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# Programmatic Upstream Liquid Biopsy Molecular 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 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 targetable driver mutation or fusion in metastatic NSCLC is present, will miss the tremendous outcome benefit of the targeted therapy and lead to the potentially wrong therapy of chemo-immune 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 therapy (RT) 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 (7-9). 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 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)

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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, less than 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 knowledge of the full molecular tumor biology. This 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 knowing the molecular tumor biology. 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. When first-line therapy is started without the availability of full molecular test results, overall survival outcomes dramatically suffer (12).

## 2. Time from DX to RX 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. 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 difference, but simply the delay in starting 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 tissue first approaches

A tissue only or first approach of molecular testing limits implementing the therapeutic advances of treating lung cancer. With all advances in cancer medicine comes new knowledge. New knowledge should spark new thinking and new ways of doing things clinically. The current model of tissue testing only, or tissue 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. Tissue testing is hampered by sampling inter-tumoral and intra-tumoral heterogeneity and potentially insufficient tissue acquisition for

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full molecular testing. That in and of itself is a limiting barrier to molecular testing in over 40% of patients (7,15).

### III. Molecular testing impactful in early-stage NSCLC

Molecular tumor biology also matters in early-stage lung cancers. Knowing the molecular tumor biology guides systemic treatment decisions in operable NSCLC. The proof of principle ADAURA trial has shown a tremendous disease-free as well as overall 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 operable NSCLC, IMpower010 has shown a significant disease-free survival benefit in stage II/IIIA with adjuvant immune checkpoint inhibitor therapy and cytotoxic chemotherapy in PD-L1 expressing resected NSCLC (18). Pre-clinical data however 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, although yet to be directly studied, this would also oncologically be expected in NSCLC.

Neoadjuvant chemo-immune therapy phase 3 trials in operable NSCLC show a significantly higher pathologic complete response (pCR) which results in improved event free as well as overall survival compared to neoadjuvant chemotherapy (21-24). As the transition to neoadjuvant chemo-immune therapy evolves in operable 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. This brings liquid biopsy plasma NGS molecular testing to the forefront in early-stage NSCLC just as in stage IIIB/IV disease.

### IV. Tumor biology matters more than anatomical stage

The number of pre-treatment ctDNA alterations in a plasma NGS are prognostic in advanced as well as earlier stage lung cancers (25-27). The greater the ctDNA shedding into the plasma, the more aggressive the tumor biology. ctDNA is also predictive of neoadjuvant chemo-immune benefit when it clears with treatment. Notably, in the neoadjuvant chemo-immune CheckMate 816 trial, the pCR doubled in those with complete clearance of any pre-treatment ctDNA shedding. Conversely, there were no pCRs if the ctDNA did not clear with neoadjuvant chemo-immune therapy (21.) In the NADIM trial, clearance of any ctDNA shedding after the pre-operative chemo-immune therapy was associated with remarkable OS outcomes that were as predictive of durable survival as the surgical pathology pCR (27).

Systemic neoadjuvant chemo-immune therapy can be greatly impacted by the presence of immune resistance mutations and potential hyperprogression closing the curative surgical window (4, 28).

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Knowing the immune checkpoint inhibitor sensitive and more importantly the potential resistant mutations is vital in neoadjuvant therapy decision making.

The molecular tumor biology also has an impact on the local modality treatment decision of NSCLC. A genomic landscape of RT sensitivity and resistant mutations are now being identified. Mutations in KEAP1, KRAS, PIK3CA, or MET amplification are associated with unfavorable SBRT benefit in anatomical stage I NSCLC (29-32). The question of post-operative radiation therapy (PORT) with occult or persisting N2 disease should also be guided by molecular tumor biology. Loco-regional control and even survival is extremely poor when the radiation resistant mutations of KEAP1, STK11, and PIK3CA are present, whereas PORT demonstrates complete locoregional control with RT sensitive mutations of POLE, ARID1A, and ATM (33).

Programmed death ligand-1 (PD-L1) expression has also evolved as an impactful predictor of neoadjuvant chemo-immune therapy benefit. In CheckMate 816, there was no survival benefit of neoadjuvant chemo-immune therapy compared to chemotherapy alone when there was a lack of PD-L1 expression. Neoadjuvant chemo-immune therapy only benefited those patients with positive PD-L1 expression. In NADIM II, there was a 31% higher mortality with neoadjuvant chemo-immune compared to chemotherapy alone when PD-L1 was negative. A plasma cell-free RNA PD-L1 assay obtained with a liquid biopsy can overcome tissue PD-L1 heterogeneity as well can provide the same predictive immunotherapy benefit as tissue (34,35).

Molecular tumor biology knowledge in all stages of lung cancer impacts treatment and survival outcomes. Not knowing or not testing for immune therapy and RT resistant alterations is clearly detrimental to individual patient outcomes in curable early-stage NSCLC. A liquid biopsy provides clinically important molecular tumor biology information that can guide the systemic and multi-modality treatment in curable NSCLC.

## Clinical Utility Pre-operative Liquid Biopsy Early-Stage NSCLC

- **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
- **No pre-operative ctDNA shedding and Stage I medically inoperable (or borderline) →**
  - No RT resistant alteration…SBRT
  - RT resistant alteration…different ablative approach (or sublobar resection)
- **EGFR mutation →**
  - Stage IB/II/III…adjuvant osimertinib

*No EGFR mutation or immune resistant mutation/fusion identified

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

Implementing a programmatic 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 when 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 tumor biology is known at the time of treatment decision making.

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. RT sensitivity and resistance mutations will impact an SBRT or PORT decision. Targeted therapy with no benefit of additional cytotoxic chemotherapy can be identified. No matter the stage, vital treatment information for each individual can be identified with liquid biopsy plasma NGS testing. Without molecular tumor biology findings, precision oncology and personalized cancer treatment does not exist.

## VI. Pulmonologists as the Fourth Pillar of Lung Cancer

Just as pulmonologists are integral in the diagnosis and staging of lung cancer, they are integral to a programmatic approach of molecular testing guiding treatment in lung cancer. A tissue diagnosis is requested of the pulmonologist. Staging of the mediastinum is expected by the pulmonologist. A request for the pulmonologist to obtain sufficient tissue for molecular testing is implicitly implied. To make the diagnosis, complete intra-thoracic staging, and provide full molecular tumor biology testing to guide treatment is within the role and expectations of the pulmonologist. A liquid biopsy for plasma NGS testing is complementary to tissue NGS molecular testing, and in fact can identify more mutations, and more mutations more quickly than tissue. Why is drawing a liquid biopsy not the role of the pulmonologist? It is clearly not getting done nor getting done in a timely manner in the majority of patients with the current model of molecular testing.

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 best multi-disciplinary treatment approach and potentially lead to a wrong treatment. This makes the pulmonologist a 'thoracic pulmonary oncologist' and a vital fourth pillar of managing and treating lung cancer.

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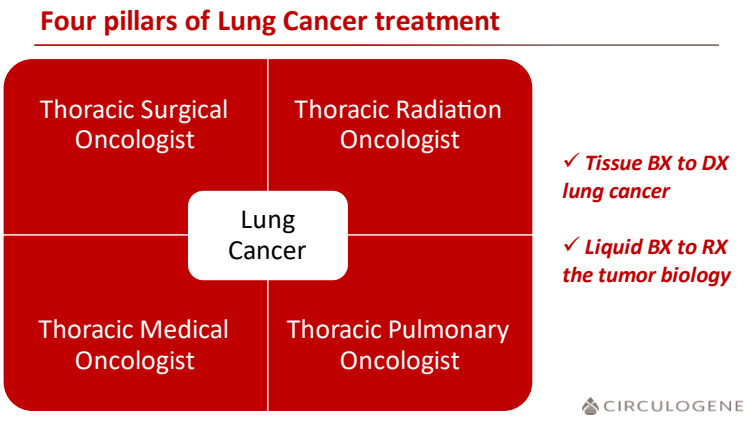
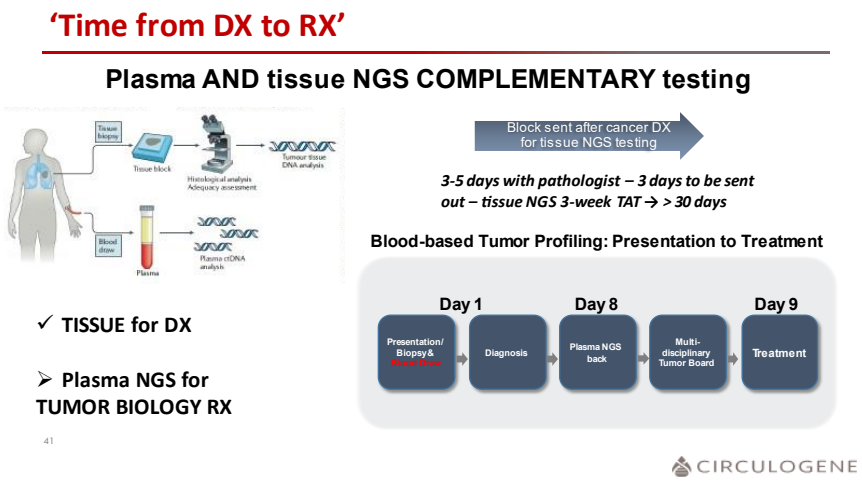



## VII. Programmatic molecular testing at the time of the tissue biopsy is the solution

The pulmonologist drawing a liquid biopsy for plasma NGS testing at the time of the confirming bronchoscopy tissue diagnosis provides an efficient and effective programmatic molecular testing approach. That is part of their role as thoracic pulmonary oncologists and the fourth pillar in the management and treatment of lung cancer. Adopting this programmatic approach of the pulmonologist drawing the liquid biopsy plasma NGS at the time of bronchoscopy tissue biopsy has been shown to increase the molecular tumor biology being available in 85% of patients at the time of the initial oncologic evaluation compared to previously being known in just 9% of cases at the same institution (36).

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



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