Precision Medicine in mNSCLC
A multidisciplinary approach to EGFR mutation testing to help inform treatment decisions

EGFR, epidermal growth factor receptor; mNSCLC, metastatic non-small cell lung cancer.
Identifying actionable biomarkers can help you provide the most appropriate treatment for your patients with mNSCLC

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend testing for EGFR mutations at diagnosis and at progression in patients with mNSCLC.

### mNSCLC at diagnosis

**NCCN Guidelines® recommendation:** Test for biomarkers at diagnosis of mNSCLC, including EGFR, ALK, BRAF, ROS1, NTRK, and PD-L1.

### mNSCLC at progression

Most patients will progress after 9 to 13 months on first-line treatment with 1st- or 2nd-generation EGFR-TKIs.\(^3\)\(^-\)\(^7\)

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#### Plasma-based testing

**Advantages**
- Less invasive and fewer limitations\(^2\)
- Potential for faster turnaround time (~3 days)\(^16\)
- May save on procedure costs\(^12\)

**Considerations**
- Results can be inconclusive due to differences in tumor biology\(^12\)
- Tumor burden and tumor shedding can influence results\(^12\)
- DNA may be insufficient for positive identification\(^12\)

If plasma-based test results are negative, NCCN Guidelines recommend tissue-based testing with rebiopsy material.\(^1\)

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#### Tissue-based testing

**Advantages**
- Established testing method\(^12\)
- High sensitivity rates\(^14\)
- No cell degradation\(^15\)

**Considerations**
- Sample heterogeneity may impact patient identification\(^12\)
- Patient may not be eligible due to performance status or tumor location\(^13\)
- Complications may develop during the collection process\(^12\)
Sample acquisition differs for tissue and plasma testing

### Tissue samples

**Sample collection**
- An interventional radiologist, pulmonologist, or thoracic surgeon collects tissue.
- Assay instructions may require using specific specimen types. Collaborate with your multidisciplinary team to ensure appropriate biopsy methods are performed.

**Sample preparation**
- Preserve tissue immediately.
  - Tissue samples are fragile, and degradation starts upon removal from the body.
  - Fix samples immediately, within 1 hour of acquisition, to preserve tumor characteristics for diagnostic evaluation.

**Sample assessment**
- Samples should be.
  - Embedded in paraffin block.
  - Cut into 5-μm sections.

**Confirm tumor cell content is sufficient**
- Tumor cellularity (i.e., the relative proportion of tumor and nontumor cells) affects the sensitivity of biomarker testing and may be more important than tumor quantity.
- Most tests require samples with >10% tumor cell content. If the sample is not sufficient, consider tumor enrichment or request a new sample.

A pathologist or a technologist performs rapid on-site evaluation (ROSE) of tissue quantity and quality by pathology/cytology, which can ensure a sufficient sample is collected.

For a diagnosis of mNSCLC without ROSE, current guidelines suggest using a minimum of 3 tranabronchial needle aspiration samples.

### Plasma samples

**Sample collection**
- Plasma testing utilizes ctDNA.
- ctDNA may be shed by tumors into the bloodstream. When blood is collected from a patient, ctDNA can be tested for EGFR mutations.
- ASCO/CAP guidelines recommend collection in cell-stabilizing tubes or EDTA anticoagulant collection tubes.

**Sample preparation**
- **Process sample as soon as possible**
  - Guidelines recommend separating plasma from the blood as soon as possible, within 6 hours of collection.
  - Blood samples are typically processed by filtration or centrifugation.
- **Store the sample**
  - After processing, isolated plasma can be frozen for storage.
  - Avoid multiple freeze-thaw cycles.

**Turnaround time can impact treatment decisions**

CAP/IASLC/AMP guidelines recommend a turnaround time of 10 working days from tissue or plasma sample receipt at testing laboratory.

Collaboration within the multidisciplinary team can ensure that critical factors, such as specimen type and turnaround time, are communicated for appropriate and timely treatment of patients.

CAP/IASLC/AMP guidelines recommend a turnaround time of 10 working days from tissue or plasma sample receipt at testing laboratory.

AMP: Association for Molecular Pathology; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; CNB, core needle biopsy; ctDNA, circulating tumor DNA; EDTA, ethylenediaminetetraacetic acid; FNA, fine needle aspiration; IASLC, International Association for the Study of Lung Cancer; NBF, neutral-buffered formalin.
A multidisciplinary approach to testing is essential to complete testing in a timely manner\(^{17}\)

According to CAP/IASLC/AMP guidelines, test reports should include the following results and interpretations\(^{21}\):

**Results**
- Clinically significant mutations identified
- Reason for assay failure (if needed)

**Interpretation**
- Assessment of tumor’s likelihood to respond to targeted therapy, based on mutation
- Requirements for repeat testing (if needed)

Multiple diagnostic assays can be used to detect EGFR mutations.

Complete reporting of EGFR test results is important for choosing an appropriate treatment.

Sample collection method may impact the ability to test for biomarkers. Consult with your multidisciplinary team to ensure collection methods are appropriate for the planned diagnostic tests\(^{17}\).

Sample requirements vary for each LDT. Always verify that your samples adhere to the individual test specifications.

**FDA-approved assays and laboratory-developed tests are available**

<table>
<thead>
<tr>
<th>FDA approved assays</th>
<th>therascreen (^{27}) EGFR RGQ PCR Kit(^{27})</th>
<th>FoundationOne CDx(^{28})</th>
<th>Oncomine(^{29}) Dx Target Test(^{30})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common EGFR mutations detected</td>
<td>Exon 19 deletions L858R T790M</td>
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<tr>
<td>Testing technology</td>
<td>qRT-PCR</td>
<td>qRT-PCR</td>
<td>NGS</td>
</tr>
<tr>
<td>Sample types</td>
<td>FFPE tissue Plasma</td>
<td>FFPE tissue FFPE tissue</td>
<td>FFPE tissue</td>
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</tbody>
</table>

**Laboratory-developed tests**

<table>
<thead>
<tr>
<th>Company</th>
<th>Guardant</th>
<th>GeneStrat(^{33,34})</th>
<th>OncoBEAM(^{35,36})</th>
<th>ExoDx(^{37}) Lung</th>
<th>Biocept Liquid Biopsy</th>
<th>Trovera(^{38}) EGFR</th>
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</thead>
<tbody>
<tr>
<td>Testing technology</td>
<td>NGS</td>
<td>PCR</td>
<td>PCR</td>
<td>PCR</td>
<td>PCR</td>
<td>NGS</td>
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<tr>
<td>Sample types</td>
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<td>Blood</td>
<td>Tissue Blood</td>
<td>Blood</td>
<td>Blood</td>
<td>Blood</td>
</tr>
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<td>Turnaround time</td>
<td>7 days</td>
<td>3 days</td>
<td>&lt;10 days</td>
<td>&lt;7 days</td>
<td>&lt;7 days</td>
<td>&lt;10 days</td>
</tr>
</tbody>
</table>

These tests are performed in laboratories that adhere to performance specifications established by the Clinical Laboratory Improvement Amendments of 1988 (CLIA) under the regulation of the Centers for Medicare & Medicaid Services. They are not FDA-approved.\(^{30,36}\)

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FDA, Food and Drug Administration; FFPE, formalin-fixed paraffin-embedded; LDT, laboratory-developed test; NGS, next-generation sequencing; PCR, polymerase chain reaction; qRT-PCR, quantitative reverse transcription PCR.
A multidisciplinary approach to EGFR mutation testing is essential to reaching informed treatment decisions.\(^{17}\)

**Testing for EGFR mutations** takes multiple disciplines, careful communication, and precise coordination.\(^{17}\)

**Options for identifying EGFR mutations** include tissue- and plasma-based testing.\(^{12}\)

**NCCN Guidelines** recommend testing for EGFR mutations at diagnosis and at progression in patients with mNSCLC.\(^{1}\)

**Complete and timely reporting** of EGFR mutation test results is important for choosing an appropriate therapy.\(^{17}\)

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**References:**
1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)® for Non-Small Cell Lung Cancer V3.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed March 19, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.