Impact of Recurrence Score on type and duration of chemotherapy in breast cancer

K. Willemsma BS c,* W. Yip BS c,† N. LeVasseur MD,‡ K. Dobosz MD,§ C. Illmann BS c,† S. Baxter MD,‡ C. Lohrisch MD,‡ and C.E. Simmons MD MSc‡

ABSTRACT

Background The use of Oncotype DX (Genomic Health, Redwood City, CA, U.S.A.) testing has been shown to change treatment decisions in approximately 30% of breast cancer (BCa) cases, but research on how Recurrence Score testing has affected the type of chemotherapy offered is limited. We sought to determine if the availability of Oncotype DX testing resulted in a change to the type and duration of chemotherapy regimens used in the treatment of early-stage hormone receptor–positive BCa.

Methods In a population-based cohort study, patients treated in the 2 years before the availability of Oncotype DX testing were compared with patients treated in the 2 years after testing availability. Charts were audited and divided into 2 groups: pre-Oncotype DX and post-Oncotype DX. The groups were compared for differences in duration of chemotherapy (12 weeks vs. >12 weeks), types of agents used (anthracycline vs. non-anthracycline), and myelosuppressive potential of the chosen regimen.

Results Of 834 patients who fulfilled the enrolment criteria, 360 fell into the pre-Oncotype DX era, and 474, into the post-Oncotype DX era. An increase of 11.2 percentage points, to 69.5% from 58.3%, was observed in the proportion of patients receiving short-course compared with long-course chemotherapy (p = 0.068). The proportion of patients prescribed anthracycline-containing regimens declined in the post-Oncotype DX era (47.7% pre vs. 32.2% post, p = 0.016). The selection of more-myelosuppressive chemotherapy protocols increased in the post-Oncotype DX era (67.4% pre vs. 78.8% post, p = 0.044).

Conclusions In the present study, the availability of Oncotype DX testing was observed to influence the choice of chemotherapy type in the setting of early-stage BCa.

Key Words Oncotype DX, Recurrence Score, early-stage breast cancer, chemotherapy choices, personalized medicine, adjuvant chemotherapy, myelosuppression

INTRODUCTION

The 21-gene Recurrence Score assay, commonly known as Oncotype DX (Genomic Health, Redwood City, CA, U.S.A.) testing, has had a significant impact on the treatment of early-stage hormone receptor–positive breast cancer (BCa) because it has been shown to quantify the risk of recurrence and to predict the benefit of adding chemotherapy to endocrine therapy when treating patients with hormone receptor–positive node-negative disease1,2. The assay is now recommended as a standard in BCa clinical guidelines for such patients3–6. Several studies have since demonstrated that use of Oncotype DX testing has resulted in a change in treatment decision in 20%–45% of cases7–25. However, the changes reported were limited to whether chemotherapy was added or omitted; whether the type of chemotherapy recommended was affected by Oncotype DX testing was not captured.

Recently, the results of the TAILORx trial were reported, demonstrating a 98.7% rate of freedom from recurrence in patients with BCa and a low Recurrence Score (0–10) who received endocrine therapy alone26. Although
women 50 years of age or younger with an intermediate Recurrence Score (16–25) received some benefit from chemotherapy, endocrine therapy alone was found to be noninferior to chemotherapy plus endocrine therapy with respect to survival outcomes overall. Although the TAILORx trial reported the percentage of patients who received docetaxel–cyclophosphamide (DC) and anthracycline-based chemotherapy regimens (56% and 36% respectively), no information was provided about how the chemotherapy type prescribed differed from the planned treatment for the patient before the Oncotype DX result was received.

To date, few research studies have investigated the effect of Oncotype DX availability on the types and durations of chemotherapy regimens used for patients who have an intermediate-to-high Recurrence Score. Little is known about the adoption of shorter-course chemotherapy regimens or the omission of anthracycline-based regimens in the setting of Oncotype DX availability. Such changes in the type of chemotherapy have broader implications for resource allocation in terms of chair time and nursing time and costs. Patient health is also affected, because shorter and less-aggressive chemotherapy regimens are less burdensome for patients in the short term and, if anthracyclines are omitted, protect patients from cardiotoxicity in the long term.

Oncotype DX testing first became available in 2004 in the United States. It became available in Canada as part of clinical studies in 2005. Despite being a standard in clinical guidelines since 2007, the Oncotype DX assay was not available in British Columbia for use outside of clinical trials until 2014. That unique situation allowed for an investigation, in a contemporary cohort, of the effect of Oncotype DX testing on the types of chemotherapy used.

The purpose of the present study was to determine if the availability of Oncotype DX testing resulted in changes to the types of chemotherapy regimens prescribed for patients with early-stage breast cancer (BCa). The primary objective of the present study was to assess any difference in the proportion of patients who received a 12-week course of chemotherapy compared with a longer course of chemotherapy. The secondary objectives were to determine the proportion of patients who received a more myelosuppressive course compared with a less myelosuppressive course of chemotherapy, an anthracycline-based regimen compared with a non-anthracycline-based regimen, and endocrine therapy plus chemotherapy compared with endocrine therapy only.

**METHODS**

**Patient Selection**

Our retrospective cohort study included patients with estrogen receptor-positive, HER2 (human epidermal growth factor receptor)–negative BCa treated at BC Cancer in the province of British Columbia. To assess the effect of the availability of Oncotype DX testing on the type of chemotherapy prescribed, a chart review of patients treated in the 2 years before and the 2 years after Oncotype DX availability was performed. Patients were divided into two groups: those who received treatment for BCa before Oncotype DX availability in 2014 (pre-Oncotype DX cohort, January 2012 to December 2013), and those who received Oncotype DX testing and treatment for BCa after Oncotype DX availability (post-Oncotype DX cohort, January 2014 to December 2015). The study received institutional ethics board approval through the University of British Columbia BC Cancer Research Ethics Board.

For the pre-Oncotype DX cohort, patients were identified using BC Cancer electronic health records in an audit of the charts of all patients with a new diagnosis of estrogen receptor–positive, HER2-negative BCa and a medical oncology consultation date between January 2012 and December 2013. Patients were included if they were 20–80 years of age, had undergone definitive surgery, and were eligible to receive adjuvant chemotherapy based on performance status. With respect to tumour characteristics, patients more than 40 years of age were included only if they had grade 2 or 3 tumours sized pT1b or greater and node-negative disease. Node-negative disease was defined as no node involvement (pN0) or isolated tumour cells only (pN0i+). Patients less than 40 years of age with node-negative disease were included in the study regardless of tumour grade and stage. Patients with a single micrometastatic deposit, defined as 0.3–2 mm in a single lymph node were also considered eligible for the study. The foregoing criteria were used in selecting the pre-Oncotype DX era cohort because they reflected the criteria adopted by BC Cancer for funding Oncotype DX testing in 2014. Patients who underwent Oncotype DX testing as part of a clinical trial and patients who paid privately for Oncotype DX testing before 2014 were excluded from the pre-Oncotype DX cohort.

Patients in the post-Oncotype DX era cohort were those who had a medical oncology consultation between January 2014 and December 2015 and who underwent Oncotype DX testing. Those patients were identified in the provincial funding database for Oncotype DX testing. The inclusion criteria for the post-Oncotype DX cohort were identical to those for the pre-Oncotype DX era, with the additional requirement of having undergone Oncotype DX testing through BC Cancer after 2014.

**Endpoint Assessment**

The charts of eligible patients were audited for demographic information, tumour characteristics, and cancer treatment details. Specifically, duration of the chemotherapy protocol, anthracycline use, and myelosuppressive potential of the regimen were recorded to determine the effect of the Oncotype DX result on the type of chemotherapy prescribed (supplemental Table 1). For the present study, a chemotherapy regimen with a greater than 20% chance of inducing febrile neutropenia without the use of growth factor support was defined as “more myelosuppressive.” In the post-Oncotype DX era, the proportions of patients who had a low, intermediate, and high Recurrence Score were documented. Patient comorbidity information was also collected to ensure that comorbidities were not confounding the chemotherapy type. Patient information was recorded in a secure password-protected database.

A priori, a “clinically meaningful change” was considered to be a 20% difference in the pattern of use from the pre-Oncotype DX era to the post-Oncotype DX era for the primary endpoint. To demonstrate such a change with a 95% confidence interval (CI) and 80% power, a minimum of 100 patients who received chemotherapy was needed.
in each cohort. Based on earlier studies, it was estimated that 30% of the patients who undergo Oncotype DX testing would be offered chemotherapy. Given that proportion, a minimum sample size of 600 patients (300 patients each in the pre- and post-Oncotype DX eras), was required. Therefore, a minimum of 600 patients had to be included to have a sample size large enough for the intended 95% CI.

Patient charts for the pre-Oncotype DX cohort were reviewed in reverse chronological order beginning with Oncotype DX availability in 2014 and working backward in time until a cohort of 360 patients was identified. Patient charts for the post-Oncotype DX cohort were reviewed in chronological order from 2014 forward in time until sufficient chemotherapy cases were included to accurately compare that cohort with the pre-Oncotype DX cohort.

**RESULTS**

**Patient Characteristics**

The 834 identified patients included 360 in the pre-Oncotype DX era and 474 in the post-Oncotype DX era. During chart review, 13 patients in the pre-Oncotype DX era and 38 patients in the post-Oncotype DX era were excluded because they did not meet the eligibility criteria (Figure 1). The eligible patients in both groups were well matched for age, grade and stage of disease, and comorbidities (Table I). The median age in both groups was 59 years. Tumour grade was similar in the two eras, with most patients having an intermediate tumour grade. Most patients had T1c or T2 tumours. Overall, the difference in T stage between the eras was minimal: in the pre-Oncotype DX era, 195 patients (54.2%) were staged T1c and 146 (40.6%) were staged T2; and in the post-Oncotype DX era, 248 (52.3%) were staged T1c, and 188 (39.7%) were staged T2. Likewise, there were minimal differences in nodal status, with 25 patients in pre-Oncotype DX era (6.9%) and 41 in the post-Oncotype DX era (8.6%) having isolated tumour cells classified as N0i+.

| TABLE I | Patient demographics in pre- and post-Oncotype DX eras |
|----------|------------------------------------------------------|
| Parameter | Oncotype DX era [n (%)] | p Value |
| | Pre | Post | Both |
| Patients (n) | 360 | 474 | 834 | — |
| Age at MO consultation (years) | | | | |
| Median | 59 | 59 | 59 | 0.052 |
| Range | 29–80 | 24–80 | 24–80 | |
| Tumour grade [n (%)] | | | | |
| Low | 0 (0) | 14b (3.0) | 14 (1.7) | 0.003b |
| Intermediate | 218 (60.6) | 295 (62.2) | 513 (61.6) | |
| High | 142 (39.4) | 165 (34.8) | 307 (36.8) | |
| Pathologic tumour stage | | | | |
| IA | 4 (1.1) | 1 (0.2) | 5 (0.6) | 0.094 |
| IB | 10 (2.8) | 29 (6.1) | 39 (4.7) | |
| IC | 195 (54.2) | 248 (52.3) | 443 (53.1) | |
| II | 146 (40.6) | 188 (39.7) | 334 (40.0) | |
| III | 5 (1.4) | 8 (1.7) | 13 (1.6) | |
| Pathologic nodal status | | | | |
| N0 | 335 (93.1) | 433 (91.4) | 768 (92.1) | 0.366 |
| N0 (i+) | 25 (6.9) | 41 (8.6) | 66 (7.9) | |
| Comorbidities | | | | |
| Diabetes | 45 (12.5) | 45 (9.5) | 90 (10.8) | 0.177 |
| Liver disease | 6 (1.7) | 5 (1.1) | 11 (1.3) | 0.545 |
| Kidney disease | 7 (1.9) | 7 (1.5) | 14 (1.7) | 0.603 |
| Previous cancer | 29 (8.1) | 55 (11.6) | 84 (10.1) | 0.092 |
| Cerebrovascular disease | 9 (2.5) | 7 (1.5) | 16 (1.9) | 0.286 |
| Cardiovascular diseasec | 8 (2.2) | 10 (2.1) | 18 (2.2) | 0.912 |

a Genomic Health, Redwood City, CA, U.S.A.
b Although they didn’t meet eligibility criteria, these 14 patients received Oncotype DX testing, which affected the chi-square p value calculation.

Tumour grade did not affect the type of chemotherapy.
c Includes angina, myocardial infarction, and congestive heart failure.

The eligible patients in both groups were well matched for age, grade and stage of disease, and comorbidities (Table I). The median age in both groups was 59 years. Tumour grade was similar in the two eras, with most patients having an intermediate tumour grade. Most patients had T1c or T2 tumours. Overall, the difference in T stage between the eras was minimal: in the pre-Oncotype DX era, 195 patients (54.2%) were staged T1c and 146 (40.6%) were staged T2; and in the post-Oncotype DX era, 248 (52.3%) were staged T1c, and 188 (39.7%) were staged T2. Likewise, there were minimal differences in nodal status, with 25 patients in pre-Oncotype DX era (6.9%) and 41 in the post-Oncotype DX era (8.6%) having isolated tumour cells classified as N0i+. Rates of diabetes, liver disease, kidney disease, cerebrovascular disease, and cardiovascular disease were comparable in the two groups. More patients with a prior history of other cancers were identified in the post-Oncotype DX cohort than in the pre-Oncotype DX era (29 in the pre-Oncotype DX cohort and 55 in the post-Oncotype DX cohort), although the difference was not statistically significant (p = 0.092).

**Recurrence Score and Chemotherapy Use**

With respect to the distribution of Oncotype DX Recurrence Score results within the post-Oncotype DX cohort,
250 patients (52.7%) had a low Recurrence Score (<18), 151 patients (31.9%) had an intermediate Recurrence Score (18–30), and 73 patients (15.4%) had a high Recurrence Score (≥31). That Recurrence Score distribution is similar to the distribution in a B.C. study by Davidson et al. and in studies conducted in other jurisdictions. In our study, 36.7% of patients in the pre-Oncotype dx era and 24.9% in the post-Oncotype dx era received chemotherapy in addition to endocrine therapy, representing an 11.8 percentage point decline in chemotherapy use between the eras (p < 0.001; 95% CI: 5.5 to 18.0).

**DISCUSSION**

The availability of Oncotype dx testing resulted in subtle but notable differences in the types and durations of chemotherapy for patients with early-stage BCa in British Columbia. Our study shows an increase of 11.2 percentage points in the choice of short-course (12-week) chemotherapy treatments in the post-Oncotype dx era compared with the pre-Oncotype dx era (for chemotherapy-eligible patients). That observation suggests a shift away from the use of longer chemotherapy regimens since the adoption of Oncotype dx testing. Most patients in the post-Oncotype dx cohort (84.5%) had either a low or intermediate Recurrence Score. Those patients were either spared chemotherapy or received a shorter course of chemotherapy compared with their counterparts in the pre-Oncotype dx era, who were

| Regimen received | Oncotype DX era [n (%)] | Percentage point change | p Value |
|------------------|------------------------|-------------------------|---------|
|                  | Pre (n=360)            | Post (n=474)            |         |
| Endocrine therapy| Only endocrine agents  | 228 (63.3)              |         |
|                  |                        | 356 (75.1)              |         |
|                  |                        | 11.8                    | <0.001  |
| Chemotherapy     | Short-course           | 77 (58.3)               | 118 (24.9) |
|                  | Long-course            | 55 (41.7)               | 82 (69.5) |
|                  | Anthracycline-based    | Yes                     | 63 (47.7) | 38 (32.2) | 11.2 | 0.068 |
|                  |                        | No                      | 69 (52.3)| 80 (67.8) |                      |
|                  |                        | 15.5                    | 0.016   |
|                  | Myelosuppressive       | More                    | 89 (67.4) | 93 (78.8) | 11.4 | 0.044 |
|                  |                        | Less                    | 43 (32.6)| 25 (21.2) |                      |

* Genomic Health, Redwood City, CA, U.S.A.
more likely to undergo longer protocols despite having the same tumour stages and grades. In the post-Oncotype DX era, more-aggressive treatment approaches, such as longer courses of chemotherapy or anthracycline-based regimens, were often reserved for patients with a high Recurrence Score.

Our study also showed a statistically significant decrease of 15.5 percentage points in the use of anthracycline-based agents in the post-Oncotype DX era compared with the pre-Oncotype DX era. Those results accord with the findings of Henry et al.34, which showed a decrease of 24 percentage points in the use of anthracycline-based chemotherapy for patients who had undergone Oncotype DX testing. Prior studies have investigated the effects of anthracycline-based chemotherapy regimens on cardiovascular health in patients, and there is a well-established link between anthracycline-based agents and increased rates of cardiotoxicity and cardiac death35. Fewer patients are being exposed to the cardiotoxicity risk associated with anthracyclines in the post-Oncotype DX era.

We observed a statistically significant decline of 11.8 percentage points in the proportion of prescribed chemotherapy in the post-Oncotype DX era, which is a smaller change than described in prior reports. Davidson et al.30 showed that Oncotype DX testing led to a change of recommendation by B.C. physicians in 30% of cases—specifically, chemotherapy was omitted in 20% of cases and added in 10% of cases. However, our study cohort included larger proportions of patients with grade 2 and 3 BCa, and stage II and III tumours. Also, the patient population in our study was older, having a median age 6 years greater than the mean age in the Davidson et al. study (59 vs. 53 years)30. Other studies have reported a change in the treatment recommendation for 20%-45% of cases, with most reporting a net decline in chemotherapy use of 10–15 percentage points7–25. Again, small variations in the cohort composition were evident between the studies, because our study restricted Oncotype DX testing to patients with grade 2 or grade 3 tumours only; other studies included patients with grade 1 tumours. Those differences might explain the subtle decline in chemotherapy use seen in our study, compared with previous studies, for the post-Oncotype DX era.

The Davidson et al.30 study also demonstrated that the use of Oncotype DX testing in the province of British Columbia was cost-effective within the context of a publicly funded health care system. Since the availability of Oncotype DX, the trend toward the prescription of shorter chemotherapy regimens might result in higher cost savings than previously reported in studies focused on the omission of chemotherapy alone. For instance, in British Columbia, the current cost of 4 cycles of dc chemotherapy is approximately $1435, which is nearly half the $2500 cost of the longer act regimen (4 cycles of doxorubicin–cyclophosphamide every 3 weeks, followed by 4 cycles of paclitaxel every 3 weeks), when nursing hours, the cost of the chemotherapy agents, and the cost of filgrastim are considered36–38. The Oncotype DX test costs CAS$4380 (Wong N. Genomic Health. Personal communication, 2019). Consequently, it is important to monitor whether the decrease in chemotherapy use since the availability of Oncotype DX testing continues to mitigate the cost of using the test in clinical practice.

Among the limitations of the present study is its status as a retrospective cohort study, in which the patient data collected were limited to those available from retrospective chart review. Additional factors affecting the type of chemotherapy being prescribed in the pre- and post-Oncotype DX eras might not have been captured. For instance, a cohort of patients in the post-Oncotype DX era might have been missed because a decision about the use of chemotherapy was made without Oncotype DX testing because of preference or comorbidity. Moreover, the present study reflects trends for the use of chemotherapy in early-stage BCa in British Columbia, although whether those trends are reflective of changes in the type of chemotherapy used in other regions or in patients with higher-stage disease remains unclear. That being said, BC Cancer encompasses 5 cancer care institutions dispersed across the province. The present study was therefore able to investigate the effect of Oncotype DX testing on the type of chemotherapy used across multiple institutions in a contemporary population-based cohort. It included patients with BCa treated immediately before and after the availability of Oncotype DX. Although changes in standard BCa treatment practices are possible, those changes should be mitigated by the negligible time difference between the two eras. In particular, the dc chemotherapy protocol was launched in British Columbia in 2007, well before the period under investigation39. Although prospective randomized studies are the “gold standard” to assess the effect of an intervention on outcomes, an analysis of the effect that the availability of a new health technology exerts on real-world behaviour can be obtained only in a careful retrospective review. The present study therefore encompasses a large group of patients eligible for Oncotype DX testing and demonstrates the effect of that test on real-world practice.

### TABLE III

| Regimen received | Recurrence Score group [n (%)] | Percentage point change | p Value |
|------------------|-------------------------------|-------------------------|---------|
|                  | Low and Intermediate (n=401) | High (n=73)             |         |
| Endocrine therapy| Only endocrine agents         |                         |         |
|                  | 350 (87.3)                    | 6 (8.2)                 | 79.1    | <0.001   |
| Chemical therapy |                           |                         |         |
| Short-course     | 51 (12.7)                     | 67 (91.8)               |         |
|                  | 42 (82.4)                     | 40 (59.7)               |         |
| Long-course      | 9 (17.6)                      | 27 (40.3)               | 22.7    | 0.008    |
| Anthracycline-based |                     |                         |         |
| Yes              | 10 (19.6)                     | 28 (41.8)               | 22.2    | 0.010    |
| No               | 41 (80.4)                     | 39 (58.2)               |         |
| Myelosuppressive|                           |                         |         |
| More             | 43 (84.3)                     | 50 (74.6)               | 9.7     | 0.205    |
| Less             | 8 (15.7)                      | 17 (25.4)               |         |

* Genomic Health, Redwood City, CA, U.S.A.
CONCLUSIONS

The availability of Oncotype dx testing has had a notable impact on the type of chemotherapy prescribed in early-stage estrogen receptor–positive, HER2-negative breast cancer. Notable trends toward an increase in the use of short-course chemotherapy and a significant decline in the use of anthracycline-based chemotherapy regimens were observed in the post-Oncotype dx era. Chemotherapy use was reduced by 11.8 percentage points, suggesting a smaller effect on the overall use of chemotherapy than has been reported in other studies. With the recent publication of the TAILORx results, which found no benefit with the use of chemotherapy for nearly all patients with an Oncotype dx low or intermediate Recurrence Score, we expect a further shift in chemotherapy prescription patterns. As we continue to monitor the effect of Oncotype dx testing and other biomarker assays in this setting, we will be able to assess the long-term implications of the foregoing trends on resource allocation.

ACKNOWLEDGMENTS

We acknowledge BC Cancer, the University of British Columbia Medical Undergraduate Program, and the University of Waterloo cooperative education program. We also thank Kristen Bystrom for her support with statistical analysis, and Julie Bedford and Linda Hamata for insights about chemotherapy treatment practices in British Columbia. We acknowledge Agena for providing unrestricted funding for this project (research grant no. 20157087 to CES). Lastly, we thank all the patients undergoing treatment for breast cancer, without whom this project would not be possible.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare the following interests: NL has received research funding from Genomic Health and AbbVie, and has received fees as an advisory board member from TerSera Canada and Pfizer. CES has received research funding from Pfizer and Agena, and has received fees as an advisory board member from Pfizer, Agena, Novartis, Roche, Merck, Lilly, Sandoz, and Mylan. CL has received materials to support clinical trials (non-financial support) from NanoString, KW, WY, KD, CI, and SB have no conflicts of interest to disclose.

AUTHOR AFFILIATIONS

*Applied Health Sciences and 1Science, University of Waterloo, Waterloo, ON; 2Medical Oncology, BC Cancer, and 3Medicine, University of British Columbia, Vancouver, BC.

REFERENCES

1. 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.
2. 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.
3. Giuliano AE, Edge SB, Hortobagyi GN. Eighth edition of the AJCC cancer staging manual: breast cancer. Ann Surg Oncol 2018;25:1783–5.
4. Andre F, Ismaila N, Henry NL, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: ASCO clinical practice guideline update—integration of results from TAILORx. J Clin Oncol 2019;37:1956–64.
5. Cardoso F, Kyriakides S, Ohno S, et al. on behalf of the ESMO Guidelines Committee. Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019;30:1672.
6. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Ver. 1.2019. Fort Washington, PA: NCCN; 2019. [Current version available online at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (free registration required); cited 8 July 2019]
7. Ademuyiwa FO, Miller A, O’Connor T, et al. The effects of Oncotype dx Recurrence Scores on chemotherapy utilization in a multi-institutional breast cancer cohort. Breast Cancer Res Treat 2011;126:797–802.
8. Albanell J, Gonzalez A, Ruiz-Borrego M, et al. Prospective transGCAM study of the impact of the 21-gene Recurrence Score assay and traditional clinicopathological factors on adjuvant clinical decision making in women with estrogen receptor–positive (ER+) node-negative breast cancer. Ann Oncol 2012;23:625–31.
9. Asad J, Jacobson AF, Estabrook A, et al. Does Oncotype dx Recurrence Score affect the management of patients with early-stage breast cancer? Am J Surg 2008;196:527–9.
10. 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.
11. Cheung PS, Tong AC, Leung RC, Yau TC. Initial experience with the Oncotype dx assay in decision-making for adjuvant therapy of early oestrogen receptor-positive breast cancer in Hong Kong. Hong Kong Med J 2014;20:401–6.
12. de Boer RH, Baker C, Speakman D, Chao CY, Yoshizawa C, Mann GB. The impact of a genomic assay (Oncotype dx) on adjuvant treatment recommendations in early breast cancer. Med J Aust 2013;199:205–8.
13. Dieci MV, Guarnieri V, Zustovich F, et al. Impact of 21-gene breast cancer assay on treatment decision for patients with T1–T3, NO–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.
14. 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 2012;24:618–24.
15. Geffen DB, Abu-Ghanem S, Sion-Vardy N, et al. Impact of the 21-gene Recurrence Score assay on decision making about adjuvant chemotherapy in early-stage estrogen-receptor–positive breast cancer in an oncology practice with a unified treatment policy. Ann Oncol 2011;22:2381–6.
16. 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.
17. 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 pN1m, ER-positive breast cancer in the UK. Br J Cancer 2013;108:2250–8.
18. Jhe JO, Esposito NN, Kilik J, et al. The effect of Oncotype dx Recurrence Score on treatment recommendations for patients with estrogen receptor–positive early stage breast cancer and correlation with evaluation of recurrence risk by breast cancer specialists. Oncologist 2011;16:1520–6.
19. Klang SH, Hamerman A, Liebermann N, Efrat N, Doberne J, Hornberger J. Economic implications of 21-gene breast cancer...
cancer risk assay from the perspective of an Israeli-managed health-care organization. Value Health 2010;13:381–7.

20. 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.

21. 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.

22. Lo SS, Mumby PB, Norton J, et al. Prospective multicenter study of the impact of the 21-gene Recurrence Score assay on medical oncologist and patient adjuvant breast cancer treatment selection. J Clin Oncol 2010;28:1671–6.

23. Oritz R, Paul D, Cohn AL, Sedlacek SM. Impact of a commercial reference laboratory test Recurrence Score on decision making in early-stage breast cancer. J Oncol Pract 2007;3:182–6.

24. Ozmen V, Atasoy A, Gokmen E, et al. Impact of Oncotype DX Recurrence Score on treatment decisions: results of a prospective multicenter study in Turkey. Curreseus 2016;8:e522.

25. Yamuchi 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.

26. 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.

27. 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;351:2817–26.

28. Butts C, Kamel-Reid S, Batist G, et al. Benefits, issues, and recommendations for personalized medicine in oncology in Canada. Curr Oncol 2013;20:e475–83.

29. BC Cancer Agency. Systemic Therapy Update. Vol. 17, No. 4, Suppl 1. Victoria, BC: BC Cancer Agency; 2014. [Available online at: http://www.bccancer.bc.ca/systemic-therapy-site/Documents/STUpdateApr2014Supplement_15Apr2014.pdf; cited 8 July 2019]

30. Davidson JA, Cromwell I, Ellard SL, et al. A prospective clinical utility and pharmacoeconomic study of the impact of the 21-gene Recurrence Score assay in oestrogen receptor positive node negative breast cancer. Eur J Cancer 2013;49:2469–75.

31. Augustovski F, Soto N, Caporale J, Gonzalez L, Gibbons L, Ciapponi A. Decision-making impact on adjuvant chemotherapy allocation in early node-negative breast cancer with a 21-gene assay: systematic review and meta-analysis. Breast Cancer Res Treat 2015;152:611–25.

32. Holmes FA, O Shaughnessy JA, Vukelja S, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. J Clin Oncol 2002;20:727–31.

33. Younus J, Vandenberg T, Jawaid M, Jawaid MA. Febrile neutropenia rates with adjuvant docetaxel and cyclophosphamide chemotherapy in early breast cancer: discrepancy between published reports and community practice—an updated analysis. Curr Oncol 2012;19:332–4.

34. Henry NL, Braun TM, Ali HY, et al. Associations between use of the 21-gene Recurrence Score assay and chemotherapy regimen selection in a statewide registry. Cancer 2017;123:948–56.

35. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. BMC Cancer 2010;10:337.

36. BC Cancer. BC Cancer Protocol Summary for Neoadjuvant or Adjuvant Therapy for Early Breast Cancer Using Doxorubicin and Cyclophosphamide Followed by Weekly Paclitaxel. Victoria, BC: BC Cancer; 2011. [Available online at: http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Breast/BRAJACTW_Protocol.pdf; cited 8 July 2019]

37. Provincial Health Services Authority (PHSA). Search Jobs [Web resource]. Victoria, BC: PHSA; n.d. [Available at: https://jobs.phsa.ca/search-jobs/Registered%20nurse%20BC%20Cancer; cited 8 July 2019]

38. Government of Ontario. Ontario Drug Benefit Formulary/Comparative Drug Index, search results for “Filgrastim” [Web resource]. Toronto, ON: Queen’s Printer for Ontario; 2019. [Available at: https://www.formulary.health.gov.on.ca/formulary/results.xhtml?q=filgrastim&type=1; cited 8 July 2019]

39. BC Cancer. BC Cancer Protocol Summary for Neoadjuvant or Adjuvant Therapy for Breast Cancer Using Docetaxel and Cyclophosphamide. Victoria, BC: BC Cancer; 2019. [Available online at: http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Breast/BRAJDC_Protocol.pdf; cited 8 July 2019]