The Journal of Molecular Diagnostics, Vol. , No. , 2023



the **Journal of Nolecular** Diagnostics

jmdjournal.org

RNA Sequencing Identifies Novel *NRG1* Fusions in Solid Tumors that Lack Co-Occurring Oncogenic **QI** Drivers

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Accepted for publication March 30, 2023.

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NRG1 gene fusions are rare, therapeutically relevant, oncogenic drivers that occur across solid tumor types. To understand the landscape of NRG1 gene fusions, 4397 solid tumor formalin-fixed, paraffinembedded samples consecutively tested by comprehensive genomic and immune profiling during standard care were analyzed. Nineteen NRG1 fusions were found in 17 unique patients, across multiple tumor types, including non-small-cell lung (n = 7), breast (n = 2), colorectal (n = 3), esophageal (n = 2), ovarian (n = 1), pancreatic (n = 1), and unknown primary (n = 1) carcinomas, with a cumulative incidence of 0.38%. Fusions were identified with breakpoints across four NRG1 introns spanning 1.4 megabases, with a mixture of known (n = 8) and previously unreported (n = 11) fusion partners. Co-occurring driver alterations in tumors with NRG1 fusions were uncommon, except colorectal carcinoma, where concurrent alterations in APC, BRAF, and ERBB2 were present in a subset of cases. The overall lack of co-occurring drivers highlights the importance of identifying NRG1 gene fusions, as these patients are unlikely to harbor other targetable alterations. In addition, RNA sequencing is important to identify NRG1 gene fusions given the variety of fusion partners and large genomic areas where breakpoints can occur. (J Mol Diagn 2023, ■: 1–13; https://doi.org/10.1016/j.jmoldx.2023.03.011)

The neuregulin 1 gene (NRG1) encodes an epidermal growth factor (EGF) family protein that mediates signaling Q8 Q9 via ERBB receptor pathways. NRG1 produces six different isoforms with expression varying across different tissue types through alternative promoters and splicing events.¹ In normal cells, NRG1 promotes the growth and differentiation of epithelial and other cell types. In human cancer, NRG1 promotes cell proliferation (CP) through gene rearrangement events that preserve the EGF domain, leading to constitutive activation of mitogen-activated protein kinase and phosphatidylinositol 3-kinase signaling pathways.² NRG1 is typically the 3' partner in these gene fusions with a wide array of genes as the 5' partner.³ There are a few recurrent partners, including CD74, SLC3A2, VAMP2, and PCM1, with many novel fusions identified in each newly

published cohort.⁴ To date, NRG1 fusions have been identified across all solid tumors at a prevalence of < 1%.^{3,5} The incidence of NRG1 fusions is higher in gallbladder

Disclosures: E.S., B.R.A., M.N., S.P., R.A.P., G.K., A.C., M.S., K.S.S., A.G., T.J.J., P.R., and S.H.R. are employed by and have equity interest in Labcorp. S.Z. and J.C. is employed by and has equity interest in Labcorp, and is employed by Roswell Park Comprehensive Cancer Center. R.K. is employed by and has equity interest in Labcorp; and has received research funding from Incyte, Genentech, Merck Serono, Pfizer, Sequenom, Foundation Medicine, Guardant Health, Grifols, and Konica Minolta; consultant fees from LOXO, X-Biotech, Actuate Therapeutics, Roche, and NeoMed; receives speaker fees from Roche; and has equity in IDbyDNA and CureMatch, Inc. B.G. is a consultant for Celgene, Cook Medical, Merrimack, 05 Foundation Medicine, Ipsen, Bristol Myers Squibb, Exelixis, Terumo Interventional Systems, and Taiho Oncology. P.S. is employed by and has **Q6 Q34** 123 124 equity interest in Illumina.

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cancer, pancreatic ductal adenocarcinoma, and renal cell carcinoma, at 0.5% in each, but is present across all solid tumors at a prevalence of approximately 0.2%.³

NRG1 fusions are key genomic drivers in patients with solid tumors that otherwise lack classic targetable alterations. As has already been shown for other clinically significant fusion genes, such as *ALK*, *NTRK1*, *NTRK2*, or *NTRK3*, variation in testing technologies can result in significant differences in the likelihood of fusion identification.⁶ Single-gene tests, hotspot panels, inadequately baited DNA-based next-generation sequencing (NGS), and panels that lack *NRG1* have technical limitations precluding accurate detection of fusions. Given these challenges, the American Society of Clinical Oncology recently released guidelines preferentially recommending RNA sequencing to detect gene fusions.⁷

Routine assessment for NRG1 fusions is not yet part of the standard workup for all solid tumors, and many available NGS panels do not assess for NRG1 fusions, so many pa-tients remain undetected. Using highly sensitive RNA-sequencing methods, such as hybrid capture, to detect fu-sions is optimal for comprehensive identification of targetable alterations, including NRG1 fusions in solid tumors. In non-small-cell lung cancer (NSCLC), National Compre-hensive Cancer Network Clinical Practice Guidelines in Oncology already recommend biomarker testing be per-formed using broad NGS panels to detect druggable rear-rangements or fusions involving ALK, NTRK, ROS1, and RET with consideration of RNA sequencing if not previously performed.⁸ In pancreatic cancer, National Comprehensive Cancer Network guidelines specifically recommend molec-ular profiling to identify uncommon, targetable genomic alterations, including NRG1 fusions.^{9,10} NRG1 testing is of particular importance in patients with locally advanced or metastatic pancreas cancer as they have a poor prognosis with standard-of-care therapies. NRG1 fusions are especially enriched in *KRAS*-negative pancreatic carcinomas.¹¹

Detection of *NRG1* fusions is important, and as is often the case with oncogenic drivers, *NRG1* fusions are typically mutually exclusive with other targetable oncogenic drivers. In rare cases, *NRG1* fusions are present with other driver alterations, such as *BRAF*, *KRAS*, or *ALK* rearrangements.^{3,12}

The immunotherapy marker landscape in patients with *NRG1* fusions is relatively unexplored, and there has been minimal investigation of treatment sequence in these patients with respect to targeted therapy versus immunotherapy. Only one prior study was identified that has examined PD-L1 expression and tumor mutation burden (TMB) in patients with *NRG1* fusions, where cases were predominantly low for both PD-L1 and TMB.¹³

Targeted therapies developed for EGF receptor and HER3 (ERBB3) have been repurposed for use in *NRG1* fusion—positive cancers.⁴ Afatinib, an EGF receptor inhibitor, has shown partial responses, including progression-free survival of 5.5 months in two patients with *NRG1*-*ATP1B1*—positive pancreatic ductal adenocarcinoma and

progression-free survival of up to 10 months in a patient with lung IMA harboring an NRG1-CD74 fusion.^{14,15} In a Q12 multicenter registry, 4 (of 12) patients treated with afatinib showed objective responses with a median progression-free survival of 3.5 months.¹⁶ Resistance to afatinib was also seen in patients with lung cancer with NRG1 fusions previously treated with anti-ERBB3 therapy.¹⁷ NRG1 fusions may also represent a resistance mechanism to alectinib, an ALK Q13 inhibitor. A recent study evaluating the novel NRG1-RALGAPA1 fusion was assessed using engineered cells and was found to be resistant to ALK inhibition through loss of phosphorylation of SHP2 ALK adaptor protein.¹⁸ Q14 Currently, patients with NRG1 fusions are actively recruited for ongoing clinical trials for seribantumab (an ERBB3 inhibitor)¹⁵ and zenocutuzumab¹⁶ (an ERBB2/ ERBB3 bispecific antibody),^{19,20} both of which have US Food and Drug Administration fast-track designation and offer a promising approach to help change the standard-ofcare clinical management based on early results showing a 34% overall response rate in solid tumors.²¹

This study describes the landscape of *NRG1* fusions detected across solid tumors by RNA sequencing, and characterizes their associations with other genomic alterations, TMB, PD-L1 status, CP signatures, and tumor immunogenic signatures (TIGSs).

Materials and Methods

Patient Cohort

Approval for this study was obtained from the Western Institutional Review Board protocol number 1340120. Comprehensive genomic and immune profiling data from 4397 formalin-fixed, paraffin-embedded patient samples tested during routine clinical care were analyzed. Patient demographics and tumor information were abstracted from the pathology reports and requisition forms submitted at the time of processing. These samples spanned a wide variety of solid tumor types, including, but not limited to, NSCLC (n = 1696), colorectal (n = 611), breast (n = 369), esophageal (n = 117), pancreatic (n = 157), ovarian (n = 105), and unknown primary (n = 233) carcinomas.

Comprehensive Genomic and Immune Profiling

Comprehensive genomic and immune profiling was performed using the OmniSeq (Buffalo, NY) INSIGHT assay performed in a laboratory accredited by the College of American Pathologists and certified by the Clinical Laboratory Improvement Amendments. As previously described, OmniSeq INSIGHT is an NGS-based *in vitro* diagnostic device for the detection of genomic variants, signatures, and immune gene expression in formalin-fixed, paraffinembedded tumor tissue.²² Briefly, DNA sequencing with hybrid capture is used to detect small variants in the full exonic coding region of 523 genes (single- and

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multi-nucleotide substitutions, insertions, and deletions), copy number alterations in 59 genes (gains and losses), as well as analysis of microsatellite instability and TMB genomic signatures. RNA is sequenced with hybrid capture approach to detect fusions and splice variants in 55 genes, in addition to mRNA expression in 64 immune genes.

Amplicon-based targeted NGS for digital gene expression (RNA sequencing) was used to interrogate a panel of 395 immune genes (64 clinically validated), including T-cell receptor signaling, tumor-infiltrating lymphocytes, and cancer testis antigens. Absolute reads were normalized using a non-transcript control to determine and subtract background and then compared with housekeeping genes to give a normalized reads per million (nRPM) for each gene. Expression ranks for each gene were calculated by converting nRPM values to a percentile rank between 0 and 100 as compared against a reference population of 735 solid tumor samples spanning 35 tumor types.²³

A TIGS based on the mean nRPM rank of 161 immune genes was calculated to describe the degree of immune activity in each tissue sample.²⁴ TIGS is considered high when \geq 67, medium when \geq 45 and <67, and low when <45. A CP signature was also calculated by taking the mean nRPM for 10 cell proliferation—related genes to characterize the tumor proliferation state in each tissue sample.²⁵ The CP signature is considered high when \geq 67, medium when \geq 35 and <67, and low when <35.

Immunohistochemical Studies

For all tumor types, PD-L1 expression on the surface of tumor cells was measured by Dako PD-L1 immunohistochemistry (IHC) 22C3 pharmDx (Agilent, Santa Clara, CA). Expression was scored by a board-certified anatomic pathologist according to published guidelines²⁶ as a tumor proportion score (TPS), which is the percentage of tumor cells with positive linear membranous staining.

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NRG1 Fusions Are Present Across Numerous Solid Tumor Types and Histologic Types

A total of 4397 unique patient samples across 34 solid tumor types were sequenced. From those cases, 19 *NRG1* fusions (involving the 3' region of *NRG1*) in 17 unique patients were identified for an overall patient prevalence of 0.4%. The median age of patients with *NRG1* fusions was 65 years (range, 41 to 86 years), with 65% women and 35% men (Table 1 and Supplemental Table S1).

Seven *NRG1* fusion cases were detected in patients with NSCLC, representing 0.41% of all NSCLC cases sequenced (Table 1 and Figure 1). Tissue specimens for six of seven NSCLC cases were from the primary site, with one distant metastasis. *NRG1* fusions in NSCLC tumors were identified

in many NSCLC histologic types, including mucinous adenocarcinoma (Figure 2A), large-cell neuroendocrine ^[F2] carcinoma (Figure 2B), poorly differentiated adenocarcinoma (Figure 2C), and squamous cell carcinoma (Figure 2D).

NRG1 fusions were also identified in tumor types other than NSCLC, including breast [n = 2 of 369 (0.54%)], colorectal [CRC; n = 3 of 611 (0.49%)], esophageal [n = 2 of 117 (1.71%)], ovarian [n = 1 of 105 (0.95%)], and pancreatic [n = 1 of 157 (0.64%)] carcinomas and carcinoma of unknown primary [n = 1 of 233 (0.43%)] (Table 1 and Figure 1). Half of the *NRG1* fusions in these cases were identified in tissue specimens from primary sites, and half were identified from distant metastatic sites.

Genomic Landscape of NRG1 Fusions

NRG1 has a complex gene structure, with six different promoters termed type I through type VI. All exons and introns were labeled with respect to the type I promoter (NM_013956.5, https://www.ncbi.nlm.nih.gov/nuccore/167 7537276, last accessed April 24, 2023).^{1,27,28} Fusion breakpoints were located in introns 1, 2, 3, and 9 as well as the intron upstream to exon 1 (intron 1 for the type II, IV, and V promoters), which collectively span 1.4 megabases (Mb) (Table 2 and Supplemental Table S2). The functional [12] EGF-like domain is in exons 6 and 7, with a transmembrane domain in exon 8 (Figure 3). NRG1 gene fusions canoni-^[F3] cally have a 5' partner gene fused to NRG1 at the 3' end. Twelve novel fusion partners were identified: DDHD2, FUT10, IKBKB, TMEM66, ZCCHC7, TNRFSF10B, BIN3, BRE, CCAR2, CD9, ERO1L, and KCTD9; two previously identified fusion partners were identified twice: CD74 and SLC3A2, and PCM1; and one previously identified fusion partner was identified once: UBXN8 (Figures 3 and 4). One [F4] fusion lacked the EGF-like domain (*PCM-NRG1*) (Figure 4). Eight of the fusions were a result of rearrangements within chromosome 8, whereas nine fusions were the result of interchromosomal rearrangements. All interchromosomal rearrangements were within intron 3, except [F5] ZCCHC7 (Figure 5 and Table 2).

On the basis of the fusion breakpoints (Figure 5), the *CD74*, *SLC3A2*, *TMEM66*, and *IKBKB* cases are predicted to be in frame with *NRG1*. The *PCM1*, *DDHD2*, and *UBXN8* cases have only the 5' untranslated region of the fusion partner and either a canonical or an internal translation start site for *NRG1*. The *TNFRSF10B*, *CD9*, *ERO1L*, *CCAR2*, *BIN3*, *BRE*, *KCTD9*, *FUT10*, and *ZCCHC7* cases all have internal translation start sites in *NRG1* exon 2 or exon 4.

NRG1 gene fusions activate HER2 and HER3 heterodimers through interaction of HER3 and the EGF-like domain of NRG1 (Figure 6). The EGF-like domain in ^[F6] exons 6 to 7 is present in all gene fusions identified with

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Table 1 Patient Demographics

		Tumor types other than NSCLC	$\frac{\text{All cases sequenced}}{(n = 4397)}$	
Variable	NSCLC ($n = 1696$)	(n = 2805)		
NRG1 fusions detected, n (%)	7 (0.41)	10 (0.35)	17 (0.38)	
Age, mean (range), years	72 (64–83)	65 (41-86)	68 (41-86)	
Sex, n (%)	· · ·		· •	
Male	2 (29)	4 (40)	6 (35)	
Female	5 (71)	6 (60)	11 (65)	
Stage, <i>n</i> (%)				
III	_	1 (10)	1 (6)	
IV	1 (14)	5 (50)	6 (35)	
Unknown	6 (86)	4 (40)	10 (59)	
Specimen site, n (%)				
Primary	6 (86)	5 (50)	11 (65)	
Distant metastasis	1 (14)	5 (50)	6 (35)	

NRG1 fusions were identified in the following tumor types: NSCLC [n = 10 (0.41%)], breast carcinoma [n = 2 of 369 (0.54%)], colorectal carcinoma [n = 3 Q33 of 611 (0.49%)], esophageal carcinoma [n = 2 of 117 (1.71%)], ovarian carcinoma [n = 1 of 105 (0.95%)], pancreatic carcinoma [n = 1 of 157 (0.64%)], and unknown primary carcinoma [n = 1 of 233 (0.43%)].

NRG1, neuregulin 1; NSCLC, non-mall-cell lung cancer.

NRG1 as the 3' fusion partner, except for one of the PCM1-*NRG1* fusions (Figures 3 and 4). Transmembrane domains are present in the following partner genes, UBXN8, CD74, SLC3A2, CD9, TMEM66, and TNFRSF10B (Figure 4), whereas 18 of 19 NRG1 fusions contain the transmembrane domain in exon 8; however, a transmembrane domain is not required for signaling.

5' NRG1 Gene Fusions

In addition to the 19 gene fusions identified with the 3'region of the NRG1 gene, six cases were identified that had fusions containing the 5' region of the NRG1 gene. Four of these fusions had a breakpoint in the large intron upstream of exon 1 (intron 1 for type II, IV, and V promoters,



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Figure 1

NRG1 Fusions in Solid Tumors



Figure 2 Representative hematoxylin and eosin sections from lung cancer cases with an *NRG1* fusion. *NRG1* fusions are found in a wide variety of tumor types and histologic types. Photomicrographs represent non-small-cell lung cancer samples where *NRG1* fusions were identified. **A:** Mucinous lung adenocarcinoma. **B:** Large-cell neuroendocrine lung carcinoma. **C:** Poorly differentiated lung adenocarcinoma. **D:** Squamous cell lung carcinoma. Scale bar = 200 μ m (**A**–**D**). Original magnification, ×20 (**A**–**D**).

approximately 1.0 Mb). One contained only the first exon from the type II, IV, and V promoters in the gene fusion, whereas one contained *NRG1* exon 1, and the last contained *NRG* exons 1 to 3.

Genomic Alterations that Co-Occur with NRG1 Fusions

Co-occurring genomic alterations across all samples with an *NRG1* fusion were evaluated (Figure 7A and Supplemental Table S3). In NSCLC, no co-occurring oncogenic driver mutations were identified, with *TP53* being the only recurrent genomic alteration (n = 2/7). The large cell neuroendocrine

lung cancer case harbored *RB1* and *TP53* co-occurring alterations (Figure 7B and Supplemental Table S3). CRC cases had co-occurring alterations in *TP53* (n = 3/3) and *APC* (n = 2/3). In addition, CRC cases had either co-occurring *BRAF* alterations (2/3) or an *ERBB2* amplification (1/3) (Figure 7C and Supplemental Table S3). For all other tumor types, *TP53* genomic alterations were most common (n = 3/7), including in 1 of 2 esophageal carcinoma cases, 1 of 2 breast carcinoma cases, and 1 of 1 ovarian carcinoma case. Driver alterations identified outside of NSCLC and CRC were all within the signaling pathway of *NRG1* and activated *HER2/HER3* heterodimers, resulting in

Table 2 Fus	ion Locations,	Fusion	Partner	Genes,	and	Intron	Sizes
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NRG1 gene	Length, kbp	Fusion partner gene
Intron 1 for type II, IV, and V NRG1 isoforms	955	UBXN8
Intron 1 for type III NRG1 isoforms	406	DDHD2, FUT10, IKBKB, PCM1, TMEM66, ZCCHC7
Intron 2 for type III NRG1 isoforms	9.5	TNFRSF10B
Intron 3 for type III NRG1 isoforms	8.8	BIN3, BRE, CCAR2, CD9, CD74, ERO1L, KCTD9, SLC3A2
Intron 9 for type III NRG1 isoforms	2.8	PCM1

Fusions found twice in the cohort are underlined; these fusions have all been previously described. Fusions previously described and only present once are in standard italic text. Novel fusions are in bold text. There were 19 fusions found in 17 patients. Two samples had two *NRG1* fusions each. NRG1, neuregulin 1.

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Figure 3 *NRG1* gene schematic and gene fusion structures. *NRG1* can be driven by six promoters, termed type I through type VI. The location of the fusion partners is listed where the fusion breakpoint occurs in the *NRG1* gene. Fusion partners are color coded where red is a novel partner, black is a known partner identified once at that location, and green is a known partner identified twice. Gene schematic and exon labels are based on the reference sequence ^{Q23} NM_013956.5 (*https://www.ncbi.nlm.nih.gov/nuccore/1677537276*, last accessed April 24, 2023). EGF, epidermal growth factor; TM, transmembrane. ^{Q24}

P13K/AKT signaling. An *ERBB2* amplification was identified in an esophageal carcinoma, whereas one of the breast carcinoma cases had a *P1K3CA* alteration (Figure 7C and Supplemental Table S3).

Immune Biomarkers in NRG1 Fusion-Positive Cases

To explore other possible treatment options for patients with *NRG1* fusions, immunotherapy-related biomarkers were investigated, including TMB, *CD274* expression, PD-L1 IHC, CP, and tumor inflammation by TIGS.

For the NSCLC cases, the median TMB was 6 mutations/ Mb (range, 0.7 to 37.7 mutations/Mb). One NSCLC case had a high TMB (≥10 mutations/Mb) (Figure 8A). PD-L1 IHC TPS by 22C3 antibody staining results was available for all NSCLC cases, with a mean TPS of 24% (range, 0% to 90%). Overall, five NSCLC cases had positive TPS scores of $\geq 1\%$, with two of five cases having high TPS scores >50% (Figure 8B). Expression of CD274, the gene that encodes for PD-L1, was also measured by RNA sequencing and scored by normalized reads per million rank.²³ Median CD274 expression was 73 nRPM (range, 14 to 95 nRPM), with five of seven cases having high expression (nRPM \geq 75) (Figure 8C). Three NSCLC samples had low levels of inflammation as measured by TIGS, and three samples had high levels of inflammation as measured by TIGS, with an overall median of 52 (range, 18 to 86) (Figure 8D). The CP signature showed low cell proliferation for two samples, with high cell proliferation for one sample with a median of 48 (range, 2 to 70) (Figure 8E). For tumor types other than NSCLC, the median TMB was 4 mutations/Mb (range, 2.3 to 10.9 mutations/Mb). One esophageal carcinoma case had a high TMB (≥10 muta-tions/Mb) (Figure 8A). PD-L1 expression results by IHC

22C3 were available for six of the non-lung cancer cases, with a mean TPS of 1.9% (range, 0% to 10%) (Figure 8B), with two cases \geq 50% TPS and five cases \geq 1% TPS. The median *CD274* nRPM rank was 26 (range, 3 to 63) among tumor types other than NSCLC. Concordant with PD-L1 protein expression by IHC, no cases had high expression of *CD274* by RNA sequencing (Figure 8C). The TIGS showed low levels of inflammation for six samples, with one sample having a high level of inflammation with an overall median of 33 (range, 15 to 73) (Figure 8D). The CP signature was low for five samples and high for two samples, with a median of 39 (range, 6 to 70) (Figure 8E). The *NRG1* fusion-positive NSCLC cases were compared with the *NRG1* fusion-negative cases for TMB, PD-L1 TPS, and CD274 expression (Figure 9). There were no significant ^[F9] differences between the *NRG1* fusion-positive and *NRG1* fusion-negative cases across these measures. There was increased *CD274* expression in the presence of an *NRG1* fusion; however, this was not statically significant (P = 0.14), likely due to small sample size. There was also increased cell proliferation as measured by the CP score in the *NRG1* fusion-positive compared with the NRG1 fusion-negative cases (mean, 49 versus 27); however, this was also not statistically significant (P = 0.28).

Discussion

NRG1 fusions are rare oncogenic drivers that occur across all solid tumor types.³ Data from 4397 patient samples after RNA sequencing using hybrid capture to interrogate 55 genes for fusions were retrospectively analyzed. Collectively, a wide array of known and novel *NRG1* fusion partners in a variety of solid tumors, including lung, breast,

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colorectal, esophageal, ovarian, and pancreatic carcinomas, were identified.^{3,17}

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NRG1 is a complex gene, with large introns and multiple promoters. There are six different promoters (type I through VI) with 33 exons and >30 isoforms generated by alternative splicing.^{1,27,28} There are not specific guidelines for determining if NRG1 fusions are oncogenic; however, basic 794 **Q16** principles from the Clin Gen NTRK Fusions Somatic Cancer Variant Curation Expert Panel can be adapted to NRG1. An *NRG1* fusion is likely oncogenic if i) *NRG1* is the 3' partner, plus ii) it contains the EGF-like domain, which is contained in exons 6 to 7 (Figure 3), and iii) there is an internal initiation site (in NRG1 exon 2 or $4^{1,3,29}$) or the reading frame is preserved.³⁰ Prior reports have identified multiple cases where translocation of a promoter region is sufficient for expression and oncogenic activity of NRG1, which can be translated off internal initiation sites.^{3,29} This is the case for several of the fusions identified in this study, where the

5' gene has only the 5' untranslated region fused to a portion of the NRG1 gene with an internal initiation site. By these criteria, 18 of the 19 fusions identified are predicted to be functional. One of the PCM-NRG1 cases lacks the EGF-like domain and may not be functional (Figure 5). This combination of a complex gene structure and minimal requirements for a functional fusion protein is likely the reason for the diversity of fusion partners.

Most NRG1 fusion breakpoints occur within the first four introns, which encompasses approximately 1.4 Mb of intronic sequencing. In addition, the intronic regions for potential structural rearrangements are large, with approximately 1.4 Mb of intronic sequence in the first four introns where NRG1 fusion breakpoints are most commonly found (Table 2).

The array of fusion partners and large intronic areas where breakpoints occur make identification of NRG1 gene fusions challenging. The potential area for rearrangements

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Figure 5 Representation of the chromosomal locations of the gene fusions identified. Of the 16 unique fusions, 10 were fusions between *NRG1* and another ^{Q26} gene on chromosome 8 and 6 were with genes on other chromosomes. The thickness of the line represents the number of fusions with that partner (two each for *SLC3A2, CD74*, and *PCM1*).

of 1.4 Mb is larger than the total size of most DNA CGP panels.^{23,31–33} Prior studies have also identified *NRG1* fusions in RNA but not DNA.¹⁷ In the eNRGy1 NSCLC *NRG1* fusion registry, most fusions (74%) were identified by RNA-based methods.¹³

In this cohort, the overall incidence of *NRG1* fusions was 0.4%, twice as high as reported in a prior RNA ampliconbased study $(0.2\%)^3$ and eight times as high as a previously reported hybrid capture DNA-based assay (0.05%).¹⁷ The higher detection frequency reported compared with DNA-based detection methods is likely due to fusions missed by DNA only methods. This is supported by the incidence of *NRG1* fusions detected on RNA but not DNA in that study.¹⁷ The increased incidence of fusions relative to the study by Jonna et al³ may be from increased sensitivity of hybrid capture versus amplicon-based



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Figure 7 NRG1 fusion case oncoprints. A: Schematic of all cases. B: Schematic depicts only non-small-cell lung carcinoma (NSCLC) cases. C: Representation of all solid tumor cases excluding NSCLC. Only genes with an alteration in at least two cases are shown. CNV, copy number variation; SNV, singlenucleotide variation.

sequencing, the relatively small numbers of *NRG1*-positive fusion samples, or a difference in the composition of the cohorts. The samples in this study were all sequenced at a reference laboratory during routine clinical care, so there is referral bias toward patients who have more advanced disease and who may have had other testing that failed to identify targetable alterations or single-gene testing that identified common alterations.

In addition to the typical fusions containing the 3' region of the *NRG1* gene, six cases were identified that had 5' *NRG1* fusions. The fusions lack the EGF-like domain required for oncogenic activity. The significance of these fusions is unclear. The fusions could be nonfunctional, they may disrupt the *NRG1* gene in a way that results in overexpression, or they may be the result of reciprocal translocations that were not identified. The BAM alignments for these cases were examined, and no evidence for a 3' NRG1 fusion transcript could be identified. Because of the unknown significance of these six cases, they were not included in any of the other analyses. Further studies of 5' *NRG1* fusions are needed to determine if they are clinically significant and whether patients will respond to targeted therapy.

For the NSCLC *NRG1* fusion-positive cases identified in this cohort, there were no co-occurring driver alterations, which is consistent with prior reports³; however, there have been rare cases of *NRG1* fusions occurring as a resistance

ALK ROS mechanism in fusion +fusion positive + NSCLC, which was not observed in this cohort.¹⁸ The only recurrent genomic alteration was the presence of TP53. Patients with NRG1 fusion-positive NSCLC respond poorly to nontargeted standard-of-care therapy,¹³ further emphasizing the importance of identifying these fusions for patient care. Other relevant biomarkers assessed in the fusion cases were TMB and PD-L1. One case had high TMB, and another had co-occurring high TMB and high PD-L1. The significance of these biomarkers co-occurring with an NRG1 fusion is unknown. In contrast to NSCLC, CRC cases had co-occurring TP53 (n = 3/3), APC (n = 2/3), and BRAF (n = 2/3) alterations, and one ERBB2 amplification. All three CRC cases had at least one co-occurring driver alteration, which is also consistent with prior reports.^{3,34} Among all non-lung cancer cases, there were three cases with alterations in ERBB2 (HER2), three cases with PTEN alterations, and two cases with BRAF alterations. This is interesting given that BRAF and PTEN are involved with the mitogen-activated protein kinase pathway, and the mechanism of action for NRG1 fusions is via an interaction with HER2/HER3 heterodimers to activate mitogen-activated protein kinase signaling pathways.²

Therapies targeting *NRG1* fusions with anti-HER2 and anti-HER3 agents are in clinical trials. *NRG1* fusion-positive tumors are being targeted with anti-ERBB3 (lumretuzumab) and ERBB2 inhibitors (lapatinib and pertuzumab), and

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Measures of potential immunotherapy response and cell proliferation in NRG1 fusion-positive cases. A-E: Tumor mutational burden (A), CD274 Q29 Figure 8 expression (B), PD-L1 score [tumor proportion score (TPS); C], tumor immunogenic signature (TIGS; D), and cell proliferation (CP) score (E) between non- Q30 -small-cell lung cancer (NSCLC) and other tumor types with NRG1 fusions. A and B: The red lines represent the threshold between high and low. D and E: The red lines represent the threshold between low, intermediate, and high. Mb, megabase; nRPM, normalized reads per million.

seribantumab (anti-ERBB3), across all solid tumors.¹⁹ Seribantumab has a pantumor US Food and Drug Administration fast-track designation, based on results from the pansolid tumor CRESTONE trial.35 In addition, the HER2-1164<mark>019</mark> HER3 bispecific humanized monoclonal antibody, zenocutuzumab (MLCA-128), showed radiographic responses in two patients with chemotherapy-resistant metastatic pancreatic cancer, and a patient with NSCLC who had progressed on six prior lines of therapies.³⁶ Zenocutuzumab also demonstrated a favorable activity and tolerability profile across NRG1 fusion-positive tumors in the phase 2 eNRGy trial, providing a second tumor agnostic option.³⁷

Taken together, these data highlight the importance of identifying NRG1 fusions as these patients often lack other driver alterations and targetable biomarkers. RNA sequencing increases the detection rate for NRG1 fusions

and offers another potential therapy option for patients with advanced cancer.

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Author Contributions

E.S. conceptualized the study, curated and analyzed data, performed investigations, developed methods, and wrote, reviewed, and edited the manuscript; B.R.A. curated data and wrote, reviewed, and edited the manuscript; M.N. and S.P. curated and analyzed data, performed investigations, developed methods, and wrote, reviewed, and edited the manuscript; R.A.P., G.K., A.C., R.K., M.S., P.S., A.G., T.J.J., K.S.S., and P.R. reviewed and edited the manuscript; S.Z. curated data, performed investigations, developed methods, and reviewed and edited the manuscript; J.C.

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Figure 9 Comparing measures of potential immunotherapy response and cell proliferation between non-small-cell lung cancer (NSCLC) cases that are NRG1 fusion positive versus negative. A-E: Comparison of tumor mutational burden (A), PD-L1 tumor proportion score (TPS; B), *CD274* expression (C), cell ^{Q31} proliferation score (D), and tumor immunogenic signature (TIGS; E) between *NRG1* fusion-positive NSCLC cases and *NRG1* fusion-negative NSCLC cases. A and C: The red lines represent the threshold between high and low. D and E: The red lines represent the threshold between low, intermediate, and high. Mb, megabase; nRPM, normalized reads per million.

conceptualized the study, curated data, and reviewed and edited the manuscript; and S.H.R. conceptualized the study, developed methods, and wrote, reviewed, and edited the manuscript.

Supplemental Data 🥿

Supplemental material for this article can be found at *http://doi.org/10.1016/j.jmoldx.2023.03.011*.

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