

Systematic Review of NTRK Fusion Prevalence across Cancer Types to Predict Impact of Histology Independent Cancer Treatment

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OBJECTIVES

Advanced cancer patients with **NTRK gene fusion biomarkers** may benefit from targeted drugs (TRK Inhibitors). These ‘Pan Cancer’ or ‘Histology Independent’ drugs are aimed at patients with any type of cancer as long as they have this biomarker.

Health Technology Assessments to facilitate public access to these drugs are challenging as these biomarkers are **very rare, have many test options, and found pan-cancer**^{1,2}. The financial implications of biomarker testing and drug uptake at a population level are uncertain³.

This study aimed to map the **current evidence for NTRK fusion prevalence pan-cancer** and to generate **point estimates for cancer types to inform Health Technology Assessments and predict impact of approving TRK inhibitors for pan cancer treatment**.

METHODS



SEARCH STRATEGY

We performed a systematic literature review with a broad database search of all NTRK fusion literature & a supplemental search of recent genomic landscape studies

- We searched Ovid Medline and Embase, and Cochrane Library in April 2021
- Key inclusion criteria: Solid Tumours, Reports rate of NTRK fusions in patients tested, year of publication 2011 and onwards
- Key exclusion criteria: Below minimum sample size, Case Reports/Abstracts, Selected by/known Fusion Status, Testing with Pan-TRK IHC only



DATA EXTRACTION

- Pan Cancer (>10 types) and specific cancer rates were extracted for all included studies
- Cancer types were recorded as per paper, and were classified into synonymous ‘unique’ types and broad tumour groups



SYNTHESIS

- In addition to a narrative summary of rates extracted;
- Rates for ‘unique’ cancer types were assessed for pooling using further ‘synthesis criteria’ to ensure robust estimates
 - Where multiple rates eligible to pool, random effect generalised linear mixed model used for meta-analysis



CRITICAL APPRAISAL

- A customised 11-item checklist was developed to assess bias and quality of studies, to ensure only optimal rates are pooled to reduce variation
- Biomarkers can vary with demographic factors (age, sex, stage, ethnicity) but associations are hard to elucidate for rare biomarkers but critical for accurate population predictions
- Checklist assessed factors that affect the following key domains of the estimated prevalence⁴;

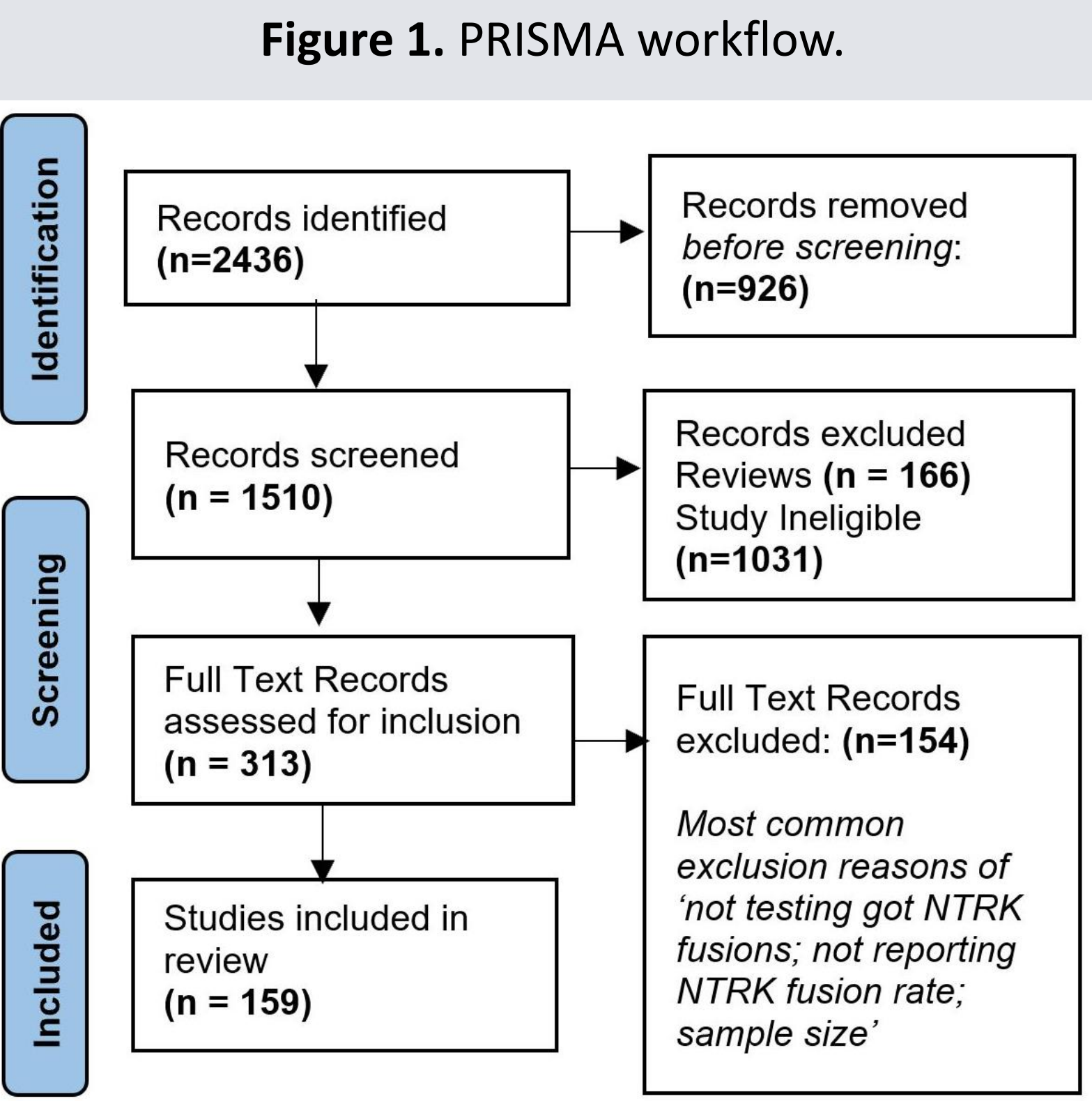
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RESULTS

STUDIES INCLUDED (Figure 1.)



159 studies were included with 443 prevalence rates extracted. These were 15 Pan Cancer (including 5 paediatric) and 428 rates in specific cancer types collated into 14 tumour groups.

Most studies (62%) were published from 2019 onwards and the majority (70%) were retrospective testing or data analysis cohorts.

PAN CANCER PREVALENCE (Figure 2.)

Pan Cancer prevalence for adult cohorts ranged from 0.03% to 0.70%.

- Higher rates seen for studies using RNA based testing (green) compared to less sensitive fusion testing
- The median rate sits around 0.30%
- Paediatric Pan Cancer rates were slightly higher and more variable (~1%)

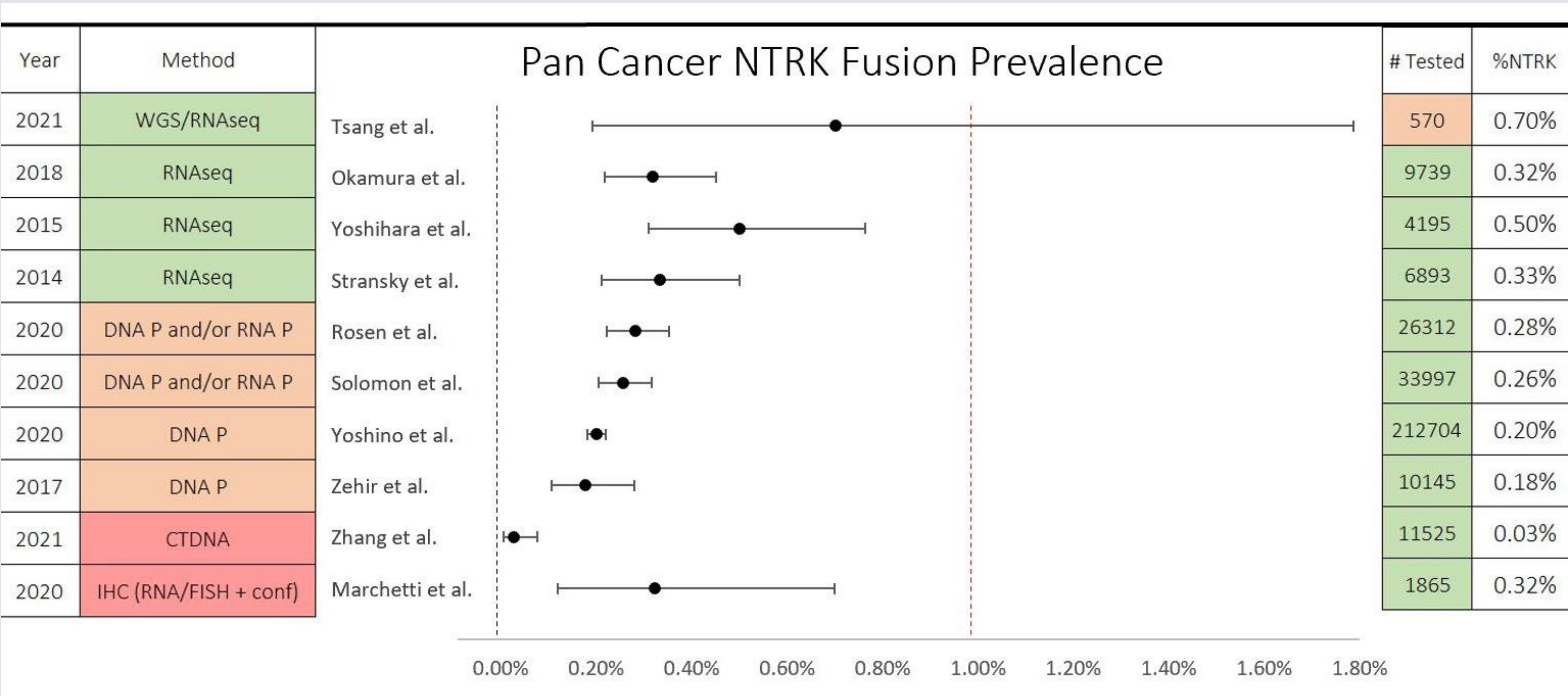


Figure 2. Pan Cancer rate summary.

CRITICAL APPRAISAL & SYNTHESIS

- 43% of cancer type rates reported zero NTRK fusions identified
- 59% of rates had sample sizes deemed insufficient to detect this rare biomarker
- No studies were judged ‘ideal’ across three domains and only 36% of rates were eligible for meta-analysis

Cancer Type	Pooled %	95% CI
Colorectal	0.22%	0.18%-0.28%
NSCLC	0.19%	0.11%-0.33%
Breast	0.21%	0.16%-0.27%
Melanoma	0.19%	0.12%-0.33%
Prostate	0.14%	0.08%-0.25%
Thyroid	1.68%	1.08%-2.63%

Figure 3. Common Cancer Point Estimates

CANCER TYPE ESTIMATES (Figure 3.)

- The greatest number of rates were extracted for Lung, Thyroid and Paediatric Tumour Groups
- Point estimates for Common Cancers were all very rare (below 0.30%)
- High rates seen for rare cancer types that should be prioritised for testing
- Enriched rates seen in some molecular subgroups but not complete mutual exclusion

CONCLUSIONS

- Prevalence of NTRK Fusions Pan Cancer is likely below 0.5%, very rare.
- Prevalence in unselected common cancers largely at 0.2%
- Due to their rarity, there is very limited data with sufficient methods and sample size for estimating prevalence.
- Additionally, variation across methods, cancer ontology and epidemiological reporting limit meaningful synthesis, our appraisal tool provides assessment framework for biomarker data to generate population prevalence estimates
- Financial impact of listing TRK inhibitors is likely minimal at population level as positive patients are rare. However the cost of identifying positive patients is significant and needs accurate data to inform optimal diagnostic algorithms

REFERENCES & FUNDING

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