

# Diagnostic and Therapeutic Utility of NTRK Fusions Detected by ThyroSeq Test in Thyroid Nodules and Cancer



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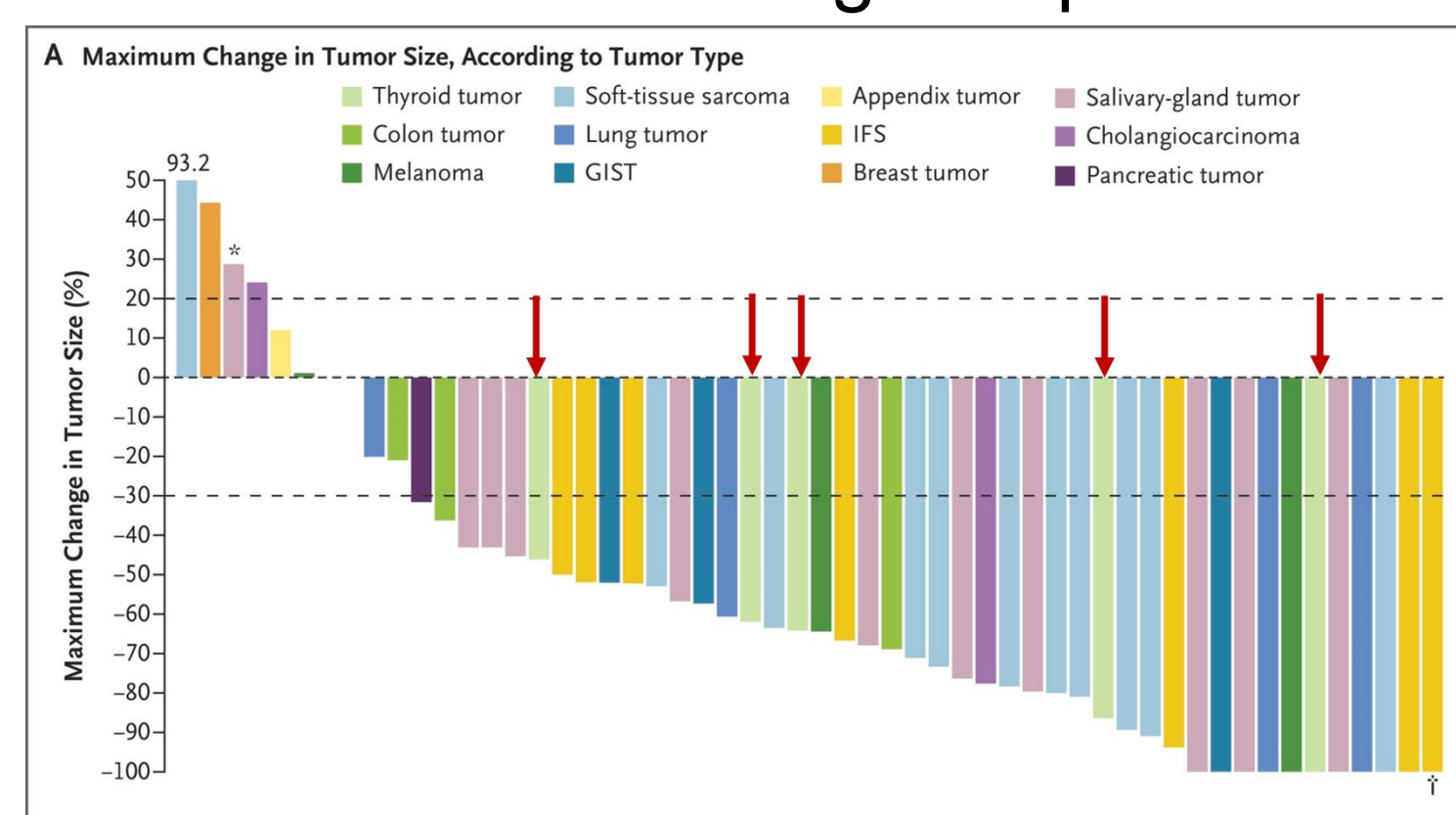
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## INTRODUCTION

In thyroid, NTRK fusions involving the NTRK1 or NTRK3 genes are found in papillary thyroid carcinomas (PTC) and poorly differentiated thyroid carcinomas. Recently, a selective pan-TRK inhibitor, Larotrectinib, was approved by the FDA for treatment of patients with TRK-positive cancers based on an overall high response rate (1).



Drilon et al. *N Engl J Med* 2018; 378:731-739.

In addition to diagnostic utility of NTRK detection in thyroid fine needle aspiration (FNA) samples, testing for NTRK fusion may be used to select patients for targeted therapy.

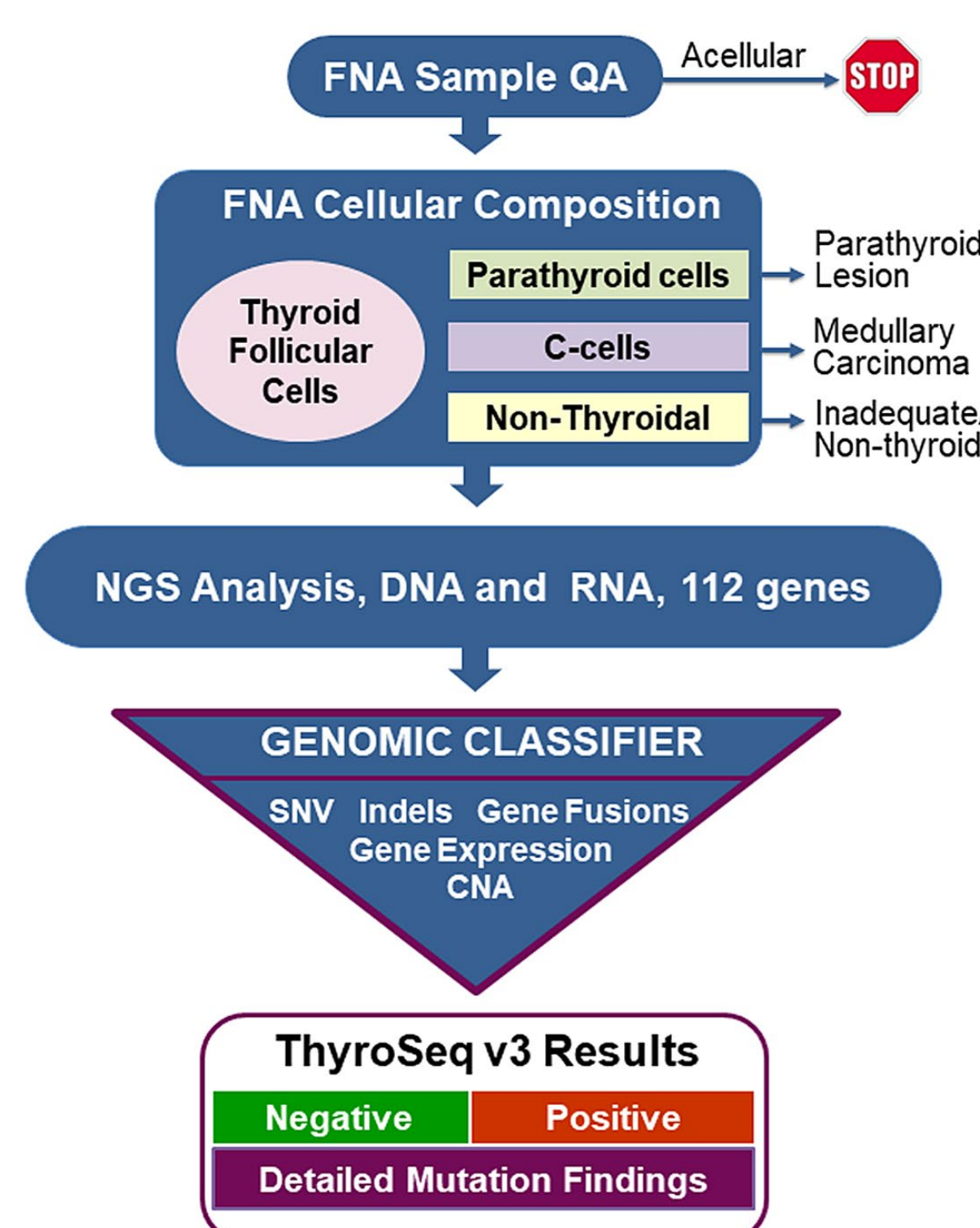
## AIMS

In this study, we evaluated the frequency of detection of NTRK fusions in FNA samples and their potential therapeutic utility.

## METHODS

ThyroSeq v3 GC test was used to detect all functional types of NTRK1 and NTRK3 fusions by sequencing known fusion types and detecting differential expression of NTRK mRNA (2).

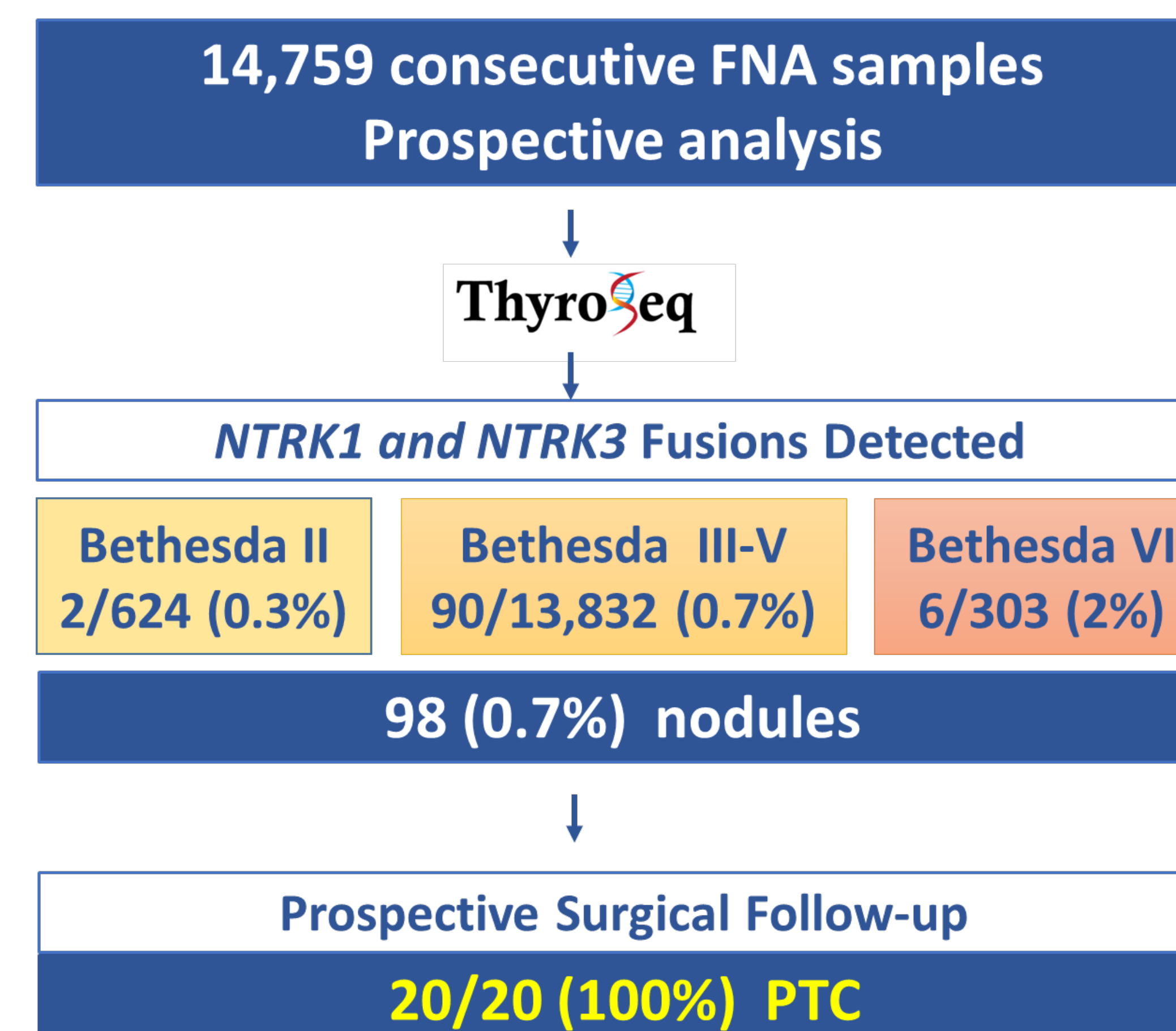
### Scheme of ThyroSeq Test Flow



## RESULTS

### Prevalence of NTRK1/3 Fusions in Consecutive Thyroid FNA Samples

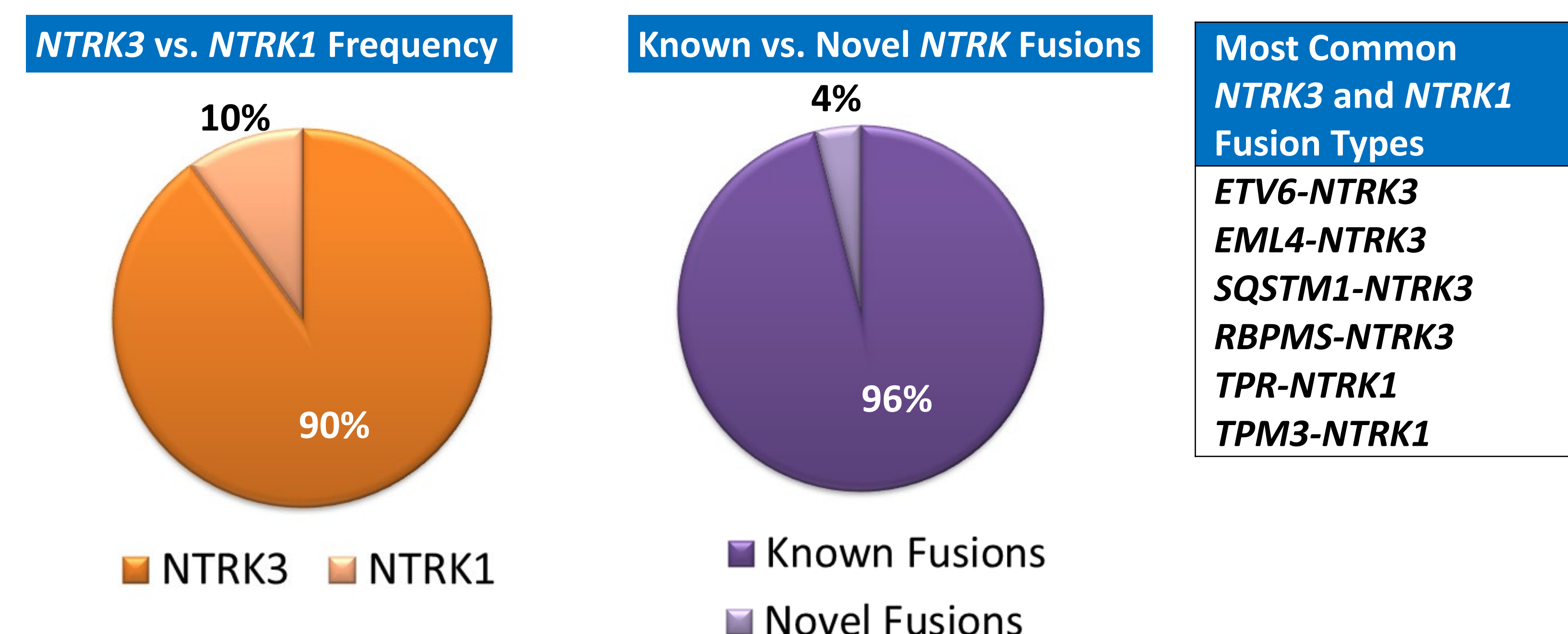
- Retrospective analysis was performed to determine frequency of NTRK fusions in consecutive FNA samples tested from November 2017 until December 2018.



- Surgical follow-up was available for 20 nodules: 1 cytologically benign (Bethesda II) nodule was diagnosed as PTC, EFV on surgery; 17 cytologically indeterminate nodules (Bethesda III-V) were diagnosed as PTCs, and 2 Bethesda VI nodules were PTC.

### Characteristics of Detected NTRK3 and NTRK1 Gene Fusions

Overall, 90% of all detected fusions were NTRK3 and 10% NTRK1. These included 96% of known fusion types and 4% of novel fusions with high expression of the tyrosine-kinase domain. Most common fusion types are listed below.



### Characteristics of Resected NTRK-Positive Tumors

In a group of surgically removed tumors, 15 PTC were positive for NTRK fusions. Among them, 6 patients had distant metastasis.

Case #	NTRK Fusion	Other Mutations	Distant Metastases	Treatment Response
1	NTRK3		No	NA
2	NTRK3		Yes	NA
3	NTRK3	TERT	Yes	Partial response, Larotrectinib
4	NTRK3		No	NA
5	NTRK3		No	NA
6	NTRK3	TERT	Yes	NA
7	NTRK1		No	NA
8	NTRK3		No	NA
9	NTRK3		No	NA
10	NTRK1		Yes	NA
11	NTRK3		No	NA
12	NTRK3		Yes	NA
13	NTRK3		No	NA
14	NTRK3		No	NA
15	NTRK3		Yes	NA

One patient with radioiodine-resistant PTC with multiple soft tissue, pulmonary, and bone metastases diagnosed 4 years after initial surgery received treatment with Larotrectinib and has a partial response.

## CONCLUSIONS

- NTRK fusions were detected by ThyroSeq in 0.7% of consecutive FNA samples (mostly with Bethesda III-V) cytology and were predictive of PTC.
- In thyroid nodules, NTRK3 fusions were more common than NTRK1, and 4% of all detected fusion types were novel functional fusions.
- NTRK fusions were found either alone or in combination with TERT mutations
- In surgically removed cancer samples, these fusions were frequently found in cases with distant metastasis and serve as a promising therapeutic target.

## REFERENCES

- Drilon et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. *N Engl J Med* 2018; 378:731-739.
- Nikiforova MN, et al. Analytical Performance of the ThyroSeq v3 Genomic Classifier for Cancer Diagnosis in Thyroid Nodules. *Cancer*. 2018 Apr;124(8):1682-1690.