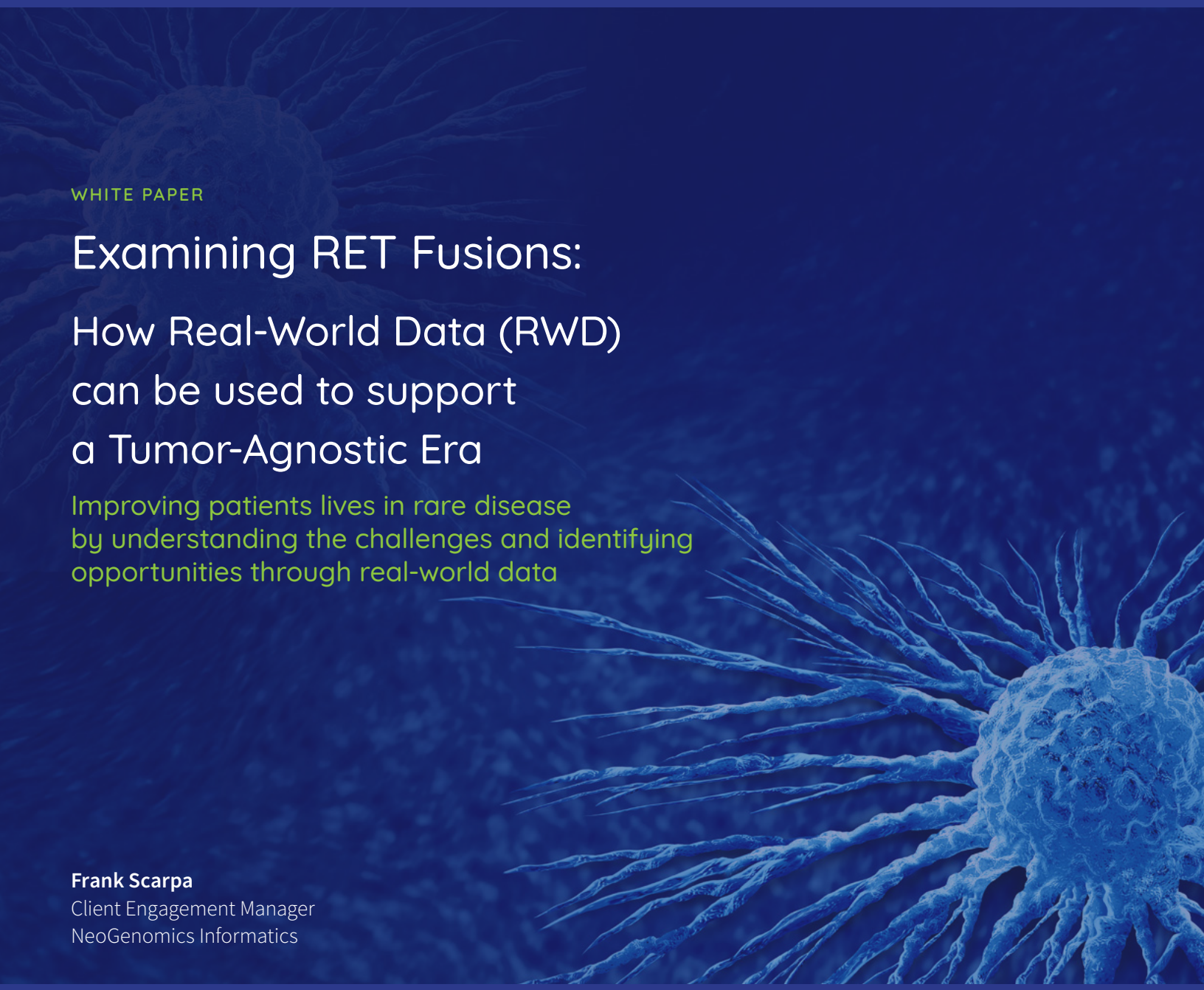
NEO GENOMICS

ONCOLOGY DATA SOLUTIONS



WHITE PAPER

Examining RET Fusions:

How Real-World Data (RWD) can be used to support a Tumor-Agnostic Era

Improving patients lives in rare disease by understanding the challenges and identifying opportunities through real-world data

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A New Era in Oncology Precision Medicines

On May 23, 2017, the FDA made a groundbreaking approval of pembrolizumab for adult and pediatric patients with unresectable/metastatic microsatellite instability-high or mismatch repair deficient tumors. This approval marked the very first targeted therapy to receive a tumor-agnostic approval and paved the way for a new paradigm in clinical oncology. To date, there are a multitude of biomarkers, preclinical drugs, and FDA approved therapies that are of intense interest due to their potential applications in a tumor agnostic setting. NTRK inhibitors larotrectinib and entrectinib received tumor agnostic approval for solid tumors harboring NTRK fusions in November 2018 and most recently, RET inhibitor selpercatinib received tumor agnostic FDA approval in September 2022 for adult patients with locally advanced/metastatic solid tumors harboring RET rearrangements. Given the novelty of this tumor agnostic approach for RET-rearranged tumors, we explored the current landscape for RET testing to identify both the challenges and prospects with a new pan-tumor indication.

Using RWD to determine testing rates and disparities in a tumor-agnostic setting

Rearranged during transfection (RET) gene fusions are rare, but highly actionable driver alterations which have most commonly been studied in lung and thyroid cancers to date. However, RET fusions have also been found to be present in a wide range of additional solid tumor malignancies. Selpercatinib and pralsetinib are two novel, highly selective tyrosine kinase inhibitors (TKIs) targeting RET that have shown robust and durable responses across multiple solid tumor types in clinical trials. Selpercatinib shows response rates of approximately 40% and progression-free survivals (PFS) of approximately 13.2 months.[1] While RET rearrangements are rare, the commercial availability of RET inhibitors, NCCN's recommendation for testing, and the durable responses they demonstrate underscore the importance of testing for RET fusions in all solid tumor types. Unfortunately, FDA approval and demonstrated clinical benefit of a therapy does not always equate to widespread adoption of testing, particularly in community settings.

5% of patients with solid tumors in the past 5 years have undergone testing for RET

Comparison of RET testing by modality

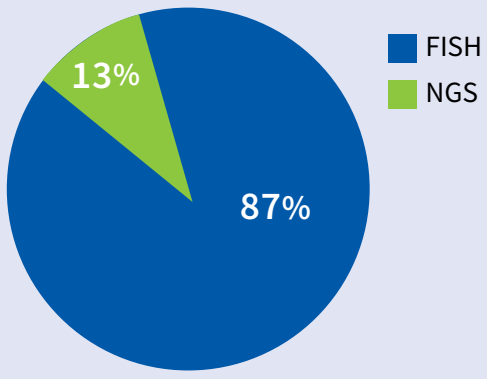


Fig. 1: *Breakdown of RET Testing by NGS vs. FISH from 2/22/2017 – 7/21/2023. RET Testing is still done overwhelmingly by FISH*

FISH vs. NGS testing YOY

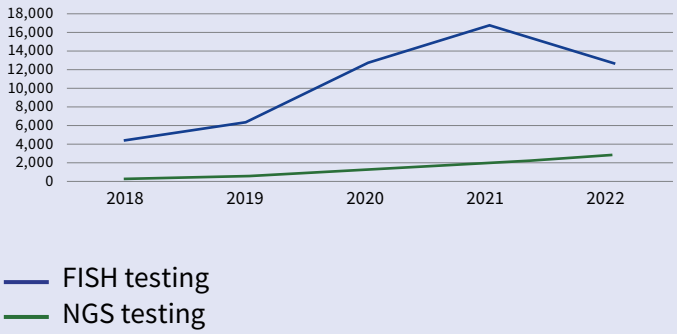
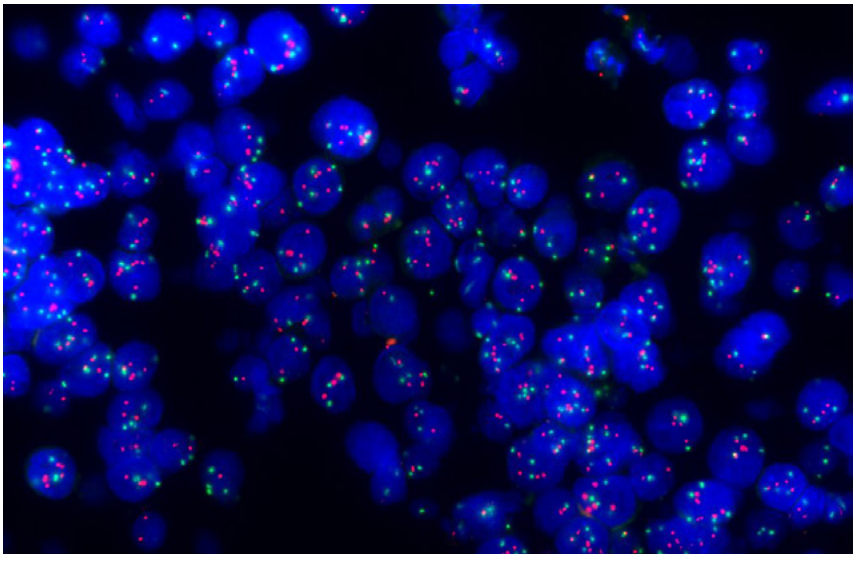


Fig. 2: *Overall RET testing volumes by NGS vs. FISH from 2/22/2017 – 7/21/2023.*

The three methods used for RET fusion detection and determining patient eligibility in the LIBRETTO-001 trial were fluorescence in situ hybridization (FISH), polymerase-chain reaction (PCR), and RNA-based next generation sequencing (NGS). Importantly, in the LIBRETTO-001 trial, 86% of RET fusions were detected using NGS while 9% were detected using PCR and only 4% were detected using FISH, indicating a preference for NGS testing in detecting RET fusions among healthcare providers. Although FISH has been shown to be an exquisitely effective modality for detection of RET fusions in some indications, the sensitivity and specificity of a FISH assay can vary depending on the RET fusion partner. Furthermore, FISH does not provide the specific RET gene fusion partner, which supports the notion that RNA NGS is considered to be the gold standard for detecting RET fusions. To understand how these assumptions translate to clinical practice, we analyzed data from our NeoNucleusTM database from the last 5 years.

From 2018 to 2019, RET testing across tumor types at NeoGenomics increased +37% and from 2019 to 2020, the testing rate more than doubled with a +127% increase. 2021 brought another increase of +36%. However, we witnessed a reduction in RET testing rates from 2021 to 2022, largely driven by a decrease in FISH-based RET testing. While overall testing rates also suffered due to the global pandemic, the decrease in RET FISH testing was coupled with an increase in NGS-based RET fusion testing as expected, highlighting the shift to the gold standard technology. Importantly, despite an upward trend over the last five years in absolute test volume and the shift to NGS, our data shows that less than 5% of patients with solid tumors in the past five years have undergone testing for RET. Furthermore, only 6% of patients have undergone RET testing since the approval of selpercatinib in September 2022, demonstrating substantial room for growth to identify therapy-eligible patients.



As one of the largest oncology testing laboratories in the US, NeoGenomics is a leading source of real-world data insights. Our team would welcome the opportunity to discuss your current programs and explore ways that we can partner to elevate the testing message in the community to make sure patients get the right test and the right treatment at the right time.

Leveraging RWD to support tumor-agnostic therapies

RET fusions have been shown to occur at varying frequencies depending on the indication and specific study. In papillary thyroid cancer, RET fusions occur in approximately 20% of patients. In non-small-cell lung cancers (NSCLCs), RET fusions occur in 1-2% of cases, while in other solid tumors, including breast, ovarian, pancreatic, salivary, colorectal, adrenal, brain, and head & neck cancers, actionable RET fusions are expected to occur at frequencies of <1%. Additionally, acquired resistance mutations in MAPK genes such as KRAS, NRAS, and BRAF have been shown to occur in approximately 35% - 50% of patients undergoing treatment with a RET inhibitor.[2,3] However, determining prevalence rates from tumor agnostic clinical trials can be challenging or even misleading due to the rarity and underrepresentation of cohorts. Additionally, tumor agnostic clinical trials are not conducive to exploring tissue-specific mechanisms of resistance and may not fully capture clinical efficacy due to patient heterogeneity (e.g. different levels of expression, prevalence, and benefit across other indications). In these instances of unmet need, RWD can be used to provide insights both across and within patient subgroups. For example, our real-world data (n = 852) shows that RET fusions occur in 1.6% of all solid tumors; when looking across 18 individual tumor types they occur at a prevalence ranging from 1% – 3.7% including in several indications which haven't yet been recommended by NCCN guidelines for RET fusion testing such as brain, bladder, and gastric cancers (See Table 1). Additionally, we show that mutations in KRAS, NRAS, and BRAF are present in 27% of RET fusion positive patients, suggesting that many of these RET-fusion positive patients will be resistant to targeted therapies against RET. By linking this detailed genomic data to medical claims or EMR records through tokenization, further insights can be drawn on outcomes and treatment response in this specific sub-population of patients which may not have been captured in published clinical studies. The importance of using RWD to supplement clinical trials data has even been underscored by the FDA, with the expanded indication approvals of pembrolizumab in 2017, blinatumomab in 2018, and palbociclib in 2019—all of which were made possible through the use of RWD.

Given the challenges that clinical trials face with tumor agnostic therapies targeting rare biomarkers, leveraging RWD is essential in order to perform holistic analyses on testing trends, therapy selection and progression, post-market surveillance, and cost-effectiveness. Improving patient care means capturing the complete picture of a patient population, and with >85% of testing coming from the community setting, NeoGenomics is uniquely positioned to explore these trends.

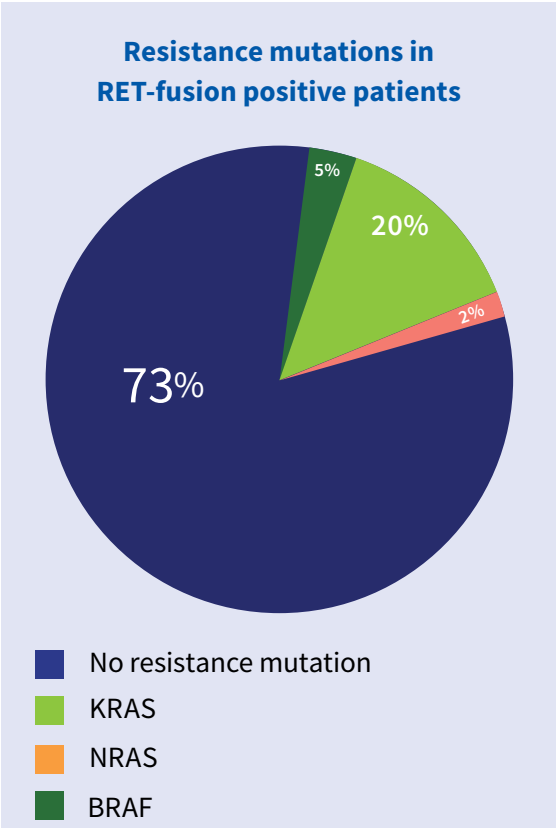


Fig. 3: *Breakdown of KRAS, NRAS, and BRAF mutations across all RET positive patients (NGS and FISH) from 2/22/2017 – 7/21/2023. KRAS, NRAS, and BRAF are associated with resistance to RET inhibitors.*

Real world prevalence rates show significant variance from published prevalence rates

Data from NeoNucleus™ shows a 1.6% RET fusion prevalence rate in all solid tumors

Table 1: Prevalence of RET fusions across 18 different tumor types from 2/22/2017 – 7/21/2023. RET prevalence in the literature and presence of NCCN guidelines recommending RET fusion testing is provided for reference.

Indication	Has NCCN Recommendation for RET Fusions?	RET Detected	RET Not Detected	Grand Total	RWD Prevalence (%)	RET Fusion Prevalence in Literature
Bladder	N	6	343	349	1.7%	N/A
Brain	N	24	980	1004	2.4%	N/A
Breast	Y	9	901	910	1.0%	0.05%
Cervical	Y	7	267	274	2.6%	N/A
Colorectal	Y	96	6804	6900	1.4%	0.46%
Gastric	Small bowel adenocarcinoma only	24	2073	2097	1.1%	N/A
HNSCC	Y	34	1950	1984	1.7%	N/A
Liver	Y	21	1204	1225	1.7%	N/A
Lung	Y	552	34315	34867	1.6%	1 – 2%
Ovarian	Y	18	539	557	3.2%	1.90%
Thyroid	Y	28	727	755	3.7%	8.20%
Unclassifiable/Other	N/A	23	1211	1234	1.9%	N/A
Grand total		852	52227	53079	1.6%	

NeoGenomics also evaluated Endometrial, Melanoma, Pancreas/Biliary, Prostate, and Sarcoma, and found a RET positivity of less than 5 for each of these indications.

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2. Lin JJ, Liu SV, McCoach CE, Zhu VW, Tan AC, Yoda S, Peterson J, Do A, Prutisto-Chang K, Dagogo-Jack I, Sequist LV, Wirth LJ, Lennerz JK, Hata AN, Mino-Kenudson M, Nardi V, Ou SI, Tan DS, Gainor JF. Mechanisms of resistance to selective RET tyrosine kinase inhibitors in RET fusion-positive non-small-cell lung cancer. Ann Oncol. 2020.
3. Rosen EY, Won HH, Zheng Y, Cocco E, Selcuklu D, Gong Y, Friedman ND, de Bruijn I, Sumer O, Bielski CM, Savin C, Bourque C, Falcon C, Clarke N, Jing X, Meng F, Zimel C, Shifman S, Kittane S, Wu F, Ladanyi M, Ebata K, Kherani J, Brandhuber BJ, Fagin J, Sherman EJ, Rekhtman N, Berger MF, Scaltriti M, Hyman DM, Taylor BS, Drilon A. The evolution of RET inhibitor resistance in RET-driven lung and thyroid cancers. Nat Commun. 2022.

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