# INCOMPLETE KNOWLEDGE HAS CONSEQUENCES

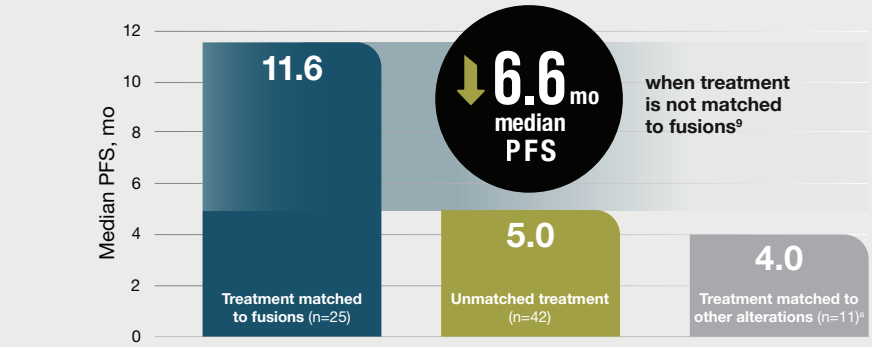
**Detecting pathogenic gene fusions in cancer is critical for patients[1-5]**

## Cancer care is evolving from thinking about cancer according to site of origin to thinking about cancer according to tumor genomics, for a more tailored approach to care[5,6]

- Genomic alterations are becoming increasingly actionable and can include point mutations and pathogenic gene fusions[6-11]
- Targeting the genomic alterations of a patient's cancer may potentially lead to improved outcomes[5-8,12]

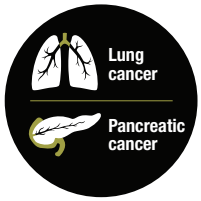

## Pathogenic gene fusions are a contributing factor in 1 in 6 cancers and can impact how tumors respond to treatment[1-5,9]

- Fusions occur across many tumor types and are an independent prognostic factor for poor outcomes in lung cancer[1,10-13]
- In patients with pathogenic gene fusions, FDA-approved fusion-targeted treatments demonstrated improved PFS[9]

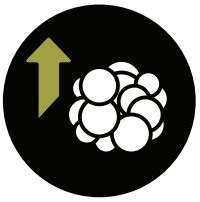



[a]Of the 79 study patients with identified pathogenic gene fusions, 12 received treatment matched to other alterations, of whom 1 had an unclear match and was excluded from pairwise comparison analysis.[9]

## A pathogenic gene fusion receiving increasing attention is *NRG1*, due to poor clinical outcomes and resistance to standard therapies[11-16]




*NRG1* fusions occur across many tumor types but are enriched in invasive mucinous lung adenocarcinoma (27%-31%) and *KRAS* wild-type pancreatic cancer (up to 6%).[11,12,15,17]

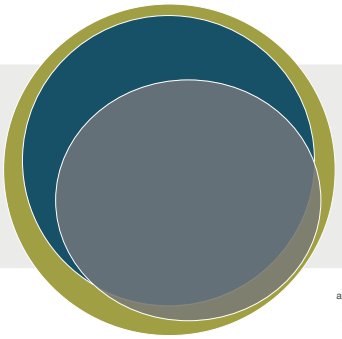


*NRG1*+ tumors have aggressive histological features associated with increased tumor growth, invasiveness, recurrence, resistance to therapy, metastasis, and worse prognosis in lung cancer.[10-15]

FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NE, not estimable; NGS, next-generation sequencing; *NRG1*, neuregulin 1; *NRG1*+, neuregulin 1 fusion positive; PFS, progression-free survival; RT-PCR, reverse transcription-polymerase chain reaction.

# Are you optimizing the detection of pathogenic gene fusions such as *NRG1*?

Comprehensive testing with RNA-based NGS, which includes DNA and RNA sequencing, is recommended to capture what DNA-based NGS alone can miss[3,14,16]



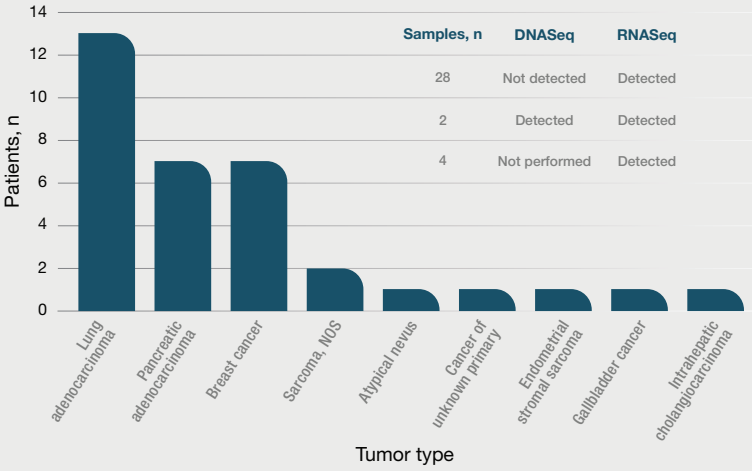

[a]Graphic for illustrative purposes only. Not drawn to scale or reflective of actual results captured by different methodologies.

**DNA-based sequencing can lead to false-negative and false-positive results in a variety of cases, particularly in the detection of pathogenic gene fusions[2-4]**

## RNA-based NGS testing is a comprehensive way to detect genomic alterations, including pathogenic gene fusions such as *NRG1*[2-4]

- Characteristics of *NRG1* can help it elude detection by conventional testing methods, including DNA-based NGS[11,13,16]
- Of 30 patients with *NRG1*+ tumors who had both DNA- and RNA-based NGS, 28 were identified by RNA-based NGS but were undetected by DNA-based NGS[16]

**Detection of *NRG1* Fusions Across Tumor Types[16]**




Results from a retrospective study by the Memorial Sloan Kettering Cancer Center.[16]

Are you using RNA-based NGS to comprehensively screen your patients? Learn more at **FindTheFusions.com**

NOS, not otherwise specified.

**References: 1.** Gao Q, Liang W-W, Foltz SM, et al. Driver fusions and their implications in the development and treatment of human cancers. *Cell Rep*. 2018;23(1):227-238.e3. doi:10.1016/j.celrep.2018.03.050 **2.** Heyer EE, Deveson IW, Wooi D, et al. Diagnosis of fusion genes using targeted RNA sequencing. *Nat Commun*. 2019;10(1):1388. doi:10.1038/s41467-019-09374-9 **3.** Bruno R, Fontanini G. Next generation sequencing for gene fusion analysis in lung cancer: a literature review. *Diagnostics (Basel)*. 2020;10(8):521. doi:10.3390/diagnostics10080521 **4.** 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 **5.** Adashek JJ, Subbiah V, Kurzrock R. From tissue-agnostic to N-of-one therapies: (R)evolution of the precision paradigm. *Trends Cancer*. 2021;7(1):15-28. doi:10.1016/j.trecan.2020.08.009 **6.** El-Deiry WS, Goldberg RM, Lenz H-J, et al. The current state of molecular testing in the treatment of patients with solid tumors, 2019. *CA Cancer J Clin*. 2019;69(4):305-343. doi:10.3322/caac.21560 **7.** Malone ER, Oliva M, Sabatini PJB, Stockley TL, Siu LL. Molecular profiling for precision cancer therapies. *Genome Med*. 2020;12(1):8. doi:10.1186/s13073-019-0703-1 **8.** Zhang R, Dong L, Yu J. Concomitant pathogenic mutations and fusions of driver oncogenes in tumors. *Front Oncol*. 2021;10:544579. doi:10.3389/fonc.2020.544579 **9.** Nikanjam M, Okamura R, Barkauskas DA, Kurzrock R. Targeting fusions for improved outcomes in oncology treatment. *Cancer*. 2020;126(6):1315-1321. doi:10.1002/cncr.32649 **10.** Dhanasekaran SM, Balbin OA, Chen G, et al. Transcriptome meta-analysis of lung cancer reveals recurrent aberrations in *NRG1* and Hippo pathway genes. *Nat Commun*. 2014;5:5893. doi:10.1038/ncomms6893 **11.** Laskin J, Liu SV, Tolba K, et al. *NRG1* fusion-driven tumors: biology, detection, and the therapeutic role of afatinib and other ErbB-targeting agents. *Ann Oncol*. 2020;31(12):1693-1703. doi:10.1016/j.annonc.2020.08.2335 **12.** Shin DH, Lee D, Hong DW, et al. Oncogenic function and clinical implications of *SLC3A2-NRG1* fusion in invasive mucinous adenocarcinoma of the lung. *Oncotarget*. 2016;7(43):69450-69465. doi:10.18632/oncotarget.11913 **13.** 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 **14.** Chang JC, Offin M, Falcon C, et al. Comprehensive molecular and clinicopathologic analysis of 200 pulmonary invasive mucinous adenocarcinomas identifies distinct characteristics of molecular subtypes. *Clin Cancer Res*. 2021;27(14):4066-4076. doi:10.1158/1078-0432.CCR-21-0423 **15.** Rosas D, Raez LE, Russo A, Rolfo C. Neuregulin 1 gene (*NRG1*). A potentially new targetable alteration for the treatment of lung cancer. *Cancers (Basel)*. 2021;13(20):5038. doi:10.3390/cancers13205038 **16.** Benayed R, Liu SV. Neuregulin-1 (*NRG1*): An emerging tumor-agnostic target. Clinical Care Options: Oncology. Accessed March 2, 2023. https://apps.clinicaloptions.com/oncology/programs/2021/nrg1-fusions/text-module/nrg1-text-module/page-1 **17.** Jones MR, Williamson LM, Topham JT, et al. *NRG1* gene fusions are recurrent, clinically actionable gene rearrangements in *KRAS* wild-type pancreatic ductal adenocarcinoma. *Clin Cancer Res*. 2019;25(15):4674-4681. doi:10.1158/1078-0432.CCR-19-0191

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