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.

AstraZeneca

Identifying actionable biomarkers can help you provide the most appropriate treatment for your patients with mNSCLC[1]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend testing for EGFR mutations at diagnosis and at progression in patients with mNSCLC[1]

mNSCLC at diagnosis

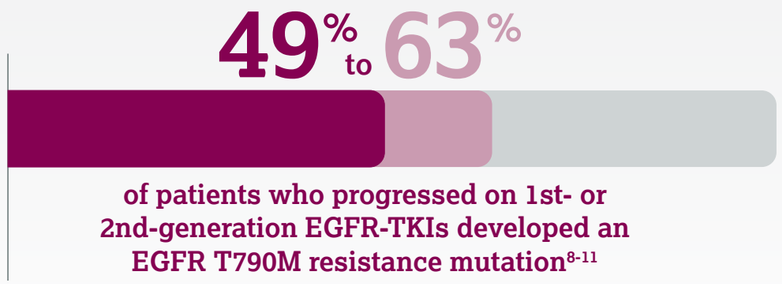
NCCN Guidelines® recommendation:
Test for biomarkers at diagnosis of mNSCLC, including EGFR, ALK, BRAF, ROS1, NTRK, and PD-L1[1]

of patients with lung adenocarcinoma have sensitizing EGFR mutations (eg, exon 19 deletions or exon 21 L858R mutations)[2]

According to NCCN Guidelines, patients with sensitizing EGFR mutation–positive mNSCLC should be treated with an EGFR-TKI[1]

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]



of patients who progressed on 1st- or 2nd-generation EGFR-TKIs developed an EGFR T790M resistance mutation[8-11]

According to NCCN Guidelines, patients with mNSCLC who progress while on a 1st- or 2nd-generation EGFR-TKI should be tested for the EGFR T790M mutation[1]

The NCCN Guidelines do not endorse specific testing modalities or techniques for biomarker tests.

AstraZeneca

Utilizing tissue and plasma samples can make EGFR mutation testing available for more patients[12]

Tissue-based testing is the gold standard for identifying sensitizing EGFR mutations, but plasma may be used if tissue testing is not feasible. Plasma testing may be preferable for patients[12,13]:

- Who are ineligible for a tissue biopsy due to performance status or tumor location
- Who are unwilling to undergo a tissue biopsy
- Whose tissue samples are inadequate for molecular testing

Tissue- and plasma-based testing methods have different advantages and considerations

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]

Plasma-based testing

Advantages

- Less invasive and fewer limitations[12]
- 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]

ALK, anaplastic lymphoma kinase; BRAF, v-Raf murine sarcoma viral oncogene homolog B; NCCN, National Comprehensive Cancer Network; NTRK, neurotrophic tyrosine kinase; PD-L1, programmed death-ligand 1; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor.

Sample acquisition differs for tissue and plasma testing

Tissue samples

Sample collection

- An interventional radiologist, pulmonologist, or thoracic surgeon collects tissue[17]
- Assay instructions may require using specific specimen types. Collaborate with your multidisciplinary team to ensure appropriate biopsy methods are performed[18]

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[17]

For a diagnosis of mNSCLC without ROSE, current guidelines suggest using a minimum of 3 transbronchial needle aspiration samples.[17]

Sample preparation

Preserve tissue immediately

- Tissue samples are fragile, and degradation starts upon removal from the body[19,20]
- Fix samples immediately, within 1 hour of acquisition, to preserve tumor characteristics for diagnostic evaluation[19,20]

CAP/IASLC/AMP guidelines recommend[21]:
Fix for 6 to 48 hours in 10% NBF

Sample assessment

Samples should be

- Embedded in paraffin block[22]
- Cut into 5-µm sections[22]

Confirm tumor cell content is sufficient

- Tumor cellularity (ie, the relative proportion of tumor and nontumor cells) affects the sensitivity of biomarker testing and may be more important than tumor quantity[23]
- Most tests require samples with >10% tumor cell content. If the sample is not sufficient, consider tumor enrichment or request a new sample[22]

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[12,13]
- ASCO/CAP guidelines recommend collection in cell-stabilizing tubes or EDTA anticoagulant collection tubes[24]

Sample preparation

Process sample as soon as possible

- Guidelines recommend separating plasma from the blood as soon as possible, within 6 hours of collection[24]
- Blood samples are typically processed by filtration or centrifugation[24]

Store the sample

- After processing, isolated plasma can be frozen for storage[24]
- Avoid multiple freeze-thaw cycles[24]

Turnaround time can impact treatment decisions[25]

CAP/IASLC/AMP guidelines recommend a turnaround time of **10 working days** *from tissue or plasma sample receipt at testing laboratory*[26]

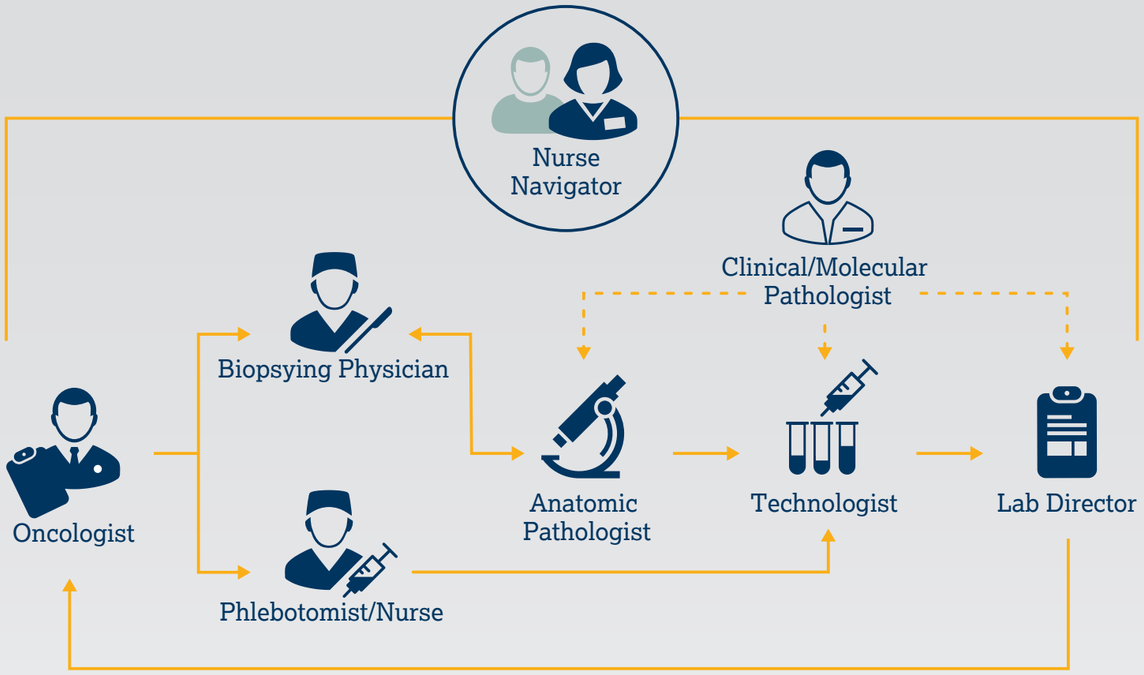
Collaboration within the multidisciplinary team can ensure that critical factors, such as specimen type and turnaround time, are communicated for appropriate and timely treatment of patients[21]

AstraZeneca

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.

Collaboration with your multidisciplinary team

A multidisciplinary approach to testing is essential to complete testing in a timely manner[17]



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

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

FDA-approved assays and laboratory-developed tests are available

	cobas® EGFR Mutation Test v2[22]	*therascreen® EGFR RGQ PCR Kit*[27]	*FoundationOne CDx™*[28]	*Oncomine™ Dx Target Test*[29]
Common EGFR mutations detected	Exon 19 deletions L858R T790M	Exon 19 deletions L858R T790M	Exon 19 deletions L858R T790M	Exon 19 deletions L858R
Testing technology	qRT-PCR	qRT-PCR	NGS	NGS
Sample types	FFPE tissue Plasma	FFPE tissue	FFPE tissue	FFPE tissue

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]

*Laboratory-developed tests**	*Guardant 360™*[30,31]	*GeneStrat®*[32,33]	*OncoBEAM™*[34,35]	*ExoDx™ Lung*[36]	*Biocept Liquid Biopsy*[37]	*Trovera™ EGFR*[38-40]
Company	Guardant	Biodesix	Sysmex Inostics	Exosome Diagnostics	Biocept	Trovagene
Testing technology	NGS	PCR	PCR	PCR	PCR	NGS
Sample types	Blood	Blood	Tissue Blood	Blood	Blood	Blood
Turnaround time	14 days	3 days	<10 days	<7 days	<7 days	<10 days

*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.[41,42]

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

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.

AstraZeneca

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]

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. **2.** Sholl LM et al. *J Thorac Oncol.* 2015;10(5):768-777. **3.** Wu YL et al. *Lancet Oncol.* 2014;5(2):213-222. **4.** Rosell R et al. *Lancet Oncol.* 2012;13(3):239-246. **5.** Mitsudomi T et al. *Lancet Oncol.* 2010;11(2):121-128. **6.** Sequist LV et al. *J Clin Oncol.* 2013;31(27):3327-3334. **7.** Zhou C et al. *Lancet Oncol.* 2011;12(8):735-742. **8.** Yu HA et al. *Clin Cancer Res.* 2013;19(8):2240-2247. **9.** Oxnard GR et al. *Clin Cancer Res.* 2011;17(6):1616-1622. **10.** Sun JM et al. *Lung Cancer.* 2013;82(2):294-298. **11.** Sequist LV et al. *Sci Transl Med.* 2011;3(75):75ra26. **12.** Diaz LA Jr, Bardelli A. *J Clin Oncol.* 2014;32(6):579-586. doi:10.1200/JCO.2012.45.2011. **13.** Bordi P et al. *Transl Lung Cancer Res.* 2015;4(5):584-597. **14.** Ellison G et al. *J Clin Pathol.* 2013;66(2):79-89. **15.** Sholl LM et al. *Arch Pathol Lab Med.* 2016;140:825-829. **16.** Sacher AG et al. *JAMA Oncol.* 2016;2(8):1014-1022. doi:10.1001/jamaoncol.2016.0173. **17.** Levy BP et al. *Oncologist.* 2015;20(10):1175-1181. **18.** Ofiara LM et al. *Front Oncol.* 2014;4:253. doi:10.3389/fonc.2014.00253. **19.** Hammond ME et al. *Arch Pathol Lab Med.* 2010;134(7):e48-e72. **20.** Chen H et al. *Cancers (Basel).* 2015;7(3):1699-1715. **21.** Lindeman NI et al. *Arch Pathol Lab Med.* 2013;137(6):828-860. **22.** cobas® EGFR Mutation Test v2 [package insert]. Branchburg, NJ: Roche Molecular Systems, Inc.; 2015. **23.** Aisner DL, Marshall CB. *Am J Clin Pathol.* 2012;138(3):332-346. **24.** Merker JD et al. *J Clin Oncol.* 2018;36(16):1631-1641 doi:10.1200/JCO.2017.76.8671. **25.** Lim C et al. *Curr Oncol.* 2017;24(2):103-110. **26.** Lindeman NI et al. *Arch Pathol Lab Med.* 2018;142(3):321-346. doi:10.5858/arpa.2017-0388-CP. **27.** *therascreen®* EGFR RGQ PCR Kit [instructions for use (handbook)]. Manchester, UK: QIAGEN; 2017. **28.** FoundationOne CDx™ [technical specifications]. Cambridge, MA: Foundation Medicine, Inc.; 2017. **29.** Oncomine™ Dx Target Test Part I: sample preparation and quantification [user guide]. Waltham, MA: Thermo Fisher Scientific Inc.; 2017. **30.** Guardant Health. http://www.guardanthealth.com/medical-professionals/#gene-panel. Accessed March 16, 2018. **31.** Guardant Health. http://www.guardanthealth.com/guardant360/#how-it-works. Accessed March 27, 2018. **32.** Centers for Medicare & Medicaid Services. https://www.biodesix.com/wp-content/uploads/2017/09/CLIA-Accreditation-cert-exp-6-20-2019-1.pdf. Accessed March 16, 2018. **33.** Biodesix. https://www.biodesix.com/genestrat. Accessed March 16, 2018. **34.** GenomeWeb. https://www.genomeweb.com/pcrsample-prep/inostics-lab-gains-clia-licensure. Published May 30, 2013. Accessed March 16, 2018. **35.** Sysmex Inostics. https://www.sysmex-inostics.com/our-services/product-single-view/oncobeamTM-egfr-3805.html. Accessed March 16, 2018. **36.** ExoDx® *Lung(ALK)* [fact sheet]. Waltham, MA: Exosome Diagnostics, Inc.; 2016. http://www.exosomedx.com/sites/default/files/uploads/alk_t790m_051716_0.pdf. Accessed March 16, 2018. **37.** Biocept. https://biocept.com/technology/lung-cancer-offering. Accessed March 16, 2018. **38.** Trovagene. https://www.trovagene.com/technology/applications/egfr-mutation-testing/egfr-clinical-evidence/assessment-of-egfr-mutations-in-matched-urine-plasma-and-tumor-tissue-in-nsclc-patients-treated-with-rociletinib-co-1686/. Accessed March 16, 2018. **39.** Trovagene. https://www.trovagene.com/technology/. Accessed March 16, 2018. **40.** Trovera. https://www.trovagene.com/faq/#trovera. Accessed March 16, 2018. **41.** Fitzgibbons PL et al. *Arch Pathol Lab Med.* 2014;138(11):1432-1443. **42.** FDA. https://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/laboratorydevelopedtests/default.htm. Updated February 4, 2018. Accessed March 16, 2018.

AstraZeneca