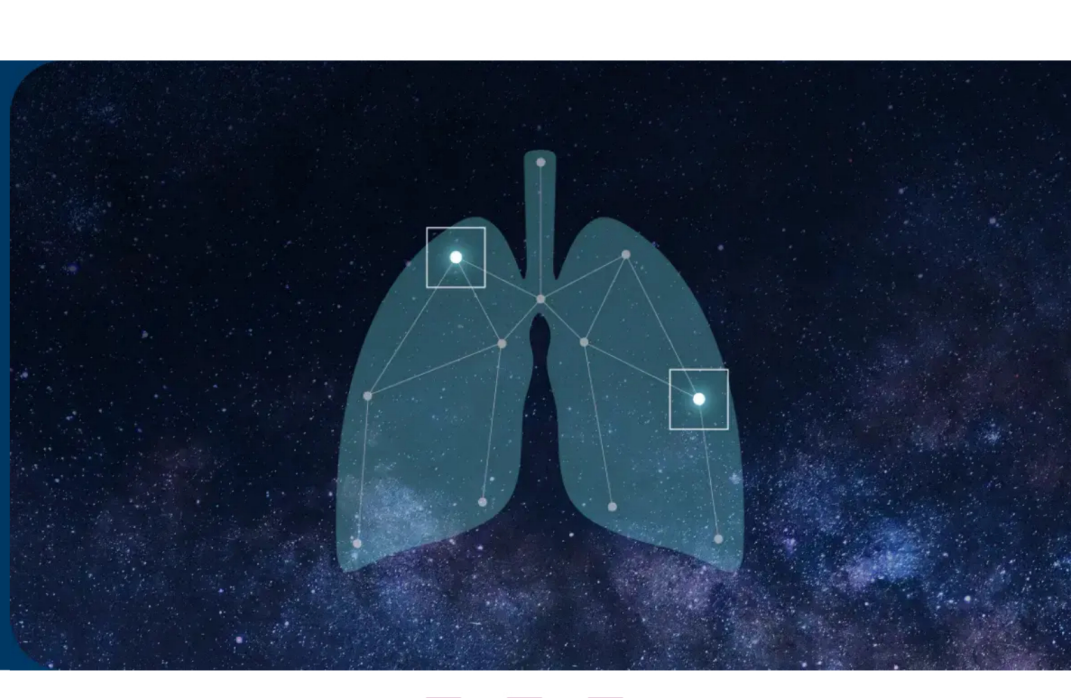
ERBB2 (*HER2*) Mutations in Metastatic NSCLC

Testing for *ERBB2* (*HER2*) mutations may contribute to improved health outcomes of patients with NSCLC by informing eligibility for targeted treatment options.[1]



Reading time: **16 min**

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Testing for *ERBB2* (*HER2*) Mutations Can Guide Treatment[1]

An activating *HER2* mutation is any mutation identified within the *ERBB2* (*HER2*) gene that is known to play a role in the oncogenic process.[2] *ERBB2* (*HER2*) mutations are reported to be mutually exclusive with other oncogenic drivers, such as *EGFR*, *KRAS*, *ALK* and *BRAF* mutations, and are recognized as an actionable biomarker in non-small cell lung cancer (NSCLC).[3,4]

ALK, anaplastic lymphoma kinase; *BRAF*, v-Raf murine sarcoma viral oncogene homolog B; *EGFR*, epidermal growth factor receptor; *ERBB2*, erb-b2 receptor tyrosine kinase 2; *HER2*, human epidermal growth factor receptor 2; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; NSCLC, non-small cell lung cancer.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Recommend Testing for *ERBB2* (*HER2*) Mutations in All Eligible Patients With mNSCLC[5]

Why test

NCCN Guidelines® recommend broad biomarker testing for eligible patients with advanced or mNSCLC to help determine appropriate treatment options.

Whom to test

NCCN Guidelines recommend *ERBB2* (*HER2*) biomarker testing for all histologic subtypes in patients with advanced or mNSCLC.[a]

How to test

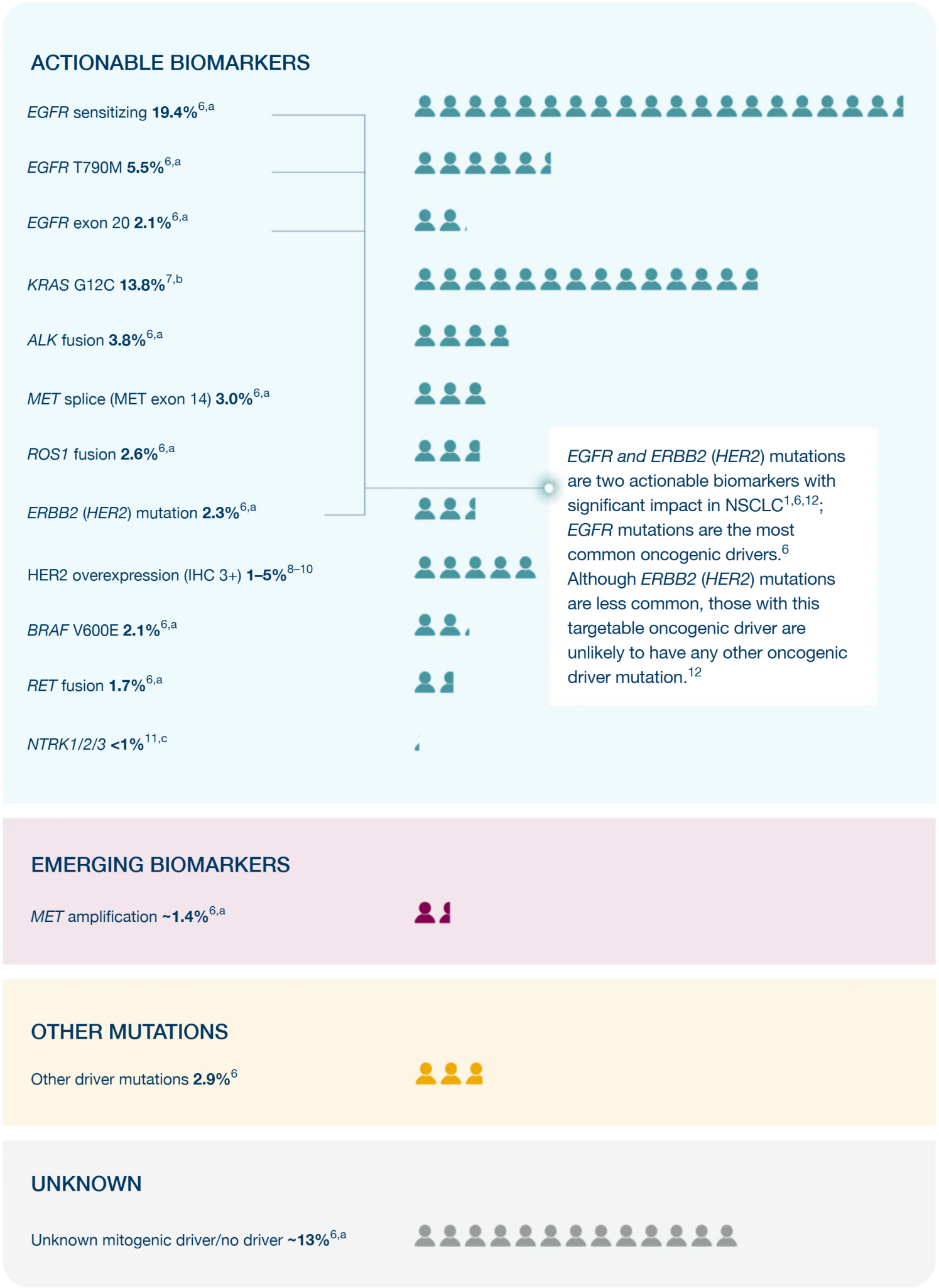
ERBB2 (*HER2*) mutations are best surveyed using Next-generation sequencing (NGS) approaches, as recommended by the NCCN Guidelines. Where NGS is not feasible, targeted PCR techniques and sanger sequencing can also be utilized.

Footnotes

[a] The NCCN Guidelines for NSCLC provide recommendations for certain individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays or commercial laboratories. NCCN also recommend testing for *EGFR* mutations, *ALK* rearrangements, *BRAF* mutations, *ROS1* gene rearrangements, *RET* gene rearrangements, *MET* exon 14–skipping mutations, *NTRK1/2/3* gene fusions, *KRAS* mutations, and PD-L1 status in eligible patients with advanced or mNSCLC.

ALK, anaplastic lymphoma kinase; *BRAF*, v-Raf murine sarcoma viral oncogene homolog B; *EGFR*, epidermal growth factor receptor; *ERBB2*, erb-b2 receptor tyrosine kinase 2; *HER2*, human epidermal growth factor receptor 2; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; *MET*, mesenchymal-epithelial transition; mNSCLC, metastatic non-small cell lung cancer; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tyrosine receptor kinase; PD-L1, programmed death-ligand 1; *RET*, rearranged during transfection; *ROS1*, ROS proto-oncogene 1, receptor tyrosine kinase.

~2% of Patients With NSCLC Have an Activating *ERBB2* (*HER2*) Mutation Known to Play a Role in the Oncogenic Process[4]



EGFR and ERBB2 (*HER2*) mutations are two actionable biomarkers with significant impact in NSCLC[1,6,12]; *EGFR* mutations are the most common oncogenic drivers.[6] Although *ERBB2* (*HER2*) mutations are less common, those with this targetable oncogenic driver are unlikely to have any other oncogenic driver mutation.[12]

Footnotes

[a] Jordan et al (2017) prospectively analyzed a total of 915 tumors from 860 patients with recurrent or metastatic lung adenocarcinoma for mutations using the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) assay, a hybridization capture-based, next-generation sequencing platform.[6] [b] Nassar et al (2021) extracted data from the registry of the American Association for Cancer Research project Genomics Evidence Neoplasia Information Exchange (GENIE) version 8.0 to study the distribution of *KRAS* mutations in 32,138 patients with cancer across race and sex. KRAS mutations were identified in 1,867 samples, most frequently in patients with NSCLC (1,443 of 10,444).[8] Stage of disease was not disclosed. [c] Farago et al (2018) examined data on 4,872 patients to determine a frequency of 0.23% (n=11) for *NTRK* gene fusions in NSCLC.[11] [d] Other driver mutations are defined as all mutations excluding actionable, emerging, and unknown driver mutations.

ALK, anaplastic lymphoma kinase; *BRAF*, v-Raf murine sarcoma viral oncogene homolog B; *EGFR*, epidermal growth factor receptor; *ERBB2*, erb-b2 receptor tyrosine kinase 2; *HER2*, human epidermal growth factor receptor 2; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; *MET*, mesenchymal-epithelial transition; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tyrosine receptor kinase; *RET*, rearranged during transfection; *ROS1*, ROS proto-oncogene 1, receptor tyrosine kinase.

ERBB2 (*HER2*) Mutations and Overexpression Are Actionable in mNSCLC[5]

ERBB2 (*HER2*) mutations in NSCLC are clustered in hotspots. Exon 20 insertion events are the most commonly identified, accounting for nearly 50%.[13–16] *ERBB2* (*HER2*) mutations independently drive tumorigenesis in NSCLC.[4,12]

ERBB2 (*HER2*) mutations are distinct from *HER2* (*ERBB2*) amplification and HER2 overexpression[3,4,17]

HER2 overexpression and *HER2* (*ERBB2*) amplification are well-established biomarkers in other tumor types.[3,4,12,17]

	ERBB2 (*HER2*) mutations[5,15]	*HER2* (*ERBB2*) amplification[12]	HER2 overexpression[5,12,17] (measured by IHC)
Alteration			
Relevance in mNSCLC	Actionable	Under investigation	Actionable (in cases of IHC 3+)[5]
Relevance in other tumor types	Under investigation in other solid tumors	Established in breast and gastric cancers	HER2 overexpression is actionable in solid tumors, including mNSCLC[5,17]

ERBB2, erb-b2 receptor tyrosine kinase 2; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mNSCLC, metastatic non-small cell lung cancer; NSCLC, non-small cell lung cancer.

Access educational resources, clinical cases and tools to evaluate your HER2 immunohistochemistry (IHC) scoring consistency in solid tumors.

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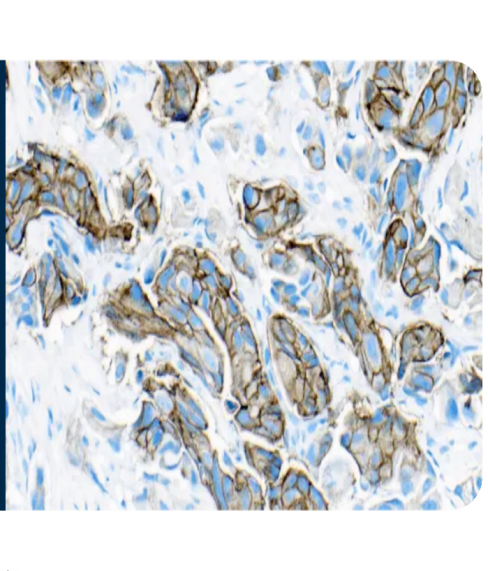


HER2, human epidermal growth factor 2; IHC, immunohistochemistry.

Histologic, Cytologic, and Liquid Biopsy Samples Are Suitable for Molecular Testing

Complementary tissue- and blood-based sample types can be used for NGS testing in mNSCLC[5,18,19]

Sample Type	Clinical Relevance	Limitations
Tissue specimen (diagnostic biopsy)	• Tissue specimens (including resections) provide high tumor volume, which may help ensure adequate tissue for molecular testing[20] • Well-established and commonly used at diagnosis when tissue is collected as part of routine workup[18,21]	Insufficient sample and/or prolonged turnaround time can pose challenges for tissue-based biomarker testing[22]
Cytology specimen (diagnostic biopsy)	• Biomarker testing of cytology specimens from pleural fluid can be used as an alternative to tissue testing[23]	Cytology specimens may provide limited material which may pose challenges for pathology[24]
Liquid biopsy (ctDNA)	• Minimally invasive, requires only a small amount of blood, and avoids complications of biopsies[25] • Likely to better reflect tumor heterogeneity[25]	Lower tumor burden may decrease sensitivity of ctDNA analysis[26]
Concurrent liquid biopsy (ctDNA) **and tissue biopsy**	• Concurrent testing may: • Deliver comprehensive results faster[5] • Help provide actionable results even in cases of tissue QNS[27,a] • Maximize the detection of therapeutically actionable mutations[19,27,a,b] • Reduce time to diagnosis which may result in earlier initiation of appropriate treatment[28,c] • Negative results by one method suggests the use of a complementary method[5]	Lack of standardization and training for liquid biopsy causes issues translating into clinical practice[29]

Unlike ctDNA analysis used in mNSCLC, liquid biopsy (ctDNA) molecular testing has not been clinically validated in the resectable NSCLC setting.[30,31]
Mutation detection in ctDNA may be challenging in the resectable setting due to lower tumor burden and less shedding of tumor DNA.[30,31]

Footnotes

[a] In a single center prospective, cohort study of 323 patients with mNSCLC, 229 received concurrent testing. Therapeutically targetable mutations were detected in 113 patients, among whom 66 had the mutation detected in plasma only, 16 patients in tissue only, and 31 patients in plasma and tissue. Mutations for 35 of 113 patients (31%) were detected in plasma only when tissue DNA was insufficient or unavailable, or no mutation was detected in tissue.[19] [b] In a prospective analysis of 282 patients with previously untreated mNSCLC undergoing physician discretion SOC tissue genotyping and submitted a pre-treatment blood sample for comprehensive cfDNA analysis, the addition of cfDNA testing identified a guideline recommended biomarker in 32% (n=90/282) of patients who otherwise would not have had guideline-complete genotyping.[27] [c] A retrospective study comparing patients with mNSCLC who underwent tissue genotyping alone (n=78) vs patients who underwent concurrent liquid and tissue genotyping (n=39) revealed a shorter mean time to diagnosis when undergoing concurrent testing (33.5 days vs 20.6 days respectively; p<0.001).[28]

cfDNA, cell free deoxyribonucleic acid; ctDNA, circulating tumor deoxyribonucleic acid; *ERBB2*, erb-b2 receptor tyrosine kinase 2; *HER2*, human epidermal growth factor receptor 2; mNSCLC, metastatic non-small cell lung cancer; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; QNS, quality not sufficient.

Utilize Diagnostic Assays That Include *ERBB2* (*HER2*) Mutations in mNSCLC

Results may be ready in hours to within 2 weeks, depending on the type of test and where it is done[a]

Laboratory and test name	Genes or alterations assessed	Minimum sample requirements	Turnaround time
Send-out			
Foundation Medicine FoundationOne® CDx[32–34,b]	324	FFPE block or ≥11 unstained slides	Median 8.8 days
Foundation Medicine FoundationOne® Liquid CDx[35,b]	>300	Blood: 2 tubes, 8.5 mL each	<2 weeks
Guardant Health Guardant360® CDx[36,37,b]	55	Blood: minimum 5 mL	≤7 days
Caris® Life Sciences Caris Molecular Intelligence® Tumor Profiling[38,39,b]	~23,000	FFPE block or 25 unstained slides	10–14 days
TEMPUS Tempus xT (RUO)[40,41,c]	648	FFPE block or 10 unstained slides + 1 H&E slide	9 days
NeoGenomics NeoTYPE® Lung Tumor Profile (RUO)[42,c]	Analyzes 49 biomarkers through a combination of methods	FFPE tissue (block)	14 days
In house			
Thermo Fisher Oncomine™ Dx Target Test[43,b]	23	10 ng DNA and RNA from FFPE tissue	4 days
Illumina TruSight™ Oncology 500 (RUO)[44,c]	523	FFPE tissue	3–4 days
Thermo Fisher Oncomine™ Precision Assay (RUO)[45,c]	50	10 ng DNA or RNA	1 day

- represents laboratories that offer concurrent testing

Footnotes

[a] This document is intended as educational information and is not intended as a complete list of available testing options. AstraZeneca is not responsible for any test provider and does not endorse any particular diagnostic test. The accuracy and results of diagnostic tests vary, and AstraZeneca shall have no liability arising from such testing. Information provided herein should in no way be considered a guarantee of coverage, reimbursement, or patient assistance. Providers should contact third-party laboratories for information on their patient assistance programs. While diagnostic testing may assist providers in identifying appropriate treatment for patients, the decision and action should be decided by a provider in consultation with the patient. All products are trademarks of their respective holders, all rights reserved. [b] FDA approved companion diagnostic. [c] This assay is not an FDA-approved companion diagnostic. The mutations detected by this assay could be informative for the treatment of NSCLC.

CDx, companion diagnostic; ctDNA, circulating tumor deoxyribonucleic acid; DNA, deoxyribonucleic acid; Dx, diagnosis; *ERBB2*, erb-b2 receptor tyrosine kinase 2; FDA, US Food and Drug Administration; FFPE, formalin-fixed paraffin-embedded; *HER2*, human epidermal growth factor receptor 2; H&E, hematoxylin and eosin; mNSCLC, metastatic non-small cell lung cancer; NSCLC, non-small cell lung cancer; RNA, ribonucleic acid; RUO, research use only.

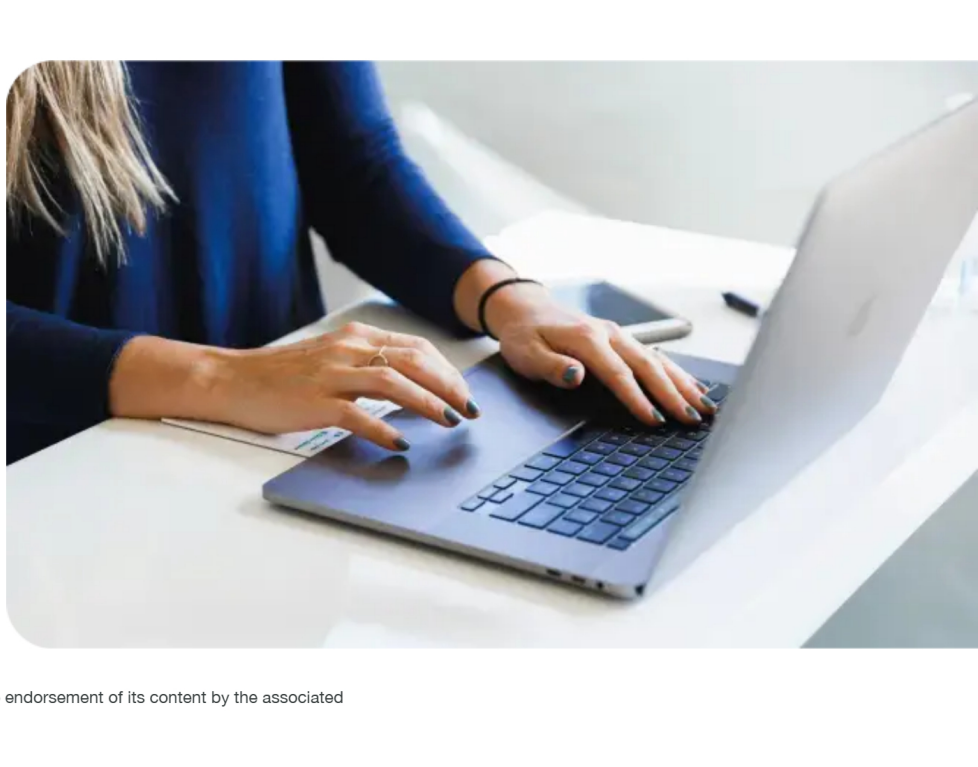
Browse a selection of major laboratories offering a range of biomarker testing options.

Find a testing lab →

This information is intended as educational and is not intended as a complete list of available testing options. AstraZeneca is not responsible for any test provider and does not endorse any particular diagnostic test. The accuracy and results of diagnostic tests vary, and AstraZeneca shall have no liability arising from such testing. Information provided herein should in no way be considered a guarantee of coverage, reimbursement, or patient assistance. Providers should contact third-party laboratories for information on their patient assistance programs. While diagnostic testing may assist providers in identifying appropriate treatment for patients, the decision and action should be decided by a provider in consultation with the patient. All products are trademarks of their respective holders, all rights reserved.

Find a list of FDA cleared or approved companion diagnostics.[46]

View diagnostic devices



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FDA, US Food and Drug Administration.

Interpret and Report *ERBB2* (*HER2*) Mutations by Their Level of Clinical Actionability

Accurately report *ERBB2* (*HER2*) mutations to help inform treatment selection

Collaborate with your multidisciplinary team (MDT) to consistently identify and record *ERBB2* (*HER2*) mutation status of all appropriate patients with mNSCLC and act on variants that are actionable biomarkers.

The American Society of Clinical Oncology (ASCO) has provided guidance on information to include for biomarker test reporting in cancer. Reports should include basic information, such as[47]:

Detection limits

Genes and gene regions evaluated

Variants detected
- Including single nucleotide variants, insertion/deletion mutations, copy number variations, gene fusions, and gene expression

Variants that may not be detected

The College of American Pathologists (CAP) provides a template for interpreting and reporting results of biomarker testing of specimens from patients with NSCLC.[48]

View CAP reporting template

Footnotes

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ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; *ERBB2*, erb-b2 receptor tyrosine kinase 2; *HER2*, human epidermal growth factor receptor 2; MDT, multidisciplinary team; mNSCLC, metastatic non-small cell lung cancer; NSCLC, non-small cell lung cancer.

Considerations for Your Practice

Implement *ERBB2* (*HER2*) mutation testing protocols or standardize existing protocols to ensure all eligible patients with mNSCLC can receive fully informed treatment options.

- Follow NCCN Guidelines recommending *ERBB2* (*HER2*) testing for all patients with advanced or mNSCLC
- Prioritize NGS testing for identifying actionable biomarkers, such as *ERBB2* (*HER2*) mutations in mNSCLC
- Observe that *HER2* (*ERBB2*) amplification and HER2 overexpression rely on different testing methodologies than *ERBB2* (*HER2*) mutations; it is important to request testing for all three HER2 outcomes as otherwise important attributes may be missed[12,17]
- Find solutions to common challenges you may face during biomarker testing

ERBB2, erb-b2 receptor tyrosine kinase 2; *HER2*, human epidermal growth factor receptor 2; mNSCLC, metastatic non-small cell lung cancer; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing.

Helpful Resources

Check out these featured resources on *ERBB2* (*HER2*) biomarker testing in lung cancer.

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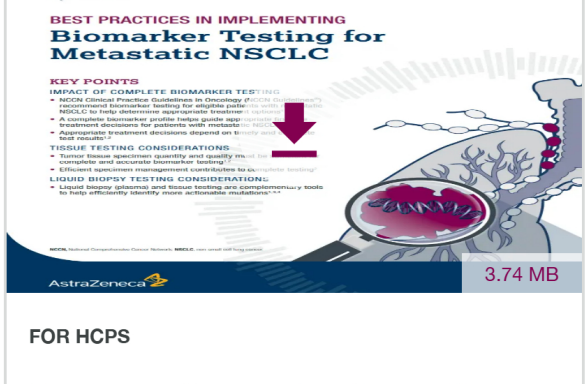
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KEY POINTS
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FOR HCPS

Best practices in implementing biomarker testing for metastatic

Read about complete biomarker profiling for informing treatment in metastatic non-small cell lung cancer (mNSCLC), and best practices for performing biomarker testing.

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FOR HCPS

Lack of evidence for use of IO therapy in first line treatment of

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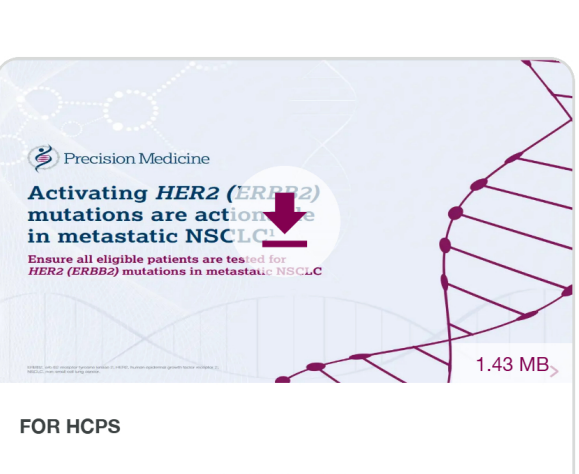
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Activating HER2 (ERBB2) mutations are actionable in metastatic NSCLC
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FOR HCPS

Testing for *ERBB2* (*HER2*) mutations in metastatic NSCLC

Learn about identification of human epidermal growth factor receptor 2 erb-b2 receptor tyrosine kinase 2 (human epidermal growth factor 2) (*ERBB2*[*HER2*]) gene in non-small cell lung cancer (NSCLC) with guideline recommendations

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References

1. Le X, et al. *Cancers (Basel)*. 2023;15(11):2917.
2. Subramanian J, et al. *The Oncologist*. 2019;24(12):e1303–e1314.
3. Jebbink M, et al. *Cancer Treat Rev*. 2020;86:101996.
4. Zhao J and Xia Y. *JCO Precis Oncol*. 2020;4:411–425.
5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. V.11.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed October 22, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org.
6. Jordan EJ, et al. *Cancer Discov*. 2017;7(6):596–609.
7. Nassar AH, et al. *N Engl J Med*. 2021;384(2):185–187.
8. Yan M, et al. *Cancer Metastasis Rev*. 2015;34(1):157–164.
9. Heinmoller P, et al. *Clin Cancer Res*. 2003;9(14):5238–5244.
10. Zinner RG, et al. *Lung Cancer*. 2004;44(1):99–110.
11. Farago AF, et al. *JCO Precis Oncol*. 2018;2018:PO.18.00037.
12. Pillai RN, et al. *Cancer*. 2017;123(21):4099–4105.
13. Peters S, et al. *J Thorac Oncol*. 2018;13(12):1897–1905.
14. Robichaux JP, et al. *Cancer Cell*. 2019;36(4):444–457.
15. Tsurutani J, et al. *Cancer Discov.* 2020;10(5):688–701.
16. Robichaux JP, et al. *Nat Med*. 2018;24(5):638–646.
17. Riudavets M, et al. *ESMO Open*. 2021;6(5):100260.
18. Rolfo C, et al. *J Thorac Oncol*. 2018;13(9):1248–1268.
19. Aggarwal C, et al. *JAMA Oncol*. 2019;5(2):173–180.
20. Lim C, et al. *Curr Oncol*. 2017;24(2):103–110.
21. Ofiara LM, et al. *Front Oncol*. 2014;4:253.
22. Gregg JP, et al. *Transl Lung Cancer Res*. 2019;8(3):286–301.
23. Ellison G, et al. *J Clin Pathol*. 2013;66:79–89.
24. Bubendorf L, et al. *Eur Respir Rev.* 2017;26(144):170007.
25. Ilié M and Hofman P. *Transl Lung Cancer Res.* 2016;5(4):420–423.
26. Semenkovich NP, et al. *J Immunother Cancer*. 2023;11(6):e006284.
27. Leighl NB, et al. *Clin Cancer Res*. 2019;25(15):4691–4700.
28. Maity AP, et al. *JCO Oncol Pract*. 2023;19(8):620–625.
29. Casagrande GMS, et al. *Int J Mol Sci*. 2023;24:2505.
30. Merker JD, et al. *J Clin Oncol*. 2018;36(16):1631–1641.
31. Chen Y, et al. *Neoplasma*. 2019;66(4):652–660.
32. Foundation Medicine. FoundationOne® CDx Technical Information. Accessed September 03, 2024. https://info.foundationmedicine.com/hubfs/FMI Labels/FoundationOne CDx Label Technical Info.pdf
33. Foundation Medicine. What is FoundationOne® CDx? Accessed September 03, 2024. https://www.foundationmedicine.com/test/foundationone-cdx
34. Foundation Medicine. FoundationOne® CDx Specimen Instructions. Accessed September 03, 2024. https://www.foundationmedicine.com/sites/default/files/media/documents/2024-04/F1CDx_Specimen_Instructions.pdf
35. Foundation Medicine. FoundationOne®Liquid CDx. Accessed September 03, 2024. https://www.foundationmedicine.com/test/foundationone-liquid-cdx#
36. Guardant Health. FDA Approved Guardant360® CDx. Accessed September 03, 2024. https://www.guardantcomplete.com/products/guardant360-cdx
37. Guardant Health. Guardant360® CDx Technical Information. Accessed September 03, 2024. https://www.guardantcomplete.com/assets/pdf/Guardant360-CDx-Technical-Information-US.pdf
38. Caris® Life Sciences. Comprehensive Molecular Profiling. Accessed September 03, 2024. https://www.carislifesciences.com/products-and-services/molecular-profiling/
39. Caris® Life Sciences. Specimen Preparation Instructions. Accessed September 03, 2024. https://www.carislifesciences.com/wp-content/uploads/2020/08/TN0252-v8_Specimen_Prep_Instructions_hi-rez.pdf
40. Tempus. Tempus xT Solid Tumor + Normal Match DNA Sequencing. Accessed September 03, 2024. https://www.tempus.com/oncology/genomic-profiling/xt-xr/
41. Tempus. Specimen Guidelines for Providers. Accessed September 03, 2024. https://www.tempus.com/wp-content/uploads/2024/11/Tempus-Onco_Specimen-Guidelines.pdf
42. NeoGenomics. NeoTYPE® Lung Tumor Profile. Accessed September 03, 2024. https://neogenomics.com/test-menu/neotype-lung-tumor-profile
43. ThermoFisher Scientific. Oncomine™ Dx Target Test. Accessed September 03, 2024. https://assets.thermofisher.com/TFS-Assets/LSG/brochures/oncomine-dx-target-test-brochure.pdf
44. Illumina. TruSight™ Oncology 500. Accessed September 03, 2024. https://www.illumina.com/products/by-type/clinical-research-products/trusight-oncology-500.html
45. ThermoFisher Scientific. Oncomine™ Precision Assay. Accessed September 03, 2024. https://assets.thermofisher.com/TFS-Assets/CSD/Flyers/oncomine-precision-assay-flyer.pdf
46. US Food and Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). Accessed September 03, 2024. https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools
47. Brown NA, et al. *Am Soc Clin Oncol Educ Book*. 2018;38:708–715.
48. College of American Pathologists. Cancer Protocol Templates. Template for Reporting Results of Biomarker Testing of Specimens From Patients With Non-Small Cell Carcinoma of the Lung. Accessed September 03, 2024. https://www.cap.org/protocols-and-guidelines/cancer-reporting-tools/cancer-protocol-templates

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