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PRECISION ONCOLOGY: From Precision Prevention to Cancer Care

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SCIENTIFIC SESSION 1: PRECISION MEDICINE

Disclosures

Research funding: BMS, Pfizer, Novartis, GSK

Scientific Board: Eurofarma, Novartis, MSD, AstraZeneca

Advisory/Consulting : BMS, Novartis, Libbs, MSD, Roche

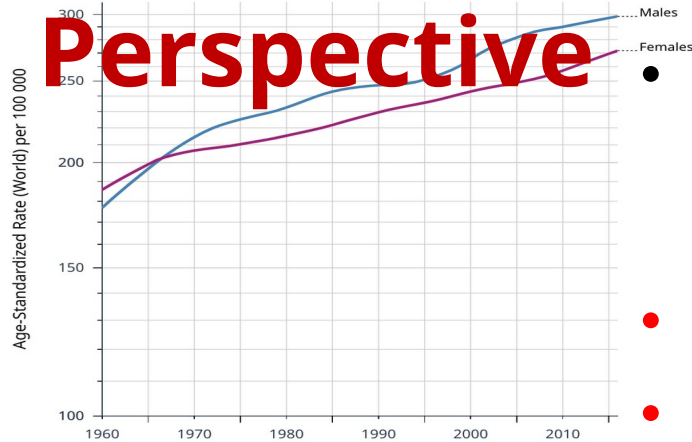
Travel Expenses: MSD, BMS, Janssen

Participation in Clinical Trials: AstraZeneca, Novartis, Janssen, MSD, Roche, BMS



March 25-26th, 2025

Epidemiology Perspective

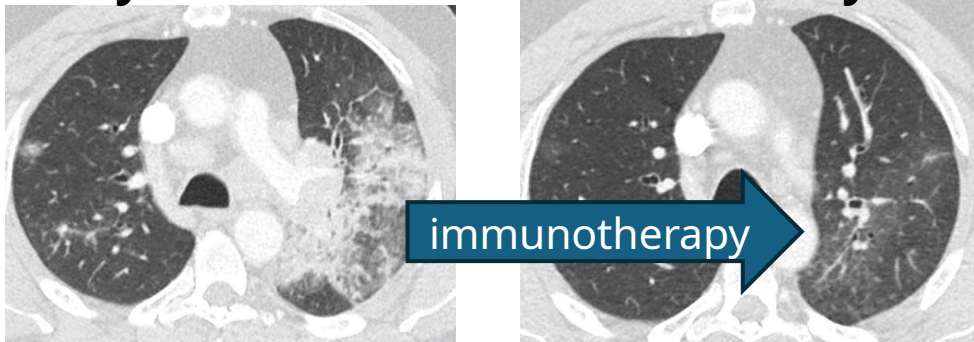


- 2nd mortality in gernal World;
- 4 / 10 people
- 1 / 6 deaths

Global Cancer Observatory - IARC

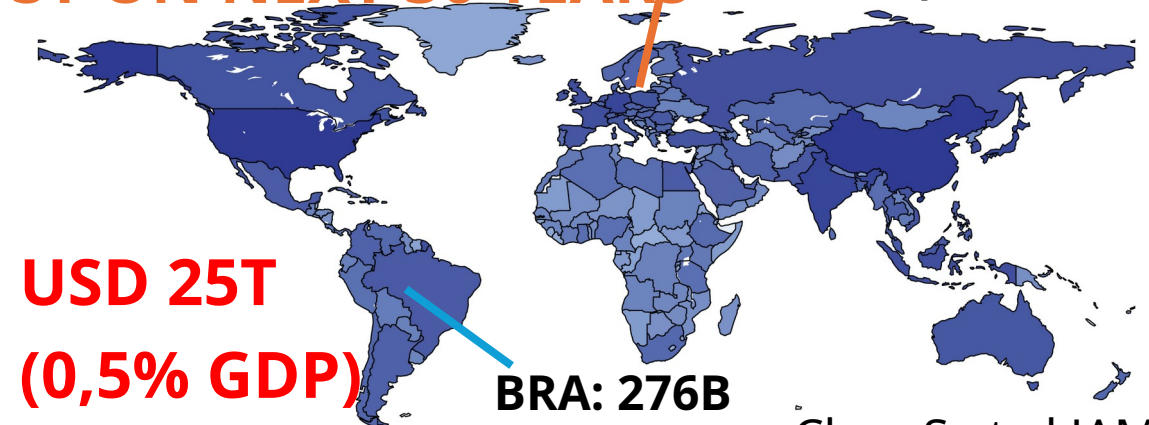
Patient Perspective

Man, 67 years, 3 kids, metastatic kidney cancer



Economic Perspective

COST ON NEXT 30 YEARS GER: 1.8T (1.1% GDP)

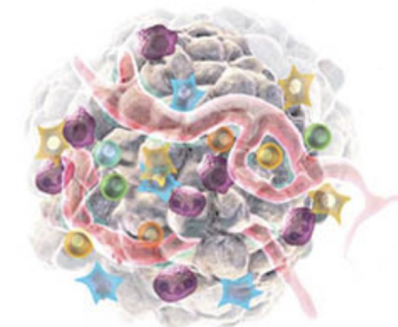


**USD 25T
(0,5% GDP)**

**BRA: 276B
(0.3% GDP)**

Chen S et al JAMA
2023

Biology Perspective





What 'type' of disease is cancer?

Cancer is a disease of the environment

Sir Percivall Pott (1775)

Increase in testicular cancer in chimney sweeps

Occupational exposure to soot.



Cancer is a disease of the genome

Theodor Boveri (1914)

Chromosomal defects lead to abnormal cell proliferation

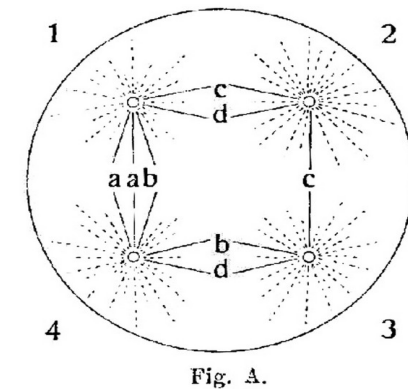


Fig. A.

Concerning the origin of malignant tumors. T. Boveri
J. Cell Sci. doi:10.1242/jcs.025742 (translated 2008)

The Burden of Cancer

The Biology Perspective

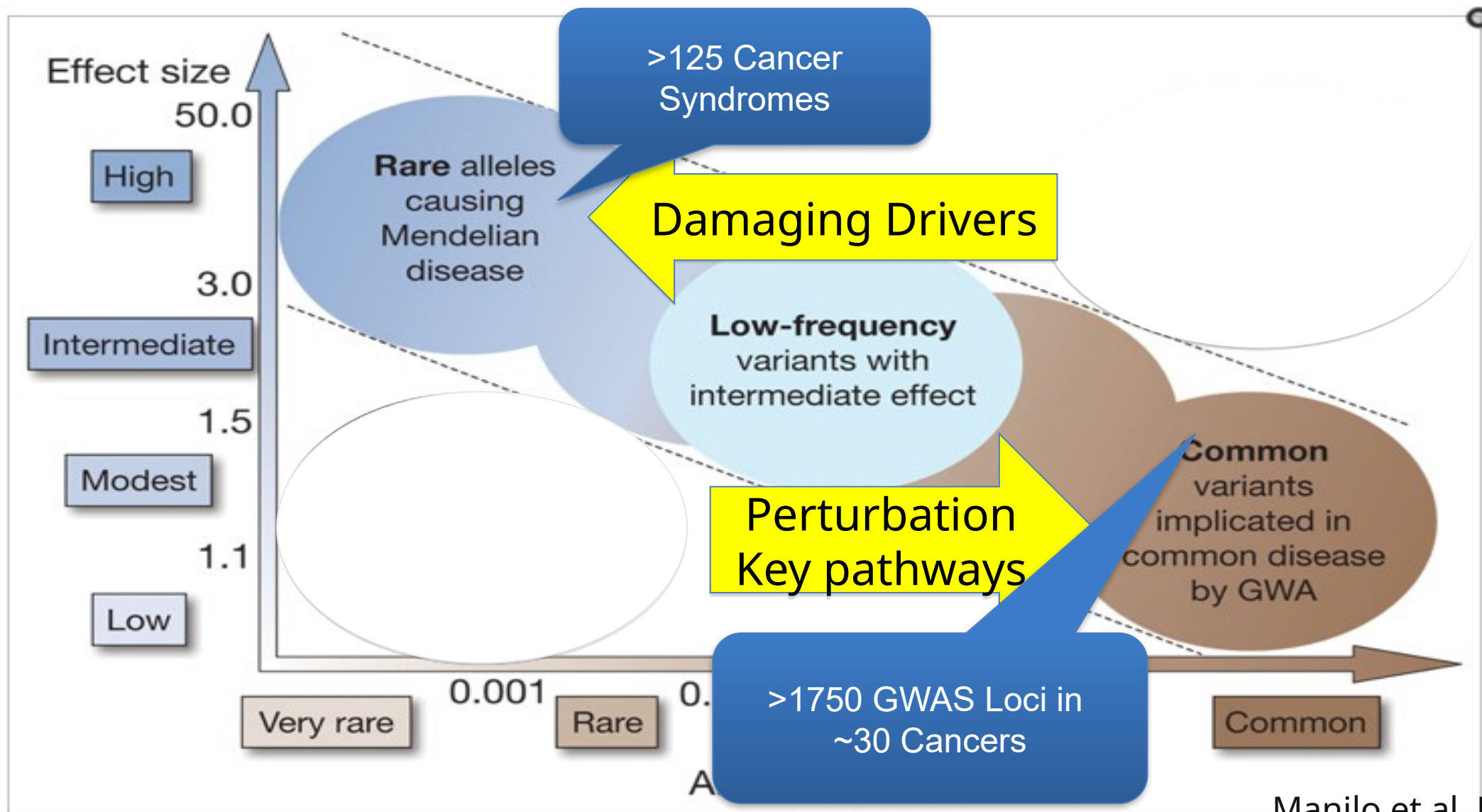
What '*type*' of disease is cancer'

- **Genetic:** two genomes
- **Celular:** all cell compartments
- **Tissue:** micro-enviroment
- **Metabolic:** energy and pathways
- **Immunology:** immune evasion
- **Evolution:** resistance
- **Infectious:** HPV, microbiome, vaccin
- **Environmental:** exposures



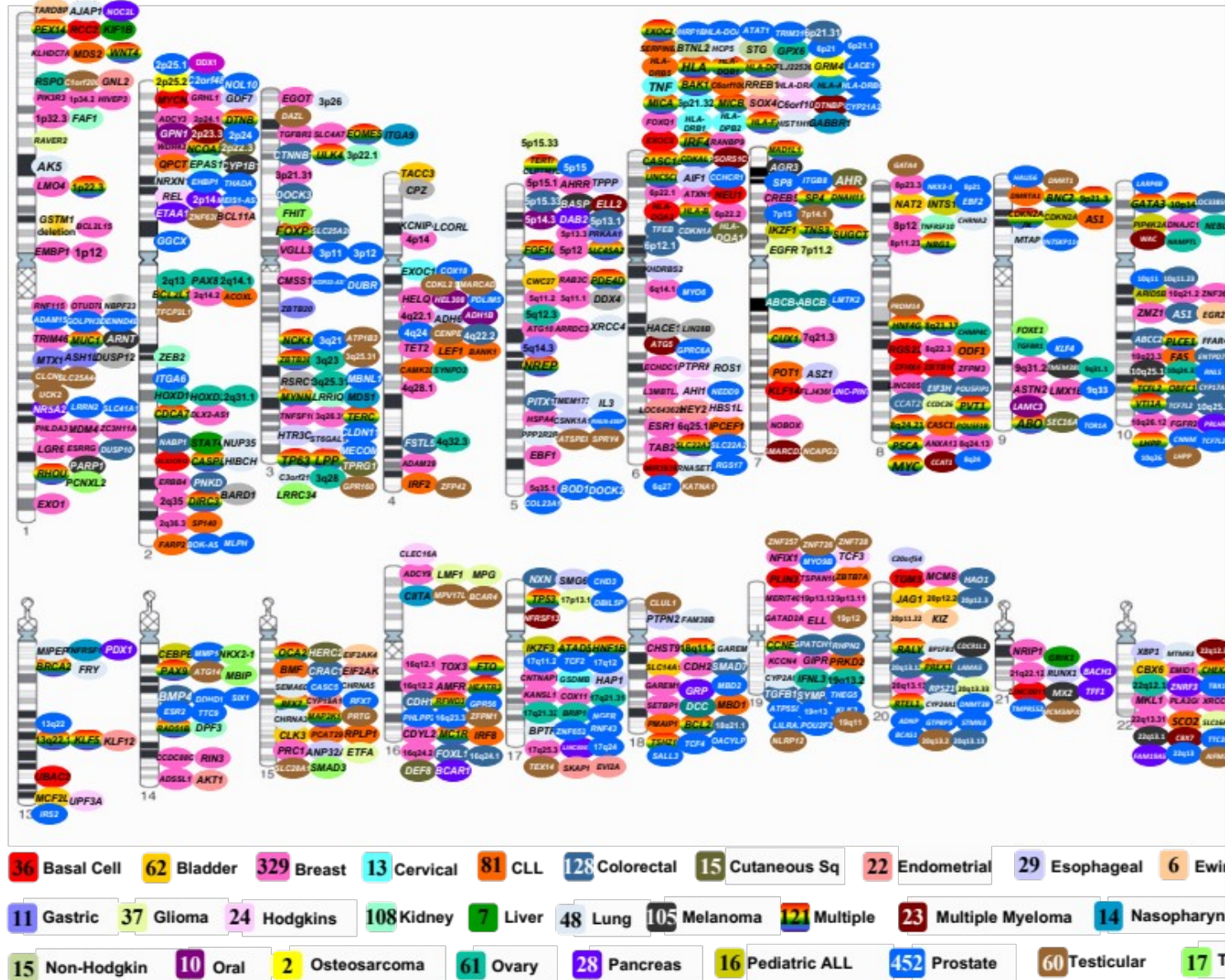


Architecture of Genetic Susceptibility





Published Cancer GWAS Etiology Hits



>1750 Disease Loci marked by SNPs

For > 30 “cancers”
Rare to Common

Adult Cancers
Estimated OR < 1.2

Vast Majority
~85% European Ancestry
~14% East Asia
~1 % African Ancestry

~15% Pleiotropy
(shared between cancers)

~5% biological mechanism
→ opportunity



Do we need to understand the biological bases of individual GWAS signals?

NO

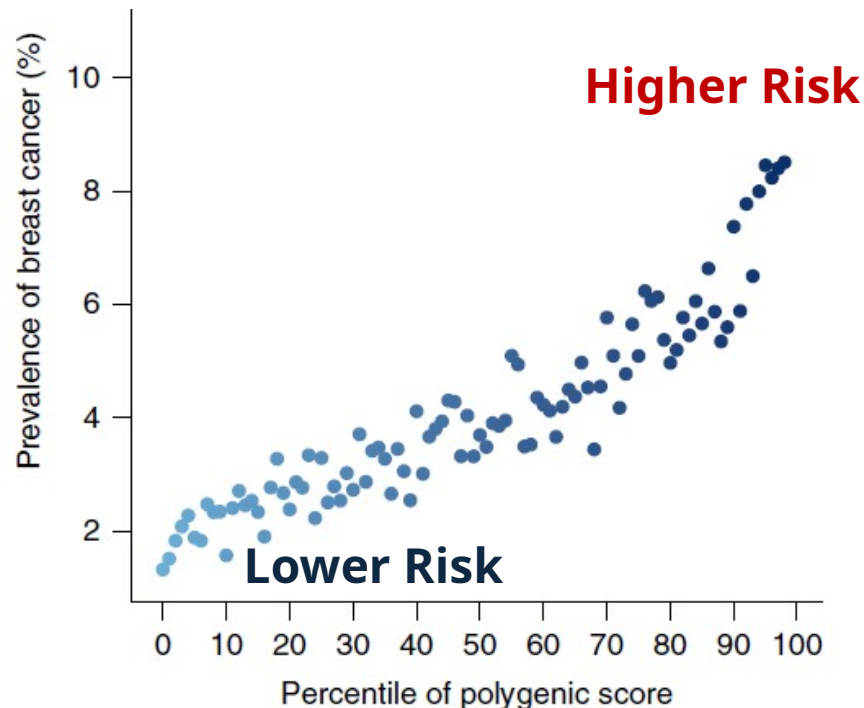
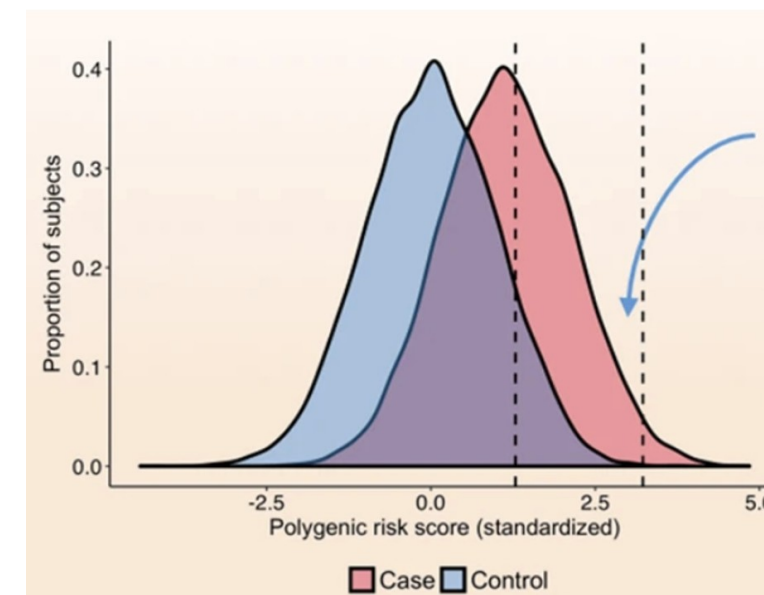
Polygenic risk score (PRS) based on *many* SNPs

Common Variants



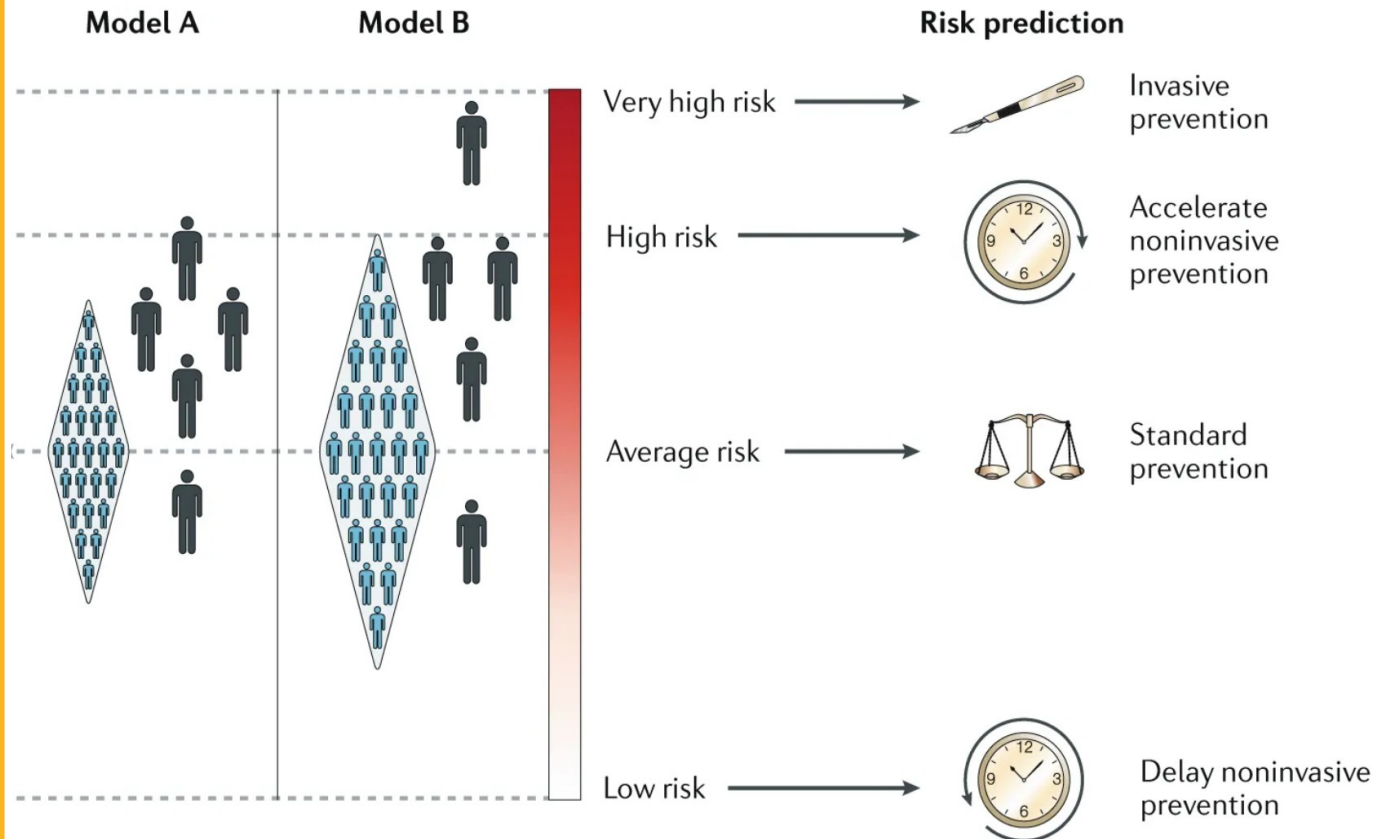
PRS

$$PRS_i = \sum_j^M \hat{\beta}_j \times dosage_{ij}$$

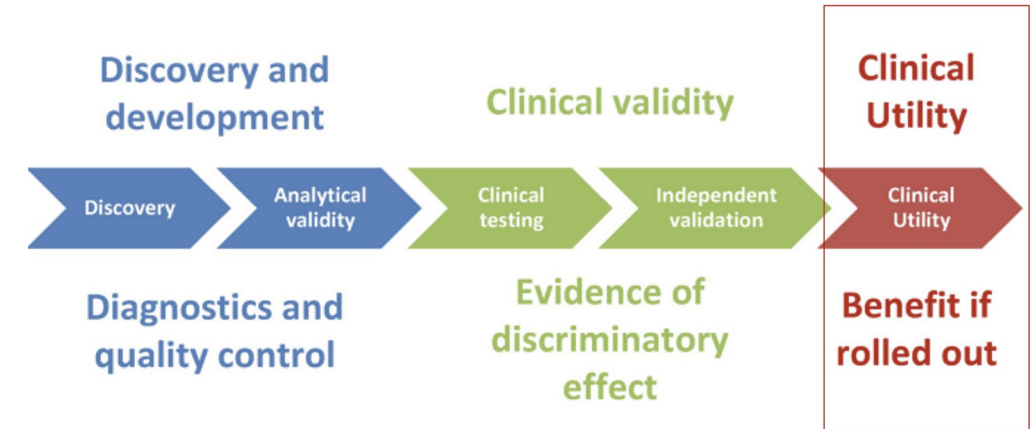
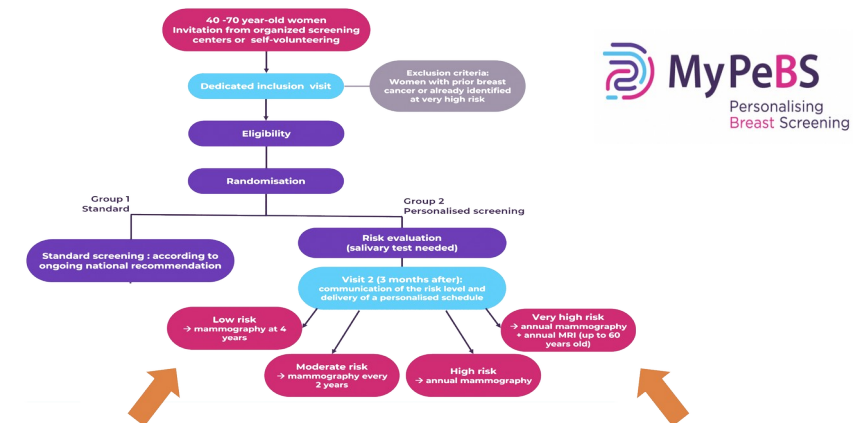




Precision Oncology Prevention



Clinical Application: Ready for patients?

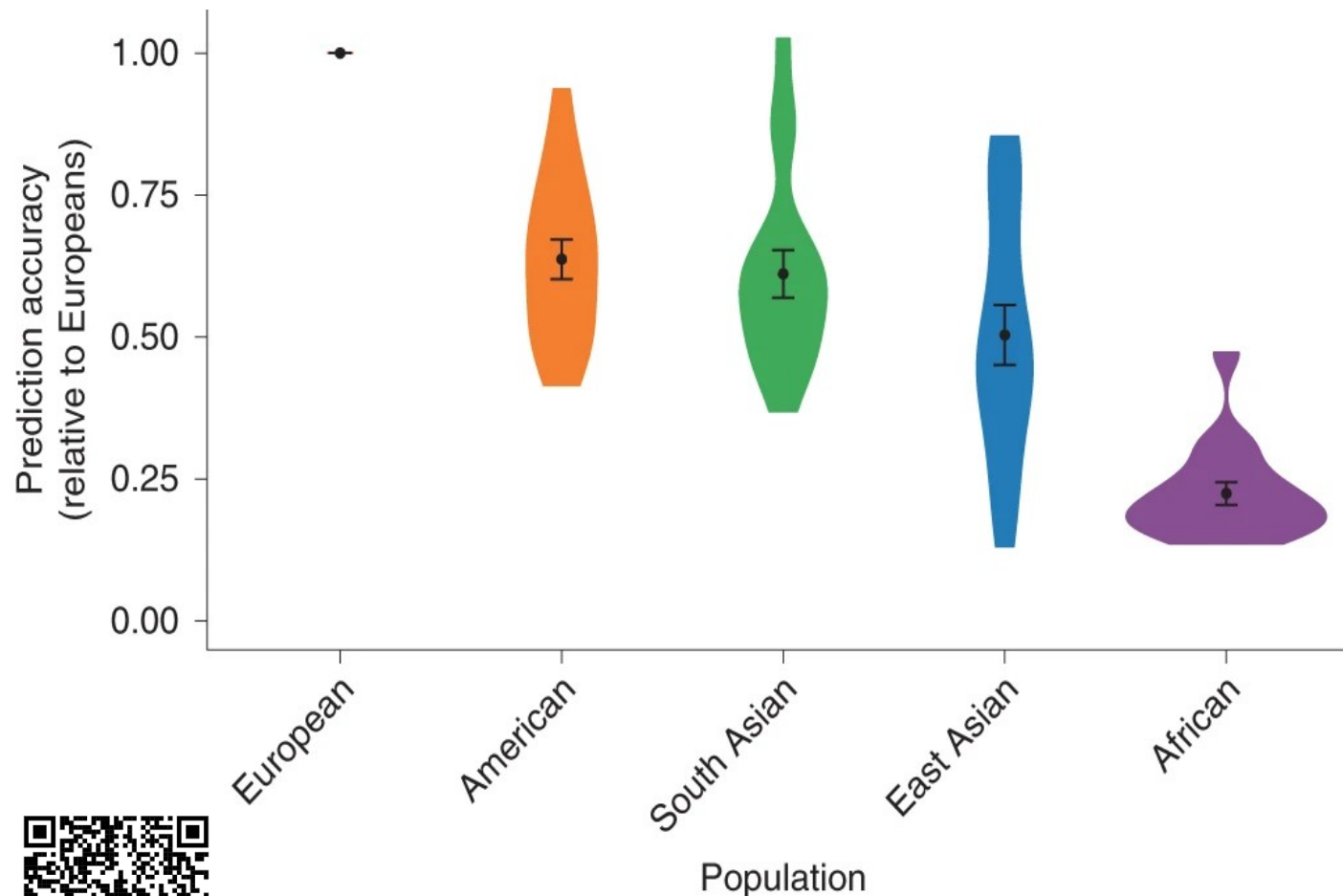


“Given the lack of validation of PRS, these should not be used to inform medical management at this time.”



Will be Brazil out of Precision Prevention?

17 quantitative traits and 5 continental populations



Operários, 1933. Tarsila do Amaral





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CoDiGO Project



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Closing the gap for diversity in genome research in Brazil

20 years of clinical data on EMR:
cancer, chronic diseases, and more

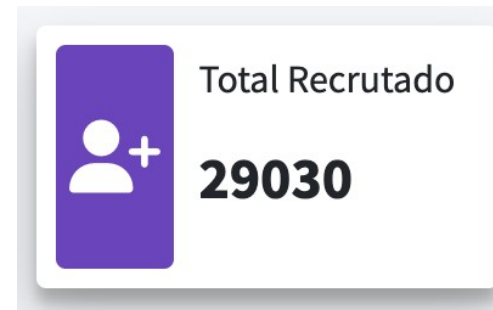


MINISTÉRIO
DA SAÚDE

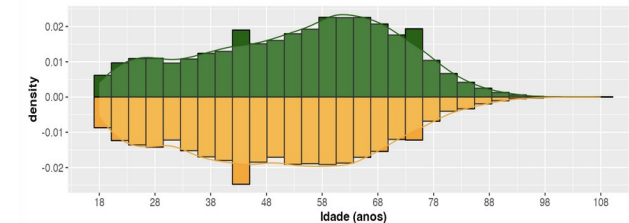
PRONON

Programa Nacional de Apoio
à Atenção Oncológica

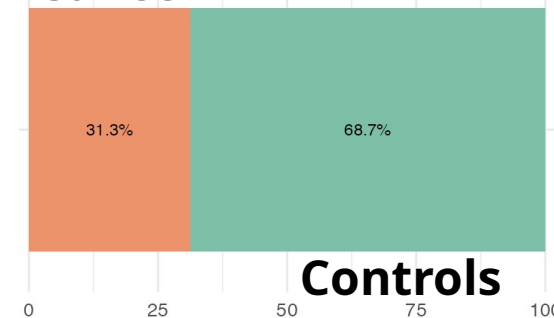
Total Recruited



18 to 108 years



Cancer

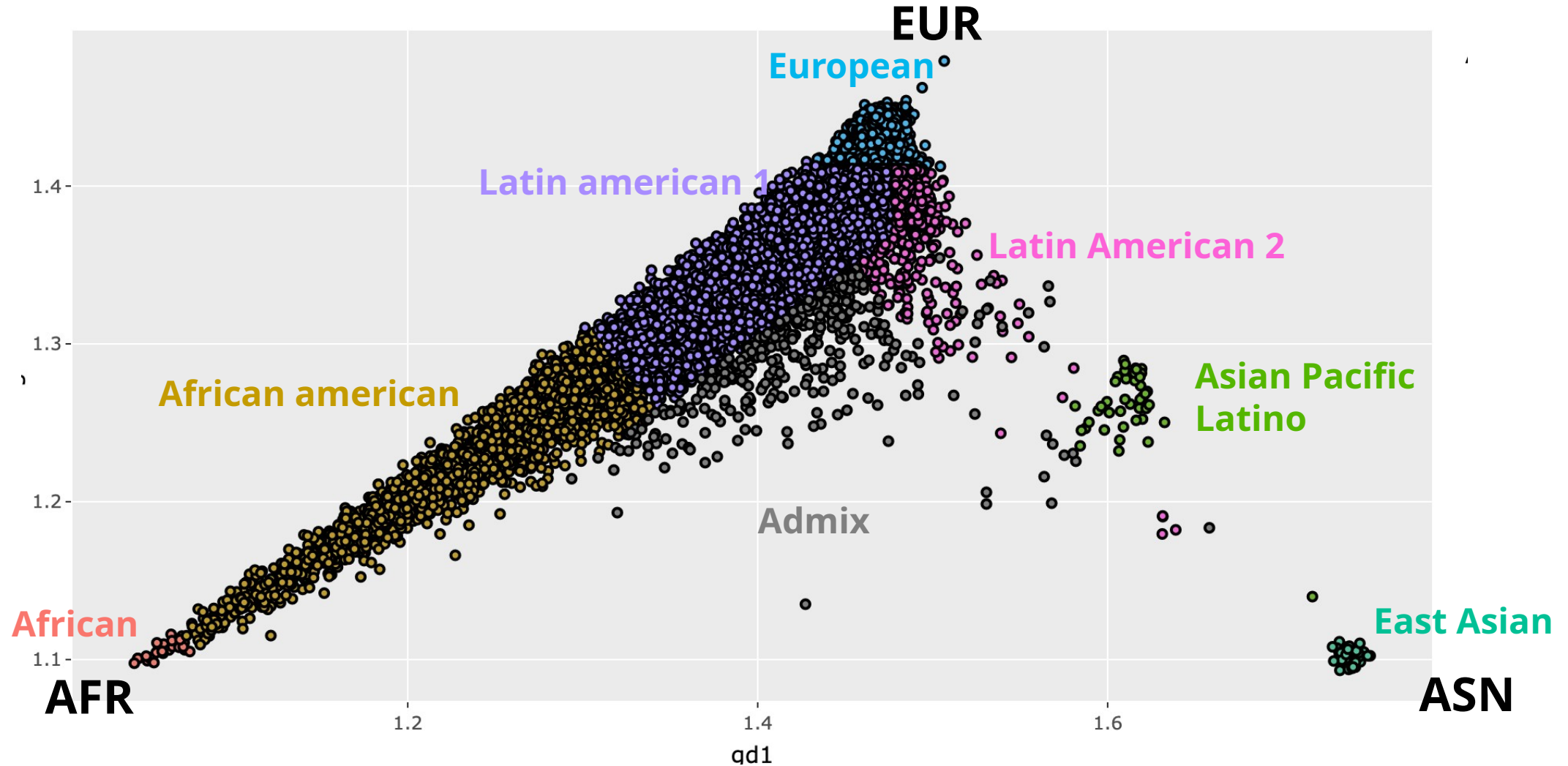


Other Diseases:

- Cardiovascular
- Metabolic
- Infectious
- Immune
- Neurological
- etc



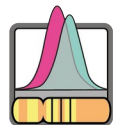
CoDiGO Project





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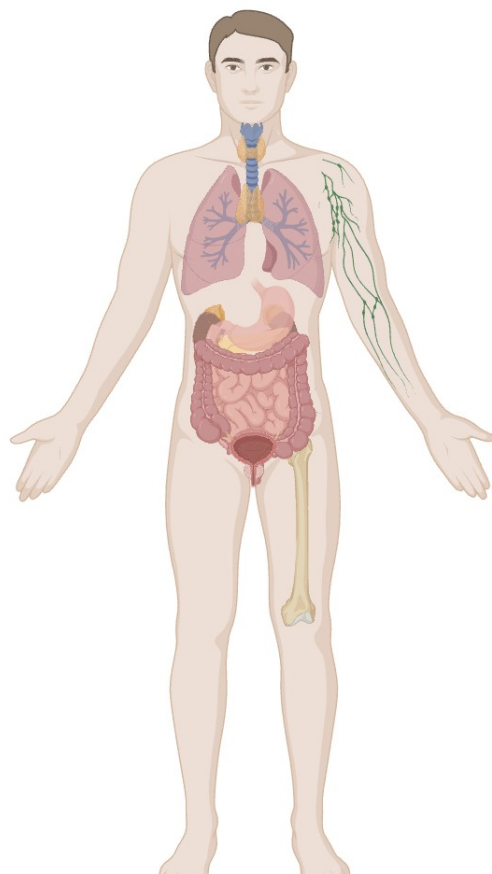
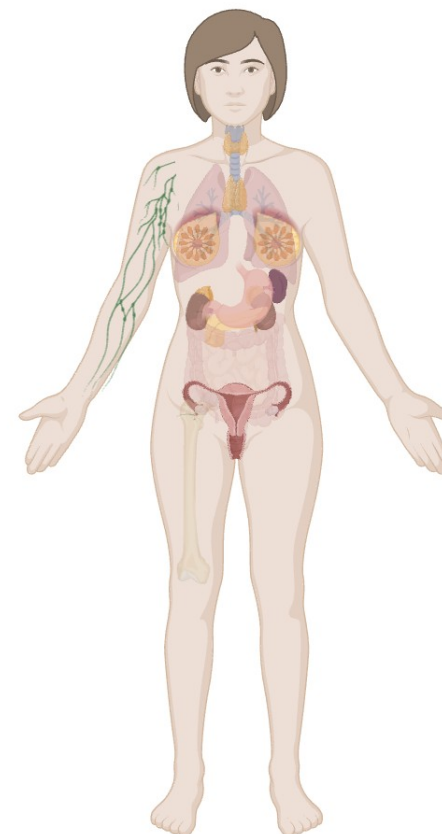


**PGS
Catalog**
~4.500 PRS
EUR-based

PRS Evaluation in BR PoP



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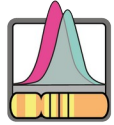
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PRS Evaluation in BR PoP



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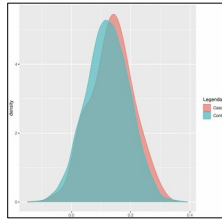
March 25-26th, 2025



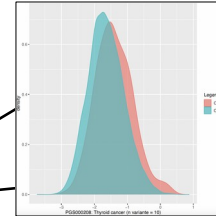
**PGS
Catalog**

**~4.500 PRS
EUR-based**

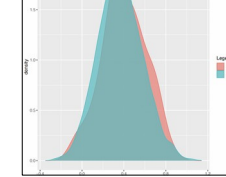
Esophageal cancer



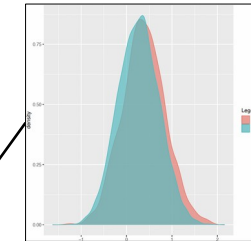
Thyroid Cancer



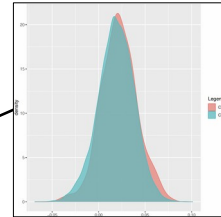
Brain Cancer



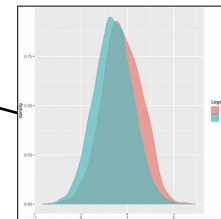
Breast Cancer



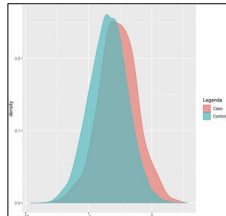
Renal Cancer



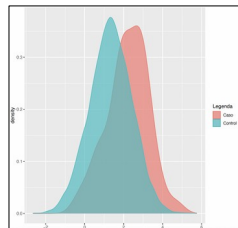
Colon Cancer



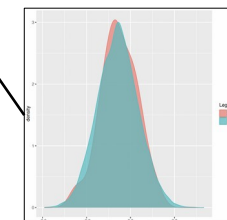
Prostate Cancer



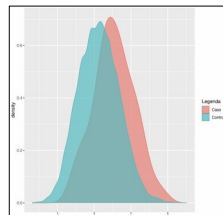
Testicular Cancer



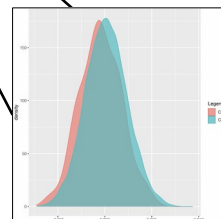
Ovarian Cancer



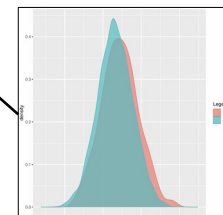
Melanoma



Bladder Cancer



Leukemia





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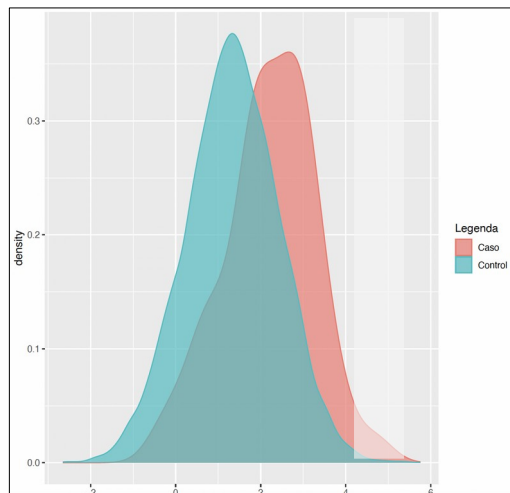
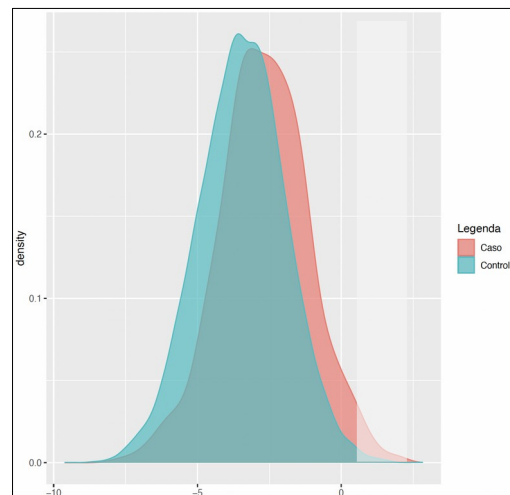


The Good, the Bad, and the Ugly

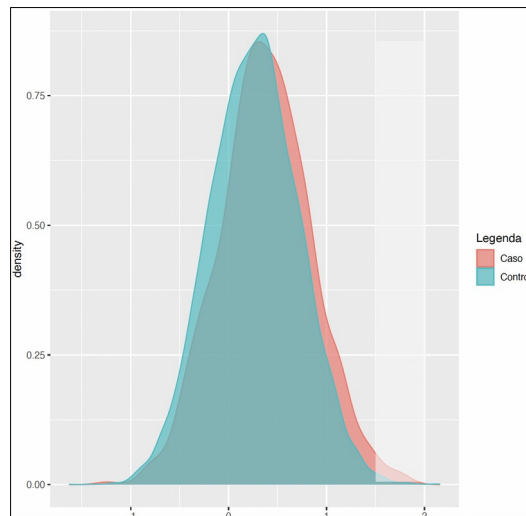


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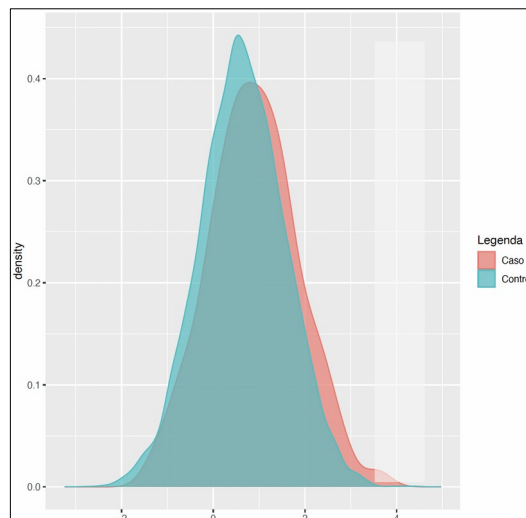
Prostate Cancer Testicular Cancer



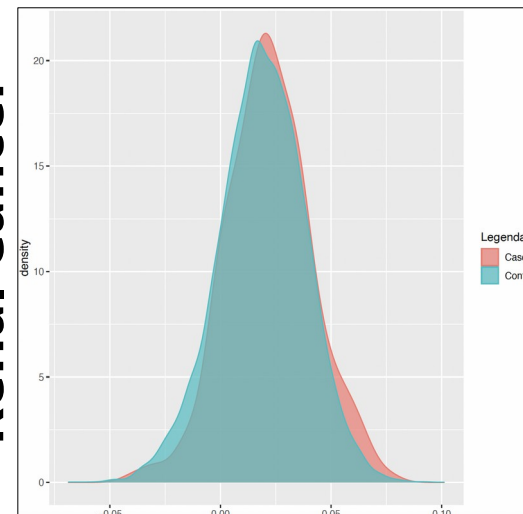
Breast Cancer



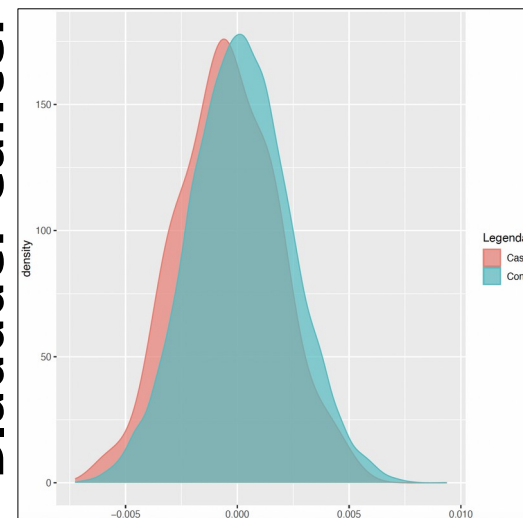
Leukemia



Renal Cancer



Bladdder Cancer

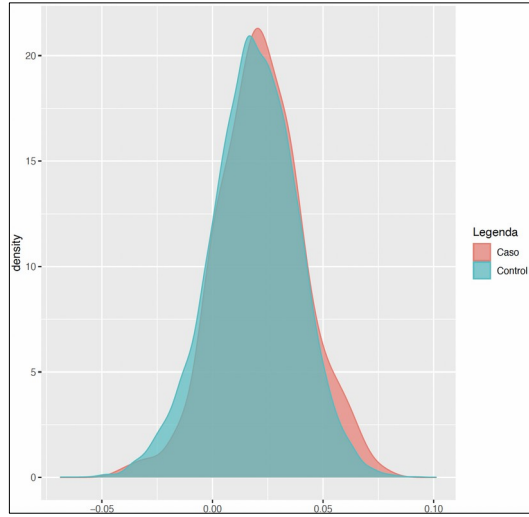




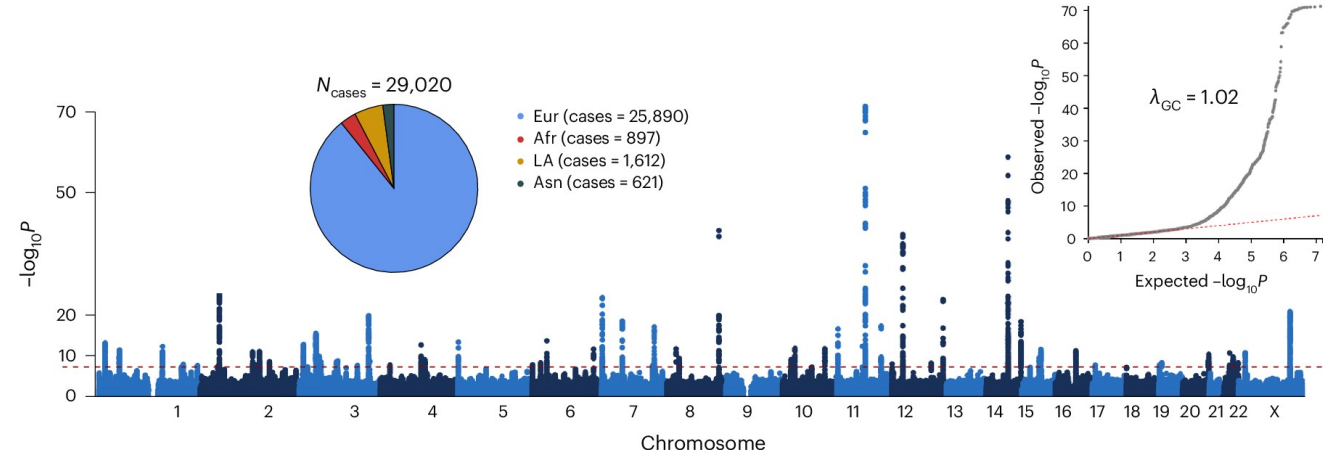
How to “solve” the Ugly?

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Renal Cancer

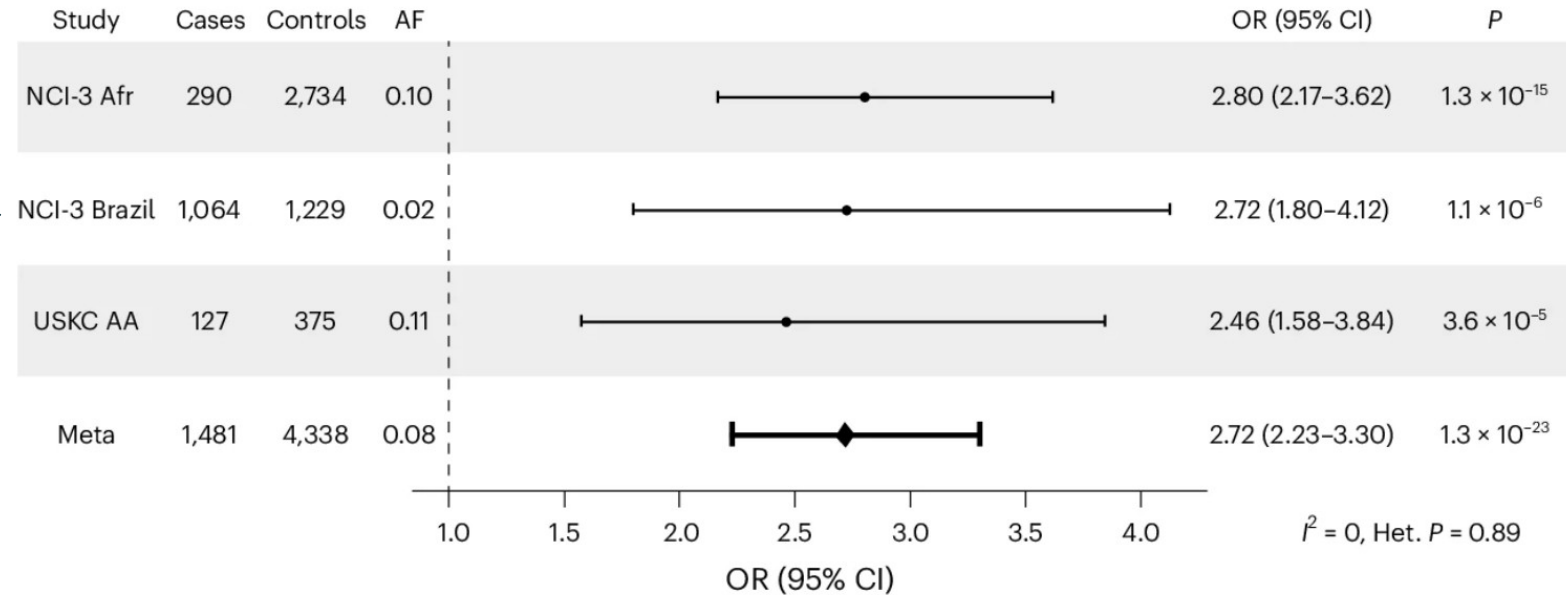


>2.000 BR Renal CA Cases
~6.000 BR Controls



a

3p25.3 rs7629500-A Nearest gene: *VHL*

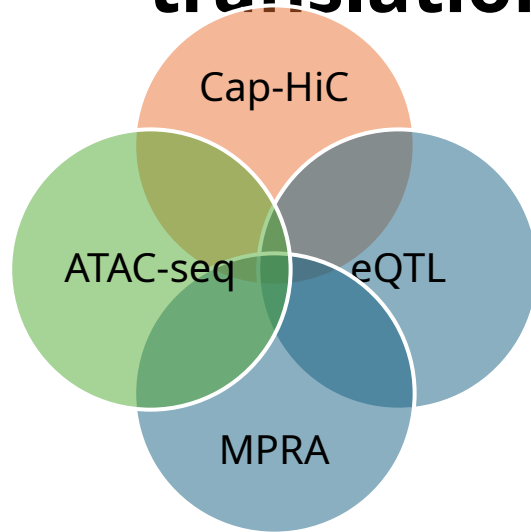
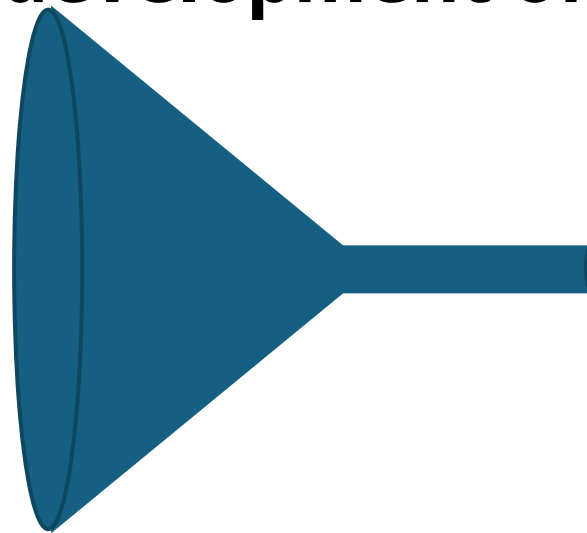


stream-line GWAS validation in-bulk per tumor type!

Purdue M et al Nat Gen 2024

Characterization of susceptibility regions is a critical opportunity for:

- **new insights into the cancer biology;**
- **translational development of new approaches.**

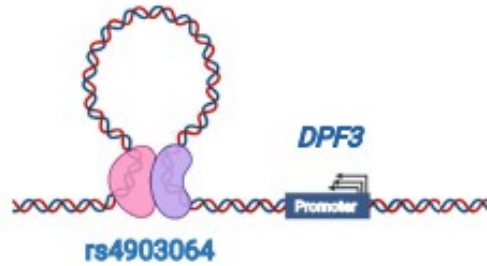


**14q24 Renal Cell
Carcinoma (RCC)
risk locus**



14q24 RCC region

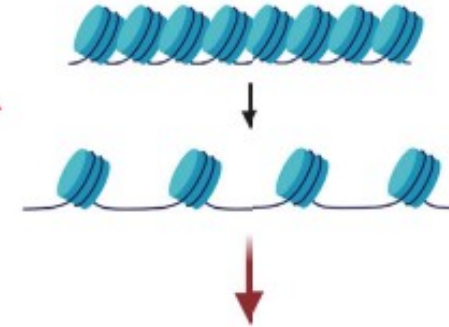
rs4903064 enhancer effect on DPF3



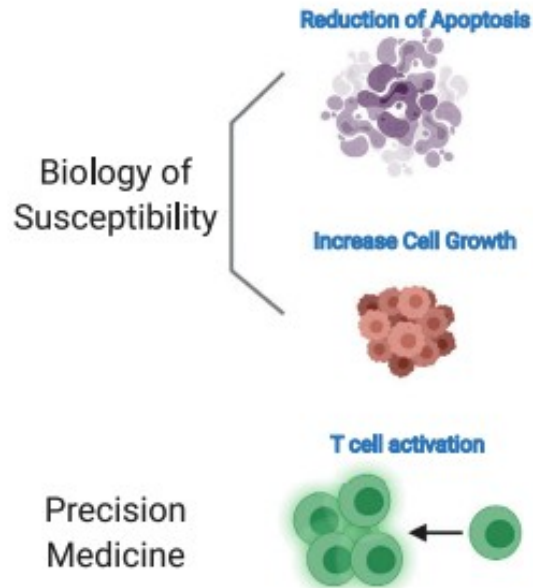
BAF Complex



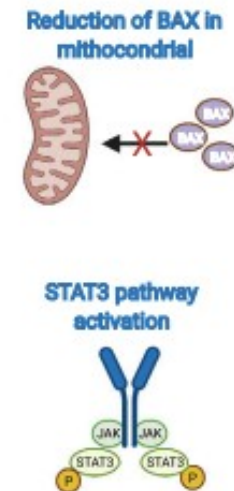
Changes in Chromatin Accessibility



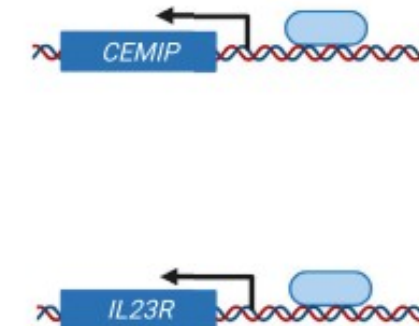
Cancer Phenotype



Molecular Phenotype



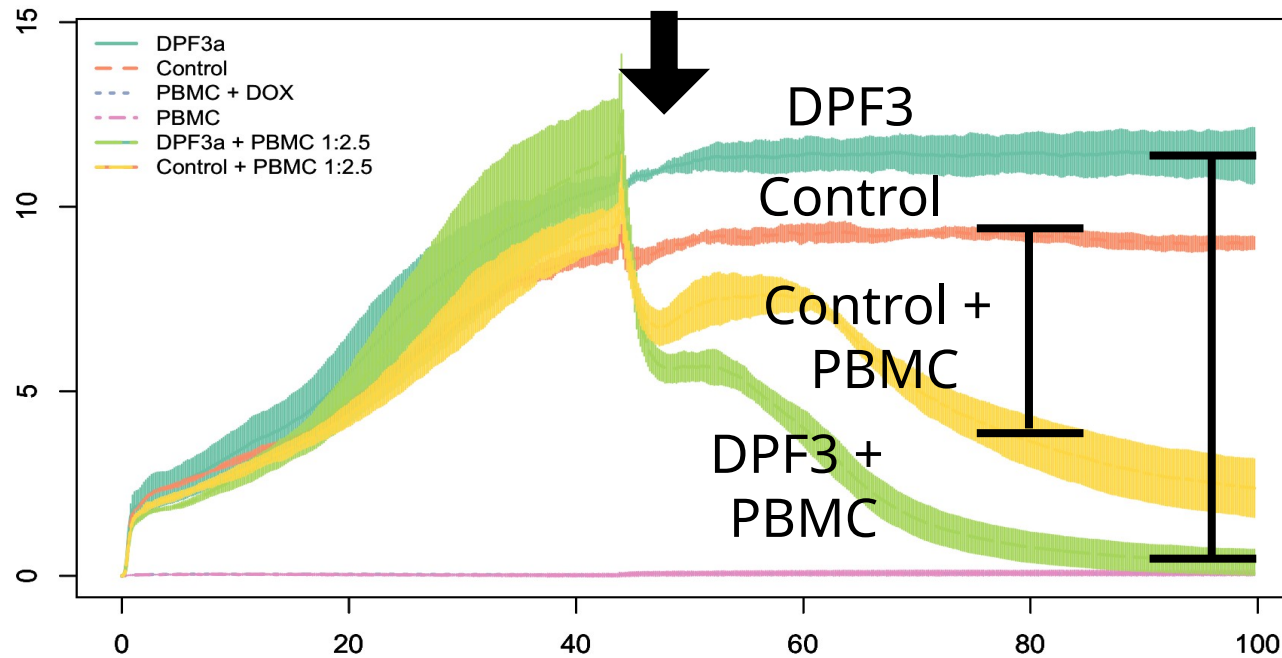
Gene expression deregulation



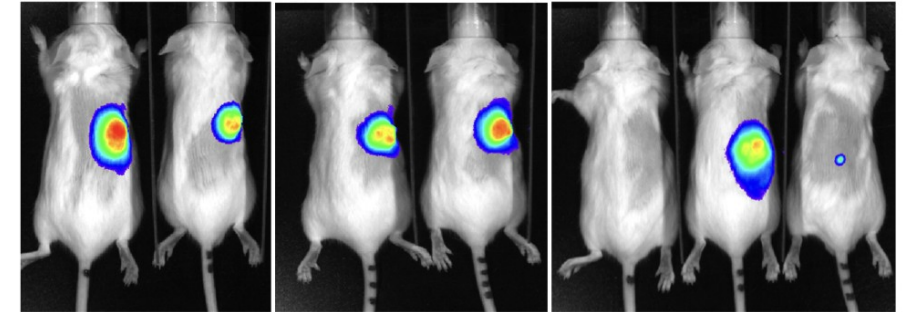


DPF3 increases T cell cytotoxicity

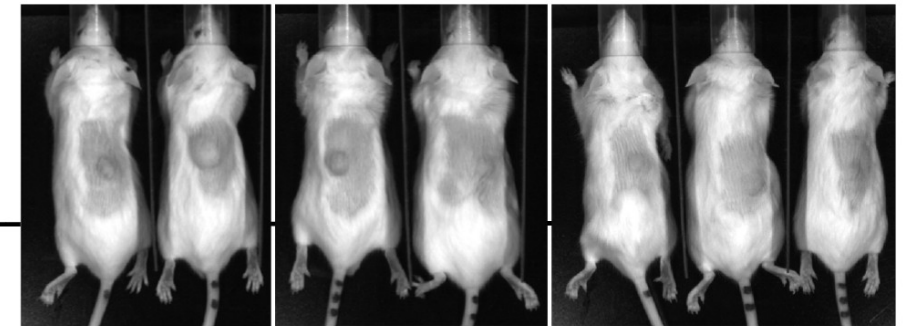
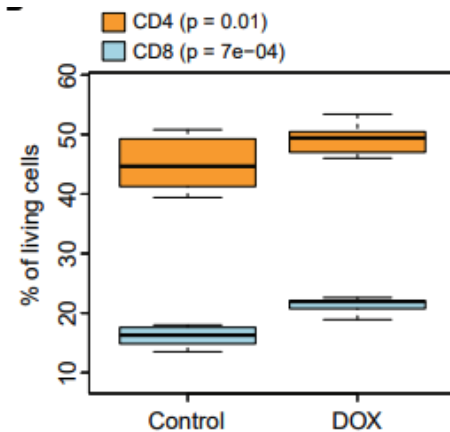
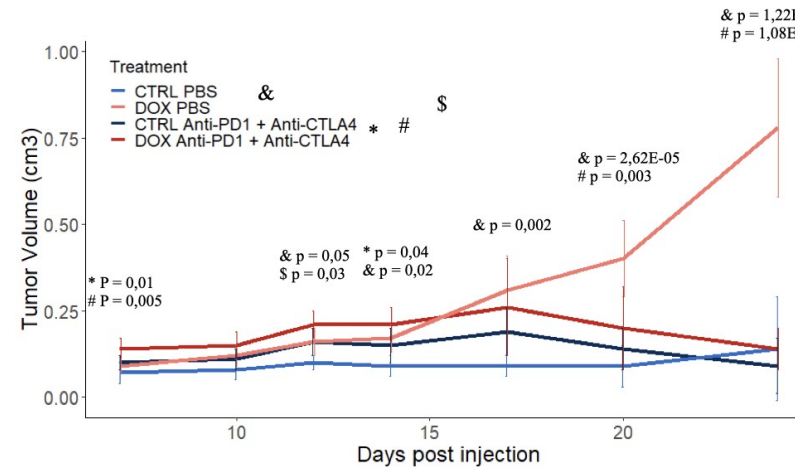
Activated PBMCs



DOX PBS



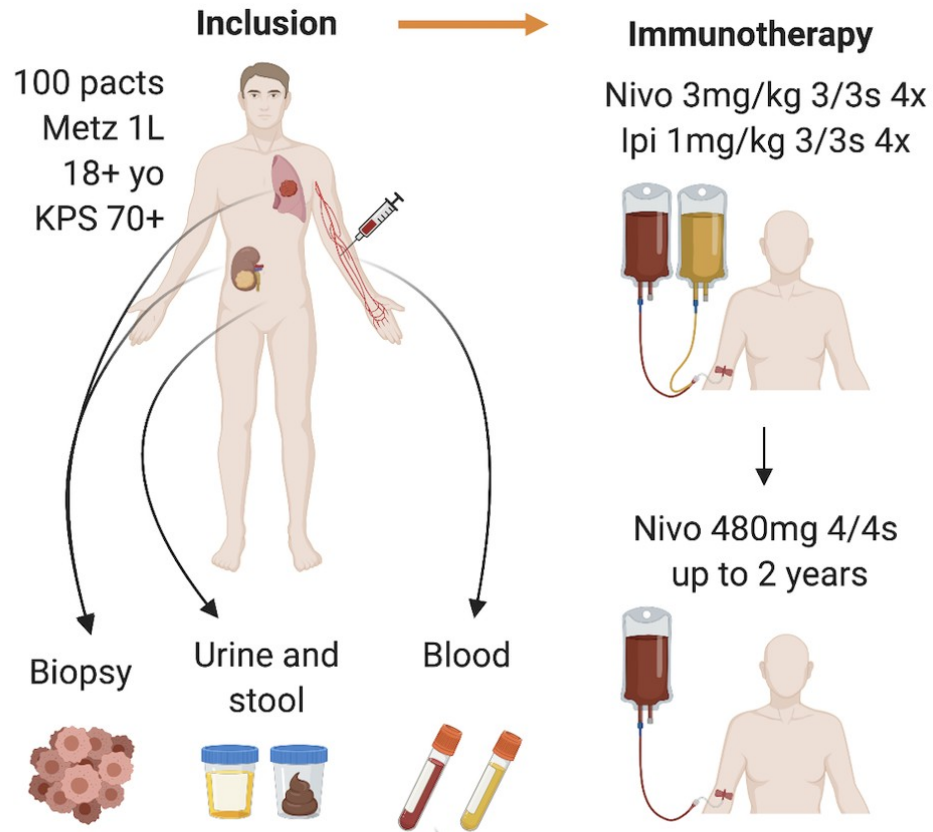
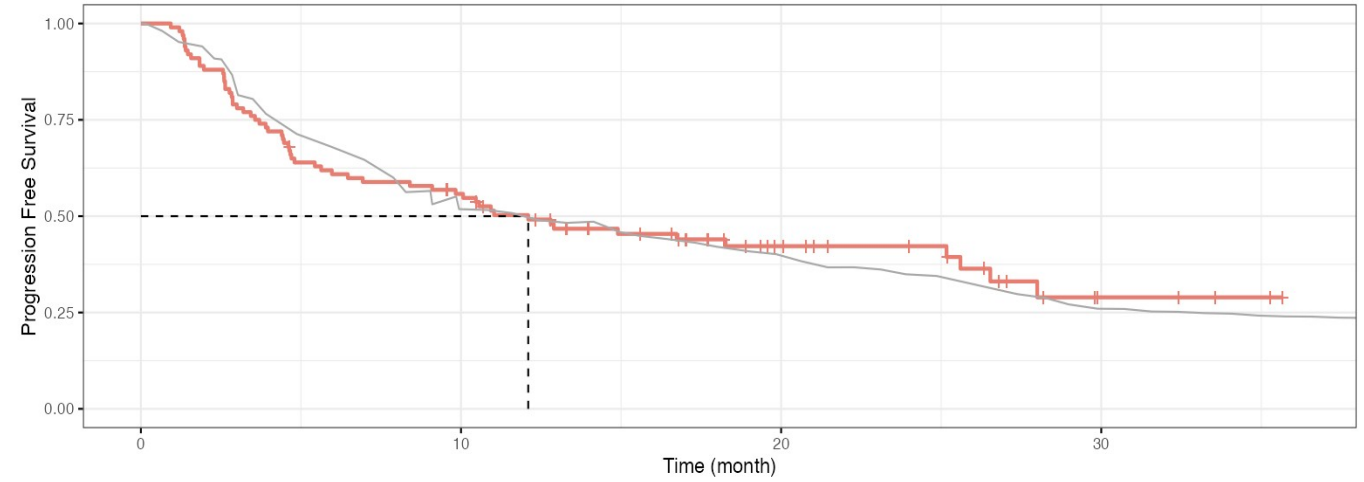
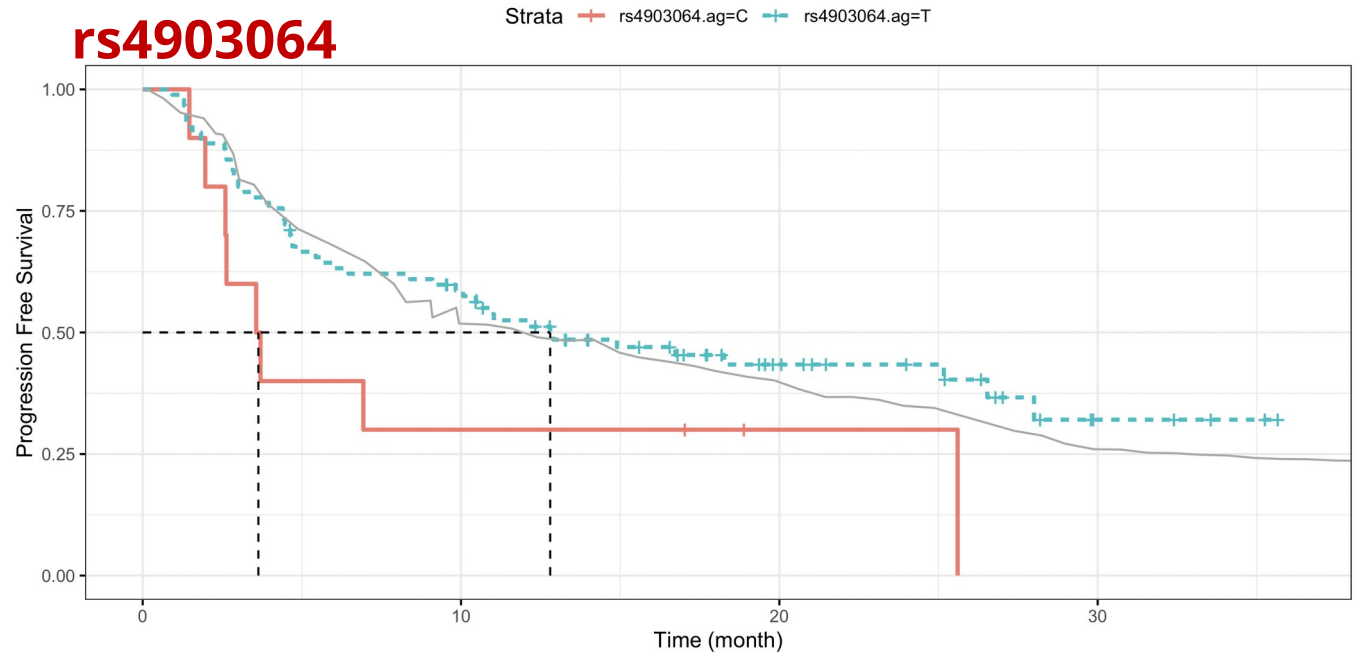
DOX IMUNO





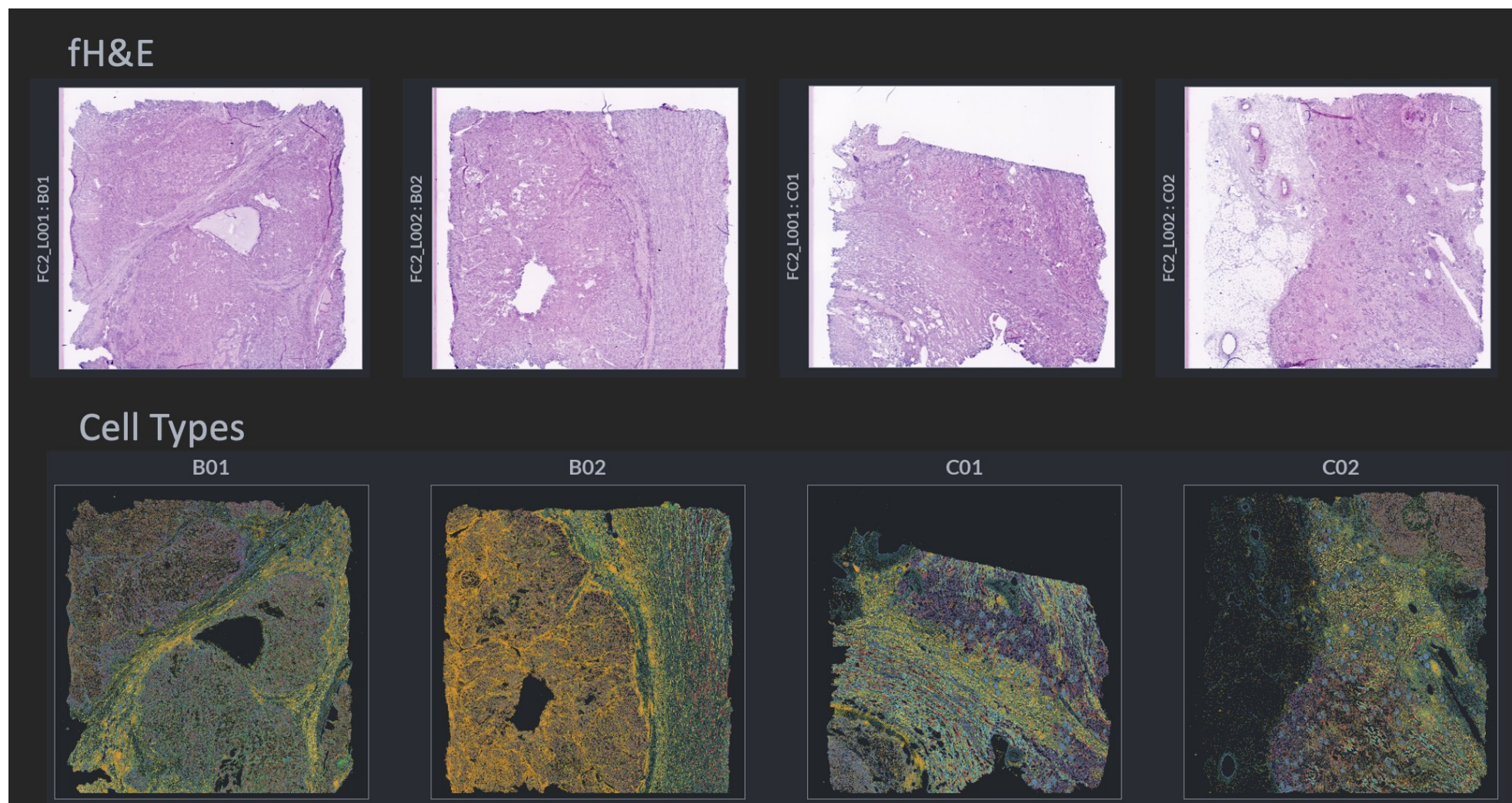
CLARA Trial

Somatic-Germline Multiomics Approach



CLARA Trial

Comprehensive Genomic Analysis of susceptibility, cancer and immune





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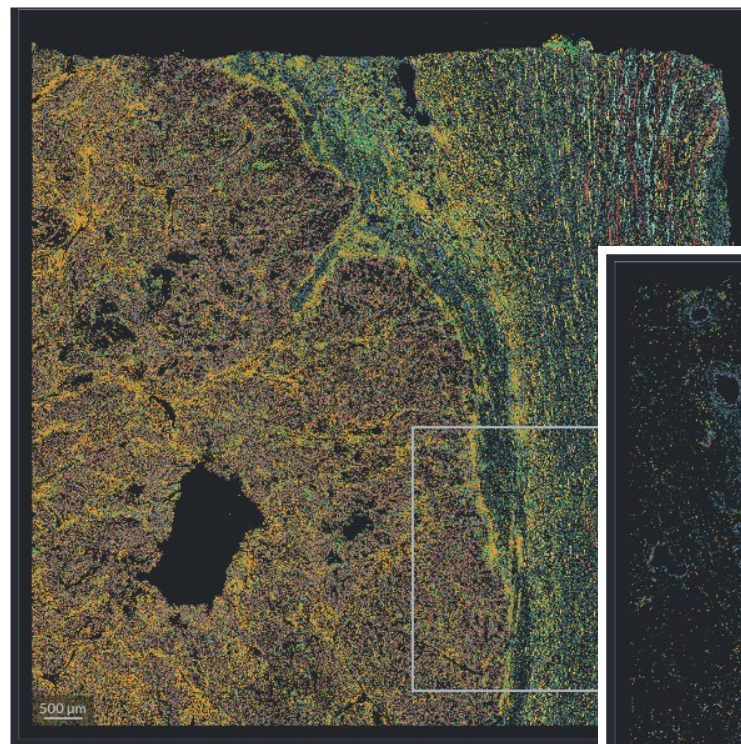
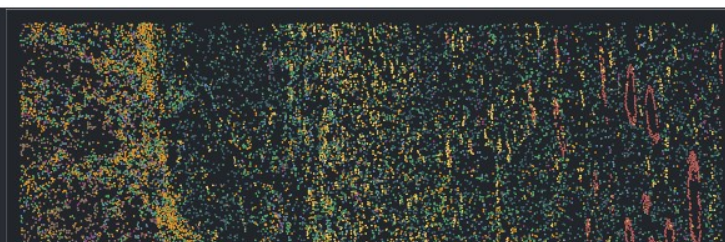
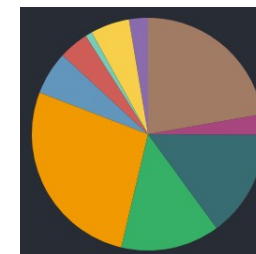
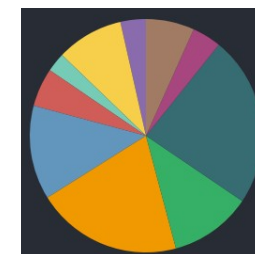
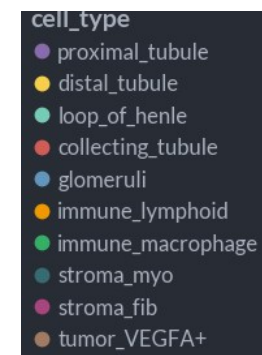
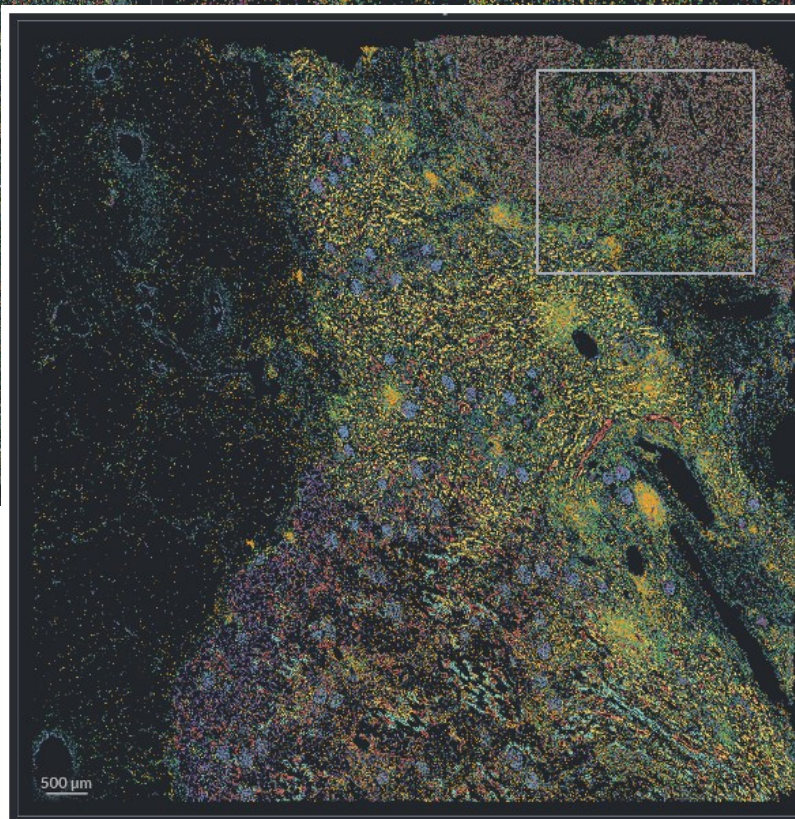
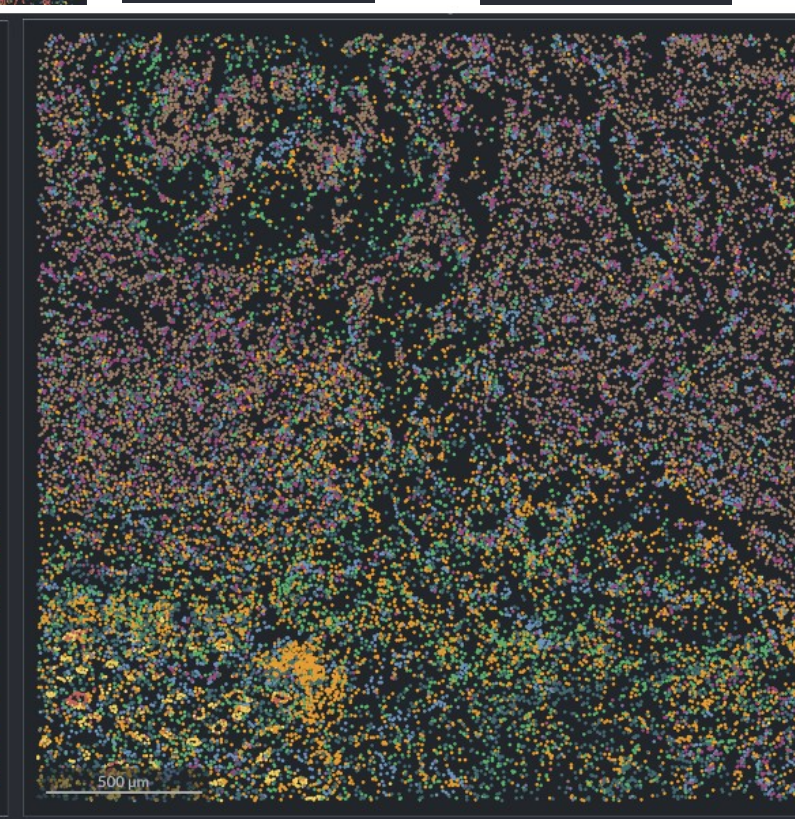
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CLARA Trial



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Exceptional responders vs non-responders





Take Home Message

- **The Burden of Cancer**

Social, Economic, Health, Biological problem

- **Cancer Susceptibility: precision prevention**

Better understanding of cancer heritability may move us to a better prevention

- **Immunotherapy plus Genomics**

Not that easy as we thought: we need more data and context

Laboratory of Translational Oncology

MEMBERS

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Pierre Bigot (Angers, FR) Rodrigo Calado (USP, BR)
Oliver Delatre (Curie, FR) Valdair Muglia (USP, BR)
Eli Van Allen (Harvard, USA)

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PRONON 19 (25000.188587/2019-19)
PRONON 21 (25000.173229/2020-45)



Newton Advanced Fellow



Breast Research Aiming Valuable Evidences



Bristol Myers Squibb™ Investigator Sponsored Research (CA209-6E3)

Thank you for the opportunity!



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RESEARCH FUNDING



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Disclosures

