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 ("signalopathies")
  - mTOR-
  - RAS-
  - Tau -
  - Ubiquitin -
  - Synuclein
  - TRPV4 -
  - PIK3CA-
  - Interferon -
  - TGF-beta -
  - SHANK3 -
Precedent: Genomically Driven Oncology Basket Trials

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.

“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 approves larotrectinib for solid tumors with NTRK gene fusions

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