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Adherence to guidelines in requesting Oncotype DX in a publicly funded health care system

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ABSTRACT

Background Oncotype DX [ODX (Genomic Health, Redwood City, CA, U.S.A.)] is an approved prognostic tool for women with node-negative, hormone receptor–positive, HER2-negative breast cancer. Because of cost, optimal use of this test is crucial, especially in a publicly funded health care system. We evaluated adherence with our provincial guidelines for ODX requests, the management of patients with an intermediate recurrence score (RS), and the cost impact of ODX.

Methods This retrospective study included 201 consecutive patients with an ODX request from two university institutions in Quebec between May 2012 and December 2014. Concordance with provincial guidelines was estimated, with its 95% confidence interval (CI). For patients with an intermediate RS, factors influencing the final treatment decision were assessed. The cost impact of ODX was derived from the proportion of patients for whom chemotherapy was not recommended.

Results
In 93.0% of patients (95% CI: 89.5% to 96.6%), ODX was ordered according to guidelines. The concordance was similar in both institutions (92.7%; 95% CI: 88.1% to 97.3%; and 93.6%; 95% CI: 88.2% to 99.0%). In 112 (55.7%), 78 (38.8%), and 9 (4.5%) patients, the RS suggested low, intermediate, and high risk respectively. In the intermediate-risk group, most patients ($n = 58$, 74.4%) did not receive chemotherapy, mainly because of patient preference and the absence of a clear proven benefit. Savings of CA$100,000 for the study period (2.5 years) were estimated to be associated with ODX use.

Conclusions In our experience, the use of ODX was concordant with published recommendations and had a positive cost impact.

Key Words Early breast cancer, node-negative disease, hormone receptor–positive disease, HER2-negative disease, Oncotype DX, multigene assays

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INTRODUCTION

At the time of diagnosis, 70% of breast cancers express hormone receptors without HER2 amplification (luminal subtype)[1]. In more than half those patients, the disease is confined to the breast, with no lymph node involvement[2]. Adjuvant endocrine therapy reduces the risk of breast cancer recurrence and is associated with better survival; hence, it is the standard of care in all patients with luminal disease[3]. In that setting, the indication for adjuvant chemotherapy is more controversial, and refinement of prognostication for the patient is crucial, considering that a 15.0% risk of distant recurrence at 10 years remains for this group of patients[4]. In the last decade, myriad gene assays have been developed to refine prognosis and to help guide decisions about adjuvant systemic treatment for breast cancer patients with luminal disease[5]. Among others, Oncotype DX [ODX (Genomic Health, Redwood City, CA, U.S.A.)], is a prognostic tool that has demonstrated clinical value. It is currently recommended by major clinical practice guidelines in patients with node-negative, hormone receptor–positive, HER2-negative breast cancer[6–8].

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As a validated multigene diagnostic assay, ODX uses reverse-transcriptase polymerase chain reaction on formalin-fixed paraffin-embedded tumour blocks to quantify the expression of 21 genes. It produces a recurrence score (RS) that can estimate the 10-year risk of distant recurrence after 5 years of adjuvant tamoxifen. The risk of distant recurrence can be approximately 6.8% in the low-risk RS category (score < 18) and up to 30.5% in the high-risk RS category (score > 30)[4]. A meta-analysis of 1154 early breast cancer patients who were candidates for adjuvant chemotherapy showed that, before ODX, 671 (58.0%) received a recommendation for adjuvant chemotherapy. Testing with ODX led to an absolute reduction in chemotherapy recommendations of 24.0%[9].

Canada's health care system is government-funded, and all residents across the country are covered[10]. The ODX test costs CA$4,200 per patient, and given that it is reimbursed by Quebec's health care system, it might represent a financial burden. To better guide the clinician in the selection of patients who could benefit from the use of ODX and in optimizing its use, guidelines were published in May 2012 by Quebec's Direction québécoise de cancérologie (DQC)[11]. So far, no data about adherence to the guidelines in a real-life setting are available. Our study aimed to evaluate the adequacy of ODX requests in an academic setting after introduction of the guidelines. We also examined the management of patients with an intermediate-risk RS, and the potential cost impact of the ODX test.

METHODS

Study Design

This retrospective multicentre study was conducted in 2 affiliated university institutions in the province of Quebec: the Centre intégré de cancérologie de la Montérégie (CICM) and the Centre hospitalier universitaire de Sherbrooke (CHUS). The study was approved by the independent ethics committees and the authorizing agencies of the participating institutions.

The study was designed as a collaborative group effort at the Breast Unit of the CICM, including oncologists, surgeons, and pathologists who are involved and specialized in the care of breast cancer patients.

Patients

Eligible patients were consecutive women with newly diagnosed early-stage breast cancer for whom an ODX was ordered between 1 May 2012 (that is, the date that the DQC guidelines were disseminated) and 31 December 2014. An archived record of the orders was obtained from the Internet platform of Genomic Health, which allows for the retrieval of all available cases. All eligible patients received their treatments at one of the participating institutions.

Baseline demographic information, clinicopathologic features of the tumour, ODX results, and treatments received were collected from medical records for all included patients. All the data required to determine adherence to the DQC criteria were also extracted from the medical records.

Objectives and Endpoints

The primary endpoint was the proportion of ODX tests ordered that accorded with the 6 eligibility criteria of the DQC guidelines (Table I) in the population overall and separately by participating institution. Secondary endpoints included a description of the factors influencing the final decision to give or not give chemotherapy to patients with an intermediate-risk RS and the absolute difference between the costs estimated for our real-world cohort and the costs estimated for a parallel fictional cohort.

Statistical Analysis

For a prescription of ODX to be considered to accord with the DQC guidelines, all 6 guideline criteria had to be met. In the presence of micrometastatic lymph node disease (N1mi), the criterion was met only if approved reasons (Table I) were clearly stated in the chart. The information related to criterion 6 (that is, would the patient accept chemotherapy if so recommended by the RS) was rarely available in the oncologist's consultation notes; it was therefore considered met by default unless divergent information was specified elsewhere in the chart.

The proportions of patients whose ODX prescription accorded with all criteria in the established guidelines are presented with 95% confidence intervals (CIs). For patients with an intermediate-risk RS, the proportion who received chemotherapy was determined, and a descriptive analysis of the factors influencing the final decision of the clinician to use or not use adjuvant systemic chemotherapy was performed. Finally, to explore potential savings or added costs associated with ODX use, we first estimated the medical expenses associated with the use of adjuvant chemotherapy in breast cancer at our institutions. We estimated a global cost related to adjuvant chemotherapy of CA$10,500 per patient. That estimate was based on 4 cycles of docetaxel and cyclophosphamide (CA$800) followed by 10 days of granulocyte colony–stimulating factor (CA$9,000). It also included nursing time (CA$700). We then added the cost of the ODX test (CA$4,200). Finally, 16 days of hospitalization was attributed to adjuvant chemotherapy in our cohort. Given that 1 day of hospitalization costs roughly CA$1,000, another CA$16,000 was added.

We then built a fictional cohort based on the assumption that 58.0% of our patients (n = 117) would have been treated with adjuvant systemic chemotherapy if ODX had not been used. That assumption was based on the meta-analysis by Hornberger and Chien[9] that evaluated the effect of RS on treatment recommendations. Provided that the number of chemotherapy-associated days of hospitalization observed in our cohort reflected reality, we extrapolated that number for the 117 patients in our fictional cohort who would have been treated with chemotherapy and obtained a total of 60 days of hospitalization. Therefore, CA$60,000 was added to the cost of our fictional cohort. Lastly, we compared the total cost for both cohorts. The impact on cost was determined after the cost for the fictional cohort was subtracted from the real-world cohort.

RESULTS

Between 1 May 2012 and 31 December 2014, an ODX test was ordered for 201 breast cancer patients, 123 (61.2%) at CICM and 78 at CHUS (38.8%).

TABLE I Guidelines from the Direction québécoise de cancérologie for the use of the Oncotype DX[a] test

Criterion	Description
1	Invasive breast cancer
2	pT1b (>0.5 cm to 1.0 cm) AND histologic grade 2 or 3, high nuclear grade, LVI OR pT1c or pT2
3	Lymph node–negative[b]
4	Hormone receptor–positive (estrogen or progesterone receptor, or both)
5	HER2-negative (defined as IHC 0 or 1+, or ISH non-amplified)
6	Patient would accept chemotherapy if recommended by the recurrence score

[a] Genomic Health, Redwood City, CA, U.S.A.
[b] A test ordered for micrometastatic lymph node involvement (stage N1mi; metastasis between 0.2 mm and 2 mm) is authorized if the clinician concludes that the use of systemic chemotherapy poses a high risk for a particular patient, or if the patient presents with an especially good prognosis (grade 1 and high hormone receptor expression).
LVI = lymphovascular invasion; IHC, immunohistochemistry; ISH = *in situ* hybridization.

Table II presents the baseline demographic characteristics of the real-world cohort. Of the 201 patients enrolled, 138 (68.6%) were between 50 and 69 years of age, and 152 (75.6%) were postmenopausal. In the cohort, 179 patients (89.0%) underwent breast-conserving surgery, and 196 (97.5%) had a sentinel lymph node biopsy. The primary tumour measured between 1.1 cm and 2 cm in most women (n = 136, 67.7%), and 160 of the tumours (79.6%) received a histopathologic grade of 2, with 200 of them (99.5%) being hormone receptor–positive and HER2-negative. The ODX test was requested mainly by oncologists (n = 119, 59.0%), and in about one third of cases, by surgeons (n = 73, 36.3%).

Concerning the distribution of patients in each ODX RS category, 112 (55.7%) had a low-risk RS, 78 (38.8%) had an intermediate-risk RS, and 9 (4.5%) had a high-risk RS. None of the 28 patients with a grade 1 tumour was found to have a high-risk RS, and 3 of 13 patients with a grade 3 tumour were found to have a low-risk RS and were thus spared adjuvant chemotherapy.

Testing in Accord with Guidelines

Overall, 93.0% (95% CI: 89.5% to 96.6%) of ODX tests were ordered in accord with the established DQC guidelines. The proportions at the 2 participating institutions were comparable: 92.7% (95% CI: 88.1% to 97.3%) at CICM, and 93.6% (95% CI: 88.2% to 99.0%) at CHUS.

Table III shows the extent to which each criterion was fulfilled independently at the 2 participating institutions. All women had invasive breast cancer. In 3 patients, the size criterion was not met because their tumours were staged either pT1a and pT1b with no unfavourable characteristics, or pT3. The lymph node criterion was respected for 195 patients (97.0%). Of the 6 patients whose tests did not comply with the lymph node criterion, 1 had macrometastatic lymph node involvement (N1a disease), and 5 had micrometastatic lymph node involvement (N1mi). Of those with N1mi disease, all had grade 2 tumours, and 4 had a high level of hormone receptor expression (range: 80%–95%). None had specific comorbidities placing them at particular risk for chemotherapy-induced toxicities. An ODX test was ordered for 1 patient whose tumour was estrogen receptor–negative (<1%), but the test was not performed by Genomic Health because of the low level of expression of the hormone receptors. An ODX test was performed for 2 patients who turned out to have HER2-positive disease. Finally, 3 patients had indicated that they would refuse chemotherapy no matter the result returned by the ODX, but the ODX test was performed despite that information.

In our real-world population overall, adjuvant systemic chemotherapy was recommended for 31 patients (15.4%). Prior reports have estimated that, in patients with similar characteristics before the use of ODX, chemotherapy would be recommended in up to 58.0% of patients[9]. In our population, had ODX not been available, that proportion would have translated into an additional 86 patients treated with adjuvant chemotherapy.

Management of Patients with an Intermediate-Risk RS

Overall, 78 patients (38.8%) had an intermediate-risk RS. Of those 78, most (n = 58, 74.3%) did not receive adjuvant systemic chemotherapy (Table IV). Many reasons were documented by the clinicians to justify their chemotherapy recommendation (Table V). Patient preference and absence of a proven benefit were the main reasons for withholding chemotherapy in this group.

Cost Impact

In the fictional and real-world cohorts, the total cost was estimated to be, respectively, CA$1,288,500 and CA$1,185,700 for the entire study period of 2.5 years (Table VI). The additional cost related to the use of more chemotherapy—and collateral costs—in the fictional cohort was CA$947,000. The additional costs related to the use of ODX in our cohort was CA$844,200. The additional costs associated with more use of adjuvant systemic chemotherapy (CA$947,000) in the fictional cohort therefore surpassed the additional costs associated with ODX (CA$844,200). Overall, we estimated that, despite its initial additional cost when ordered, use of the ODX test led to savings of approximately CA$100,000 in 2.5 years.

DISCUSSION

In the present study, we investigated adherence to DQC guidelines about the use of ODX for patients with node-negative, hormone receptor–positive, HER2-negative breast

TABLE II Baseline characteristics of the study patients

Characteristic	Patient group		
	CICM	CHUS	Combined
Patients *(n)*	123	78	201
Age group [*n* (%)]			
<40 Years	0 (0.0)	3 (3.8)	3 (1.5)
40–49 Years	20 (16.2)	7 (9.0)	27 (13.4)
50–59 Years	39 (31.7)	23 (29.5)	62 (30.8)
60–69 Years	46 (37.4)	30 (38.5)	76 (37.8)
70–79 Years	18 (14.6)	15 (19.2)	33 (16.4)
Female sex [*n* (%)]	123 (100.0)	78 (100.0)	201 (100.0)
Menopausal status [*n* (%)]			
Menopausal	88 (71.5)	64 (82.1)	152 (75.6)
Premenopausal	35 (28.5)	14 (17.9)	49 (24.4)
Surgery [*n* (%)]			
Breast conservation	111 (90.2)	68 (87.2)	179 (84.8)
Total mastectomy	10 (8.1)	10 (12.8)	20 (10.0)
Modified radical mastectomy	2 (1.6)	0 (0.0)	2 (1.0)
Histology [*n* (%)]			
Invasive ductal carcinoma	92 (74.8)	50 (64.1)	142 (70.6)
Invasive lobular carcinoma	19 (15.4)	15 (19.2	34 (16.9)
Lymph node assessment [*n* (%)]			
Sentinel lymph node biopsy	121 (98.4)	75 (96.2)	196 (97.5)
Node dissection	1 (0.8)	1 (1.3)	2 (1.0)
None	1 (0.8)	2 (2.6)	3 (1.5)
Tumour stage [*n* (%)]			
T1a	0 (0)	1 (1.3)	1 (0.5)
T1b	20 (16.3)	15 (19.2)	35 (17.4)
T1c	81 (65.9)	55 (70.5)	136 (67.7)
T2	21 (17.1)	6 (7.7)	27 (13.4)
T3	1 (0.8)	1 (1.3)	2 (1.0)
Nodal stage [*n* (%)]			
N0	112 (91.1)	74 (94.9)	186 (92.5)
N0i+	4 (3.3)	2 (2.6)	6 (3.0)
N1mi	6 (4.9)	2 (2.6)	8 (4.0)
N1a	1 (0.8)	0 (0.0)	1 (.5)
Histopathologic grade [*n* (%)]			
1	14 (11.4)	14 (17.9)	28 (13.9)
2	102 (82.9)	58 (74.4)	160 (79.6)
3	7 (5.7)	6 (7.7)	13 (6.5)
Hormone receptor status [*n* (%)]			
Positive	123 (100.0)	77 (98.7)	200 (99.5)
Negative	0 (0.0)	1 (1.3)	1 (0.5)
HER2 status [*n* (%)]			
Positive	2 (1.6)	0 (0.0)	2 (1.0)
Negative	121 (98.4)	78 (100)	199 (99.0)

TABLE II Continued

Characteristic	Patient group		
	CICM	CHUS	Combined
Chemotherapy [*n* (%)]			
TC×4	10 (8.1)	12 (15.4)	22 (10.9)
AC×4	0 (0.0)	3 (38.4)	3 (1.5)
FEC×6	1 (0.8)	0 (0.0)	1 (0.5)
AC-T or FEC-D	0 (0.0)	2 (2.6)	2 (1.0)
Trastuzumab-based CTx	3 (2.4)	0 (0.0)	3 (1.5)
Oncotype DX recurrence score [*n* (%)]			
Low-risk (<18)	71 (57.7)	41 (52.6)	112 (55.7)
Intermediate-risk (18–30)	47 (38.2)	31 (39.7)	78 (38.8)
High-risk (>30)	5 (4.1)	4 (5.1)	9 (4.5)
Indeterminate	0 (0.0)	2 (2.6)	2 (1.0)
Oncotype DX request [*n* (%)]			
Oncologist	105 (85.4)	14 (17.9)	119 (59.2)
Surgeon	18 (14.6)	55 (70.5)	73 (36.3)
Other	0 (0.0)	8 (10.3)	8 (4.0)

CICM = Centre intégré de cancérologie de la Montérégie; CHUS = Centre hospitalier universitaire de Sherbrooke; N0i+ = isolated tumour cells (malignant cells in regional lymph node or nodes not >0.2 mm); N1mi = micrometastasis (>0.2 mm or >200 cells, but not >2.0 mm); HER2 = human epidermal growth factor receptor; TC = docetaxel–cyclophosphamide; AC = doxorubicin–cyclophosphamide; FEC = 5-fluorouracil–epirubicin–cyclophosphamide; AC-T = doxorubicin–cyclophosphamide–taxane; FEC-D = 5-fluorouracil–epirubicin–cyclophosphamide–docetaxel; CTx = chemotherapy.

TABLE III Criteria of the Direction québécoise de cancérologie respected

Variable	Value [*n* (%)]		
	CICM	CHUS	Combined
Requests	123	78	201
Criteria met by requests			
Invasive breast cancer	123 (100.0)	78 (100.0)	201 (100.0)
pT1b with unfavourable characteristics[a] OR pT1c or pT2	122 (99.2)	76 (97.4)	198 (98.5)
Lymph node–negative OR N1mi in special situation	118 (95.9)	77 (98.7)	195 (97.0)
Hormone receptor–positive	123 (100.0)	77 (98.7)	200 (99.5)
HER2-negative	121 (98.4)	78 (100.0)	199 (99.0)
Patient would accept CTx	122 (99.2)	76 (97.4)	198 (98.5)
All 6 criteria met by requests	114 (92.7)	73 (93.6)	187 (93.0)

[a] Grade 2 or 3, high nuclear grade, lymphovascular invasion.
CICM = Centre intégré de cancérologie de la Montérégie; CHUS = Centre hospitalier universitaire de Sherbrooke; CTx = chemotherapy.

cancer in 2 university institutions in Quebec. Overall, we observed good concordance between the theoretical and real-life use of ODX. Both participating institutions performed equally in that regard. Most patients in the intermediate-risk RS category did not receive chemotherapy. We estimated that, with the use of ODX, 86 patients were spared chemotherapy and that, despite the price, use of ODX led to substantial savings of approximately CA$100,000 during the 2.5-year study period.

Not all provinces in Canada officially reimburse the ODX test for N1mi disease[8]. In contrast, in Quebec, ODX can be used in the presence of N1mi disease only in special situations—for example, for patients thought to be at low risk of recurrence because of certain good pathologic

TABLE IV Risk categorization and use of adjuvant systemic chemotherapy

Risk group	Pts (*n*)	Chemotherapy [*n* (%)]	
		Yes	No
Low-risk			
CICM	71	0 (0.0)	71 (100.0)
CHUS	41	2 (4.9)	39 (95.1)
Combined	112	2 (1.8)	110 (98.2)
Intermediate-risk			
CICM	47	10 (21.3)	37 (78.7)
CHUS	31	10 (32.3)	21 (67.7)
Combined	78	20 (25.6)	58 (74.4)
High-risk			
CICM	5	4 (80.0)	1 (20.0)
CHUS	4	4 (100.0)	0 (0.0)
Combined	9	8 (88.9)	1 (11.1)
Undetermined			
CICM	0	0 (0.0)	0 (0.0)
CHUS	2	1 (50.0)	1 (50.0)
Combined	2	1 (50.0)	1 (50.0)

Pts = patients; CICM = Centre intégré de cancérologie de la Montérégie; CHUS = Centre hospitalier universitaire de Sherbrooke.

TABLE V Reasons for decision-making in the group with an intermediate recurrence score

Reason	Cited by [*n* (%)]		
	CICM (*n*=47)	CHUS (*n*=31)	Combined (*n*=78)
Patient's comorbidities	0 (0.0)	1 (3.2)	1 (1.3)
No proven scientific benefit	12 (25.5)	5 (16.1)	17 (21.8)
Other worrisome pathology features	3 (6.4)	2 (6.5)	5 (6.4)
Shared decision-making with patient	20 (42.6)	12 (38.7)	32 (41.0)
Absolute value of Oncotype DX[a]	8 (17.0)	8 (25.8)	16 (20.5)
None	4 (8.5)	2 (6.5)	6 (7.7)

[a] Genomic Health, Redwood City, CA, U.S.A.
CICM = Centre intégré de cancérologie de la Montérégie; CHUS = Centre hospitalier universitaire de Sherbrooke.

features (grade 1 and high positivity for hormone receptors), or for those who, if given chemotherapy, would be at high risk of complications because of comorbidities.

Despite the low number of patients included in the analysis, our study showed that the clinicopathologic criterion with the highest discordance was the one concerning lymph node status. That observation reflects the fact that the utility of ODX in this population is highly controversial. Even though ODX also has prognostic value in node-positive disease, the actual low-risk RS cut-off in the latter group has been shown to be associated with a substantial risk of distant recurrence[12]. The results of the RXPONDER S1007 trial, an ongoing phase III trial that aims to determine a low-risk RS cut-off at which chemotherapy could be spared in node-positive luminal breast cancer, are awaited to better define the role of ODX in that group of patients (see NCT01272037 at http://ClinicalTrials.gov).

Notably, a distinction is seldom made between macrometastasis and micrometastasis: they are globally referred to as "node-positive," and N1mi patients are sometimes included with N0 patients, blurring even more the possibility to draw conclusions[13]. Patients with N1mi involvement are not eligible for the RXPONDER trial; hence, no additional information will be obtained from that trial for those patients. Nonetheless, in a population-based study by Petkov *et al.*[14] using U.S. Surveillance, Epidemiology, and End Results program data, the 5-year breast cancer–specific mortality for patients with node-positive disease (micrometastases and 1–3 positive nodes) was just 1.0% for patients with a RS of less than 18. In March 2016, the Institut national d'excellence en santé et en services sociaux, an organization that promotes the optimal use of technologies, pronounced itself in favour of approving ODX in patients with micrometastatic lymph node involvement[15]. Our analysis does not take into account that recent recommendation.

Interestingly, 2 patients with HER2-positive breast cancer received an ODX test. In both cases, the gene assay had been requested by the clinician while he was waiting for the result of *in situ* hybridization after an intermediate result by immunochemistry. In those cases, the RSS were 47 and 22, and trastuzumab was given. Also, 1 patient received adjuvant trastuzumab despite having a HER2-negative result on immunochemistry and on *in situ* hybridization; that decision was based on a HER2-positive result by reverse-transcriptase polymerase chain reaction from ODX. Even though quite uncommon, such a finding has previously been observed and occurs in approximately 1.0% of cases[16]. The optimal management of such patients,

TABLE VI Analysis of costs

Cost component	Medical expense (CA$)		
	Real-world cohort	Fictional cohort	Difference (real – fictional)
Adjuvant CTx[a]	325,500 (31 pts × 10,500)	1,228,500 (117 pts × 10,500)	–903,000
Hospitalization	16,000 (16 days × 1000)	60,000 (60 days × 1000)	–44,000
Oncotype DX	844,200 (201 pts × 4200)	0 (0 × 4200)	+844,200
TOTAL	1,185,700	1,288,500	–102,800

[a] Chemotherapy agents, nursing, granulocyte colony–stimulating factor.
CTx = chemotherapy; pts = patients.

including the potential benefit of anti-HER2 targeted therapy, is currently unknown.

In addition, 3 patients received a costly ODX test despite mentioning that they would have refused chemotherapy. Of those 3 patients, 2 had confided to a third party that they did not want chemotherapy; however, after an interdisciplinary meeting, the test was prescribed based only on clinicopathologic criteria. The 3rd patient refused chemotherapy, and the test was ordered with the hope that the result could be used to convince her to accept chemotherapy, considering her high-risk clinical characteristics at diagnosis.

In line with prior reports, approximately half our patient cohort (55.7%) was categorized as having a low-risk RS. The distribution of patients in the intermediate- and high-risk groups was, however, respectively higher (38.8%) and lower (4.5%) than in prior reports[4]. Current guidelines neither recommend nor forbid adjuvant systemic chemotherapy in patients with an intermediate RS. Results of the prospective TAILORX trial are awaited to clarify whether additional benefit could be gained from chemotherapy in this group of patients[6]. Our cohort illustrates this area of uncertainty, with 58 of the patients in that group (74.4%) not receiving adjuvant chemotherapy. Importantly, the physician's final decision was based mainly on a shared decision-making process that included the patient.

So far, rigorous analyses have shown that ODX is cost-effective. In Canada, Tsoi *et al.*[17] reported an incremental cost-effectiveness ratio per quality-adjusted life-year of CA$63,064 with ODX. In Canada, the threshold for governmental willingness to pay is approximately CA$50,000–CA$80,000 per quality-adjusted life-year[18,19]. In the present study, we investigated potential savings with the use of ODX. Despite the increased initial cost that inevitably comes with ODX, the added expense might be offset by less adjuvant chemotherapy being prescribed. However, that analysis contains some potential biases. We estimated a fixed cost for chemotherapy that did not take into account the various regimens that are commonly used in daily practice. The decision to include a cost for granulocyte colony–stimulating factor for all patients is debatable, as is the decision to extrapolate hospitalization days from our population to the hypothetical cohort. Notably, those results do not take into account the psychological burden associated with the use of adjuvant chemotherapy and with its potential long-term toxicities (for example, cognitive impairment, fertility issues, and peripheral neuropathy) that sometimes require specialized care or treatment. Those additional elements could further increase the positive cost impact of ODX.

Recently, efforts have been made to optimize ODX use by integrating standard clinicopathologic features (estrogen receptor, progesterone receptor, Ki-67 index, HER2, and Bloom–Richardson–Elston grade) in the RS prediction[20]. Identifying a group of patients with a highly predictive ODX result is appealing, because the use of ODX could then be restricted solely to patients for whom it could really add value, while at the same time diminishing its financial burden. For example, some data suggest that ODX does not add useful information for low-grade tumours[21]. Interestingly, in our cohort, none of the patients with grade 1 tumours were found to have a high-risk RS, and none of them received chemotherapy. Further validation of such models is required before they can be recommended in daily practice.

CONCLUSIONS

Our study showed a good adherence rate to published guidelines for ODX prescription in 2 academic hospitals in Quebec. Although most patients in the intermediate-risk RS category did not receive chemotherapy, data to clarify the optimal management of such patients are eagerly awaited. Prescription of ODX according to guidelines seemed to have a positive impact on costs by balancing its price with the savings produced by chemotherapy sparing. Further savings might even be achieved by using ODX as a complementary tool together with well-known prognostic clinicopathologic features. More and larger real-world studies investigating adherence to available guidelines for the use of multigene assays should be considered a research priority not only to improve patient management, but also resource management from the perspective of a publicly funded health care system.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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