CO-OP 2025

Chloe Flamm

PARKER INSTITUTE FOR CANCER IMMUNOTHERAPY

Our mission is to accelerate the development of breakthrough immune therapies to turn all cancers into curable diseases.

WHAT IS PICI?

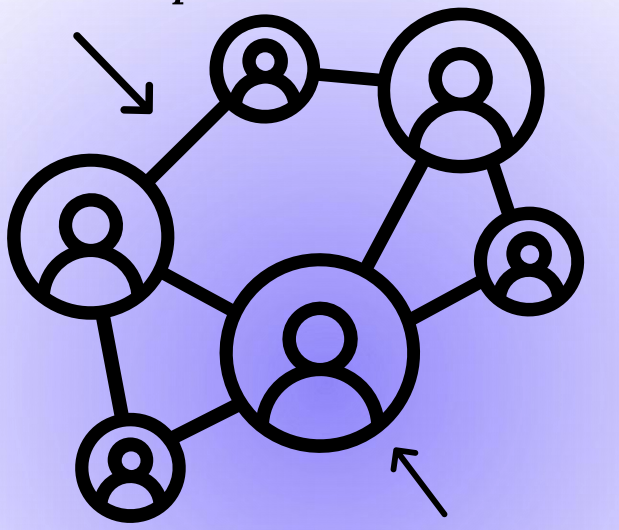
- Patient-centric, grant-giving non-profit organization
- 700+ Cross-Institutional PICI Investigators
- Supports innovative research and clinical trials
- Investments in emerging companies
- Funds early-career scientists

MEASURING PICI'S IMPACT ON THE FIELD OF CANCER IMMUNOTHERAPY

- KEY QUESTIONS:
  - Who is PICI collaborating with?
  - How can we quantify scientific output and collaboration across institutions?
- WHAT METRICS BEST INDICATE COLLABORATION?
  - PICI Center Publications
  - (External) Co-authorships
- VISUALIZING COLLABORATION
  - Network Graph to visualize institute and author relationships
  - Sizing nodes by meaningful metrics

PICI PUBLICATIONS NETWORK GRAPH

Publication
Co-Authorship



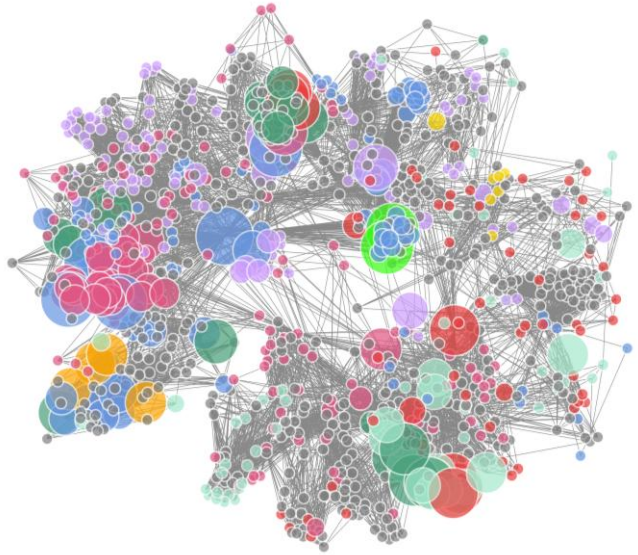
Author

- Color: PICI Center
- Size: External Co-Authorship

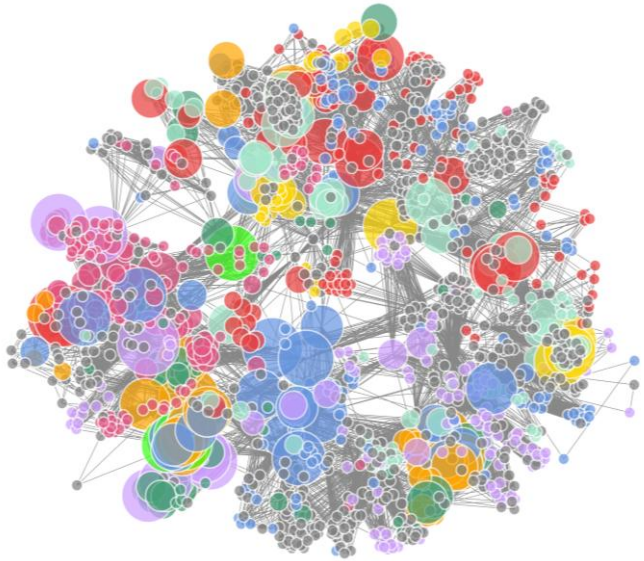
- PubMed API
- All Publications with PICI listed in authorship, as grant-funders, or full-members
- 2016 – mid 2025
  - Filtered by H4 Index
  - 11,000+ Publications
  - 10 PICI Centers
- Highlights PICI's ongoing contributions to collaboration between institutions

PUBLICATION NETWORK BY YEAR

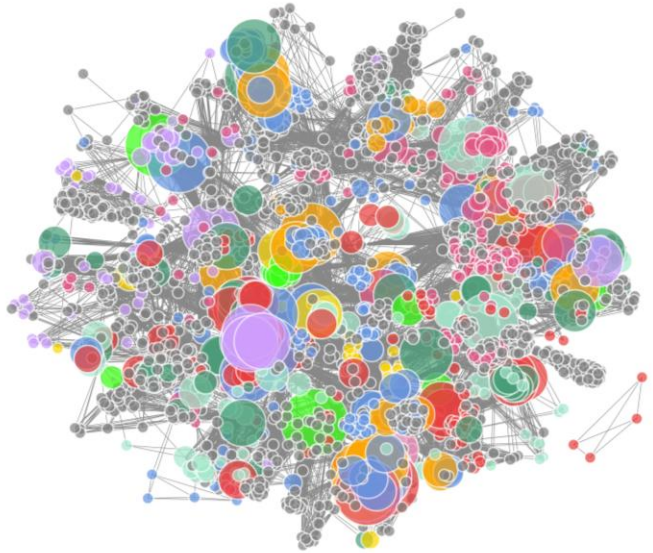
- Nodes = Authors
- Color = Institution
- Edges = Publication Co-Authorships
- Node Size = Num of External Co-Authorships



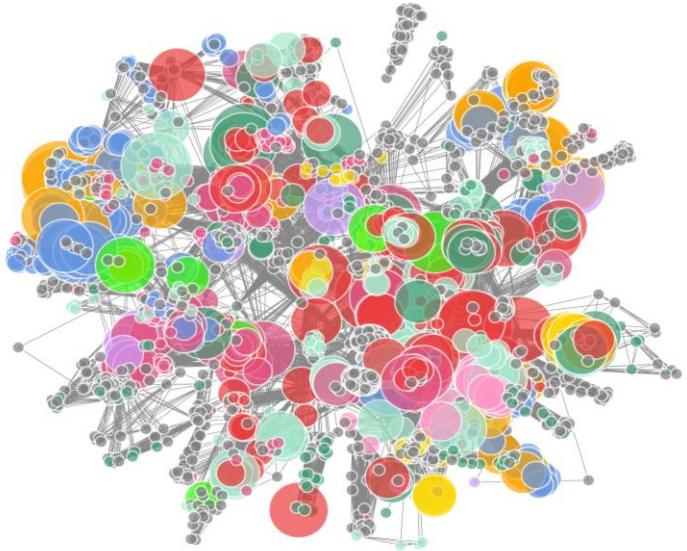
2016-2017



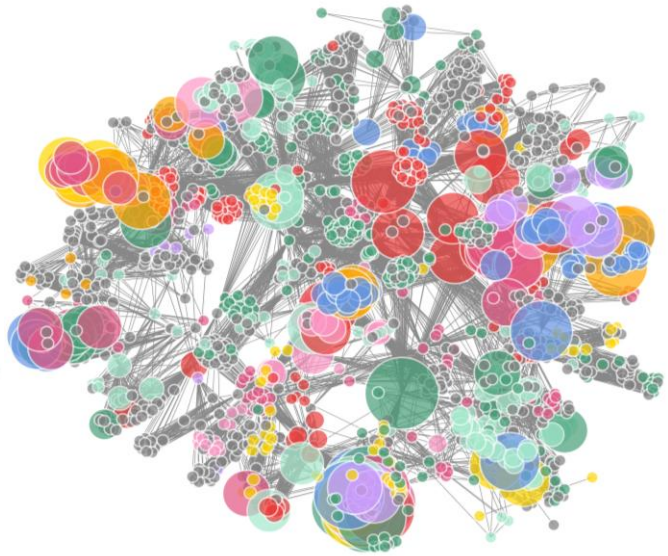
2018-2019



2020-2021



2022-2023

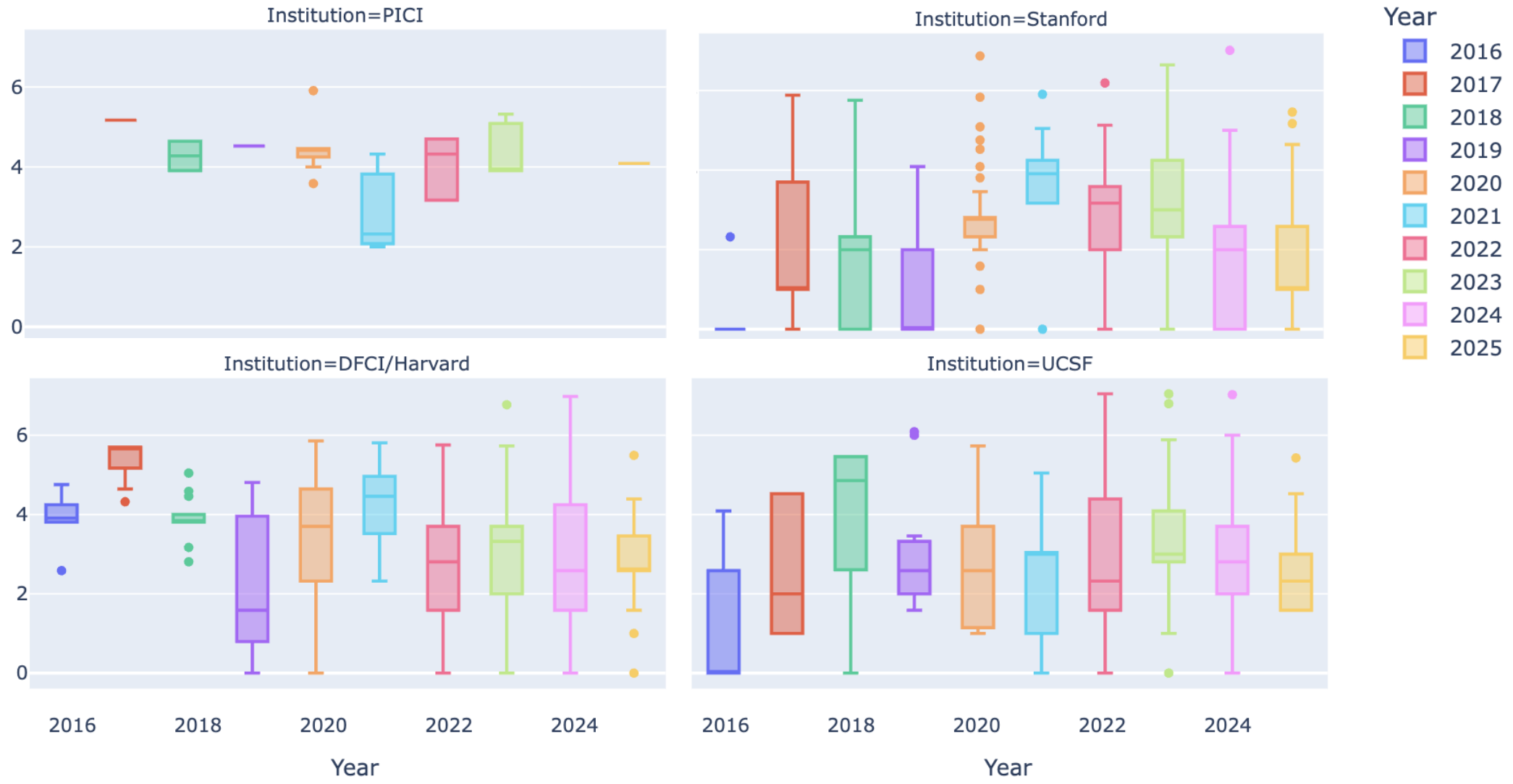


2024-2025*

* pulled mid-2025

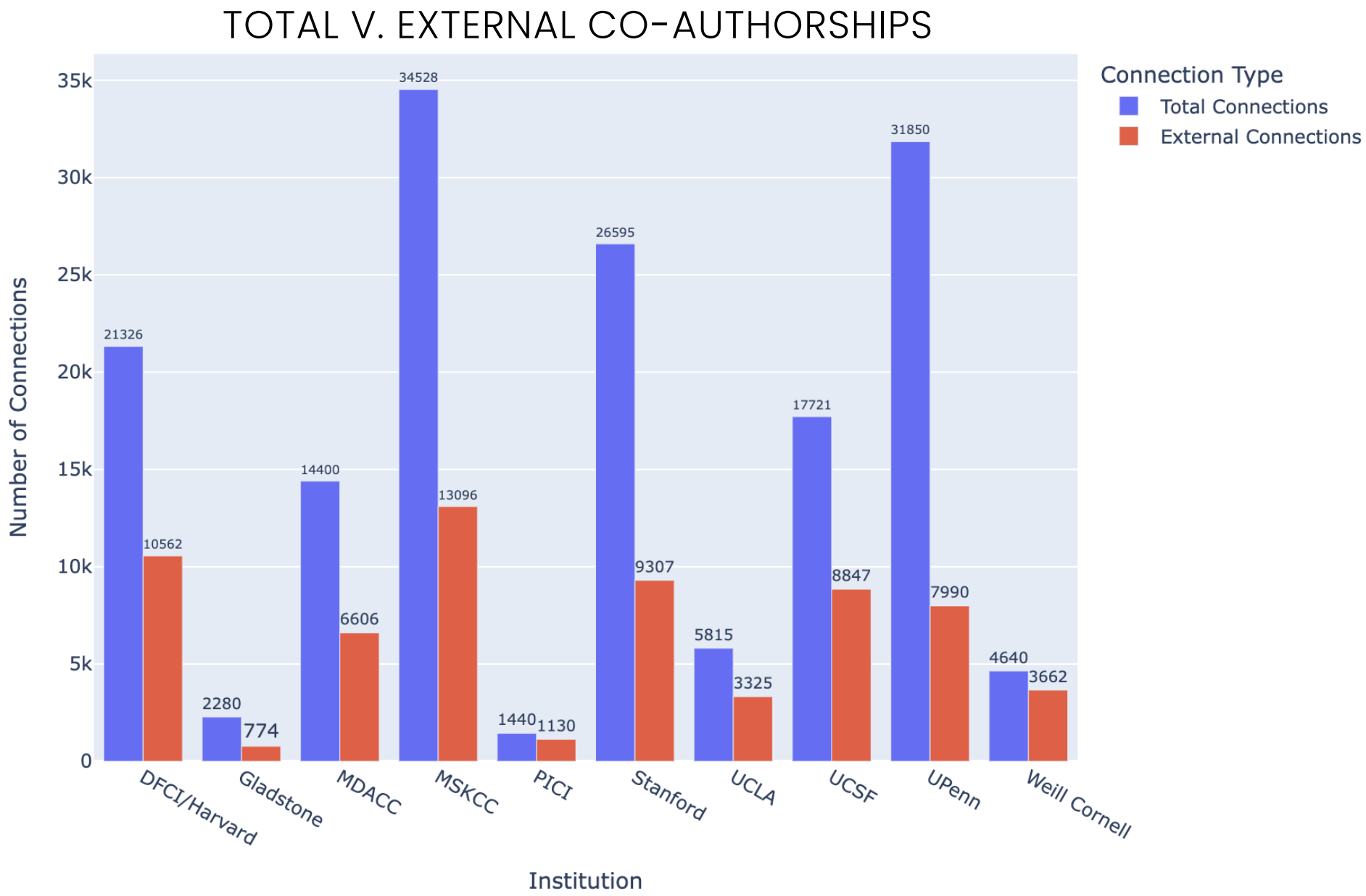
PICI Institutes Individual Collaboration Over *Time*

(LOG_2) OF EXTERNAL CO-AUTHORSHIPS



External Compared to *Overall* Collaboration

- Institutional connections represent the total sum of all co-authorship edges
- Count reflects collaboration volume, not the number of unique publications
- High overall co-authorship does not guarantee strong cross-institutional collaboration



Data Bias and Assumptions

- So, does this mean certain institutions are less collaborative than others? No.
- Number of connections is skewed by the length of authorship per publication
- Certain publications for one institute may have several more internal collaborators while still be collaborative with other institutes
- In this case, longitudinal analysis may be more useful than total
- Still a good indicator of how collaboration has progressed over time for external sharing

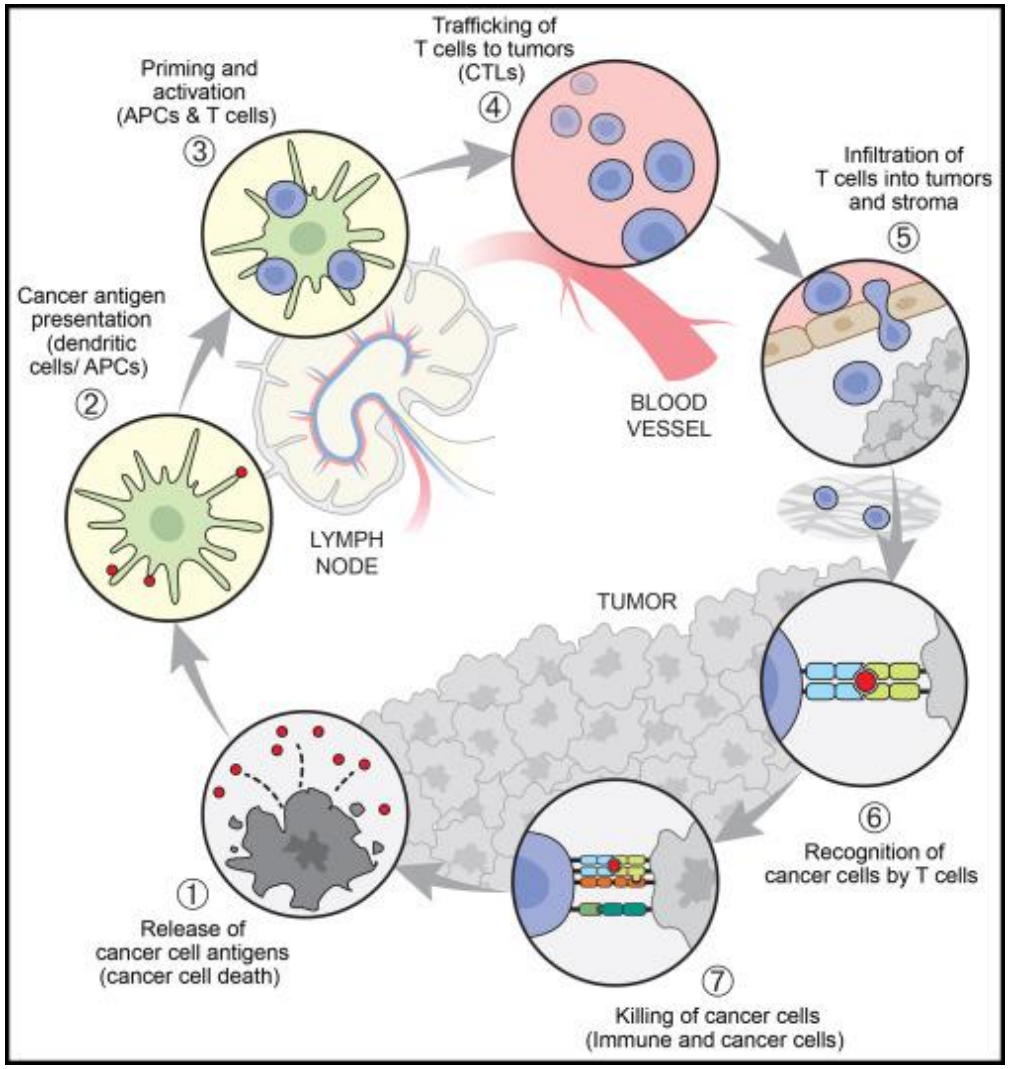
How Does Immunotherapy *Work*?

- Immunotherapy harnesses your own immune system to fight cancer

- The Immune Cycle
  - Recognition: Immune cells (T-cells) must identify markers (antigens) from cancer cells
  - Activation: The immune system signals T-cells to multiply and prepare to attack
  - Attack: T-cells travel to the tumor, infiltrate malignant cells, and destroy, thus releasing antigens and continuing the cycle.

- Challenges: Cancer cells can evade detection by disguising themselves or expressing conflicting signals

- Immunotherapy Treatments aim to expose cancerous cells or enable the immune system to overcome these challenges



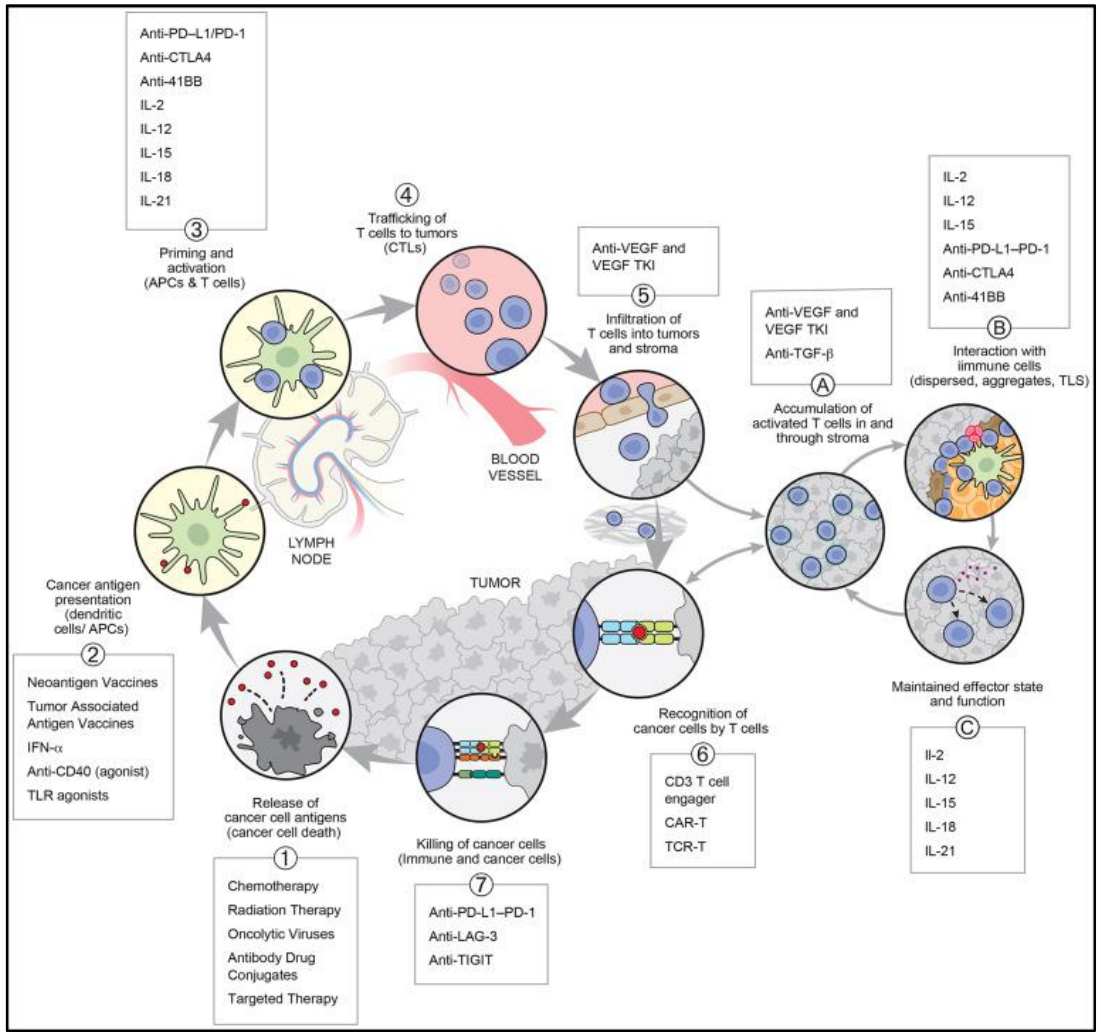
The Cancer Immunity Cycle

Immune Checkpoint Inhibitors (ICIs) *Simplified*

- Checkpoints:
  - Proteins found on immune cells that regulate response
  - Keep the immune system in balance
  - Prevent immune cycle from becoming overly responsive

- To avoid detection, cancer cells express these proteins to turn off the immune system's ability to attack them

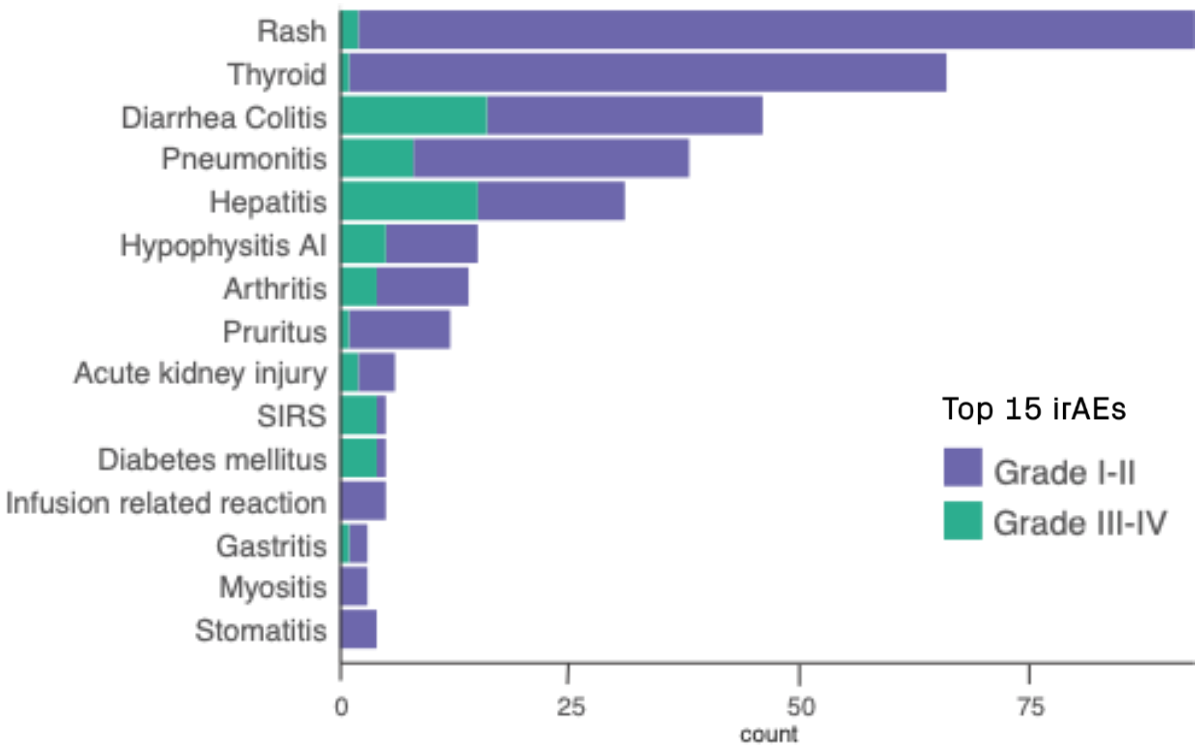
- Immune Checkpoint Inhibitors block these "off" signals to enable the immune system to respond to cancer cells



Targeted Cancer Immunity Therapies

Challenges with Immunotherapy

- Immune-related Adverse Events (irAEs)
  - Overactivation from ICIs to stimulate the immune system can cause inflammation and the body to mistakenly attack healthy tissues and organs
  - 25.4% of RADIOHEAD patients experienced irAEs
  - Potentially underreported
  - irAEs can span from mild rash to severe life-threatening effects on organ function, leading to hospitalization or steroid treatment



RADIOHEAD

RESISTANCE DRIVERS FOR IMMUNO-ONCOLOGY PATIENTS INTERROGATED BY HARMONIZED MOLECULAR DATASETS

1070 Patients
3500+ Timepoints

70K+ Sample Aliquots Banked

- Patient Information
- Treatment Detail
- Outcomes Data
- Additional Metadata

- Whole Blood
- Plasma
- Serum
- PBMC

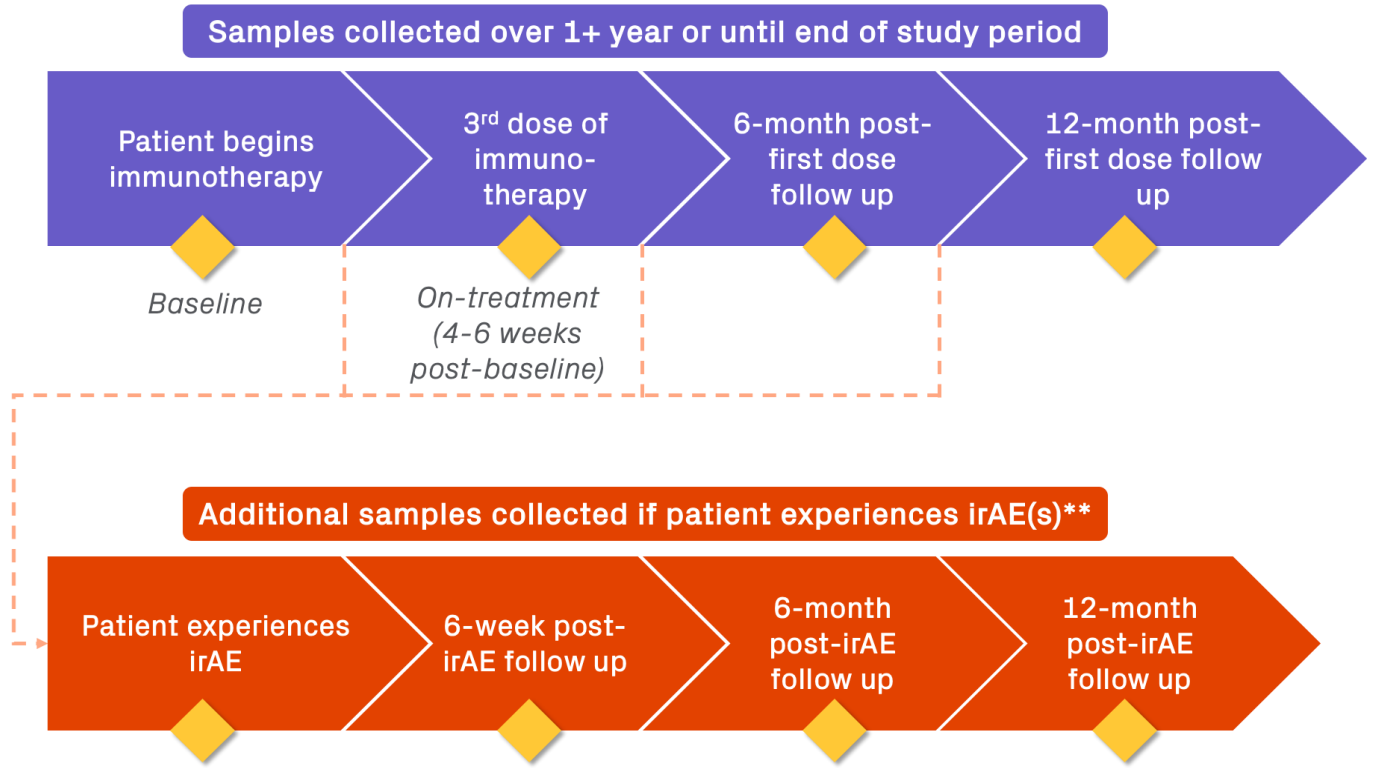
THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

Bristol Myers Squibb™

UNIVERSITY OF UTAH HUNTSMAN CANCER INSTITUTE

UCSF



RADIOHEAD Study Planning

Study Support and Goals:

- Funded by the Helmsley Charitable Trust, JDRF, and Bristol Myers Squibb.
- **Goal:** Identify **biomarkers** to prevent or intervene in:
  - Cancer immunotherapy-induced **Type 1 Diabetes**.
  - Severe **Immune-Related Adverse Events (irAEs)**.

Academic Guidance and Study Direction:

- UCSF: data collection and trial objectives.
- Huntsman Cancer Institute: data cleaning and curation work.

Key Challenges:

- Recruitment for a Rare Event was difficult: 12 Expected, 3 Recruited.

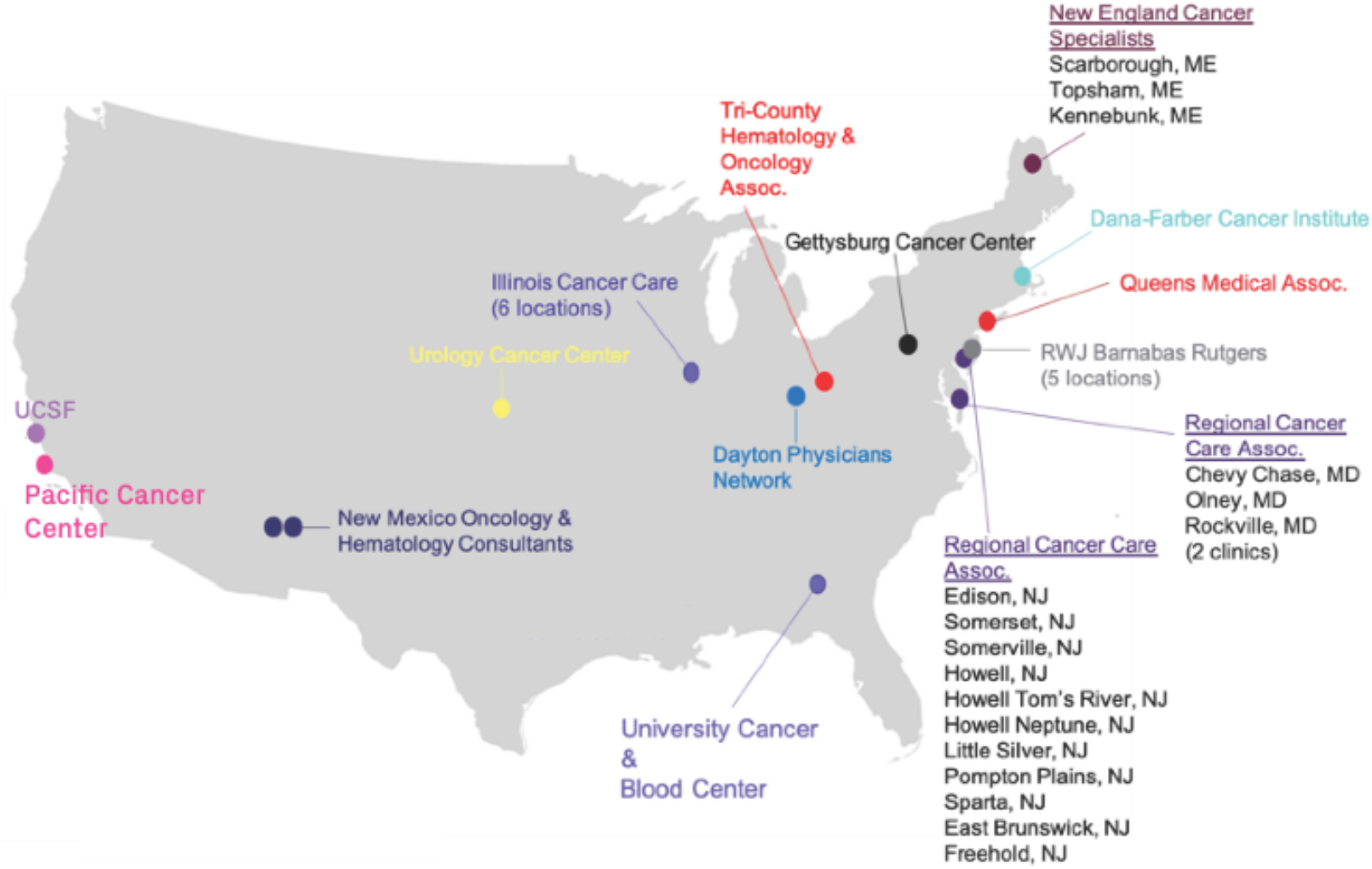
Root Cause Analysis:

- Patient Behavior
- COVID Impact
- Technical Issues
  - Difficulty in diagnosing T1D in community centers lacking specialized experience.

New Focus: Association between all Immune-Related Adverse Events (irAEs) and Cancer Treatment Response.

What Makes RADIOHEAD *Unique*?

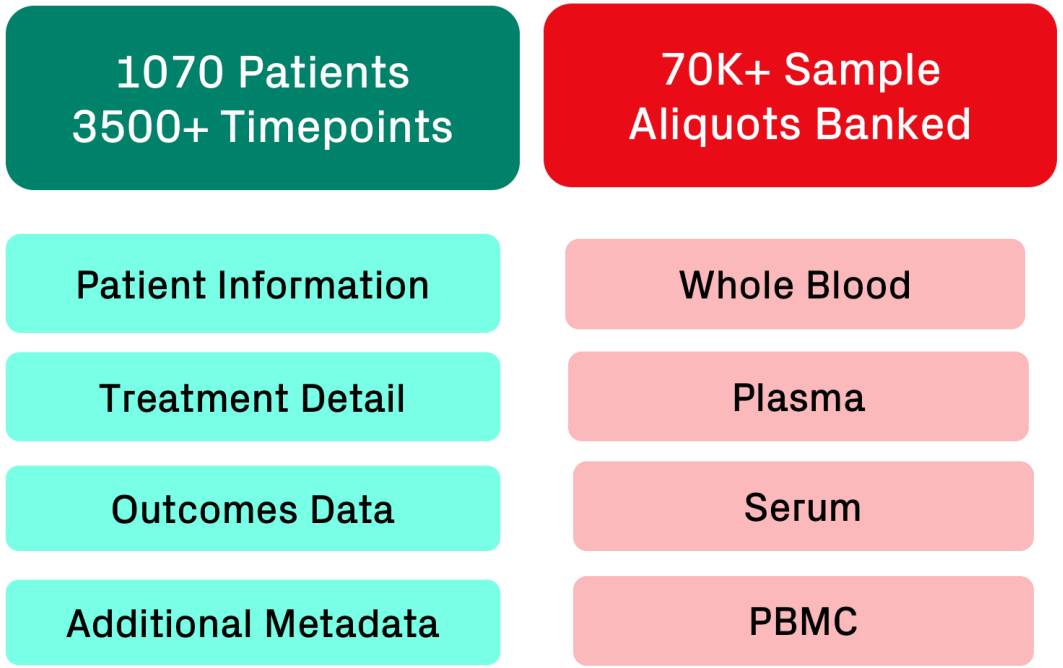
- Real-World Setting
  - 49 *Community* Hospitals
  - Patients already receiving standard-of-care immunotherapy
  - Large pan-cancer cohort
  - Representative of population
- Standardized Processes
- All blood samples shipped overnight to ensure consistency across sites
- Central Laboratory: Usage of a single central facility to eliminate processing variables
- Batch Effect Analysis
- Event-Driven Sampling
  - Additional samples collected in the event of an adverse event (irAE)



Sample Collection and Biases

- **Geographic Bias:** Study privileges expensive, resource-rich urban hubs
- **Demographic Gap:** Underrepresentation of minority
- **Economic Barriers:** Cost of Access
- **IRAE Potentially Underreported**
- **Lack of Longitudinal Data:** Patient follow up is inconsistent because of pandemic
- **Clinical Limitations:** Additional disease information was often a free textbox

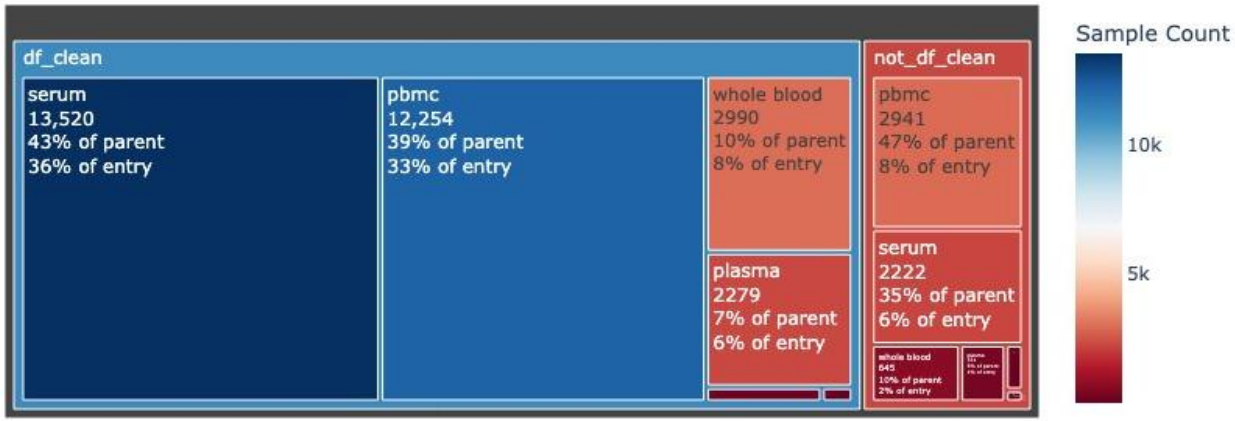
- **Scale and Data:**
  - Data collected from **1,070** patients.
  - Generated over **70,000** samples across **3,500+** unique combinations of patients and timepoints
  - Samples were collected over one year



Datasets

1. **REDCap:** clinical annotations of RADIOHEAD patients
2. **Biorepository:**
   - Multiple pulls: keeping track of sample shipments
   - Samples with unique barcode (PBMC, plasma, serum…)
   - Further sequencing datasets from partnering corporations
3. **df_clean:** cleaned REDCap with 1,070 patients of all patients with a pre-treatment sample

Sample Material Types in PICI 009 Biorepository
(from df_clean patients: 83.3% of all samples)



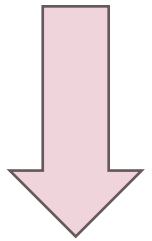
Comprehensive Multiomic Analyses

ctDNA	~750 genes, completed — GUARDANT
Serum Proteomics	600+ proteins, completed — nomic
WES / SNP-panel	completed — Genentech (A Member of the Roche Group) Teiko.bio
HD Flow Cytometry	80 markers, in progress (complete by mid-2025) — BostonGene
Bulk-RNAseq	In progress (complete by mid-2025)
Single cell RNA-seq	Projected to start in April 2025 – partner TBA
Metabolomics	Evaluating partners

Clinical Data Cleaning Priorities

- Cleaning REDCap Clinical Annotations
- Unifying cleaned data with df_clean
  - Merged on PICI Patient ID
  - Standardized free-text previous and concurrent cancers
  - Patient pre-treatment dates
  - Jittered pre-treatment dates for confidentiality
  - Separated (PD-1/PD-L1) Line 1 Therapies
  - Remaining therapy specifications

Clinical Annotations

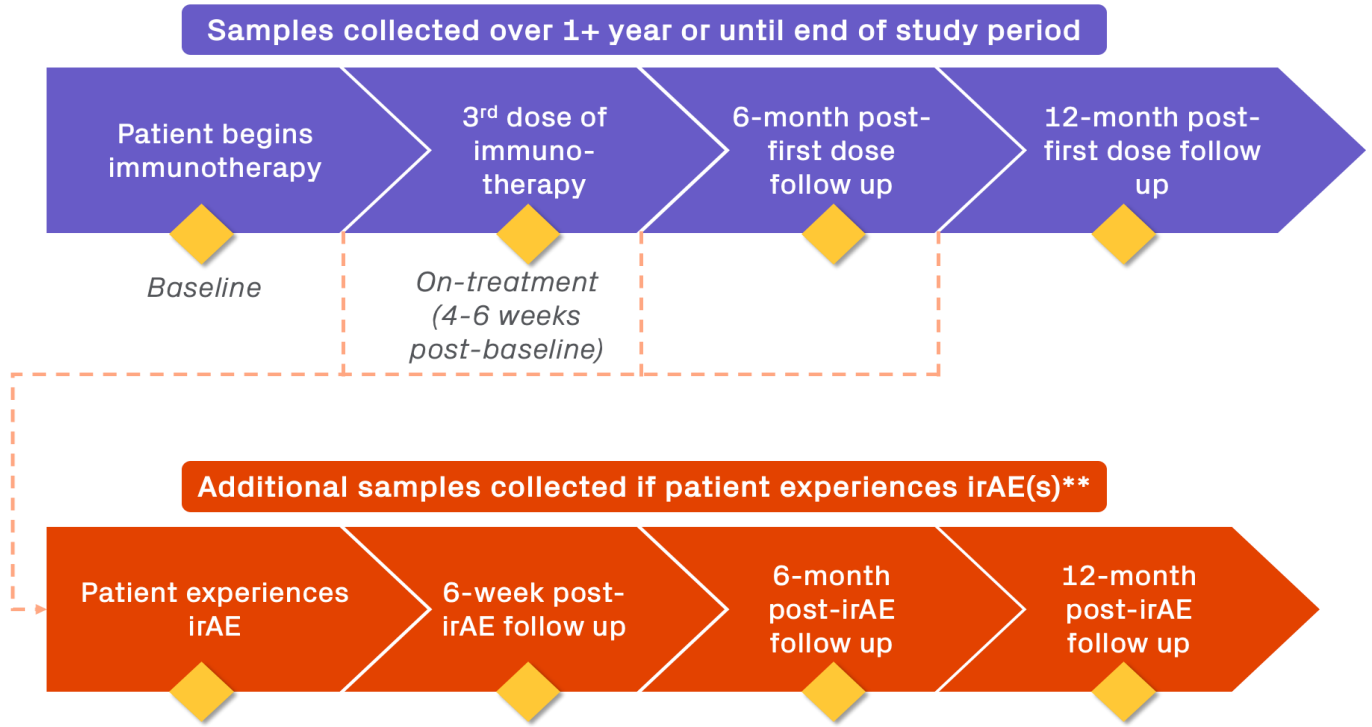


df_clean

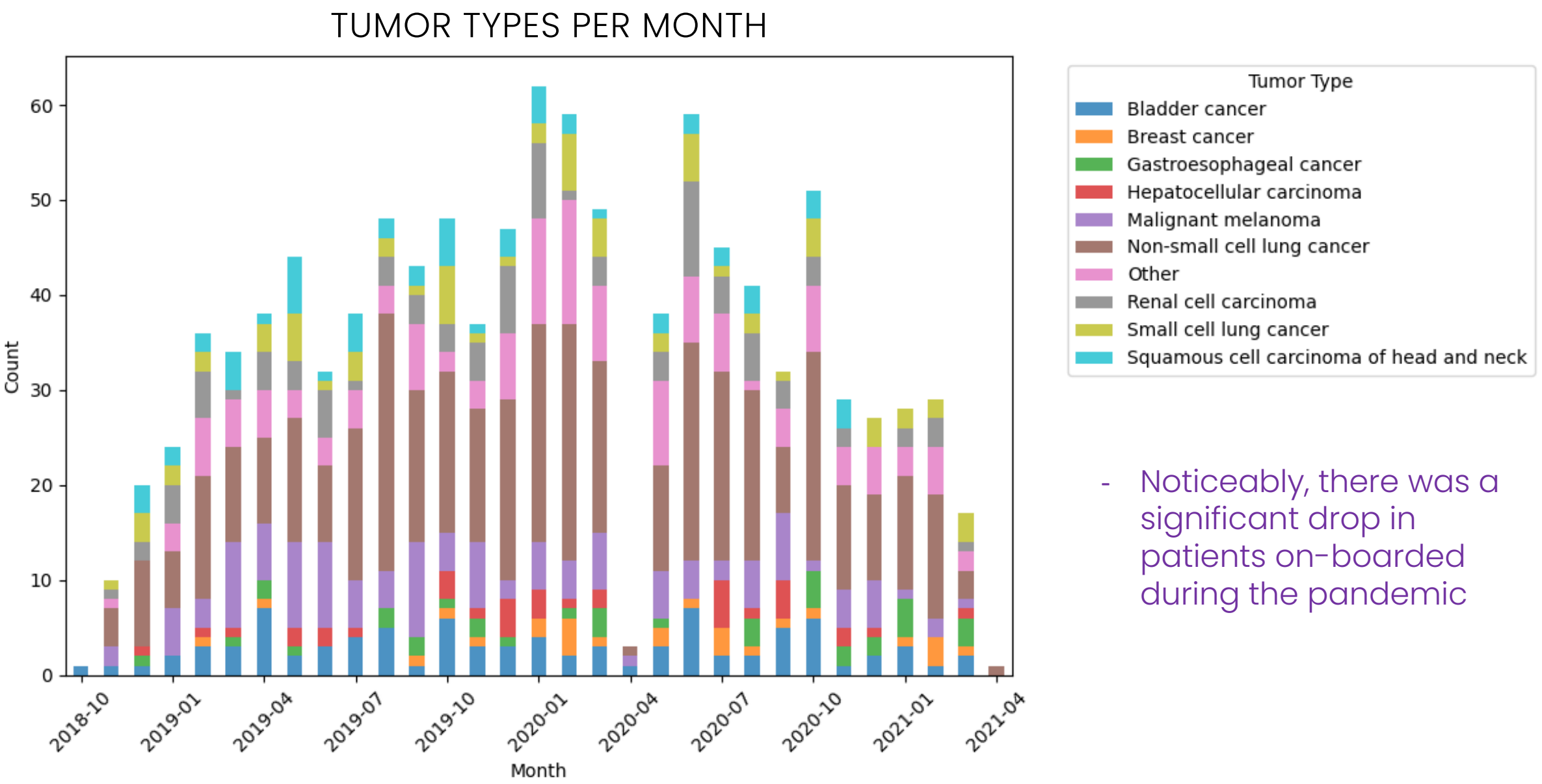
Cleaned Annotations for 1070 Patients

What is Pre-Treatment Date?

- RADIOHEAD requires patients to be immune-naïve before entering study
- Patients came in at different time points
- Pre-treatment dates are entered into REDCap Clinical Annotations
- Collecting a Pre-treatment sample is important for normalization and longitudinal analysis
- Therefore, Patients without Pre-treatment samples were excluded from the study
- When merging dates with df_clean, dates were randomized within a certain number of days to ensure patient confidentiality

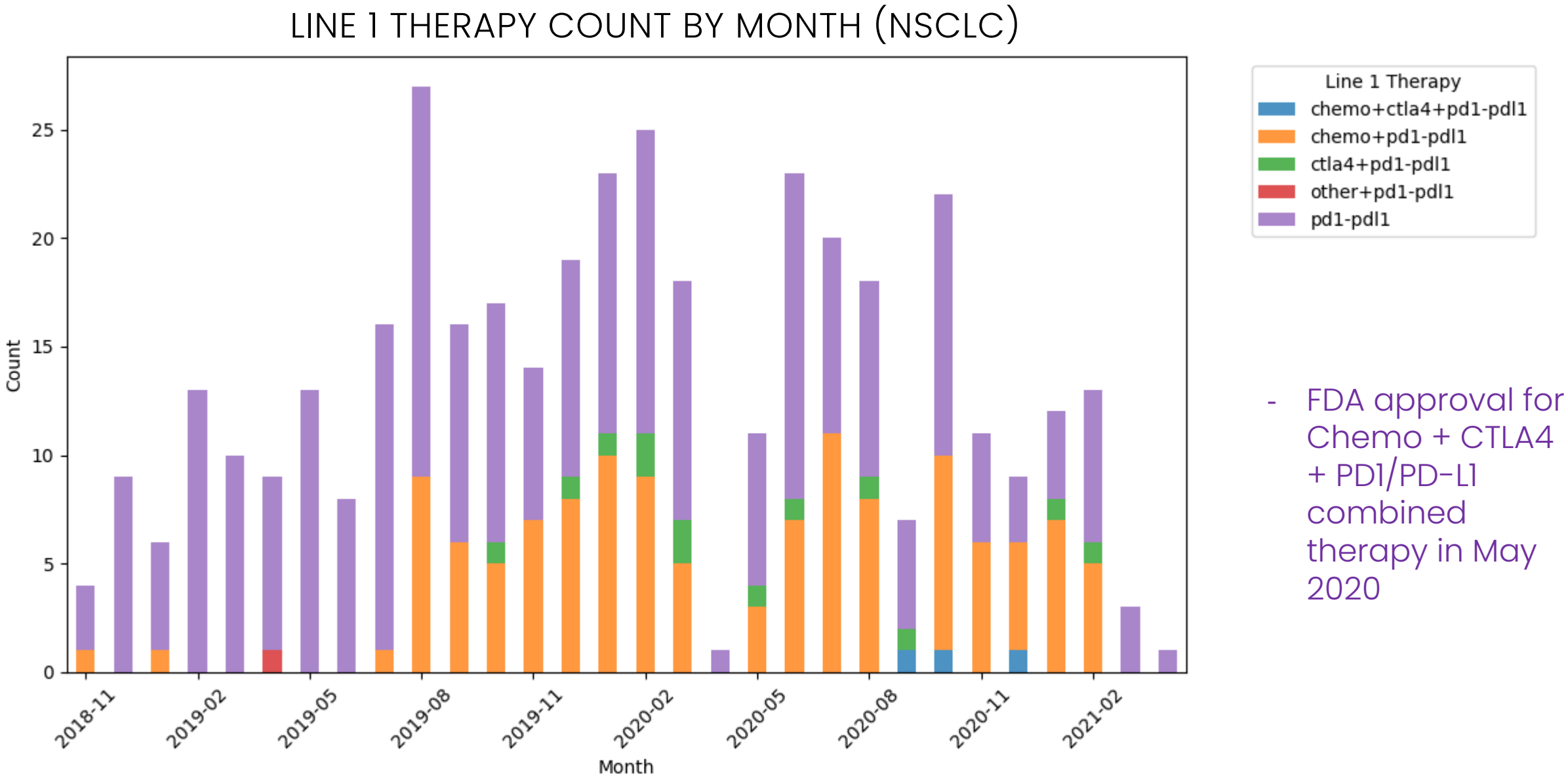


Pre-treatment Timeline by Tumor Type



- Noticeably, there was a significant drop in patients on-boarded during the pandemic

Pre-treatment Timeline by Line 1 ICI Therapy



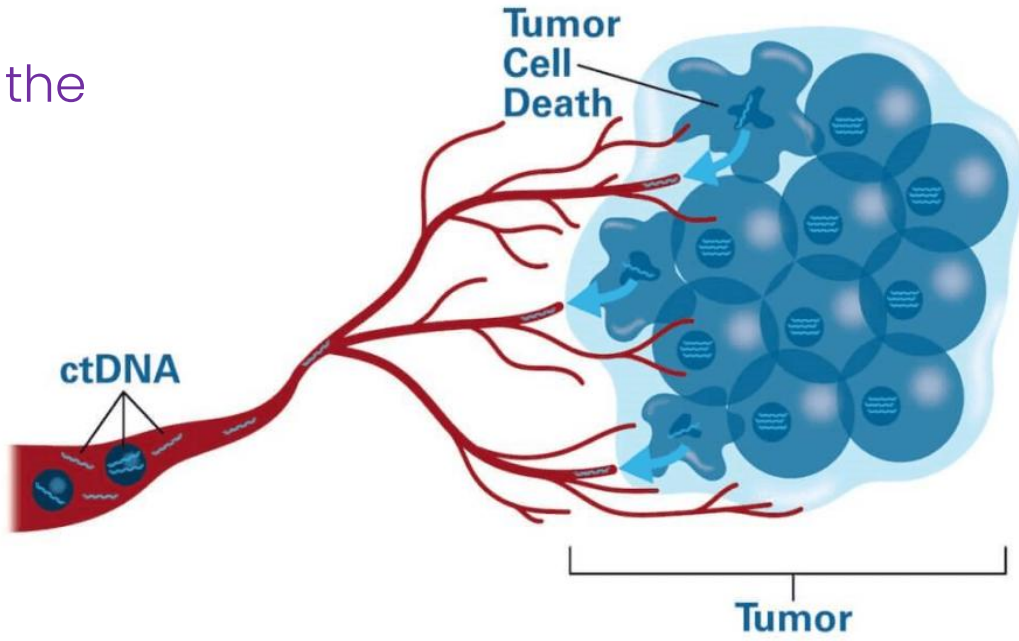
- FDA approval for Chemo + CTLA4 + PD1/PD-L1 combined therapy in May 2020

What is ctDNA?

- Circulating tumor DNA
  - Tumors grow and cells die rapidly
  - When cells die, they shed fragments of their DNA into the bloodstream
  - ctDNA contains genetic mutations specific to the respective tumor type
  - Total ctDNA levels are correlated with cancer progression

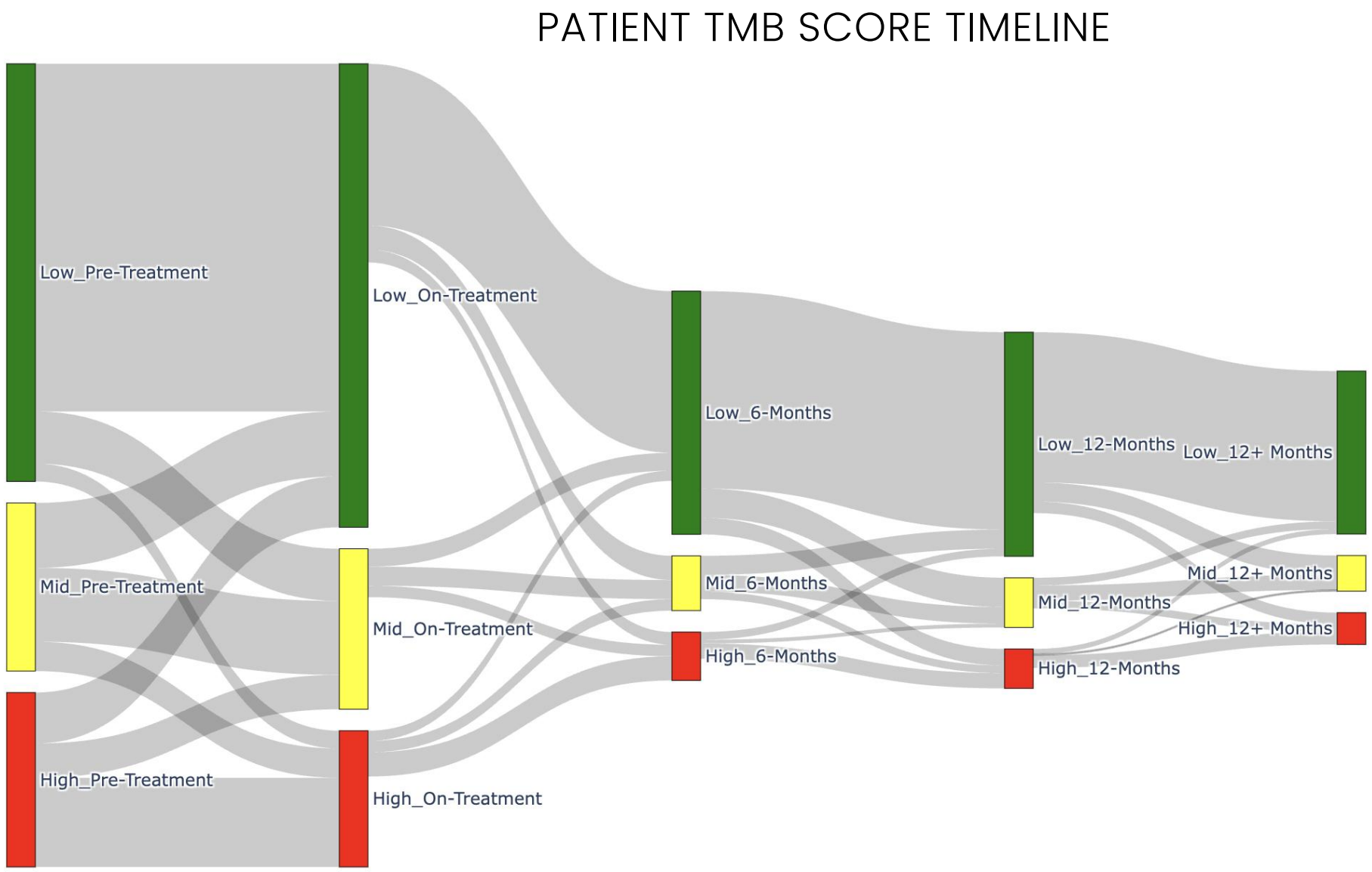
- Tumor Mutational Burden (TMB)
  - TMB is the total number of somatic gene mutations within a genome sequence

- Utility
  - Clinically useful, only requires a blood sample to track tumor progression
  - Potential for targeted therapies



CtDNA (TMB SANKEY)

- How does Tumor Mutational Burden (TMB Score) change over time by Severity?
- Uses Patient Sample data bucketed by time interval
- Diagram only reflects patients with samples between each time point, does not account for missing samples



CtDNA Gene Mutation Workflow

Utilized NCBI Entrez API to collect Gene IDs

Leveraged gene functional annotations from Gene Ontology (GO) Databases

Categorized genes by keywords found in annotations using a dictionary

Prioritized category assignment by critical gene functions

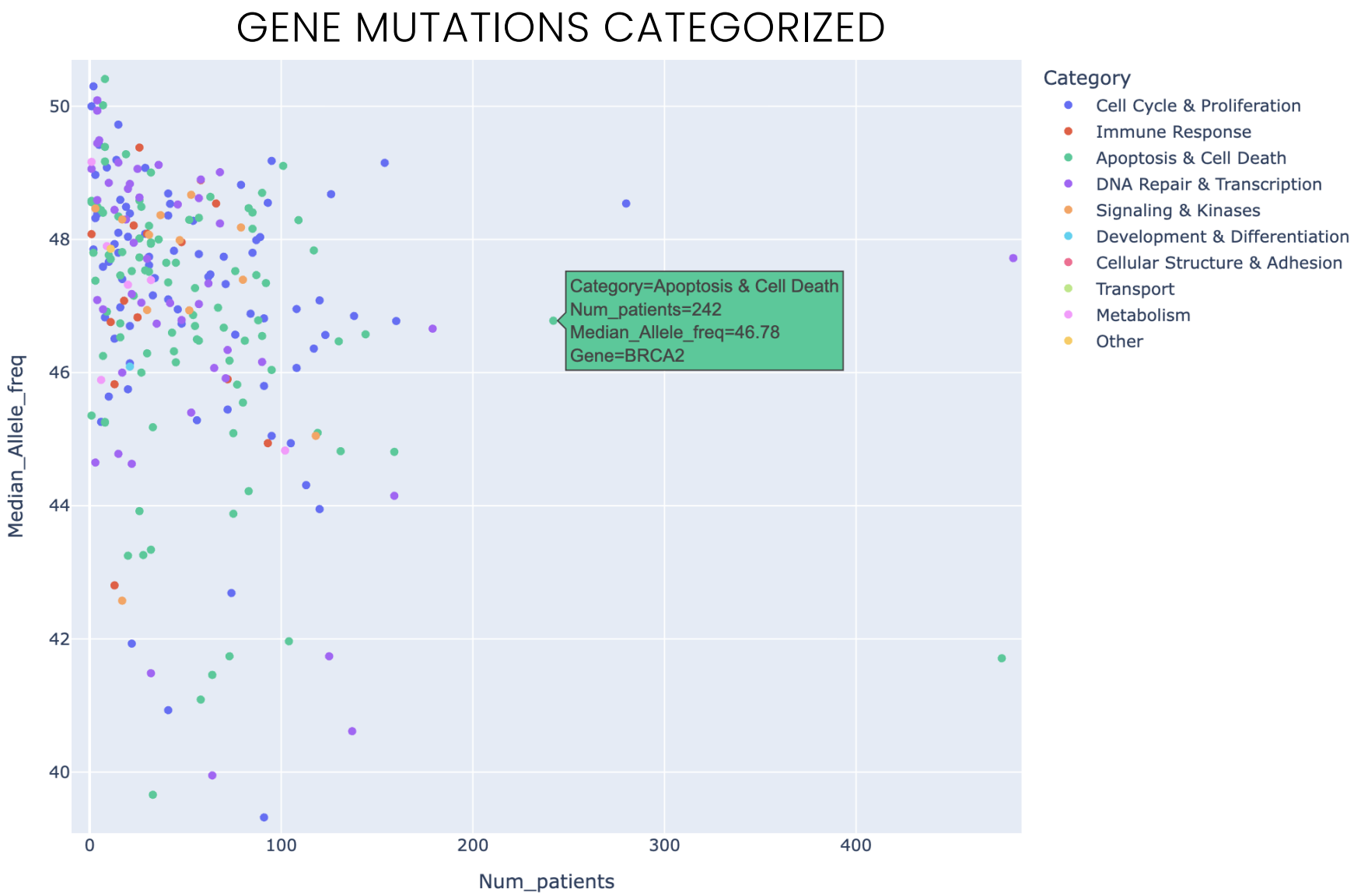
Merged Gene and Gene Categories back with Patient IDs for further analysis

Gene	Gene ID	Category
ADARB2	105	DNA Repair & Transcription
EPS8	2059	Signaling & Kinases
SLC34A2	10568	Development & Differentiation

GENEONTOLOGY
Unifying Biology

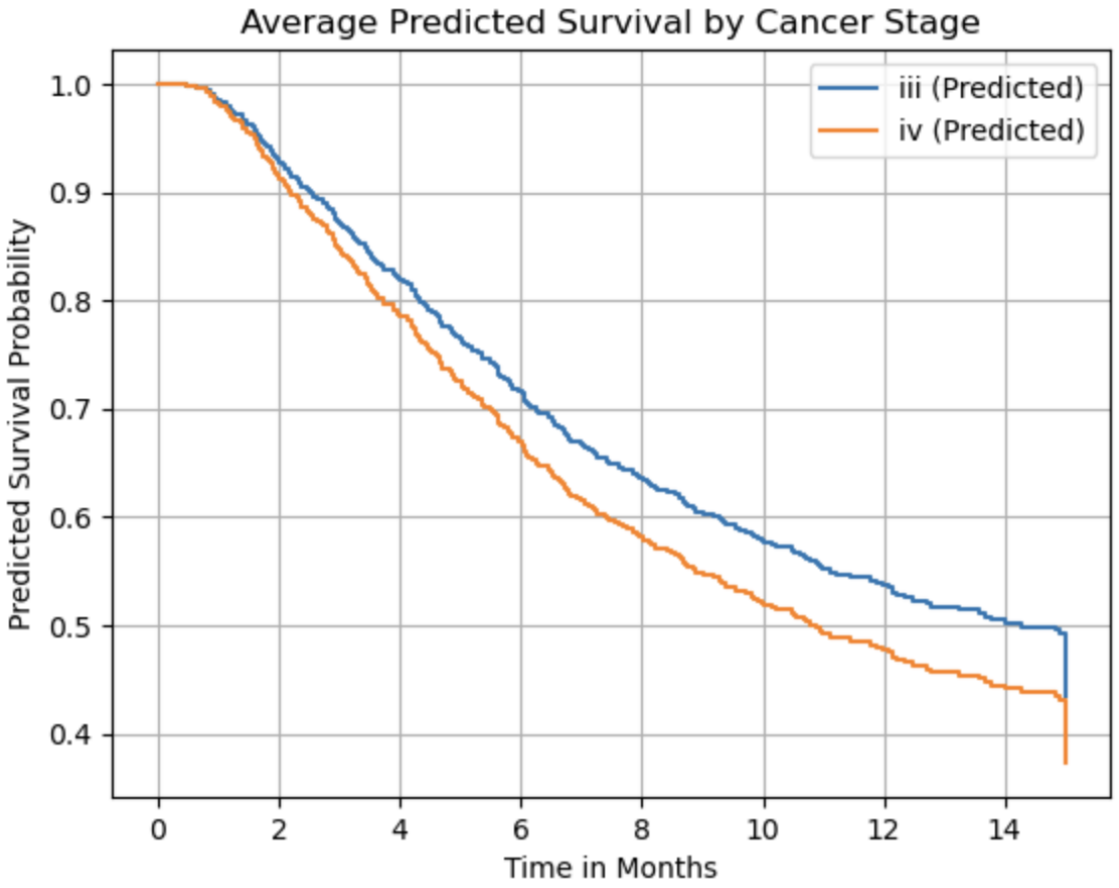
CtDNA (Gene Mutations)

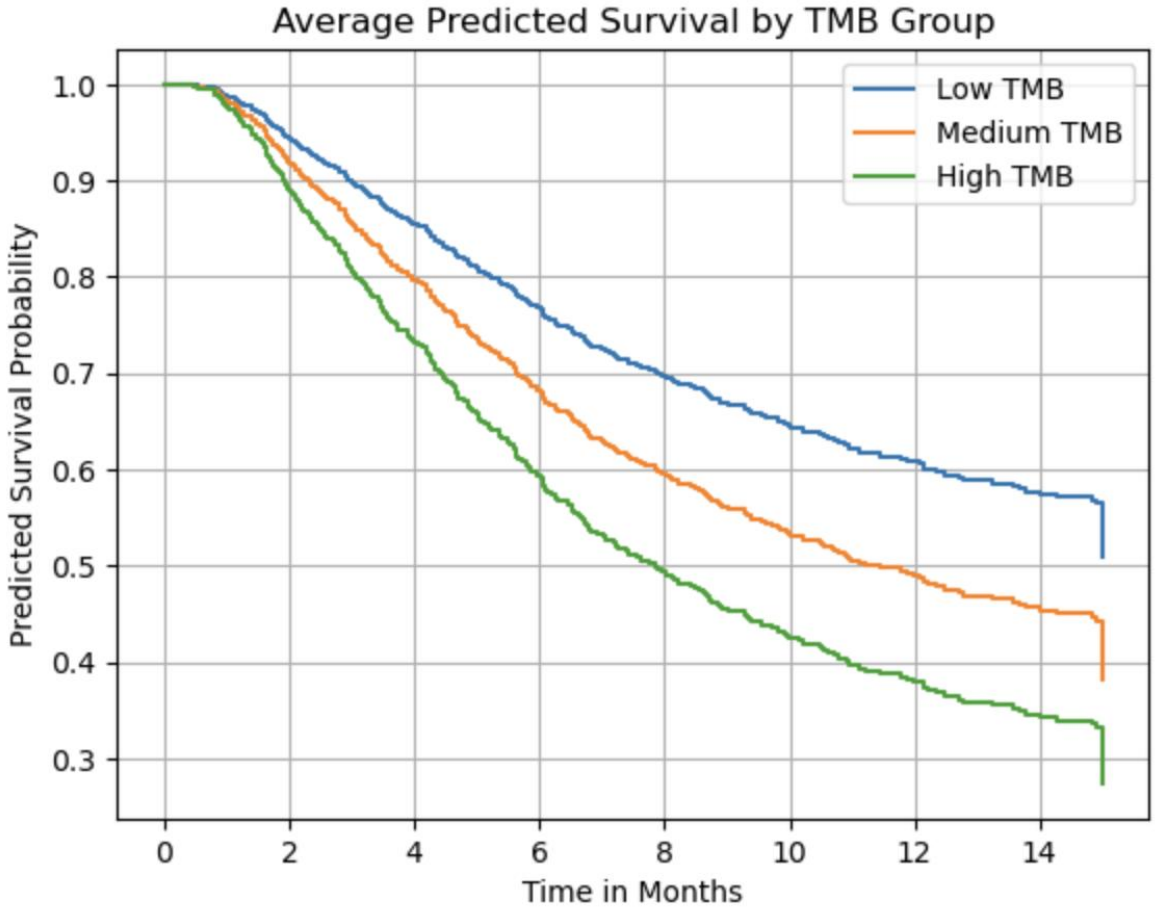
- Filtered ~50% Allele Frequency to investigate for Heterozygosity
- Interested in Genes with high enough allele frequency and prevalent in a significant number of patients
- Genes may fall into several categories, but are sorted by priority



Survival Analysis (Cox PH)

USING PROGRESSION FREE SURVIVAL & GENE FUNCTIONAL CATEGORIZATION





Can Gene Mutation Category Affect Survival?

- Truncated at 15 mo. (Immortal Time Bias)
- Pre-treatment TMB Score is the predominant feature
- C-index: 0.635, where 0.5 is Random
- N size is too low for accurate predictions

Next Steps

Network Graph

- Control for Length of Authorship
- Optimize and Clean script for pulling from PubMed API

Radiohead

- Explore relationships between datasets and fully harmonized df_clean
- Signaling pathways, connecting bio pathways across modalities
- More survival analysis
- Practice feature reduction techniques

Software & Tools | Python

Data Curation & Processing

- Pandas & NumPy: Data manipulation and structuring
- PubMed API: Publication data retrieval
- NCBI Entrez: Gene ID data retrieval
- Gene Ontology (GO): Categorization using gene2go and go-basic.obo

Visualization

- Plotly: Primary visualization tool (Sankey diagrams, Boxplots, etc.)
- Matplotlib: Static plotting
- NetworkX: Network structure and layout algorithms

Survival Analysis (scikit-survival)

- Scikit-learn Utilities: StandardScaler, MultiLabelBinarizer, train_test_split
- Models: Cox Proportional Hazards , Random Survival Forests, Gradient Boosting
- Metrics: Concordance Index, Permutation Importance

THANK YOU!

CONTACT ME

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Sources

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- Fig. X. Immune-related adverse events and impact on survival outcomes. Image from Zoe Quandt et al., Associations between immune checkpoint inhibitor response, immune-related adverse events, and steroid use in RADIOHEAD: a prospective pan-tumor cohort study, Journal for ImmunoTherapy of Cancer, vol. 13, no. 5, 12 May 2025, e011545, doi:10.1136/jitc-2025-011545. PubMed, https://pubmed.ncbi.nlm.nih.gov/40355283/