Molecular Testing in Non–Small-Cell Lung Cancer: A Call to Action

Arani Sathiyapalan, MD, MSc[1,2] and Peter Michael Ellis, MBBS, MMed, PhD[1,2]

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It has been nearly 15 years since the IPASS trial first demonstrated the importance of molecular testing to identify the population of patients with non–small-cell lung cancer (NSCLC) that benefit from molecularly targeted therapy.[1] Molecular genomic testing has become more widespread since then, with an increasing number of molecular targets and molecularly targeted therapies. As many as 50% of patients with advanced NSCLC are found to have an actionable oncogenic driver (including *KRAS* mutations).[2] In these patients, targeted treatments with tyrosine kinase inhibitors (TKIs) have been shown to improve overall response rates and progression-free survival (PFS) and are generally more tolerable than chemo(immuno)therapy.

Current clinical guidelines (European Society for Medical Oncology, ASCO) recommend broad-based molecular subtyping for patients with nonsquamous NSCLC.[3,4] There are different approaches to molecular genomic testing with variable availability, including single-gene testing (ie, sequential) or multigene testing, such as next-generation sequencing (NGS). Traditionally, tumor tissue samples have been tested. However, advances in technology allow molecular analysis, including NGS, of circulating tumor DNA in blood samples (liquid biopsies). Analysis of real-world data though suggests that there is incomplete uptake of molecular testing in NSCLC.[5] In addition, turnaround time (TAT) from the receipt of a biopsy sample to the receipt of results and initiation of targeted therapy can range from 5.1 weeks for NGS and 9.2 weeks for single-gene strategies.[6] These time frames though create concerns as delays to treatment in advanced NSCLC are associated with poorer outcomes, with population modeling on the basis of lung cancer kinetics estimating approximately 4% death rate per week.[7] As a result, National Comprehensive Cancer Network guidelines recommend empiric up-front therapy while awaiting molecular genomic testing results.[8]

In the article that accompanies this editorial, Smith et al[9] examine the association between availability of molecular testing before treatment decisions and outcomes such as time to next treatment (TTNT) and overall survival (OS). The data represent a retrospective real-world observational study from the Integra Connect Database. Patients were classified into three groups: those in whom treatment decisions were made after results of molecular testing, those who started empiric therapy (chemo[immuno]therapy) and switched to a TKI within 35 days, and those who continued empiric therapy. A total of 4,415 patients were identified, for whom actionable molecular abnormalities (*EGFR, ALK, ROS1, BRAF, MET, RET, HER2, NTRK*) were identified through tissue-based or blood-based NGS or single-gene testing of tumor. Molecular abnormalities were identified in 791 patients (18%); however, treatment records were available in only 510 (64.5%) of these patients.

This study was able to demonstrate that patients whose treatment decisions were made after molecular testing results had a longer TTNT and improved OS, in comparison with patients starting on empiric therapy with chemotherapy, immune checkpoint inhibitors (ICI), or combined chemotherapy and ICI treatment. The median OS for patients waiting for molecular test results before therapy was 28.8 months, in comparison with patients commencing empiric therapy, regardless of whether they switched to a TKI within 35 days (median OS, 21.7 months) or continued with empiric therapy (median OS, 15.3 months). Multiple randomized trials have demonstrated longer PFS for molecularly directed therapy compared with chemotherapy.[10,11] Therefore, it is not surprising that the longest TTNT was seen in patients who waited for the results of molecular testing.

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While it is possible that the differences in OS observed in this trial may represent real differences in outcomes for patients with molecularly driven NSCLC, it is very likely that the retrospective study design has contributed to a variety of selection biases that magnify any observed differences in outcomes between the groups. Only 18% of patients with single-gene panels had a molecular abnormality compared with 23% of tissue-based NGS and 24% of blood-based NGS. Approximately 40% of patients in this study had single-gene testing, which is less likely to identify fusion abnormalities such as *RET*, *MET*, and *NTRK*. These molecular abnormalities might not have the same positive prognostic implications as *EGFR* mutations or *ALK* translocations. This would seem apparent as there were clear differences between the groups in the proportion of patients with *EGFR* mutations (62% in group A *v* 28.6% in group C). ECOG PS appeared balanced across groups; however, there are likely other patient and physician factors, such as burden of disease, that both influenced the apparent urgency to commence therapy and are associated with poorer outcomes.

The apparent large improvement in OS is not consistent with data from randomized trials comparing molecularly targeted therapy with chemotherapy in NSCLC. Multiple randomized trials in patients with *EGFR* mutations and *ALK* translocations have demonstrated large improvements in PFS but no differences in OS.[10,11] This is likely due to the receipt of TKI therapy on progression. Therefore, it is not clear why this study would observe such large differences in OS. A significant limitation of the current study is that it does not provide information on the treatment received by patients on disease progression. It would be very informative to know what proportion of patients who received empiric therapy went on to receive TKI therapy at the time of progression. It would be important to know in the real world if patients do not go on to receive TKI therapy and have worse OS.

Nevertheless, the current report by Smith et al[9] suggests that waiting for the results of molecular testing before commencing therapy might result in improved OS for patients with advanced NSCLC. This should be a call to action. The findings challenge us to think about our current approach to patient management and question the diagnostic and testing systems that currently exist. The TATs for testing results vary depending on the type of testing (tissue *v* blood) and whether testing is conducted in house or through commercial laboratories. In general, results from liquid biopsies are available sooner (mean, 10 days; range, 1-17). TATs for tissue-based NGS range from a mean of 19 days (6-55) for in-house testing to 25 days (6-55) for outside NGS testing. TAT for sequential gene testing was not reported, but others have reported even longer times for sequential testing.[6]

We need to critically examine the overall systems that are in place to improve efficiency in molecular testing. There are many questions to be asked. Who orders molecular testing? The earlier in the diagnostic pathway this is ordered, the shorter any delays will be to commence treatment. Is molecular testing ordered reflexively at the time of diagnosis? Should liquid biopsy be the preferred initial test? The Blood First Assay Screening Trial demonstrated the feasibility of blood-based NGS testing to identify molecular abnormalities in patients with NSCLC.[12] Blood-based testing is usually recommended when tissue-based testing fails or if there is insufficient tissue for testing. Perhaps we need to reverse the sequence, perform blood-based NGS, and only proceed with tissue testing if the results are negative. If local testing is not available, we need to send samples earlier and minimize the steps involved to lower the turnaround time.

Sheffield et al identified key areas in which the systemic workflow could be streamlined to reduce delays. These include pursuing NGS versus sequential single-gene testing, which is associated with shorter TAT, reduced economic burden, and up-front identification of nonstandard mutations in NSCLC. In addition, reflex ordering of molecular genomic testing simultaneously with diagnostic IHC with the use of an automated gene sequencing system improved TAT. This workflow was shown to improve TAT to approximately 3 business days for all samples.[9] The challenge is to see if these local solutions are transferable to a broad number of institutions.

The findings by Smith et al[9] also question current guideline recommendations that support starting empiric therapy while awaiting the results of molecular testing.[8] In an ideal world, we would have rapid access to the necessary information to make clinical treatment decisions at the time of initial consultations. A survey of US oncologists reported that most oncologists feel a wait of <14 days for molecular testing results was acceptable.[13] There is a sense of urgency to treat though, perhaps due to perceived poor outcomes in untreated advanced NSCLC. Perhaps oncologists and patients need to be more patient and await molecular testing results before finalizing treatment decisions. This will require some adjustment in expectations and system improvements. While the current study has limitations, it does suggest that commencing the best therapy first will optimize patient outcomes. It will also help to minimize the potential risks of harm from commencing immunotherapy and switching to TKI-based therapy.[14] The challenge for us all now is how to improve our systems to achieve improved patient outcomes.

AFFILIATIONS

[1]Division of Medical Oncology, Juravinski Cancer Centre, Hamilton, ON, Canada
[2]Department of Oncology, McMaster University, Hamilton, ON, Canada

CORRESPONDING AUTHOR

Peter Michael Ellis, MBBS, MMed, PhD, Juravinski Cancer Centre, 699 Concession St, Hamilton, ON L8V 5C2, Canada; e-mail: ellisp@hhsc.ca.

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Arani Sathiyapalan
Honoraria: AstraZeneca
Consulting or Advisory Role: AstraZeneca

Peter Michael Ellis
Honoraria: AstraZeneca, Pfizer, Lilly, Bristol Myers Squibb, Merck, Jazz Pharmaceuticals, Novartis Canada Pharmaceuticals Inc, Janssen Oncology, Sanofi/Aventis, Roche Canada

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