

Assessing copy number changes in High Grade Serous Ovarian Cancer with a shallow whole genome workflow



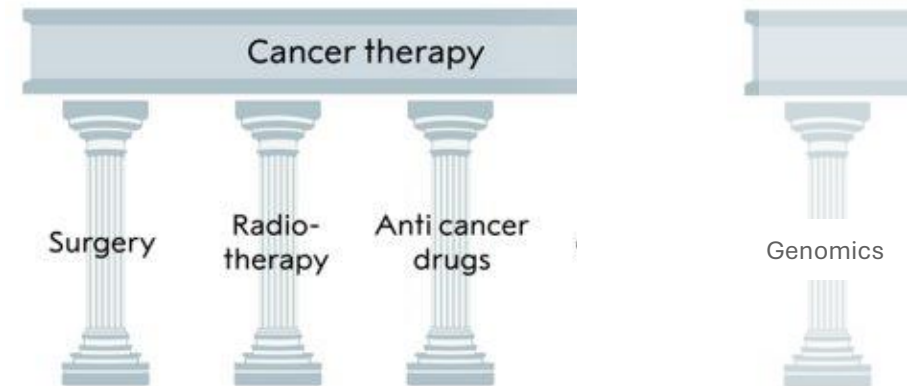
Merridee Wouters
Lowy Cancer Research Centre
Women's Health Initiative
University of New South Wales



From the depressing 1980s to the dawn of precision medicine

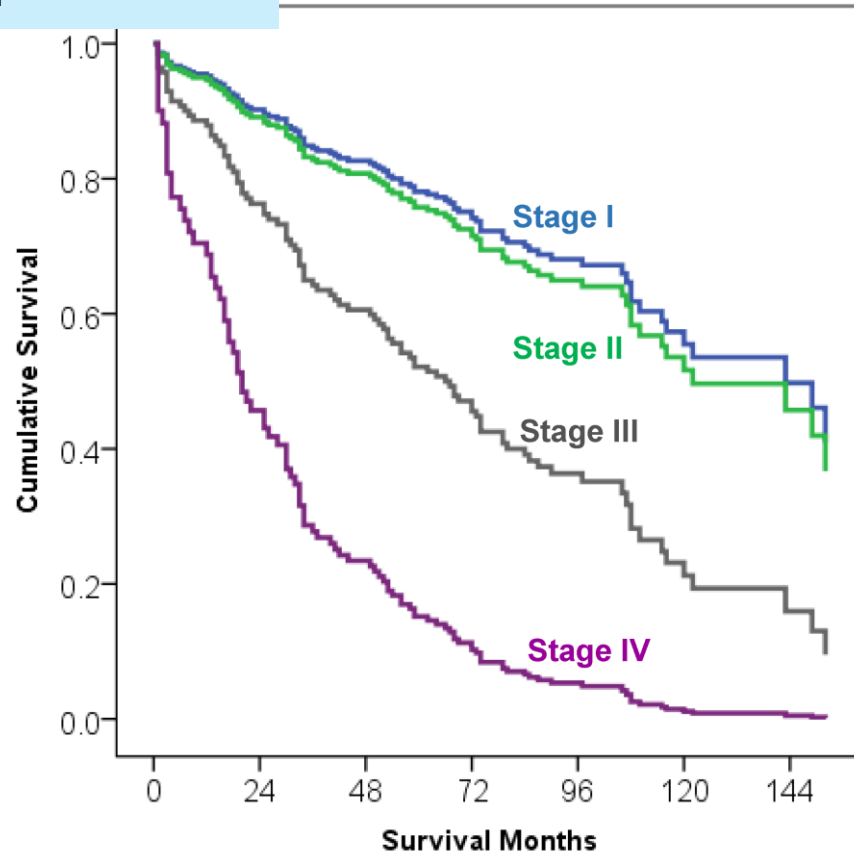
The rise of genomics

2001-2024



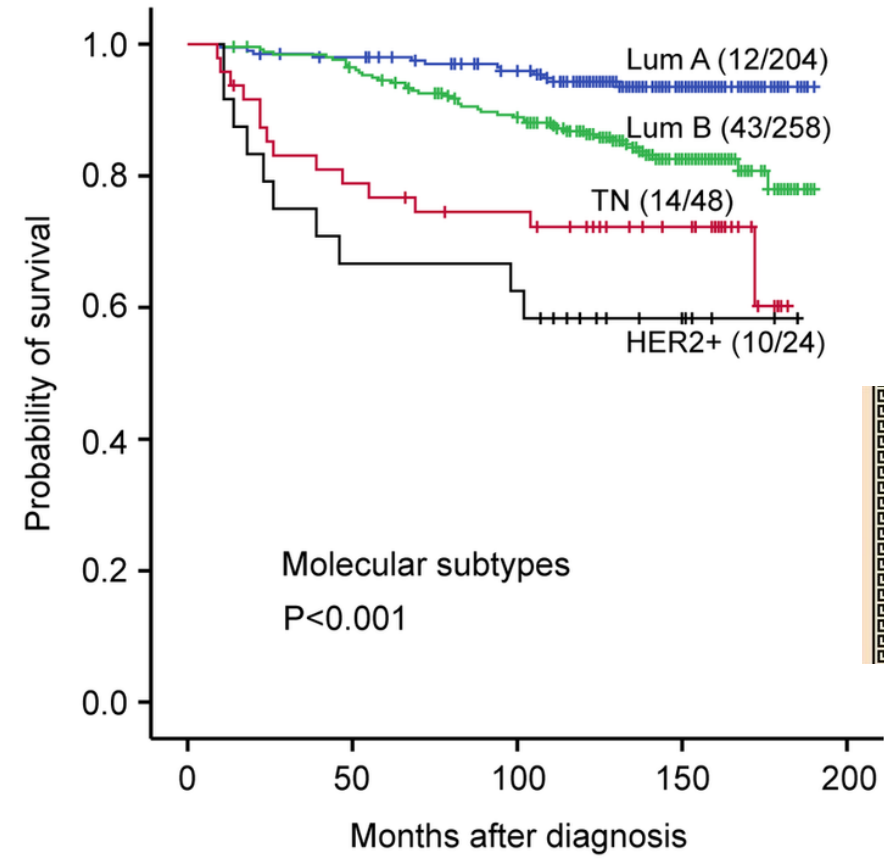
1st 10 years of genomics – better classification brings precision treatments

Breast cancer



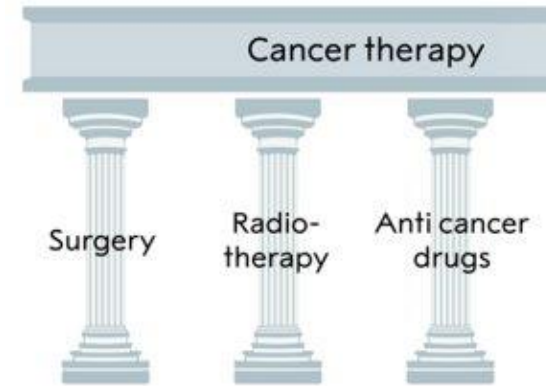
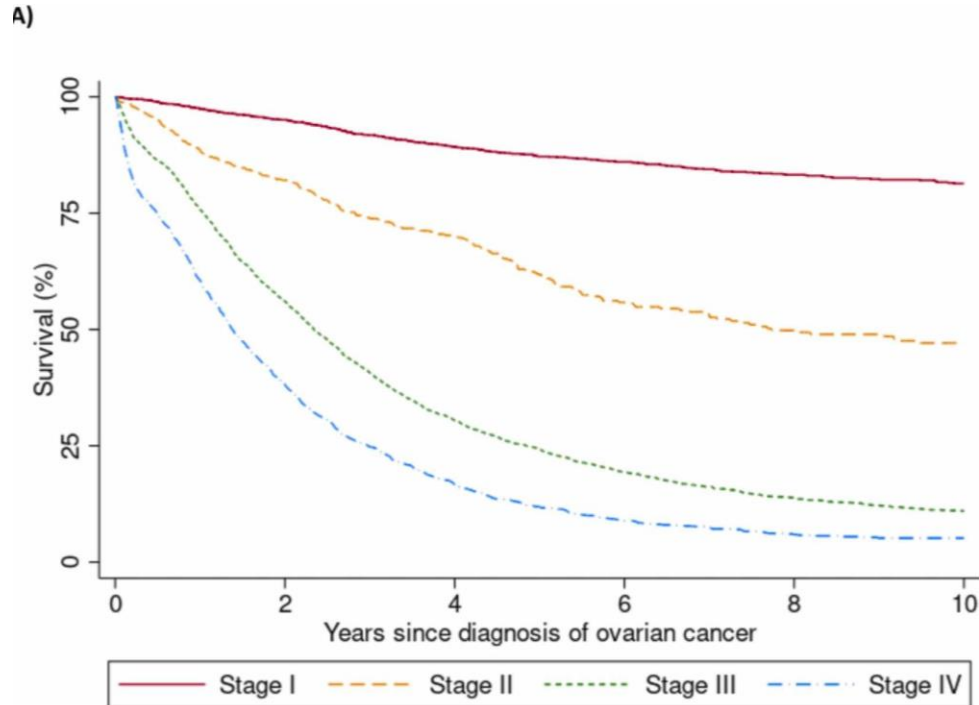
(b)

Pre-genomics classification < 2000



Post-genomics classification > 2000

Ovarian cancer – diagnosis & treatment



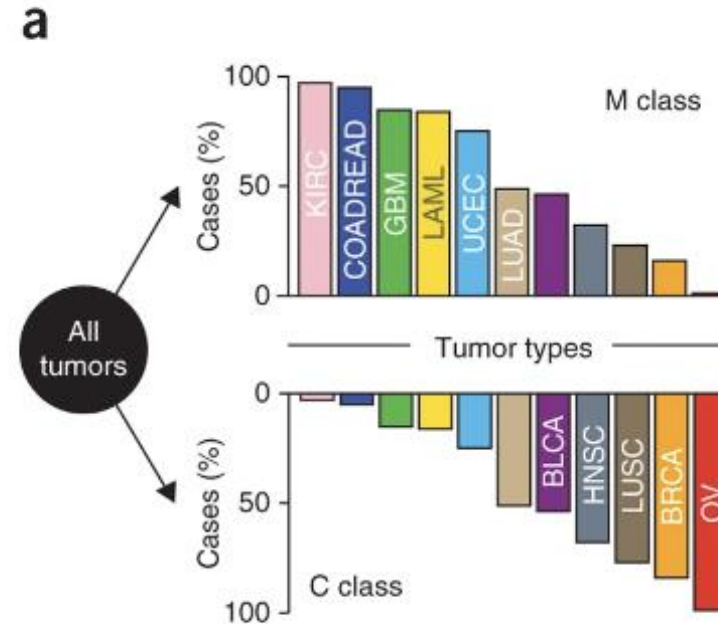
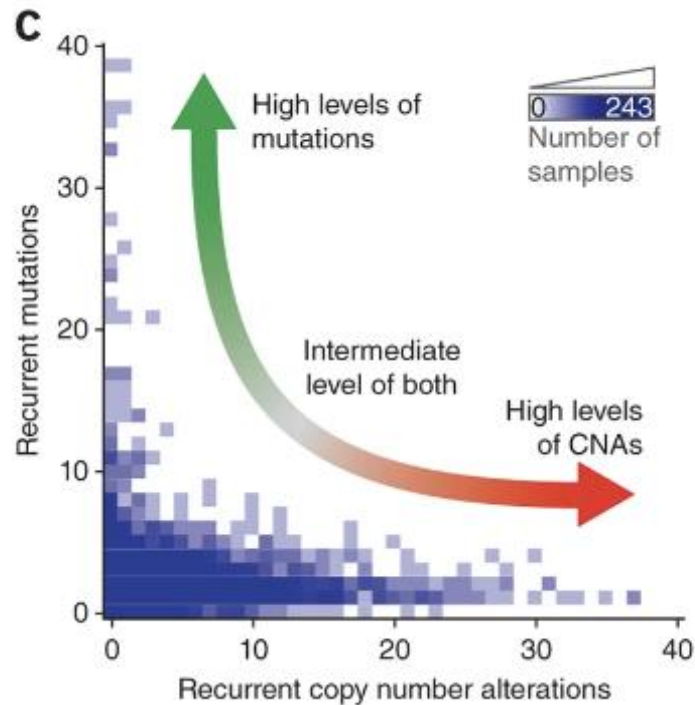
Stage I-II Adjuvant therapy surgery -> chemotherapy

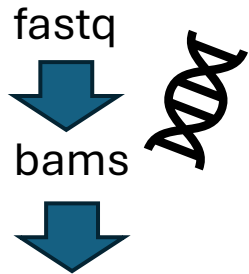
Stage III-IV Neoadjuvant therapy chemo -> surgery -> chemotherapy

Stage at diagnosis

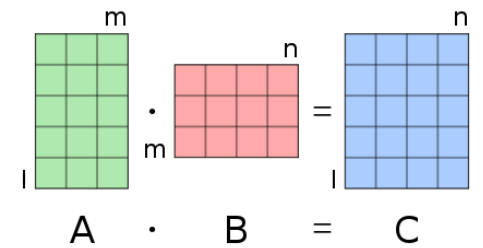
Stage I	1349	45
Stage II	498	60
Stage III	3674	890
Stage IV	1755	690

The need to assess chromosomal instability

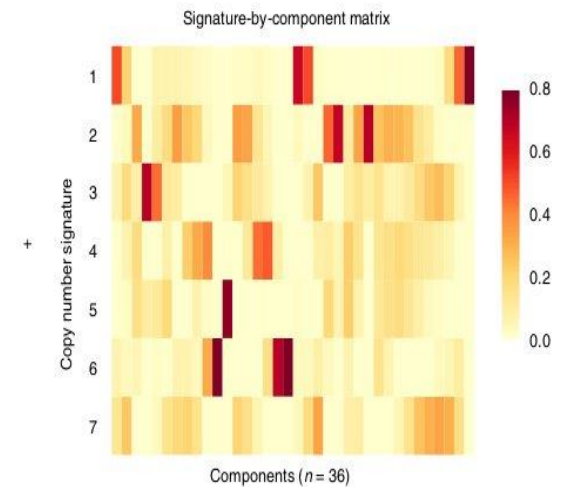
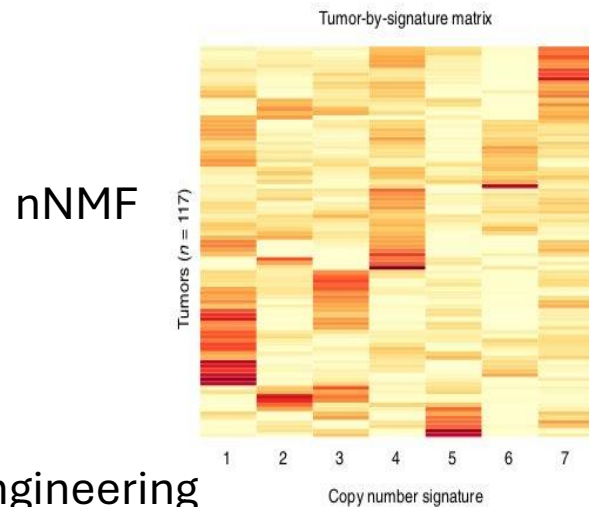
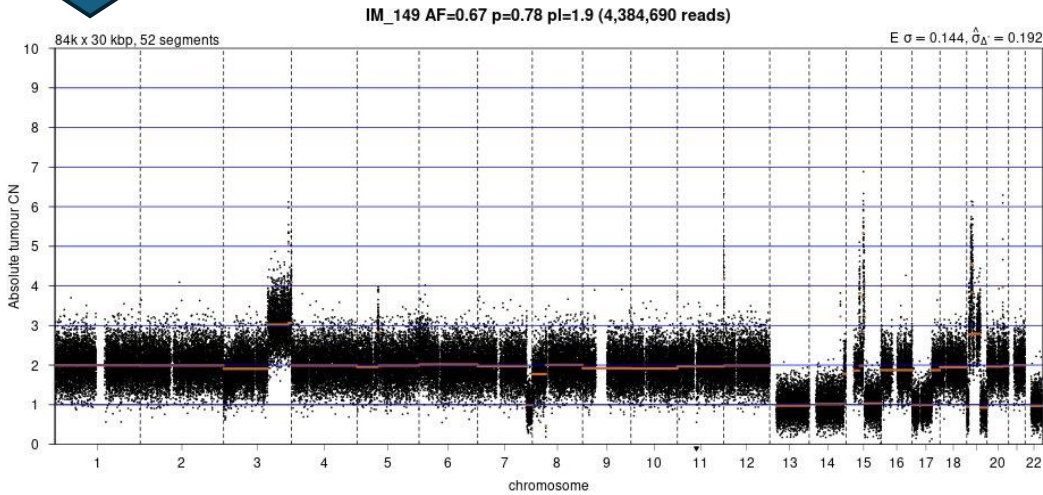




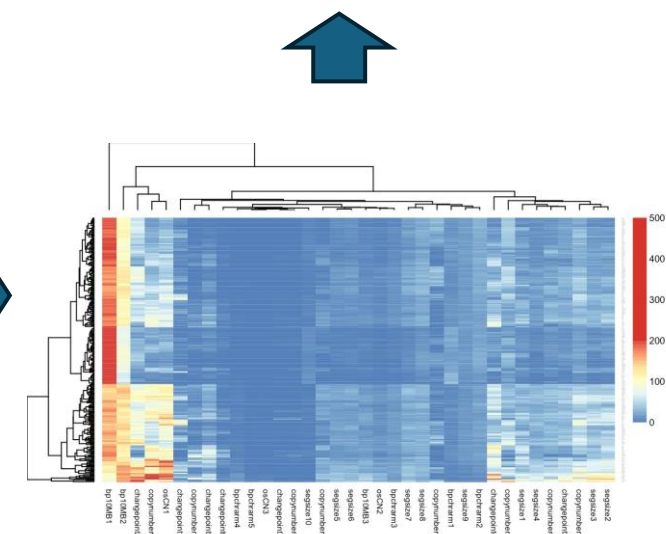
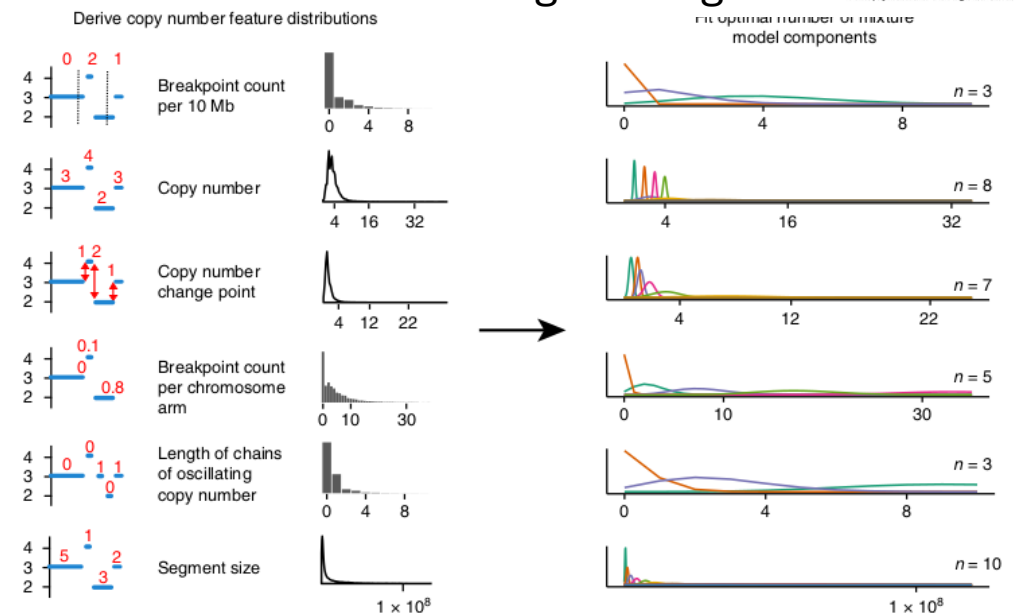
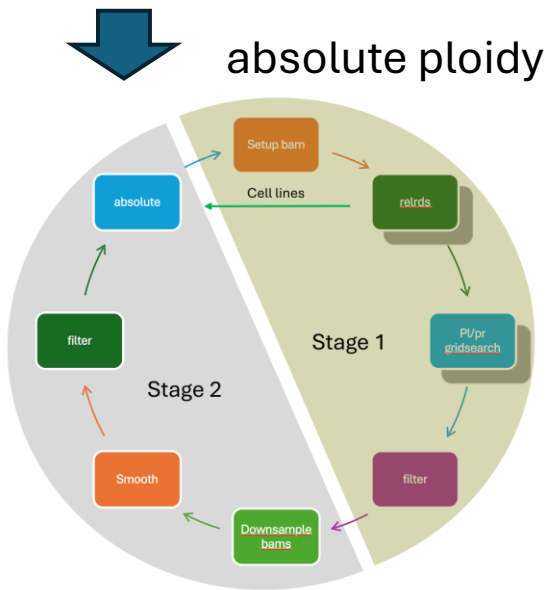
Derivation of signatures



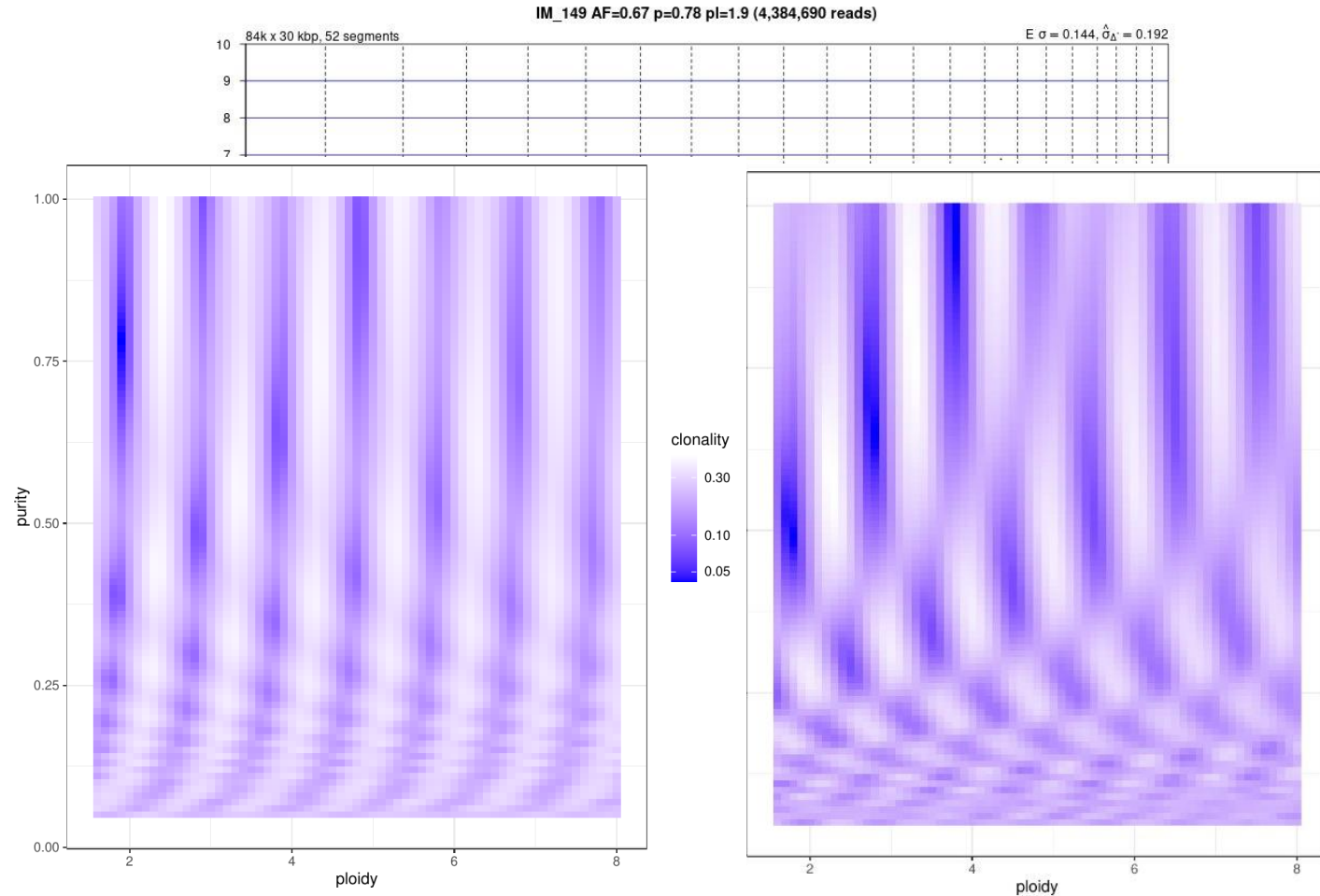
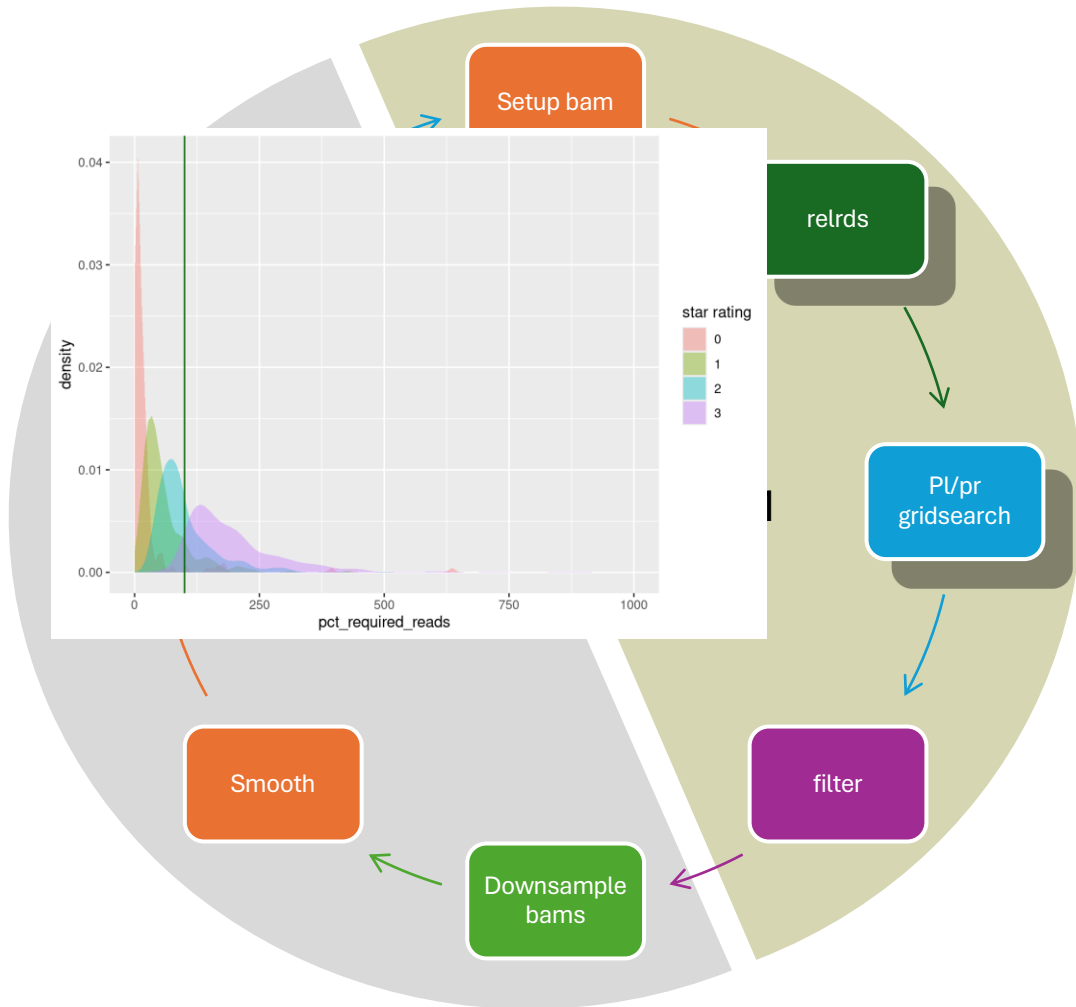
Perform non-negative matrix factorization



Feature engineering



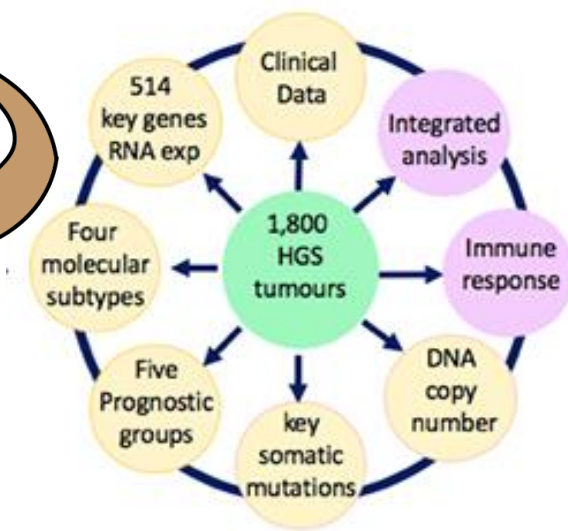
Assigning copy number with qDNAseqmod and Rascal



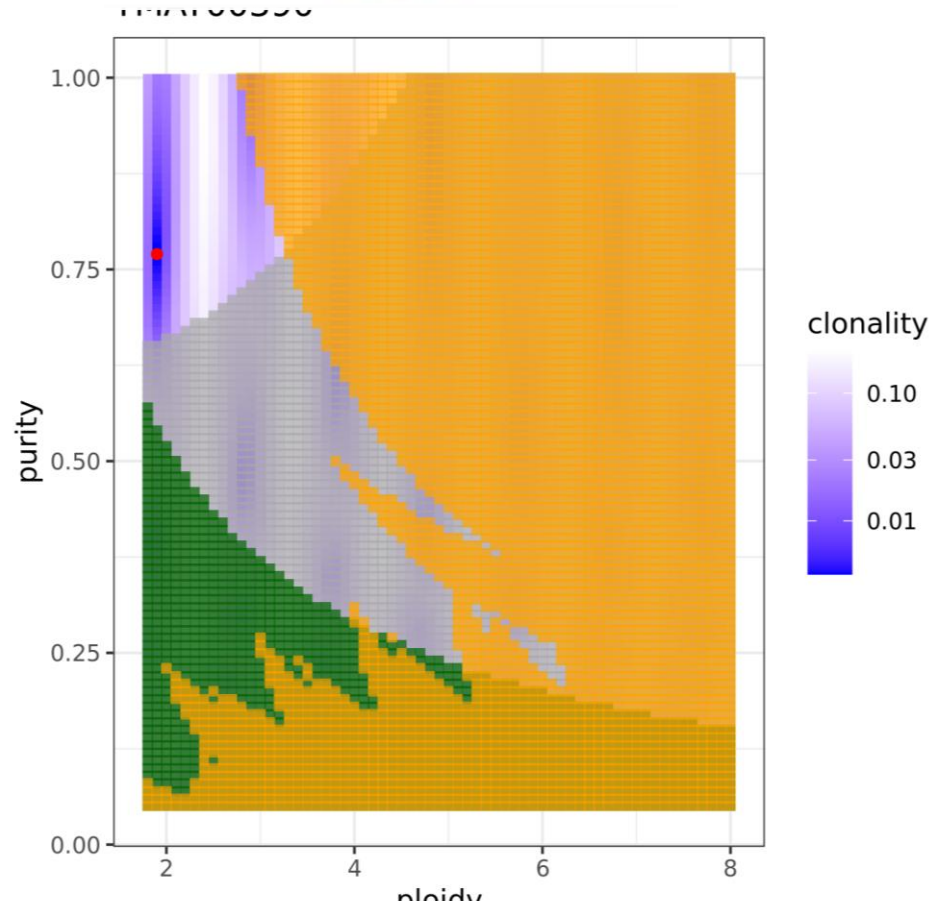
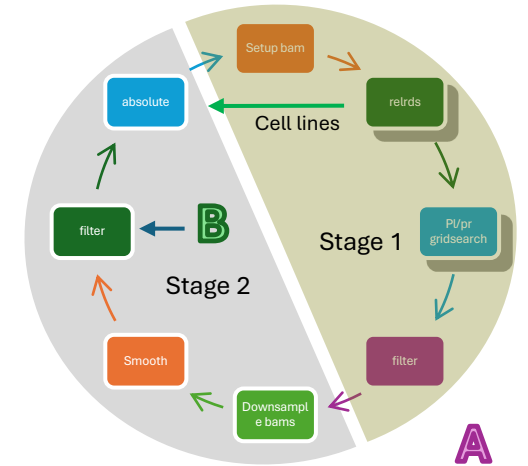
<https://github.com/markowetzlab/QDNAseqmod>

<https://www.biorxiv.org/content/10.1101/2021.07.19.452658v1.full>

$\tilde{purity, ploidy} \quad J \quad \underline{j=1}$



Filtering of ploidy solutions



- underpowered
- **> 10Mb of homozygous loss**
- **does not have at least one genomic segment at every integer copy number state from 1 to ploidy**

<https://www.biorxiv.org/content/10.1101/2021.07.19.452658v1>

Disclosure: JB is a founder of Tailor Bio

Characterizing chromosomal instability in cancer using sWGS data

[markowetzlab/CINSignatureQuantification](https://doi.org/10.1038/s41588-022-04789-9)

ARTICLES

<https://doi.org/10.1038/s41588-018-0179-8>

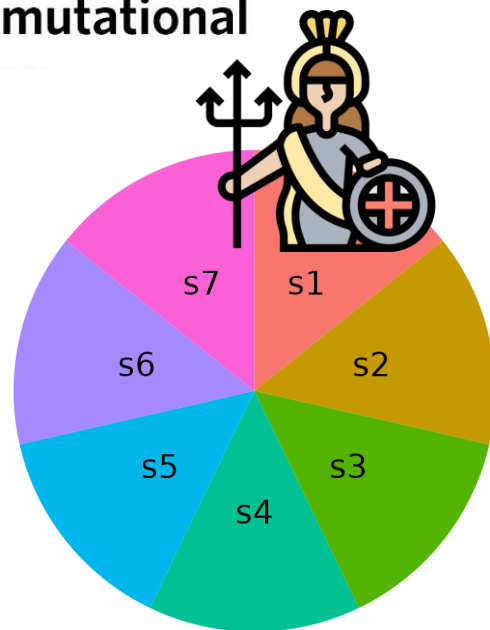
nature
genetics

Copy number signatures and mutational processes in ovarian cancers

Geoff Macintyre^{1,24}, Teodora E. Goranova^{1,24}, Dili Matthew Eldridge¹, Daoud Sie³, Liz-Anne Lewsley⁴, Suzanne Dowson², Rosalind M. Glasspool⁵, Miel Axel Walther¹⁰, Sudha Sundar¹¹, Richard Edmondson Charlie Gourley¹⁶, Marcia Hall¹⁷, Christina Fotopoulou David Millan²⁰, Aoisha Hoyle²⁰, Gareth Bryson²⁰, Cruz Luis Navarro Sanchez², Bauke Ylstra³, Mercedes Jim Florian Markowitz^{1*}, Iain A. McNeish^{2,5,18*} and J

The genomic complexity of profound copy number aberrations in high-grade serous ovarian cancer (HGSOC) cases, which were varied by multiple mutational processes. Copy number signature exposures at diagnosis predict both overall survival and progression-free survival. Measurement of signature exposures provides a rational framework for understanding the underlying mutational processes.

Macintyre



Article

A pan-cancer compendium of chromosomal instability

<https://doi.org/10.1038/s41588-022-04789-9>

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Accepted: 21 April 2022

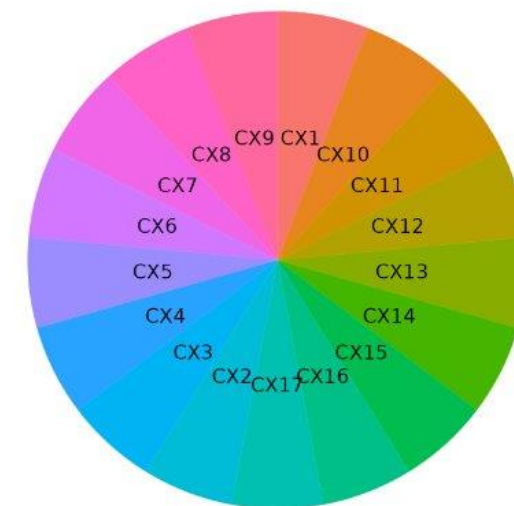
Published online: 15 June 2022

Check for updates

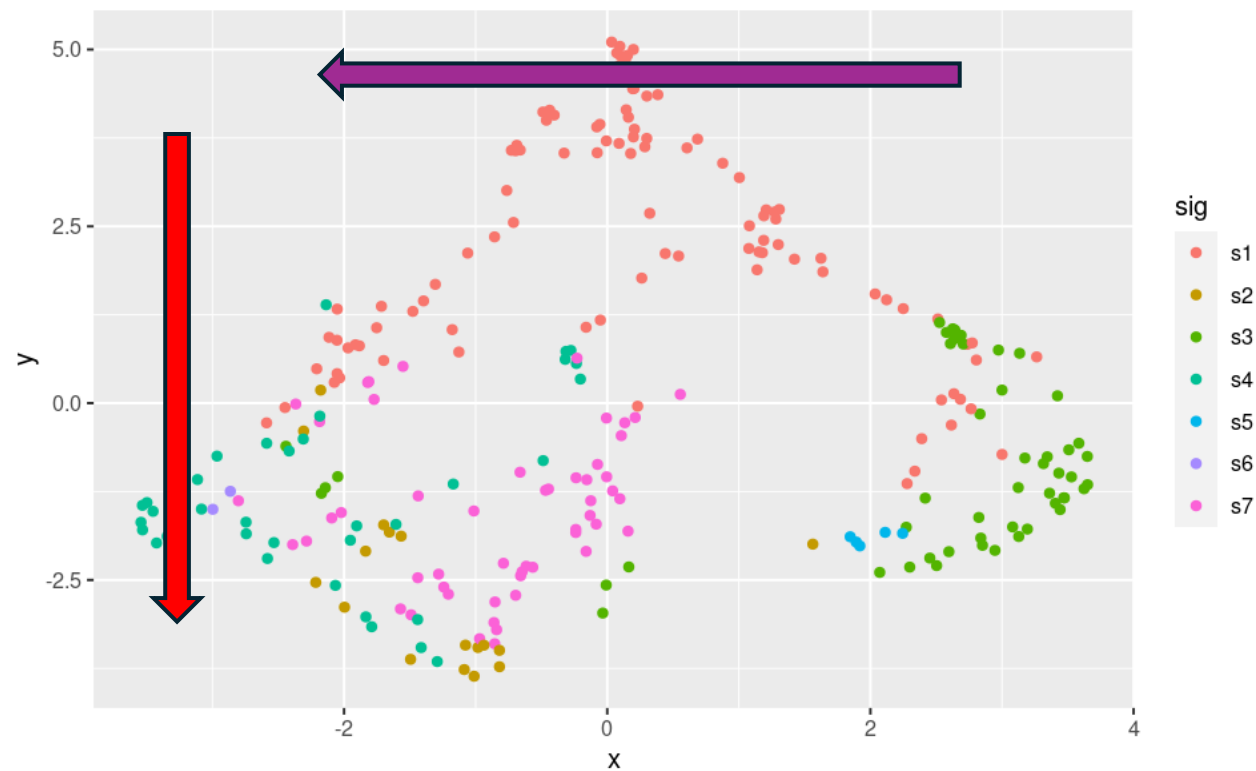
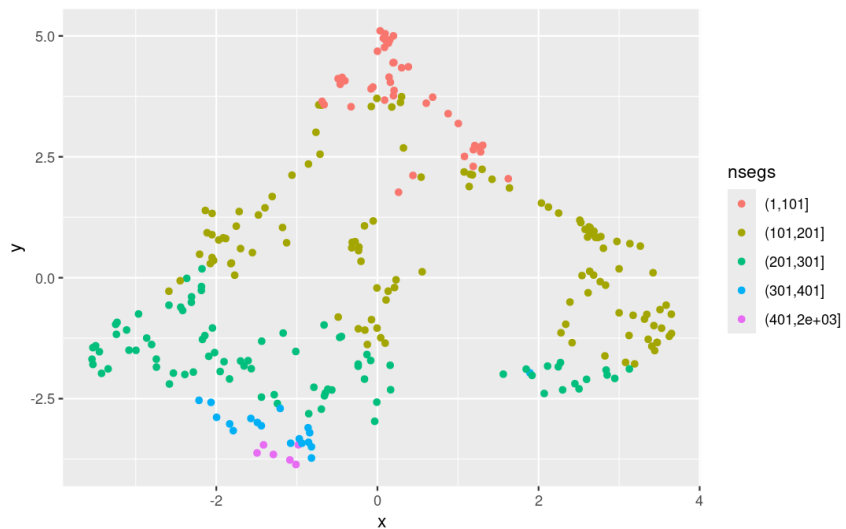
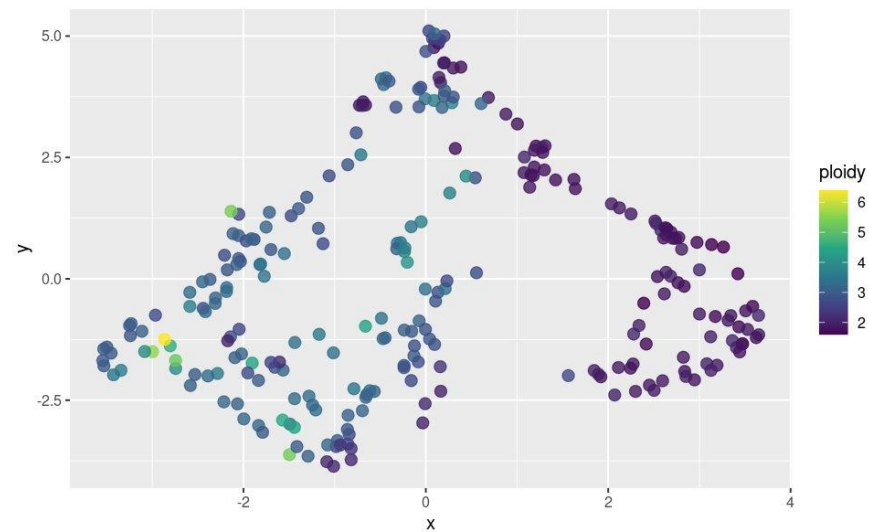
Ruben M. Driessens
Philip S. Smith
Michael Schumacher
Florian Markowitz

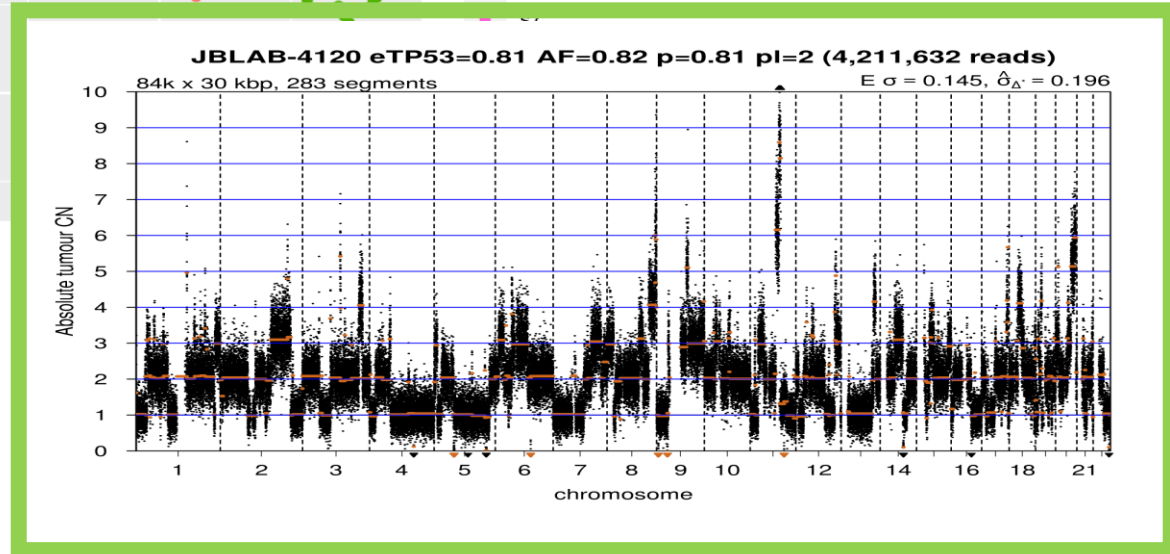
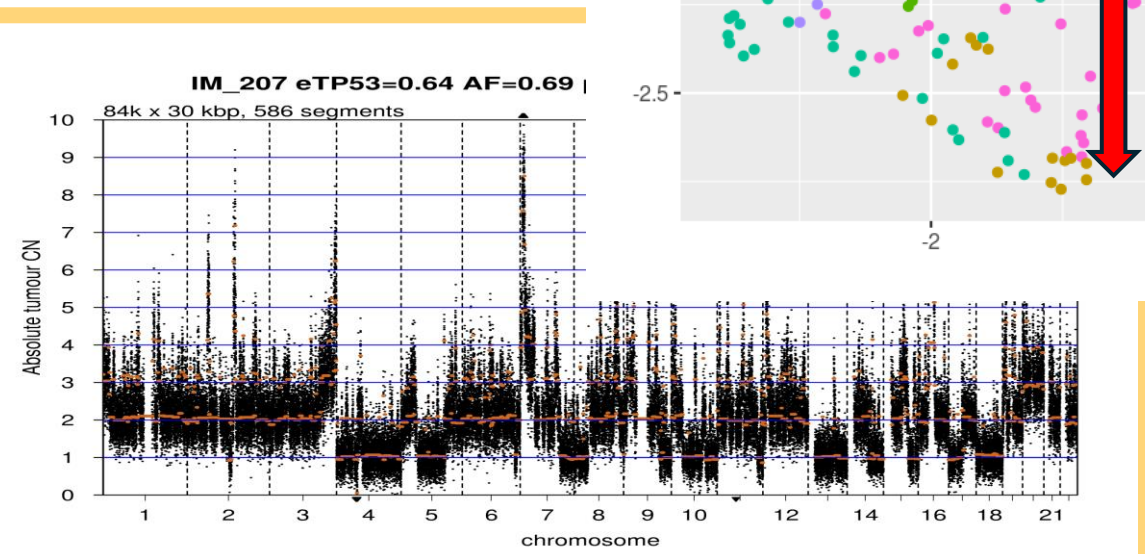
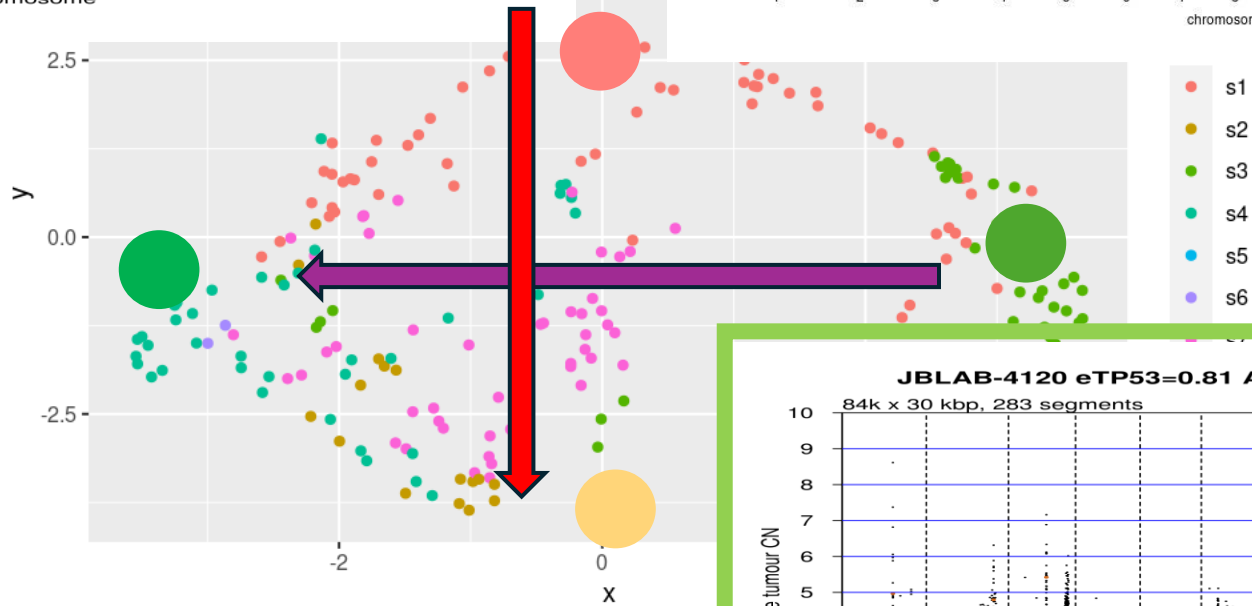
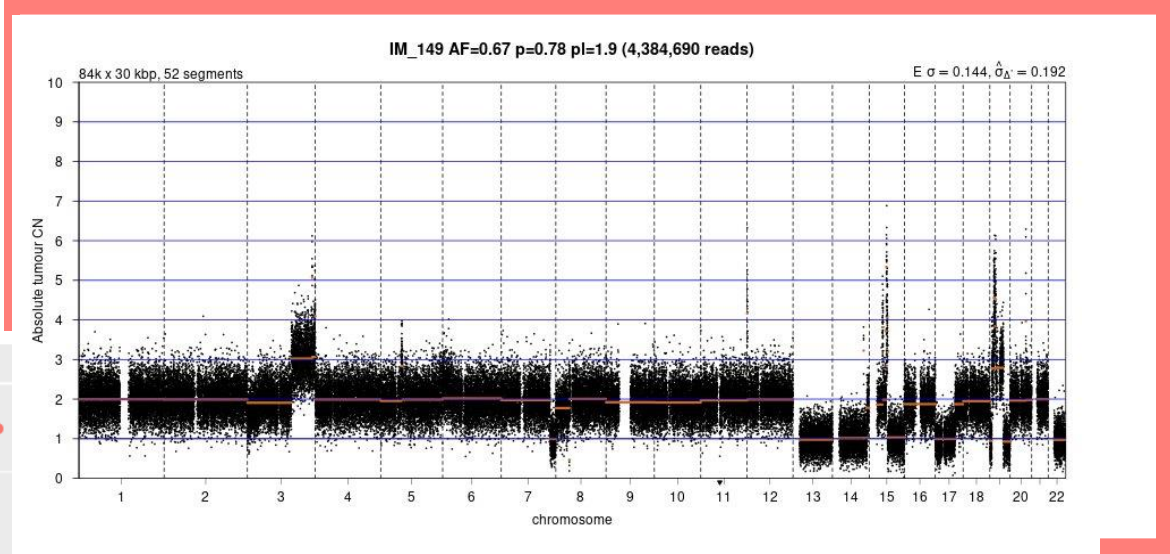
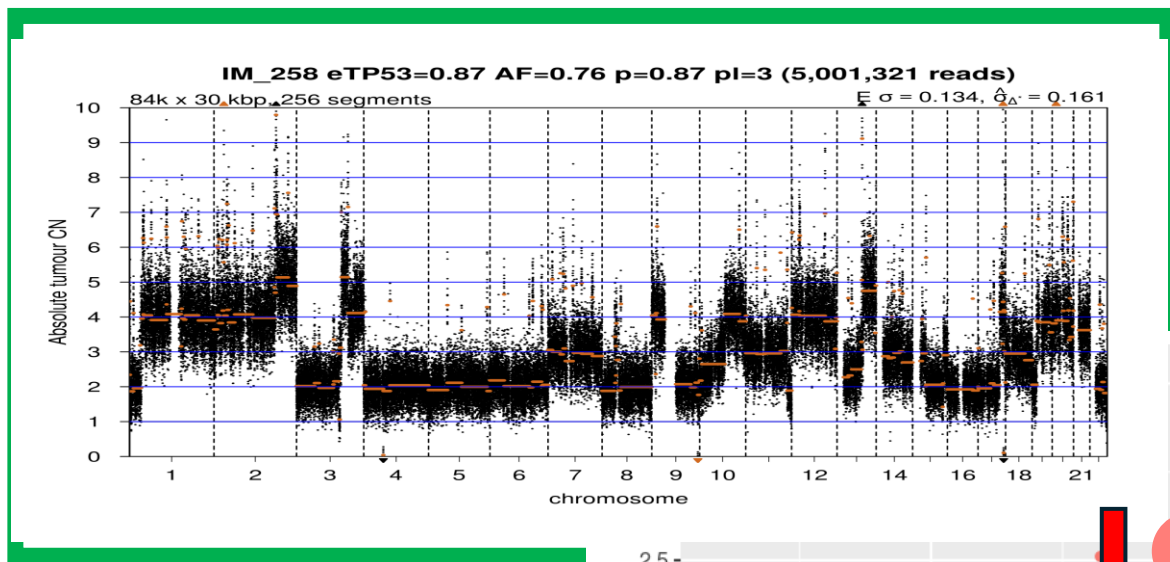
Chromosomal instability (CIN) is a hallmark of cancer. We present a pan-cancer compendium of CIN types and their sources. This framework is one of the fundamental tools to provide a rational

Dreus

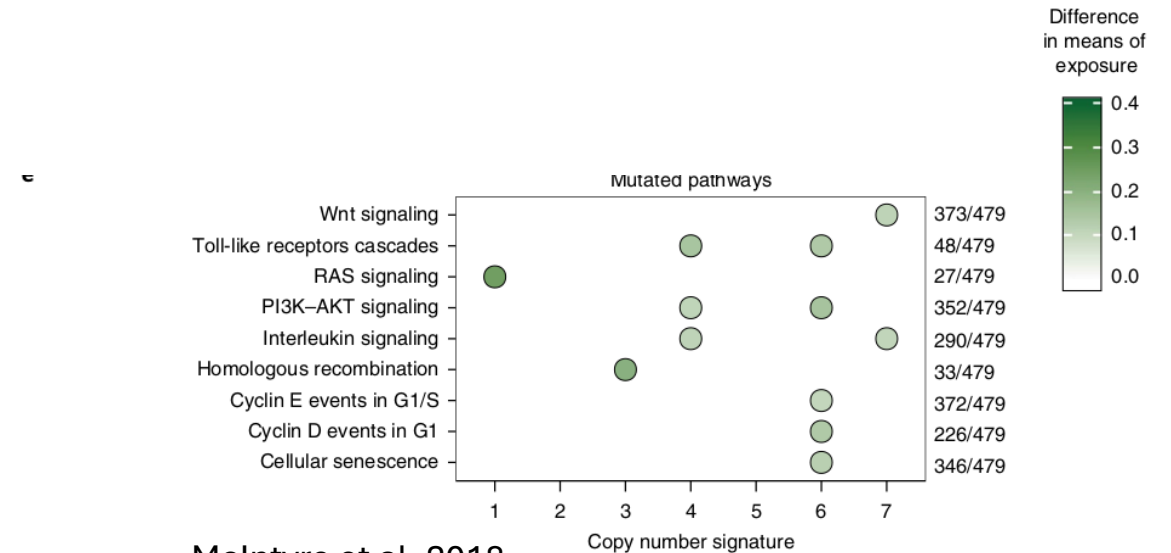
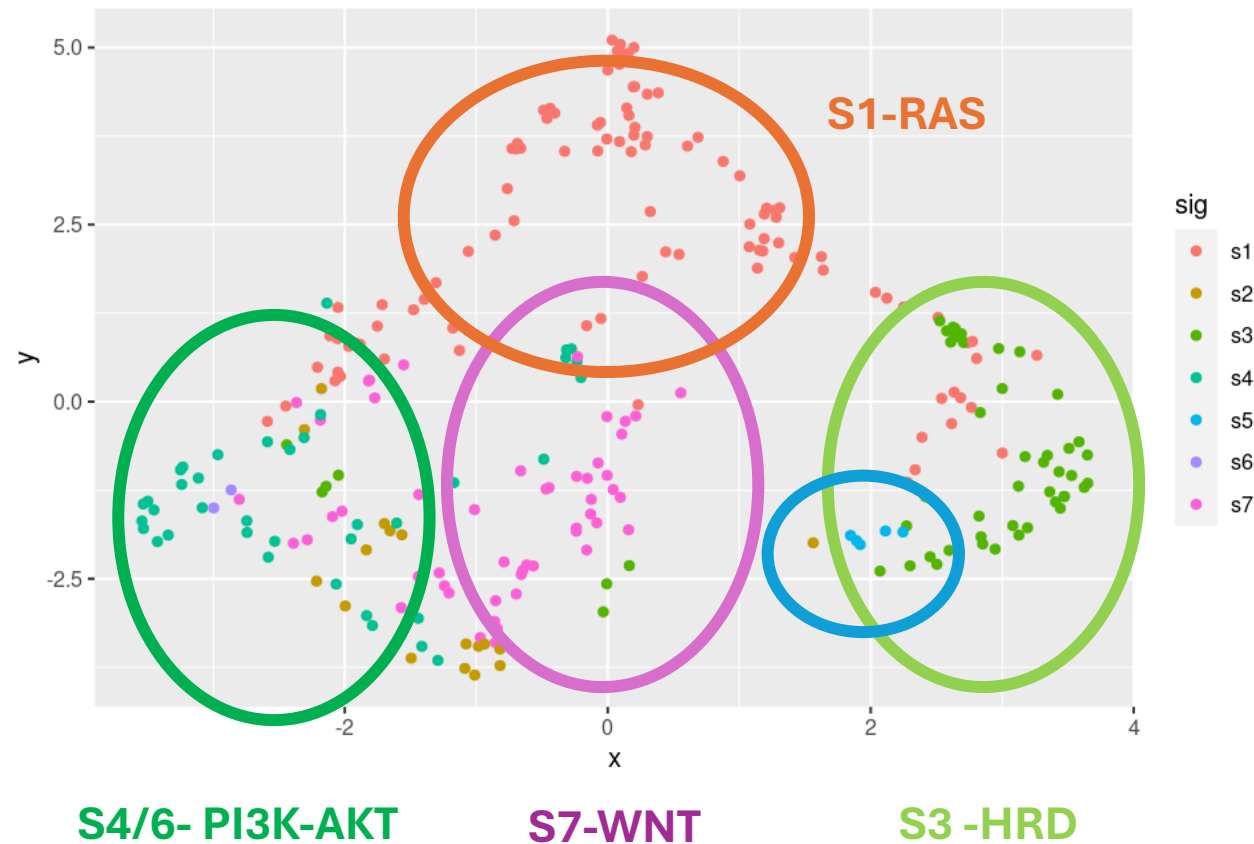


Major axes related to **segmentation**, **ploidy**

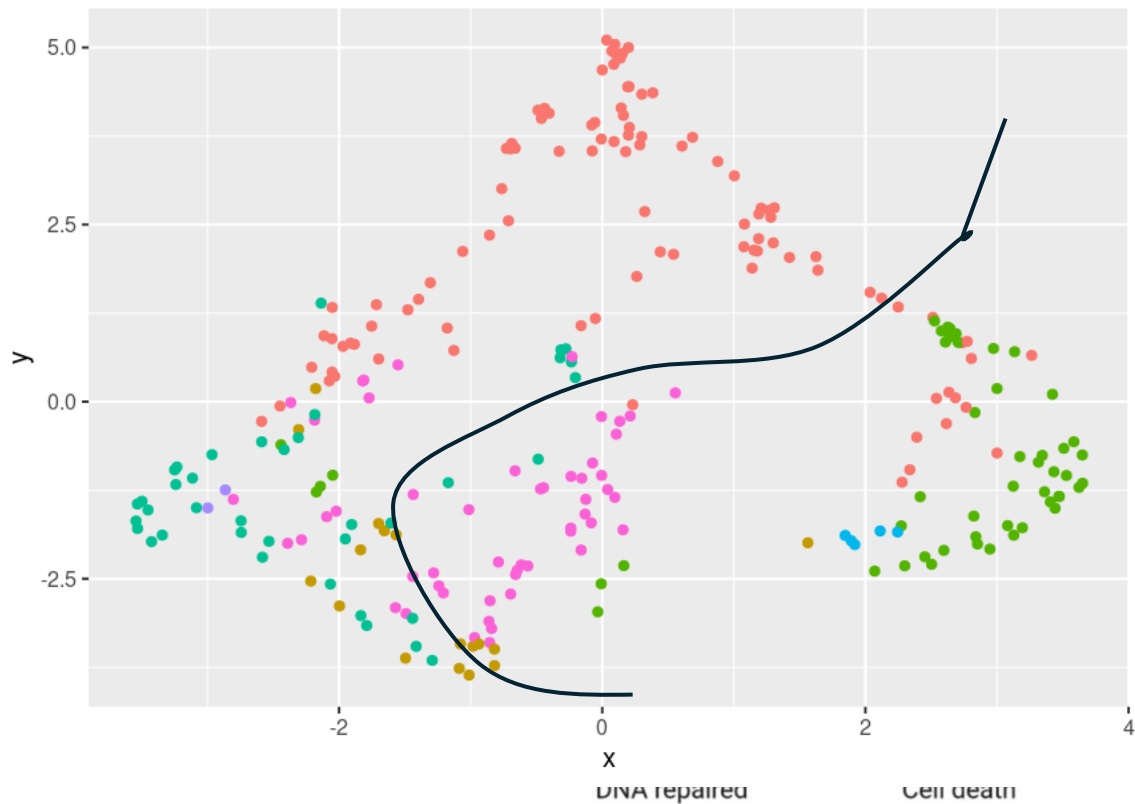
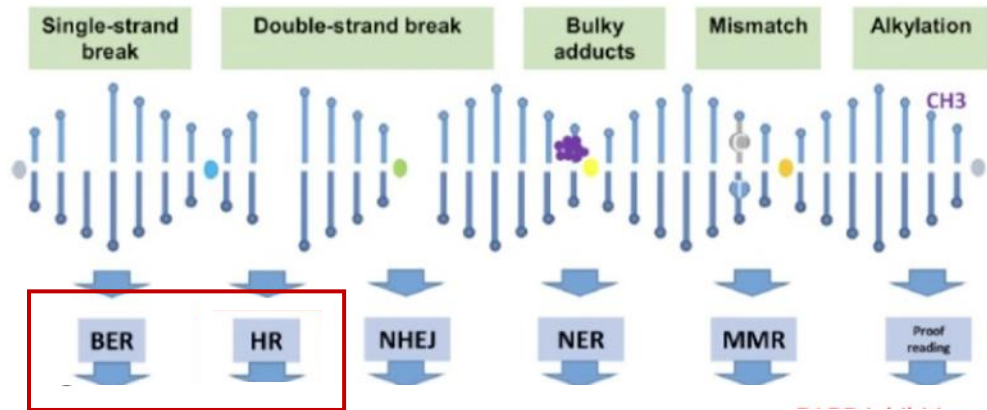




Pathways associated with specific signatures



Current standard of care – Ovarian cancer



Stage I-II Adjuvant therapy

surgery -> chemotherapy

Stage III-IV Neoadjuvant therapy chemo -> surgery -> chemotherapy

• + PARP inhibitors?

50%

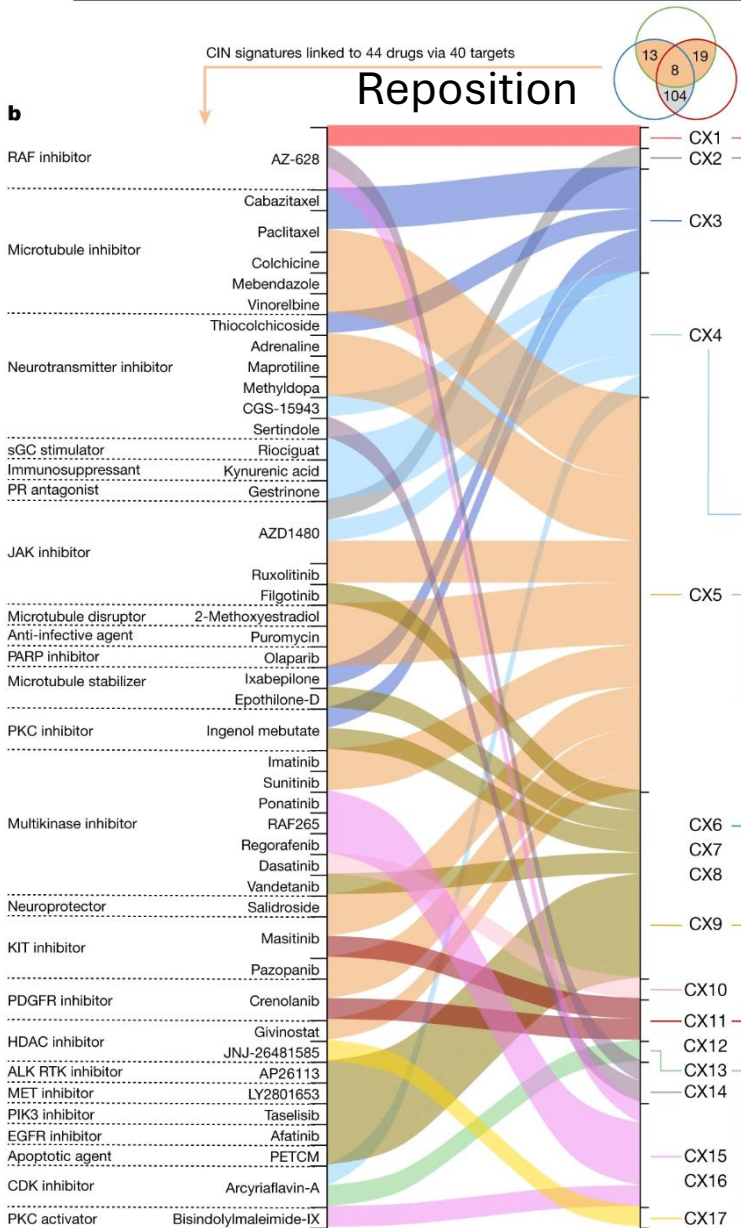
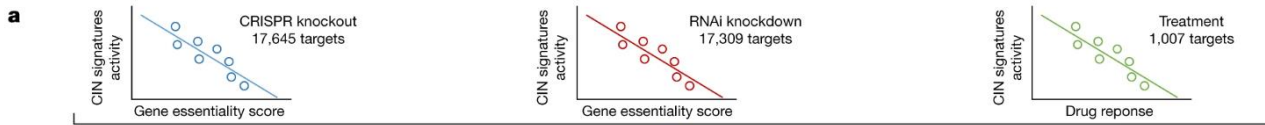
of HGSCs have a defect in HR repair



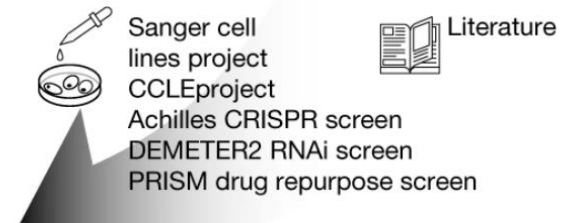
▪ 12.5% have a *BRCA1* mutation

▪ 11.5% have a *BRCA2* mutation

Myriad MyChoice

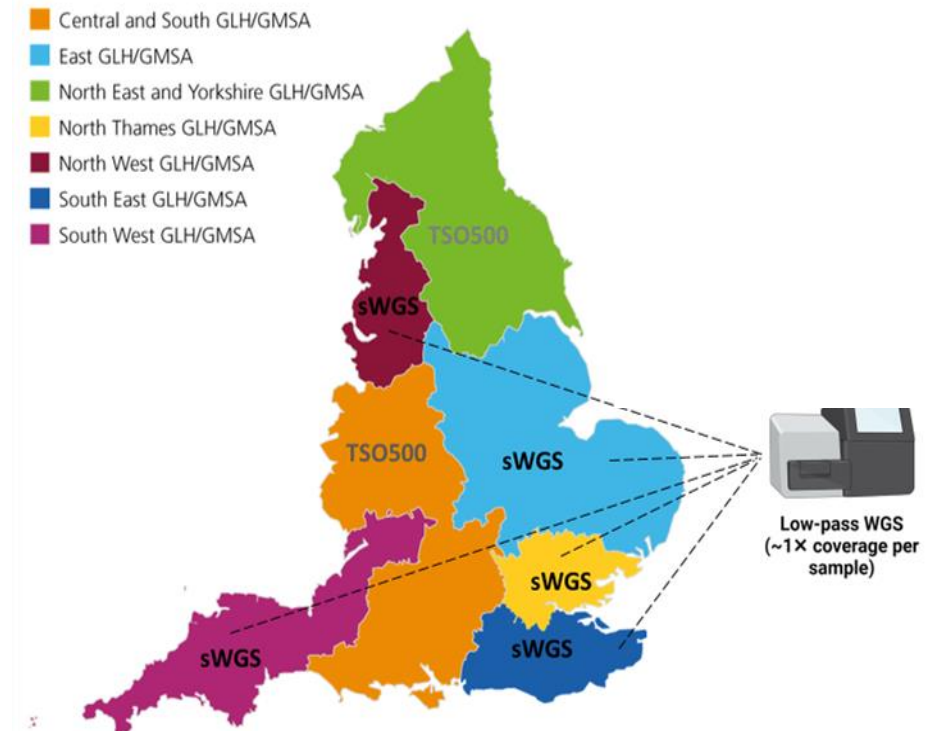


Can we use signatures to stratify for drug treatment?



Summary

- Developing a pipeline to better classify CIN using sWGS
- Aim of developing better precision medicine treatments for ovarian cancer
 - Esophageal cancer, head and neck cancer, small cell lung cancer, lymphoma, neuroblastoma, triple negative breast cancer.
- Hope to move into the clinic in next 5 years



Acknowledgements



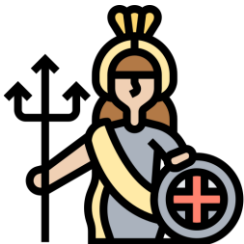
Patients and Consumers

UNSW

- Susan Ramus
- Adelyn Bolithon
- Nicki Meagher (Daffodil Centre)
- Gordana Popovic
- Amir Ariff
- Brittney Harrington

University of Cambridge

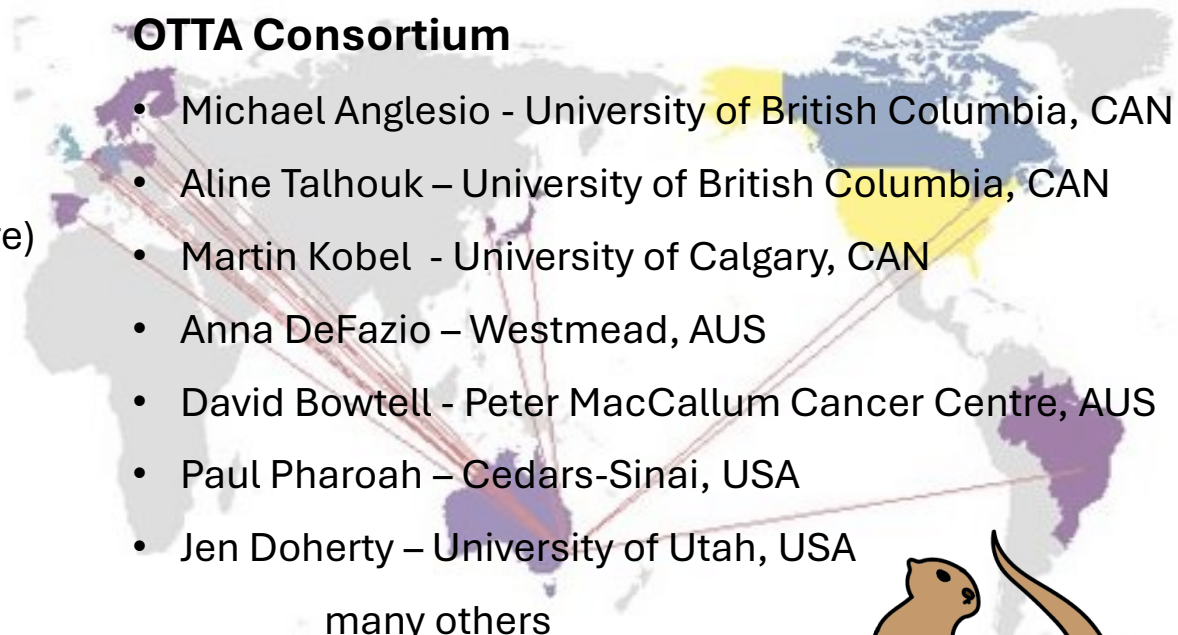
- James Brenton
- Thomas Bradley
- Ania Piskorz
- Philip Smith



OTTA Consortium

- Michael Anglesio - University of British Columbia, CAN
- Aline Talhouk – University of British Columbia, CAN
- Martin Kobel - University of Calgary, CAN
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- David Bowtell - Peter MacCallum Cancer Centre, AUS
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- Jen Doherty – University of Utah, USA

many others



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