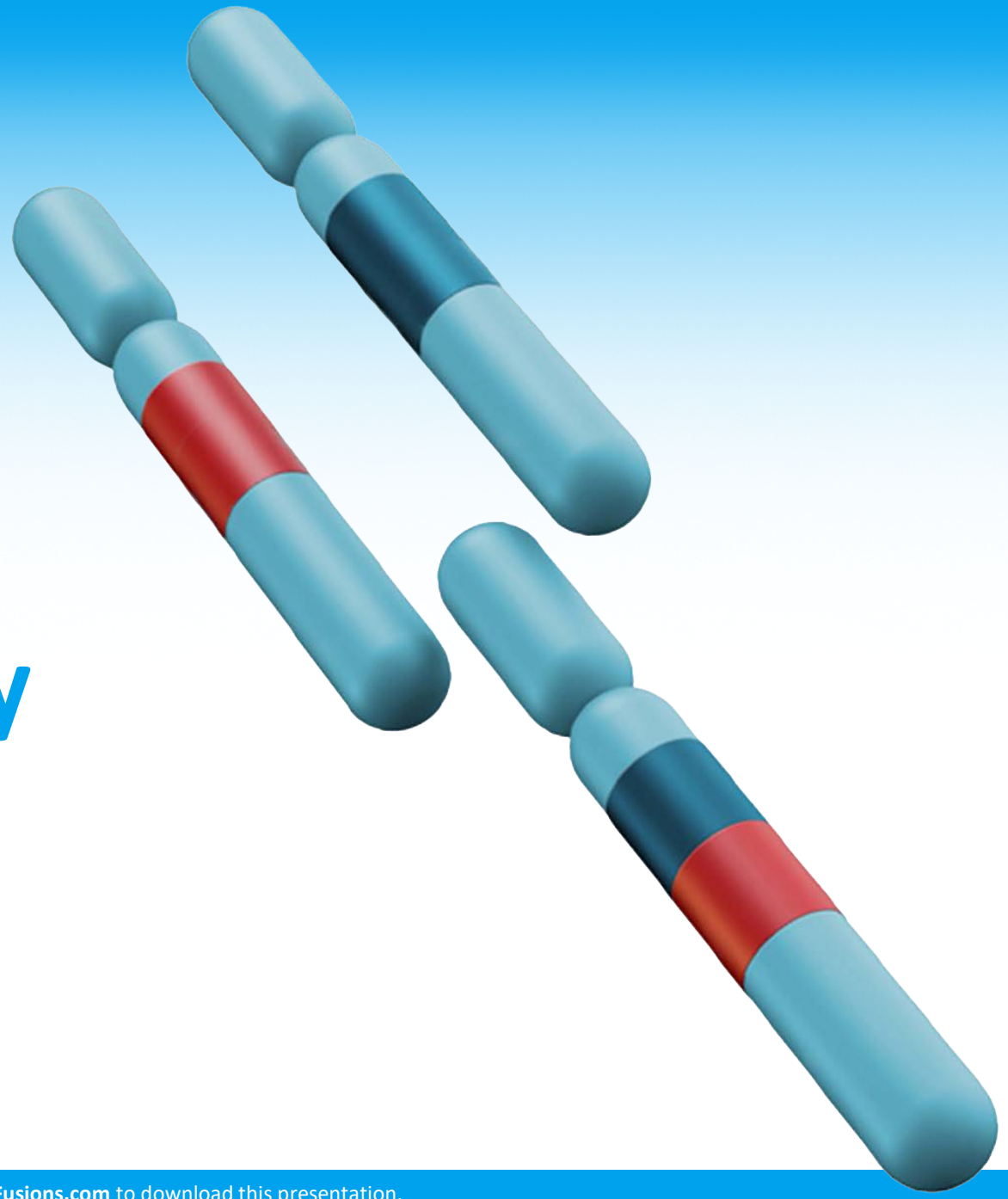
Simplifying Your Approach to Precision Oncology



The Importance of a Precision Oncology Approach

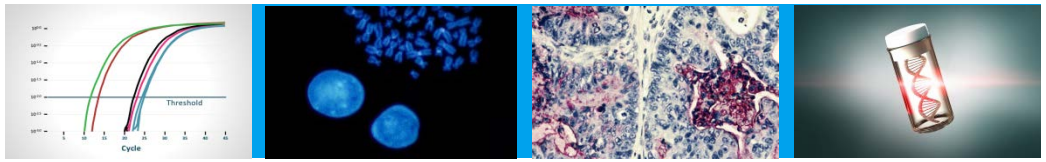
Cancer Is Driven by Genomic Alterations[1]

- 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]

Personalized Cancer Therapy

MOLECULAR PROFILING



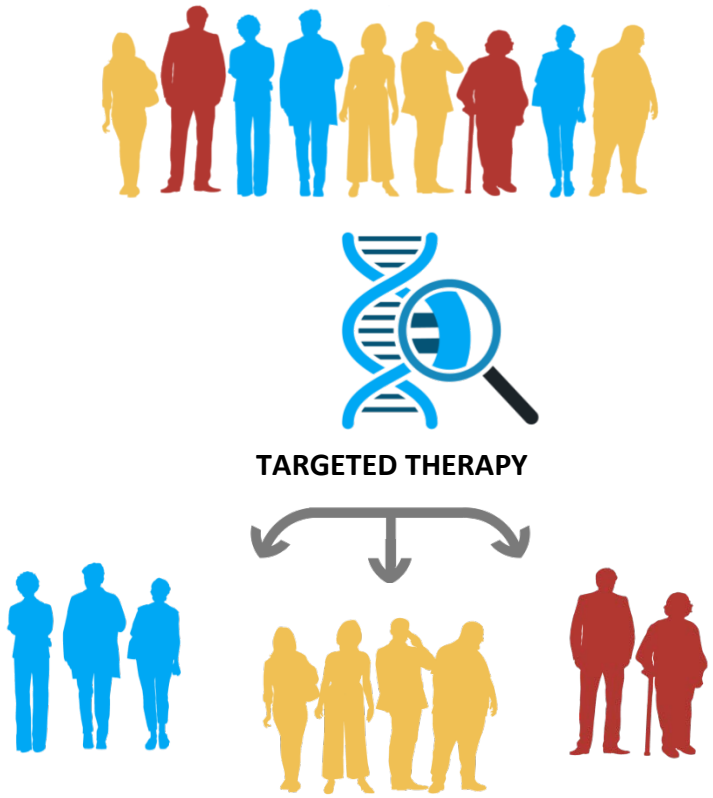
RT-PCR | FISH | IHC | NGS

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]

Precision Treatment Approach

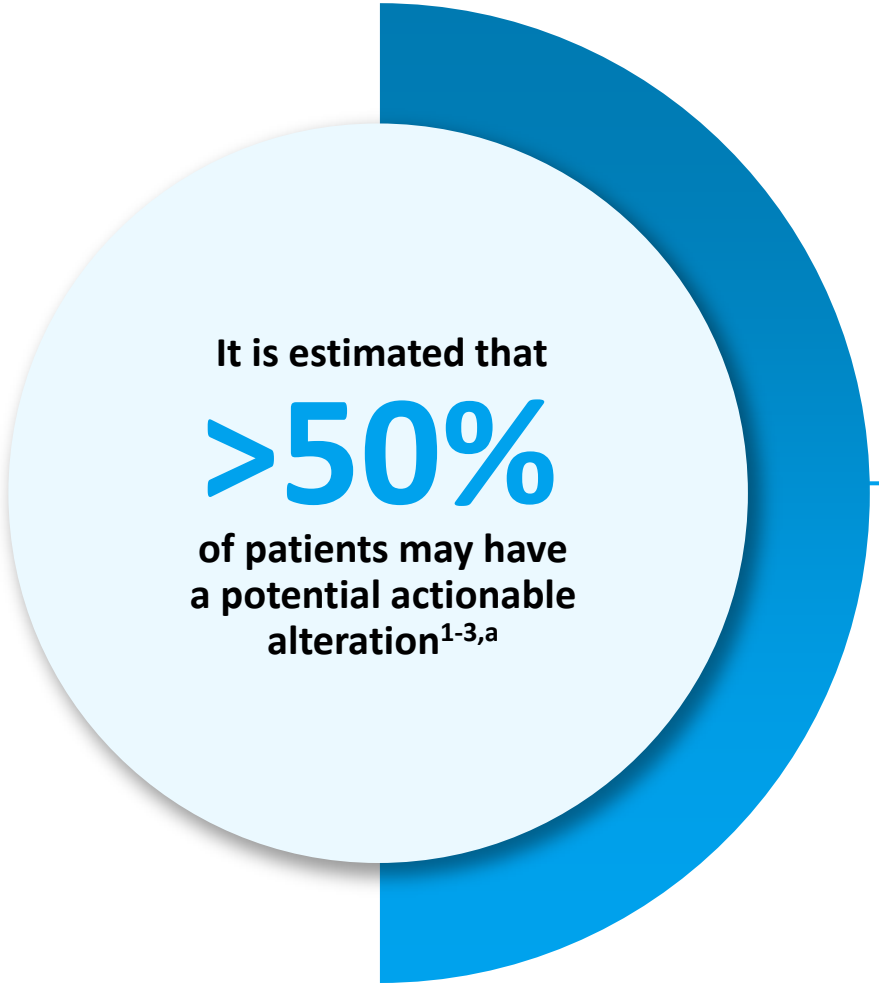


Precision oncology **aims to optimize and tailor each patient's treatment approach** based on the genomic profile of the patient's cancer[3]

- 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

Number of Actionable Genomic Alterations Continues to Rise

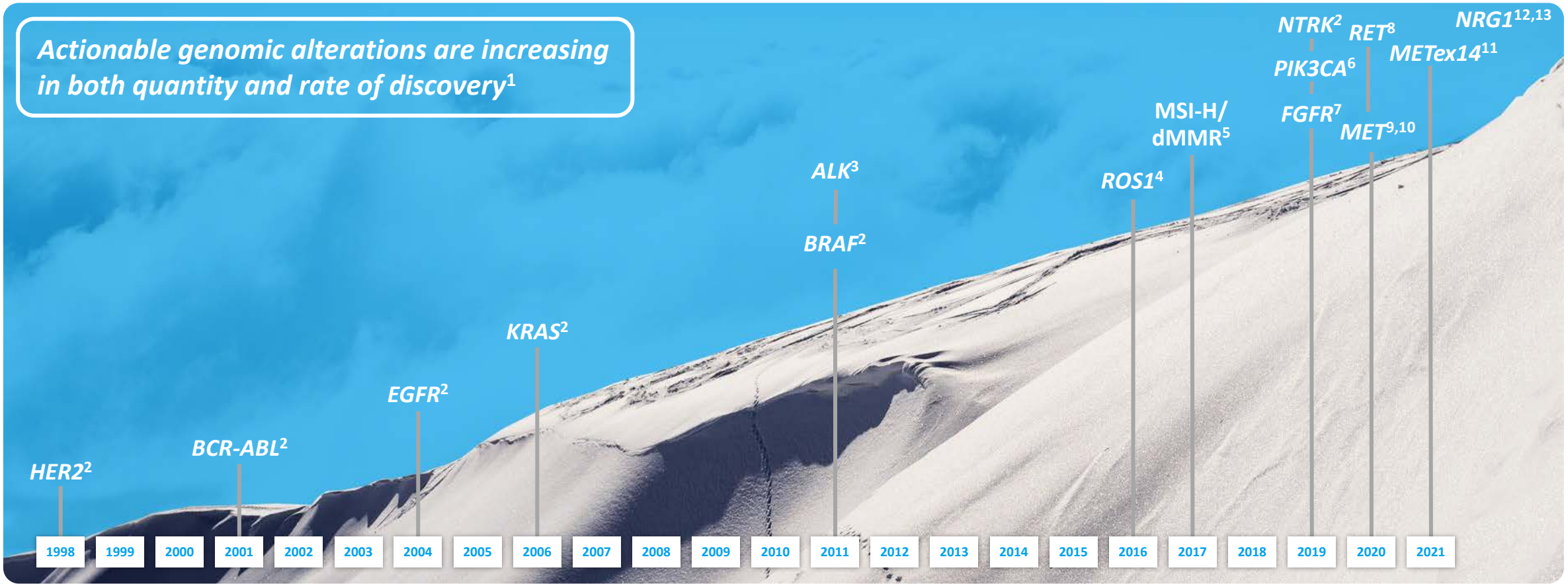


- Individual genomic alterations may be rare; however, alterations in totality are found in a significant percentage of patients with cancer[1,3-6]
  - **A genomic alteration is defined as actionable when there is a potential therapeutic target that <u>will mitigate oncogenic consequences</u> of the disrupted pathway[7]**
    - Genomic alterations may be treated directly with a targeted agent, or the aberrant pathogenic pathway caused by the genetic defect may be treated instead
- **>50 oncology drugs** with genomic indications were approved between 2006 and 2020[8]

[a]Large retrospective series have documented that 80% to 90% of patients tested will have potentially actionable genomic alterations, although the definition of actionable can vary substantially.[1]

1. Schwartzberg L et al. *Am Soc Clin Oncol Educ Book*. 2017;37:160-169. doi:10.1200/EDBK_174176 **2**. Kris MG et al. *JAMA*. 2014;311(19):1998-2006. doi:10.1001/jama.2014.3741 **3**. Priestley P et al. *Nature*. 2019;575(7781):210-216. doi:10.1038/s41586-019-1689-y **4**. Tuxen IV et al. *Clin Cancer Res.* 2019;25(4):1239-1247. doi:10.1158/1078-0432.CCR-18-1780 **5**. Bertucci F et al. *Genome Med*. 2021;13(1):87. doi:10.1186/s13073-021-00897-9 **6**. Cobain EF et al. *JAMA Oncol.* 2021;7(4):525-533. doi:10.1001/jamaoncol.2020.7987 **7**. Yates LR et al. *Ann Oncol*. 2018;29(1):30-35. doi:10.1093/annonc/mdx707 **8**. Haslam A et al. *Eur J Cancer*. 2022;160:175-179. doi:10.1016/j.ejca.2021.10.028

Data Establishing the Role of Clinically Actionable Genomic Markers Are Increasing[1]

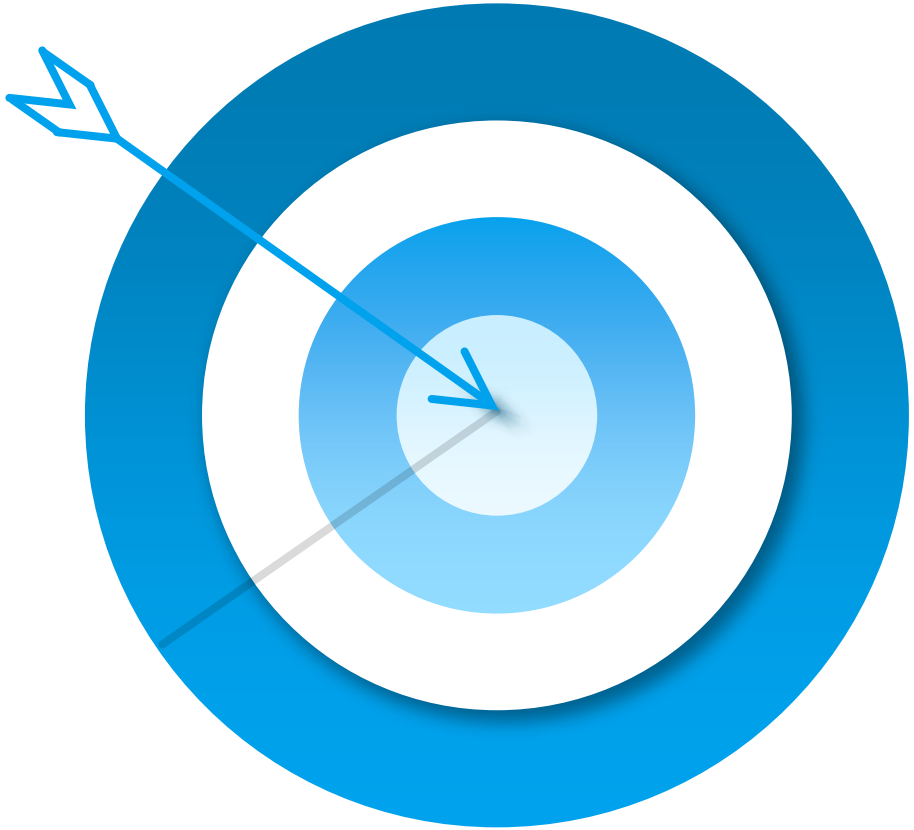


ALK, anaplastic lymphoma kinase; *BCR-ABL*, breakpoint cluster region-Abelson murine leukemia homolog 1; *BRAF*, rapidly accelerated fibrosarcoma B1; *EGFR*, epidermal growth factor receptor; *FGFR*, fibroblast growth factor receptor; *HER2*, human epidermal growth factor receptor 2; *KRAS*, Kirsten 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**. Colomer R et al. *EClinicalMedicine*. 2020;25:100487. doi:10.1016/j.eclinm.2020.100487 **3**. Kazandjian D et al. *Oncologist*. 2014;19(10):e5-e11. doi:10.1634/theoncologist.2014-0241 **4**. Kazandjian D et al. *Oncologist*. 2016;21(8):974-980. doi:10.1634/theoncologist.2016-0101 **5**. Marcus L et al. *Clin Cancer Res*. 2019;25(13):3753-3758. doi:10.1158/1078-0432.CCR-18-4070 **6**. Narayan P et al. *Clin Cancer Res*. 2021;27(7):1842-1849. doi:10.1158/1078-0432.CCR-20-3652 **7**. Sayegh N et al. *Onco Targets Ther*. 2022;15:1047-1055. doi:10.2147/OTT.S318332 **8**. Bradford D et al. *Clin Cancer Res*. 2021;27(8):2130-2135. doi:10.1158/1078-0432.CCR-20-3558 **9**. MET. Accessed April 24, 2023. https://www.mycancergenome.org/content/gene/met/ **10**. Recondo G et al. *Cancer Discov*. 2020;10(7):922-934. doi:10.1158/2159-8290.CD-19-1446 **11**. Desai A, Cuellar S. *J Adv Pract Oncol*. 2022;13(5):539-544. doi:10.6004/jadpro.2022.13.5.8 **12**. Schram AM et al. *Cancer Discov*. 2022;12(5):1233-1247. doi:10.1158/2159-8290.CD-21-1119 **13**. Geuijen CAW et al. *Cancer Cell*. 2018;33(5):922-936. doi:10.1016/j.ccell.2018.04.003

Visit **FindTheFusions.com** to download this presentation.

Genomic Profile-Guided Treatment Decisions Are the Future of Precision Oncology



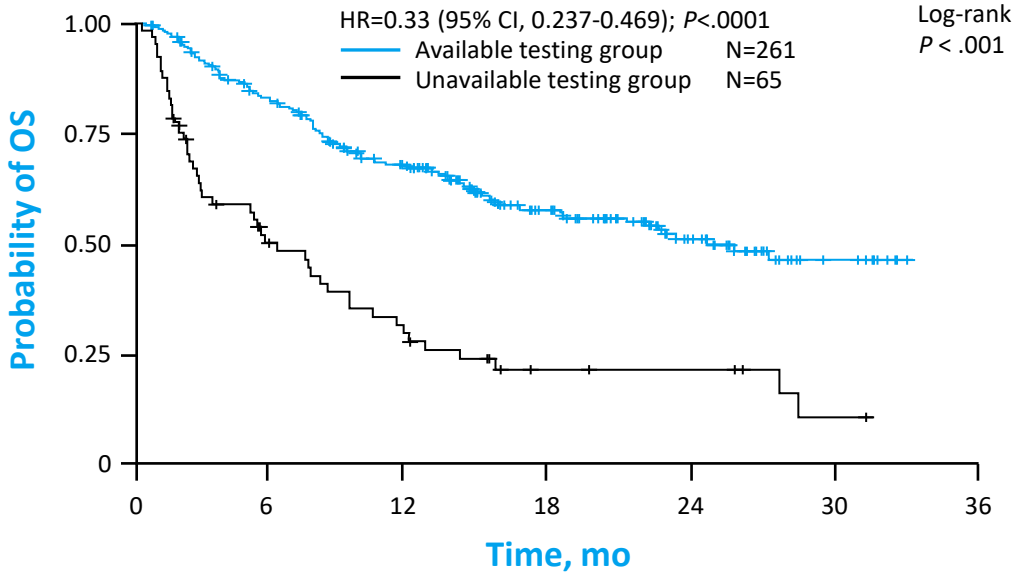
- **Understanding a patient's genomic profile and their oncogenic drivers can guide physicians toward a more tailored treatment approach[1,2]**
- Knowledge of a patient's genomic profile can also eliminate inappropriate or less effective treatment choices[3]

1. El-Deiry WS et al. *CA Cancer J Clin*. 2019;69(4):305-343. doi:10.3322/caac.21560 **2**. Faulkner E et al. *Value Health*. 2020;23(5):529-539. doi:10.1016/j.jval.2019.11.010 **3**. Thomas DM et al. *Public Health Genomics*. 2022;25:70-79. doi:10.1159/000520000

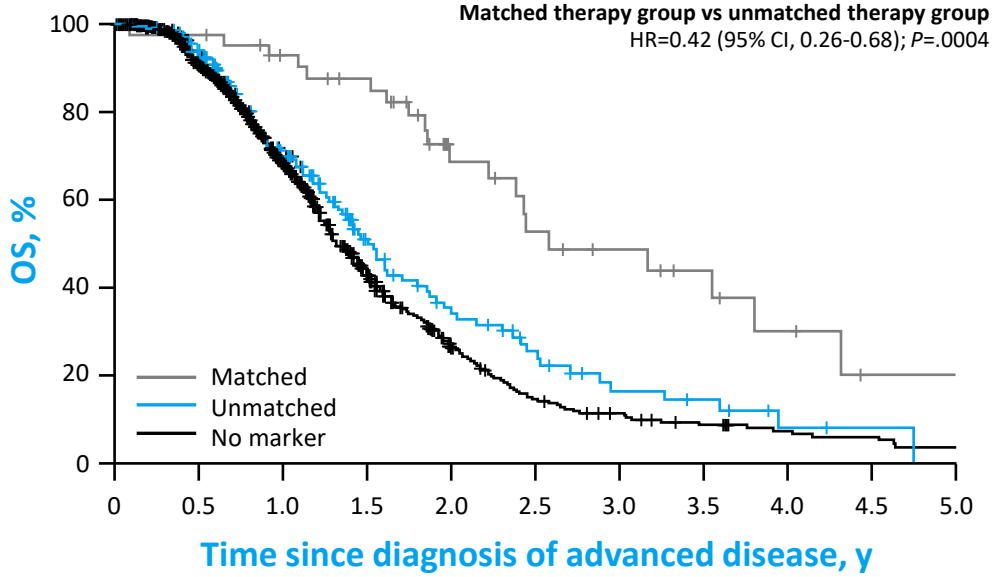
Targeting Genomic Alterations Can Lead to Better Outcomes for Patients[1,2]

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

OS Based on Availability of Molecular Test Results Before 1L Therapy (mNSq NSCLC)[1,*]



OS in Pancreatic Cancer With Matched vs Unmatched Therapy[3]



In both studies, OS was improved in patients who received therapies directed toward their specific alterations.[1,3]

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

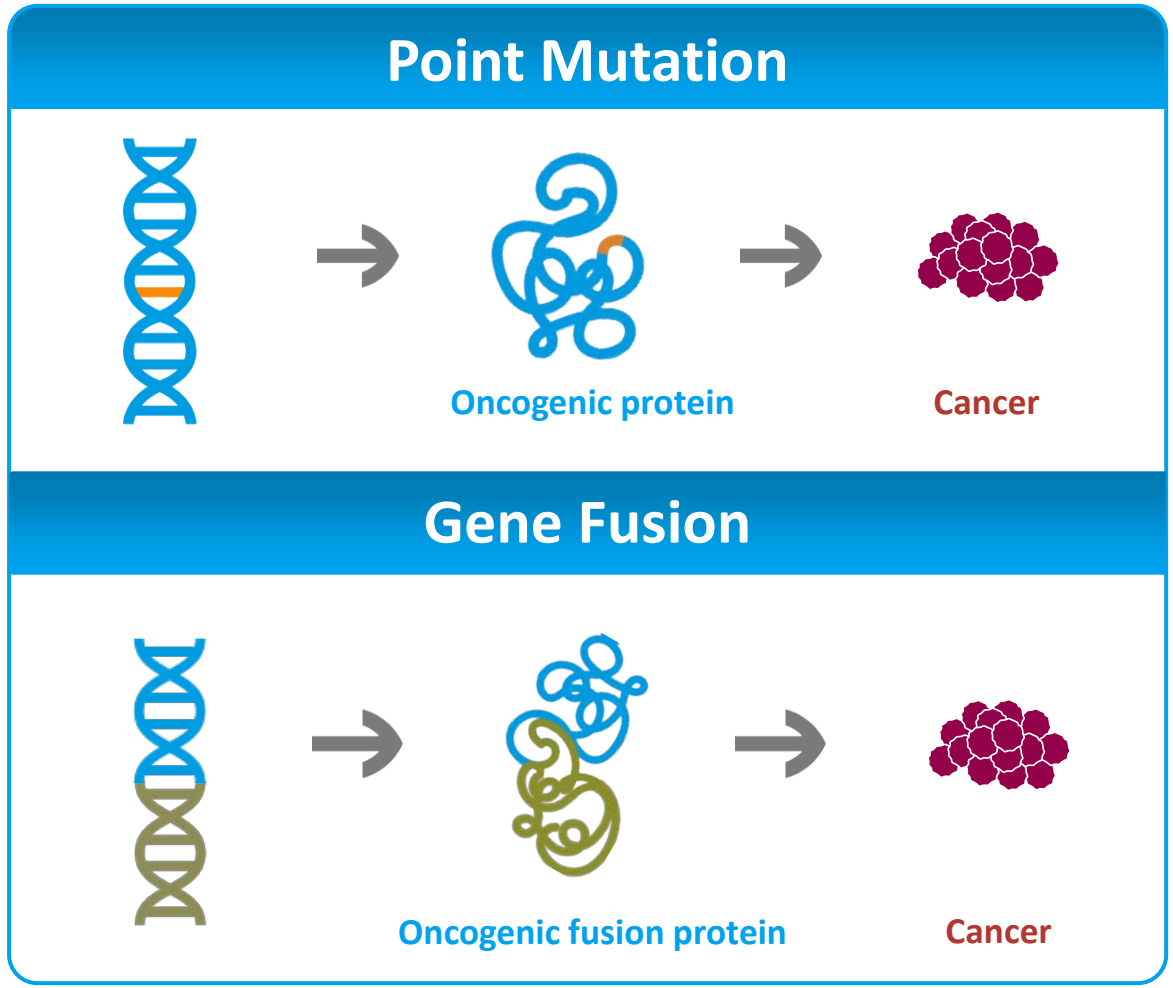
*Retrospective data collected between January 1, 2019 and December 31, 2020.

1. Aggarwal C et al. *JCO Precis Oncol*. 2023;7:e2300191. doi:10.1200/PO.23.00191 **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

There Are Different Types of Genomic Alterations That Drive Cancer

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

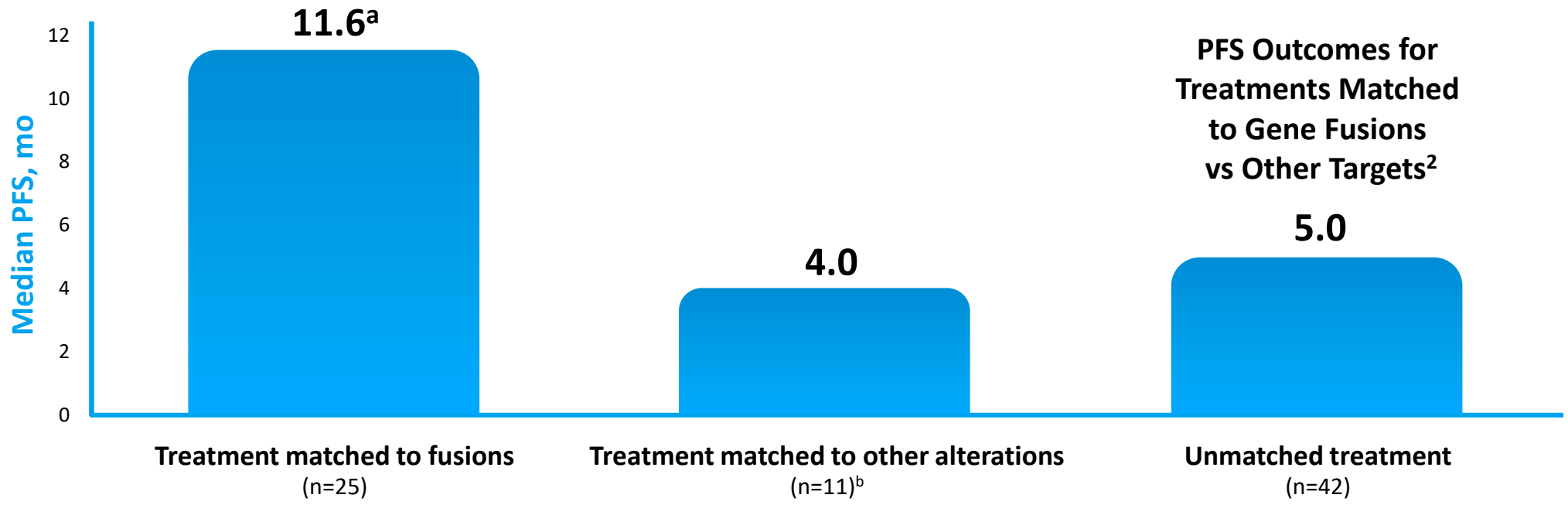
- Point mutations are changes in DNA base pairs[2]
  - Examples include *BRAF* and *EGFR*[3]
- Pathogenic gene fusions typically occur when 2 different genes join to form an abnormal hybrid gene[4]
  - Examples include ALK, NTRK, ROS1, and NRG1[3,5]
    - Genes involved in fusions are not located next 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]

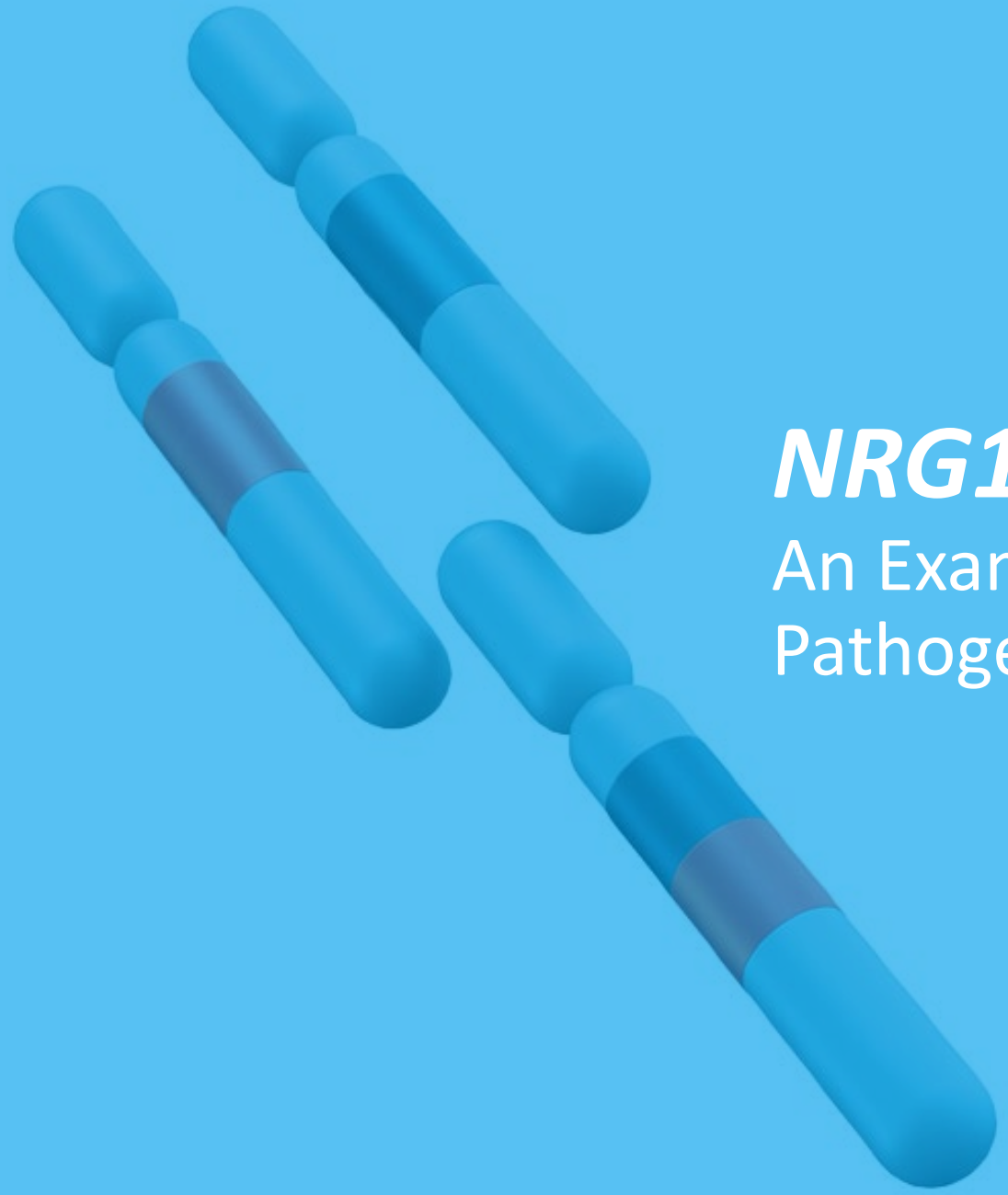


PFS, progression-free survival.

[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 one 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 Example of an Important Pathogenic Gene Fusion

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 induces receptor dimerization and activation of PI3K- and RAS-mediated growth pathways[3,4]

Wild Type NRG1 Formation and Signaling

(WT) Pro-NRG1 cleavage to active NRG1

Pro-NRG1

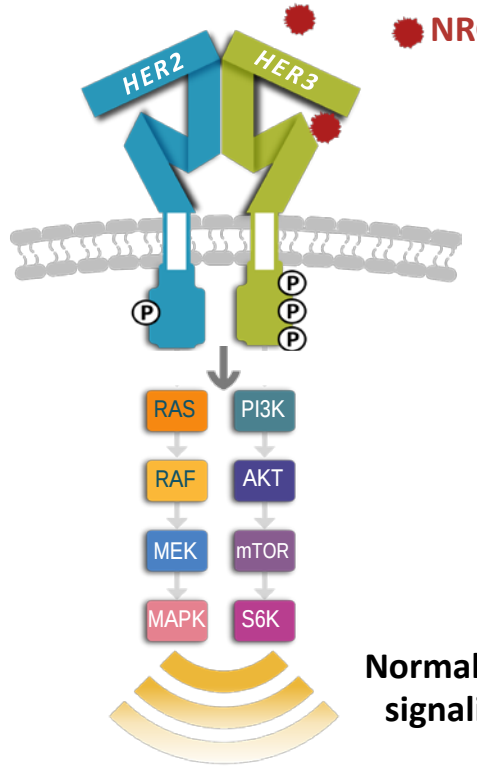
Cleavage

NRG1

WT NRG1 unbound (extracellular)

NRG1

WT NRG1-HER3 binding and receptor dimerization



Normal cell 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 Fusions Result in Increased Cell Signaling and Growth[1,2]

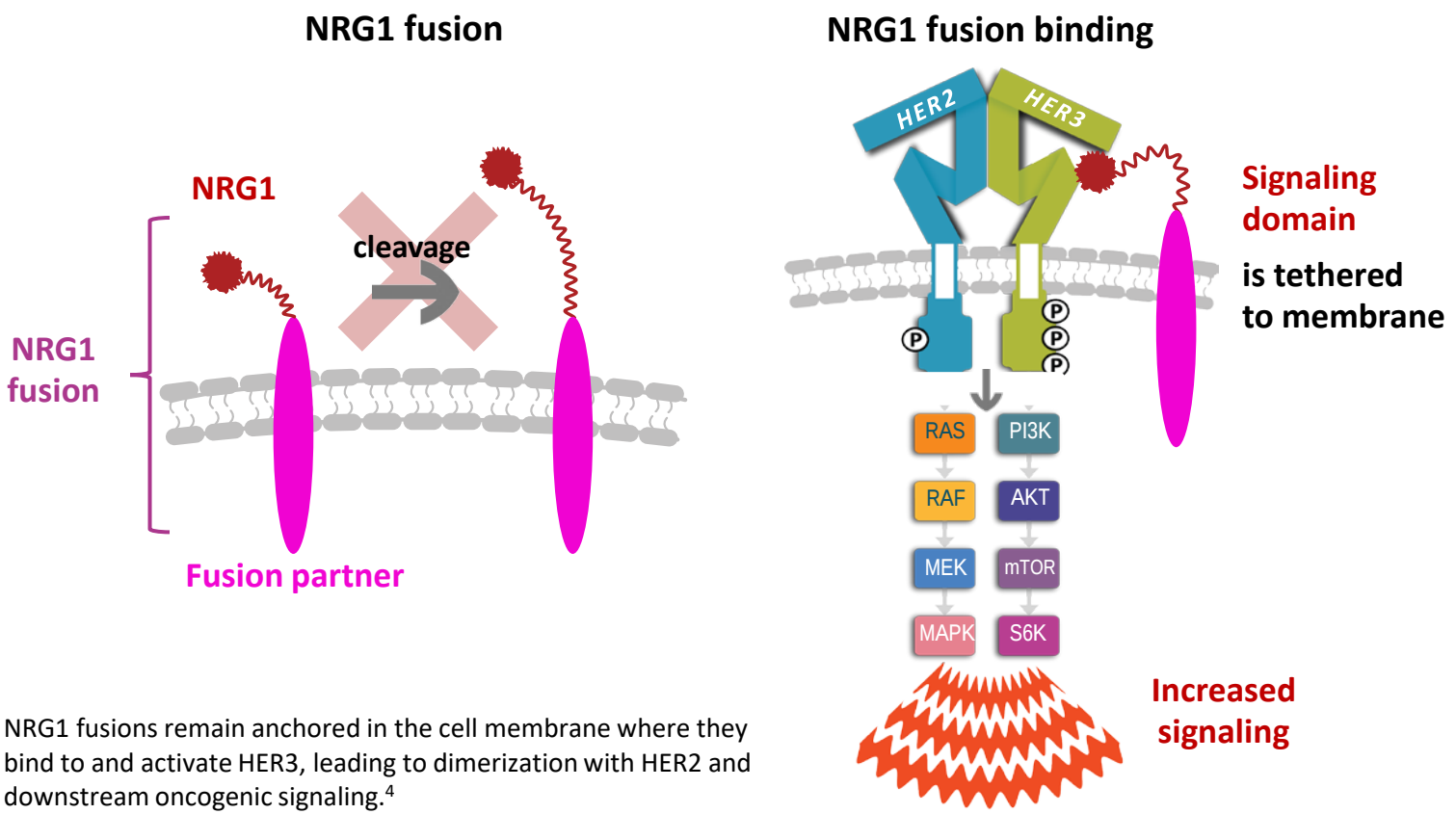
NRG1 fusions induce receptor dimerization and result in aberrant cell signaling[3,4]

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 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.[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

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 outcomes[3-7]

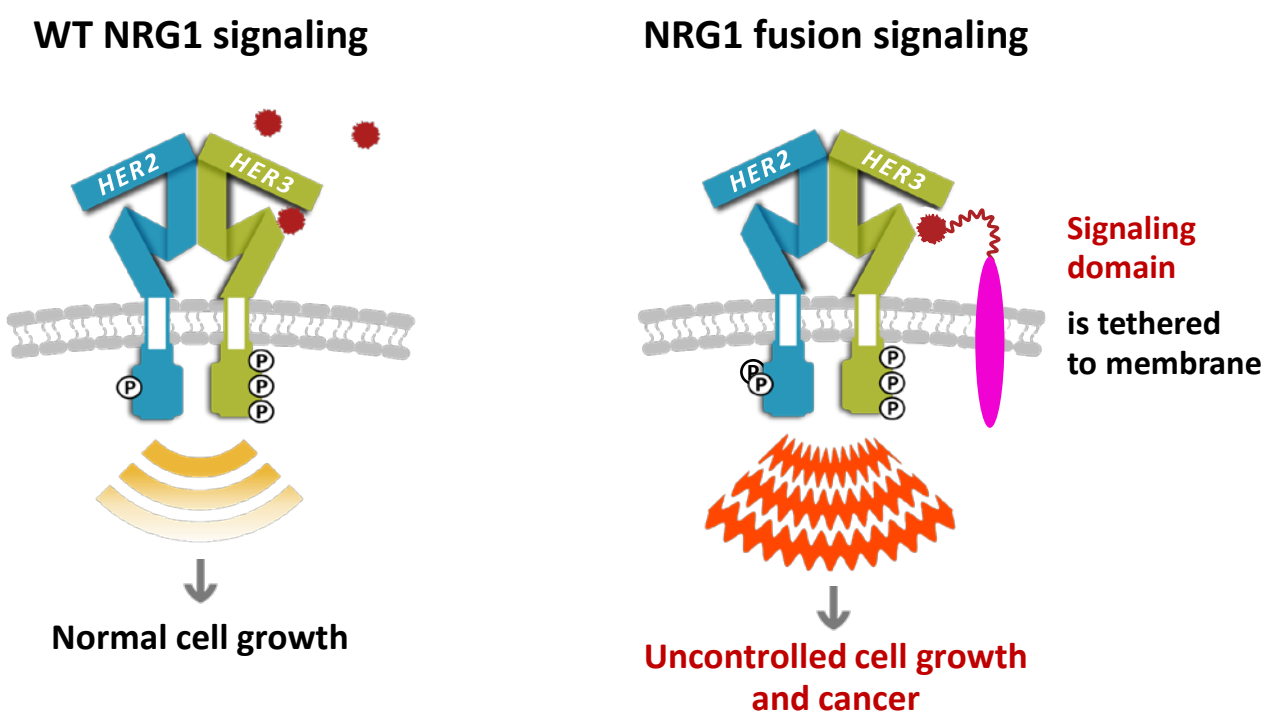
NRG1 fusions can lead to

- 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

NRG1 Gene Fusions Can Occur in Many Types of Solid Tumors[1]

NRG1 Fusion Frequency Estimates[a]

	Overall	Enrichment
	Lung cancer (0.3%-1.7%)[1,2]	**Invasive mucinous lung adenocarcinoma** (27%-31%)[3]
	Pancreatic cancer (0.5%-1.8%)[2,4]	***KRAS* wild-type pancreatic cancer** (up to 6%)[5]
	Other (<1%, eg, breast, cholangiocarcinoma, colorectal cancers)[2]	

- Enrichment is observed in some tumors, particularly[2,6]
  - Invasive mucinous lung adenocarcinoma
  - NSCLC that is **negative for other driver mutations**
  - KRAS wild-type pancreatic cancer
- *NRG1* fusions generally occur in the absence of other driver mutations[6]

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

1. Drilon A et al. *Cancer Discov*. 2018;8(6):686-695. doi:10.1158/2159-8290.CD-17-1004 **2**. Jonna S et al. *Clin Cancer Res*. 2019;25(16):4966-4972. doi:10.1158/1078-0432.CCR-19-0160 **3**. Laskin J et al. *Ann Oncol*. 2020;31(12):1693-1703. doi:10.1016/j.annonc.2020.08.2335 **4**. Knepper TC et al. *J Clin Oncol*. 2022;40(suppl 16):4155. doi:10.1200/JCO.2022.40.16_suppl.4155 **5**. Jones MR et al. *Clin Cancer Res*. 2019;25(15):4674-4681. doi:10.1158/1078-0432.CCR-19-0191 **6.** 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,*]

	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)

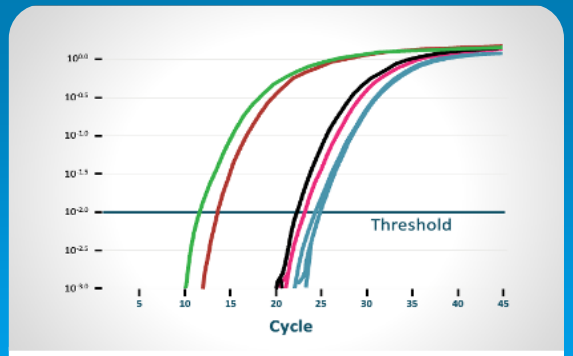
ORR, overall response rate.

*Patients either diagnosed with or who developed metastatic disease during the course of their disease.

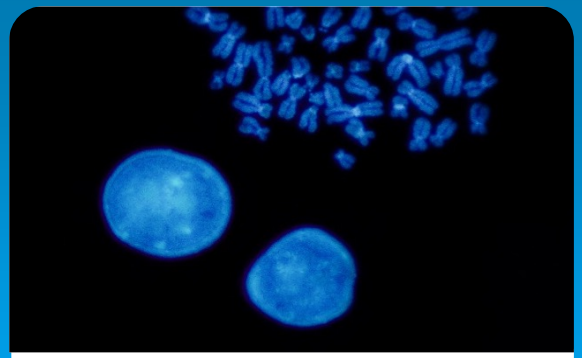
1. Rosas D et al. *Cancers (Basel)*. 2021;13(20):5038. doi:10.3390/cancers13205038 **2**. National Institutes of Health, National Cancer Institute. Accessed April 24, 2023. https://www.cancer.gov/types/lung/patient/non-small-cell-lung-treatment-pdq **3**. Drilon A et al. *J Clin Oncol*. 2021;39(25):2791-2802.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

Testing With Both DNA and RNA (RNA-Based NGS) Is the Key to Finding Actionable Alterations

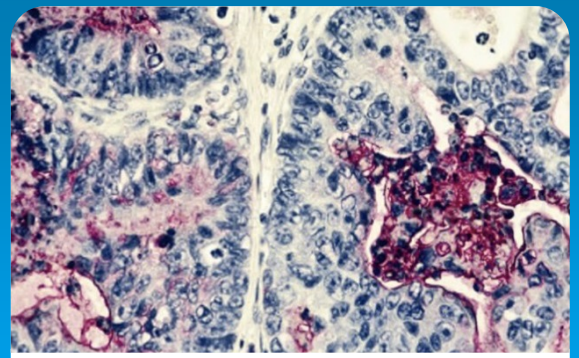
Classical Biomarker Screening Methods Were Developed to Detect Single Molecular Targets[1,2]



RT-PCR



FISH



IHC

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 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/article/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

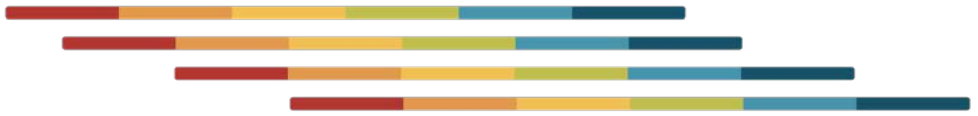
NGS Can Detect a Broad Range of Genomic Alterations[1]

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

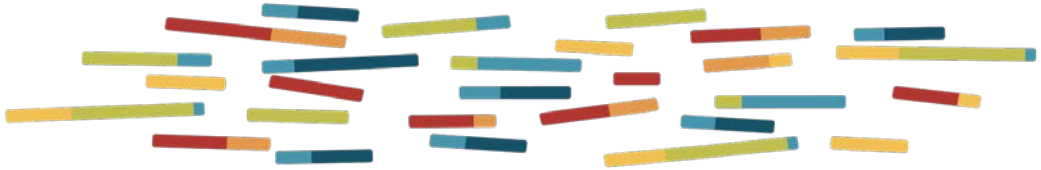
- NGS is a high-throughput genomic sequencing technology that allows for the simultaneous analysis of numerous alterations that[2]
  - Can be performed with DNA or RNA[3]
  - Has several advantages over current conventional methods in detecting pathogenic gene fusions[3]

There are clear
DIFFERENCES BETWEEN
DNA- and RNA-based NGS[3]

NGS Process



Nucleic acid extraction and isolation



Fragmentation and library creation

Amplifying and sequencing the libraries

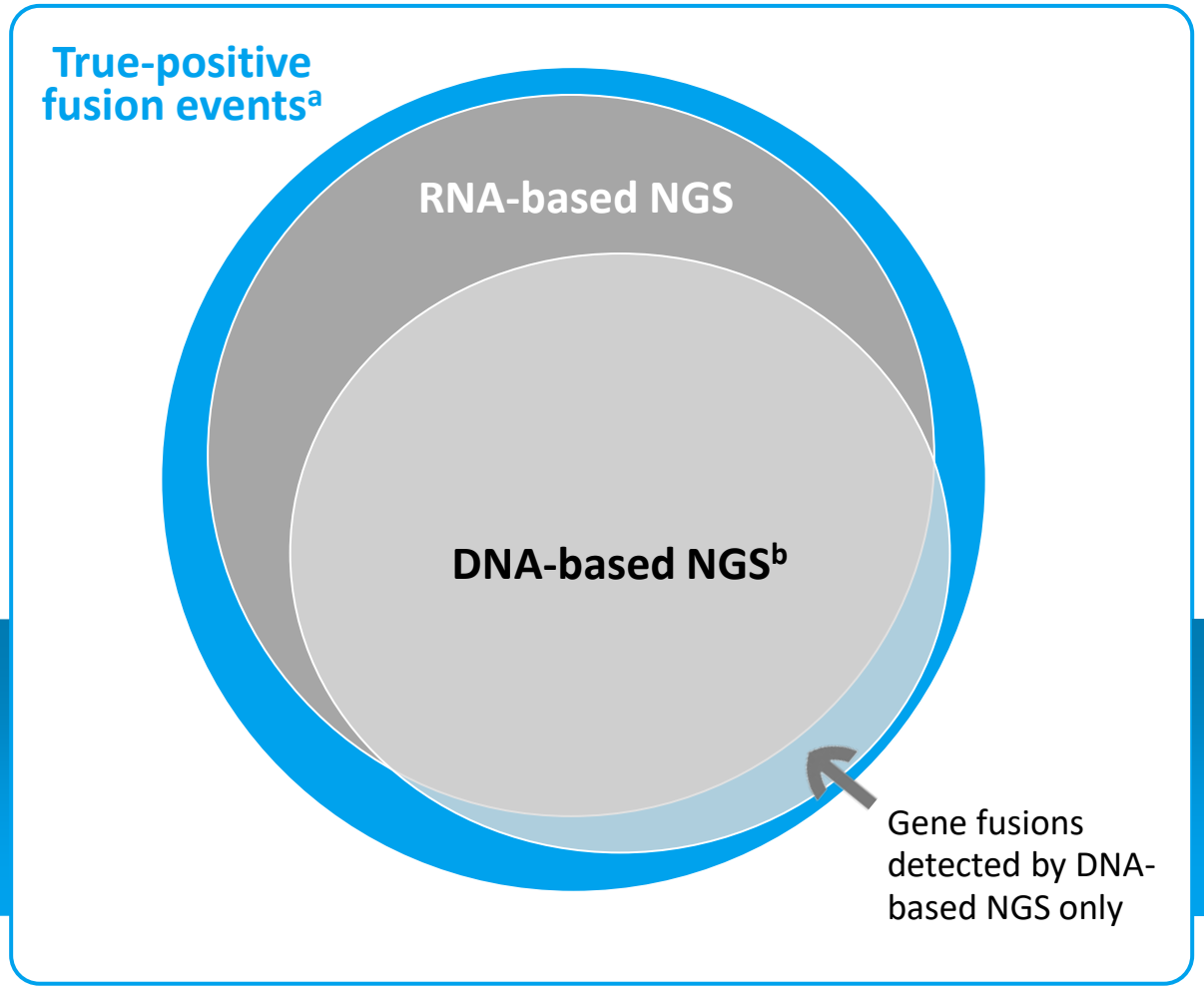
1. Singh RR. *J Mol Diagn*. 2020;22(8):994-1007. doi:10.1016/j.jmoldx.2020.04.213 **2**. Goswami RS et al. *Am J Clin Pathol.* 2016;145(2):222-237. doi:10.1093/ajcp/aqv023 **3**. Bruno R, Fontanini G. *Diagnostics (Basel)*. 2020;10(8):521. doi:10.3390/diagnostics10080521

DNA-Based NGS Alone Can Miss Pathogenic Gene Fusions[1]

DNA-based sequencing can lead to false-negative and false-positive results in a variety of cases, particularly in the detection of gene fusions[1,2]

- Commercially available NGS for liquid biopsies relies on analysis of circulating cfDNA and lacks the sensitivity of RNA-based NGS[3]

RNA-based NGS
is recommended to capture
WHAT DNA-BASED NGS CAN MISS[1]



cfDNA, cell-free DNA.

[a]Graphic for illustrative purposes only. Not drawn to scale or reflective of actual results captured by the different methodologies.
[B]DNA-based NGS can detect some fusions not found by certain RNA-based NGS.[2]

1. Benayed R et al. *Clin Cancer Res*. 2019;25(15):4712-4722. doi:10.1158/1078-0432.CCR-19-0225 **2**. Heydt C et al. *BMC Med Genomics*. 2021;14:62. doi:10.1186/s12920-021-00909-y **3**. Choudhury Y et al. Poster presented at: 2022 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL.

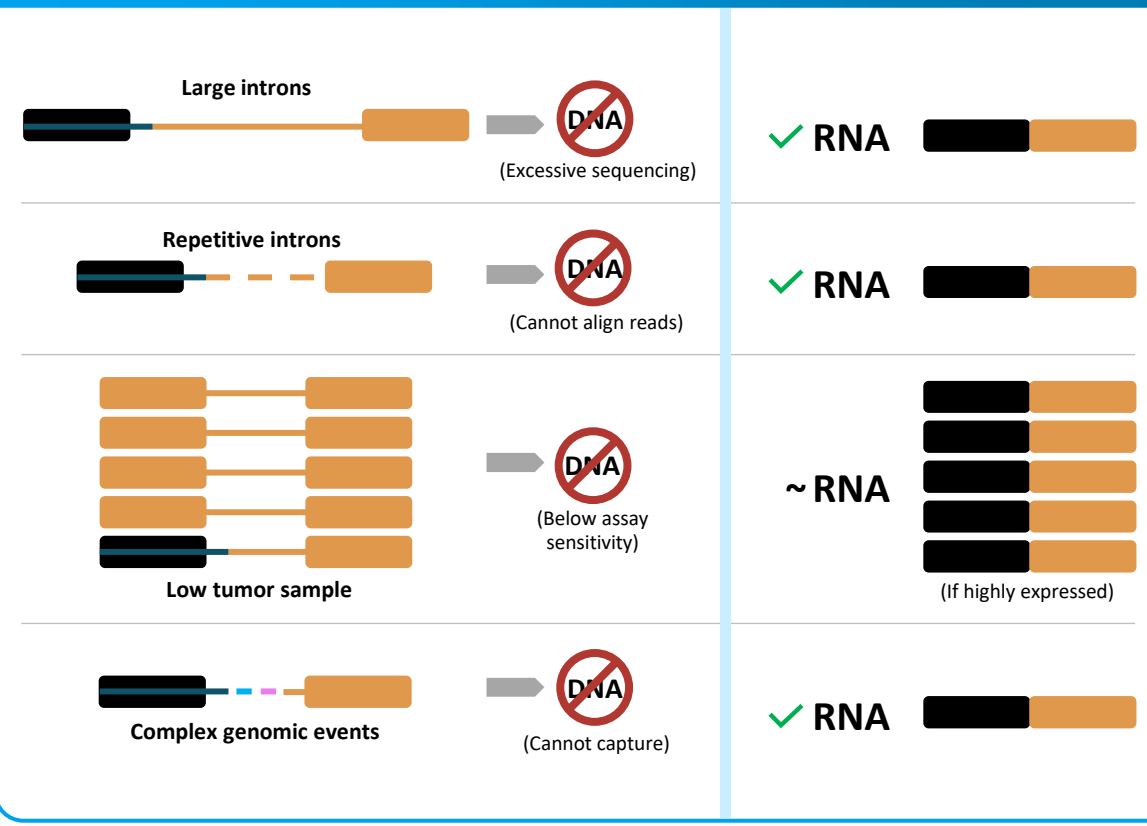
RNA-Based NGS Is More Sensitive Than DNA-Based NGS Alone for Detecting Pathogenic Gene Fusions[1]

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 sensitive 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

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; Vendor	Analyte[a]	Genes on Panel
Altera™[3]; Natera	DNA/RNA	440
Caris®[4]: Caris Life Sciences	DNA/RNA	WES/WTS
Neo Comprehensive™[5]; NeoGenomics Laboratories	DNA/RNA	517
OncoExTra™[6]; Exact Sciences	DNA/RNA	WES/WTS
Oncomine™ Dx[7]; Thermo Fisher Scientific	DNA/RNA	23
OmniSeq INSIGHT℠[8]; Labcorp Oncology	DNA/RNA	523
StrataNGS™[9]; Strata Oncology	DNA/RNA	437
Tempus xT[10]; Tempus	DNA/RNA	648
FoundationOne® CDx[11]; Foundation Medicine	DNA	324
FoundationOne® Liquid CDx[12]; Foundation Medicine	cfDNA	318
Guardant360® CDx[13,14]; Guardant Health	cfDNA	74
MSK-IMPACT®[15]; Memorial Sloan Kettering Cancer Center	DNA	468
NeoGenomics NeoTYPE® Discovery[16]; NeoGenomics Laboratories	DNA	336
Northstar Select™[17]; NorthstarOnc/BillionToOne	DNA	84
Paradigm Dx PCDx™[18]; Paradigm Diagnostics	DNA	234
PathGroup SmartGenomics™ Complete[19]; PathGroup	DNA	160

WES, whole exome sequencing; WTS, whole transcriptome sequencing.

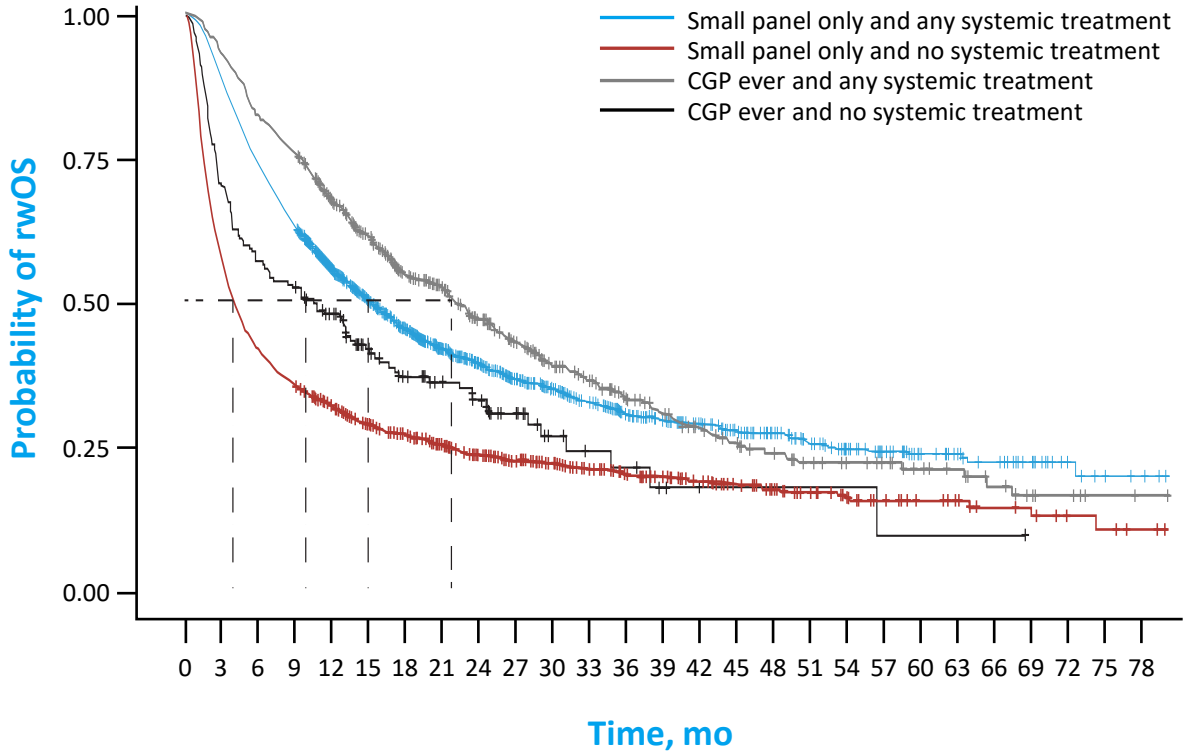
[a]Tests in gray have a limited ability to identify a broad range of gene fusions.[2]

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.CCR-19-0225 **3**. Natera. Accessed April 24, 2023. https://www.natera.com/oncology/signatera-advanced-cancer-detection/clinicians/altera **4**. Caris Life Sciences. Accessed April 24, 2023. https://www.carislifesciences.com/products-and-services/molecular-profiling/tissue-profiling/ **5**. Neogenomic. Accessed April 24, 2023. https://neogenomics.com/test-menu/neo-comprehensive-solid-tumor **6**. Exact Sciences. Accessed April 24, 2023. https://precisiononcology.exactsciences.com/healthcare-providers/therapy-selection/advanced-solid-tumors/oncomapextra?_ga=2.112104071.A2014766495.1671548515-1652124340.1671548515 **7**. ThermoFisher Scientific. Accessed April 24, 2023. https://assets.thermofisher.com/TFS-Assets/CSD/Flyers/odxtt-us-pathologists-flyer **8**. OnmiSeq. Accessed April 24, 2023. https://www.omniseq.com/wp-content/uploads/2021/05/OmniSeq-INSIGHT-INTENDED-US-PERFORMANCE-SPECS **9**. StrataNGS. Accessed April 24, 2023. https://static1.squarespace.com/static/5eb03a8225db790ffcb446cf/t/61688603a2642a5336a46881/1634240003520/Gene_List_SO-SPEC-003v5.pdf **10**. Tempus. Accessed April 24, 2023. https://www.tempus.com/oncology/genomic-profiling/ **11**. Foundation Medicine. Accessed April 24, 2023. https://www.foundationmedicine.com/test/foundationone-cdx **12**. Foundation Medicine, Accessed October 2, 2023. https://www.foundationmedicine.com/test/foundationone-liquid-cdx **13**. Guardant Health. Accessed April 24, 2023. https://guardant360cdx.com/gene-list/ **14**. US Food and Drug Administration. Accessed April 24, 2023. https://www.fda.gov/medical-devices/recently-approved-devices/guardant360-cdx-p200010s001 **15**. US Food and Drug Administration. Accessed April 24, 2023. https://www.fda.gov/news-events/press-announcements/fda-unveils-streamlined-path-authorization-tumor-profiling-tests-alongside-its-latest-product-action **16**. NeoGenomics. Accessed April 24, 2023. https://neogenomics.com/sites/default/files/NeoGenomicsTestCatalog.pdf **17**. Northstar Onc. Accessed Sept 14, 2023. https://northstaronc.com/wp-content/uploads/2023/07/BTO-Northstar-Select-Spec-Sheet-_072623.pdf **18**. Paradigm. Accessed April 24, 2023. https://www.therapyselect.de/sites/default/files/downloads/pcdx/pcdx_tumor-profiling-menu_en.pdf **19**. PathGroup. Accessed April 24, 2023. http://www.pathgroup.com/oncology/smartgenomics/

Visit FindTheFusions.com to download this presentation.

Comprehensive Genomic Profiling Is Associated With Improved OS in NSCLC Patients[1]

rwOS From aNSCLC Diagnosis, by Testing Type and Receipt of Systemic Therapy[1]



Treated patients receiving CGP testing during follow-up **had greater median rwOS (22 months vs 15 months)[1]**

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)

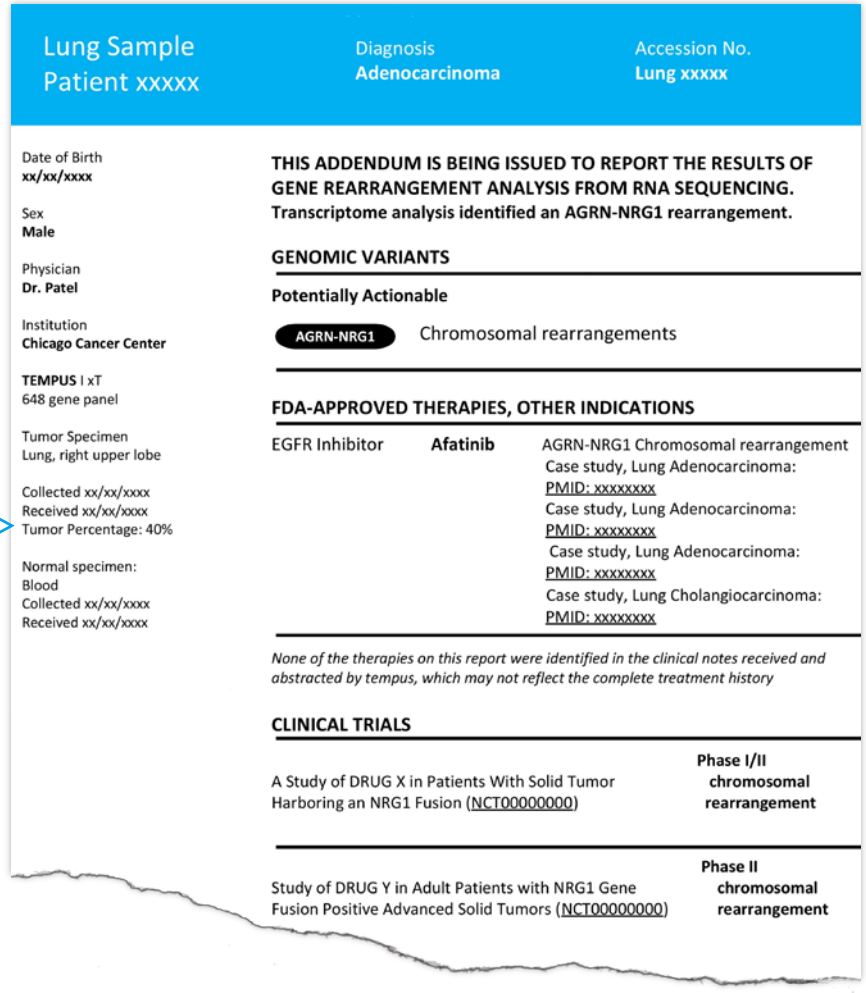
Predictors of rwOS by Testing Type (Cox proportional hazards model)

	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. Simon G et al. Poster presented at: European Society for Medical Oncology; October 21, 2023; Madrid, Spain. Poster #1422P.

Most NGS Reports Highlight Actionable Information



Lung Sample
Patient xxxxx

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**

Study of DRUG Y in Adult Patients with NRG1 Gene Fusion Positive Advanced Solid Tumors (NCT00000000) — **Phase 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 September 1, 2022. Accessed April 24, 2023. 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 health 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

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 outcomes[4]
- ***NRG1* is an important pathogenic gene fusion that can occur across tumor types** and is reported to be associated with poor 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

Thank you!