Mutational Status Now Directs Lung Cancer Treatment Decisions

Mutational status in non-small-cell lung cancer is critically important in determining the most effective therapy, similar to that of breast cancer. Oncologists do not treat breast cancer without first determining the patient’s HER2 status. Now, status for EGFR, KRAS, and EML4-ALK in NSCLC has taken on a similar role as HER2, becoming an integral component in treatment decisions.

Significant progress has been made during the last 20 years in the molecular characterization of lung tumors. Previously, tumors were identified only as KRAS positive/negative; now physicians are empowered with 3 mutations of actionable significance.

Histology Is the First Step

Leading experts in lung cancer, such as Dr. David Ettinger – Chair of NSCLC NCCN guidelines, are now stressing the importance of histology before mutational testing. The NCCN guidelines specifically states that a patient’s tumor should be classified as adenocarcinoma or squamous cell carcinoma before mutational testing.

Which Histology Classifies Your Patient’s Tumor?

<table>
<thead>
<tr>
<th>Histology</th>
<th>Percent of NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>40-50%</td>
</tr>
<tr>
<td>Squamous</td>
<td>30-35%</td>
</tr>
<tr>
<td>Large Cell</td>
<td>10-20%</td>
</tr>
</tbody>
</table>

85% of all Lung Cancers are NSCLC

Pathology departments can regularly provide histology sub-typing. If they do not, GENPATH as a full-service oncology laboratory can provide the most comprehensive histological classification, categorizing the tumor as either adenocarcinoma or squamous.

NSCLC Histology Classification: Test Code A130

When resection specimens are not available, lung specimens for testing are obtained by either endobronchial or percutaneous needle biopsies both yielding small amounts of tissue. The scarcity of specimen places particular importance on selecting appropriate tests.

Testing according to clinical treatment selection priority has multiple benefits:

- Does not deplete specimen with unnecessary tests
- Ensures most relevant & actionable tests are run first
- Cost saving

### Reflex Dx: Adenocarcinoma

GenPath has designed a testing algorithm specifically for adenocarcinoma histology subtypes. The Reflex Dx test looks for EGFR, KRAS mutations, and EML4-ALK fusion proteins in a reflexive manner that takes into account clinical relevance and likely incidence. For example, EGFR and KRAS are mutually exclusive; a patient that is EGFR positive should NOT have a KRAS mutation. Therefore testing both together would not be practical.

#### Treatment Implications

- **EGFR**
  - Positive
  - if negative, run

- **KRAS**
  - Positive
  - if negative, run

- **EML4-ALK**
  - Positive

#### References

Squamous Cell Carcinoma

The classification of a NSCLC tissue as squamous cell carcinoma has significant implications for treatment decisions. NCCN guidelines do not recommend mutational testing for squamous cell due to the extremely low incidence (1% or less) of EGFR or KRAS mutations, and EML4-ALK fusions.

Patients with squamous cell carcinoma histology are:

- At significant risk for toxicity when treated with bevacizumab (Avastin).
- May be resistant to treatment with pemetrexed.
- Primary first line treatment plans include cisplatin doublet based combination regimens that include with gemcitabine or docetaxel or paclitaxel.

80% of Oncologists Regularly Use Practice Guidelines to Guide Patient Care.

ERCC1: All Histology Subtypes

Test Code : A300-6

GenPath offers ERCC1 mRNA expression level testing by RT-PCR that provides both prognostic value and prediction of therapeutic response to DNA damaging agents such as carboplatin/gemcitabine or gemcitabine alone.

ERCC1 (RT-PCR)

High Level of ERCC1:

1. Favorable Prognosis
   
   Patients with high tumoral ERCC1 levels had an overall survival of 55 months vs. 42 months for patients with low ERCC1 expression.

2. Unfavorable Therapeutic Response to DNA Damaging Agents

   High tumoral ERCC1 expression had poor response to cisplatin based therapy vs. patients with low ERCC1 levels.

Low Level of ERCC1:

Unfavorable prognosis and favorable response to cisplatin based therapy vs. patients with high ERCC1 levels.

Methodology Matters

GenPath utilizes the most clinically appropriate methodology to identify the relevant mutation or quantitate the target expression level.

<table>
<thead>
<tr>
<th>Test</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>PCR</td>
</tr>
<tr>
<td>KRAS</td>
<td>PCR</td>
</tr>
<tr>
<td>EML4-ALK</td>
<td>FISH</td>
</tr>
<tr>
<td>ERCC1</td>
<td>RT-PCR</td>
</tr>
</tbody>
</table>

PCR can miss EML4-ALK mutations for patients who achieve significant response from treatment.

GenPath uses FISH for EML4-ALK

“An EML4-ALK fusion transcript could not be confirmed on RT-PCR in 9 patients, and the analysis failed in 2 additional patients. *RT-PCR assays were unable to detect all known ALK rearrangements*.”