Challenges to Implementation of an Epidermal Growth Factor Receptor Testing Strategy for Non–Small-Cell Lung Cancer in a Publicly Funded Health Care System

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Background: Data from seven recent randomized clinical trials have demonstrated that epidermal growth factor (*EGFR*) mutation status is predictive of improved progression-free survival and quality of life from first-line EGFR tyrosine kinase inhibitor therapy compared with platinum-based chemotherapy. We examined barriers to the initial implementation of a national *EGFR* testing policy in Canada.

Methods: Five laboratories across Canada underwent a validation and quality-control exercise for *EGFR* mutation testing using reverse transcriptase–polymerase chain reaction with financial support from the pharmaceutical industry for the initial 12 months. Oncologists registered patients with nonquamous histology for *EGFR* mutation testing using a Web-based platform. Basic demographics were collected including age, histology, sex, smoking status, and ethnicity. The decision to prescribe gefitinib was subsequently registered on the system.

Results: Between March and December 2010, 2104 requests were received for *EGFR* mutation testing. Demographic details are as follows: adenocarcinoma (91.6%); Asian ethnicity (13.9%); female (58%); light/never smoker (41.3%); stage IV disease (87.1%). The number of tests requested each month ranged from 200 to 250. Mutation testing was conducted in 1771 of 2104 requests (84%). The median turnaround time for *EGFR* testing was 18 days (standard deviation 9.7). Gefitinib was prescribed in 302 patients (17.1%). The number of test requests dropped to 50 to 100 per month at the end of the initial 12 months.

Conclusion: There was rapid uptake of *EGFR* mutation testing into routine clinical practice in Canada. Uptake of *EGFR* mutation testing dropped substantially once funding from pharmaceutical industry was discontinued. There is a need for a national strategy to ensure resources are in place to implement molecular testing for new molecularly targeted agents.

Key Words: Non–small-cell lung cancer, Epidermal growth factor mutations, Molecular testing,Implementation.

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Significant advances have taken place in the management of patients with advanced and metastatic non–small-cell lung cancer (NSCLC) over the last 5 years. Traditionally, all advanced NSCLC patients were treated in a similar manner, in which a platinum-based two-drug combination was given as first-line therapy,[1,2] docetaxel or pemetrexed as second-line therapy,[3,4] and erlotinib as second- or third-line therapy for patients who remained well enough for treatment.[5] More recently, the importance of pathologic subtype has been recognized. Data from several randomized trials demonstrate that pathologic subtype is predictive of improved survival with selected systemic therapies.[6,7] These changes were rapidly incorporated into treatment algorithms.

There have also been major advances in the understanding of the molecular pathogenesis of NSCLC, resulting in intense research efforts to evaluate molecularly targeted agents for defined subsets of patients. Tyrosine kinase inhibitors (TKIs) of the epidermal growth factor receptor (*EGFR*) gene were initially shown to have modest improvements in survival in an unselected population of NSCLC patients.[5] Further analysis suggested that clinical characteristics such as Asian ethnicity, adenocarcinoma histology, female sex, and never-smoking status, were associated with a higher likelihood of response to EGFR TKIs.[8] However, the discovery of activating mutations of the *EGFR* gene in 2004[9,10] identified a subgroup of patients who seemed to derive dramatic benefits from EGFR TKI therapy.

Historical data suggested that the addition of EGFR TKI therapy to patients with *EGFR* mutation–positive NSCLC improved survival.[11] Multiple trials have since been conducted comparing EGFR TKIs with platinum-based chemotherapy as first-line therapy for advanced/metastatic NSCLC

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TABLE 1. Summary of Trials of First-Line Trials of EGFR TKI Versus Chemotherapy

Trial	Treatment	Population	RR	PFS (m)	PFS (HR)	QoL
IPASS[16]	Gef vs. Cb/Pac	Mut$^+$	71% vs. 47%		0.48	↑
		Mut$^-$	1% vs. 23%		2.85	
First Signal[12]	Gef vs. Cis/Gem	Mut$^+$	85% vs. 37%		0.61	↑
		Mut$^-$	26% vs. 52%		1.52	
NEJ002[13]	Gef vs. Cb/pac	Mut$^+$	74% vs. 31%	10.8 vs. 5.4 m	0.30	
WJTOG 3405[15]	Gef vs. Cb/Doc	Mut$^+$	62% vs. 32%	9.2 vs. 6.3 m	0.49	
Optimal[18]	Erl vs. Cb/Gem	Mut$^+$	83% vs. 36%	13.1 vs. 4.6 m	0.16	
EURTAC[17]	Erl vs. plt doub	Mut$^+$	58% vs. 15%	9.7 vs. 5.2 m	0.37	Not reported
Lux Lung 3[14]	Afat vs. Cis/Pem	Mut$^+$	56% vs. 23%	11.1 m vs. 6.9 m	0.58	↑

↑QoL better for EGFR TKI.

Gef, gefitinib; Erl, erlotinib; Cb, carboplatin; Cis, cisplatin; Pac, paclitaxel; Gem, gemcitabine; Doc, docetaxel; Afat, afatanib; Pem, pemetrexed; mut, mutation; plat doub, platinum doublet; PFS, progression-free survival; QoL, quality of life; HR, hazard ratio; RR, reponse rate.

(Table 1).[12–18] The initial trials, Iressa Pan Asian Study (IPASS) and First Signal,[12,16] selected patients based on clinical characteristics associated with a higher probability of harboring an *EGFR* mutation. The IPASS trial demonstrated that patients with *EGFR* mutation–positive NSCLC had significantly longer progression-free survival (PFS) if they received gefitinib compared with carboplatin and paclitaxel chemotherapy (hazard ratio 0.48; 95% confidence interval 0.36–0.64; $p < 0.001$).[16] Of equal importance was the finding that patients with *EGFR* wild-type NSCLC randomized to initial therapy with gefitinib had inferior outcomes (PFS hazard ratio 2.85, 95% confidence interval 2.05–3.98; $p < 0.001$). Five subsequent trials, performed exclusively in *EGFR* mutation–positive patients, have all confirmed that EGFR TKI therapy is the preferred first-line therapy in this molecularly defined subgroup of NSCLC patients, with higher response rates, PFS,

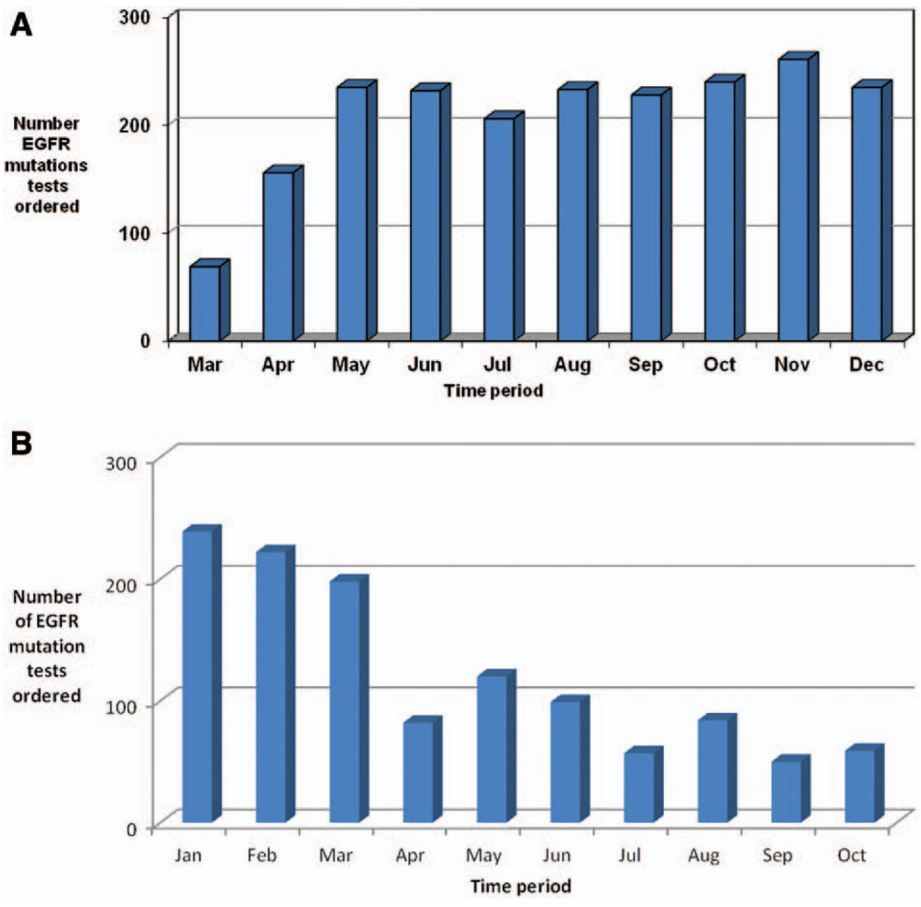

FIGURE 1. *A*, Initial uptake of *EGFR* mutation testing (March–December 2010). *B*, Number of *EGFR*-mutation tests performed upon completion of sponsored program (April–September 2011). EGFR, epidermal growth factor receptor.

and improved symptom control and/or quality of life.[13–15,17,18] Because of high rates of treatment crossover in these trials, survival differences were not seen.

The findings from these trials gained broad acceptance among oncologists worldwide. International and Canadian consensus recommendations,[19–21] as well as an Ontario Health Technology Assessment Committee report[22] recommended that tumor samples from patients with advanced/metastatic NSCLC should be tested for the presence of an activating mutation of the *EGFR*. Although gefitinib received Health Canada approval for the first-line treatment of advanced *EGFR* mutation–positive NSCLC in 2009, there was no mechanism in place in Canada to perform *EGFR* mutation testing in clinical laboratories. A national network of laboratories was set up across Canada, with funding support from AstraZeneca Canada, to perform *EGFR* mutation testing.[23] This was linked to compassionate supply of gefitinib for those patients with *EGFR* mutation–positive tumors. This article reports on the uptake of *EGFR* testing in Canada.

PATIENTS AND METHODS

The Canadian health care system is publicly funded through each province or territory. *EGFR* mutation testing was not available in Canada outside of research laboratories before March 2010. Five laboratories across the country undertook validation and quality-control processes to establish a network for *EGFR* mutation testing using reverse transcriptase–polymerase chain reaction (British Columbia Cancer Agency [BC], Alberta Cancer Agency, University Health Network, Centre de Lutte Contre le Cancer du CHUM Quebec, and Jewish General Hospital Quebec).[23] Laboratories were reimbursed for testing by AstraZeneca Canada for an initial 12 months.

Patients were eligible for *EGFR* mutation testing if they had advanced/metastatic NSCLC and nonsquamous histology. Requests for testing were made through an electronic Web-based platform. Information was collected on age, histology, sex, smoking status, and ethnicity, in addition to specimen location and identification number. A request was sent to the original reporting pathology laboratory to forward tumor samples (blocks or slides) to one of the five validated laboratories for *EGFR* mutation testing. Results were forwarded directly from the testing laboratory to the requesting physician, as well as the initial reporting laboratory. Subsequently, the decision to prescribe gefitinib for *EGFR* mutation positive patients was entered into the system. From March 2010 until March 2011, gefitinib was provided free of charge to *EGFR* mutation–positive patients. Dates of initial test request, receipt of sample at the testing laboratory, and completion of the test were recorded.

Data in this report were collected from the initial 10 months of the *EGFR* testing program (March–December 2010). Additional data on the number of tests performed up until 6 months after completion of the funded program are also available. The analysis was descriptive, and summary information is provided in this report. Testing turnaround times were calculated from the recorded dates. The number of *EGFR* mutation–positive tests was not accessible, but was inferred from the number of patients for whom gefitinib was prescribed. Patients with inadequate tissue for testing were not included when calculating the proportion of patients with an *EGFR* mutation.

RESULTS

Approximately 22,000 new lung cancer cases were diagnosed in Canada in 2010.[24] Assuming 85% of cases were NSCLCs, 40% had metastatic disease at diagnosis and 75% had nonsquamous histology, then approximately 5600 patients were potentially eligible for *EGFR* mutation testing during 2010. There was rapid uptake of *EGFR* testing across Canada (Fig. 1*A*). Between March and December 2010, 2104 requests were received for *EGFR* mutation testing. Demographic information is summarized in Table 2. The proportion of light-/never-smokers (41.3%), women (58%), and Asian ethnicity (14%) suggests that Canadian physicians did incorporate clinical characteristics when selecting patients for testing.

EGFR mutation testing was not conducted in 251 patients (12%) because specimens were not sent to the testing laboratory (n = 106; 5%), or samples were deemed inadequate by the testing laboratory (n = 145; 7%). At the time of data cutoff, test results were pending for an additional 82 samples (4%). The median time to transport the sample to the testing laboratory was 7 days (standard deviation [SD] 9.6).

TABLE 2. Summary of Patient Demographics

Patient Demographics	N	Proportion (%)
Age (yr)		
<49	135	6.5%
50–59	379	19.8%
60–69	573	27.2%
70–79	712	33.8%
≥80	303	14.5%
Sex		
Female	1221	58%
Male	883	42%
Smoking status		
Light/never	868	41.3%
Current/former	1236	58.7%
Histology		
Adenocarcinoma	1927	91.6%
Nonadenocarcinoma	177	8.4%
Ethnicity		
Asian	292	14%
Non-Asian	1812	86%
Laboratory		
BC	410	19.5%
AB	178	8.5%
ON	1239	58.9%
QC-CHUM	95	4.5%
QC-Jewish General	182	8.7%

BC, British Columbia Cancer Agency; AB, Alberta Cancer Agency; ON, University Health Network; CHUM QC, Centre de Lutte Contre le Cancer du CHUM Quebec; JGH QC, Jewish General Hospital Quebec.

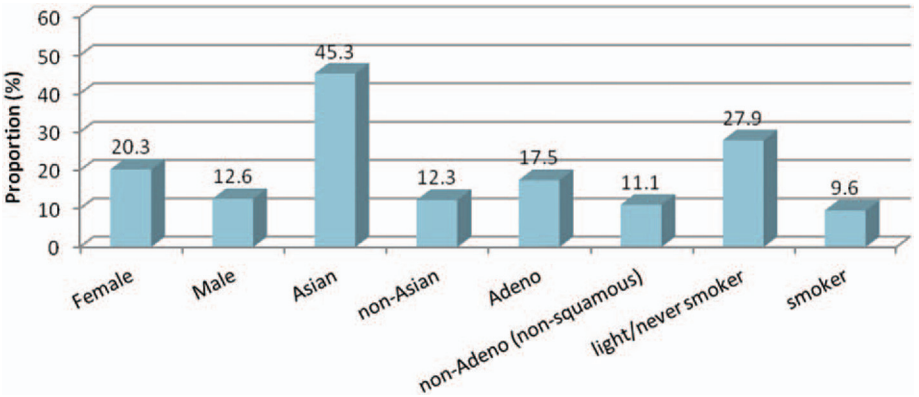

FIGURE 2. Frequency of epidermal growth factor receptor mutations in clinical subgroups. Adeno, adenocarcinoma.

In the initial experience, the median time to perform *EGFR* mutation testing at the test laboratory was 11 days (SD 5.5). Overall, the median turnaround time from initial request to *EGFR* result was 18 days (SD 9.7). Across the five laboratories, this ranged from 15 to 26 days. Three hundred two of 1771 samples (17.1%) tested positive for a mutation. The highest mutation-positive rates were seen in patients of Asian ethnicity and light-/never-smokers (Fig. 2). There was some variation in the rate of *EGFR*-positive test results across the provinces, with the highest rates observed in BC (Fig. 3). This likely reflects variation in ethnicity among the provinces.

At the end of 12 months, when the *EGFR* mutation testing and associated compassionate gefitinib program supported by AstraZeneca were completed, there was a substantial drop in the number of *EGFR* test requests (Table 3). Over the next 6 months, the number of tests performed monthly ranged from 50 to 120 (Fig. 1*B*) in comparison to 200 to 250 tests per month in the first 12 months.

DISCUSSION

The management of NSCLC has undergone substantial changes in the past few years. The idea that one approach can be used to treat all NSCLC patients is no longer valid. Chemotherapy algorithms are now dependent on histologic subtype. There is increasing recognition that there are distinct molecular phenotypes of lung adenocarcinomas.[25] To date, identification of mutations of the *EGFR* gene and translocations of the anaplastic lymphoma kinase gene have resulted in specific therapies targeting these molecular abnormalities.[16,26] Identification of other molecular phenotypes, such as *KRAS* mutations[27] and *ROS1* translocations,[28] are also important in identifying patient eligibility for ongoing clinical trials. However, challenges exist in the ability to test for and identify these molecularly defined subsets of NSCLC.

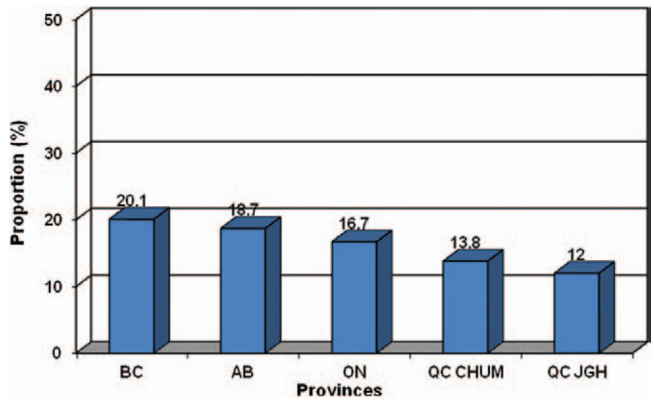

FIGURE 3. Variation across provinces in rate of positive epidermal growth factor receptor mutation tests. AB, Alberta Cancer Agency; BC, British Columbia Cancer Agency; ON, University Health Network Ontario; QC CHUM, Centre de Lutte Contre le Cancer du CHUM Quebec; QC JGH, Quebec Jewish General Hospital.

TABLE 3. Summary of Number of *EGFR* Mutation Tests Ordered Per Month, Broken Down by Province

Date	*EGFR* Test Lab					
	AB	BC	CHUM	JGH	ON	Total
2010						
March	8	27	0	0	34	69
April	10	40	5	13	88	156
May	10	50	6	16	150	235
June	22	44	5	21	152	232
July	20	38	9	20	119	206
August	32	44	14	18	135	233
September	18	36	20	22	132	228
October	16	48	12	30	134	240
November	16	40	14	21	170	261
December	26	43	10	21	135	235
2011						
January	27	45	13	18	136	239
February	14	45	5	20	138	222
March	14	37	5	20	122	198
April	0	32	3	11	47	93
May	3	49	0	18	54	124
June	2	43	2	21	36	104
July	0	20	1	15	35	71
August	0	2	1	29	47	79
September	0	0	6	20	48	74

AB, Alberta Cancer Agency; BC, British Columbia Cancer Agency; CHUM QC, Centre de Lutte Contre le Cancer du CHUM Quebec; JGH, Jewish General Hospital QC; ON, University Health Network Ontario.

TABLE 4. Challenges to the Implementation of *EGFR* Mutation Testing in Canada

Challenge	Suggestion
Use of clinical characteristics to select patients for molecular testing	Test all patients with advanced/metastatic nonsquamous NSCLC
Patients too symptomatic to wait for results of testing	Initiate testing at the time of diagnosis rather than time of referral to medical oncology
Inadequate diagnostic tissue for molecular testing	Improve the amount of diagnostic tissue
Policy issues	
Testing at the time of referral to medical oncology	Initiate testing at the time of diagnosis rather than the time of referral.
Limited number of testing laboratories or limited access to *EGFR* testing	Increase availability of molecular testing
Government funding for *EGFR* testing	Provision of funding for molecular testing
Ability to rapidly implement change in response to new clinical data	Governmental policies that enable rapid implementation of new molecular tests
Lack of national molecular testing strategy	Development of national molecular testing strategy for oncology

EGFR, epidermal growth factor receptor; NSCLC, non–small-cell lung cancer.

The results presented in this article suggest that medical oncologists in Canada rapidly adopted these new data into clinical practice. The number of *EGFR* mutations tests ordered rose rapidly in the initial 2 months of testing and reached a plateau around 200 to 250 cases per month. However, the patient demographics from this report, suggest that physicians were using clinical characteristics, such as Asian ethnicity, smoking status, and sex, to select patients for whom *EGFR* mutation testing was to ordered. Although this strategy increases the yield for testing, it inevitably results in some mutation-positive patients being missed. Given the strong predictive value of *EGFR* mutation results, *EGFR* mutation testing should be considered in all patients with advanced nonsquamous NSCLC with adequate performance status (Eastern Cooperative Oncology Group 0–3).

The knowledge translation literature suggests that passive knowledge translation strategies such as meeting presentations and publications are not particularly effective in changing physician behavior.[29] However, these findings would suggest that the major limitations to the adoption of *EGFR* mutation testing seem to be access to and reimbursement for testing. There was a rapid decline in the number of *EGFR* mutation tests ordered after completion of the sponsored testing and compassionate drug-supply program. The fact that there was still no provincial funding mechanism for testing or first-line EGFR TKI treatment in place at the end of a year indicates that governments need to be more responsive to rapidly evolving clinical data if Canadian cancer patients are going to have access to new personalized medicines. The cost of *EGFR* mutation testing in Canada is approximately $400 to $450 per case. On the basis of earlier assumptions to limit testing to patients with advanced or metastatic nonsquamous NSCLC, this would result in an incremental cost to the health care system of $2.2 to $2.52 million. Nevertheless, to approve a drug that is only appropriate to a subgroup of NSCLC patients, without a mechanism to identify those patients or make treatments affordable and accessible to Canadians in the context of a publicly funded system is a major impediment to adoption of new therapies.

Given the observational nature of this study, there are some limitations. There may be other factors contributing to these findings. The rate of testing early in the program may have been higher if physicians were testing prevalent cases rather than just newly diagnosed cases. However, this seems less likely given the abrupt drop in the number of tests ordered in April 2011. Additionally, data were no longer captured by the program in some provinces after the initial 12-month period. In Alberta, *EGFR* mutation testing was supported through provincial funds after the initial 12 months. Data were not captured in BC after July 2011. Funding for mutation testing was still coming from the pharmaceutical industry in several provinces in 2013. These changes likely impact on the lower rates of testing observed in August and September of 2011, although drug access almost certainly also plays a key role.

Multiple challenges exist in implementing *EGFR* mutation testing (Table 4). Although uptake of *EGFR* testing was high, there were still a significant number of patients not able to access testing. There were some barriers to adoption of testing. The limited number of testing laboratories meant that tissue needed to be sent between laboratories for the majority of patients. Eligibility for testing was often not determined until patients were seen by a medical oncologist. This factor, in combination with the median time to obtain test results of nearly 3 weeks, limited the feasibility of testing for patients who were already symptomatic and could not wait 2 to 3 weeks to begin systemic therapy. Many of these patients could not wait for test results and needed to start urgent chemotherapy instead of receiving personalized cancer therapy. Expansion of the number of testing laboratories and allowing for testing to be initiated by pathologists at the time of diagnosis would help improve access to testing for Canadian lung cancer patients. In addition, *EGFR* testing could not proceed in approximately 12% of cases because of inadequate tissue samples. This highlights the need to obtain appropriate tissue samples to provide adequate amounts of tissue for molecular testing at diagnosis. Molecular testing is an issue for the majority of disease sites in oncology. Coordinated approaches that link reimbursement of molecular testing with approval of clinically important molecularly targeted agents seems essential to allow adoption of new and novel therapies for oncology patients.

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