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,

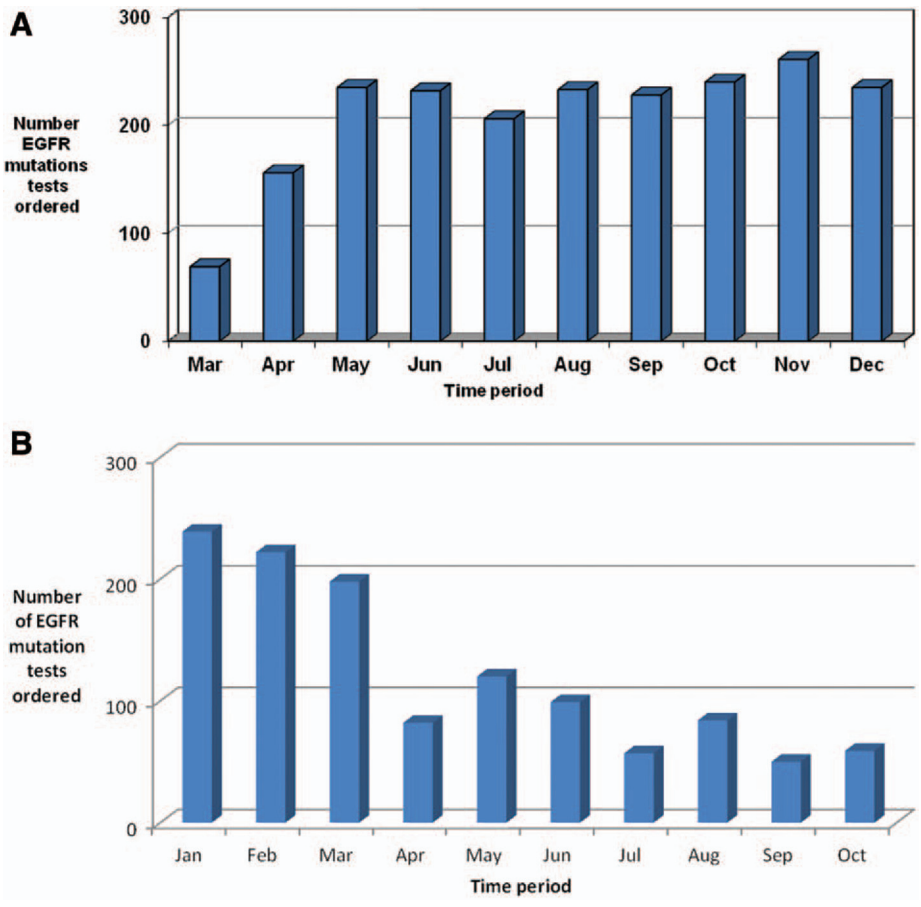

FIGURE 1. *A*, Initial uptake of *EGFR* mutation testing (March–December 2010). *B*, Number of *EGFR*-mutation tests performed upon completion of sponsored program (April–September 2011). EGFR, epidermal growth factor receptor.

