ABSTRACT

The advent of personalized therapy for non-small-cell lung carcinoma (NSCLC) has improved patient outcomes. Selection of appropriate targeted therapy for patients with NSCLC now involves testing for multiple biomarkers, including EGFR. EGFR mutation status is required to optimally treat patients with NSCLC, and thus timely and accurate biomarker testing is necessary. However, in Canada, there are currently no standardized processes or methods in place to ensure consistent testing implementation. That lack creates challenges in ensuring that all appropriate biomarkers are tested for each patient and that the medical oncologist receives the results for making informed treatment decisions in a timely way.

An expert multidisciplinary working group was convened to create consensus recommendations about biomarker testing in advanced NSCLC in Canada, with a primary focus on EGFR testing. Recognizing that there are biomarkers beyond EGFR that require timely identification, the expert multidisciplinary working group considered EGFR testing in the broader context of integration into complex lung biomarker testing. Primarily, the panel of experts recommends that all patients with nonsquamous NSCLC, regardless of stage, should undergo comprehensive reflex biomarker testing at diagnosis with targeted next-generation sequencing. The panel also considered the EGFR testing algorithm and the challenges associated with the pre-analytic, analytic, and post-analytic elements of testing. Strategies for funding testing by reducing silos of single biomarker testing for EGFR and for optimally implementing the recommendations presented here and educating oncology professionals about them are also discussed.

Key Words Biomarker testing, comprehensive biomarker testing, non-small-cell lung cancer, NSCLC, targeted therapy, EGFR T790M, epidermal growth factor receptor, EGFR

INTRODUCTION

Lung cancer is the most commonly diagnosed cancer in Canada, with approximately 29,800 new cases expected in 2020. It is the leading cause of cancer death for both men and women. Approximately 70% of lung cancers are diagnosed at a late stage (stage III or IV), leading to poor 5-year survival rates of 19%.

Non-small-cell lung cancer (NSCLC), the most common type, is a model for the application of precision medicine to clinical oncology. The standard of care, which used to be platinum doublet chemotherapy, has shifted to personalized therapy based on histology and biomarker testing results. Genetic alterations that are oncogenic drivers are found in a higher percentage of lung adenocarcinomas than of squamous cell carcinomas or other histologic subtypes, and receiving matched targeted therapies for the genomic alterations improves response, progression-free survival, quality of life, and in many cases, overall survival.

The first targetable mutations to be identified in NSCLC were sensitizing mutations in the EGFR (epidermal growth factor receptor) gene. Those mutations are found in 10%–20% of patients with nonsquamous NSCLC in Canada overall, although they are more common in patients of Asian
testing to identify and treat EGFR-mutated lung cancer. The group had pan-Canadian representation and included medical oncologists, pathologists, a clinical laboratory scientist, and a clinician educator. A targeted literature review was performed to identify relevant literature about the topics that the group identified as essential for optimizing biomarker testing in EGFR-mutated lung cancer, including reflex testing, biomarker testing algorithms, liquid biopsy, and TAT. The expert multidisciplinary working group convened in person to discuss draft recommendations and to reach consensus.

CONSENSUS RECOMMENDATIONS FROM THE EXPERT MULTIDISCIPLINARY WORKING GROUP

Treatment of EGFR-Mutated NSCLC

The purpose of biomarker testing, including EGFR, in NSCLC is to guide personalized therapy for patients. Testing recommendations should therefore align with current treatment algorithms. Thus, the expert multidisciplinary working group began by reviewing a recently published Canadian consensus treatment algorithm for systemic therapy in advanced EGFR-mutated NSCLC\textsuperscript{14}. The expert multidisciplinary working group endorsed the algorithm and recommendations summarized in the next subsection and used those recommendations as the context for determining optimal biomarker testing practices.

The Canadian guidelines consider specific EGFR mutations and the presence of central nervous system metastases for treatment decisions. To summarize, based on the phase III FLAURA trial, osimertinib is the preferred first-line treatment for patients with advanced NSCLC harbouring common EGFR mutations (exon 19 deletion or exon 21 L858R mutation) and for patients with the de novo EGFR T790M mutation, because of improved overall survival and a favourable toxicity profile compared with first-generation EGFR TKIs\textsuperscript{12}. Because of its activity in the central nervous system, osimertinib is also recommended for patients with brain metastases or leptomeningeal disease\textsuperscript{12,18,19}. First- and second-generation TKIs are options for patients with common EGFR mutations when osimertinib is not available or not tolerated. For patients with uncommon EGFR sensitizing mutations, afatinib is recommended as first-line therapy based on the LUX-Lung 3 and 6 trials\textsuperscript{20}, which included patients harbouring uncommon EGFR mutations such as G719X, L861Q, and S768I. For patients with exon 20 insertions, a heterogeneous group of alterations that are generally resistant to currently available EGFR TKIs, the preferred treatment is a platinum doublet chemotherapy regimen or enrolment in a clinical trial.

Biomarker results also guide treatment selection after progression on EGFR TKIs. Based on data from the AURA3 clinical trial, patients who receive a first- or second-generation TKI in the first line and who develop the EGFR T790M resistance mutation should receive osimertinib\textsuperscript{21}. For patients who develop resistance to TKIs and who do not have the T790M mutation, the preferred treatment is a platinum doublet chemotherapy regimen.
Recommendations for Biomarker Testing

*Identifying the Presence or Absence of EGFR Mutations*

- **EGFR** mutation testing should be performed as part of a comprehensive panel that includes the current standard-of-care biomarkers as summarized by international guidelines, including the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology.\(^{12}\)

- To avoid delay in treatment initiation, single-gene testing for **EGFR** could, at the discretion of the treating oncologist, be performed first in patients with advanced NSCLC who are at imminent risk of clinical deterioration while awaiting comprehensive testing results.

- Comprehensive reflex biomarker testing, including **EGFR**, is recommended for all patients diagnosed with nonsquamous NSCLC regardless of disease stage and should be initiated by the pathologist at the time of initial diagnosis. Biomarker test results should be reported without delay, but should also be compiled by the pathologist and listed sequentially in a single comprehensive lung biomarker report, regardless of the type of testing [immunohistochemistry, fluorescence in situ hybridization, next-generation sequencing (NGS), etc.]. The PD-L1 biomarker report should state that PD-L1 results should be interpreted in the context of other biomarker results.

- When tissue biopsy harbours scarce tumour cells, when time for a tissue biopsy is too lengthy, or when invasive procedures for tissue procurement are contra-indicated, liquid biopsy for the detection of activating **EGFR** mutations and other biomarkers is recommended at baseline, if available. A positive liquid biopsy result for an actionable biomarker alteration should be regarded as a true positive. A negative liquid biopsy result should be confirmed using a tissue biopsy.

- Optimal treatment decision-making requires results from biomarker testing that assesses actionable driver mutations; systemic therapy should therefore not be initiated in patients with metastatic NSCLC based on PD-L1 expression level until actionable driver mutation results (at a minimum, aberrations in **EGFR**, **ALK**, and **ROS1**) are also available, unless patient deterioration is imminent or patients require urgent initiation of therapy.

- If a patient with advanced lung adenocarcinoma has to start systemic therapy and cannot wait for **EGFR** test results, it is recommended to start platinum doublet chemotherapy. The panel consensus is, if possible, to avoid checkpoint inhibitors in the first-line setting because of the risk of subsequent pneumonitis if treatment is changed to a TKI after checkpoint inhibitor therapy.

- At the time of progression after a first- or second-generation **EGFR** TKI, testing for the identification of the **EGFR** T790M resistance mutation should be performed. Liquid biopsy is recommended as the initial test, but tissue biopsy should be obtained when liquid biopsy is negative. The liquid biopsy or circulating tumour DNA (ctDNA) assay should include both **EGFR** T790M and common **EGFR** sensitizing mutations, for which identification serves as confirmation of tumour shedding.\(^{18}\)

The expert multidisciplinary working group recommends that all patients with NSCLC undergo reflex biomarker testing, wherein comprehensive biomarker testing using a tissue sample is ordered by the pathologist at the time of diagnosis, regardless of disease stage. For cases in which squamous cell histology is confirmed, but for which the clinical parameters are atypical (for example, nonsmoking patient or a peripheral lesion), it might still be relevant to request a complete biomarker assessment that includes **EGFR**. Liquid biopsy could be used if available. The expert multidisciplinary working group recommends that the comprehensive testing panel should incorporate, at a minimum, **EGFR** and biomarkers based on the current standard of care and guideline recommendations\(^{12,14,19,22,23}\). Current recommendations include biomarkers currently approved by Health Canada and emerging actionable NSCLC targets to identify patients for clinical trials or early drug access programs, understanding the limitations of funding that might attend such testing.

Initiation of reflex testing by pathologists for confirmed NSCLC optimizes sample processing by eliminating the need to retrieve archived tissue, bypasses the need (and associated delay) for oncology consultation to initiate testing\(^{24}\), and has been shown to increase rates of testing\(^{25}\). When ordered at the time of initial diagnosis, it can improve time to treatment\(^{19,24–27}\). Findings from one Canadian centre showed a median reduction in time to testing of 10 days (to 26 days from 36 days) when **EGFR** and **ALK** testing was requested by pathologists at the time of diagnosis regardless of clinical stage, and a significant improvement in time to optimal systemic therapy according to guidelines (24 days vs. 36 days)\(^{19}\). Although, in general, the expert multidisciplinary working group recommends reflex testing for all patients with NSCLC regardless of stage, rare institutions at which biomarker results are consistently available to treating clinicians within 21 calendar days could consider reflex testing for advanced-stage disease only.

The expert multidisciplinary working group recommends parallel testing with a comprehensive NGS panel rather than single-gene **EGFR** testing, in line with current guidelines\(^{12,19,22,23}\). That approach makes efficient use of the sample, improves timely access to results, bypasses delays for ordering follow-up testing, and can be cost-effective if enough targets are included\(^{19}\). New technologies enable concurrent testing for all relevant biomarkers, at moderate additional expense compared with single-gene testing\(^{26}\), and overall higher assay success rates (95% vs. 71%)\(^{29}\). Failure of single-gene tests is largely attributed to an inadequate or insufficient sample for the full complement of an algorithm of single-gene tests\(^{26}\). In contrast, NGS uses input material comparable to that for a single-gene test to detect oncogenic driver mutations across multiple genes, which could be beneficial for patients because it reduces the need for, and risks associated with, rebiopsy\(^{29}\). Comprehensive NGS testing has been demonstrated to be feasible, with acceptable TATs in line with current guidelines\(^{12,26,28}\).

The expert multidisciplinary working group recommends that clinically actionable biomarker results should
be reported immediately as they become available, and that the pathologist should also compile lung biomarker results, including EGFR, to be summarized in a comprehensive final synoptic report. Thus, the medical oncologist and the patient are provided with the information required to make informed treatment decisions. For patients with metastatic NSCLC, treatment should not be based on PD-L1 expression levels alone, but rather considered in the context of actionable driver mutation results, including EGFR and ALK results at a minimum, to prevent suboptimal immunotherapy treatment of patients with actionable driver mutations. Approximately 27% of patients with PD-L1 expression also have actionable genomic targets\(^{29}\). In addition, PD-L1 expression should not be used as a biomarker to determine eligibility for checkpoint inhibitor therapy in patients with certain actionable alterations, including EGFR, ALK, and ROS1\(^{30}\).

Rapid results might be urgently needed in certain clinical scenarios—for example, if there is a risk of clinical deterioration in patients with advanced nonsquamous NSCLC. In such cases, single-gene testing for EGFR might be appropriate while awaiting comprehensive testing results and could lead to avoidance of unacceptable delay in treatment decision-making or treatment initiation\(^ {24}\). If a patient has to start systemic therapy and cannot wait for biomarker testing, the expert multidisciplinary working group recommends starting platinum doublet chemotherapy without an immune checkpoint inhibitor and tailoring treatment once biomarker results are available, because of the risk of pneumonitis in patients receiving TKIs after checkpoint inhibitor therapy\(^ {30}\). The maximum acceptable time to wait for biomarker results for each individual patient should be at the clinician’s discretion and be based on the risks of waiting (for example, patient deterioration or missed treatment opportunities). Clinicians should follow patients closely for signs of deterioration while awaiting results.

At disease progression after a first- or second-generation EGFR TKI, the expert multidisciplinary working group recommends broad comprehensive molecular testing, including for the EGFR T790M mutation, using a new biopsy. The rationale is to identify emerging resistance mechanisms for which clinical trial options might be available. Liquid biopsy is preferred because it reduces the inherent risks and discomfort of tissue biopsy and is more cost-effective for follow-up testing and monitoring\(^ {31,32}\). High pairwise concordance has been demonstrated for liquid biopsy and matched tissue for EGFR mutational analysis in resistance settings\(^ {31,33–37}\). Circulating biomarkers have an advantage, in that they are theoretically more likely to reflect the intratumoural heterogeneity in actively growing metastatic tumours that might be missed by single-site tissue biopsies\(^ {31,32,38,39}\). Typically, ctDNA represents less than 0.5% of total circulating free DNA in a liquid biopsy\(^ {31}\). Moreover, shedding of ctDNA differs between tumours and can be lower in patients whose disease is not progressing or who are responding to therapy, potentially leading to false negative results\(^ {31}\). The EGFR testing should therefore, where possible, include testing for activating EGFR mutations that would serve as controls to confirm tumour shedding and the presence of adequate ctDNA in the sample. A tissue biopsy is recommended when a liquid biopsy does not detect T790M; the tissue biopsy should also evaluate the specimen for small-cell transformation. In situations in which a patient cannot wait for a sequential approach, tests on both sample types can be performed simultaneously\(^ {40}\).

### Turnaround Time

- Lung cancer working groups should consider local contextual factors and define a target TAT for biomarker results, starting when a diagnosis of NSCLC is issued until when the report is received by the treating oncologist.
- The total TAT from ordering EGFR testing to reporting the results and making the report available to the ordering physician should not exceed 21 calendar days.
- The pre-laboratory TAT, from test request to sample receipt by the testing laboratory, should not exceed 3 business days. The intra-laboratory TAT, from sample receipt to generation of the report, should not exceed 10 business days. The post-laboratory TAT, from result reporting to report receipt by the ordering physician, should be less than 24 hours.

A rapid TAT for biomarker testing results in NSCLC is extremely important for timely treatment initiation. In a study at one Canadian centre, biomarker testing results were available for only 21% of patients at the time of first consultation with a medical oncologist\(^ {24}\). Patients with biomarker test results available had a mean time to treatment initiation of 16 days, compared with 29 days for those whose biomarker test results were not available at that time. In some cases, lack of timely biomarker test results led to unnecessary initiation of chemotherapy: one study reported that 19% of patients with EGFR- and ALK-positive disease had initiated first-line chemotherapy before biomarker results were available\(^ {34}\).

Current guidelines recommend a 10-day TAT from sample receipt in the laboratory to generation of the report (intra-laboratory TAT)\(^ {12}\). The expert multidisciplinary working group recommends that TAT in the context of reflex testing should be defined from when biomarker tests are ordered at the time of diagnosis of NSCLC to when the treating clinician receives the report. The impact of lengthy administrative aspects of EGFR testing is significant and influences the ability of oncologists to obtain results and make treatment decisions for patients. To ensure timely access to testing year-round, even during periods with multiple holidays, the expert multidisciplinary working group recommends a maximum of 21 calendar days from ordering the EGFR testing and comprehensive biomarker panel to receiving the report. However, particularly when testing is not performed in-house, breaking the overall TAT into its component parts can be useful, because it allows for the identification of processes whose efficiency has to improve. The intra-laboratory TAT typically has the least variability; in contrast, archival specimen handling and transportation to the testing laboratory are highly variable\(^ {41}\). In addition, there is a need for more efficient release of results from testing laboratories to the medical record\(^ {41}\). A recent Canadian study found that implementing in-house testing was associated with a median reduction of 2 months in biomarker report TAT, demonstrating that, when tests are sent to an outside laboratory, the pre-laboratory and post-laboratory processes...
can significantly increase the overall time for the oncologist to receive results\(^{46}\). The expert multidisciplinary working group therefore recommends that the pre-laboratory TAT should not exceed 3 business days, the intra-laboratory TAT should not exceed 10 business days (in line with current guidelines\(^{12}\)), and the post-laboratory TAT should be less than 24 hours (Figure 1). Taking into account weekends, holiday periods, and other resource constraints, the full TAT should be less than 21 calendar days.

**Pre-analytic Considerations**

- All pathology reports in NSCLC should include, in the diagnostic comment, information about the tumour content and identification of best tumour block or blocks for further testing. Diagnostic reports in NSCLC should specify the best tumour block, the total number of viable neoplastic cells, and the percentage of viable neoplastic cells among all viable nucleated cells in the slide.
- Basic training for assessing and reporting tissue adequacy parameters for biomarker testing should be provided to all anatomic pathologists, regardless of their place of practice.
- Laboratories should, whenever possible, avoid using decalcification. When necessary, use of molecular-friendly decalcification methods, such as EDTA, is recommended.
- Any cytology sample with adequate cell block tumour cellularity can be used for molecular testing. However, immunohistochemistry-based biomarkers usually require formalin-fixed cytology samples.
- Requisitions of samples obtained upon progression for the investigation of resistance mechanisms should state the reason for tissue procurement and mention current and previous treatments.
- To preserve the specimen for molecular testing, additional samples obtained in the context of resistance mechanisms assessment should not be re-evaluated extensively with immunohistochemistry stains.
- Specimens should be sent through a courier that uses a digital tracking system, so as to track specimens from the referring laboratory to the reference laboratory.

Pre-analytic considerations, including sample collection and handling upon receipt into the laboratory and prior to testing, are important to ensure that the best specimen is selected for testing\(^{43}\). The International Organization for Standardization’s 15189 standard is one of the most cited guidelines for molecular diagnostics\(^{43}\) and specifies that laboratories should provide information about acceptable specimen types and volumes, TAT, specimen transportation requirements, rejection criteria, and factors affecting test performance and interpretation, and should allow for access to laboratory personnel with expertise in providing clinical advice on test ordering and interpretation.

The expert multidisciplinary working group considered the foregoing elements in the setting of nonsquamous NSCLC and highlighted essential pre-analytic elements in that setting. Those elements include recommendations about sample procurement, fixation, transportation, and processing. Pathologists should become familiar with tumour requirements for specific biomarker tests in NSCLC and subsequently be trained in the process of selecting the tumour tissue block best-suited for testing. To provide immediate feedback on tissue quality, real-time assessment of tissue quality at the time of procedures, such as rapid on-site evaluation, should be performed where possible. Radiology–pathology, respirology–pathology, or surgery–pathology correlation rounds are encouraged as ongoing education for tissue providers and as a way to improve the quality of tissue samples obtained by various techniques. Cytology samples with adequate cell block tumour cellularity should be used for testing, with results comparable to those obtained with histology samples\(^{12}\).

Specimen adequacy parameters should be assessed by all pathologists. If a local laboratory is unsure of the specimen adequacy parameters for specific tests and methods, the specimen should still be sent to the testing laboratory. An effort should be made to educate community pathologists to assess parameters of sample adequacy for testing\(^{44}\).

Laboratories should follow standard operating procedures to control tissue storage and handling, including fixation method and ischemia and fixation times, and should avoid the use of decalcification methods that will preclude molecular testing. Acid decalcification should be avoided, because it extensively fragments DNA and renders samples unsuitable for molecular testing\(^{12,32,45}\).

Previous treatments can alter tumour gene expression. For example, **EGFR** resistance mutations are associated

\(\leq 21\) calendar days

\(\leq 3\) days*  \(\leq 10\) days*  \(\leq 24\) hours*

*business days

**FIGURE 1** Turnaround time from ordering EGFR testing to receipt of report by the ordering physician. Total turnaround time should not exceed 21 calendar days. NSCLC = non-small-cell lung cancer.
with NSCLC progression after first- or second-line treatment with an EGFR TKI\(^{46}\). Samples obtained upon progression to investigate resistance mechanisms should therefore clearly state on the requisition the reason for the biopsy and should list previous treatments to assist pathologists in deciding on appropriate use of ancillary testing. Clear communication on requisitions for treatment resistance also helps to ensure that the specimen is not re-evaluated unnecessarily with immunohistochemistry stains. Each specimen should be collected so as to assure a short ischemia time, should be submitted to the laboratory in an appropriate fixative, and should be properly fixed per current guidelines. Specimen transportation to the reference laboratory should be digitally recorded and tracked to ensure timely and accurate tracking of specimens between laboratories.

**Analytic Considerations**

- A targeted NGS panel, including EGFR, is preferred over single-gene testing. Copy number variations and gene rearrangements should also be considered for comprehensive gene analysis. Single-gene testing for EGFR T790M could be appropriate in the context of treatment resistance.

EGFR testing can be performed by NGS using tumour tissue or blood. It is beyond the scope of this guideline to review the analytic characteristics of the various NGS platforms. The expert multidisciplinary working group considers that each laboratory should choose the method of testing best suited to their clinical practice and in accordance with the samples to be tested, the local technical and professional expertise, and access to equipment. The advantage of screening all samples for all EGFR mutations is the detection of all known and novel mutations\(^{46}\). The disadvantages are the potential for lower sensitivity than could be achievable with targeted methods and a labour-intensive process requiring extensive expertise and longer TAT. Targeted EGFR testing takes less time and uses fewer resources, generally has higher sensitivity for detection of mutations, and uses a technology that is fairly widely available\(^{46}\). Its disadvantage, however, is that rare mutations are not detected, and reagents might be more costly than those for other screening methods. The expert disciplinary working group therefore recommends a combination of EGFR screening methods and targeted EGFR testing, on tissue and plasma, which could be adapted by the pathologist to each clinical scenario as detailed in other parts of this guideline.

**Post-analytic Considerations**

- The biomarker report should use both standard Human Genome Variation Society and commonly recognized nomenclature.
- The biomarker report should not make recommendations for or against the use of specific therapies, but could comment on expected drug sensitivities based on the biomarker results.

A primary purpose of the molecular pathology report is to provide testing results to the medical oncologist in a manner that allows the oncologist to easily ascertain the information required to select therapy for the patient, while also communicating the limitations of the testing results. Existing reporting guidelines should be followed when reporting biomarker testing results in NSCLC\(^{3,16,32,47}\). Additionally, as stated earlier, the pathologist should summarize the results of all biomarker testing, including EGFR, in a comprehensive report. The summarized results allow the medical oncologist to find, in one location, all the information needed to make treatment decisions. Although existing provincial accreditation programs require results to be communicated according to Human Genome Variation Society nomenclature\(^{46}\), the expert multidisciplinary working group recommends that the report also use commonly recognized nomenclature for ease of interpretation by the medical oncologist. For example, the commonly recognized name EGFR T790M should be used in the report as should the Human Genome Variation Society nomenclature NC_000007.14:g.55181378C>T. In addition, specific therapies should not be recommended in the report, but expected sensitivities can be noted based on biomarker results.

**Funding for Biomarker Testing in EGFR-Mutated NSCLC**

Although funding for EGFR testing does exist in Canada, the expert multidisciplinary working group recommends comprehensive biomarker testing to optimally perform genomic profiling in NSCLC, including identifying the presence or absence of EGFR mutations, and to allow for timely treatment. Funding is a major challenge for comprehensive biomarker testing in Canada; it is often reserved to single-gene testing. Effective biomarker testing requires funding from provincial reimbursement bodies not just funding for the test itself, but also funding for other aspects of testing such as human resources, infrastructure, digital tracking of specimens, and bioinformatics. A recently published Canadian guideline on the use of NGS assays in oncology identified an unmet need in funding for NGS infrastructure, local expertise, methodologic validation, and test implementation\(^{48}\). Although the clinical utility of concurrent testing for a panel of biomarkers is recognized, funding for comprehensive biomarker testing is not yet standard in Canada; the expert multidisciplinary working group therefore recommends that provincial reimbursement bodies should support comprehensive testing rather than single-gene assays.

**Optimal Biomarker Testing Implementation**

- Translating guidelines into clinical practice requires a multidisciplinary effort, adapting to provincial and local contexts.

Despite publication of practice guidelines, large gaps between the recommended care and the care that patients receive often remain\(^{49}\). Barriers to guideline implementation include not just physician factors such as lack of knowledge of guidelines, but also external factors such as resource and organizational constraints\(^{50}\).

Although education about new recommendations is required, education is not sufficient for implementation, which also requires teamwork at an institutional level to develop context-specific solutions. Such a systemic and
A collaborative approach was used at one hospital in Canada to support process improvement throughout the lung cancer diagnostic pathway. That effort ultimately resulted in a decrease of 48% in the time from referral to initial treatment. Recognizing that a collaborative approach is key to implementation of the recommendations in the present guideline, the expert multidisciplinary working group recommends review of the guideline recommendations by a multidisciplinary team at each institution and conduct of a local needs assessment to identify the needs of all target groups and stakeholders. Such an approach ensures that the perspectives of health care professionals involved in various aspects of lung cancer diagnosis, biomarker testing, and treatment will be considered in the implementation of the guidelines. That “community of practice” should be the focus of education and implementation strategies, in which social interaction will facilitate behavioural change, the identification of contextual constraints, and the proposal of solutions that take into account the local care setting.

Effective education about these guidelines also requires interprofessional collaboration. The expert multidisciplinary working group recommends that the design and delivery of educational meetings should be interprofessional, practice-based, focused on outcomes that are relevant to the professional practice of each health care discipline, and be underpinned by the “communities of practice” learning theory. Factors that might increase the effectiveness of educational meetings include strategies to increase attendance by various health care professionals; using mixed interactive and didactic formats; and having multiple, spaced, and longer exposures. Faculty development is critical to prepare and support facilitators in the delivery of interprofessional education, and educators should be consulted to design effective educational interventions.

Accurate and timely biomarker testing is multifactorial: education and implementation strategies should extend beyond the medical facets of testing to include coordination of care, tissue procurement and handover, requisition and report design, clear workflow within and between services, automatic information exchange between electronic health systems, and improved communication, with fast feedback loops between health care practitioners. In addition, education has to be extended beyond physicians to include nurse navigators, clerks, and laboratory technologists. The implementation strategies should include decision-support systems and standardized orders. There is a need to approach implementation with a continuing quality improvement lens, to perform robust program evaluation, to measure processes and products, and to monitor critical quality indicators so as to guide future educational interventions for individuals and the team.

**SUMMARY**

Comprehensive reflex biomarker testing for patients with confirmed nonsquamous NSCLC is important for the selection of appropriate therapies. To guide optimal patient care, each biomarker result, including *EGFR*, should be interpreted in the context of the full set of biomarker data. Lung Cancer Canada’s *Policy on Molecular Testing in Lung Cancer*, published in 2014, highlighted the 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. The organization also recommended that, in Canada, reflex testing be performed at diagnosis. That effort was followed by Canadian guidelines for the standardization of biomarker testing in patients with advanced NSCLC and best-practice recommendations for *EGFR*-positive NSCLC were published. Our recommendations align with those guidelines in that they encourage both comprehensive reflex molecular testing for all patients with nonsquamous NSCLC at diagnosis to rapidly identify patients with *EGFR*-mutated NSCLC, and molecular testing for resistance mutations during treatment. Here, we have made recommendations for *EGFR* mutation testing and focused on breaking silos of single-gene testing with the use of more comprehensive panels. Recommendations for the optimization of the pre-analytic, analytic, and post-analytic elements of testing are also provided to complement existing guidelines in the setting of NSCLC. The importance of standardizing those elements and the impact that such standardization can have on the timeliness and accuracy of the biomarker report and the time to treatment is highlighted. Review of the present guideline by a multidisciplinary team is important to ensure that perspectives from all relevant stakeholders are considered for the successful local implementation of its recommendations.

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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: PKC reports consultancies and honoraria from AstraZeneca, Bristol Myers Squibb, Amgen, Roche, Novartis, Merck, Pfizer, Takeda, and EMD Serono. MG reports grants and personal fees from AstraZeneca and Hoffmann–La Roche, unrestricted educational grants from AstraZeneca, Hoffmann–La Roche, Eli Lilly, Boehringer Ingelheim, Pfizer, and Merck, and nonprofit and nonfinancial support from Merck, outside the submitted work. SB reports personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, GlaxoSmithKline, Lilly, Merck, Novartis, Pfizer, Roche, and Takeda, outside the submitted work. NBL reports institutional research funding from AstraZeneca, Pfizer, Roche, and Merck Sharp and Dohme; and honoraria for continuing medical education lectures from Merck Sharp and Dohme. BM reports advisory board fees or honoraria from Boehringer Ingelheim, Pfizer, AstraZeneca, Roche, and Novartis. BSS reports personal fees from AstraZeneca during the conduct of the study; grants and personal fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, EMD Serono, Novartis, and Pfizer; and personal fees from Bayer and Roche, outside the submitted work. TS reports personal fees from AstraZeneca during the conduct of the study. DNI reports personal fees from AstraZeneca during the conduct of the study; grants, personal fees, and nonfinancial support from AstraZeneca; grants and...
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