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Rate of *EGFR* mutation testing for patients with nonsquamous non-small-cell lung cancer with implementation of reflex testing by pathologists

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ABSTRACT

Background Testing for mutation of the *EGFR* (epidermal growth factor receptor) gene is a standard of care for patients with advanced nonsquamous non-small-cell lung cancer (NSCLC). To improve timely access to *EGFR* results, a few centres implemented reflex testing, defined as a request for *EGFR* testing by the pathologist at the time of a nonsquamous NSCLC diagnosis. We evaluated the impact of reflex testing on *EGFR* testing rates.

Methods A retrospective observational review of the Web-based AstraZeneca Canada EGFR Database from 1 April 2010 to 31 March 2014 found centres within Ontario that had requested *EGFR* testing through the database and that had implemented reflex testing (with at least 2 years' worth of data, including the pre- and post-implementation period).

Results The 7 included centres had requested *EGFR* tests for 2214 patients. The proportion of pathologists requesting *EGFR* tests increased after implementation of reflex testing (53% vs. 4%); conversely, the proportion of medical oncologists requesting tests decreased (46% vs. 95%, $p < 0.001$). After implementation of reflex testing, the mean number of patients having *EGFR* testing per centre per month increased significantly [12.6 vs. 4.9 (range: 4.5–14.9), $p < 0.001$]. Before reflex testing, *EGFR* testing rates showed a significant monthly increase over time (1.37 more tests per month; 95% confidence interval: 1.19 to 1.55 tests; $p < 0.001$). That trend could not account for the observed increase with reflex testing, because an immediate increase in *EGFR* test requests was observed with the introduction of reflex testing ($p = 0.003$), and the overall trend was sustained throughout the post–reflex testing period ($p < 0.001$).

Conclusions Reflex *EGFR* testing for patients with nonsquamous NSCLC was successfully implemented at multiple centres and was associated with an increase in *EGFR* testing.

Key Words Reflex testing, *EGFR*, biomarkers, non-small-cell lung cancer

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INTRODUCTION

Several biomarkers have emerged as prognostic and predictive in advanced nonsquamous non-small-cell lung cancer (NSCLC). Of those biomarkers, the most widely studied has been the epidermal growth factor receptor (EGFR). The presence in NSCLC tumours of somatic activating mutations in the kinase domain of the *EGFR* gene, particularly small in-frame deletions in exon 19 (deletion 19) and a missense mutation in exon 21 (L858R), strongly correlate with increased responsiveness to EGFR tyrosine kinase inhibitors (TKIs)[1–3]. Such mutations are found predominately in tumours with nonsquamous histology and more commonly in never-smoker women of East Asian ethnicity[4].

Based on consistent data showing that, compared with standard chemotherapy, EGFR TKIs improve clinical outcomes for patients with tumours harbouring *EGFR* activating mutations, the recommended systemic therapy for advanced nonsquamous NSCLC takes a personalized approach: Recommended first-line treatment for patients with advanced *EGFR*-mutated nonsquamous

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NSCLC is an EGFR TKI (erlotinib, gefitinib, or afatinib); for patients with advanced *EGFR*-negative nonsquamous NSCLC, chemotherapy or other targeted therapies are chosen[5–7].

In line with this personalized approach, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology (CAP/IASLC/AMP) published consensus guidelines recommending that *EGFR* mutation testing be performed at time of diagnosis of nonsquamous NSCLC for patients with advanced-stage disease who are suitable for therapy, with the results guiding treatment decisions[8,9].

Despite those recommendations, a recent international survey of medical oncologists found that *EGFR* testing was not performed for 1 in 4 patients with advanced NSCLC in North America (24%)[10]. One of the main barriers to *EGFR* testing identified by medical oncologists was the long turnaround time for results; oncologists and patients were both uncomfortable with delaying therapy because of the risk of clinical deterioration during that time[10]. In Canada, the time from initiation of *EGFR* testing to results was found to be 18 days (range: 15–26 days)[11]. Also, to add to the delay, tests might be cancelled because of an insufficient tumour sample or the sample not being sent from the holding lab to the testing lab.

The first EGFR TKI approved by Health Canada for the treatment of advanced *EGFR* mutation–positive NSCLC was gefitinib in December 2009. Subsequently, on 18 March 2010, *EGFR* mutation testing became readily available through a Web-based platform managed and funded by AstraZeneca Canada: the AstraZeneca Canada EGFR Database. A request for *EGFR* testing would be initiated using a Web-based portal, and then a notice would be sent to the original reporting pathology ("holding") laboratory to forward tumour samples to one of the validated laboratories in Canada. Patient age, sex, smoking status, ethnicity, and tumour histology were captured in the database, as was the date the test was requested and an indicator of whether the test was completed or cancelled. The database did not include the *EGFR* test result, and testing was limited to patients with nonsquamous NSCLC. That Web-based portal for ordering *EGFR* testing was discontinued in September 2014 once public funding for *EGFR* testing was available.

Currently, given that *EGFR* results affect treatment choice only for patients with advanced-stage disease, *EGFR* testing has generally been initiated by medical oncologists once a patient is deemed eligible for an EGFR TKI (that is, the patient is known to have advanced-stage disease). Earlier receipt of biomarker results by medical oncologists has been shown to significantly improve time-to-treatment decisions and treatment for patients with advanced nonsquamous NSCLC[12,13]. Thus, in an effort to improve timely access to *EGFR* test results, a few centres in Ontario adopted centre-specific protocols for reflex *EGFR* mutation testing. "Reflex testing" was defined as a request for *EGFR* testing by the pathologist at the time of a nonsquamous NSCLC diagnosis, regardless of a patient's clinical stage.

The objective of the present study was to evaluate *EGFR* testing rates associated with the implementation of reflex testing by pathologists.

METHODS

Patients and Centres

This observational retrospective review used data from the AstraZeneca Canada EGFR database for *EGFR* test requests reported through the database from 1 April 2010 to 31 March 2014. The data analysis protocol was approved by the Sunnybrook Health Sciences Centre research ethics board. Patient privacy was ensured and protected per research ethics board guidelines. Centres within Ontario that had adopted centre-specific protocols for reflex *EGFR* mutation testing were included in the study. It was mandatory that centres requesting *EGFR* testing through the AstraZeneca Canada EGFR Database have at least 2 years of data available, including periods before and after implementation of reflex testing.

Study Outcomes

The primary outcome of our study was the rate of *EGFR* testing before and after implementation of reflex testing at centres in Ontario. One *EGFR* test request per patient was included in the analysis, and based on date, the first *EGFR* request for the patient was included. Any subsequent *EGFR* tests requested for the same patient were categorized as duplicates. In the sensitivity analysis April–August 2011 was excluded, because during that period, Ontario had no public funding for EGFR TKIs, and an associated decrease in *EGFR* testing was documented for that period[11]. Secondary analyses compared the number of *EGFR* tests requested by medical oncologists, by pathologists, and by other specialties; the number of *EGFR* tests reported as completed; the number of duplicate *EGFR* tests; and changes in patient demographics before and after implementation of reflex testing.

Duplicate *EGFR* requests for a patient were categorized as necessary or unnecessary. "Necessary requests" were those for patients whose earlier *EGFR* test was cancelled or inconclusive and for which a different tumour sample was sent for testing, or alternatively, those for patients whose tumour sample was not received by the testing lab and for whom the test request was reinitiated. "Unnecessary requests" were *EGFR* tests requested for a patient by the same or a different physician despite a previously completed *EGFR* test, or *EGFR* tests requested for a tumour sample that had already been tested with an inconclusive result.

Sample Size

Sample size for examining the difference in the monthly rate of *EGFR* testing before and after the introduction of reflex testing was based on an ARIMA(1,1,0) model, using the formula derived by McLeod and Vingilis[14]. Assuming a type I error of 0.05 (alpha) and a series of 36 monthly data points, with an average of 24 points before the intervention and 12 after the intervention, the study would have 80% power to detect a 1.5 standard deviation change in the number or rate of *EGFR* tests. The study actually had greater power to detect smaller changes, because approximately 36 data points were available for each of 7 centres (that is, 36 * 7 = 252 data points). Site-specific analyses were also possible.

Statistical Analysis

The ecologic denominator data (for example, the total number of NSCLC cases) required to estimate true *EGFR* testing rates (that is, accounting for changes in the incidence of NSCLC during the study period by hospital-level geography) could not be determined at the level of hospital catchment area. We therefore made the assumption that, during the 2-year study period, the incidence of NSCLC did not change appreciably.

Monthly counts of *EGFR* tests were used as the primary outcome of the analysis. Integer-valued autoregressive Poisson models were therefore used to evaluate overall changes in *EGFR* testing over time[15]. Such models are appropriate for count data, particularly when monthly counts are low (that is, at the level of the individual hospital). The resulting time-series analysis will be sensitive to changes in level of *EGFR* testing in real time as hospitals change their protocols.

To evaluate the effect of site-specific changes in protocol, a Poisson-based generalized estimating equations approach was used to identify any differences in *EGFR* testing before and after the introduction of reflex testing[16]. In that analysis, the index date was the date of implementation of reflex testing, and the total number of tests before and after implementation were compared, accounting for the amount of time before and after implementation.

To evaluate differences in secondary outcomes, generalized estimating equations models were used to account for serial correlation of errors and clustering by centre. The form of the generalized estimating equations model depended on the outcome being evaluated (for example, logit for binary outcomes, normal for continuous outcomes).

All analyses were conducted using the SAS software application (version 9.3: SAS Institute, Cary, NC, U.S.A.), and a p value less than 0.05 was used as an indicator of statistical significance.

RESULTS

Centres

At 6 of the 7 included Ontario centres, reflex testing was implemented during these months: May 2012—Royal Victoria Regional Health Centre, Barrie; April 2013—Health Sciences North (HSN), Sudbury; October 2013—North York General Hospital, Toronto; November 2013—Toronto East General Hospital, Toronto, and Thunder Bay Regional Health Sciences Centre, Thunder Bay; December 2013—Southlake Regional Hospital, Newmarket. At Sunnybrook Health Sciences Centre (SHSC), University of Toronto, Toronto, reflex testing by pathologists was initially instituted during February 2013 for tissue samples that were diagnosed as NSCLC nonsquamous histology and were found outside of lung (for example, in brain, bone, and liver biopsies); in June 2013, the policy was amended to reflex test all tissue samples regardless of biopsy site.

All centres initially sent tumour samples for *EGFR* testing outside their centre to either the University Health Network, Toronto (which began testing during March 2010); the Bay Area Genetics Laboratory, Hamilton (which began testing during April 2012); or the HSN laboratory, Sudbury (which began testing during April 2013). Before developing their in-house testing, HSN sent samples to outside testing laboratories.

EGFR Testing

The included centres sent *EGFR* test requests for 2214 patients during the study period (1330 patients before and 884 patients after implementation of reflex testing). Overall, the mean number of tests per centre per month increased to 12.6 after implementation from 4.9 before implementation, for a mean difference of 7.7 tests (range: 4.5–14.9 tests; $p < 0.001$; Table I). From April 2011 to August 2011, a statistically significant decrease in the pre-implementation rate of *EGFR* testing occurred (mean monthly count April–August 2011: 2.3 ± 1.6; mean monthly count outside the April–August 2011 window: 5.1 ± 5.4; $p < 0.001$). Excluding the April–August 2011 window from the analysis, the increase in tests in the post-implementation period remained statistically significant, with a mean difference per month of 7.5 tests (range: 3.9–14.8 tests; $p < 0.001$). Individually, all centres showed a significant increase in the mean number of *EGFR* tests per centre per month after implementation of reflex testing. The exception was Southlake Regional Hospital, although it showed a trend favouring increased testing (Table I).

Over time, before the introduction of reflex testing, the monthly rate of *EGFR* testing increased statistically significantly for all Ontario centres individually and combined (1.37 more tests per month; 95% confidence interval: 1.19 to 1.55 more tests per month; $p < 0.001$). However, time series modelling demonstrated that the increase during that period did not account for the increase seen after the implementation of reflex testing. After implementation, an immediate increase in *EGFR* test requests was observed ($p = 0.003$), and that increase was sustained throughout the post-implementation period ($p < 0.001$, Figure 1).

EGFR Test Requests by Medical Specialty

Of *EGFR* test requests before the implementation of reflex testing, 4% were made by pathologists; that proportion increased to 53% after implementation ($p < 0.001$). Conversely, fewer tests were requested by medical oncologists after implementation of reflex testing (95% of tests before implementation vs. 46% after). With the exception of HSN, each individual centre showed the same significant trend (Table II). At HSN, no tests appeared to have been requested by pathologists; however, most tests were in fact ordered by pathologists, but the database requests were made under a medical oncologist's identifier.

Demographics

An increased proportion of women were tested for *EGFR* mutation status after implementation of reflex testing; no other significant differences in the demographics of tested patients were observed (Table III). Also, the proportion of patients less likely to be tested for *EGFR* mutation if demographics were to be used as selection criteria—for example, smokers or non-Asians—was no different after implementation. The proportion of non-Asian, male, smokers was similarly unchanged.

TABLE I *EGFR* mutation tests performed per centre per month before and after implementation of reflex testing

Centre	Mean test requests per month			*p* Value
	Before reflex testing	After reflex testing	Mean difference	
Sunnybrook Health Sciences Centre	9.9±5.8	14.8±4.9	4.9	0.004
Health Sciences North	2.6±2.5	13.0±4.8	10.4	<0.001
North York General Hospital	2.1±2.1	9.2±4.3	7.1	<0.001
Royal Victoria Regional Health Centre	2.2±1.6	10.7±4.3	8.5	<0.001
Southlake Regional Hospital	10.2±6.7	19.8±5.0	9.6	0.055
Thunder Bay Regional Health Sciences Centre	2.5±2.6	7.0±3.8	4.5	0.026
Toronto East General Hospital	3.9±3.2	18.8±3.3	14.9	<0.001
OVERALL	4.9±5.2	12.6±5.5	7.7	<0.001

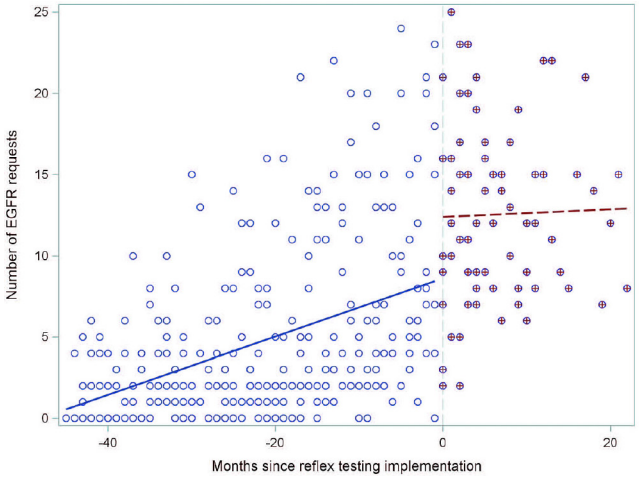

FIGURE 1 Number of *EGFR* test requests per month from time of implementation of reflex testing at all centres.

Completion of *EGFR* Tests

Implementation of reflex testing did not affect the completion of *EGFR* tests (81.9% completed before reflex testing vs. 79.4% completed after, $p = 0.15$) or the proportion of inconclusive tests (5.3% before vs. 5.0% after). Also, the occasions on which a tumour sample was not received by the testing lab, leading to cancellation of the test was not significantly affected (6.2% before reflex testing vs. 7.2% after reflex testing, $p = 0.35$). The odds of tests being completed, inconclusive, or cancelled because a tumour sample was not sent to the testing lab did not change over time.

Duplicate Tests

During the study period, 8.2% ($n = 198$) of *EGFR* test requests were duplicates. Of those 198 tests, 60.6% were unnecessary (5% of all test requests). Reflex testing had no effect on the proportion of *EGFR* test requests that were duplicates (8.2% before and after implementation, $p = 0.99$). Similarly, post-implementation, no significant difference in unnecessary *EGFR* tests requests was observed (4.3% of all tests before vs. 5.9% after, $p = 0.081$). The proportion of duplicate test requests was equally distributed by requester (medical oncologists, pathologists, and other specialties; $p = 0.56$), and the distribution did not change with the implementation of reflex testing ($p = 0.82$).

DISCUSSION

The Lung Cancer Mutation Consortium found that two thirds of NSCLC patients have an oncogenic driver and that overall survival improves if patients receive matched targeted therapy[17]. Therefore, to implement personalized medicine, the first step is to ensure that molecular tests are conducted for appropriate patients. In the present study, we specifically focused on *EGFR* mutation, understanding that other biomarkers such as *ALK* and *ROS1* are equally important in the management of advanced nonsquamous NSCLC[7].

Ideally, all patients with advanced NSCLC of nonsquamous histology who are fit for treatment should have their tumour tested for *EGFR* mutation. Our study demonstrated that, for multiple centres, implementation of reflex testing was associated with an increase in *EGFR* tests, which is consistent with reports from two single-institution studies[13,18]. Our analysis also found an increase in testing over time, which suggests improved knowledge translation of data supporting *EGFR* testing; however, that pre-existing trend did not statistically account for the sudden rise and sustained increase in test requests observed after the implementation of reflex testing.

In addition to its design as a retrospective observational study, this study is limited by an inability to determine how much of the increase in *EGFR* test requests after the implementation of reflex testing concerned patients having early-stage disease compared with patients having advanced-stage disease who would immediately benefit from the test results. Notably, the CAP/IASLC/AMP guideline encourages *EGFR* testing for patients with early-stage disease, because the availability of the result enables rapid initiation of treatment in patients who experience a recurrence[8,9]. Another limitation is the inability of the study to determine whether the increase in *EGFR* testing led to improved patient-related outcomes, because those data were not captured in the AstraZeneca Canada EGFR Database. The proportional increase in *EGFR* test requests made by pathologists compared with medical

TABLE II *EGFR* mutation test requests by medical specialty before and after implementation of reflex testing

Centre	Specialty [*n* (%)] making requests						*p* Value
	Before reflex testing (*n*=1330)			After reflex testing (*n*=884)			
	Pathologists	Medical oncologists	Other specialties	Pathologists	Medical oncologists	Other specialties	
Sunnybrook Health Sciences Centre	8 (2.4)	310 (91.2)	22 (6.5)	92 (42.0)	120 (54.8)	7 (3.2)	<0.001
Health Sciences North	0 (0.0)	97 (100.0)	0 (0.0)	0 (0.0)	156 (100.0)	0 (0.0)	—
North York General Hospital	0 (0.0)	91 (98.9)	1 (1.1)	43 (78.2)	11 (20.0)	1 (1.8)	<0.001
Royal Victoria Regional Health Centre	0 (0)	58 (100)	0 (0)	137 (55.7)	108 (43.9)	1 (0.4)	<0.001
Southlake Regional Hospital	0 (0.0)	460 (100.0)	0 (0.0)	67 (84.8)	12 (15.2)	0 (0.0)	<0.001
Thunder Bay Regional Health Sciences Centre	33 (30.0)	77 (70.0)	0 (0.0)	35 (100.0)	0 (0.0)	0 (0.0)	<0.001
Toronto East General Hospital	6 (3.5)	165 (95.4)	2 (1.2)	92 (97.9)	2 (2.1)	0 (0.0)	<0.001
OVERALL	47 (3.5)	1258 (94.6)	25 (1.9)	466 (52.7)	409 (46.3)	9 (1.0)	<0.001

TABLE III Characteristics of patients for whom *EGFR* mutation tests were requested before and after implementation of reflex testing

Characteristic	Reflex testing		*p* Value
	Before (*n*=1330)	After (*n*=884)	
Smoking [*n* (%)]			0.18
Yes	489 (40.5)	126 (44.8)	
No	720 (59.5)	155 (55.2)	
Unknown[a]	121	603	
Female [*n* (%)]			0.009
Yes	650 (51.0)	318 (57.6)	
No	624 (49.0)	242 (42.4)	
Unknown[a]	56	313	
Asian [*n* (%)]			0.412
Yes	164 (13.2)	45 (11.6)	
No	1079 (86.8)	343 (88.4)	
Unknown[a]	87	496	
Group [*n* (%)]			0.488
Asian, female, nonsmoker	65 (15.6)	16 (18.6)	
Non-Asian, male, smoker	352 (84.4)	70 (81.4)	
Unknown[a]	913	798	

[a] These individuals were not taken into account in the calculation of percentages or in statistical comparisons between time periods.

oncologists supports the success of the Ontario centres in implementing their centre-specific protocols; however, our study cannot determine if that change resulted in *EGFR* results being available earlier for treatment decisions by medical oncologists. However, a previous report from the SHSC found that reflex testing increased the proportion of patients whose biomarker results were available to medical oncologists at the time of first consultation and lowered the time to optimal first-line treatment for patients with advanced nonsquamous NSCLC[13].

Reflex testing did not altogether eliminate *EGFR* test requests from medical oncologists, indicating that room for improvement in centre protocols remains. Such requests might reflect requests from medical oncologists for patients who had a diagnosis of early-stage nonsquamous NSCLC before reflex testing and who subsequently developed advanced-stage disease after their centre had implemented the reflex protocol; it might also be attributable to requests for patients whose diagnostic tumour sample was obtained outside their centre, in a facility where reflex testing was not implemented.

The proportion of medical oncologists requesting *EGFR* tests might in fact be lower than reported here if tests actually requested by pathologists were entered as requests on behalf of medical oncologists, which occurred at HSN. But the corollary is also possible: as pathologists became comfortable with ordering *EGFR* tests after the implementation of reflex testing, verbal or written requests to pathologists from medical oncologists might have occurred and been captured as pathologist-initiated.

The CAP/IASLC/AMP guidelines discourage *EGFR* testing based on demographics because that approach inherently leads to patients receiving suboptimal first-line therapy[8,9]. Reflex testing could eliminate physician bias in centres that use demographics to make the decision for *EGFR* testing. In our study, the demographics of tested patients did not dramatically change with the implementation of reflex testing. The dataset might not have captured the true benefit of testing initiated by pathologists; after implementation, a considerable number of data points were missing, likely because the pathologists were unaware of the smoking status and ethnicity of patients.

Given that pathologists directly handle tumour specimens, one potential benefit of reflex testing might be an increase in the success rate of *EGFR* testing because of an assurance that tissue is conserved for molecular testing and because appropriate high-yield tissue samples are sent to the testing lab. However, we did not find that reflex testing modified the proportion of tests cancelled because tumour samples were not sent from holding labs, or that it improved the number of inconclusive tests. Interestingly, HSN, the only centre in our study that developed in-house testing for *EGFR* simultaneously with the implementation of reflex testing, demonstrated improvement in both those

indices—an observation suggesting that in-house testing could be a solution. Unfortunately, however, that approach is not practical for most centres. Also, those data contradict a single-institution report from SHSC, which noted an improvement in successful completion of both *EGFR* and *ALK* tests with implementation of reflex testing[19]. The present database study made the assumption that an *EGFR* test recorded as "test completed" meant successfully completed; in contrast, the SHSC study determined its completion rate directly from patient charts and pathology reports.

The benefit of reflex testing must be balanced against the extra cost incurred for *EGFR* testing in patients with early-stage disease who do not experience a relapse. Unfortunately, that concern extends to a small proportion of patients, given that the 5-year survival of all patients with NSCLC is 18%[20]. Thus, a significant number of patients with early-stage disease will progress to advanced disease in which *EGFR* mutation results will eventually guide their therapy.

There is also the possibility that, with reflex testing, unnecessary *EGFR* tests might be conducted for patients with multiple tumour samples, thus further increasing costs. However, our study found no change in the rate of unnecessary duplicate *EGFR* test requests after the implementation of reflex testing. In addition, unnecessary test requests were often recognized by the testing lab and cancelled. The fact that approximately 4%–6% of all test requests during the study period were unnecessary duplicates suggests uncertainty at the physician level about whether *EGFR* testing has already been requested for a patient. That observation highlights the need to standardize ordering, tracking, and reporting of *EGFR* tests to reduce redundancy; ideally, standardization could be established at a national level.

CONCLUSIONS

Reflex testing by pathologists for *EGFR* mutation was successfully implemented across multiple centres and resulted in an increase in *EGFR* testing. Thus, reflex testing could be considered by centres to reduce barriers to implementation of a personalized approach to systemic therapy for patients with advanced nonsquamous NSCLC.

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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 the following interests: This study was funded by AstraZeneca Canada. PKC has received research grants, honoraria, and conference support from AstraZeneca; ADo and ADz are employees of AstraZeneca. The remaining authors have no conflicts to declare.

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