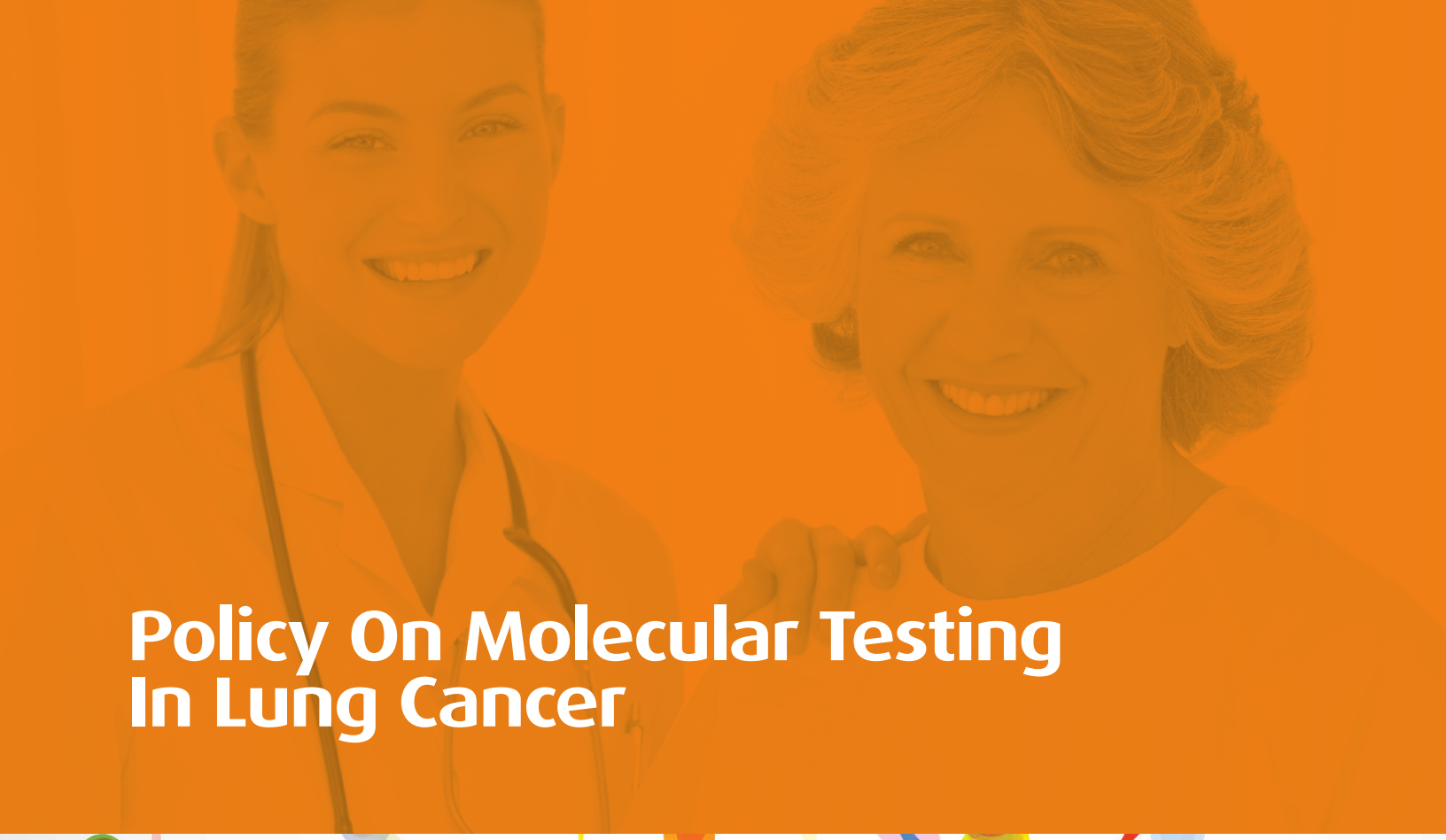

Policy On Molecular Testing In Lung Cancer

LUNG CANCER CANADA
Awareness. Support. Education.

Lung Cancer Canada is a national charitable organization that serves as Canada's leading resource for lung cancer education, patient support, and advocacy. Based in Toronto, Lung Cancer Canada is a member of the Global Lung Cancer Coalition and is the only organization in Canada focused exclusively on lung cancer.

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Lung Cancer Canada wishes to thank the working group members who contributed to writing this paper:

Chair: Dr. Barb Melosky, Medical Oncologist, BC Cancer Agency, Vancouver, British Columbia
Dr. Ron Burkes, Medical Oncologist, Mount Sinai Cancer Center, Toronto, Ontario
Dr. Rob El-Maraghi, Medical Oncologist, Simcoe Muskoka Regional Cancer Center, Barrie, Ontario
Dr. Vera Hirsh, Medical Oncologist, McGill University, Montreal, Quebec
Dr. Diana Ionescu, Pathologist, BCCA and University of British Columbia, Vancouver, British Columbia
Dr. Shantanu Banerji, Medical Oncologist, Cancer Care Manitoba, Winnipeg, Manitoba

Lung Cancer Biomarker Testing in Canada: An Evolution in Treatment

Lung cancer is globally the leading cause of cancer death for both men and women, surpassing colorectal, breast, and prostate cancer combined.[1] One in 11 Canadian males and 1 in 15 females will develop lung cancer, accounting for more than 25,000 new cases annually. The probability of a male dying from lung cancer is 1 in 13, compared with prostate cancer as the next most likely cause of death at 1 in 28; in females, the probability of dying from lung cancer is 1 in 18, compared with breast cancer as the next most likely cause of death at 1 in 29.[2] The majority of patients present with advanced, incurable disease, with most presenting histologically with non-small cell lung cancer (NSCLC). Although the most important risk factor remains tobacco use, the incidence of lung cancer in non-smoking young women is increasing.[3]

Although cytotoxic chemotherapy remains the standard of care for most patients, there has been a shift towards personalized therapy with our increased understanding of the molecular diagnosis and treatment of lung cancer. This has been realized by the identification of a number of actionable mutations, including the genes EGFR and ALK, that has revolutionized therapy in those patients who harbor these mutations.[4, 5, 6] As demonstrated by the Lung Cancer Mutation Consortium, two thirds of NSCLC patients have an oncogenic driver mutation and patients with these mutations live longer if they receive the corresponding targeted agent.[7]

Unfortunately, the majority of patients present to the medical oncologist without knowledge of their EGFR or ALK mutation status, potentially delaying the start of treatment. Furthermore, a movement towards minimally invasive diagnostic methods has increased the number of patients whose biopsy samples yield insufficient tissue to conduct the appropriate molecular analysis. This further delays treatment and often requires commencement of cytotoxic chemotherapy in patients who would otherwise be eligible for targeted therapy, thereby increasing toxicity, adversely affecting quality of life, and exposing them to an inferior treatment. In a review by Lim et al[8] at one Toronto institution, 10% of patients had inadequate diagnostic tissue for biomarker analysis; 56% of these went on to have a repeat biopsy and of those with an EGFR mutation, 16% started chemotherapy prior to results becoming available to the clinician. Therefore, it is important for all physicians involved in the diagnosis and treatment of lung cancer to be aware that maximizing tissue yield for histologic and molecular subtyping is essential to be in the modern era of personalized care for all patients with lung cancer. There is a need for national policy standards and a sustainable public funding model for lung cancer molecular testing so that all patients across Canada are treated in a timely fashion, now and in the future.

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Personalized Medicine: An Analogy of Current Standard Practice

Personalized care is not new to medicine. Laboratory testing to assess the sensitivity of infectious agents to various antibiotics is an established cornerstone in determining therapy that ultimately improves patient outcomes, avoids side effects, shortens hospital stays, and minimizes unnecessary physician visits. In the long term, the testing process helps to limit antibiotic resistance, avoid health care complications (including death), and prevent unnecessary expenses. This entire chain of medical events is most efficiently and effectively directed by relatively inexpensive but highly reliable and specialized tests that are implemented in a timely fashion.

As lung cancer treatment evolves, biomarker testing increasingly dictates therapy. Determining which party is responsible for paying for the biomarker test often sparks debate nationally.

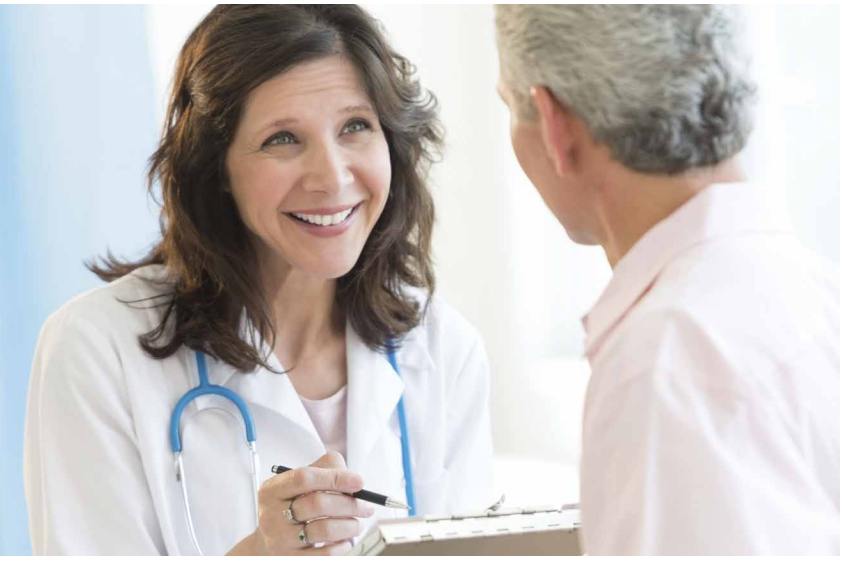
Similarly, the greater our understanding of the molecular diversity of cancers, the greater our awareness of their unique sensitivity and resistance to specific drugs. Oncology is undergoing a revolution that started with the advent of targeted therapy. The role of oncologic pathology is increasingly important with the introduction of mandatory companion diagnostic tests to identify patients who will best benefit from a given anticancer drug. As with antibiotics, a relatively inexpensive laboratory test can determine the best use of health care resources just as we have adopted HER2 molecular testing for identifying the appropriate targeted treatment with Herceptin in breast cancer. As Sir William Osler noted more than a century ago, "As is your Pathology, so is your Medicine".

Sustainable Program is a Public Program

As lung cancer treatment evolves, biomarker testing increasingly dictates therapy. Determining which party is responsible for paying for the biomarker test often sparks debate nationally. The main arguments for non-pharma (i.e. government) payment of biomarker companion tests are sustainability, accessibility, and control. Sustainability: Reliance on pharmaceutical companies to pay for testing is not sustainable long-term, as this approach generally means the costs are placed back on the patient and the payer through drug cost. Accessibility: Testing should be available regardless of geography (availability is currently dependent on provincial approval of tests and is inconsistent across Canada). Stipulations on the populations to be tested should be determined by best evidence via a national molecular testing policy and review board, rather than pharma-determined eligibility. Control of testing: With government-funded testing, the procedures followed and the eligibility criteria applied can be better controlled, ensuring the evidence-based use of these tests. Additionally, the costs of testing can be better controlled and efficiencies can be realised with centralized, publicly funded molecular testing.

Targeted Therapy Impact on Quality of Life

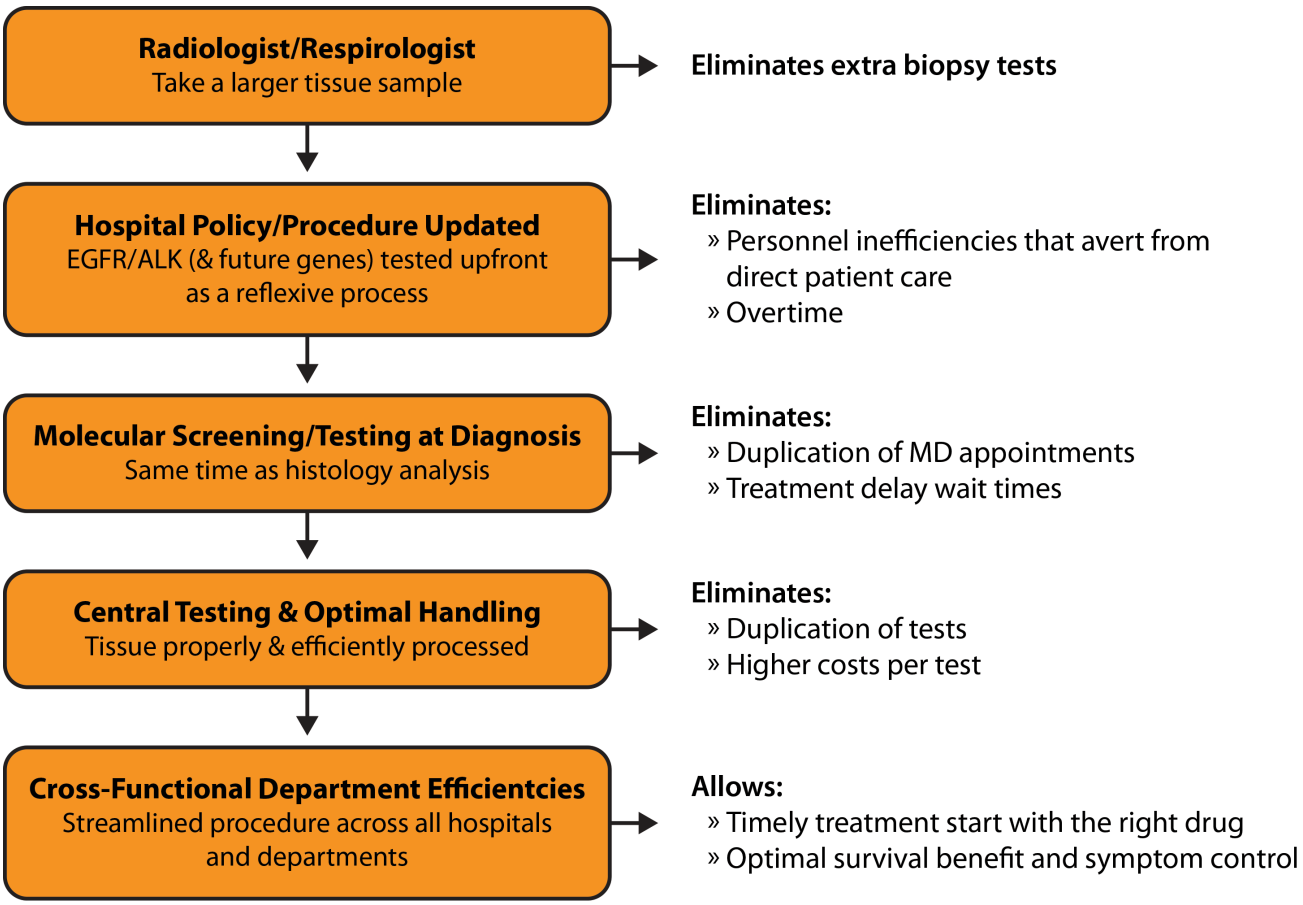
Clinically speaking, Health-Related Quality of Life (HRQOL) has a particularly significant impact in lung cancer when compared to other cancer types due especially to its direct effect on airway and breathing. Approximately 90% of patients with the most common type of advanced cancer, non-small cell lung cancer (NSCLC), experience 2 or more symptoms, especially shortness of breath, cough, chest pain, and fatigue, which are often then associated with psychological distress. In one survey, 68% of patients said that they would choose chemotherapy ONLY IF it improved their



symptoms.[9] This is significant when considering adverse events of palliative chemotherapy or treatment with EGFR inhibitors (targeted therapy) on HRQOL and the clinical benefits from these treatments in advanced NSCLC patients. In randomized phase III trials using the oral EGFR targeted therapy where the data on disease related symptoms and HRQOL data were properly collected and conducted (i.e. LUX-LUNG 3 and LUX-LUNG 6),[10,11,12,13] this treatment provided superior symptom improvements, delayed symptom deterioration, and also showed improvements of global HRQOL and patient functioning on EGFR therapy compared to a standard chemotherapy. This is of the utmost importance for this palliative group of patients with advanced NSCLC and impacts the need on supportive health services like emergency rooms, radiotherapy and other palliative care services. The impact being a decrease or delay of medical interventions like frequent hospitalizations and surgical procedures for pathologic bone fractures; spinal cord compression; and removal of pleural and pericardial fluids. Initiating treatment as soon as possible is imperative for positive clinical HRQOL impact; this cannot occur if molecular testing is delayed or inaccessible, highlighting the need to conduct this testing at diagnosis as part of routine diagnostic pathology review.

REFLEX Testing Model

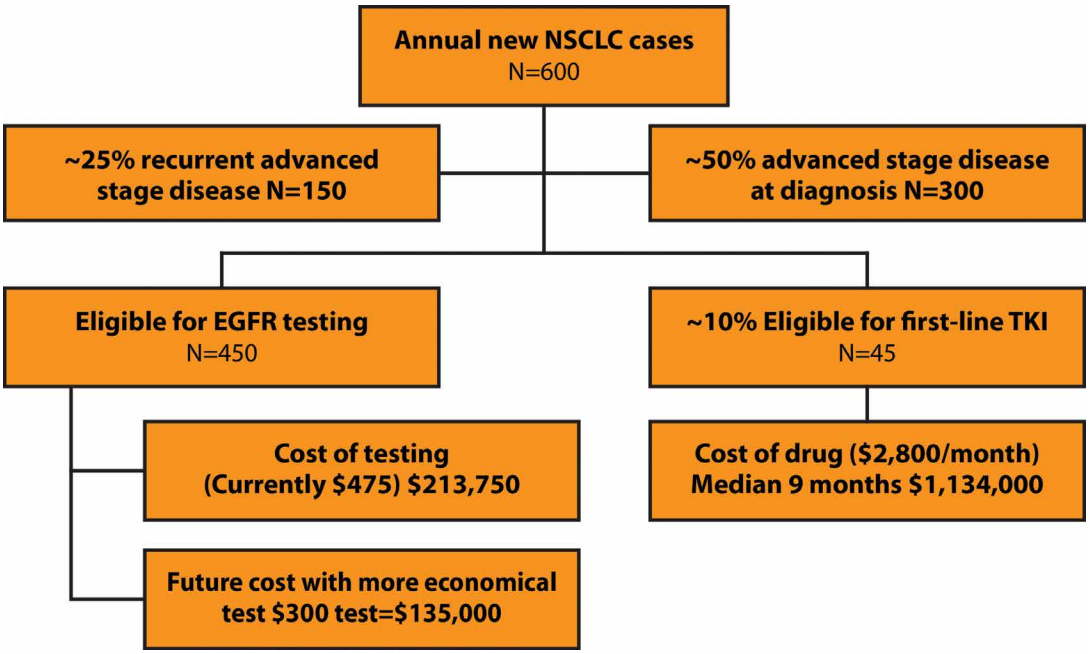
As targeted therapy evolves oncology experts in lung cancer strongly believe that molecular testing in Canada, specifically EGFR and ALK testing, should be done at diagnosis. This diagnostic information is as imperative to direct therapy decisions as a chest x-ray that identifies the lung cancer. Reflex testing should be a standard of care. Ultimately, reflex testing has direct patient impact on specialists initiating the right chemotherapy/targeted therapy within acceptable treatment wait time standards for optimal survival outcomes. Inherently, the reflex model also has budget impact savings on hospital department efficiencies and personnel by reducing the number of extra biopsy tests; streamlining pathology and clerical personnel roles/responsibilities furthermore reducing overtime costs; and reduces extra physician appointments/tests for the patient.



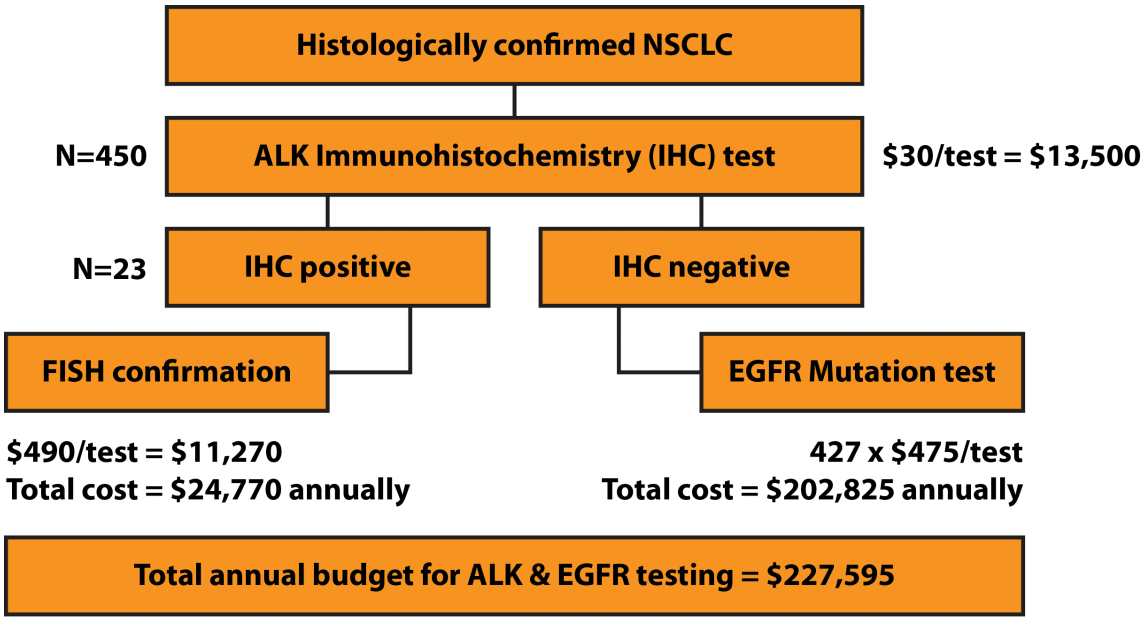
REFLEX testng model provided courtesy of CARE faculty, a group of oncology clinical experts in lung cancer.

Budget Impact of Molecular Testing in NSCLC

What are the costs of molecular testing versus the targeted drug costs? The example below demonstrates the budget impact of EGFR testing in the Manitoba lung cancer population (Manitoba's population roughly represents 1:28 of Canadian population).[15]



Proposed testing Algorithm for ALK and EGFR testing in Manitoba using the reflex model:



A Case In Point

Early and consistent access to molecular testing is of critical importance to the effective delivery of lung cancer therapy in Canada, as exemplified in the following case example.[16] It is imperative to understand that this unfortunate woman, who is a productive member of society and with a young family, would not have survived without early access to the molecular tests that identified her ALK mutation and predicted her response to crizotinib targeted therapy.

The patient is a 40 year old non-smoking woman of Chinese origin who works as an accountant. She developed a cough and pleuritic chest pain in May of 2013 that did not resolve after a trial of antibiotics. A chest X-ray was performed demonstrating a right lower lobe lung mass. She subsequently had a CT scan in September 2013 that confirmed that the mass was 7.9 x 7.1 cm and was metastatic involving the liver, with the largest lesion measuring 5.0 x 3.5 cm. A biopsy was performed, confirming adenocarcinoma. Because upfront molecular testing is the practice in this institution, EGFR and ALK mutation testing were completed by an efficient reflex process in the pathology department. This patient's disease was very aggressive and by mid-October she was clinically declining and lesions were growing rapidly. Her molecular studies returned 21 days after the biopsy which confirmed the diagnosis of her lung cancer and identified the presence of an ALK mutation by immunohistochemistry (a low-cost test for ALK screening). Unfortunately, she was deteriorating rapidly and was admitted to the coronary care unit (CCU) with hypoxia, blood clots in both lungs, and a large pericardial effusion. Her molecular test results were finalized 7 days later with ALK positive gene rearrangement being confirmed by fluorescence in situ hybridization (FISH genomic testing). However, given the speed at which her disease was progressing, her significant complications, and her resultant poor performance status, she was not a candidate for traditional systemic chemotherapy (no treatment could be initiated until all the molecular pathology testing was completed to determine which treatment would be best to control her disease).

The drug crizotinib, a targeted drug for ALK mutation, was initiated 34 days after the biopsy in late October, 2013 and the response was remarkable. The patient rapidly improved and was discharged home off oxygen less than 2 weeks after drug initiation. One month later, a chest X-ray confirmed partial re-expansion of her lung and, apart from some very mild nausea, she had no side effects from the drug. By mid-December, her disease in the lung had shrunk more than 50% (3.5 x 2.1 cm), the pleural effusion cleared completely, and her liver lesion had no enhancement or liquid density consistent with non-viable tissue (i.e. necrotic). By January 2014, she was completely asymptomatic, had an almost complete response, and requested a physician note so that she could return to work.

This case report highlights several key features:

- Molecular testing traditionally takes between 3 - 4 weeks from time of the request until results are reported.
- Molecular driver mutations promote the malignant phenotype and are modifiable with currently available drugs, even in extremely ill patients who are too unwell for traditional systemic chemotherapy.
- Early access to molecular testing (i.e. at diagnosis, similar to breast cancer) allows for identification of these driver mutations at the time of the initial consultation with the oncologist, thus avoiding delays in initiation of effective targeted drug therapy.
- Without reflexive testing, an efficient "biopsy to pathology reporting process" that involved re-alignment of health services, this patient would likely have died before the results of her ALK mutation status were available and would have died if she had not been treated with the right drug for her cancer type.

In conclusion, from the 2012-2013 Report Card on Cancer in Canada[17]:

"If a Health-Canada approved targeted therapy is shown to be safe and effective and is linked to a biomarker that can be tested clinically, then every province and territory should publicly fund the test." Lung cancer represents the largest area of research with 17 molecular targets in active clinical trials, compared to breast cancer and melanoma, with 15 and 13 new targets, respectively. Upfront molecular testing is the new standard of cancer disease management with systemic therapy.

"If a Health-Canada approved targeted therapy is shown to be safe and effective and is linked to a biomarker that can be tested clinically, then every province and territory should publicly fund the test."

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