Thousands of Rare Diseases, far fewer etiologies

- Limited number of mutation types
  - Nonsense mutations - premature stop codon
  - Missense mutations → abnormal protein folding
  - Abnormal RNA splicing
  - Dominant (gain of function) mutations

  - Biochemical signaling pathway defects (“ signallopathies”)
    - mTOR-
    - RAS-
    - Tau -
    - Ubiquitin –
    - Synuclein
    - TRPV4 –
    - PIK3CA-
    - Interferon -
    - TGF-beta -
    - SHANK3 -

Precedent : Genomically Driven Oncology Basket Trials

ORIGINAL ARTICLE

Efficacy of Larotrectinib in TRK Fusion–Positive Cancers in Adults and Children

Alexander Drilon, M.D., Theodore W. Laetsch, M.D., Shivaani Kummar, M.D., Steven G. DuBois, M.D., Ulrik N. Lassen, M.D., Ph.D., George D. Demetri, M.D., Michael Nathenson, M.D., Robert C. Doebele, M.D., Ph.D., Anna F. Farago, M.D., Ph.D., Alberto S. Pappo, M.D., Brian Turpin, D.O., Afshin Dowlati, M.D., et al.

Tumor type — no. (%)	
Salivary-gland tumor	12 (22)
Other soft-tissue sarcoma‡	11 (20)
Infantile fibrosarcoma	7 (13)
Thyroid tumor	5 (9)
Colon tumor	4 (7)
Lung tumor	4 (7)
Melanoma	4 (7)
GIST	3 (5)
Cholangiocarcinoma	2 (4)
Appendix tumor	1 (2)
Breast tumor	1 (2)
Pancreatic tumor	1 (2)

February 22, 2018 N Engl J Med 2018; 378:731-739

" Larotrectinib had marked and durable antitumor activity in patients with TRK fusion–positive cancer, regardless of the age of the patient or of the tumor type "

FDA

FDA approves larotrectinib for solid tumors with NTRK gene fusions

https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions-0