SIMPLIFYING YOUR APPROACH TO PRECISION ONCOLOGY

Understanding Pathogenic Gene Fusions and the Role of RNA-Based Genomic Testing



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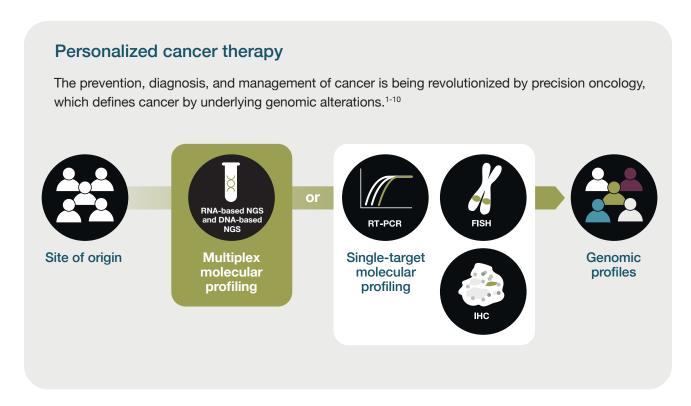
NGS, next-generation sequencing; NRG1, neuregulin 1.

FIGHTING CANCER STARTS BY FINDING ITS FINGERPRINT

HOW ARE GENOMICS CHANGING THE FUTURE OF ONCOLOGY?

Oncology is evolving from thinking about cancer according to site of origin to thinking about cancer according to tumor genomics¹⁻⁹

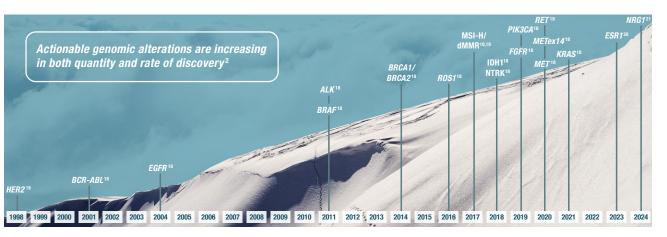
Tumors can have distinct histologies, sites of origin, and genomic signatures. Over the course of the past decade, the understanding of the centrality of tumor genomics has been increasingly driving oncology, including disease classification, patient selection, and clinical trial design. With 18 new FDA-approved personalized treatments in 2024, these therapies comprise at least a quarter of all new drug approvals annually for the past decade. Just over 10 years ago, they represented less than 10% of approvals. This rapid growth underscores the increasingly central role of tumor genomics in guiding treatment decisions.



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.⁶

Understanding the genomic and oncogenic drivers of a patient's cancer can help clinicians develop a more tailored approach to care^{5-7,10}

As the understanding of cancer biology has advanced, both the quantity and rate of discovery of genomic alterations have accelerated.² In response, investigators are meeting the demand for ways to target them.^{2-8,11} More recent studies have estimated higher percentages of actionable alterations, which are only expected to increase as new molecular entities are developed.^{8,12-17}



MSI-H/dMMR, microsatellite instability-high/mismatch repair deficiency.

Individual genomic alterations may be rare, but alterations in totality are found in a significant percentage of patients with cancer¹²⁻¹⁷

While treatments are still being developed, it is estimated that \sim 38% of patients have an actionable genomic alteration.²²

A genomic alteration is typically defined as actionable when there is a potential therapeutic target that can mitigate the oncogenic consequences of the disrupted pathway; although across clinical studies, the definition of actionable can vary substantially.^{12,17}

Point mutations and pathogenic gene fusions are among the most common genomic alterations driving cancer²³

Point mutations (eg, KRAS, BRAF, EGFR) are changes in DNA base pairs.^{2,24}

Pathogenic gene fusions (eg, *ALK*, *NTRK*, *ROS1*, *RET*, *NRG1*) typically occur when 2 different genes join to form an abnormal hybrid gene. ^{2,25,26} Genes involved in fusions are not located next to one another but are from separate chromosomal loci. ²⁷ Gene fusions can be comprised of multiple fusion partners. ²⁸

PRECISION ONCOLOGY PROVIDES A UNIQUE OPPORTUNITY TO IMPROVE CLINICAL OUTCOMES^{1-12,17,26,29-33}

Targeting genomic alterations can lead to better outcomes for patients

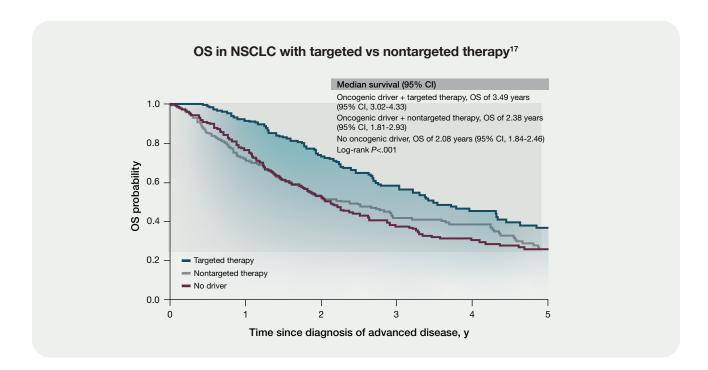
Precision oncology benefits have been reported to potentially include significant improvements in objective response rate (ORR), overall survival (OS), progression-free survival (PFS), and quality of life (QOL) for certain well-characterized molecular alterations with approved targeted therapies compared with conventional chemotherapies approved for the same or overlapping indication and line of therapy. 1-5,7-10,12 With improved outcomes, patients may potentially be able to avoid cycles of trial and error, as well as adverse physical and financial impacts from the cumulative effects of multiple rounds of conventional therapies.8

From 2006 to 2018, there was a 7x increase in the number of patients estimated to benefit from genome-based therapy.³¹

In both of the following studies on NSCLC and pancreatic cancer, OS was improved in patients who received therapies directed toward their specific alterations. 17,32

Overall survival in NSCLC

In a study of 938 patients with metastatic lung adenocarcinomas and a Southwest Oncology Group (SWOG) performance status of 0 through 2, tumors were tested for 10 oncogenic drivers. The study collected information from patients, therapies, and OS. Three-hundred sixty (38%) patients had no identified oncogenic driver, while 578 (62%) had actionable oncogenic drivers. Of those with actionable oncogenic drivers,



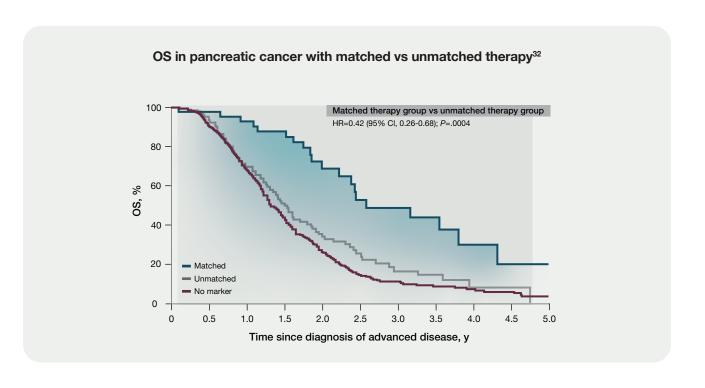
decision-making in cancer care for 318 patients (55%) was not impacted, while 260 patients (45%) had identified drivers that impacted cancer management. Patients who received a matched therapy for their actionable molecular alterations had longer OS of 3.49 years (95% CI, 3.02-4.33) vs 2.08 years (95% CI, 1.84-2.46) for those with no known oncogenic drivers (log-rank *P*<.001).¹⁷

Overall survival in pancreatic cancer

Of 1856 patients with pancreatic cancer who were referred to the Know Your Tumor (KYT) program between June 16, 2014, and March 31, 2019, 1082 (58%) received personalized reports based on their molecular testing results.³²

With a median follow-up of 383 days (IQR, 214-588), patients with actionable molecular alterations who received a matched therapy (n=46) had significantly longer median OS than patients who only received unmatched therapies (n=143; 2.58 years [95% CI, 2.39 to not reached] vs 1.51 years [95% CI, 1.33-1.87], respectively; HR=0.42 [95% CI, 0.26-0.68]; P=.0004).³²

The 46 patients who received a matched therapy also had longer OS than the 488 patients who did not have an actionable molecular alteration (2.58 years [95% CI, 2.39 to not reached] vs 1.32 years [95% CI, 1.25-1.47], respectively; HR=0.34 [95% CI, 0.22-0.53]; P<.0001). Median OS did not differ between patients who received unmatched therapy and those without an actionable molecular alteration (HR=0.82 [95% CI, 0.64-1.04]; P=.10).



NSCLC, non-small cell lung cancer.

THE CLINICAL CONSEQUENCES OF PATHOGENIC GENE FUSIONS

NRG1: A DANGEROUS PATHOGENIC GENE FUSION

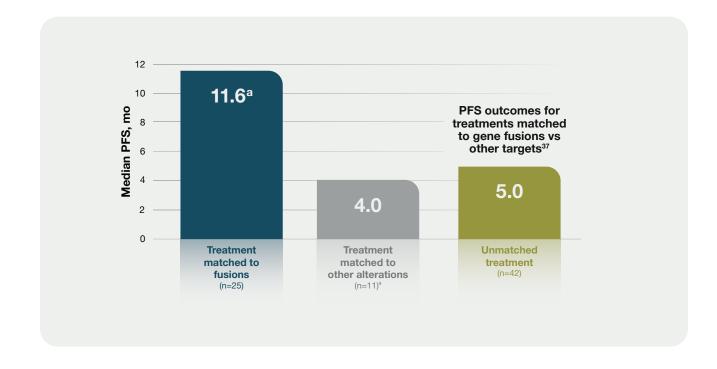
Pathogenic gene fusions are a contributing factor in 1 in 6 cancers³³

Among 9624 patients who had their tumors genetically tested with RNA-based sequencing, pathogenic gene fusions were found in 16.5% of samples.³³ Fusions can occur across tumor types and account for approximately 20% of cancer morbidity.^{26,33-37}

Pathogenic gene fusions are an independent poor prognostic factor

A study of 594 patients with fusion-driven lung cancer measured outcomes over time. Patients with a high number of fusions had shorter median OS (35.6 months; 95% CI, 27.2-43.9) compared with patients with an intermediate (49.5 months; 95% CI, 23.9-75.1) or low number of fusions (62.3 months; 95% CI, 44.6-80.1; likelihood ratio test, P=.008). This relationship persists even when controlled for factors such as age, sex, stage, cancer type, and smoking status.³⁶

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.³⁷



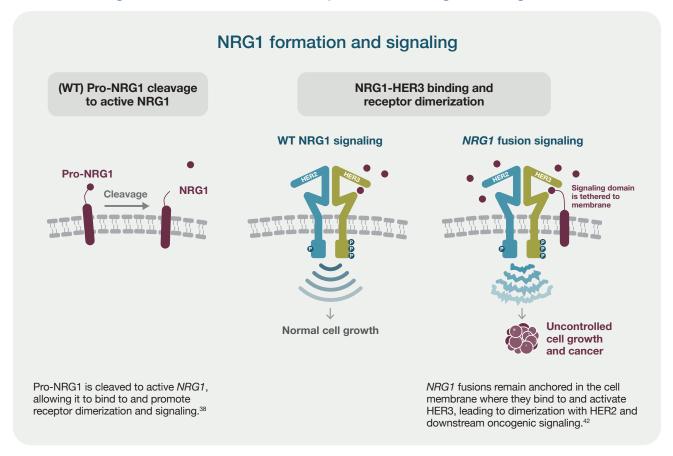
A pathogenic gene fusion receiving increasing attention is *NRG1*, which has been associated with aggressive features and poor outcomes^{25,36,38-41}

NRG1 is a key signaling protein involved in proliferation and survival. Normal NRG1 signaling is tightly controlled.^{35,38} NRG1 is normally inactive until it is cleaved by proteases at the cell surface. Extracellular binding of NRG1 activates tightly regulated cell growth pathways, including PI3K, AKT, and mTOR. When these pathways are dysregulated, they are capable of becoming oncogenic drivers.^{38,39}

Abnormal *NRG1* fusions can lead to uncontrolled growth and cancer.³⁵ They can induce the formation of heterodimers, leading to the pathologic activation of signaling pathways and abnormal cell proliferation.^{38,41}

NRG1 fusions are heterogenous and can have many different partners and breakpoints.^{25,38,39} *NRG1*+ NSCLC possesses histologic features associated with growth, recurrence, invasiveness, metastasis, resistance to therapy, and worse prognosis.^{9,25,36,38-40} *NRG1*+ NSCLC responds poorly to available therapies and is associated with lower OS, DFS, and PFS.^{9,25,26,29-41}

Pathogenic NRG1 fusions are capable of driving cancer growth³⁵⁻³⁸



DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; NE, not estimable; *NRG1*+, neuregulin 1 fusion positive; WT, wild type.

^aTwelve 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 pairwise comparison analysis.³⁷

NRG1 ACROSS TUMOR TYPES

AGGRESSIVE HISTOLOGICAL FEATURES

NRG1 gene fusions have been identified across many solid tumors and generally occur in the absence of other driver mutations^{25,35,38}

NRG1 fusion frequency estimates



Overall (<1%)^{42,43}
Enrichment
Invasive mucinous lung
adenocarcinoma



Overall (<2%)^{43,46}
Enrichment
KRAS wild-type pancreatic cancer (up to 3%)^{46,47}



Overall (<1%)⁴³

(up to 31%)9,44,45

Breast, cholangiocarcinoma, colorectal, gallbladder, sarcoma, ovarian cancers, renal cell carcinoma, etc⁴³

NRG1 fusions are associated with poor outcomes and resistance to therapies²⁵

In a retrospective global registry study, *NRG1*+ NSCLC was associated with limited response to available therapies. Of 110 patients with *NRG1*+ lung cancer included in the eNRGy1 global multicenter registry, 103 had adenocarcinoma, of which 59 (57%) were IMA, 29 (28%) were nonmucinous, and 15 (15%) were "other" or "unspecified."²⁵

Activity of systemic therapy in NRG1+ NSCLC ^{25,a}	ORR, %	Median PFS, mo (95% CI)
Platinum-doublet chemotherapy (n=15)	13	5.8 (2.2-9.8)
Taxane-based chemotherapy (∩=7)	14	4.0 (0.8-5.3)
Combination chemotherapy and immunotherapy (n=9)	0	3.3 (1.4-6.3)
Single-agent immunotherapy (∩=5)	20	3.6 (0.9-undefined)
Targeted therapy with kinase inhibitor (n=20)	25	2.8 (1.9-4.3)

^aPatients either diagnosed with or who developed metastatic disease during the course of their disease.²⁵

NRG1 fusions have aggressive histological features

Chang et al conducted a molecular and clinicopathologic analysis of 200 cases of pulmonary IMA diagnosed between 2009 and 2019. Genomic analysis was conducted using hotspot mutation testing, targeted DNA sequencing, and targeted RNA sequencing. The investigators found that 92% of the IMA tumors that were *NRG1+* possessed aggressive histological features associated with poor outcomes compared with 54% of *KRAS+* tumors and 61% of tumors with other driver alterations. Findings were consistent with other studies suggesting that *NRG1+* lung and gastric tumors are associated with increased infiltrative tumor growth, as well as lymphovascular, neural, and desmoplasmic stromal invasion, which are associated with poor outcomes. 99

Growth

In the same study, Chang et al also measured primary tumor size pathologically in resected tumors and radiologically in unresected tumors. Among all tumors tested, gene fusions were identified in a total of 24 IMAs, including 12 (50%) with *NRG1*, 6 (25%) with *ALK*, 2 (8%) with *ROS1*, and 1 each with *ERBB2*, *NTRK1*, *FGFR2*, and *FGFR3*. The investigators found dramatically increased primary tumor size at diagnosis for *NRG1*+ vs *KRAS*+ and other IMA tumors (7.7 cm vs 3.9 cm vs 5.5 cm, respectively; *P*=.0004).^b This study documented more aggressive histological and clinical characteristics of IMAs with *NRG1* fusions. The presence of these characteristics has been found to correlate with worse prognosis for patients with IMA.⁴⁴

Migration

Shin et al studied a cohort of 59 patients with IMA who underwent curative surgical resection, 16 of whom had *NRG1* fusions. The majority of cases with *NRG1*+ samples had pathological stage I disease. Investigators found that an *SLC3A2-NRG1* fusion promoted increased tumor volume, as well as cancer cell proliferation and migration, using a shedding and juxtacrine method through *ERBB2-ERBB3* heterocomplexes. This association strengthened with increased *NRG1* fusion protein expression.° Cancer cell migration induced by the *SLC3A2-NRG1* fusion protein was due to an increase in pFAK and pSrc by the *SLC3A2-NRG1* fusion protein—this was not induced by *SLC3A2-NRG1* EGF. Results indicated that the EGF domain in the *NRG1* part of the *SLC3A2-NRG1* fusion augmented cell proliferation and migration.°

EGF, epidermal growth factor; IMA, invasive mucinous adenocarcinoma.

^bIn a study by Chang et al (2021), samples from 200 IMA cases were reviewed by 2 thoracic pathologists. Primary tumor size was measured pathologically in resected tumors and radiologically in unresected tumors. Presence of tumor necrosis and stromal invasion, defined by stromal desmoplasia surrounding invasive glands or nests of tumor cells, were recorded.⁴⁴

^oShin et al (2016) tested 59 IMA samples obtained from patients who underwent curative surgical resection, identifying 13 *SLC3A2-NRG1* fusions (27% frequency). Tumor xenografts in nude mice were generated for measuring tumor volume and tumor weight. Tumor proliferation, volume, and weight were analyzed in cancer cells ectopically expressing *SLC3A2*, *NRG1*, and *SLC3A2-NRG1*.⁹

UNIQUE PATTERNS OF METASTASIS

THE EVOLUTION OF GENOMIC TESTING

Metastatic potential in NRG1+ tumors

IMA has been reported to represent 3% to 5% of adenocarcinomas overall. A recent study evaluated the histology and genomic profiles of tissue samples from 200 cases of IMA. *KRAS* alterations were identified in 151 of the IMA samples, and gene fusions were identified in 24 samples. Half of the fusions (12) were *NRG1+*. *NRG1* fusions were associated with significantly lower cigarette exposure compared with *KRAS* fusions (5.9 vs 20 pack-years, respectively). Presence of metastasis at diagnosis, as well as the frequency of extrathoracic metastases, were higher for *NRG1* vs *KRAS*.⁴⁴



NRG1+ tumors have a higher rate of metastasis at diagnosis compared with KRAS+ tumors (67% vs 32%, respectively)⁴⁴



NRG1+ tumors are 10x more likely to have concurrent intra- and extrathoracic metastases than KRAS+ tumors (50% vs 5%, respectively)⁴⁴

Similar results were observed in a study by Drilon et al about the clinicopathologic features of *NRG1* fusion–driven lung cancers, in which data were collected from a consortium of 22 centers from 9 countries. At the time of diagnosis, most (71%, n=58/82) patients had nonmetastatic (stages I-III) disease. In patients with metastatic *NRG1*-driven disease diagnosed at any time during their disease course (n=44), extrathoracic metastases were found in 43% (n=19/44) of patients.²⁵

Most common sites of NRG1+ extrathoracic metastases in IMA²⁵







Conventional testing methods

RT-PCR, FISH, and IHC are biomarker screening methods that were developed to detect single molecular targets and may fall short of detecting pathogenic gene fusions.^{34,48,49}

Specifically, limitations include:

- Inability to identify the full breadth of genomic alterations^{34,50}
- Limited ability to identify the full breadth of fusion partners and breakpoints^{34,49}
- May require a significant amount of tissue and can exhaust tissue samples⁵¹







The advent of next-generation sequencing

Since the completion of the National Human Genome Project was announced in 2003, genome sequencing technology has improved dramatically. In particular, the decade that followed saw revolutionary advances in sequencing technologies that fundamentally changed the nature of genomics. The advent of "next-generation" sequencing in 2008 welcomed significant improvements in both accuracy and efficiency, bringing with it a rapid reduction in costs and turnaround time.⁵²

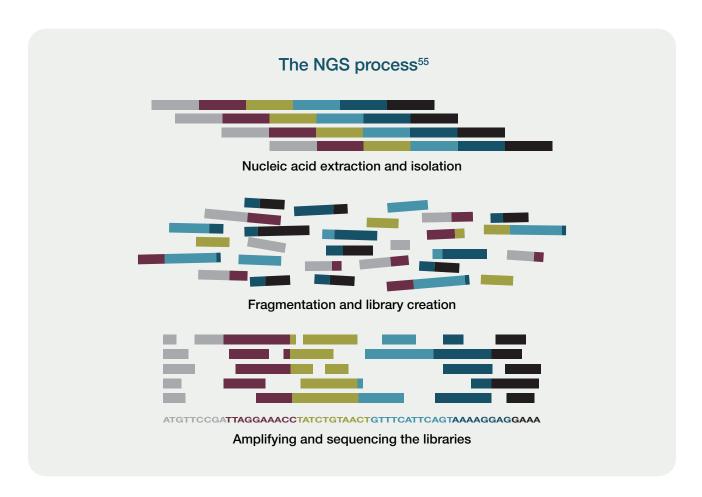
NEXT-GENERATION SEQUENCING CAN DETECT A BROAD RANGE OF GENOMIC ALTERATIONS^{2,5,48,53}

DNA-BASED NGS ALONE CAN MISS PATHOGENIC GENE FUSIONS^{57,58}

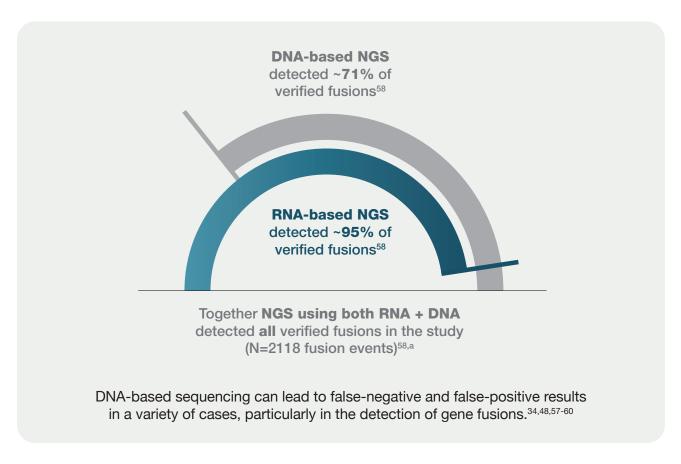
NGS has emerged as a key tool in profiling many solid tumors⁵³

NGS is a high-throughput genomic sequencing technology that allows for the simultaneous analysis of numerous alterations; NGS can be DNA-based, RNA-based, or both^{48,54}

NGS is a young field, with the first machines entering the market less than 2 decades ago. In less than a decade, NGS became a cornerstone of molecular biology and genetics. More recently, NGS systems have been introduced that allow for massively parallel sequencing reactions. These systems are capable of analyzing millions, or even billions, of sequencing reactions at the same time, dramatically increasing the efficiency of sequencing genomes. Unlike some tools, NGS is flexible and can be applied in different situations, ranging from exome to small RNAs.^{6,55,56}



Comprehensive testing with RNA-based NGS, including DNA and RNA sequencing, is recommended to capture what DNA-based NGS alone can miss^{25,57}



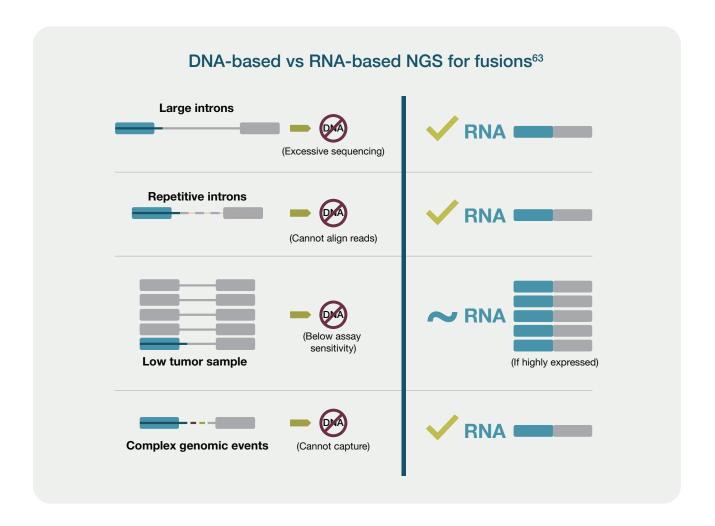
Comprehensive genomic sequencing—a more efficient option that sequences both RNA and DNA simultaneously—should take place at diagnosis, or as early as possible in the course of disease, to maximize the range of treatment options available to patients.^{29,60}

WHY IS RNA-BASED NGS MORE COMPREHENSIVE FOR DETECTING PATHOGENIC GENE FUSIONS? 57,59-63

RNA-BASED NGS IS ESSENTIAL FOR OPTIMIZING DETECTION OF MANY *NRG1* FUSIONS^{57,59-63}

Advantages of RNA-based NGS

- Detects gene expression and many structural variants^{1,34,57,61}
- Reduces many of the technical challenges involved in sequencing long introns^{48,57,59-63}
- Can improve the detection rate of DNA-based NGS alone and provide more comprehensive detection results^{16,57,59-63}
- May enable oncologists to match therapy to the driving fusion, which wouldn't have otherwise been identified, potentially leading to improved clinical responses¹⁶



Detecting NRG1 pathogenic gene fusions

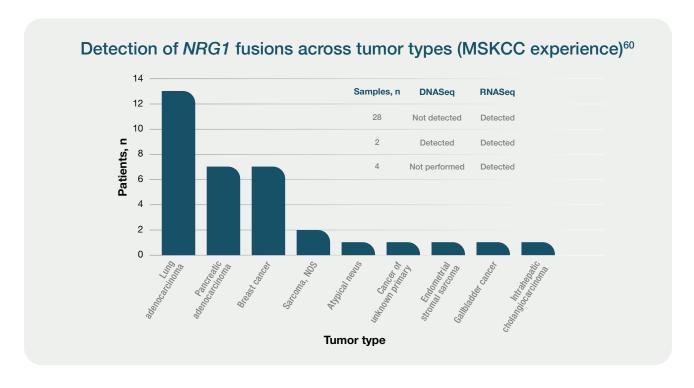
- NRG1 fusions are more likely to be missed without the use of RNA-based NGS^{57,59-63}
- The diversity of *NRG1* fusion partners and breakpoints and the large intronic regions of the *NRG1* gene can make detection more challenging^{48,57,59-61,63}



In a retrospective study by the Memorial Sloan Kettering Cancer Center,

RNA-based NGS detected more *NRG1* fusions than DNA-based NGS⁶⁰

Both DNA-based and RNA-based NGS were performed on 30 *NRG1*+ IMA samples. Of these, 28 were detected by RNA-based NGS but not DNA-based NGS. The remaining 2 were detected by both. Four additional samples that did not undergo DNA-based NGS were detected by RNA-based NGS.⁶⁰



Of the 60,000 tumor specimens that have undergone molecular profiling by DNA-based NGS at MSKCC, *NRG1* fusions were detected at a rate of just 20% of the estimated prevalence in the population. This further indicates that DNA-based NGS by itself is not the optimal approach for the comprehensive detection of *NRG1* fusions. It can be a challenge to detect *NRG1* fusions with standard assays, and the tests that can detect them are not always performed.⁶⁰

MSKCC, Memorial Sloan Kettering Cancer Center; NOS, not otherwise specified

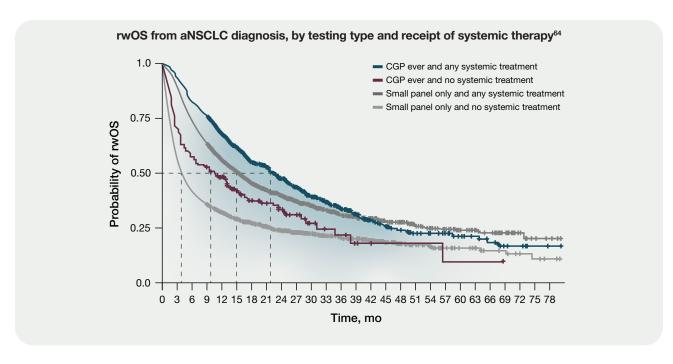
COMPREHENSIVE GENOMIC PROFILING IS ASSOCIATED WITH IMPROVED OUTCOMES⁶⁴

IT IS TIME TO TEST FOR *NRG1* FUSIONS

The impact of genomic profiling

A real-world, retrospective study evaluated the clinical impact of CGP vs small panel testing in patients with aNSCLC. Using data from community oncology settings, researchers compared outcomes related to biomarker detection, use of targeted therapies, and rwOS.⁶⁴

Patients tested with CGP were more likely to have actionable biomarkers identified (32% vs 14%; P<.001) and to receive matched targeted therapies (39% vs 29%; P<.001).



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)



Treated patients receiving CGP testing during follow-up had higher median rwOS (22 months vs 15 months)⁶⁴

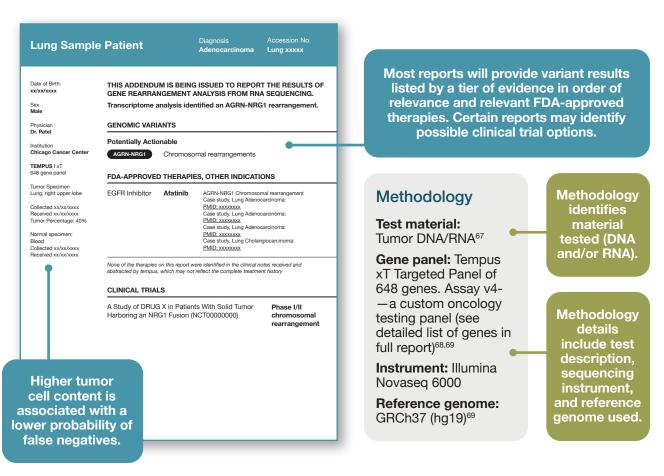
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) include RNA-based NGS^{65,66}

- Pancreatic adenocarcinoma: RNA-based NGS is a preferred option to detect gene fusions⁶⁵
- NSCLC: RNA-based NGS should be considered to maximize detection of fusion events⁶⁶



Detecting *NRG1* fusions through comprehensive testing is a critical step toward optimizing care and potentially improving outcomes^{65,66}

Most NGS reports highlight actionable information⁶⁷



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

NCCN, National Comprehensive Cancer Network.

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INCOMPLETE KNOWLEDGE HAS CONSEQUENCES

Detecting pathogenic gene fusions in cancer is critical to help improve outcomes for patients^{16,33,44}



Oncology is evolving from thinking about cancer according to site of origin to thinking about cancer according to tumor genomics.¹⁻⁹

- Pathogenic gene fusions are becoming increasingly actionable^{2,18,21}
- Targeting these genomic alterations may potentially lead to improved outcomes^{17,32}



NRG1 is an important pathogenic gene fusion that can occur across solid tumors and is associated with poor outcomes and resistance to therapies in NRG1+ NSCLC.^{25,39,43}



RNA-based NGS is capable of supporting broader identification of genomic alterations, including pathogenic gene fusions such as *NRG1*, when compared with DNA-based methods.^{48,53,54,57}

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