
OPTIMIZING YOUR APPROACH
TO PRECISION ONCOLOGY
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THE IMPORTANCE OF A
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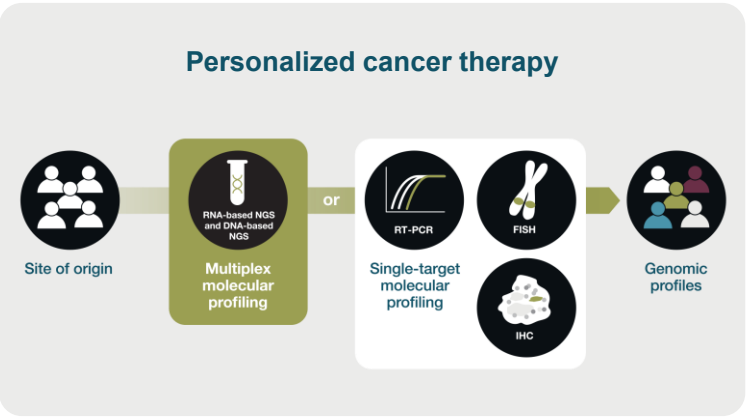
CANCER IS DRIVEN BY GENOMIC ALTERATIONS[1]

- Historically, cancer has been defined by its **site of origin**[2]
- Today, certain cancers are increasingly being **defined by genomic alterations** (eg, point mutations, gene fusions) capable of driving proliferation[1-3]

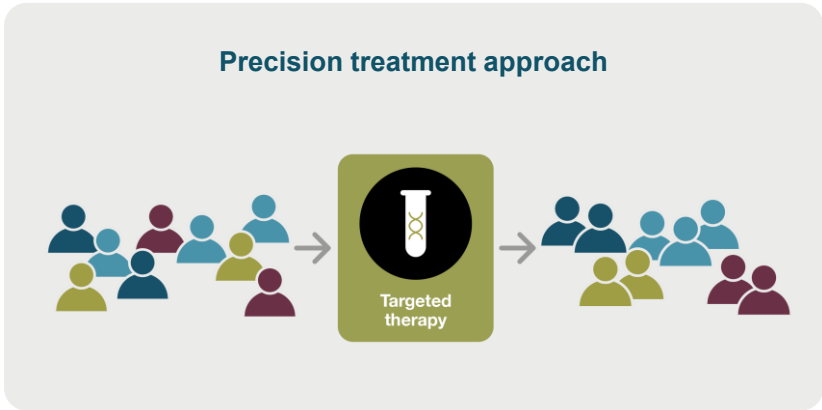
Precision oncology defines cancers by their underlying genomic changes[2,4]



FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; RT-PCR, reverse transcription-polymerase chain reaction.

1. Zhang R et al. *Front Oncol*. 2021;10:544579. doi:10.3389/fonc.2020.544579 **2**. Adashek JJ et al. *Trends Cancer*. 2021;7(1):15-28. doi:10.1016/j.trecan.2020.08.009 **3**. Zhang B et al. *Medicine (Baltimore)*. 2022;10(43):e31380. doi:10.1097/MD.0000000000031380 **4**. Malone ER et al. *Genome Med*. 2020;12:8. doi:10.1186/s13073-019-0703-1

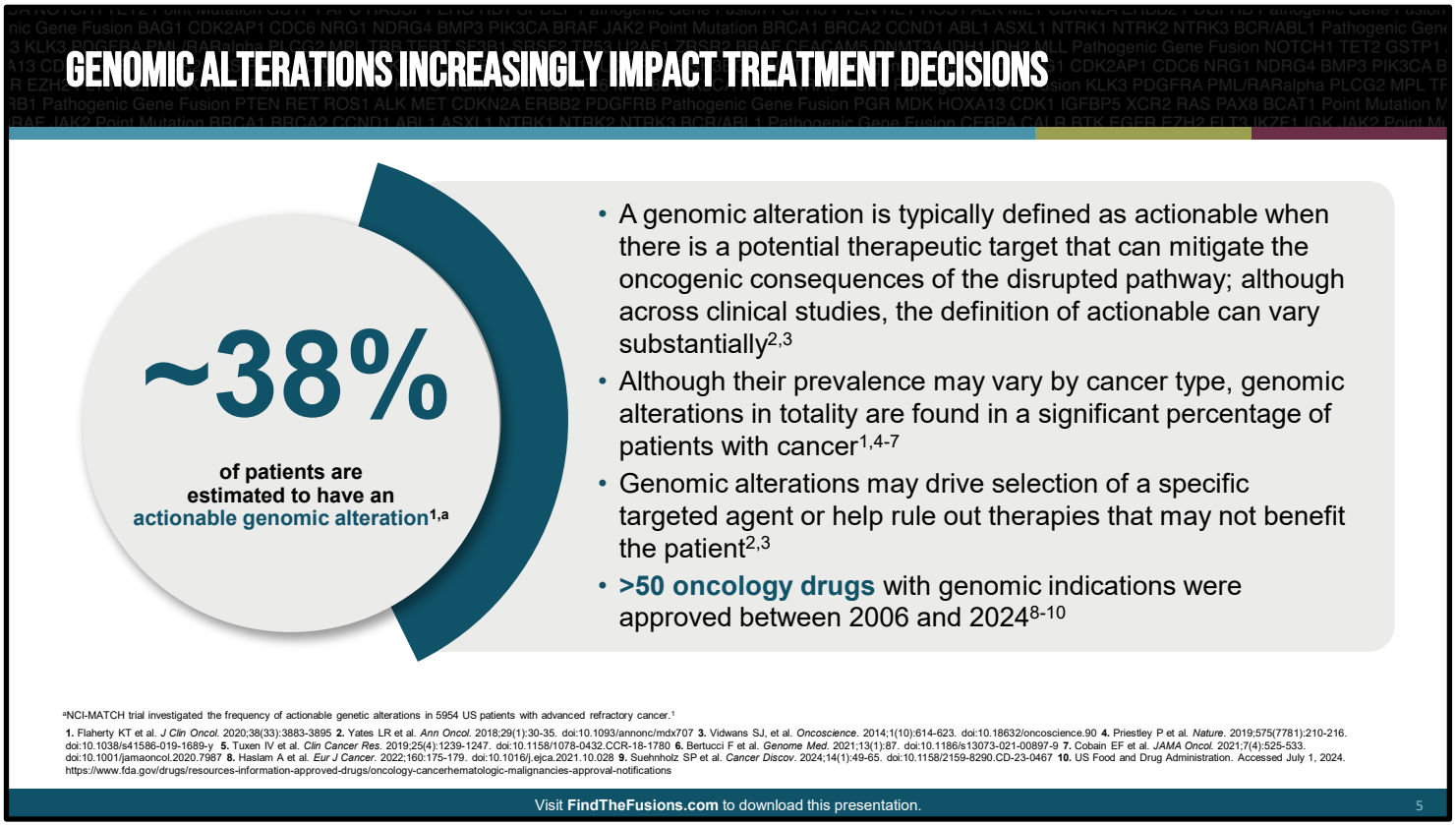
PRECISION ONCOLOGY FOCUSES ON A TUMOR'S SPECIFIC GENOMIC PROFILE[1,2]



The goal of precision oncology is **to optimize and tailor each patient's treatment approach** based on the genomic profile of the patient's cancer[3]

- Genomic profiles can[4]
  - Assist in optimal patient selection
  - Inform treatment decision making

1. Adashek JJ et al. *Trends Cancer*. 2021;7(1):15-28. doi:10.1016/j.trecan.2020.08.009 **2**. Malone ER et al. *Genome Med*. 2020;12:8. doi:10.1186/s13073-019-0703-1 **3**. Rodriguez-Rodriguez L et al. In: Rodriguez-Rodriguez L, ed. Rutgers University Press; 2019:ix. **4**. El Deiry WS et al. *CA Cancer J Clin*. 2019;69(4):305-343. doi:10.3322/caac.21560



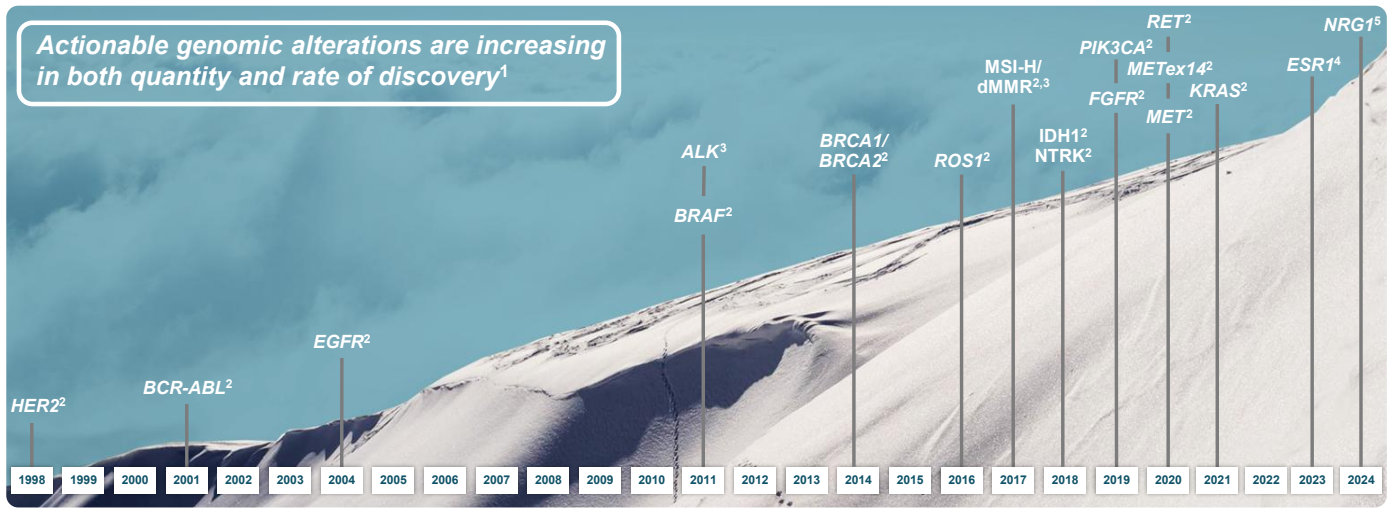
Thus, when we test and find a genomic alteration, we may be able to treat that alteration directly with a targeted therapy, or we may be able to treat the disease-causing biological pathway that is resulting from the alteration that we detected in our test.[1]

Are there any patients that should not be tested for genomic alterations? If so, which ones and why?

Reference:

1. Yates LR, Seoane J, Le Tourneau C, et al. The European Society for Medical Oncology (ESMO) precision medicine glossary. *Ann Oncol*. 2018;29(1):30-35. doi:10.1093/annonc/mdx707

DATA ESTABLISHING THE ROLE OF CLINICALLY ACTIONABLE GENOMIC MARKERS ARE INCREASING[1]



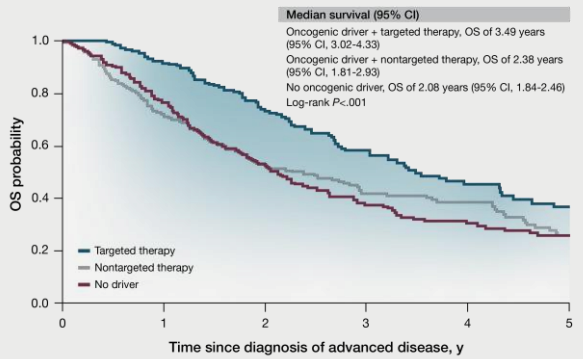
ALK, anaplastic lymphoma kinase; *BCR-ABL*, breakpoint cluster region-Abelson murine leukemia homolog 1; *BRAF*, rapidly accelerated fibrosarcoma B1; *EGFR*, epidermal growth factor receptor; *FGFR*, fibroblast growth factor receptor; *HER2*, human epidermal growth factor receptor 2; *KRAS*, Kirsten rat sarcoma; *MET*, mesenchymal-epithelial transition; *METex14*, mesenchymal-epithelial transition exon 14 skipping; MSI-H/dMMR, microsatellite instability-high/mismatch repair deficiency; *NRG1*, neuregulin 1; *NTRK*, neurotrophic tyrosine receptor kinase; *PIK3CA*, phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha; *RET*, rearranged during transfection; *ROS1*, repressor of silencing 1.

1. Malone ER et al. *Genome Med*. 2020;12:8. doi:10.1186/s13073-019-0703-1 **2.** Suehnholz SP et al. *Cancer Discov*. 2024;14(1):49-65. doi:10.1158/2159-8290.CD-23-0467 **3.** Marcus L et al. *Clin Cancer Res*. 2019;25(13):3753-3758. doi:10.1158/1078-0432.CCR-18-4070 **4.** Hoy SM. *Drugs*. 2023;83(6):555-561. doi:10.1007/s40265-023-01861-0 **5.** Kucharczyck T et al. *Cancers (Basel)*. 2024;16(15):2766. doi:10.3390/cancers16152766

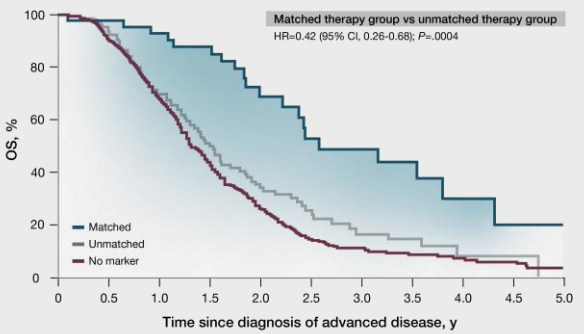
TARGETING GENOMIC ALTERATIONS CAN LEAD TO BETTER OUTCOMES FOR PATIENTS[1,2]

Knowledge of a tumor's genomic profile may substantially impact disease management decisions and patient outcomes[1,2]

OS in NSCLC with targeted vs nontargeted therapy[1]



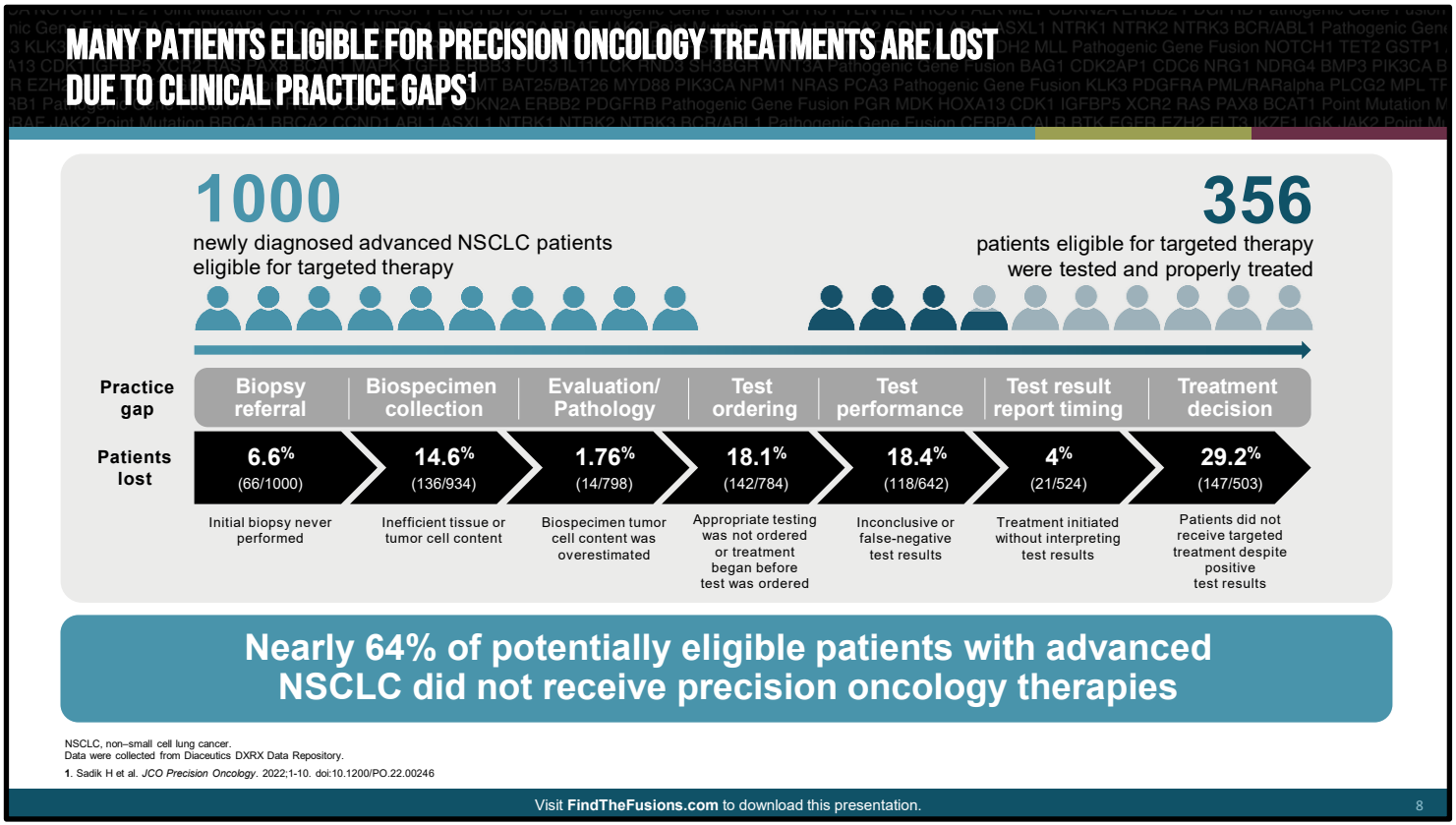
OS in pancreatic cancer with matched vs unmatched therapy[3]



In both studies, patients who received therapies directed toward their specific alteration lived longer.[1,3]

1L, first-line; HR, hazard ratio; NSCLC, non–small cell lung cancer; OS, overall survival.

1. Kris MG et al. *JAMA*. 2014;311(19):1998-2006. doi:10.1001/jama.2014.3741 **2.** Zhao S et al. *BMC Med.* 2021;19:223. doi:10.1186/s12916-021-02089-z **3.** Pishvaian MJ et al. *Lancet Oncol.* 2020;21(4):508-518. doi:10.1016/S1470-2045(20)30074-7

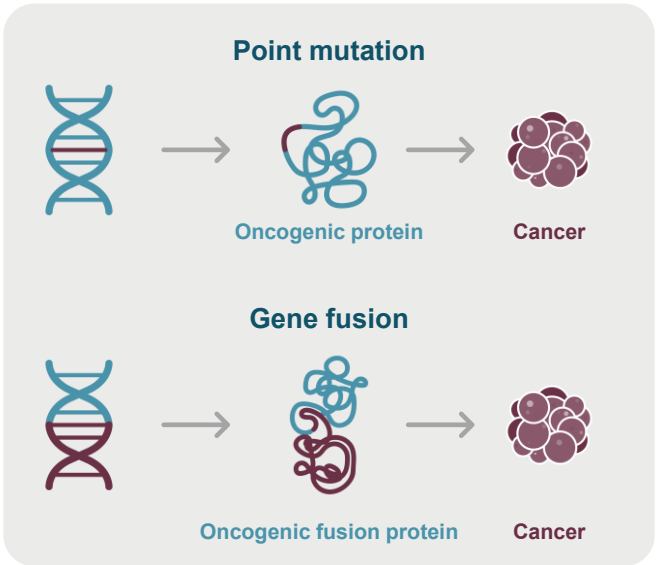


Why do you think such a high percentage of patients identified with a gene fusion do not receive targeted therapy? What solutions could be implemented to improve access to precision oncology therapies or solve for the identified practice gap?

THERE ARE DIFFERENT TYPES OF GENOMIC ALTERATIONS THAT DRIVE CANCER

Common types of genomic alterations include point mutations and pathogenic gene fusions[1]

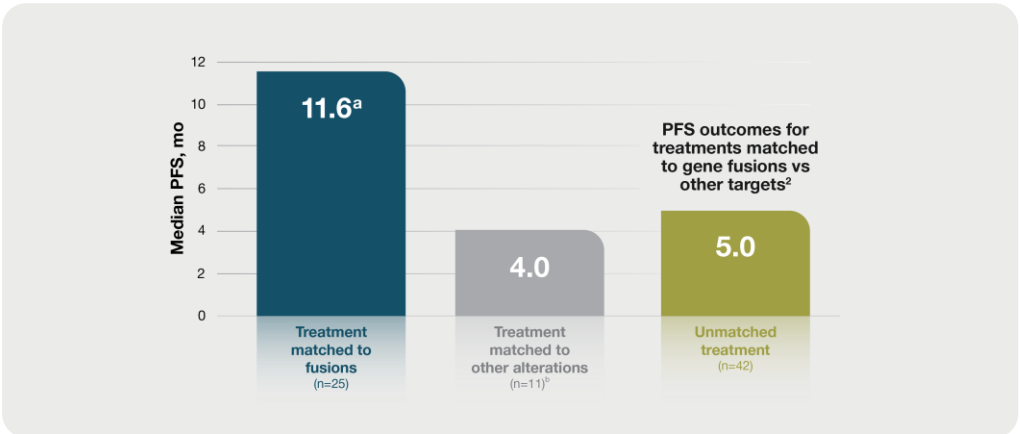
- Point mutations are changes in DNA base pairs[2]
  - Examples include *BRAF* and *EGFR*[3]
- Pathogenic gene fusions typically occur when 2 different genes join to form an abnormal hybrid gene[4]
  - Examples include *ALK*, *NTRK*, *ROS1*, and *NRG1*[3,5]
    - Genes involved in fusions are not located next to one another but are from separate chromosomal loci[6]
    - Gene fusions can be comprised of multiple fusion partners[7]



1. Zhang R et al. *Front Oncol.* 2021;10:544579. doi:10.3389/fonc.2020.544579 **2**. Gunter C. Updated December 8, 2022. Accessed April 24, 2023. https://www.genome.gov/genetics-glossary/Point-Mutation **3**. Malone ER et al. *Genome Med.* 2020;12:8. doi:10.1186/s13073-019-0703-1 **4**. Latysheva NS, Babu MM. *Nucleic Acids Res.* 2016;44(10):4487-4503. doi:10.1093/nar/gkw282 **5**. Drilon A et al. *J Clin Oncol.* 2021;39(25):2791-2802. doi:10.1200/JCO.20.03307 **6**. Barr FG. *Expert Rev Mol Diagn.* 2016;16(9):921-923. doi:10.1080/14737159.2016.1220835 **7**. Stangl C et al. *Nat Commun.* 2020;11(1):2861. doi:10.1038/s41467-020-16641-7

PATHOGENIC GENE FUSIONS CAN BE STRONG ONCOGENIC DRIVERS[1,2]

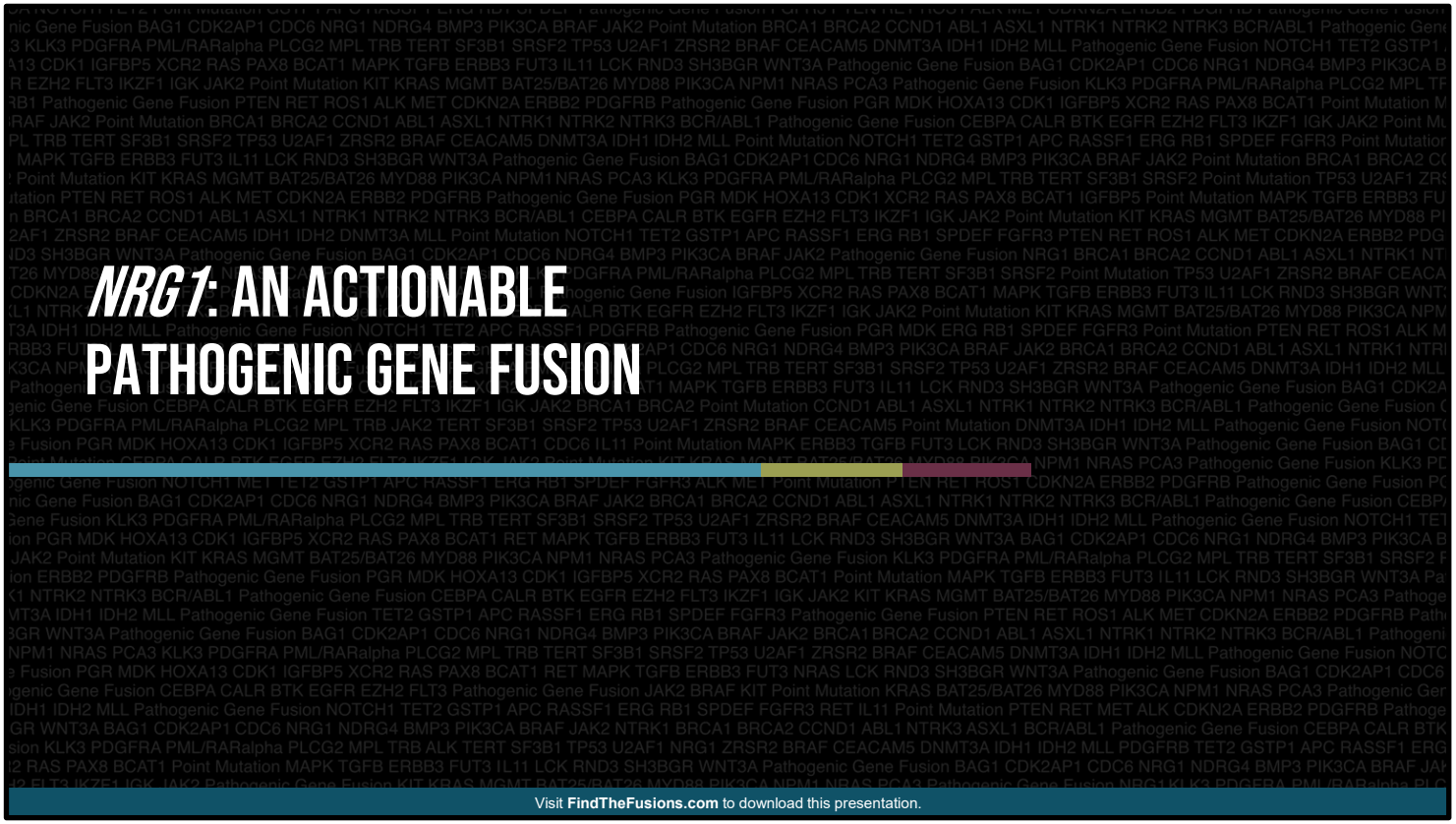
In an analysis of 79 patients with identified gene fusions, poorer outcomes were observed in patients with pathogenic gene fusions who were not matched to an FDA-approved fusion-targeted therapy[2]



PFS, progression-free survival.

[a]Comparison of patients matched to fusions vs those unmatched to fusions, including unmatched to other alterations or unmatched, was significant by log-rank test (*P*=.034).[2]
[b]Twelve of the 79 patients received treatment matched to other alterations, but 1 patient in the matched group had an unclear match and was excluded from the pair-wise comparison analysis.[2]

1. Gao Q et al. *Cell Rep*. 2018;23(1):227-238. doi:10.1016/j.celrep.2018.03.050 **2**. Nikanjam M et al. *Cancer*. 2020;126(6):1315-1321. doi:10.1002/cncr.32649


NRG1: AN ACTIONABLE
PATHOGENIC GENE FUSION
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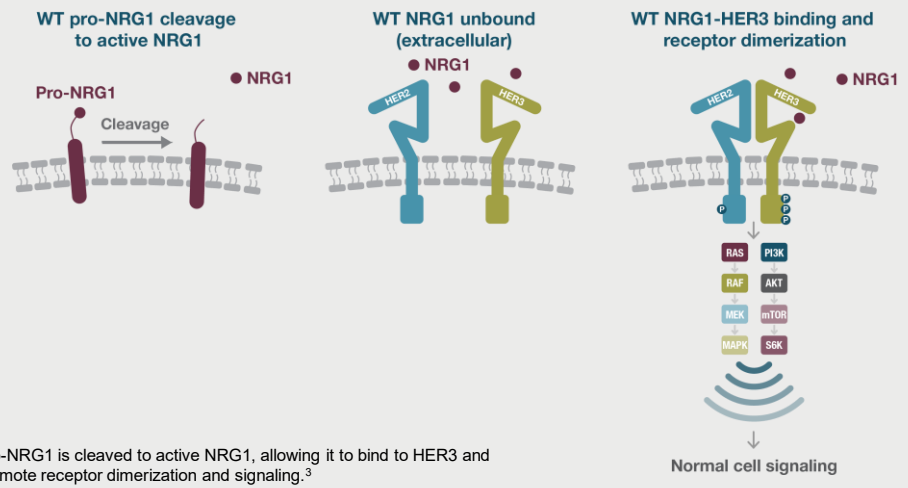
NRG1 IS IMPORTANT FOR NORMAL CELLULAR DEVELOPMENT[1,2]

NRG1 is a key signaling protein involved in proliferation and survival[1,2]

- NRG1 normally is inactive until it is cleaved by proteases at the cell surface[3]
- Extracellular binding of NRG1 activates tightly regulated cell growth pathways, including PI3K, AKT, and mTOR[3,4]

WT NRG1 formation and signaling



Pro-NRG1 is cleaved to active NRG1, allowing it to bind to HER3 and promote receptor dimerization and signaling.[3]

HER3, human epidermal growth factor receptor 3; WT, wild type.

1. Mujoo K et al. *Oncotarget*. 2014;5(21):10222-10236. doi:10.18632/oncotarget.2655 **2.** Teo JCM et al. In: Lee SJ et al, eds. Academic Press; 2016:313-344. **3.** Laskin J et al. *Ann Oncol*. 2020;31(12):1693-1703. doi:10.1016/j.annonc.2020.08.2335 **4.** Zhang C et al. *Biochim Biophys Acta Rev Cancer*. 2022;1877(3):188707. doi:10.1016/j.bbcan.2022.188707

NRG1 signaling:

- NRG1 is an extracellular ligand that binds to HER receptors, leading to the activation of downstream signaling pathways that cause cell growth

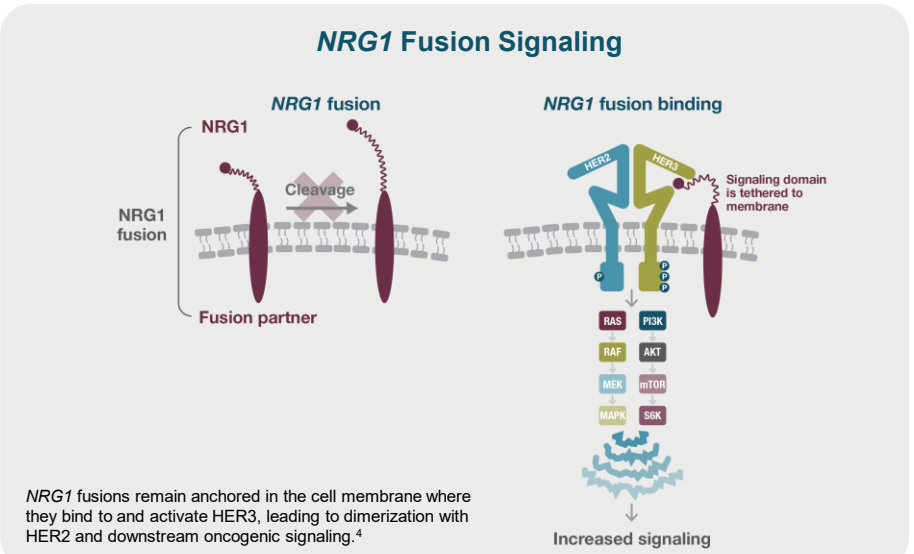
NRG1 FUSIONS RESULT IN INCREASED CELL SIGNALING AND GROWTH[1,2]

NRG1 fusions induce receptor dimerization and result in aberrant cell signaling[3,4]

NRG1 fusions

- Are heterogenous and have many different gene partners and breakpoints[5]
- **Cannot be cleaved by cell surface proteases** resulting in increased expression of the fusions at the cell surface[3]
- Retain the signaling domain of WT NRG1[4,6]

Certain _NRG1_ fusions are membrane bound, resulting in increased cell signaling[4]



NRG1 fusions remain anchored in the cell membrane where they bind to and activate HER3, leading to dimerization with HER2 and downstream oncogenic signaling.[4]

1. Schram AM et al. *Cancer Discov*. 2022;12(5):1233-1247. doi:10.1158/2159-8290.CD-21-1119 **2.** Geuijen CAW et al. *Cancer Cell*. 2018;33(5):922-936. doi:10.1016/j.ccell.2018.04.003 **3.** Laskin J et al. *Ann Oncol*. 2020;31(12):1693-1703. doi:10.1016/j.annonc.2020.08.2335
4. Zhang C et al. *Biochim Biophys Acta Rev Cancer*. 2022;1877(3):188707. doi:10.1016/j.bbcan.2022.188707 **5.** Drilon A et al. *J Clin Oncol*. 2021;39(25):2791-2802. doi:10.1200/JCO.20.03307 **6.** Howarth KD et al. *Breast Cancer Res*. 2021;23(1):3. doi:10.1186/s13058-020-01377-5

Normal (wild-type) *NRG1* binds to HER3, leading to dimerization with HER2 and subsequent signaling. In *NRG1* fusions, the *NRG1* signaling domain (EGF domain) remains localized to HER3 and tethered in the cell membrane via its fusion partner resulting in heightened HER2-HER3 signaling.

EGF, epidermal growth factor.

NRG1 FUSIONS CAN LEAD TO UNCONTROLLED GROWTH AND CANCER[1,2]

Cancers resulting from *NRG1* gene fusions are reported to be aggressive and associated with poor clinical outcomes[3-7]

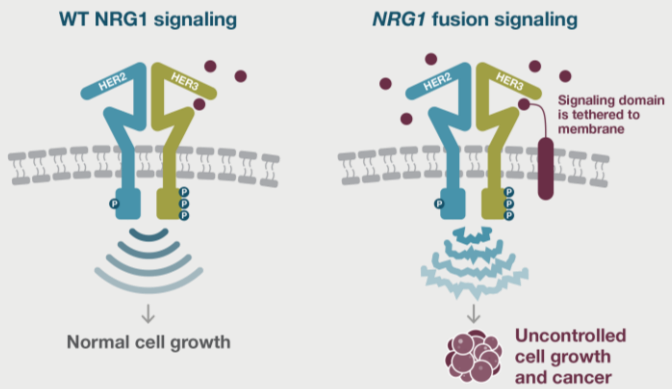
***NRG1* fusions can lead to**

- Enhanced pathologic activation of PI3K- and RAS-mediated pathways[6,8]
- Abnormal cell proliferation[6,8]

***NRG1*+ tumors**

- Have histologic features associated with growth, recurrence, invasiveness, metastasis, resistance to therapy, and worse prognosis[3-7]
- Respond poorly to available therapies and are associated with lower OS, DFS, and PFS in lung cancer[4-7,9]

An example of WT *NRG1* and *NRG1* fusion signaling



NRG1 fusions remain anchored in the cell membrane where they bind to and activate HER3, leading to dimerization with HER2 and downstream oncogenic signaling.[8]

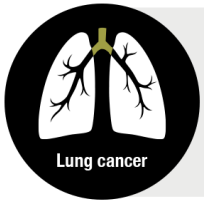
DFS, disease-free survival; *NRG1*+, neuregulin 1 fusion positive.

1. Schram AM et al. *Cancer Discov*. 2022;12(5):1233-1247. doi:10.1158/2159-8290.CD-21-1119 **2.** Geuijen CAW et al. *Cancer Cell*. 2018;33(5):922-936. doi:10.1016/j.ccell.2018.04.003 **3.** Dhanasekaran SM et al. *Nat Commun*. 2014;5:5893. doi:10.1038/ncomms6893 **4.** Rosas D et al. *Cancers (Basel)*. 2021;13(20):5038. doi:10.3390/cancers13205038 **5.** Drilon A et al. *J Clin Oncol*. 2021;39(25):2791-2802. doi:10.1200/JCO.20.03307 **6.** Laskin J et al. *Ann Oncol*. 2020;31(12):1693-1703. doi:10.1016/j.annonc.2020.08.2335 **7.** Shin DH et al. *Oncotarget*. 2016;7(43):69450-69465. doi:10.18632/oncotarget.11913 **8.** Zhang C et al. *Biochim Biophys Acta Rev Cancer*. 2022;1877(3):188707. doi:10.1016/j.bbcan.2022.188707 **9.** Jones MR et al. *Clin Cancer Res*. 2019;25(15):4674-4681. doi:10.1158/1078-0432.CCR-19-0191

Normal (wild-type) *NRG1* binds to HER3, leading to dimerization with HER2 and subsequent signaling. In *NRG1* fusions, the *NRG1* signaling domain (EGF domain) remains localized to HER3 and tethered in the cell membrane via its fusion partner resulting in heightened HER2-HER3 signaling.

NRG1 GENE FUSIONS CAN OCCUR IN MANY TYPES OF SOLID TUMORS[1]

NRG1 fusion frequency estimates[a]



Overall (<1%)[1,2]

Enrichment
Invasive mucinous lung adenocarcinoma (up to 31%)[3-5]

Overall (<2%)[1,6]

Enrichment
KRAS wild-type pancreatic cancer (up to 3%)[6,7]

Overall (<1%)[1]
Breast, cholangiocarcinoma, colorectal, gallbladder, sarcoma, ovarian cancers, renal cell carcinoma, etc[1]

- Enrichment is observed in some tumors, particularly
  - Invasive mucinous lung adenocarcinoma[3-5]
  - NSCLC that is **negative for other driver mutations**[8]
  - KRAS wild-type pancreatic cancer[6,7]
- *NRG1* fusions more commonly occur in the absence of other driver mutations[8]

[a]The frequency of *NRG1* tumors is still under investigation and can vary significantly based on testing methodology.[2]

1. Jonna S et al. *Clin Cancer Res*. 2019;25(16):4966-4972. doi:10.1158/1078-0432.CCR-19-0160 **2.** Severson E et al. *J Mol Diagn*. 2023;25(7):454-466. doi:10.1016/j.jmoldx.2023.03.011 **3.** Chang J et al. *Clin Cancer Res*. 27(14):4066-4076. doi:10.1158/1078-0432.CCR-21-0423 **4.** Shin DH et al. *Oncotarget*. 2016;7(43):69450-69465. doi:10.18632/oncotarget.11913 **5.** Trombetta D et al. *Oncotarget*. 2018;9(11):9661-9671. doi:10.18632/oncotarget.23800 **6.** Knepper TC et al. *J Clin Oncol*. 2022;40(suppl 16):4155. doi:10.1200/JCO.2022.40.16_suppl.4155 **7.** Philip PA et al. *Clin Cancer Res*. 2022;28(12):2704-2714. doi:10.1158/1078-0432.CCR-21-3581 **8.** Drilon A et al. *J Clin Oncol*. 2021;39(25):2791-2802. doi:10.1200/JCO.20.03307

NRG1+ TUMORS CAN BE AGGRESSIVE AND RESPOND POORLY TO EXISTING STANDARD OF CARE[1,2]

In a retrospective global registry study of 110 patients, *NRG1*+ NSCLC was associated with limited response to available therapies[3]

Activity of systemic therapy in *NRG1*+ NSCLC[3,a]

	ORR, %	Median PFS, mo (95% CI)
Platinum-doublet chemotherapy (n=15)	**13**	**5.8** (2.2-9.8)
Taxane-based chemotherapy (n=7)	**14**	**4.0** (0.8-5.3)
Combination chemotherapy and immunotherapy (n=9)	**0**	**3.3** (1.4-6.3)
Single-agent immunotherapy (n=5)	**20**	**3.6** (0.9-undefined)
Targeted therapy with kinase inhibitor (n=20)	**25**	**2.8** (1.9-4.3)

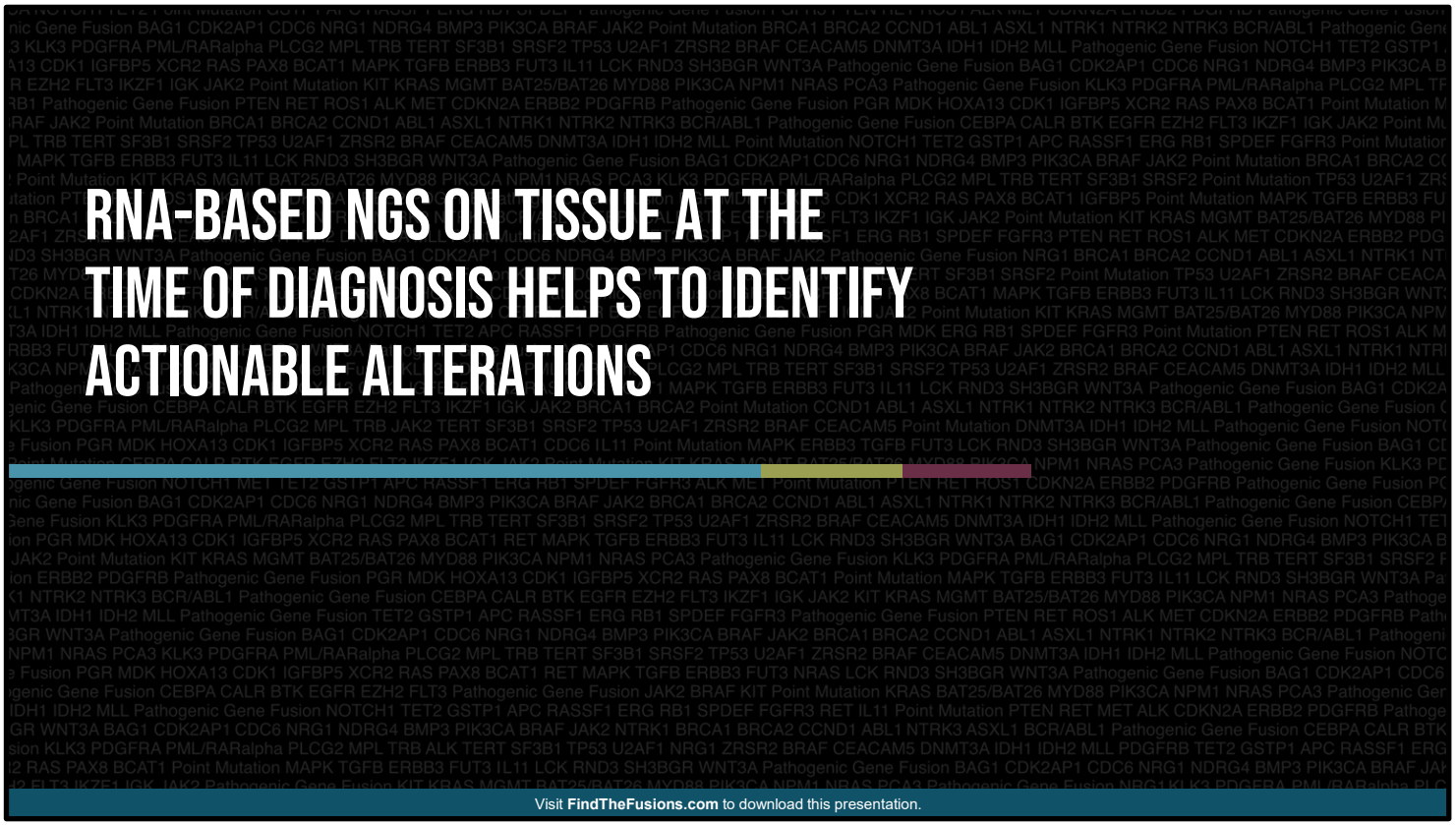
ORR, overall response rate.

[a]Patients either diagnosed with or who developed metastatic disease during the course of their disease.

1. Rosas D et al. *Cancers (Basel)*. 2021;13(20):5038. doi:10.3390/cancers13205038 **2**. National Institutes of Health, National Cancer Institute. Accessed April 24, 2023. https://www.cancer.gov/types/lung/patient/non-small-cell-lung-treatment-pdq **3**. Drilon A et al. *J Clin Oncol*. 2021;39(25):2791-2802. doi:10.1200/JCO.20.03307

Do you consider the possibility of pathogenic gene fusions in your patients who fail to respond to standard of care?

RNA-BASED NGS ON TISSUE AT THE TIME OF DIAGNOSIS HELPS TO IDENTIFY ACTIONABLE ALTERATIONS



CLASSICAL BIOMARKER SCREENING METHODS WERE DEVELOPED TO DETECT SINGLE MOLECULAR TARGETS[1,2]

Conventional test methods limit the ability to detect many pathogenic gene fusions.

Limitations include

- Inability to identify the full breadth of genomic alterations[3]
- Limited ability to identify the full breadth of fusion partners and breakpoints[1]
  - *May require a significant amount of tissue and can exhaust tissue samples*[4]

1. Su D et al. *J Exp Clin Cancer Res*. 2017;36(1):121. doi:10.1186/s13046-017-0591-4 **2**. Bruno R, Fontanini G. *Diagnostics (Basel)*. 2020;10(8):521. doi:10.3390/diagnostics10080521 **3**. Personalized Medicine in Oncology. Accessed April 24, 2023. https://www.personalizedmedonc.com/supplements/faculty-perspectives-next-generation-sequencing-testing-in-oncology-part-4-of-a-4-part-series/next-generation-sequencing-testing-in-oncology **4**. Yu TM et al. *Clin Lung Cancer*. 2018;20(1):20-29. doi:10.1016/j.cllc.2018.08.010

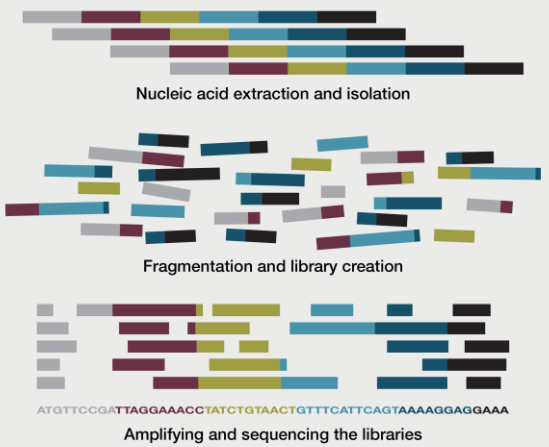
NGS CAN DETECT A BROAD RANGE OF GENOMIC ALTERATIONS[1]

NGS has emerged as a key tool in profiling many solid tumors[2]

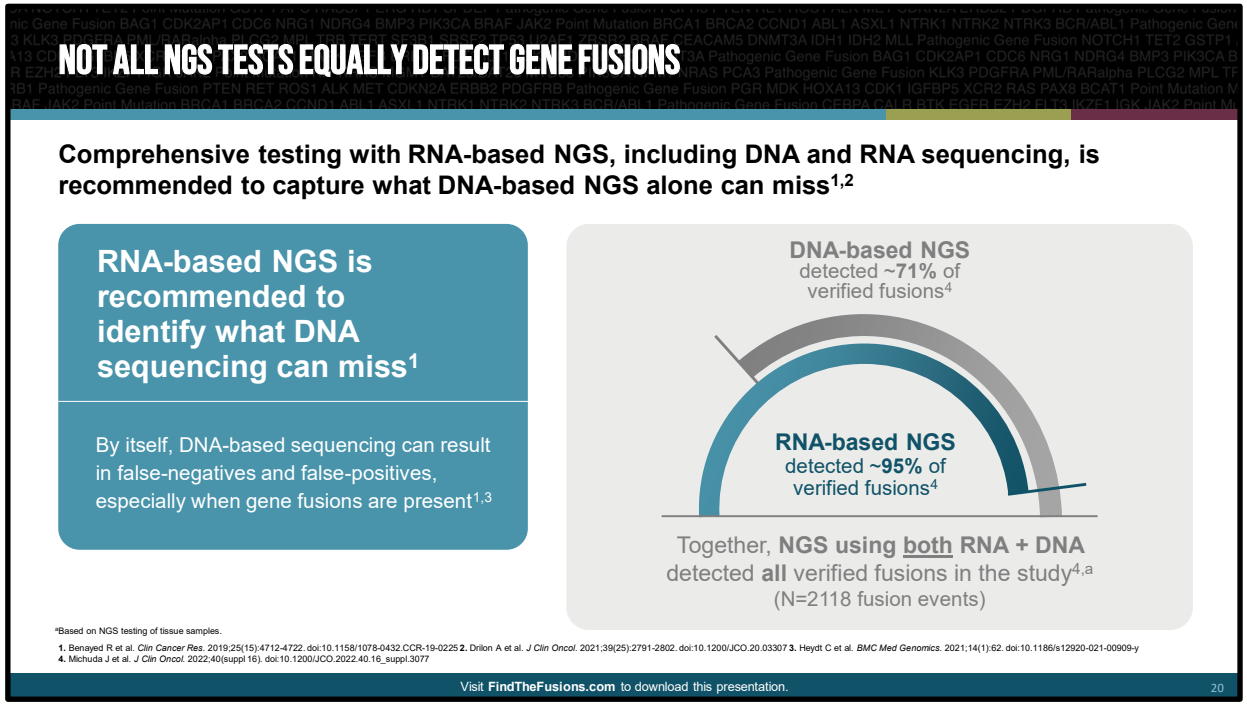
- NGS is a high-throughput genomic sequencing technology that allows for the simultaneous analysis of numerous alterations that[2]
  - Can be performed with DNA or RNA[3]
  - Has several advantages over current conventional methods in detecting pathogenic gene fusions[3]

There are clear differences between DNA- and RNA-based NGS[3]

The NGS process



1. Singh RR. *J Mol Diagn*. 2020;22(8):994-1007. doi:10.1016/j.jmoldx.2020.04.213 2. Goswami RS et al. *Am J Clin Pathol*. 2016;145(2):222-237. doi:10.1093/ajcp/aqv023 3. Bruno R, Fontanini G. *Diagnostics (Basel)*. 2020;10(8):521. doi:10.3390/diagnostics10080521



Comprehensive testing with RNA-based NGS, including DNA and RNA sequencing, is recommended to capture what DNA-based NGS alone can miss.[1,2]

By itself, DNA-based sequencing can result in false-negatives and false-positives, especially when gene fusions are present.[1,3]

RNA-based NGS is recommended to identify what DNA sequencing can miss.[1]

NOTE: The point of the illustration is to reinforce the need for both RNA and DNA testing.

References:

1. Benayed R, Offin M, Mullaney K, et al. High yield of RNA sequencing for targetable kinase fusions in lung adenocarcinomas with no mitogenic driver alteration detected by DNA sequencing and low tumor mutation burden. *Clin Cancer Res.* 2019;25(15):4712-4722. doi:10.1158/1078-0432.CCR-19-0225

2. Drilon A, Duruisseaux M, Han J-Y, et al. Clinicopathologic features and response to therapy of *NRG1* fusion–driven lung cancers: the eNRGy1 global multicenter registry. *J Clin Oncol*. 2021;39(25):2791-2802. doi:10.1200/JCO.20.03307

3. Heydt C, Wölwer CB, Velazquez Camacho O, et al. Detection of gene fusions using targeted next-generation sequencing: a comparative evaluation. *BMC Med Genomics*. 2021;14(1):62. doi:10.1186/s12920-021-00909-y

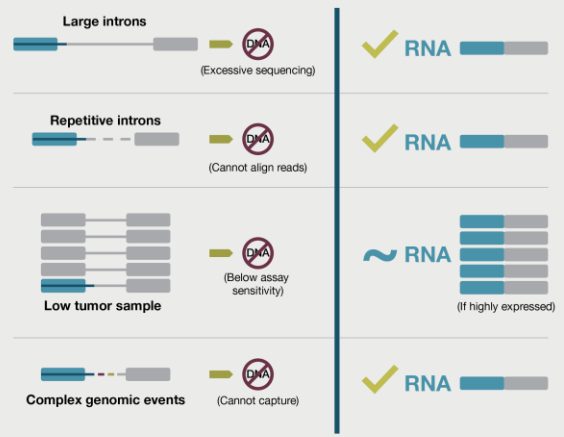
RNA-BASED NGS IS MORE SENSITIVE THAN DNA-BASED NGS ALONE FOR DETECTING PATHOGENIC GENE FUSIONS[1]

RNA-based NGS can detect genomic alterations missed by DNA-based NGS[1,2]

- RNA-based NGS detects gene expression and many structural variants[3]
  - RNA-based NGS is inclusive of both DNA and RNA sequencing
- RNA-based NGS reduces the technical challenges that occur with DNA-based NGS when sequencing long introns[3]
- RNA-based NGS can improve the detection rate of DNA-based NGS alone and provide more comprehensive detection results[1,4,5]

***NRG1* fusions are more likely to be missed unless testing with RNA-based NGS[2]**

DNA-based vs RNA-based NGS for fusions[6]



1. Benayed R et al. *Clin Cancer Res*. 2019;25(15):4712-4722. doi:10.1158/1078-0432.CCR-19-0225 **2**. Drilon A et al. *J Clin Oncol*. 2021;39(25):2791-2802. doi:10.1200/JCO.20.03307 **3**. Mahmoud M et al. *Genome Biol*. 2019;20(1):246. doi:10.1186/s13059-019-1828-7
4. El-Deiry WS et al. *CA Cancer J Clin*. 2019;69(4):305-343. doi:10.3322/caac.21560 **5**. Hindi I et al. *Exp Mol Pathol*. 2020;114:104403. doi:10.1016/j.yexmp.2020.104403 **6**. Davies KD, Aisner DL. *Clin Cancer Res*. 2019;25(15):4586-4588. doi:10.1158/1078-0432.CCR-19-1361

OPTIMIZING FUSION DETECTION THROUGH TISSUE, RNA-BASED TESTING[1,2]

RNA-based NGS may improve detection of *NRG1*, *NTRK*, *RET*, *ROS1*, and other gene fusions.[1-3]

ASCO guidelines considered RNA-based methods generally superior for fusion detection across multiple targets.[4]

- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) include RNA-based NGS[1,2]
  - **Pancreatic adenocarcinoma:** Tumor/somatic molecular profiling, preferably using NGS assay, is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify clinically actionable and/or emerging alterations. These alterations include, but are not limited to, *NRG1* fusions. RNA sequencing assays are preferred for detecting RNA fusions because gene fusions are better detected by RNA-based NGS[1]
  - **NSCLC:** RNA-based NGS may increase novel fusion detection and can be performed concurrently or sequentially with DNA-based NGS. If no identifiable driver oncogenes with DNA-based broad molecular profiling are identified, RNA-based testing is recommended[2]

- Tissue-based NGS remains the gold standard for identifying genomic alterations[5]
  - Relying solely on ctDNA or liquid biopsy may miss targetable alterations, including fusions[5-7]

Liquid biopsy could miss actionable mutations in up to 20% of patients[5-7]

RNA-based NGS on tumor tissue provides the most comprehensive view of the genomic landscape to help enable detection of clinically actionable alterations and providing insights that guide care[1,2]

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ASCO, American Society of Clinical Oncology; ctDNA, circulating tumor DNA; NCCN, National Comprehensive Cancer Network.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pancreatic Adenocarcinoma V.2.2025. © National Comprehensive Cancer Network, Inc. 2025. All right reserved. Accessed October 31, 2025. To view the most recent and completeversion of the guideline, go 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.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.3.2026. ©National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed January 15, 2026. 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. **3.** Owen D et al. *JAMA Netw Open*. 2024;7(11):e242970. doi:10.1001/jamanetworkopen.2024.42970 **4.** Chakravarty D et al. *J Clin Oncol*. 2022;40:1231-1258. doi:10.1200/JCO.21.02767 **5.** Iams WT et al. *JAMA Netw Open*. 2024;7(1):e2351700. doi:10.1001/jamanetworkopen.2023.51700 **6.** van der Leest P et al. *Commun Med*. 2025;5:204. doi:10.1038/s43856-025-00921-8 **7.** Park S et al. *Cancer*. 2021;127(16):3019-3028. doi:10.1002/cncr.33571

ORDERING RNA-BASED NGS IS A KEY TO OBTAINING COMPREHENSIVE RESULTS[1,2]

- Commercial vendors are increasing their NGS testing options[1]
- However, **not all vendors offer combined RNA + DNA NGS**
- Clinicians need to stay up to date on testing modalities to achieve the most comprehensive testing results[1]

Test Name; Commercial Vendor	Analyte	Genes on Panel
Altera™[3]; Natera	**DNA/RNA**	440 (WES/WTS)
Caris®[4]; Caris Life Sciences	**DNA/RNA**	WES/WTS
FoundationOne®RNA[5]; Foundation Medicine	**RNA**	318
NEO PanTracer™ Tissue[6]; NeoGenomics Laboratories	**DNA/RNA**	517/55 (DNA/RNA)
OncoExTra®[7]; Exact Sciences	**DNA/RNA**	WES/WTS
Oncomine™ Dx Express[8]; Thermo Fisher Scientific	**DNA/RNA**	46
OmniSeq® INSIGHT[9]; Labcorp Oncology	**DNA/RNA**	523
StrataNGS™[10]; Strata Oncology	**DNA/RNA**	417/59 (DNA/RNA)
Tempus xR RNA[11]; Tempus	**RNA**	>100
FoundationOne®CDx[12]; Foundation Medicine	**DNA**	324
FoundationOne®Liquid CDx[13]; Foundation Medicine	**cfDNA**	311
Guardant360® CDx[14,15]; Guardant Health	**cfDNA**	74
MSK-IMPACT®[16]; Memorial Sloan Kettering Cancer Center	**DNA**	505
Northstar Select™[17]; Northstar	**cfDNA**	84
PathGroup Endeavor[18]; PathGroup	**DNA**	>500
Paradigm Dx PCDx™[19]; Paradigm Diagnostics	**DNA**	234
Tempus xT CDx[11,20]; Tempus	**DNA**	648

Information in this table is current as of August 2025.

- Indicates DNA/RNA analyte
- Indicates RNA analyte
- Indicates DNA or cfDNA analyte and a limited ability to identify a broad range of gene fusions

This table is intended to summarize known available tests and may not be all inclusive. All trademarks are property of their respective owners. Not all tests on this list are known to identify *NRG1* fusions.

cfDNA, cell-free DNA; WES, whole exome sequencing; WTS, whole transcriptome sequencing.

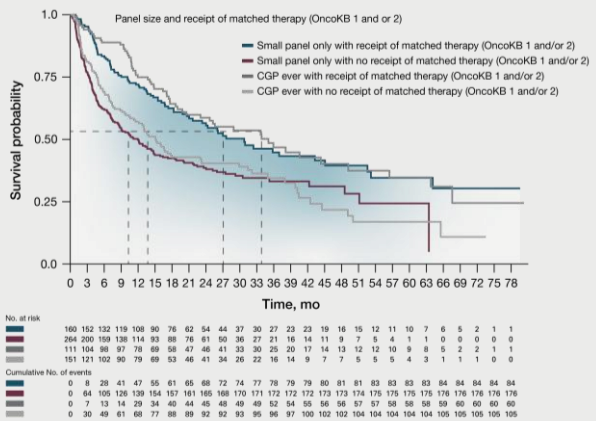
1. Park HJ et al. *J Mol Diagn*. 2021;23(11):1443-1451. doi:10.1016/j.jmoldx.2021.07.027 **2.** Benayed R et al. *Clin Cancer Res*. 2019;25(15):4712-4722. doi:10.1158/1078-0432. **3.** Natera, Inc. Altera™ comprehensive genomic profiling. Accessed August 27, 2025. https://www.natera.com/oncology/altera **4.** Caris Life Sciences. Physician tests. Accessed August 27, 2025. https://www.carislifesciences.com/physicians/physician-tests **5.** Foundation Medicine, Inc. FoundationOne®RNA. Accessed August 27, 2025. https://www.foundationmedicine.com/test/foundationone-rna **6.** NeoGenomics Laboratories. NEO PanTracer™ Tissue (formerly Neo Comprehensive - Solid Tumor). Accessed August 27, 2025. https://www.neogenomics.com/providers/test/NTG-PTTT-03AX/neo-pantracer-tissue-formerly-neo-comprehensive-solid-tumor/ **7.** Exact Sciences Corporation. OncoExTra®. Accessed August 27, 2025. https://precisiononcology.exactsciences.com/healthcare-providers/therapy-selection/advanced-solid-tumors/oncoextra **8.** Thermo Fisher Scientific Inc. Oncomine Dx Express Test. Accessed August 27, 2025. https://documents.thermofisher.com/TFS-Assets/CSD/Flyers/oncomine-dx-express-test-pathologist-info.pdf **9.** Laboratory Corporation of America® Holdings (Labcorp). OmniSeq® INSIGHT - improving outcomes for patients with solid tumors. Accessed August 27, 2025. https://oncology.labcorp.com/cancer-care-team/test-menu/omniseq-insight **10.** Strata Oncology, Inc. StrataNGS®: gene list. Accessed August 27, 2025. https://strataoncology.com/wp-content/uploads/2022/12/Gene_List_SO-SPEC-003v7.pdf **11.** Tempus. xR whole transcriptome RNA sequencing. Accessed August 27, 2025. https://www.tempus.com/oncology/genomic-profiling/xt-xr/ **12.** Foundation Medicine, Inc. FoundationOne®CDx. Technical specifications. Accessed August 27, 2025. https://www.foundationmedicine.com/sites/default/files/media/documents/2025-06/F1LCDx_Tech Specs_SPEC-01746_R4.pdf **13.** Foundation Medicine, Inc. FoundationOne®Liquid CDx. Accessed August 27, 2025. https://www.foundationmedicine.com/test/foundationone-liquid-cdx **14.** US Food and Drug Administration (FDA). Guardant360 CDx –P200010/S008. Accessed August 27, 2025. https://www.fda.gov/medical-devices/recently-approved-devices/guardant360-cdx-p200010s008 **15.** Guardant Health, Inc. Guardant360® CDx. Accessed August 27, 2025. https://www.guardantcomplete.com/products/guardant360-cdx **16.** Memorial Sloan Kettering Cancer Center. MSK-IMPACT: a targeted test for mutations in both rare and common cancers. Accessed August 27, 2025. https://www.mskcc.org/msk-impact **17.** Northstar Onc by Billion to One, Inc. Therapy selection for solid tumor. Accessed August 27, 2025. https://www.northstaronc.com/northstar-select **18.** PathGroup. Endeavor. Accessed August 27, 2025. http://www.pathgroup.com/oncology/endeavor/ **19.** Paradigm Diagnostics. Paradigm Cancer Diagnostic (PCDx)™. Accessed August 27, 2025. https://www.therapyselect.de/sites/default/files/downloads/pcdx/pcdx_tumor-profiling-menu_en.pdf **20.** Tempus. Tempus xT CDx Assay. Accessed August 28, 2025. https://www.tempus.com/life-sciences/xt-cdx/?srsltid=AfmBOoq0FlKXNvIKE-5pH1WmQ9nkW52PD2nPR4bqGCnO_F6IB8JNPTo

Speaker note: After presenting this slide, ask the following questions for comments from the audience:

Do you know what is included on your NGS platform? How do you stay up to date on testing vendor capabilities and platforms? How would you go about educating your institution or colleagues on this information?

COMPREHENSIVE GENOMIC PROFILING IS ASSOCIATED WITH IMPROVED OS IN NSCLC PATIENTS[1]

rwOS from aNSCLC diagnosis, by testing type and receipt of matched vs unmatched therapy



Treated patients receiving CGP testing during follow-up **had greater median rwOS (34 months vs 14 months)**

No. at risk at index	Testing/treatment group	Median, mo (95% CI)
1852	Small panel with any systemic therapy	15 (14-16)
1253	Small panel and no systemic therapy	4 (4-5)
603	CGP with any systemic therapy	22 (18-25)
176	CGP and no systemic therapy	10 (6-15)

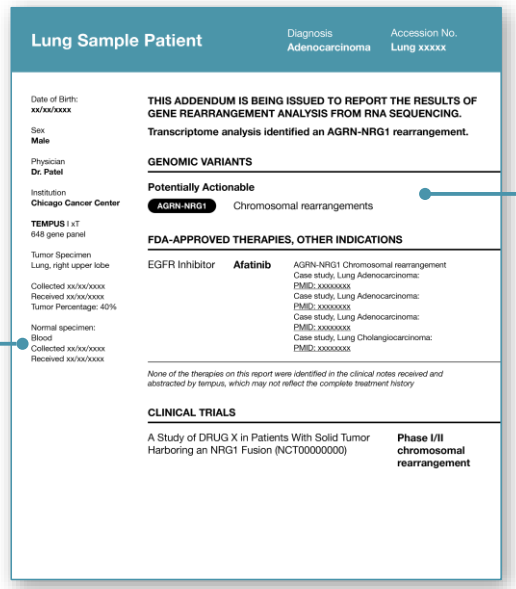
Predictors of rwOS by Testing Type (Cox proportional hazards model)

	Alive N=1186	Deceased N=2698	HR (95% CI)
CGP Testing, No. (%)			
No	906 (76%)	2199 (82%)	1.00
Yes	280 (24%)	499 (18%)	0.80 (0.72-0.89)

aNSCLC, advanced non–small cell lung cancer; CGP, comprehensive genomic profiling; HR, hazard ratio; rwOS, real-world overall survival.

1. Law JW et al. *JCO Precis Oncol.* 2024;8:e2400075. doi:10.1200/PO.24.00075

MOST NGS REPORTS HIGHLIGHT ACTIONABLE INFORMATION



Lung Sample Patient

Diagnosis: **Adenocarcinoma**
Accession No.: **Lung xxxxx**

Date of Birth: **xx/xx/xxxx**
Sex: **Male**
Physician: **Dr. Patel**
Institution: **Chicago Cancer Center**
TEMPUS I xT
648 gene panel
Tumor Specimen
Lung, right upper lobe
Collected xx/xx/xxxx
Received xx/xx/xxxx
Tumor Percentage: 40%
Normal specimen:
Blood
Collected xx/xx/xxxx
Received xx/xx/xxxx

THIS ADDENDUM IS BEING ISSUED TO REPORT THE RESULTS OF GENE REARRANGEMENT ANALYSIS FROM RNA SEQUENCING.

Transcriptome analysis identified an AGRN-NRG1 rearrangement.

GENOMIC VARIANTS

Potentially Actionable

AGRN-NRG1 — Chromosomal rearrangements

FDA-APPROVED THERAPIES, OTHER INDICATIONS

EGFR Inhibitor — **Afatinib** — AGRN-NRG1 Chromosomal rearrangement
Case study, Lung Adenocarcinoma: PMID: xxxxxxxx
Case study, Lung Adenocarcinoma: PMID: xxxxxxxx
Case study, Lung Adenocarcinoma: PMID: xxxxxxxx
Case study, Lung Cholangiocarcinoma: PMID: xxxxxxxx

None of the therapies on this report were identified in the clinical notes received and abstracted by tempus, which may not reflect the complete treatment history

CLINICAL TRIALS

A Study of DRUG X in Patients With Solid Tumor Harboring an NRG1 Fusion (NCT00000000) — **Phase I/II chromosomal rearrangement**

Higher tumor cell content is associated with a lower probability of false negatives.

Most reports will provide variant results listed by tier of evidence in order of relevance, and relevant FDA-approved therapies. Certain reports may identify possible clinical trial options.

Methodology

Test material: Tumor DNA/RNA[1]

Gene panel: Tempus xT Targeted Panel of 648 genes. Assay v4—a custom oncology testing panel (see detailed list of genes in full report)[2,3]

Instrument: Illumina Novaseq 6000[1]

Reference genome: GRCh37 (hg19)[3]

Methodology identifies material tested (DNA and/or RNA).

Methodology details include test description, sequencing instrument, and reference genome used.

1. National Library of Medicine. Updated November 8, 2024. Accessed November 4, 2025. https://www.ncbi.nlm.nih.gov/gtr/tests/558436/overview/ **2**. Tempus. Accessed April 24, 2023. https://www.tempus.com/oncology/genomic-profiling/ **3**. Tempus. Accessed April 24, 2023. https://www.tempus.com/wp-content/uploads/2022/09/Tempus-Onco_Clinical-Report-Sample.pdf

RNA-BASED NGS IS IMPORTANT TO IDENTIFY A WIDE RANGE OF PATHOGENIC FUSIONS, INCLUDING *NRG1*[1]

The **diversity of *NRG1* fusion partners and breakpoints and the large intronic regions** of the *NRG1* gene can make detection more **challenging**[1,2]

NRG1 fusions **may be missed** unless testing accounts for these characteristics[1,2]

Technologic and methodologic improvements, such as **RNA-based NGS**, are reported to capture significantly more actionable fusions[1,2]

1. Drilon A et al. *J Clin Oncol.* 2021;39(25):2791-2802. doi:10.1200/JCO.20.03307 **2**. Jonna S et al. *Clin Cancer Res.* 2019;25(16):4966-4972. doi:10.1158/1078-0432.CCR-19-0160

COLLABORATION IS IMPORTANT TO HELP IDENTIFY ACTIONABLE INFORMATION IN NGS REPORTS

- Maximizing the clinical use of NGS reports is best achieved through a multidisciplinary approach[1,2]
- Collaboration between key experts facilitates the most informed decision making[2,3]
  - Oncologists
  - Pathologists
  - Pharmacists
  - Radiologists
  - Allied healthcare professionals
- Molecular tumor boards may provide key learning opportunities for identifying actionable genomic alterations[1,2]

1. Perakis SO et al. *ESMO Open.* 2020;5(5):e000872. doi:10.1136/esmoopen-2020-000872 **2.** Malone ER et al. *Genome Med.* 2020;12:8. doi:10.1186/s13073-019-0703-1 **3.** Specchia ML et al. *BMC Health Serv Res.* 2020;20(1):73. doi:10.1186/s12913-020-4930-3


SUMMARY
Visit FindTheFusions.com to download this presentation.

KEY TAKEAWAYS

- **Precision oncology** defines cancer according to its genomic profile rather than by the organ or tissue of origin[1,2]
  - Pathogenic gene fusions are becoming increasingly actionable[3]
  - Targeting these genomic alterations may lead to improved patient outcomes[4]
- ***NRG1* is an important pathogenic gene fusion that can occur across tumor types** and is reported to be associated with poor clinical outcomes, including increased mortality and resistance to currently available therapies in lung cancer[5-9]
- **RNA-based NGS tests can improve identification of genomic alterations over DNA-based methods**, including pathogenic gene fusions such as *NRG1*[9,10]
- Precision oncology benefits from **collaboration** between **oncologists** and **pathologists** to deliver appropriate genomic analysis that can lead to actionable results and potentially meaningful outcomes for patients[2,11]

1. Adashek JJ et al. *Trends Cancer*. 2021;7(1):15-28. doi:10.1016/j.trecan.2020.08.009 **2**. Malone ER et al. *Genome Med*. 2020;12:8. doi:10.1186/s13073-019-0703-1 **3**. Nikanjam M et al. *Cancer*. 2020;126(6):1315-1321. doi:10.1002/cncr.32649 **4**. Zhao S et al. *BMC Med*. 2021;19(1):223. doi:10.1186/s12916-021-02089-z **5**. Drilon A et al. *Cancer Discov*. 2018;8(6):686-695. doi:10.1158/2159-8290.CD-17-1004 **6**. Jonna S et al. *Clin Cancer Res*. 2019;25(16):4966-4972. doi:10.1158/1078-0432.CCR-19-0160 **7**. Rosas D et al. *Cancers (Basel)*. 2021;13(20):5038. doi:10.3390/cancers13205038 **8**. Shin DH et al. *Oncotarget*. 2016;7(43):69450-69465. doi:10.18632/oncotarget.11913 **9**. Drilon A et al. *J Clin Oncol*. 2021;39(25):2791-2802. doi:10.1200/JCO.20.03307 **10**. Benayed R et al. *Clin Cancer Res*. 2019;25(15):4712-4722. doi:10.1158/1078-0432.CCR-19-0225 **11**. Perakis SO et al. *ESMO Open*. 2020;5(5):e000872. doi:10.1136/esmoopen-2020-000872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