Positive Predictive Value of *NTRK*, *RET*, *BRAF*, and *ALK* Fusions in Bethesda III/IV Thyroid Fine-Needle Aspirates

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INTRODUCTION

The prevalence of thyroid cancer, as determined by excision, among biopsied Bethesda III/IV nodules with fusions of *ALK, BRAF, NTRK* or *RET* (other than *RET/PTC1* and *RET/PTC3*), is unknown. The Afirma Genomic Sequencing Classifier and Xpression Atlas report 130 fusion pairs, including these fusions. Here we report their PPVs in real-world clinical practice.

METHODS

Consecutive cohorts of Bethesda III/IV nodules with *ALK, BRAF, NTRK* or *RET* fusions (other than *RET/PTC1* and *RET/PTC3*) submitted to Veracyte for molecular analysis were identified. Local surgical pathology diagnoses were sought with IRB approval. Only one nodule per patient was included. PPV calculations did not consider NIFTP as malignant. Gene pairs are listed alphabetically.

RESULTS

Local surgical pathology diagnoses were available for 58 thyroid nodules from 58 patients. No sample had a concurrent variant or second fusion. Twelve *ALK* fusion partners included 8 *STRN* and 4 *EML4*. Eight (67%) were malignant while 4 were adenomatoid or hyperplastic (3 *STRN* and 1 *EML4*). Sixteen *BRAF* fusion partners included 5 *AGK*, 5 *SND1*, 2 *CCNY*,2 *MKRN1*, 1 *POR*, and 1 *MACF1*; 12 carcinomas (75%), 1 NIFTP (*AGK*), and 3 adenomas (1 each *AGK, SND1, MKRN1*). Twenty-three *NTRK* fusion partners included 19 *ETV6*, 2 TPM3, and 2 *RBPMS*; 22 carcinomas (96%) and 1 hyperplastic nodule. Seven *RET* fusion partners included 3 *ERC1*, 1 *TRIM33*, 1 *AKAP13*, 1 *PRKAR1A* and 1 *FKBP15*; 6 carcinomas (86%) and 1 NIFTP (*ERC1*).

CONCLUSION

NTRK and *RET* fusions among Bethesda III/IV nodules were associated with malignancy in 28 of 30 nodules. Risk of malignancy was lower among nodules with *ALK* (67%) or *BRAF* (75%) fusions. We found it notable that two nodules with fusions expected to be *BRA*FV600E-like were diagnosed as NIFTP. Additionally, 4 nodules were reported as hyperplastic despite harboring fusions expected to drive neoplasia (2 *ALK/STRN*, 1 *ALK/EML4*, 1 *ETV6/NTRK3*). With a modest sample size, our findings highlight the local histopathology risk of malignancy associated with several fusions among nodules with indeterminate cytopathology. Future studies with expert histopathologists may provide additional comparative insight, as will long term clinical outcomes associating fusion partners with biological risk for recurrence.

FIGURE 1.
Relative Fusion Partner Frequency

Relative Frequency of Fusion Partners of *ALK*, *BRAF*, *NTRK* or *RET* (other than *RET/PTC1* and *RET/PTC3*) among consecutive Bethesda III/IV nodules.

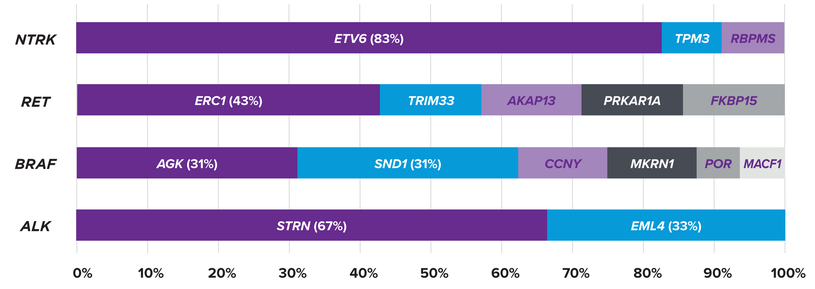

FIGURE 2.
Positive Predictive Value

Percent of consecutive Bethesda III/IV nodules with *ALK*, *BRAF*, *NTRK* or *RET* fusions (other than *RET/PTC1* and *RET/PTC3*) demonstrating cancer or Non-Invasive Follicular Thyroid neoplasm with Papillary-like features (NIFTP) on local surgical histopathology.

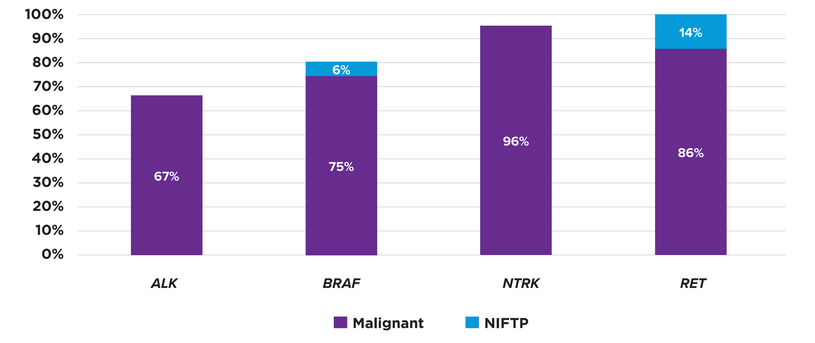

Table 1.

Local histopathological diagnosis of consecutive Bethesda III/IV nodules with *ALK*, *BRAF*, *NTRK* or *RET* fusions with available diagnoses. NIFTP: Non-Invasive Follicular Thyroid neoplasm with Papillary-like features.

Fusion Kinase Domain	Local Histology
ALK	Papillary thyroid cancer (PTC) 42% Hyperplasia 25% Follicular variant PTC 8% Adenomatoid nodule 8% Follicular thyroid cancer 8% Unspecified thyroid malignancy 8%
BRAF	Papillary thyroid cancer 56% Follicular variant PTC 19% Adenoma 19% NIFTP 6%
NTRK	Follicular variant PTC 48% Papillary thyroid cancer 48% Hyperplasia 4%
RET (not *RET/PTC1* or *RET/PTC3*)	Papillary thyroid cancer 57% Follicular variant PTC 29% NIFTP 14%