

# Approach to biomarker testing: perspectives from various specialties

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## ABSTRACT

**Background** Despite its importance for patient outcomes, biomarker testing for lung cancer is not uniformly integrated into the Canadian health care system. To better understand current practice patterns for lung cancer biomarker testing, we assessed physician perspectives by specialty and region.

**Methods** A national survey of Canadian lung cancer specialists was conducted to understand their perspectives on biomarker testing in lung cancer. The 11-item survey assessed the current practice and challenges of testing. The survey was sent to 375 specialists.

**Results** The overall response rate for the survey was 36%. Nearly all specialists reported that knowing tumour genotyping results affects patient outcome and influences the treatment decision. Medical oncologists most commonly initiated molecular testing; however, most respondents suggested a shared model involving medical oncologists and pathologists. More than half of all responding specialists had the perception that fewer than 25% of test results are available for first-line treatment decisions. Identified barriers to routine testing for all lung cancer patients included cost, lack of funding, tissue availability, and sample quality.

**Conclusions** There was clear agreement that biomarker testing is important in determining appropriate treatment for patients. There is a need for general consensus on who should initiate molecular testing. Clear clinical guidance for pathologists has to be established for molecular testing, including defining the population to be tested, the timing of testing, and the tests to be performed. Testing could be facilitated by including more information on diagnostic sample requisitions, such as clinical suspicion of primary lung cancer, cancer history, and other samples already collected.

**Key Words** Advanced lung cancer, biomarker testing, testing patterns, testing barriers

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## INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality in both Canadian women and men, with a 5-year survival rate of only 18% for non-small-cell lung cancer (NSCLC)<sup>1</sup>. However, the management of NSCLC has significantly evolved since the early 2000s. Enhanced understanding of the molecular pathogenesis of NSCLC has resulted in intense interest in, and evaluation of, molecularly targeted therapies in specific subsets of patients<sup>2</sup>. Multiple trials have demonstrated that first-line therapy with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors is superior to standard platinum-based chemotherapy in patients with EGFR-mutation positive

NSCLC, improving response rates, quality of life, lung-cancer-specific symptoms, and median progression-free survival<sup>3-9</sup>. Similarly, patients with a translocation of the anaplastic lymphoma kinase (ALK) gene have experienced improved progression-free survival and other secondary outcomes when treated with the ALK inhibitor crizotinib (compared with first- and second-line chemotherapy)<sup>10</sup>. Additional molecularly-directed therapies currently in clinical development also show promise in selected patient subgroups, including those with KRAS mutations<sup>11</sup>, MET overexpression<sup>12</sup>, and ROS1 translocations<sup>13</sup>.

Customizing treatment based on histology and molecular genotype has become the standard of care for treating lung cancer patients. As a result, biomarker testing

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has increasingly been adopted in Canada to reflect those advances. Challenges exist, though, in the implementation of molecularly directed therapies. Use of those therapies depends on both the identification of, and the ability to test for, biomarkers predicting treatment benefit. The Canadian *EGFR* testing program, initiated in 2010, estimated that testing was initiated for only 38% of potentially eligible patients, and 12% of tests did not proceed because samples did not arrive at the test centre or were insufficient<sup>14</sup>. Furthermore, Ellis *et al.*<sup>14</sup> reported that uptake of *EGFR* mutation testing dropped substantially across Canada once funding from the pharmaceutical industry was discontinued in 2011.

There is an urgent need to develop a systematic and timely approach to testing in the appropriate population, with access to molecular test results in time for treatment decision-making for lung cancer patients and their providers of care. Currently, there is no national strategy or algorithm in place to ensure that biomarker testing is uniformly integrated into the Canadian health care system. Funding for biomarker testing varies by province. The result is inconsistency in access to and delivery of therapies across provinces. Notably, a molecular laboratory was only recently introduced in Eastern Canada. In Ontario, *EGFR* testing was publically funded by the provincial government only as of 18 September 2014.

Further questions about who should initiate requests for biomarker testing for *EGFR* mutations and *ALK* translocations remain. Additionally, the optimal strategy to ensure timely access to biomarker results is unclear. There is a need to understand current practice patterns for biomarker testing and to examine the perspectives of the various lung cancer-related specialties about this issue. That information will allow for an improved understanding of factors that have to be addressed in order to establish appropriate clinical guidance for biomarker testing.

## METHODS

In early 2013, a short 11-item survey (Table 1) was mailed to a cross-sectional list of 375 Canadian specialists involved in the treatment of lung cancer, including 150 medical oncologists, 75 pathologists, and 150 respirologists or thoracic surgeons. After the initial mailing, no further prompts were sent, and no incentives were provided for survey completion. To return the completed surveys, recipients were given the option either to use the postage-paid envelope provided in the mailing or to fax their responses to a designated number.

The aim of the survey, which was developed by 3 academic medical oncologists (NBL, PME, SV), was to better understand the current approach and related barriers to biomarker testing. The questionnaire assessed selected issues relating to *EGFR* and *ALK* testing:

- The specialty that generally orders *EGFR* and *ALK* testing at the respondent's centre
- How frequently testing is ordered
- How patients are selected for testing
- How testing is funded
- Perceived barriers to testing

Certain questions allowed respondents to choose more than one option. Recommendations for system improvement were constructed based both on respondent and on investigator feedback.

The data analysis was descriptive. The frequency of responses to each question is reported. Responses were examined by specialty (medical oncology, pathology, respirology) and region (Western Canada, Ontario, Quebec, Eastern Canada). Consent was implied by return of the questionnaire. The sample size was determined by the number of specialists identified.

## RESULTS

### Demographics of Survey Respondents

Of the 375 surveys distributed, 135 were completed and returned (either by mail or by fax), yielding a response rate of 36%. Responses were obtained from 38% of medical oncologists, 24% of pathologists, and 40% of respirologists. Of all respondents, 26% were from the Western provinces, 40% from Ontario, 28% from Quebec, and 6% from the Eastern provinces.

### Ordering Molecular Testing for Lung Cancer

In all regions, most specialists reported that medical oncologists initiate *EGFR* mutation testing at their centres (Table 1). Of all specialist groups, specialists in respiratory medicine were the most likely (46%) to identify themselves as one of the initiators of *EGFR* testing. That finding could be reflective of regional differences in the specialties involved in lung cancer treatment, because 52% of Quebec respondents indicated that *EGFR* testing is initiated by respirologists. However, regional responses showed similar overall patterns, with the largest proportion of respondents agreeing that medical oncologists most commonly order *EGFR* testing.

When asked who *should* order *EGFR* mutation testing, most respondents suggested a shared model for the testing process involving multiple specialties. Up to 75% of pathologists and 70% of respirologists indicated that medical oncologists should initiate *EGFR* testing. On the other hand, medical oncologists suggested that pathologists were key: 53% of medical oncologists indicated that pathologists should always routinely order *EGFR* testing as part of the lung cancer diagnostic procedure.

With the exception of Quebec, regional analysis of responses revealed similar patterns, with pathologists and medical oncologists most consistently being identified as those who should always order *EGFR* testing. In a reflection of the large number of respirologists who treat lung cancer in Quebec, 53% of respondents from Quebec believed that specialists in respiratory medicine should have a significant role in initiating the testing process, similar to the 58% of Quebec respondents who chose medical oncology.

### Impact on Outcome and Treatment Decision

Nearly all respondents (98%) agreed that having knowledge of a patient's molecular status significantly affects outcome and influences the treatment decision. Those factors were recognized as important by all specialists surveyed.

**TABLE I** The study questionnaire

Dear Dr. [name],  
 Please take a few moments to share your thoughts on molecular testing in non-small-cell lung cancer (NSCLC, emphasis on metastatic lung cancer) by filling in this survey and returning it either by using the postage-paid envelope or by faxing your response to 1-800-xxx-xxxx. The responses will be used to form the basis of a needs assessment for future. Your experience and insights on diagnosis, management, and treatment are valuable.

Thank you for your participation.  
 Drs. Peter Ellis, Natasha Leighl and Sunil Verma

1. Do you treat lung cancer?  Yes  No

**EGFR mutation**

2. a. Who orders *EGFR* mutation testing at your centre? (please check all that apply)

Respiratory medicine  Pathology  Medical oncology  Thoracic surgeon  Radiation oncology

b. Do you agree that knowing mutation status at the time of initial medical oncology consultation impacts outcome and influences treatment decision?  Yes  No

c. Who do you think should order *EGFR* mutation testing? (please check all that apply)

	ALWAYS	SOMETIMES	NEVER
ALL	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Respiratory medicine	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pathology	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Medical oncology	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Thoracic surgeon	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Radiation oncology	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. What are the barriers to having someone other than medical oncologists order the testing?  
 \_\_\_\_\_

4. Approximately what proportion of your locally advanced or metastatic NSCLC patients were potentially suitable for *EGFR* mutation testing this year?  < 10%  11%–25%  26%–40%  41%–60%  61%–80%  81%–100%

5. How many *EGFR* tests were ordered by you through the year?  < 10  11–25  26–40  41–60  61–80  81–100

6. How many delivered results in time for first-line treatment decisions?  <25%  25%–50%  51%–75%  76%–100%

7. a. Which of the following factors influence your decision to test for *EGFR*? (please check all that apply)

Asian ethnicity  Light/never smoker  Female sex

Adenocarcinoma histology  ALL

2 or more options: \_\_\_\_\_

Other: \_\_\_\_\_

b. What are the barriers to testing ALL patients?  
 \_\_\_\_\_

8. Are you testing patients regardless of stage?  Yes  No

9. Who is funding the *EGFR* testing in your region?  
 \_\_\_\_\_

**ALK mutation**

10. a. Which of the following factors influence your decision to test for *ALK*? (please check all that apply)

Asian ethnicity  Light/never smoker  Female sex

Adenocarcinoma histology  ALL

2 or more options: \_\_\_\_\_

Other: \_\_\_\_\_

b. When do you test for *ALK*?  Newly referred  Prior to 1st-line treatment  2nd-line  3rd-line  Beyond

c. What are the current barriers to *ALK* testing?  
 \_\_\_\_\_

d. Does your centre routinely test for *ALK*?  Yes  No

e. What tests are performed?  
 \_\_\_\_\_

11. Who is funding the *ALK* testing in your centre or region?  
 \_\_\_\_\_

More than half of all responding specialists (57%) had the perception that fewer than 25% of test results are available at the time of first-line treatment decision-making (Table III). Although 21% of medical oncologists reported that results almost always arrive in time for treatment decisions, most medical oncologists and other specialists did not have similar experiences. Similar delays were also indicated for the various regions. Specifically, 100% of specialists in Eastern Canada indicated that fewer than 25% of test results are delivered in time for first-line treatment decisions. Notably, our survey was conducted before the molecular laboratory was introduced in Eastern Canada, and our results might not reflect the associated changes in molecular testing practice in the region.

### Barriers to Testing All Lung Cancer Patients

As indicated by the respondents, the main barriers to testing all lung cancer patients are cost and lack of systematic

funding for molecular testing. Tissue availability and quality of tissue sample were additional key concerns, particularly among pathologists. Significant concerns reported by medical oncologists included time delays associated with the testing process, and clinician knowledge about the importance of molecular testing in treatment selection. Other barriers included a lack of clinical information given to pathologists indicating whether a lung cancer diagnosis is suspected and whether the case is advanced.

### DISCUSSION

Our survey was designed and conducted with the aim of better understanding the current reality of biomarker testing, gaining insight into the testing practices of various lung cancer–related specialties, and assessing barriers to biomarker testing. Almost all responding specialists acknowledged the importance to treatment selection of

**TABLE II** Who orders *EGFR* mutation testing, by specialty and region

Respondent category (n of 135 surveyed)	Response [n (%)] <sup>a</sup>				
	Respiratory medicine	Thoracic surgery	Radiation oncology	Pathology	Medical oncology
All respondents (116)	30 (26)	16 (14)	22 (19)	26 (22)	105 (91)
Specialty					
Pathology (15)	1 (7)	1 (7)	5 (33)	3 (20)	14 (93)
Medical oncology (51)	6 (12)	9 (18)	9 (18)	8 (16)	50 (98)
Respiratory medicine (50)	23 (46)	6 (12)	8 (16)	15 (30)	41 (82)
Region					
West (35)	4 (11)	2 (6)	10 (29)	8 (23)	32 (91)
Ontario (43)	10 (23)	8 (19)	9 (21)	6 (14)	40 (93)
Quebec (31)	16 (52)	5 (16)	3 (10)	10 (32)	26 (84)
East (7)	0 (0)	1 (14)	0 (0)	2 (29)	7 (100)

<sup>a</sup> More than one response was permitted.

**TABLE III** How many *EGFR* mutation tests deliver results in time for first-line treatment decisions, by specialty and region

Respondent category (n of 135 surveyed)	Response [n (%)]			
	<25%	25%–50%	51%–75%	76%–100%
All respondents (88)	50 (57)	16 (18)	7 (8)	15 (17)
Specialty				
Pathology (6)	4 (67)	0 (0)	0 (0)	2 (33)
Medical oncology (48)	23 (48)	10 (21)	5 (10)	10 (21)
Respiratory medicine (34)	23 (67)	6 (18)	2 (6)	3 (9)
Region				
West (23)	11 (48)	4 (17)	2 (9)	6 (26)
Ontario (30)	15 (50)	5 (17)	4 (13)	6 (20)
Quebec (29)	18 (62)	7 (24)	1 (4)	3 (10)
East (6)	6 (100)	0 (0)	0 (0)	0 (0)

knowing the patient's molecular status and the crucial effect of that status on outcome. However, the current system of biomarker testing practice poses significant challenges: more than half of all responding specialists reported that fewer than 25% of test results are provided in time for first-line treatment decisions.

An American Society of Clinical Oncology review panel recently endorsed the guidelines for molecular testing published by the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology, which recommended testing for *EGFR* mutations and *ALK* fusions in all patients with advanced-stage adenocarcinoma to guide patient selection for targeted therapies<sup>15</sup>. That endorsement highlighted the clinical importance of early molecular diagnosis in determining appropriate treatment plans for patients with advanced lung cancer. A recent study by Lim *et al.*<sup>16</sup>, which assessed the effect of testing on time to treatment decisions, demonstrated that waiting for biomarker testing results can delay the decision and treatment initiation for patients with advanced NSCLC. The lack of biomarker results at the time of first-line treatment decision is therefore a significant concern, because it can result in the unnecessary initiation of chemotherapy and an inferior outcome, including quality of life and potentially even survival.

Most specialists indicated that medical oncologists order *EGFR* mutation testing at their centres; however, opinions on who should order *EGFR* mutation testing were mixed. Although most pathologists still felt that medical oncologists should order testing, one third of respirologists and more than half the medical oncologists suggested that pathologists should initiate testing. With most patients lacking biomarker results at the time of first-line treatment decisions, there are significant opportunities for greater collaboration between specialists to incorporate biomarker testing into the lung cancer diagnostic pathway early, at the level of the pathologist. Seizing that opportunity will require that more detailed clinical information—including clinical suspicion of primary lung cancer, other cancer history, and other samples already collected (and tested) or planned (for instance, by resection)—be provided on diagnostic sample requisitions, thus assisting pathologists in making timely molecular diagnoses. Empowering pathologists to initiate molecular testing early can help to streamline the testing process and will offer greater opportunities to deliver appropriate and timely treatment plans for lung cancer patients.

The present study identified several barriers that hindered implementation of molecular testing for all patients, including a lack of tissue availability, poor sample quality, insufficient funding for biomarker testing, lack of access to testing, and the significant length of time required. To optimize the analysis of limited tissue available for biomarker testing, communication between the pathologist and the rest of the multidisciplinary team is critical<sup>17</sup>. Thoughtful prioritization of how the tissue sample will be used will help to preserve sufficient biopsy material for molecular analysis and ensure rapid diagnosis<sup>18</sup>.

The desire for minimally invasive testing procedures should also be balanced with the requirement for a tissue

yield sufficient to obtain necessary molecular diagnostic information. With the exception of resistant mutations necessitating repeat biopsies, the molecular testing process requires only a single pathology result, but has profound impact on patient outcomes<sup>19</sup>. The inherent difficulty in obtaining repeat biopsies has also led to the evaluation of circulating biomarkers, including circulating tumour cells and cell-free circulating tumour DNA, as methods of less-invasive sampling for molecular testing<sup>20</sup>. To support the current standard of molecular testing required for lung cancer, sufficient dedicated laboratory funding is required throughout the Canadian public health care system. Sufficient funding will promote greater access to, and standardization of, molecular testing practices across the country. Additional recommendations for system improvement (Table IV) were derived both from participants and from the investigators.

Limitations of the present study include regional differences in response rates, which might vary depending on the availability of on-site molecular testing and on differences between academic and community centres. The subjective nature of the study could result in variations in within-institution responses, because certain questions might be more opinion-based. We did not look at clinical and prognostic factors that might affect treatment urgency and that could influence views about which specialty or specialties should initiate testing. All of those factors could have had an effect on the representativeness of the sample in the wider Canadian context.

**TABLE IV** Recommendations

<b>Step 1</b>	Establish clear clinical guidance for pathologists and other clinicians involved in lung cancer diagnosis and treatment about molecular testing in lung cancer. The guidance should include the population to be tested, timing, and tests to be performed. International and national guidelines must be adapted for local use.
<b>Step 2</b>	Ensure that diagnostic requisitions from respirologists, thoracic surgeons, and interventional radiologists indicate whether there is clinical suspicion of primary lung cancer, other cancer history, and other samples collected (and tested) previously or planned (for example, pending surgical resection).
<b>Step 3</b>	To facilitate molecular testing, pathologists have to incorporate routine <i>EGFR</i> and <i>ALK</i> testing into the diagnostic lung cancer algorithm, minimizing unnecessary sections and immunohistochemistry. As with HER2 testing in breast cancer, molecular testing in lung cancer should be funded through provincial health care systems and should be considered routine.
<b>Step 4</b>	Clearly establish and monitor turnaround times: guidelines from the Canadian Association of Pathologists recommend 3 days for transport from diagnosing lab to the molecular testing lab, followed by a 10-day turnaround for results to be delivered to the ordering pathologist and clinician.
<b>Step 5</b>	Provide feedback to clinicians about tissue volume, quality, whether testing was successful, and molecular results in a timely manner. Provincial or national molecular databases (or both) should be maintained to ensure that molecular testing is performed for all appropriate patients.



## CONCLUSIONS

Information from early molecular diagnosis is essential in determining appropriate treatment options for patients with advanced NSCLC. There is an urgent need to establish clear guidelines about who should initiate the testing process and to ensure that sufficient resources are in place to implement molecular testing at the right time for lung cancer patients. The standardization of molecular testing practices and their integration into the routine diagnostic pathway for lung tumours will facilitate early initiation of molecular testing in the appropriate patient population, allow for more efficient molecular diagnosis and treatment of lung cancer, and most importantly, improve outcomes for Canadians with lung cancer.

## CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interests: NBL's institution (University Health Network) has received funding from Novartis Canada for an investigator-initiated trial. SV has served on advisory boards for Astra Zeneca, Roche, Novartis, Boehringer Ingelheim, Eli Lilly, Bristol-Myers Squibb, and Merck. MRS, PME, and ED declare that they have no conflicts of interest.

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