St. Jude Children's Research Hospital

Genomic Methods to Understand the Genetic Origins of Pediatric Cancers

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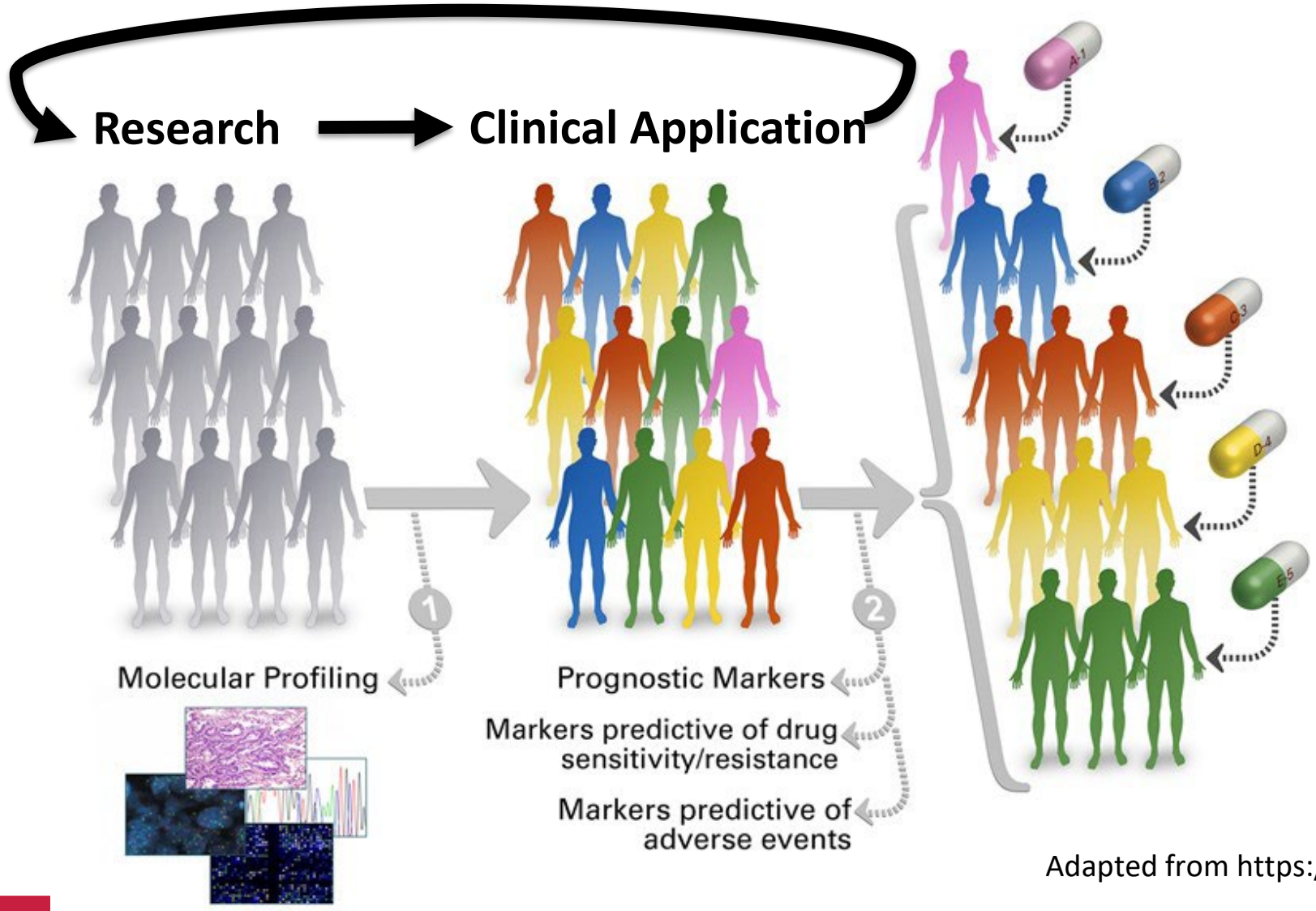
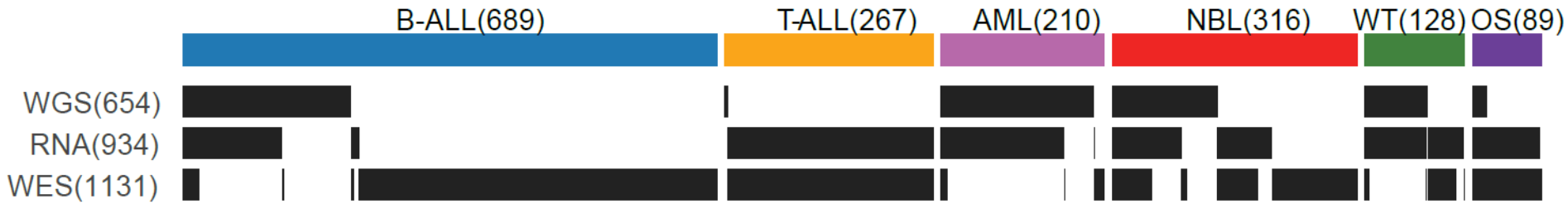
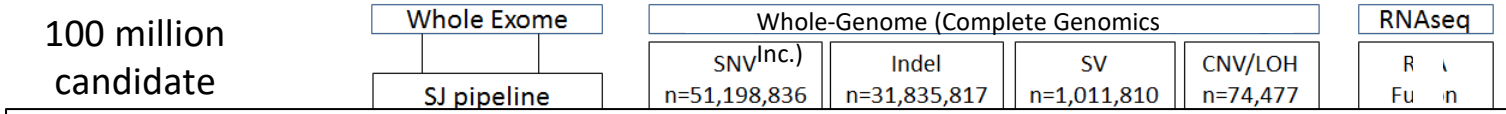
Genomic Analysis in Research & Clinic



Adapted from https://pct.mdanderson.org/#/

Map the Genetic Drivers in Tumor Genome by Variant Enrichment Analysis





Of the 142 statistically significant driver genes:

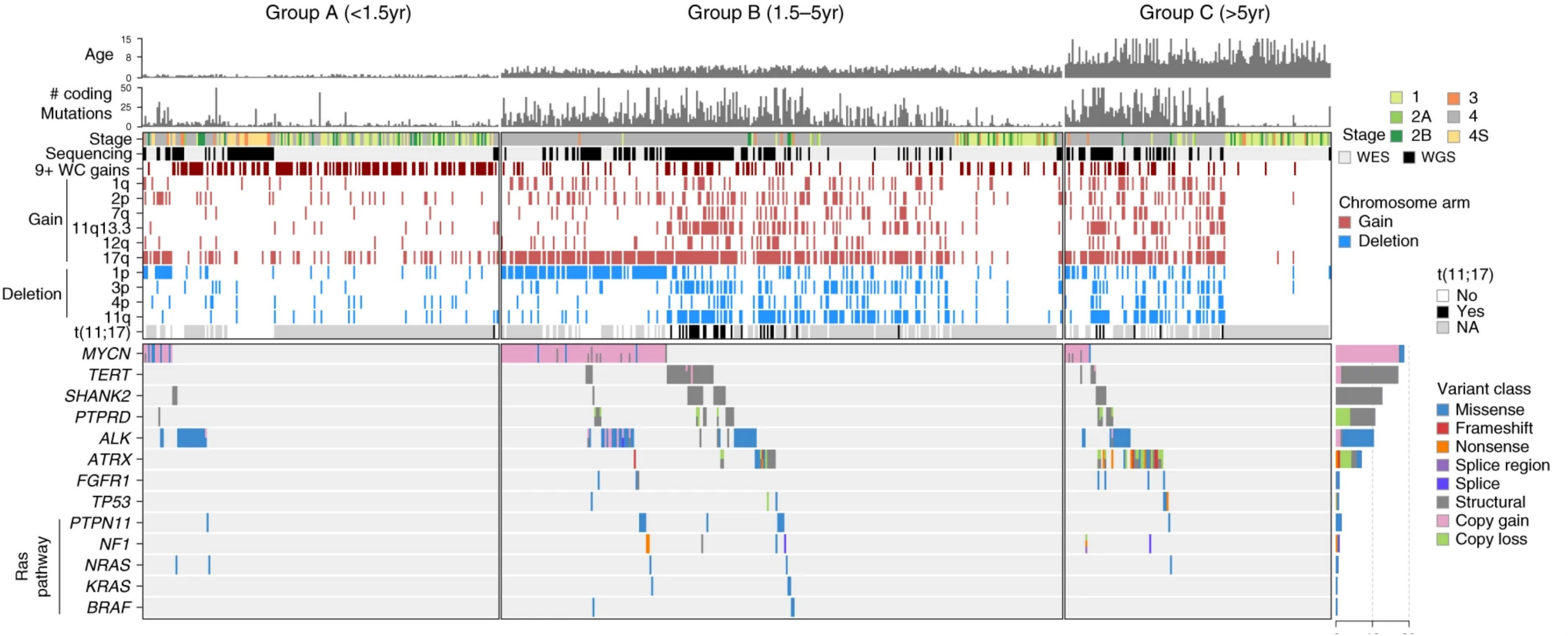
- 78 (55%) absent in three adult pan-cancer studies
  - Kandoth et al Nature (2013)
  - Lawrence et al Nature (2013)
  - Zack et al Nature Genetics (2013)
- 62% are Structural/Copy Number Variations (SVs/CNVs)

142 driver genes ← Statistical analysis (MutSigCV, GRIN) ← Pathogenicity classification → 82 additional driver genes with P/LP variants

Ma et al, Nature 2018

Define Genetic Basis by Age of Onset

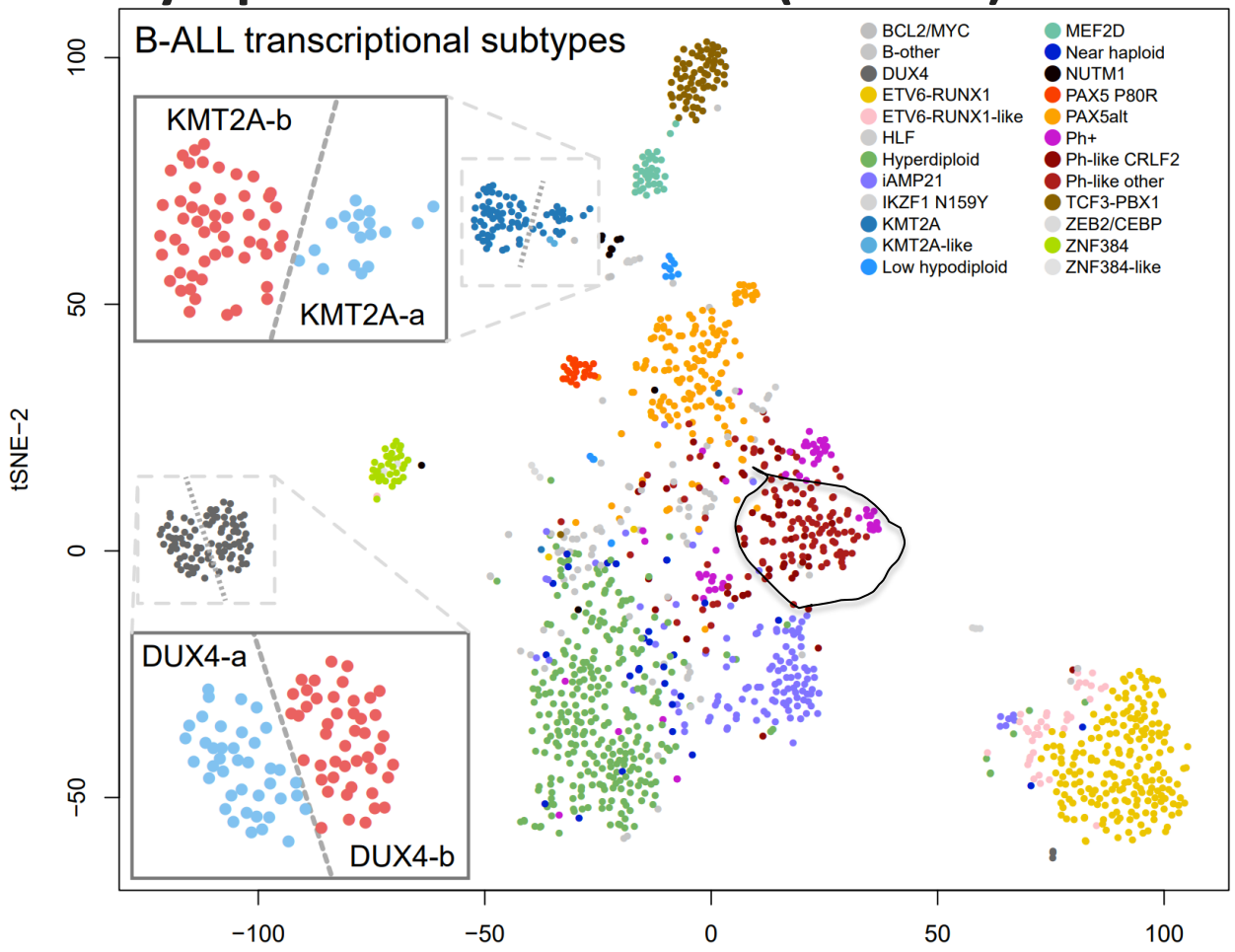
Pan-neuroblastoma Study of ~700 Patients



Brady et al, Nat. Comm. 2020

Define Genetic Basis by Following the Cluster Pattern of Expression/Methylation Data

The genomic landscape of pediatric acute lymphoblastic leukemia (n=2754)

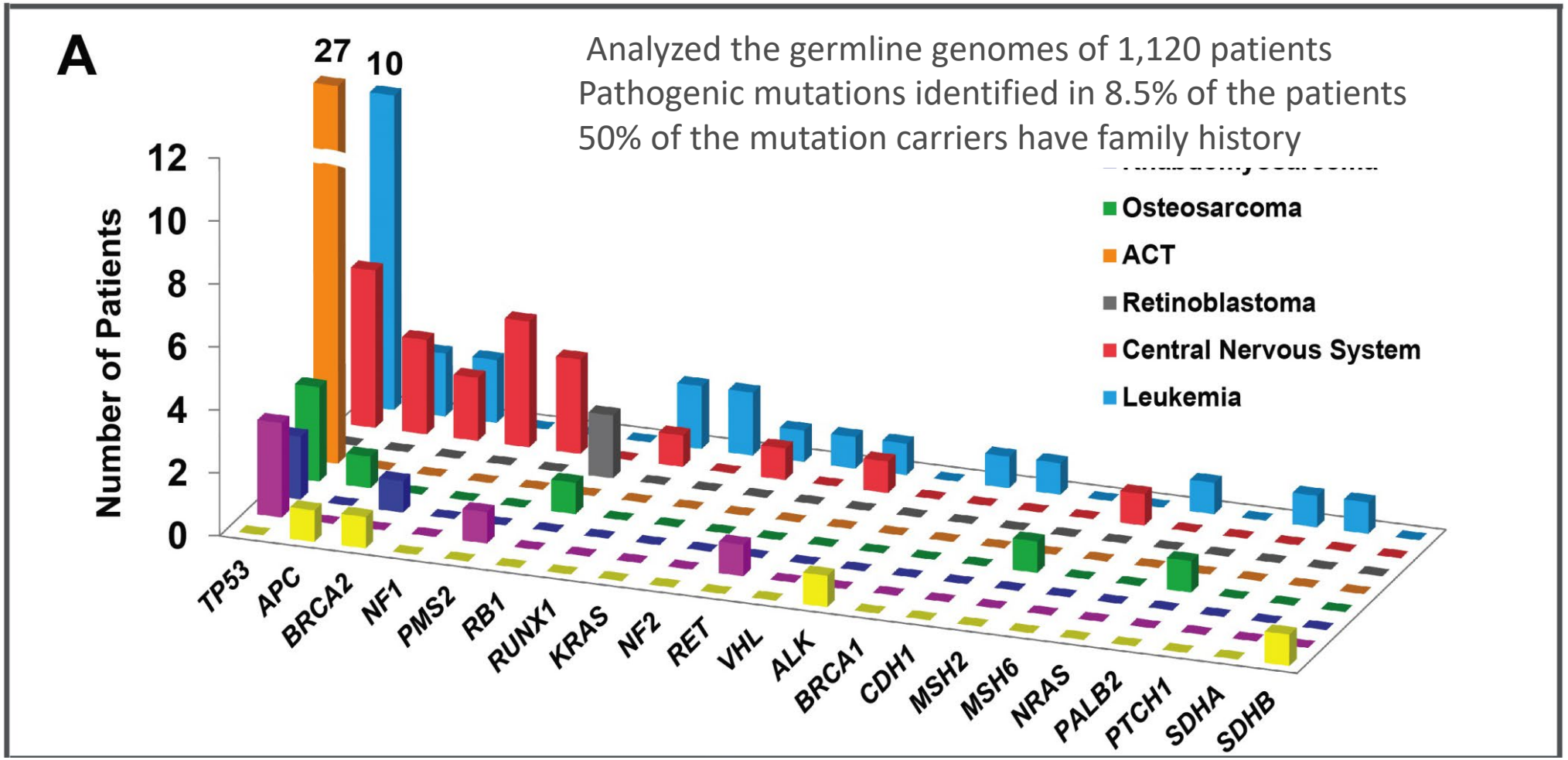


Brady et al, Nat. Gen. 2022

Approaches

1. Perform clustering using RNA-seq expression of methylation data.
   - ➢ Samples are organized by genetic alterations or cell of orgin or both
2. Analysis of genetic variants for samples within a cluster can identify cluster-specific recurrent drivers (e.g. NUMT1 fusion)
3. Heterogeneous drivers affecting the same program can be identified (e.g. Ph-like ALL)
4. Additional collaborative mutations led to substructure within a cluster

Germline Predisposition in Pediatric Cancer

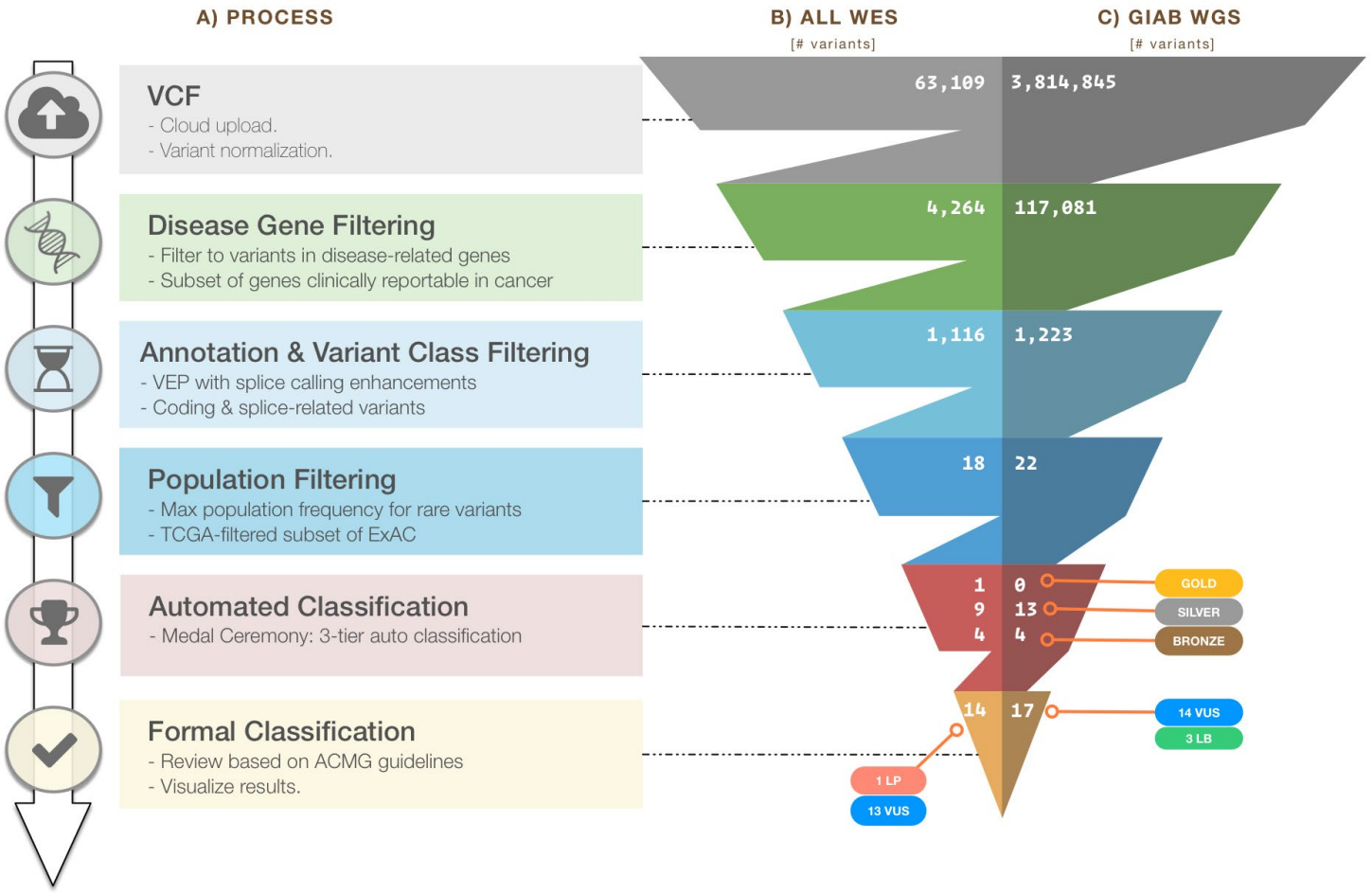


J. Zhang et al, NEJM 2015

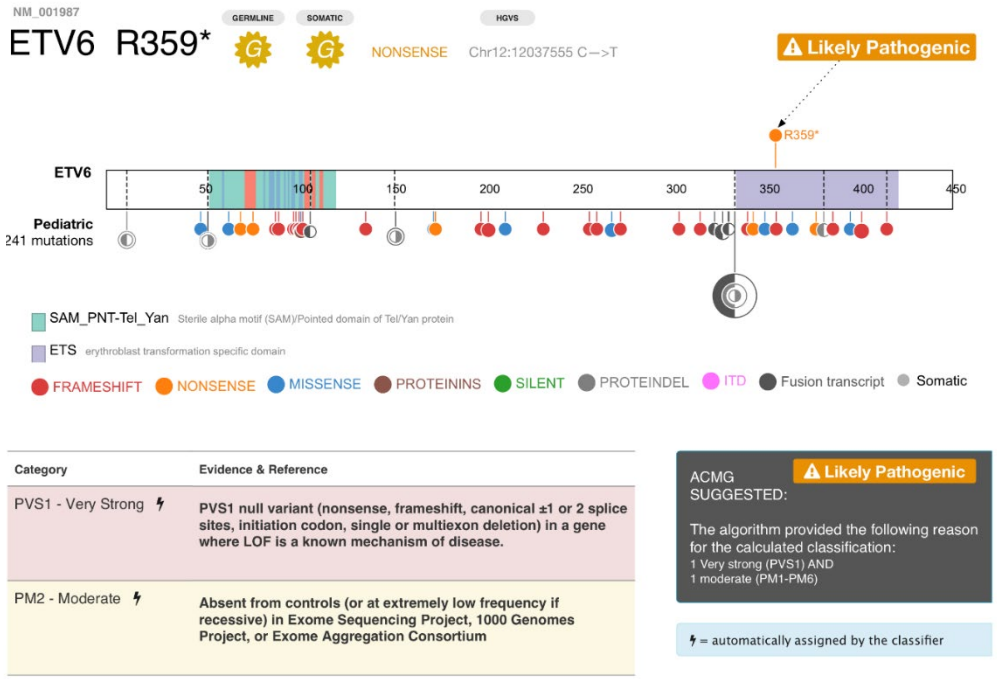
Germline Variant Classification by PeCanPIE

Pediatric Cancer Variant Pathogenicity Information Exchange

https://platform.stjude.cloud/tools/pecan_pie

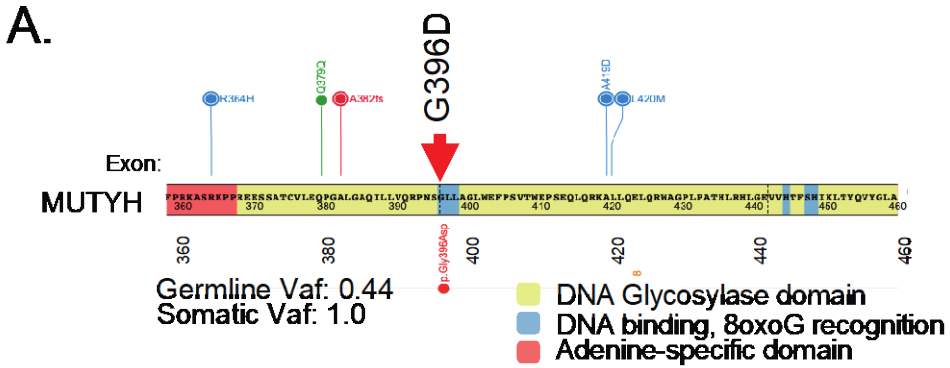


- ❑ Used for JCO 2018, Lancet Oncology 2015, Cancer Discovery 2021
- ❑ Used for clinical and research



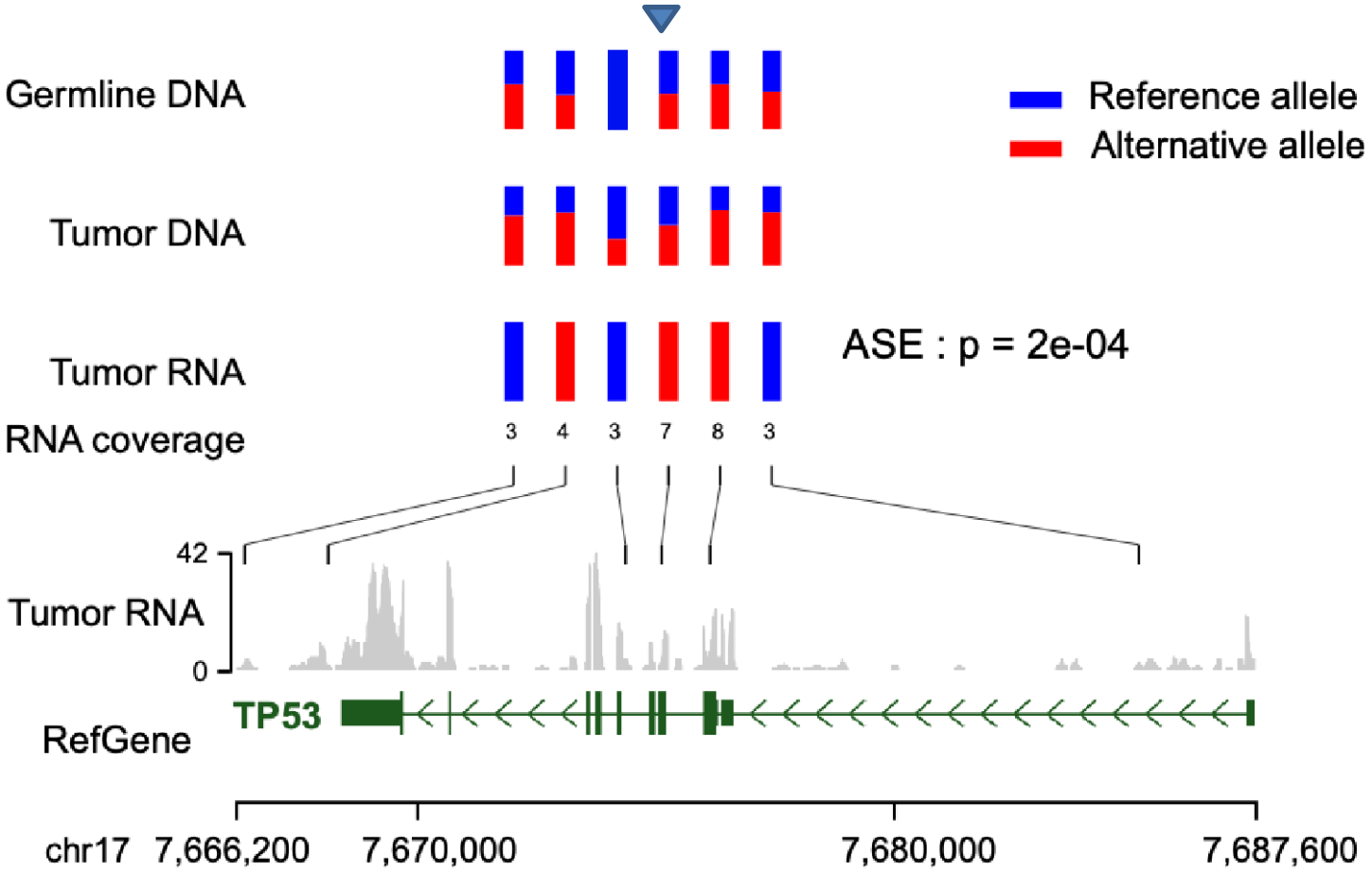
Edmonson et al, Genome Research 2019

Tumor WGS Mutational Signature for Germline Variant Classification



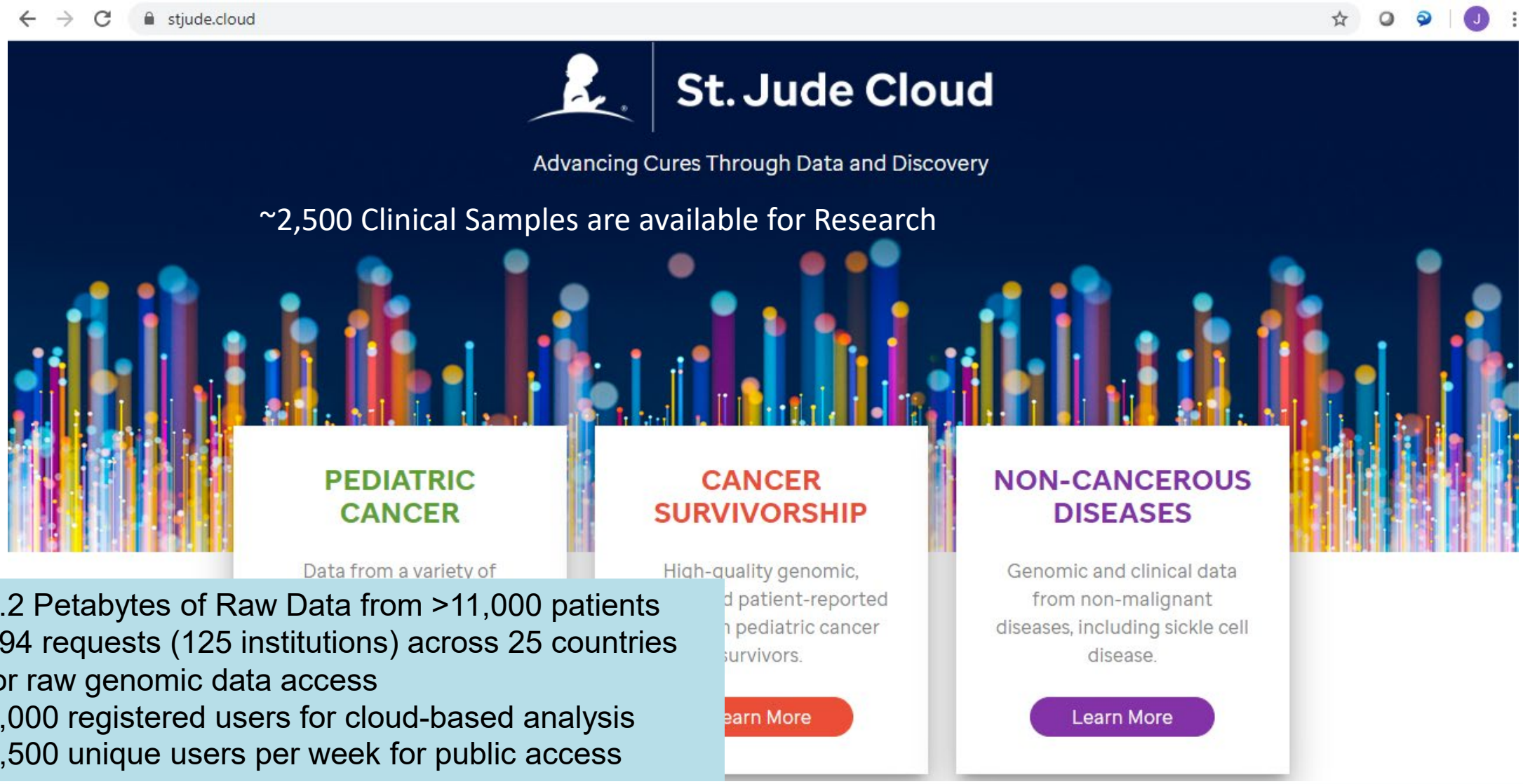
Tumor Allelic-Specific Expression (ASE) for Germline Variant Classification

TP53 A161T in a ganglioneuroblastoma patient.



Data Sharing & Visualization on St Jude Cloud

https://www.stjude.cloud/



- 1.2 Petabytes of Raw Data from >11,000 patients
- 394 requests (125 institutions) across 25 countries for raw genomic data access
- 3,000 registered users for cloud-based analysis
- 2,500 unique users per week for public access