



# Tumor Immune Microenvironment: A Holistic Approach Workshop

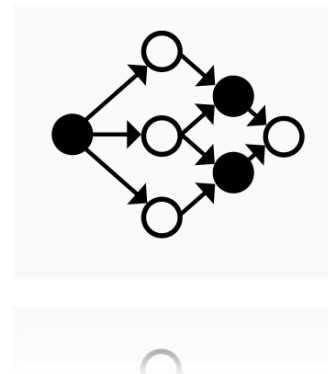
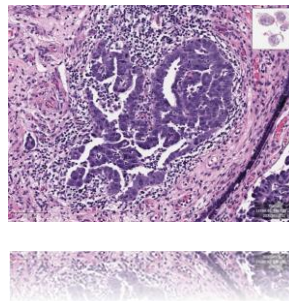
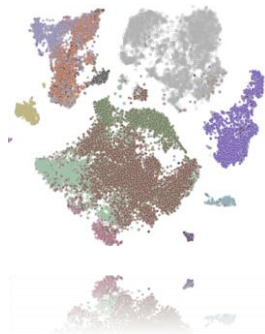
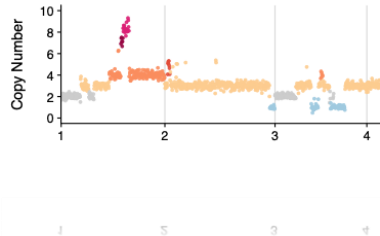
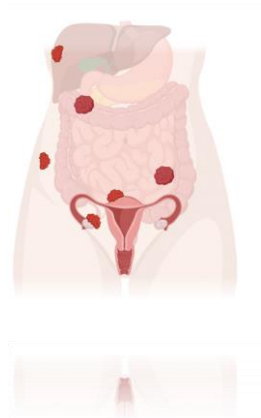
April 21-22, 2022 • San Diego and Virtually

#SITCworkshop



Society for Immunotherapy of Cancer

# Malignant and immune cell phenotypic states in high grade serous ovarian cancer



**Sohrab P Shah PhD**

Chief Computational Oncology

Epidemiology & Biostatistics

Nicholls-Biondi Chair in Computational Oncology

Memorial Sloan Kettering Cancer Center

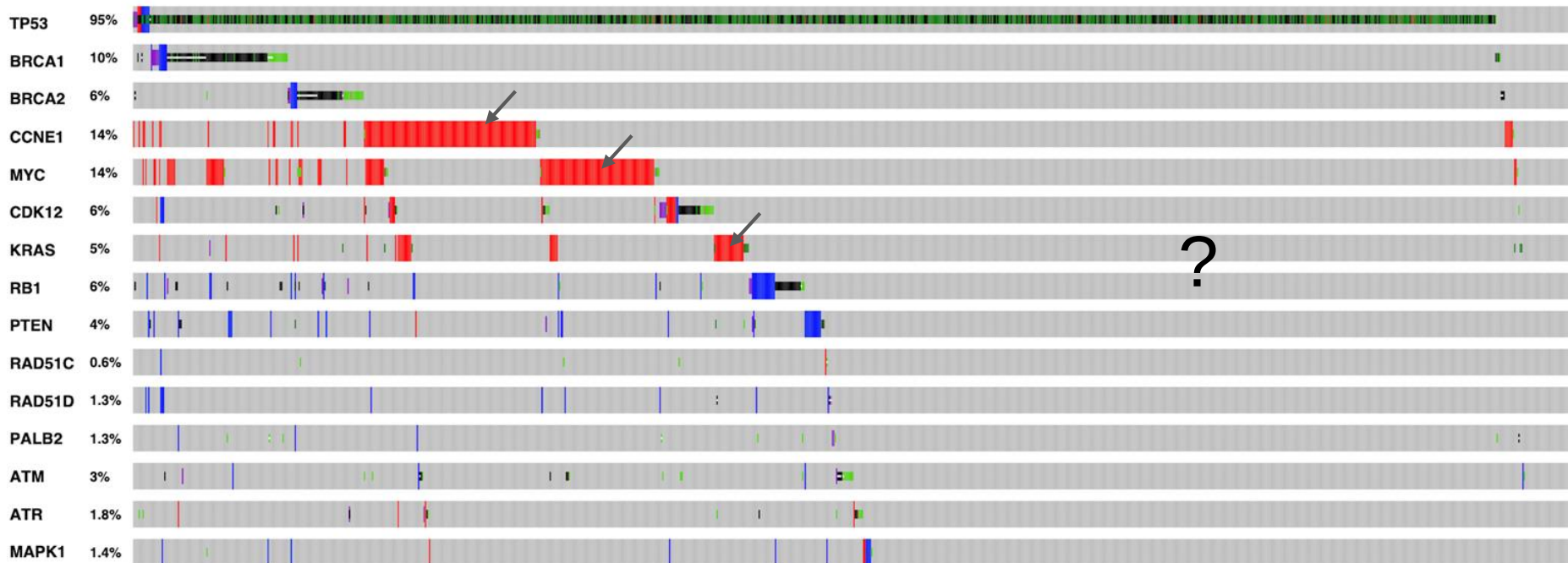
# Financial Relationships

| Commercial Interest: | Nature of Relationship:     |
|----------------------|-----------------------------|
| Canexia Health Inc   | Stock ownership, Consultant |
|                      |                             |
|                      |                             |
|                      |                             |
|                      |                             |

| Off Label Discussion: |
|-----------------------|
| None                  |

# HGSOC harbors LoF mutations in tumor suppressors and amplifications of oncogenic drivers

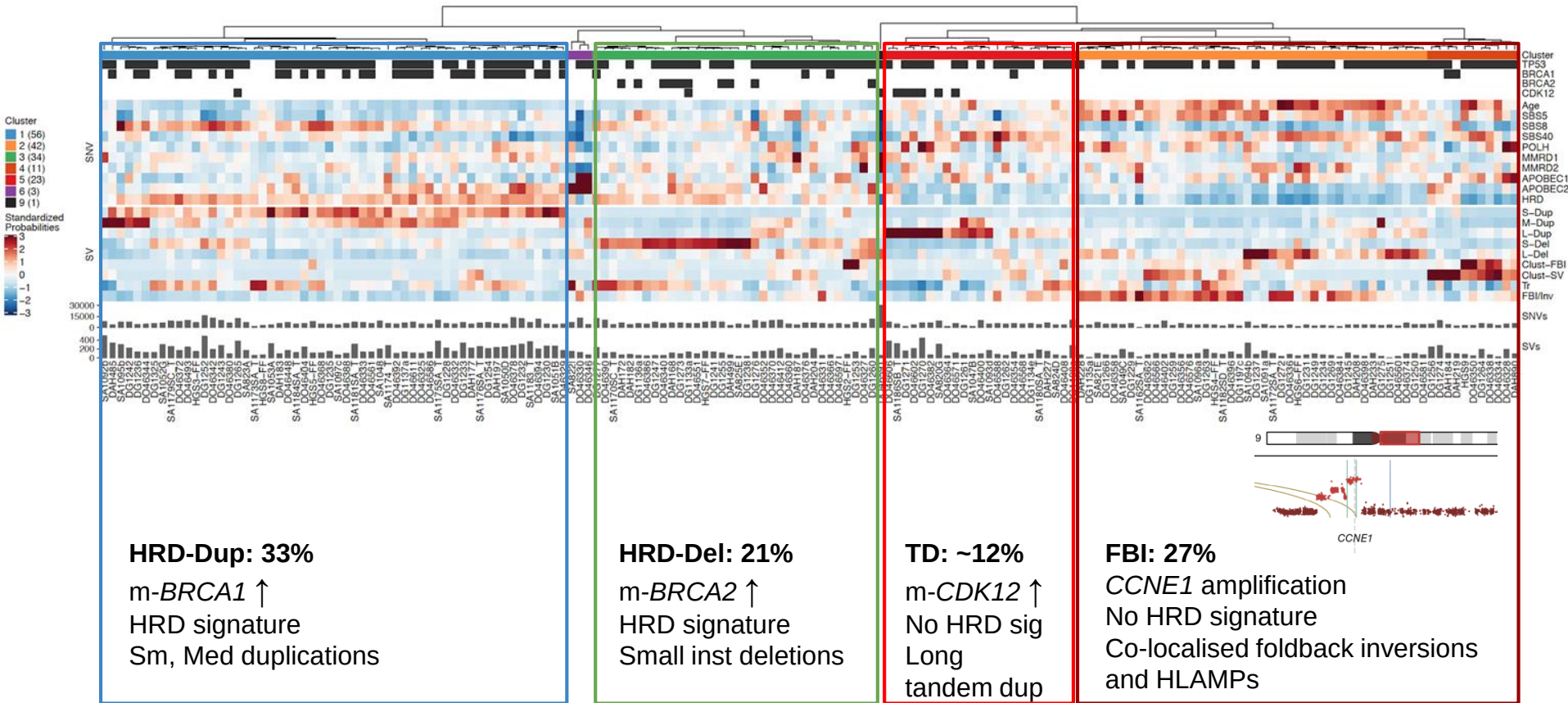
MSK-IMPACT



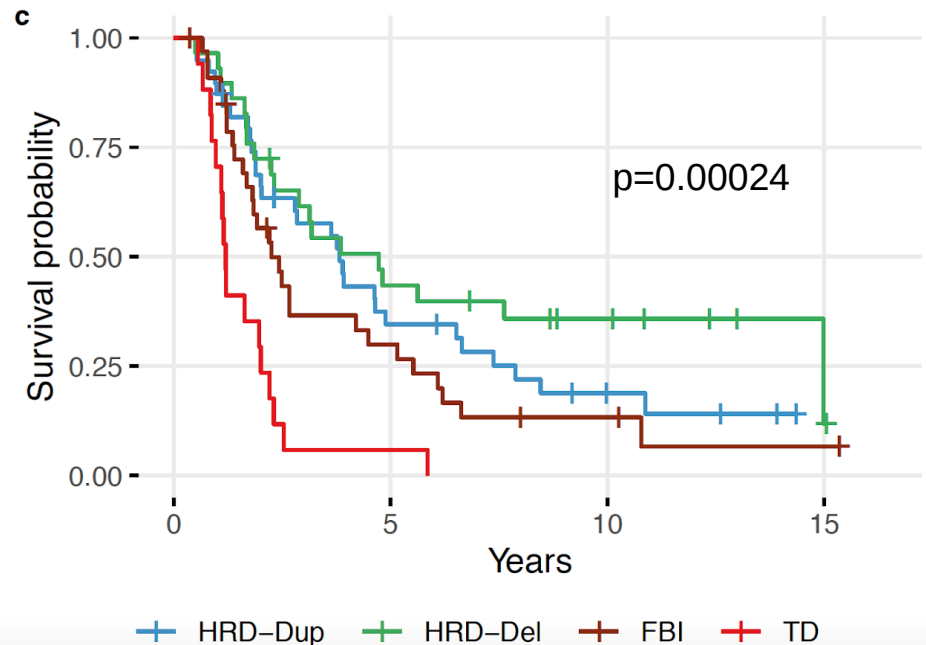
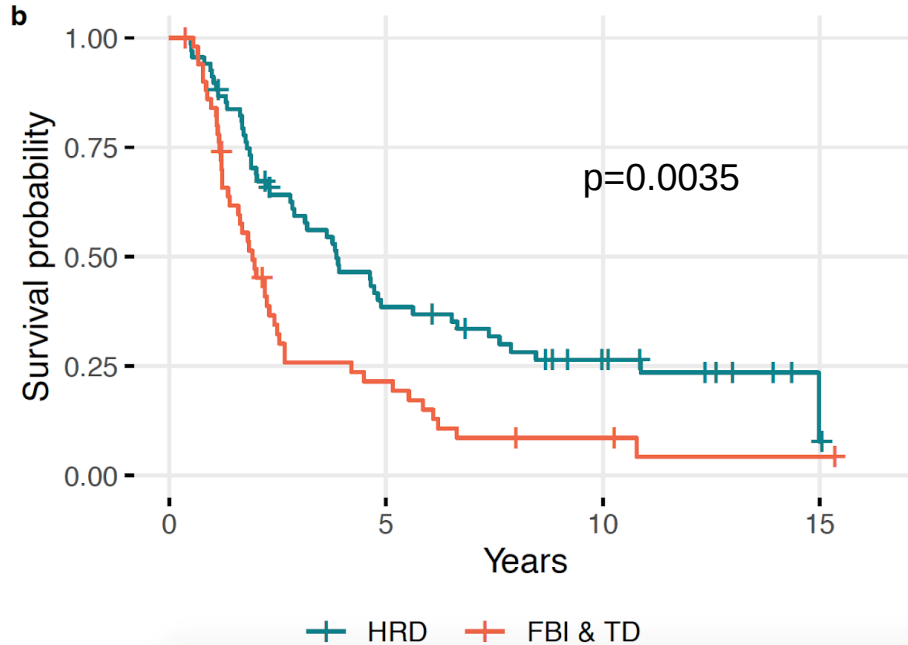
Legend:

- Inframe Mutation (putative driver)
- Inframe Mutation (unknown significance)
- Missense Mutation (putative driver)
- Missense Mutation (unknown significance)
- Other Mutation
- Truncating Mutation (putative driver)
- Truncating Mutation (unknown significance)
- Fusion
- Germline Mutation
- Amplification
- Deep Deletion
- No alterations

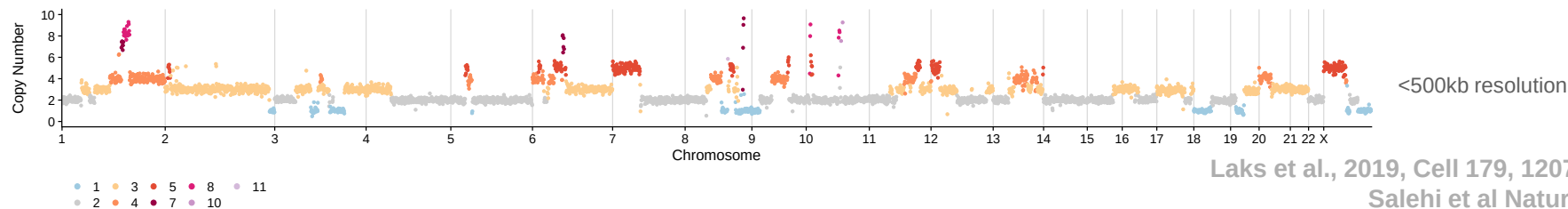
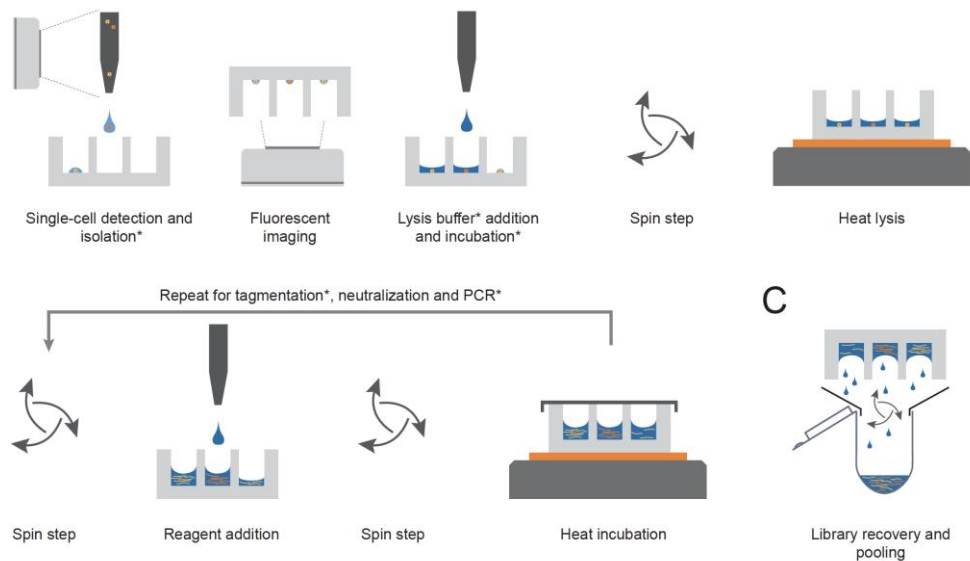
# Mutational processes inferred from WGS stratify HGSOC (n=170)



# Mutational processes associate with therapeutic response to cisplatin chemotherapy



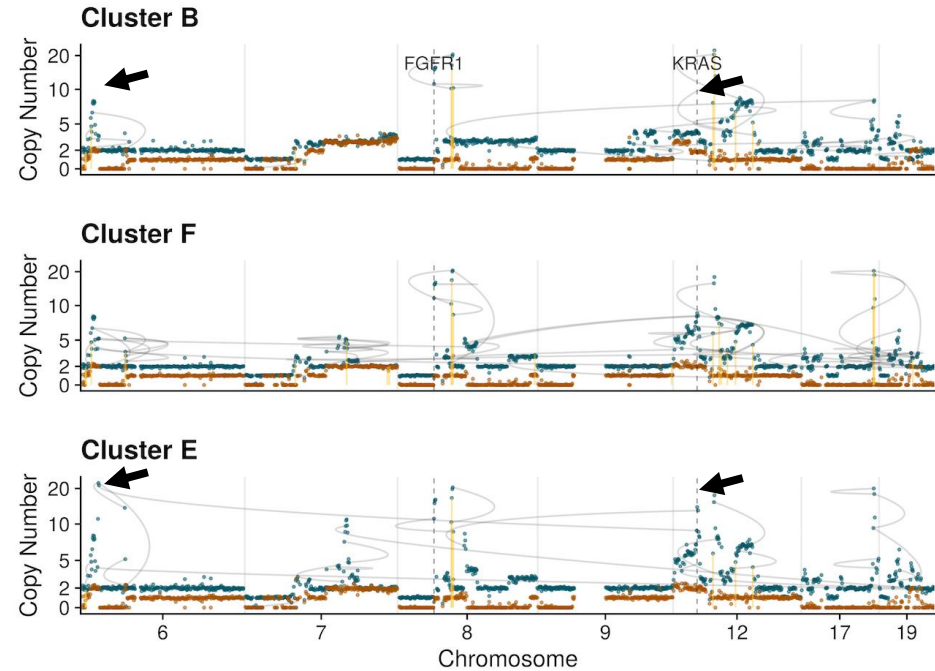
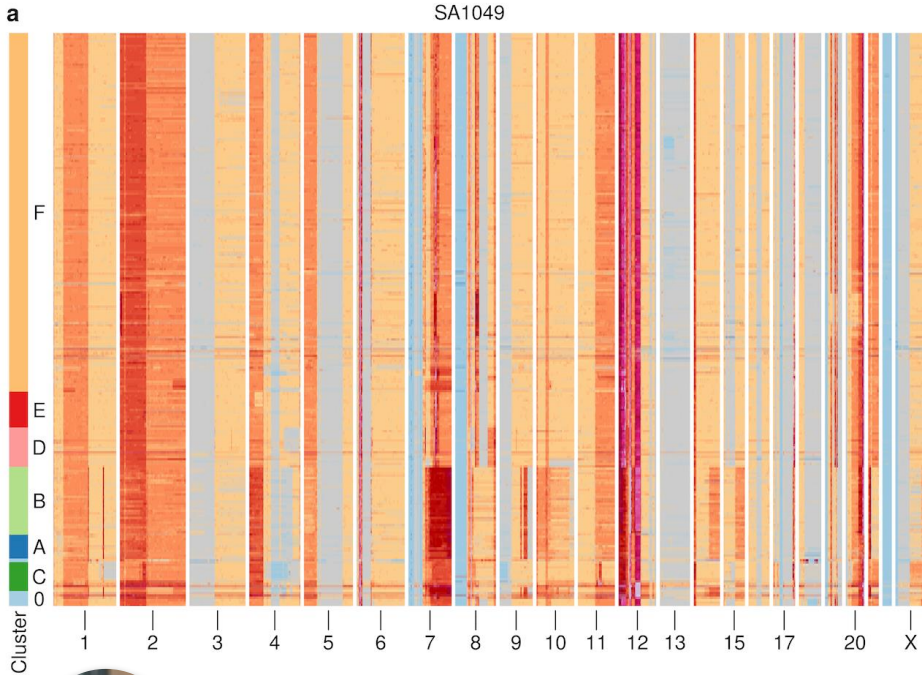
# Technology advances: single cell whole genome sequencing



Laks et al., 2019, Cell 179, 1207–1221  
Salehi et al Nature 2021



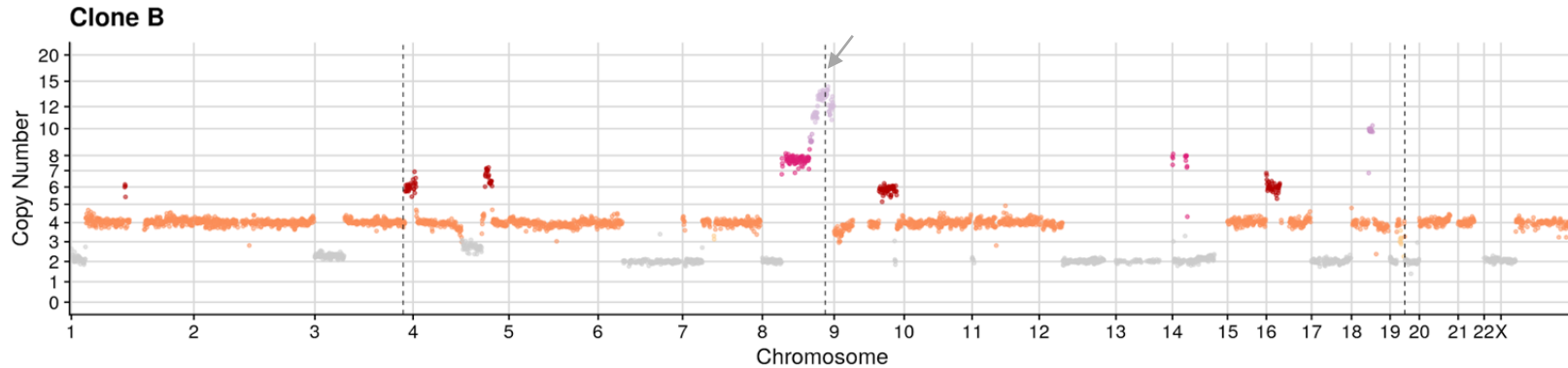
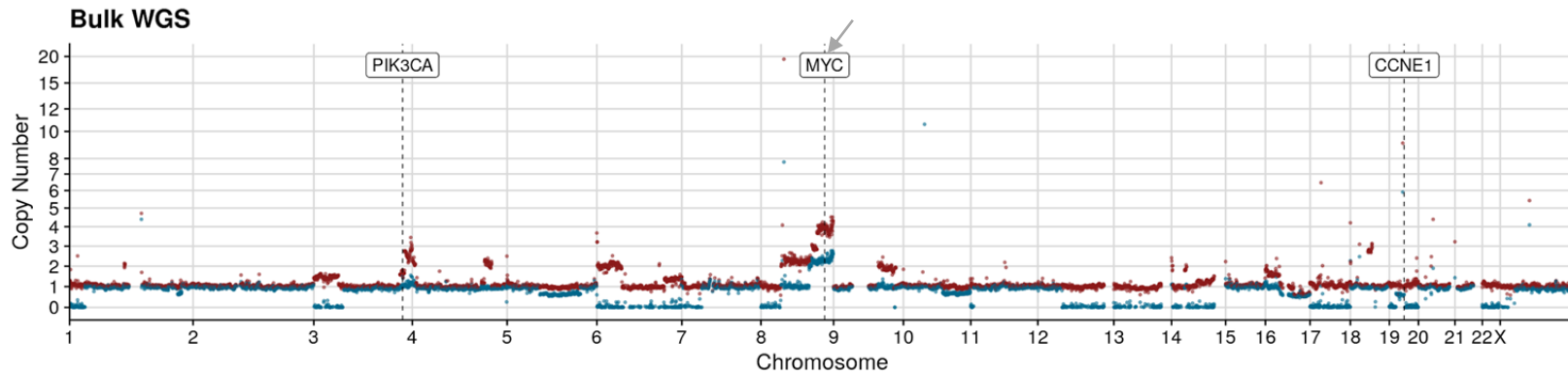
# Single cell structural variation profiling



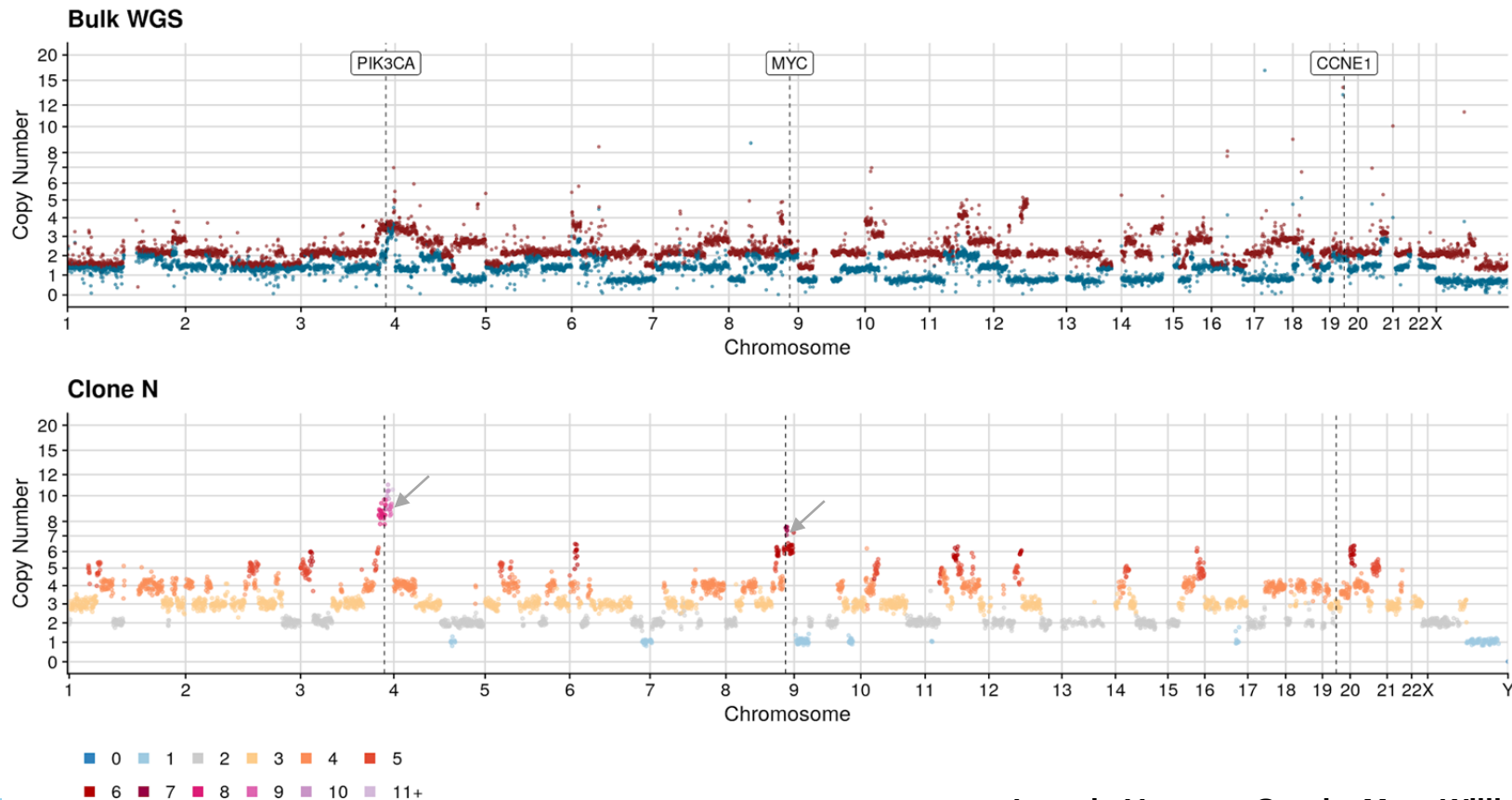
**Marc  
Williams**



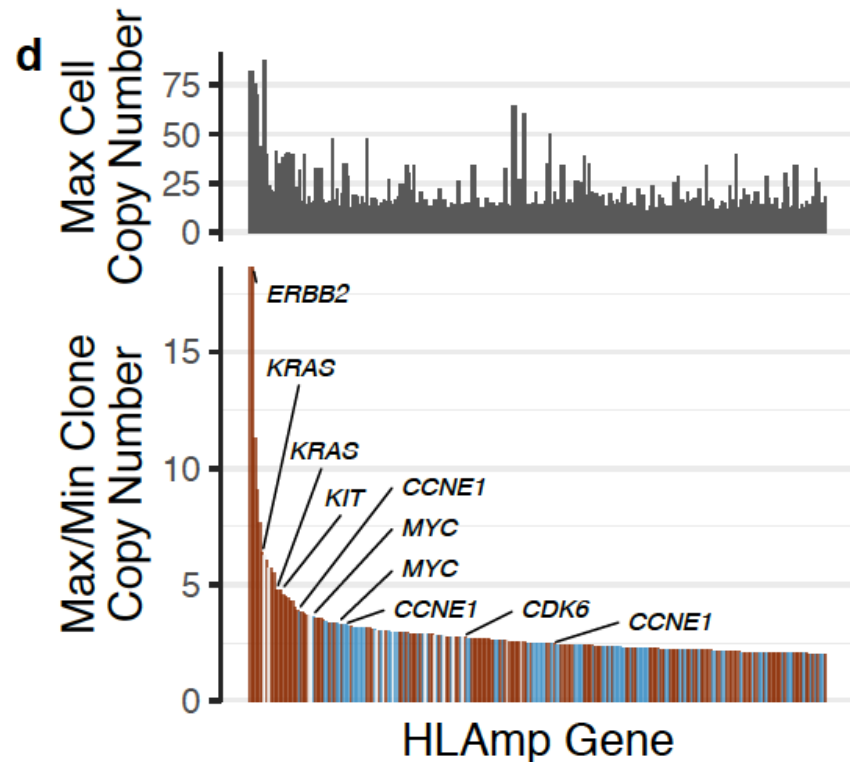
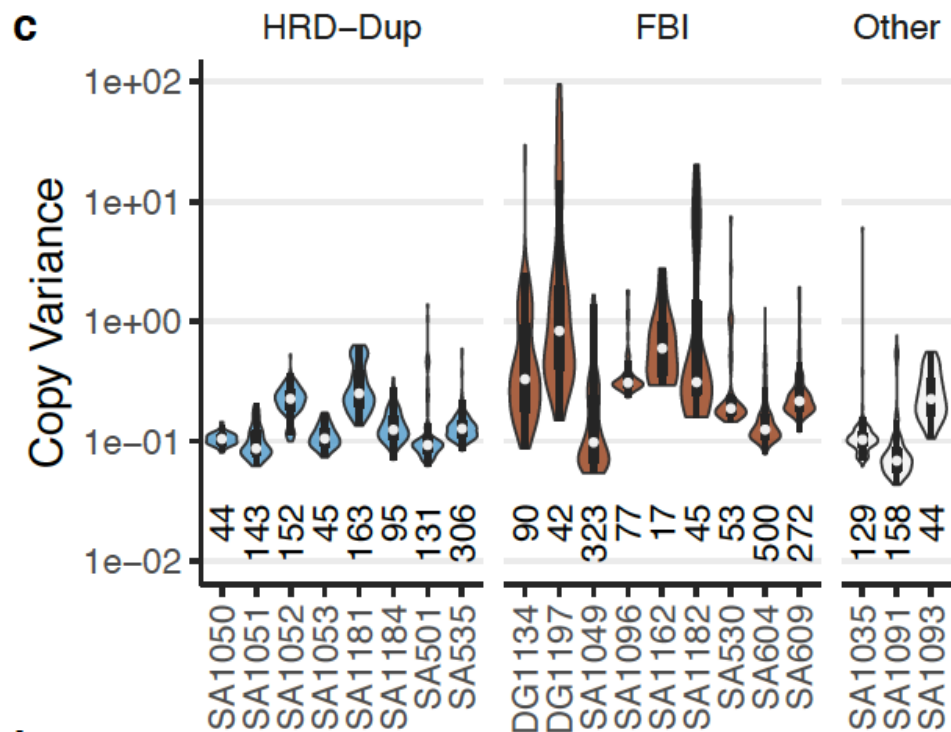
# High level amplifications are composites of varying clonal constituents



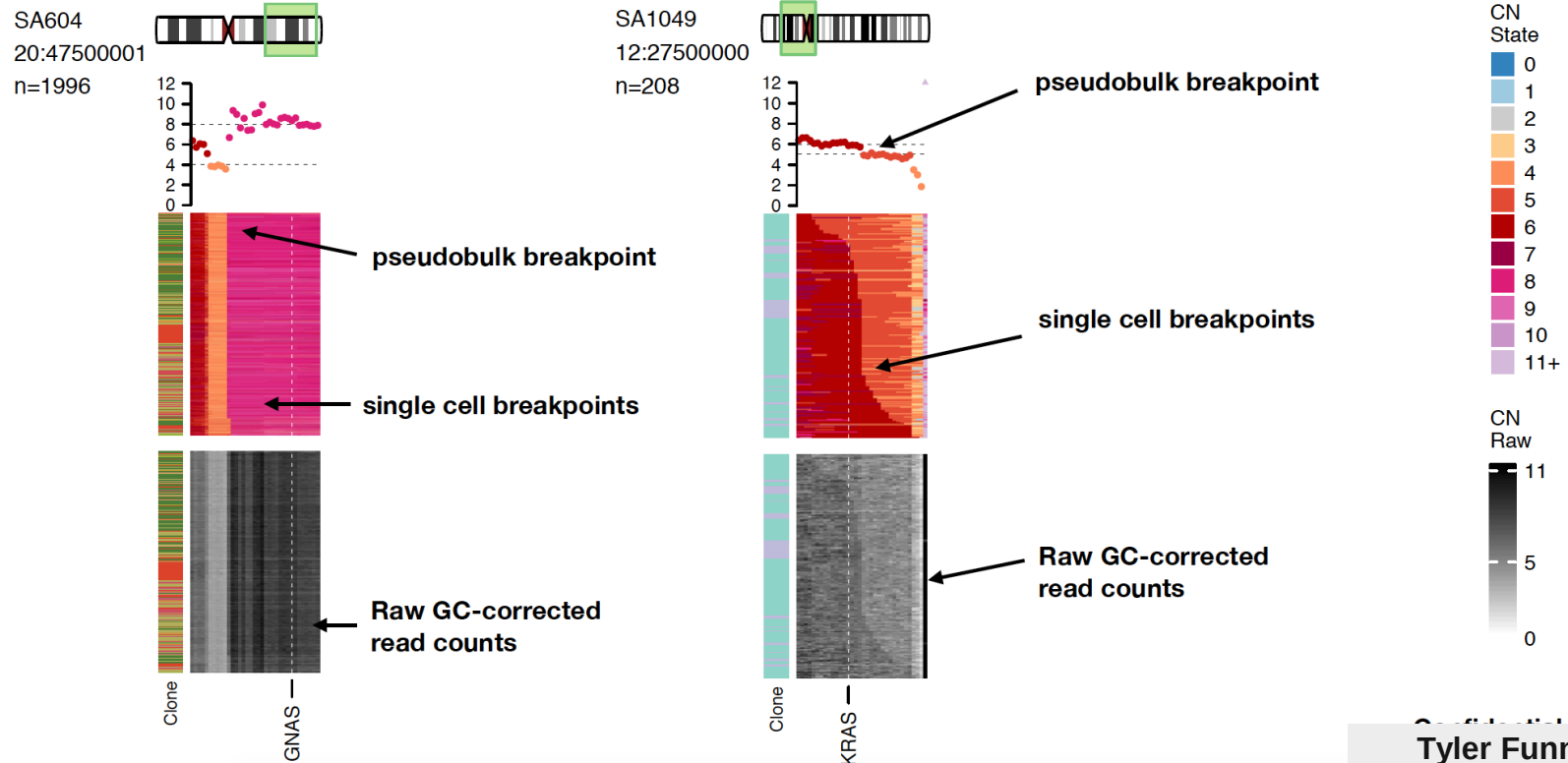
# Bulk sequencing will miss clone-specific amplifications of oncogenic drivers



# FBI tumors exhibit higher intra-tumor variation in HLAMP amplitude

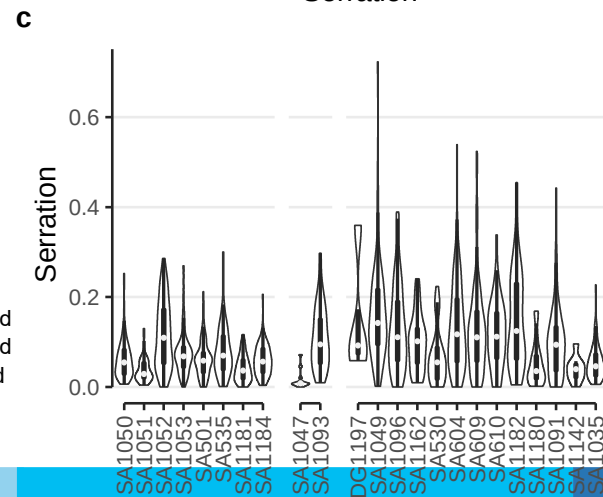
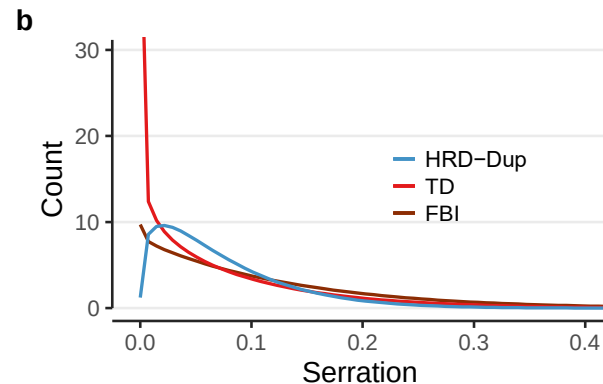
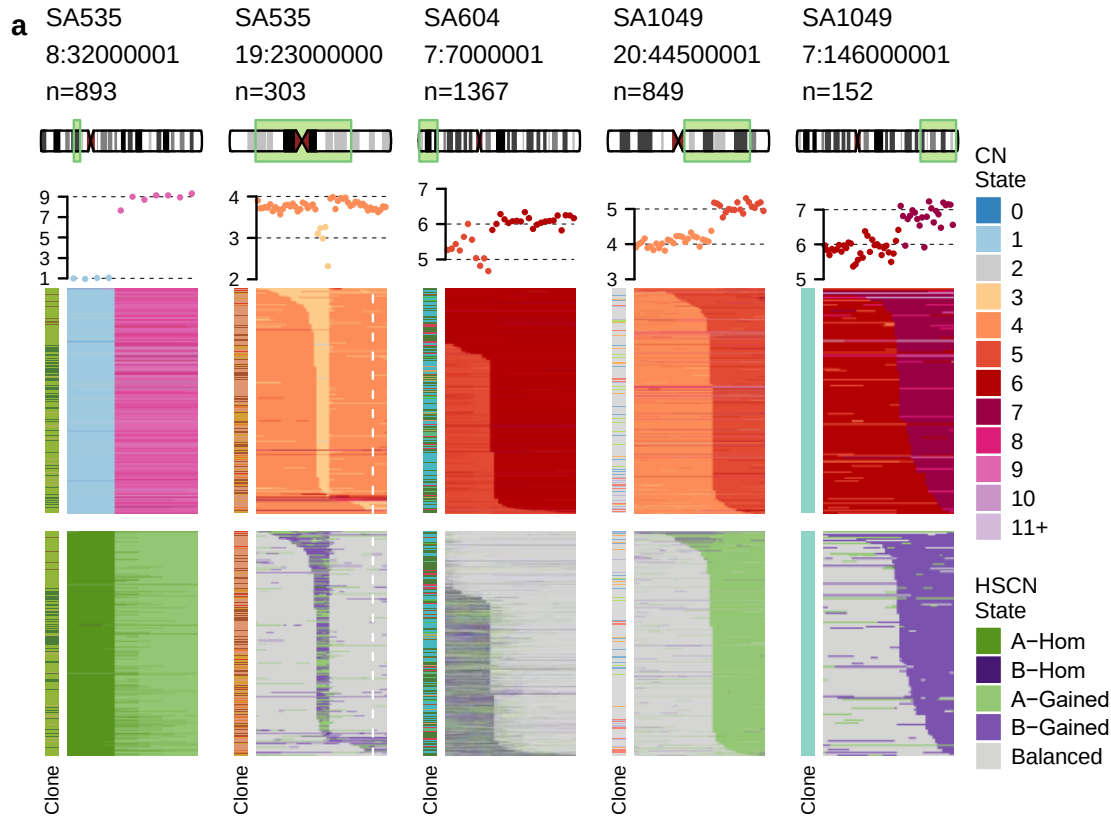


# Serriform patterns indicate 'progressive' genomic variation

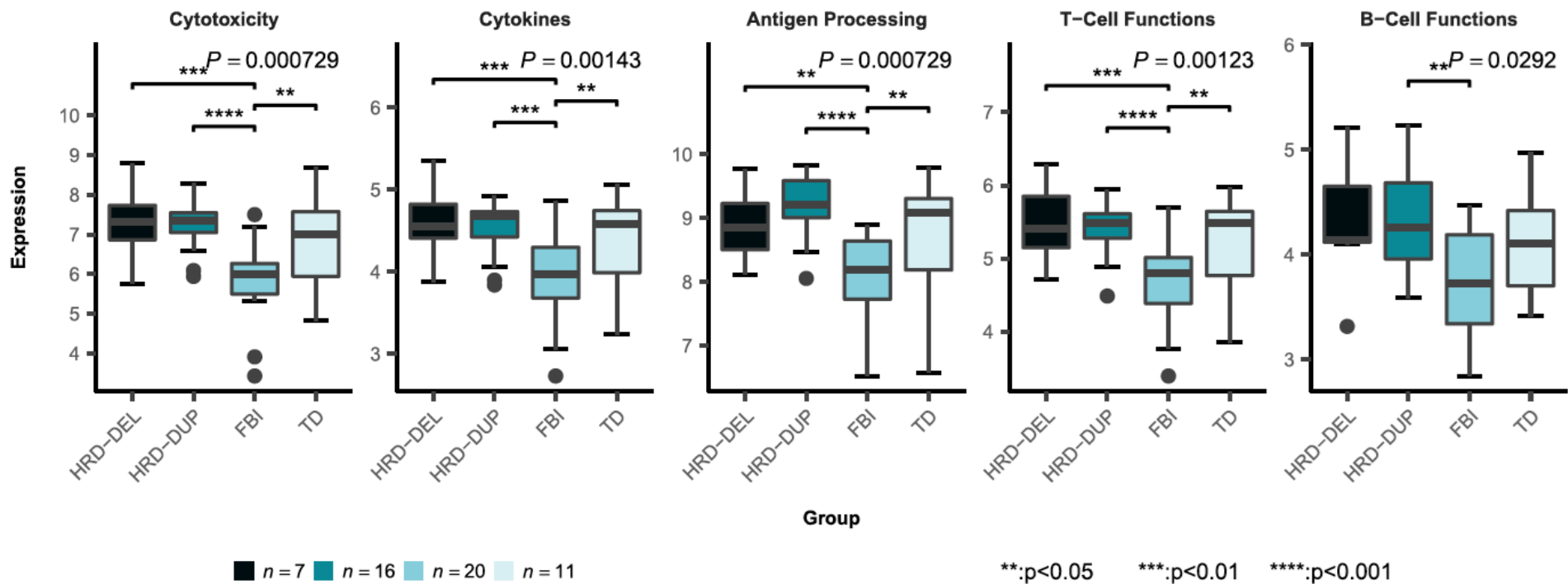


Tyler Funnell  
Ciara O'Flanagan

# Serriform patterns indicate progressive genomic variation



# Mutational processes elicit different immune infiltration profiles from bulk gene expression

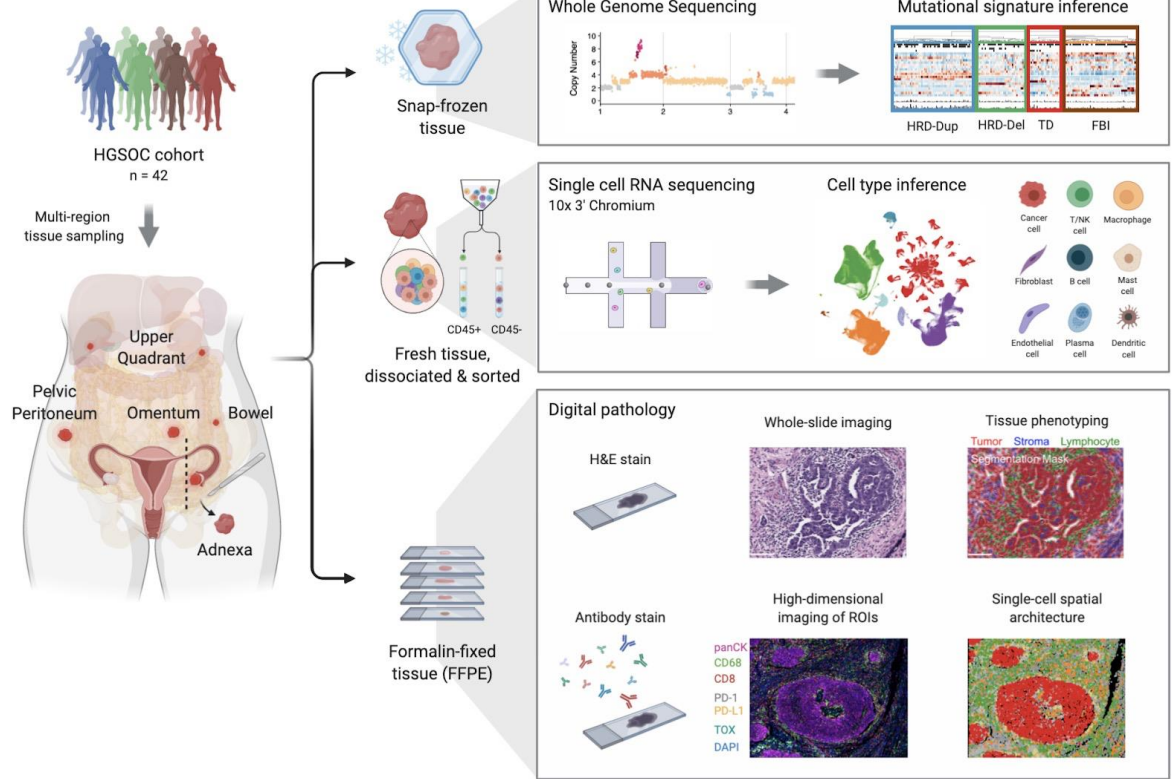


How do mutational processes impact cell intrinsic and cell extrinsic phenotypic states of the TME?



# How do mutational processes impact the immune microenvironment?

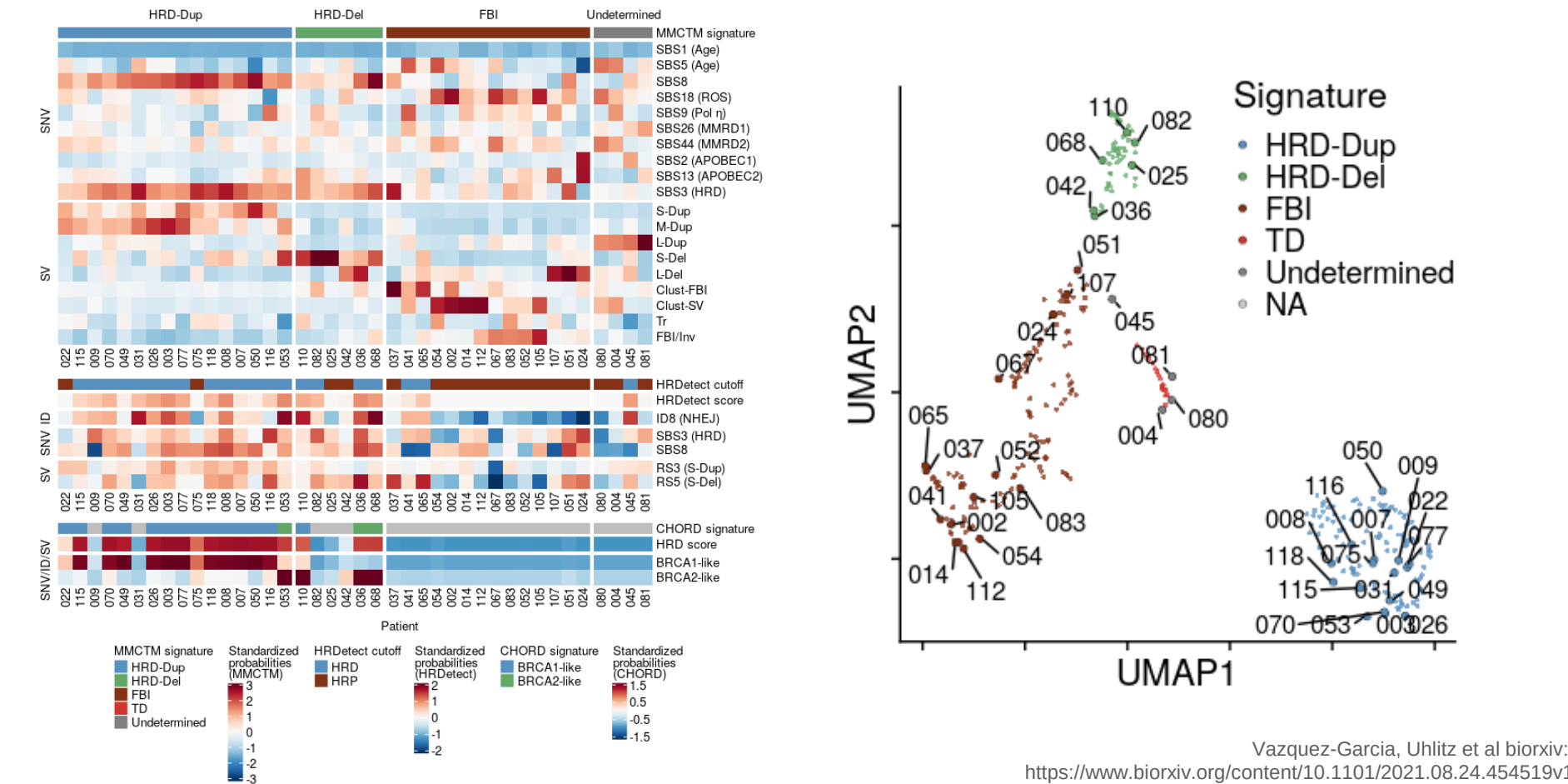
## MSK SPECTRUM



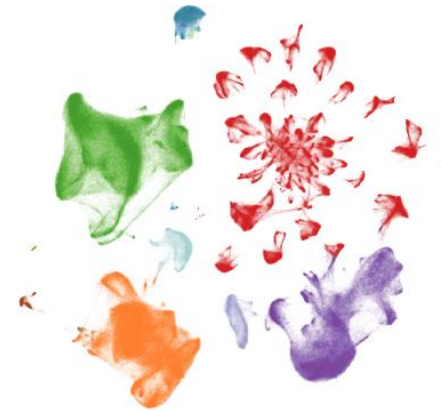
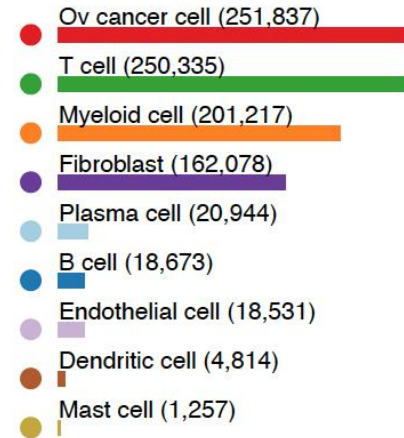
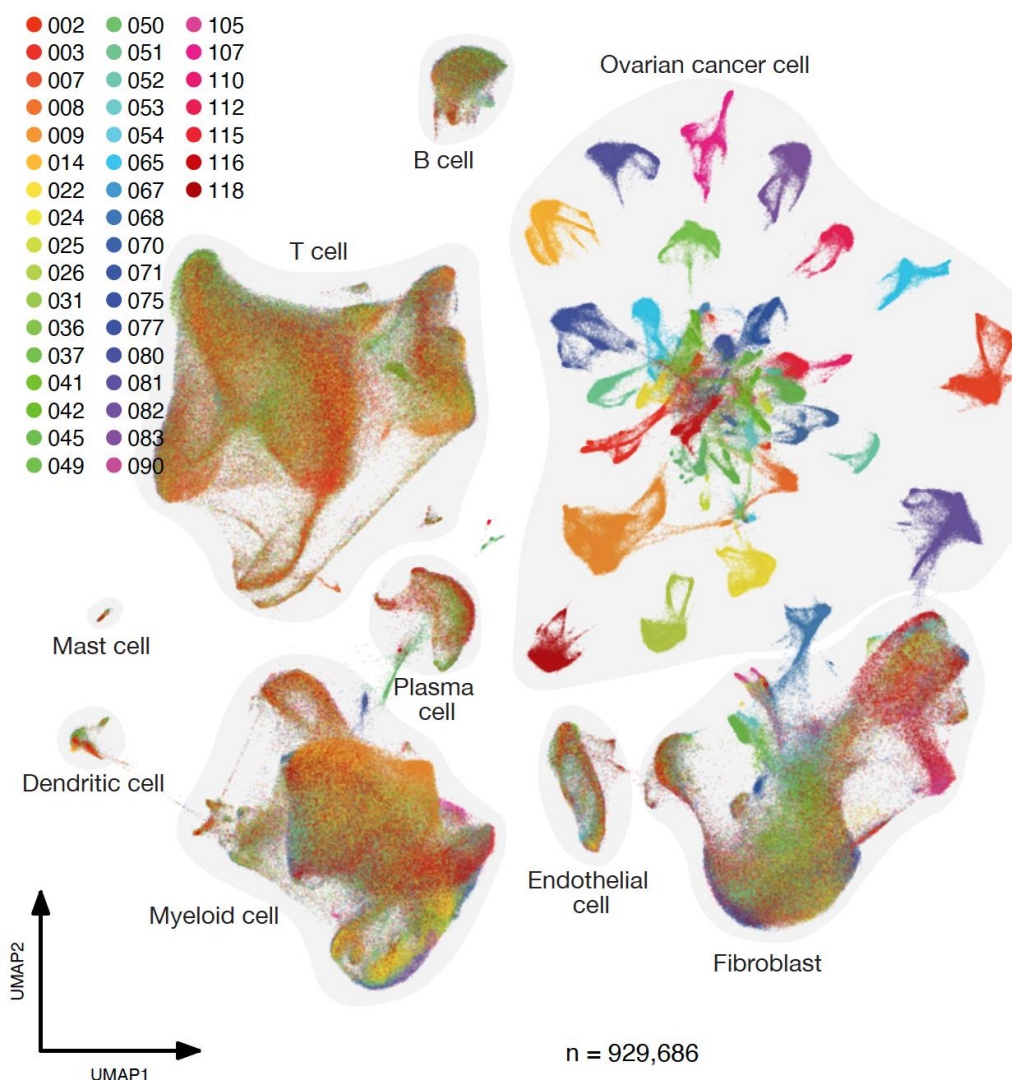
### Single-cell and spatial profiling

- 10x 3' scRNA-seq**
  - >1M cells
  - 42 patients
  - 335 samples
- Digital H&E**
  - 42 patients
  - ~300 samples
- AkoyaBio Vectra mPLIF**
  - 20 patients
  - 67 samples
  - 1,023 FOVs
  - >7M cells
  - panCK, CD8, CD68, PD1, PDL1, TOX, DAPI
- scDNA-seq (DLP+)**
  - 7 patients
  - 11 samples
- Tumor-normal whole-genome sequencing**
  - 30 patients
- Targeted gene panel (MSK IMPACT)**
  - 42 patients

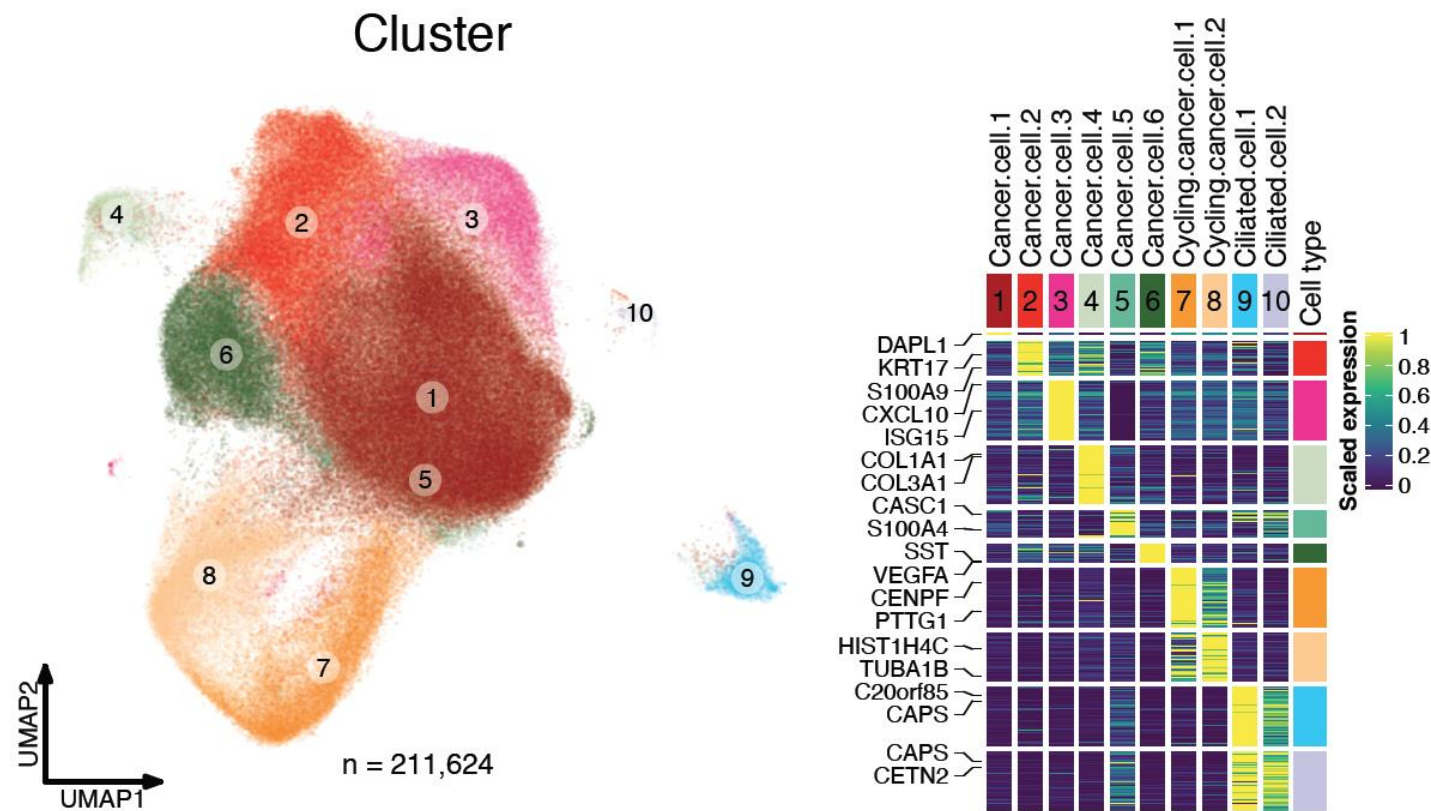
# How do mutational processes impact the immune microenvironment?



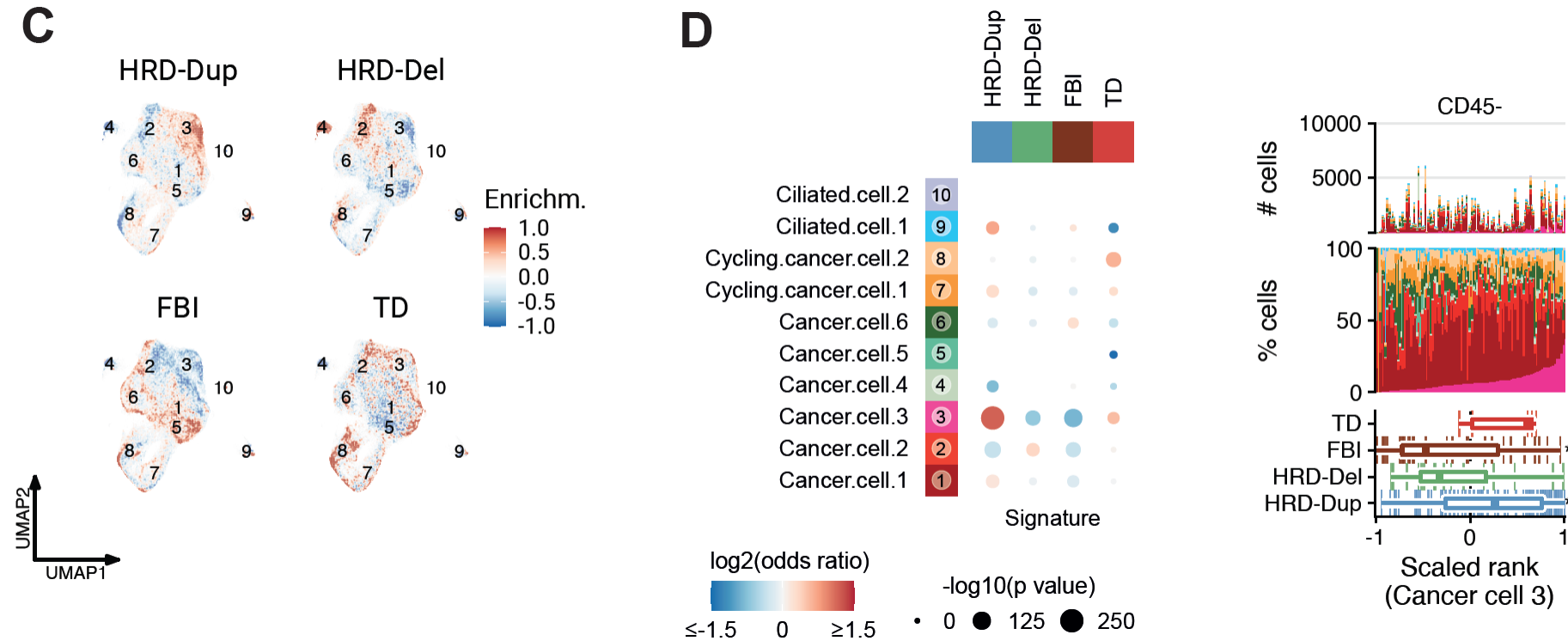
# Single cell deconstruction of tissues



# Malignant cell intrinsic phenotypic states are associated with mutational processes

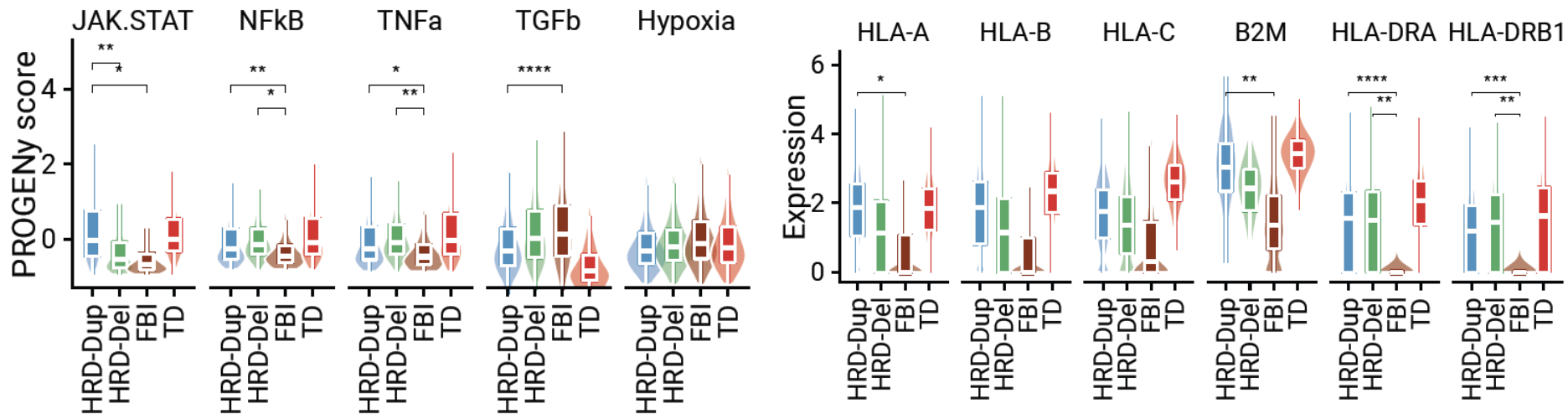


# Malignant cell intrinsic phenotypic states are associated with mutational processes

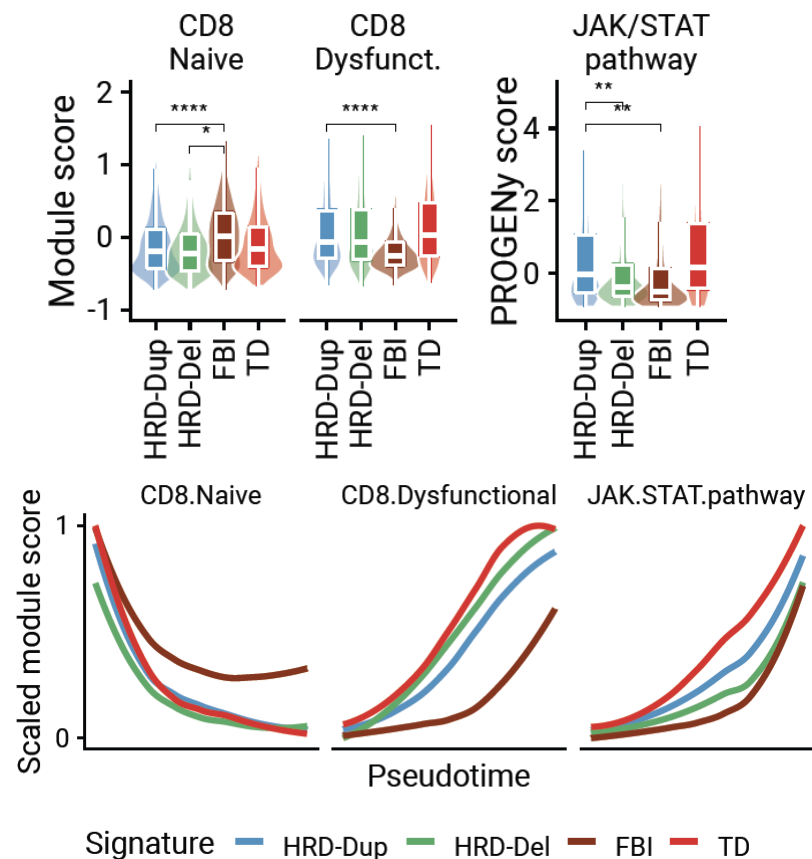
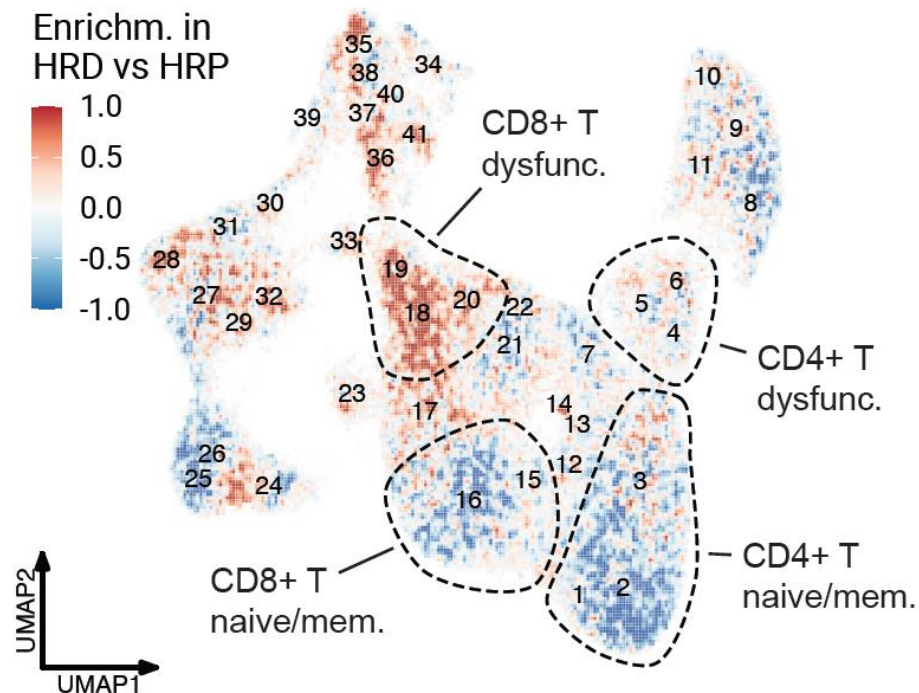




# Malignant cell intrinsic phenotypic states are associated with mutational processes

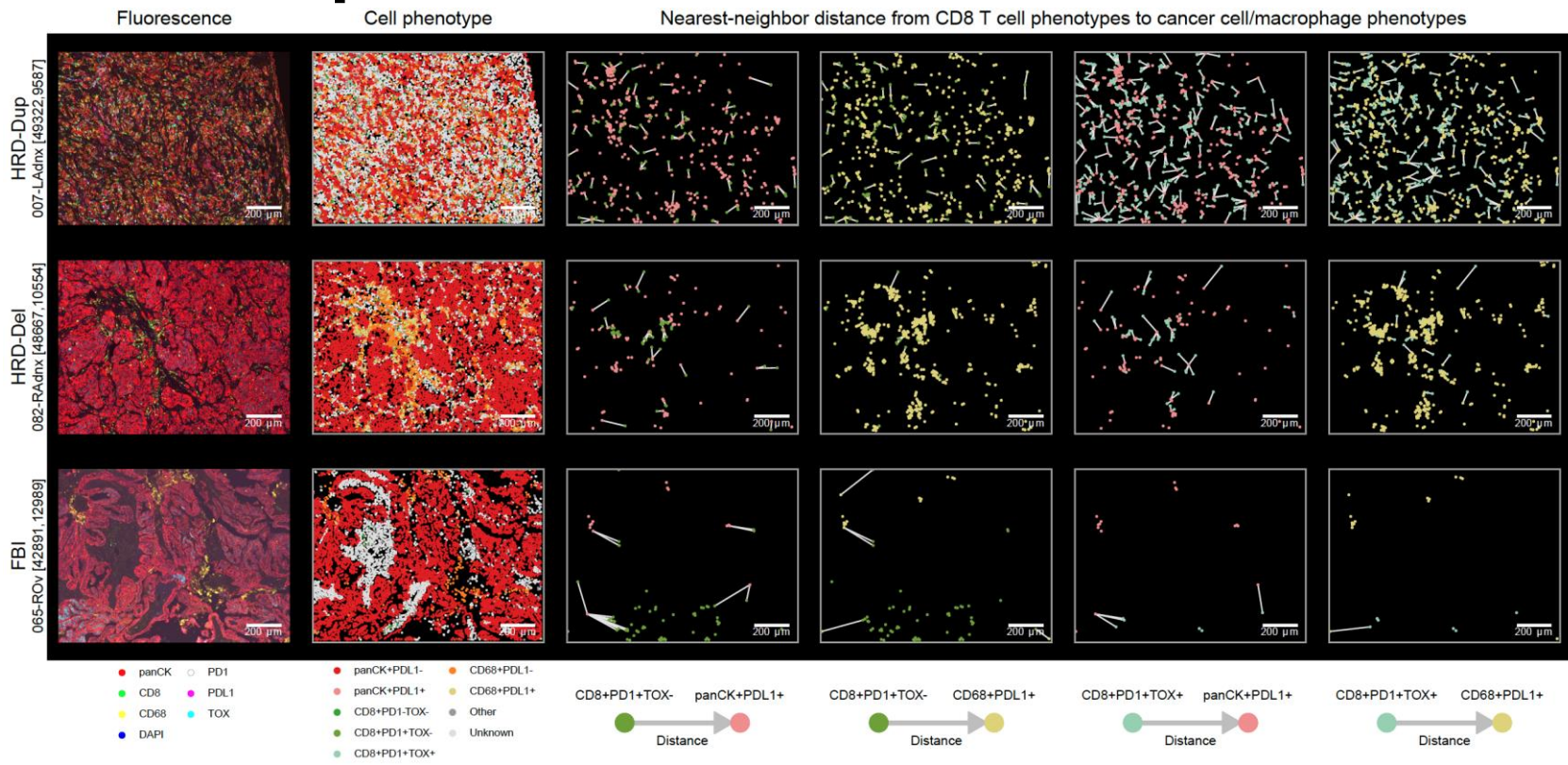


# Immune cell phenotypic states are associated with mutational processes



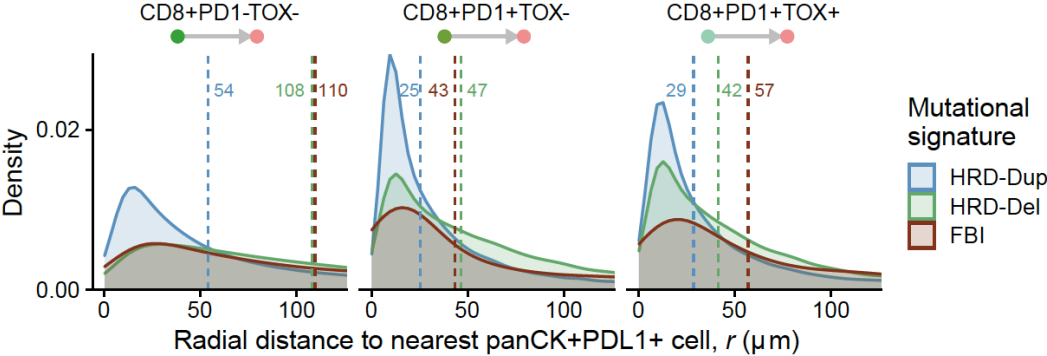


# Tissue architectures are associated with mutational processes

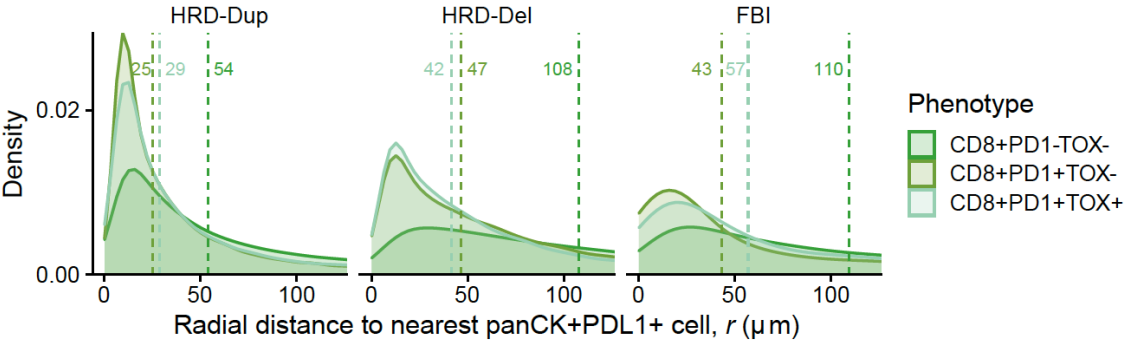


# Tissue architectures are associated with mutational processes

D

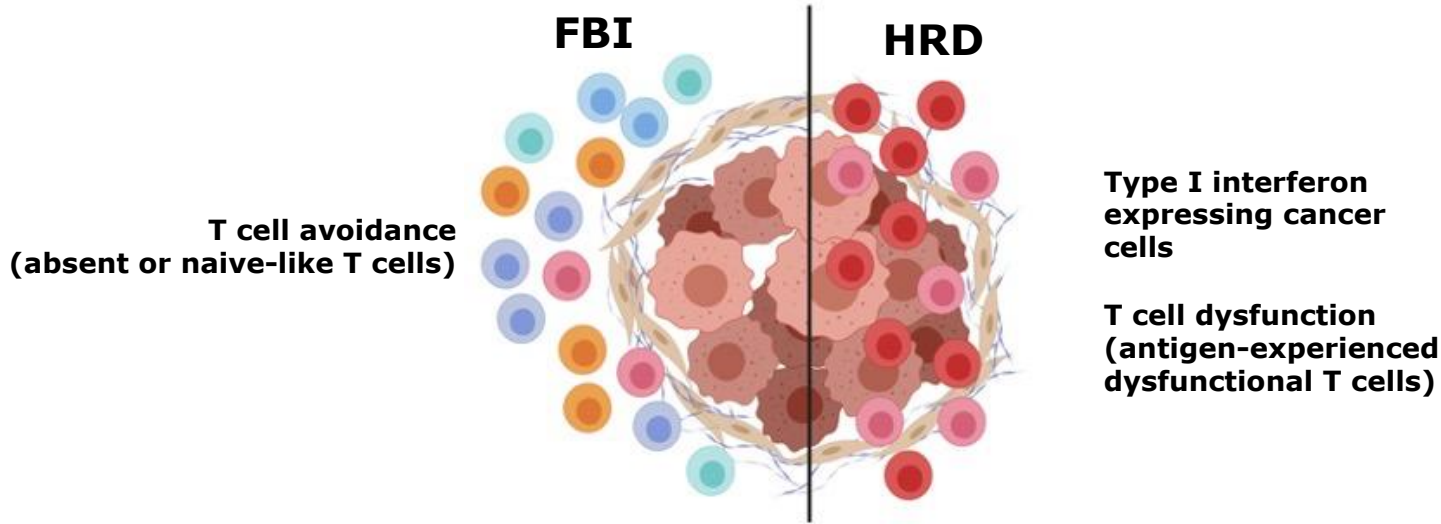


E



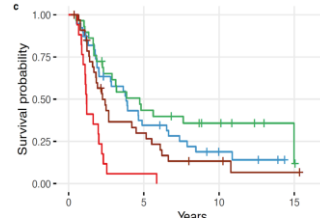
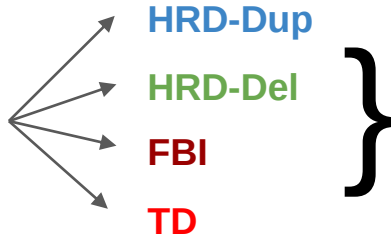
# Lessons and take home messages:

## An emerging model for how mutational processes impact immuno-reactivity

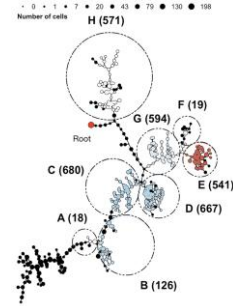


- Refined mutational processes impact response to standard of care chemo
- Mutational processes lead to distinct cell-intrinsic signaling pathways
- Mutational processes associate with immune cell phenotypic states
- Mutational processes associate with distinct tissue architecture

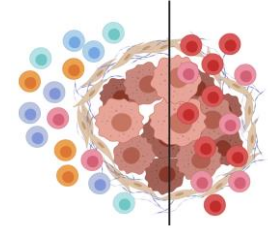
**TP53**  
mutation



**Prognostic  
implications**



**Evolutionary  
dynamics, phenotypic  
diversity, treatment  
resistance**



**Variation in immune  
response in disease  
natural history**

**Predicting response to genotoxic chemotherapy +/- immunotherapy will require multi-factorial biomarkers combining mutational processes and immune-phenotypes**

# Team science: clinical + computational groups

## GYN Surgery

Nadeem Abu-Rustum  
Kara Long-Roche  
Dennis Chi  
Oliver Zivanovic  
Yukio Sonoda  
Ginger Gardner  
Vance Broach

Elizabeth Jewell  
Jennifer Mueller  
Carol Brown  
Mario Leitao  
Kaity Chang

## Bakhoun Lab

Melody DiBona  
Ninjit Dhanota  
Jun Li

## Shah Lab

Diljot Grewal  
Minsoo Kim  
Kevin Boehm  
Jessica Urraca

Eli Havasov  
Arfath Pasha  
Samantha Leung  
Viki Bojilova  
Maryam Pourmaleki  
Allen Zhang  
Sohrab Salehi  
Gryte Satas

## Data analysis team



Ignacio  
Vazquez-Garcia



Florian Uhlitz



Marc Williams



Hongyu Shi



Nicholas Ceglia

## GYN Med Onc

Carol Aghajanian  
Dmitriy Zamarin  
Claire Friedman  
Ying Liu

## DigITs

Stu Gardos  
Theodora Bakker  
John Philip  
Jonathan Wills  
Daniel Kelly  
Joseph Schmeltz



Andrew McPherson

## GYN Pathology

Lora Ellenson  
Robert Soslow  
Rahelly Nunez

## PPBC

Joachim Silber  
Cora Mariano  
Michael Roehrl

## Lab Medicine

Chintan Patel



Tyler Funnell

## GYN/ Weigelt Lab

Britta Weigelt  
**Anthe Stylianou**  
Sarah Kim  
GYN Onc Fellows  
Fresia Pareja  
Mahsa Vahdatinia

## Papaemmanuil Lab

Juan Medina  
Max Levine  
Gunes Gundem  
Joe Zhou  
Juanes Arango

## Radiology

Yulia Lakhman  
Ines Nikolovski

## iGO Lab (CMO)

Agnes Viale  
Neeman Mohibullah  
Darrell Nabors

## MSK MIND

Rami Vanguri  
Chris Fong

## Dept of Pathology

Luke Geneslaw  
Travis Hollmann  
Mike Berger  
Dana Tsui

## Sam Aparicio Lab (BC Cancer)

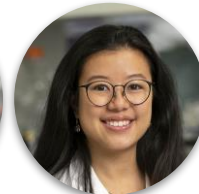
Ciara O'Flanagan  
Jazmine Brimhall  
Jecy Wang  
Justina Biele

## Alexandre Bouchard-Cote (UBC)

## Patient consent and sample procurement team



Michelle Wu



Jamie Lim



Jessica Urraca



Ana Maroldi

# Funding



Canadian  
Cancer  
Society



HENRY M. JACKSON FOUNDATION  
FOR THE ADVANCEMENT OF MILITARY MEDICINE



Thank you to the patients and their families