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Thoracic Surgeons and Programmatic Liquid Biopsy Testing in Lung Cancer

The survival outcome benefit in advanced non-small cell lung cancer (NSCLC) from molecular testing is immense with a doubling of median overall survival (OS) and potential 5-year durability with targeted and immune-based therapies (1,2). Just as important as knowing the right therapy, it is equally important to avoid the wrong therapy. Not testing for or not knowing a driver mutation or fusion target in metastatic NSCLC is present, will miss the tremendous outcome benefit of the targeted therapy and lead to the potentially wrong therapy of chemoimmune therapy by default. Not knowing immune resistance mutations are present such as STK11 or KEAP1 and co-mutations will lead to ineffective immune-based therapy and potential disease hyperprogression (3,4). Not knowing radiation resistant mutations will lead to poorer survival in curative stage NSCLC. Not knowing the molecular tumor biology at the time of treatment decision making will miss a patient's best treatment and may lead to a wrong treatment with a much poorer survival outcome. Molecular testing is necessary in advanced lung cancer and is now becoming equally important in earlier curative stages of lung cancer. Not testing or not knowing the molecular tumor biology in the 'Precision Oncology' era of lung cancer before starting treatment is no longer an acceptable standard of care.

I. Advances have facilitated an ease of molecular testing in lung cancer

Next-generation technology (NGS) makes molecular testing complete, efficient, and more cost effective than individual sequential molecular testing approaches (5). Individual pathogenic driver mutations, gene rearrangement fusions, or gene amplifications do not need to be individually remembered and ordered. A broad all-encompassing NGS panel provides the complete molecular testing needed.

Liquid biopsy with plasma NGS molecular testing has further extended this needed full molecular testing with a simple blood test. Although tissue and plasma NGS testing remains complementary, completeness and timing of results have led the International Association for the Study of Lung Cancer (IASLC) to publish a consensus statement advocating and supporting a 'plasma first' molecular testing approach in NSCLC (6). Comparative simultaneous tissue and plasma NGS testing unexpectedly has indicated that tissue molecular testing will miss 33-43% of the mutations present, whereas testing plasma first will identify 80-87% of the targetable mutations/fusions (7,8,9). Tissue is still the 'gold standard' in making a diagnosis of cancer. However, given this data, the true 'gold standard' of molecular tumor biology testing has evolved to plasma. More complete molecular findings and a much quicker turnaround time of the

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molecular tumor biology results make a liquid biopsy with plasma NGS an ideal molecular testing approach.

II. Problems with the current model of molecular testing that need to be overcome

1. Molecular testing not getting done

The biggest problem with the current molecular testing approach is that the molecular testing is simply not getting done. Chart review data continues to show National Comprehensive Cancer Network (NCCN) guideline recommended molecular testing is not being performed by medical oncologists in the majority of patients. At the American Society of Clinical Oncology (ASCO) in 2019, a chart review of 1,203 advanced NSCLC patients from five community oncology practices of 289 oncologists, identified full NCCN guideline recommended biomarker testing in only 22% of advanced NSCLC patients (10). Even in the MYLUNG (Molecularly Informed Lung Cancer Treatment in a Community Cancer Network) consortium of US Oncology practices with a structured care pathway system, still under half of advanced NSCLC patients had recommended molecular testing performed (11).

This has led to multi-disciplinary thoracic tumor board discussions and treatment decisions being made without the full molecular tumor biology knowledge. This lack of knowing the full molecular tumor biology can lead to missing the best therapy for an individual and lead to a wrong treatment decision even in earlier stage NSCLC where the curative impact is more profound. How can a multidisciplinary thoracic tumor board begin to consider a treatment recommendation without knowing the molecular tumor biology?

Even more unsettling is medical oncologists are starting treatment without having knowledge of PD-L1, EGFR, or other mutations/fusions. In the MYLUNG consortium, only 35% of patients had the ordered tissue molecular testing results available before initiating first-line treatment (11). Testing but not knowing is no different than not testing and not knowing. The molecular tumor biology will be a guess and the right therapy will be a guess and thus potentially missed. The right therapy matters but also the right therapy first matters. Cross over treatment does not make up the lost survival that occurs when the best therapy is not undertaken first (12).

2. Time matters

The time from diagnosis to treatment matters. It is not the turnaround time of a molecular test that matters. It is the time from diagnosis of the cancer to starting treatment of the cancer that matters. Studies identify a 30-day window from the time from diagnosis to starting treatment as the critical period before survival outcomes begin to fall. Not because of any treatment

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difference, but simply the delay in starting a treatment. Kasymjanova et al reported that starting treatment within 30 days from diagnosis more than doubled the 4-year OS compared to a delay of more than 30 days across all stages of NSCLC (13). A meta-analysis of thirty-four studies across seven major cancer types, including NSCLC, noted a significant association between increased cancer mortality and delaying cancer treatment beyond 4 weeks from diagnosis (14).

3. Tissue only or first approaches

A tissue only or first approach of molecular testing is limiting implementing the therapeutic advances of treating lung cancer. With all advances comes new knowledge. New knowledge should spark new thinking and new ways of doing things. The current model of tissue testing only or first should no longer be an acceptable model of molecular testing in lung cancer. Tissue misses more mutations than plasma NGS testing. Tissue molecular testing is still not being performed in over half of advanced NSCLC patients. Tissue NGS testing takes too long with turnaround times of 3+ weeks leading to starting treatment greater than 30 days from diagnosis.

This 30-day time window starting from diagnosis to starting treatment is vitally important to survival outcome yet is not being achieved when tissue only or first molecular testing is performed. Tissue NGS testing typically has a 3-week turnaround time, when tissue is sufficient for molecular testing. With a needed pathology review for a histologic diagnosis of 3-5 days, followed by a request for tissue NGS testing, this delays initiation of treatment past the 30-day mark in the majority of patients (or patients start on treatment without knowing the molecular tumor biology findings). In the ASCO 2021 presentation and 2022 subsequent publication of the MYLUNG consortium study, the median time from diagnosis to treatment was 36 days (range 25-65 days) (11). Tissue testing also relies on sufficient tissue acquisition for full molecular testing. That in and of itself can be a limiting barrier to molecular testing in over 40% of patients (7,15).

4. Molecular testing impactful in earlier stage NSCLC

Molecular tumor biology also matters in earlier stage lung cancers. Knowing the molecular tumor biology to guide adjuvant treatment matters in resected NSCLC. The proof of principle ADAURA trial has shown a tremendous disease-free survival benefit of an EGFR TKI in EGFR mutant resected NSCLC compared to chemotherapy (16). The original adjuvant cytotoxic chemotherapy trials did not identify a survival benefit in the setting of a KRAS or TP53 mutation. In fact, there was a significant detrimental OS outcome with adjuvant chemotherapy if both KRAS and TP53 mutations were present (17).

Now in the ‘immune era’ of treating NSCLC, IMpower010 has shown a significant disease-free survival benefit in stage II and medically operable stage IIIA of adjuvant immune checkpoint

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inhibitor therapy with cytotoxic chemotherapy in PD-L1 expressing resected NSCLC (18). Pre-clinical data supports a better pre-operative immune-based therapy approach than post-operative approach due to the importance of the intact tumor draining lymph nodes for T-cell priming (19). SWOG S1801 in resectable stage III-IV melanoma showed a significantly improved 72% 2-year event free survival utilizing the same immune therapy in the neoadjuvant setting compared to 49% with the same therapy in the adjuvant setting (20). Given immune tumor biology and immune checkpoint inhibitor therapy, this would also oncologically be expected in NSCLC.

The two phase 3 neoadjuvant chemoimmune therapy trials in operable NSCLC both show a significantly higher pathologic complete response (pCR) resulting in remarkably improved event free as well as overall survival compared to neoadjuvant chemotherapy, supporting a neoadjuvant immune therapy approach. (21,22). As the transition to neoadjuvant chemoimmune therapy evolves in resectable NSCLC, knowing the molecular tumor biology becomes critical in decision making. Unlike the adjuvant setting where surgical tissue is bountiful, small bronchoscopy biopsies may well be fraught with insufficient tissue for full molecular testing, bringing liquid biopsy plasma NGS molecular testing to the forefront just as in stage IIIB/IV disease.

There is now an evolving understanding of immune therapy sensitive but even more importantly immune therapy resistant alterations that need to be known before making a group therapy decision of neoadjuvant chemo-immune treatment. Neoadjuvant chemo-immune therapy can be impacted by the presence of the immune resistance mutations EGFR, KEAP1, STK11 with a KRAS co-mutation, JAK2, PTEN mutations and oncogenic fusions (23). In addition to the immune therapy resistance, STK11 carries a potential for immune hyperprogression closing the curative surgical window (4). Phase 2 neoadjuvant chemo-immune trials have shown poor outcomes when an immune therapy resistant alteration is present. In a phase 2 trial of neoadjuvant atezolizumab with chemotherapy none of the patients with an STK11 mutation had a major pathologic response with one patient still having 100% tumor viability and half of the EGFR mutated patients did not have a major pathologic response (24). The only patients who recurred after neoadjuvant chemo-immune therapy in another phase 2 study each had targetable driver mutations identified (EGFR exon 20 insertion, EGFR exon 21 L858R substitution, and a MET exon 14 skipping mutations), despite 2 of these 3 having a major pathologic response (25). Knowing the immune checkpoint inhibitor potential resistant mutations/fusions is vital to know in neoadjuvant treatment decision making.

The molecular tumor biology also has an impact on the local modality treatment decision of NSCLC. A genomic landscape of radiation therapy sensitivity and resistant mutations are now being identified. Mutations in KEAP1, KRAS, PIK3CA, or MET amplification are associated with unfavorable stereotactic radiation treatment benefit in anatomical stage I NSCLC (26-29). The question of post-operative radiation therapy (PORT) with occult or persisting N2 disease is answered by the molecular tumor biology. Loco-regional control and even survival is extremely

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poor when the radiation resistant mutations of KEAP1, STK11, and PIK3CA are present, whereas PORT demonstrates complete locoregional control with radiation sensitive mutations of POLE, ARID1A, and ATM (30). Molecular tumor biology knowledge in all stages of lung cancer impacts treatment and survival outcomes. Not knowing or not testing for immune therapy and radiation therapy resistant alterations is clearly detrimental to patient outcomes in curable NSCLC. Liquid biopsy for plasma NGS testing in resectable NSCLC is important for patients to get their best curative outcome possible.

III. Surgical management of pre-operative ctDNA shedders and non-shedders

Even beyond identifying targetable mutations/fusions or immune/radiation therapy sensitive or resistant mutations, pre-surgical liquid biopsy testing also provides important findings that can guide neoadjuvant or adjuvant treatment decision making. Any pre-operative shedding of ctDNA into plasma, even when not a therapeutic target or treatment modality sensitive/resistant mutation, can identify those patients with potential lymph node involvement and those who have a far more aggressive underlying tumor biology beyond the anatomical stage. If there is pre-operative ctDNA shedding, neoadjuvant chemo-immune treatment can dynamically clear the plasma ctDNA changing an otherwise poor surgical outcome to a very favorable surgical outcome. If there is no pre-operative ctDNA shedding, the tumor biology is far less aggressive leaving open an adjuvant treatment decision based upon the stage specific surgical pathology.

Shedding will occur more frequently the higher the tumor burden and anatomical stage. In anatomical stage I NSCLC, shedding of ctDNA will occur in half of patients. With N1 and N2 lymph node involvement, the frequency of identifying ctDNA shed into the plasma increases to the 75% range. That is on par to even stage IV NSCLC with 80% shedding (31).

The simple number of pre-treatment plasma ctDNA mutations being shed into plasma and the higher the mutant allele fraction percentage are also prognostic of an underlying aggressive tumor biology with much poorer outcomes in advanced as well as earlier stage lung cancers compared to non-shedders (32-34). In the phase 2 NADIM neoadjuvant chemo-immune therapy trial in stage IIIA disease, baseline positive ctDNA shedding was associated with just a 45% Kaplan-Meier 4-year OS even with the neoadjuvant chemo-immune therapy (34). This is not any better than the seminal IALT adjuvant chemotherapy trial in stage I/II/III NSCLC trial with a 44.5% 5-year OS with adjuvant chemotherapy or compared to 40% in those who did not receive adjuvant chemotherapy (35). Yet non-shedder patients with a negative baseline plasma NGS in the same NADIM trial had a remarkable Kaplan-Meier 4-year OS of over 80%. In a study of plasma NGS testing in early-stage NSCLC, the anatomical stage I NSCLC patients who were shedding pre-operative plasma ctDNA had a 75% recurrence rate within 5 years of surgery. Comparatively, the non-shedders with a negative pre-operative plasma NGS in this study had an 80% 5-year freedom from recurrence rate (33).

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A negative pre-operative liquid biopsy plasma NGS is a particularly good oncologic finding with a less likelihood of nodal or other metastatic disease and is associated with a much less aggressive tumor biology and higher curative outcomes. Conversely, the finding of any pre-operative plasma ctDNA is associated with a much poorer outcome and should be viewed as having a more aggressive tumor biology with micro-metastatic disease warranting a more aggressive multi-modality treatment approach.

Pre-operative plasma ctDNA has a vital role in guiding neoadjuvant versus adjuvant treatment decision making in resectable NSCLC. When pre-operative ctDNA shedding is identified, there is a strong tumor biology rationale supported by clinical phase 3 trial data for a neoadjuvant chemo-immune treatment approach (provided there are no immune checkpoint inhibitor resistant mutations/fusions). Given the tumor biology impact of pre-operative ctDNA shedding even in stage I NSCLC, it is oncologically very compelling to step forward with neoadjuvant chemo-immune therapy irrespective of the anatomical stage.

This unfavorable tumor biology and evident poor OS outcome of pre-operative ctDNA shedders can be greatly improved by neoadjuvant chemo-immune therapy. Clearing of the baseline ctDNA findings upon repeat plasma NGS testing after the neoadjuvant chemo-immune therapy results in a greatly improved pCR and OS changing the unfavorable outcome prognosis to a very favorable OS outcome. In the CheckMate 816 trial, the pCR doubled in those with complete clearance of pre-treatment ctDNA shedding improving progression-free and OS (21). In the NADIM II trial, clearance of baseline ctDNA shedding after the pre-operative chemoimmune therapy, was associated with remarkable improvement from 45% to a 3-year 90% OS outcome that was as predictive as the surgical pathology pCR (22).

For the shedders who do not clear their ctDNA with neoadjuvant chemo-immune therapy, strong consideration of either PORT (provided no radiation therapy resistant mutation) if any persisting ypN2 disease or a step to more aggressive and extended (chemo-) immune options or any targetable findings options with ongoing monitoring of ctDNA is warranted.

Another important clinical caveat can be made in PET and/or EBUS confirmed stage IIIA NSCLC patients. The markedly higher OS of pre-operative non-shedders in stage IIIA studies treated with neoadjuvant chemo-immune therapy, compared to outcomes in adjuvant chemotherapy and chemo-immune trials, is very compelling to step forward with a neoadjuvant chemo-immune approach in IIIA disease irrespective of ctDNA shedding or not (18,21,22,34,35).

Conversely, in stage I/II pre-operative ctDNA non-shedders, given the more favorable underlying tumor biology and outcomes data, can be managed with an adjuvant treatment approach guided by stage specific surgical pathology findings.

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Neoadjuvant or adjuvant treatment?

- **Pre-operative ctDNA shedding →**
  Aggressive tumor biology and poor outcome
  Stage I/II/III…Neoadjuvant *chemo-immune treatment

- **No pre-operative ctDNA shedding →**
  Stage IIIA…neoadjuvant *chemo -immune treatment
  Stage I/II…adjuvant treatment based upon stage specific surgical pathology

- **EGFR mutation →**
  Stage I/II/III…adjuvant osimertinib

*No EGFR mutation or immune resistant mutation/fusion identified

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IV. Programmatic molecular testing makes a difference across all stages of NSCLC

Implementing a programmatic upstream approach to molecular testing of lung cancer is a vital foundation for a 'center of excellence' lung cancer program. The survival outcome benefits that precision oncology, immune oncology, and aggressive multi-disciplinary treatment of lung cancer provide will be lost if molecular testing is not fully done. With a consistent programmatic approach of molecular testing, all members of the lung cancer program team will know what needs to be done, when it needs to be done, and will ensure it gets done. This will provide the needed molecular tumor biology at the time when the treatment discussions and decisions are being made. A programmatic approach to molecular testing will allow one to see the molecular tumor biology never seen or known before. Just as we think and provide better lung cancer care and treatment together as a multi-disciplinary team, having a consistent programmatic approach to molecular testing will ensure the needed molecular testing gets done.

Anatomical staging may not be known at the time of diagnostic bronchoscopy. EBUS frequently identifies unexpected nodal involvement. Beyond the anatomical stage, the aggressiveness of the NSCLC can be identified by the number of ctDNA alterations being shed into the plasma. This impacts a decision regarding the aggressiveness of the treatment decisions as well as the liquid biopsy plasma NGS can guide the best treatment approach. Immune therapy sensitive and resistant mutations make a difference in decision making. Radiation therapy sensitivity and resistance mutations will impact a stereotactic radiation therapy or a PORT decision. Targeted therapy with no benefit of additional cytotoxic chemotherapy can be identified. No matter the

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stage, vital treatment information for each individual can be identified with liquid biopsy plasma NGS testing.

How can you have a multi-disciplinary treatment discussion, let alone make a treatment decision, without knowing the molecular tumor biology findings? Without molecular tumor biology findings, precision oncology and personalized cancer treatment does not exist.

V. Programmatic molecular testing at the time of the tissue biopsy is the solution

Drawing a liquid biopsy for plasma NGS testing at the time of the confirming tissue diagnosis provides an efficient and effective programmatic molecular testing approach. Adopting this programmatic approach of having the liquid biopsy plasma NGS drawn at the time of bronchoscopy tissue biopsy increased the molecular tumor biology being known in 85% of patients at the time of the initial oncologic evaluation. Previously it was known in just 9% of cases at this institution (36).

Even though the final stage is frequently unknown at the time of diagnosis, all stages of lung cancer need and can benefit from molecular testing. Just as not fully staging for extra-thoracic disease with PET and CNS imaging and not fully staging the mediastinum with EBUS can lead to a wrong treatment and poorer outcome, not knowing the molecular tumor biology of lung cancer, may miss the right and best treatment and potentially lead to a wrong treatment. And patient survival outcomes suffer.

A programmatic approach with a liquid biopsy for plasma NGS testing at the time of the tissue diagnosis and EBUS mediastinal staging provides the solution of making sure the needed molecular testing gets done. It provides the molecular tumor biology at the time of multi-disciplinary treatment decision making. It shortens the time from diagnosis to treatment. A best treatment can be identified. A wrong treatment avoided. And patient survival outcomes across all stages of lung cancer will improve.

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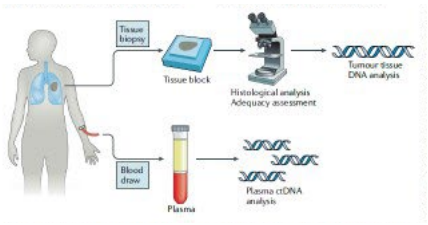
'Time from DX to RX'

Plasma AND tissue NGS COMPLEMENTARY testing



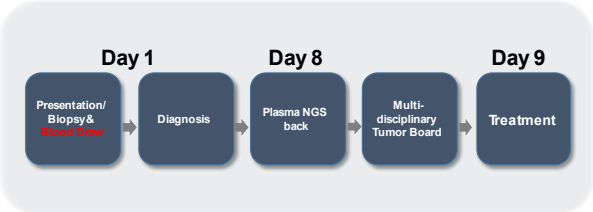
✓ **TISSUE for DX**

➢ **Plasma NGS for TUMOR BIOLOGY RX**

Block sent after cancer DX for tissue NGS testing

3-5 days with pathologist – 3 days to be sent out – tissue NGS 3-week TAT → > 30 days

Blood-based Tumor Profiling: Presentation to Treatment



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