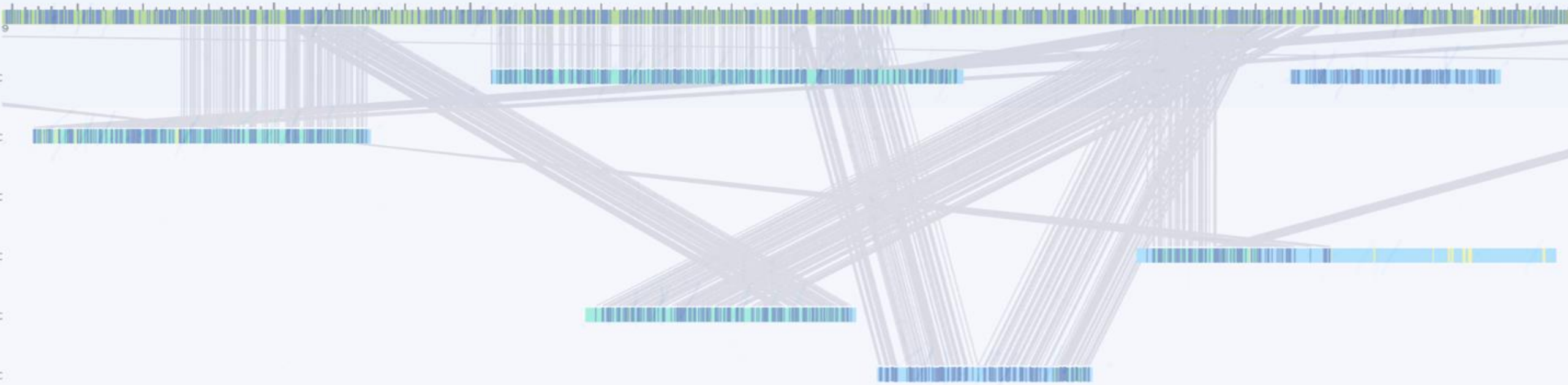
Deciphering the Complexity of Genomic Aberrations in Human Breast Cancer for Precision Oncology



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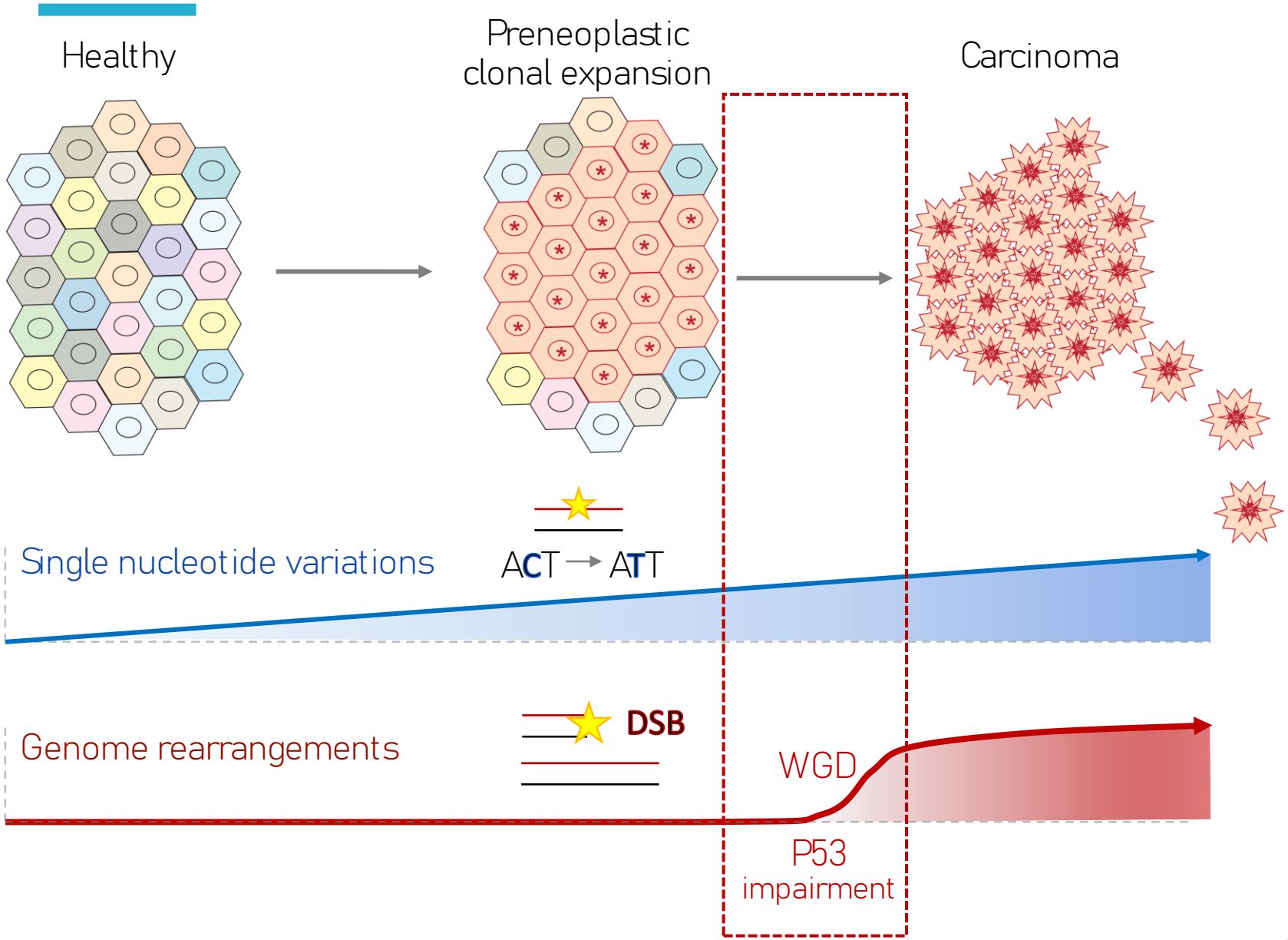
National Cancer Advisory Board Presentation

February 8, 2024

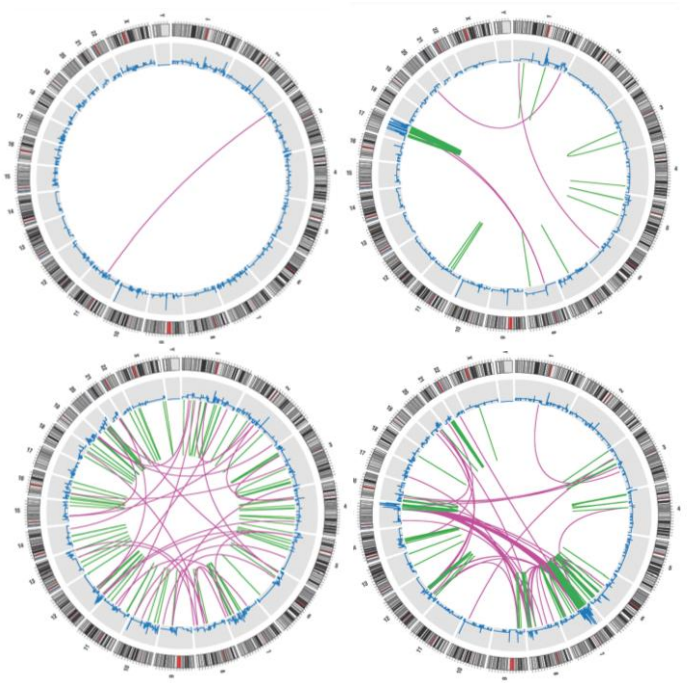
UNC

LINEBERGER COMPREHENSIVE CANCER CENTER

Genome Rearrangements in Breast Cancer



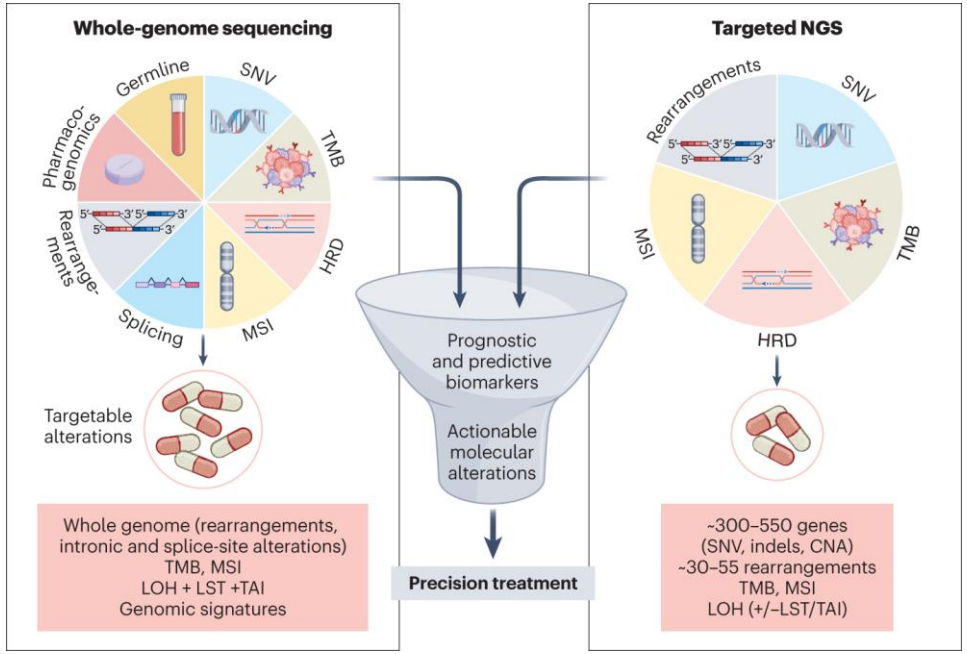
What are the causes and clinical implications of different genome rearrangement patterns?



Stephens, et al, Nature 2009
PMCID PMC3398135

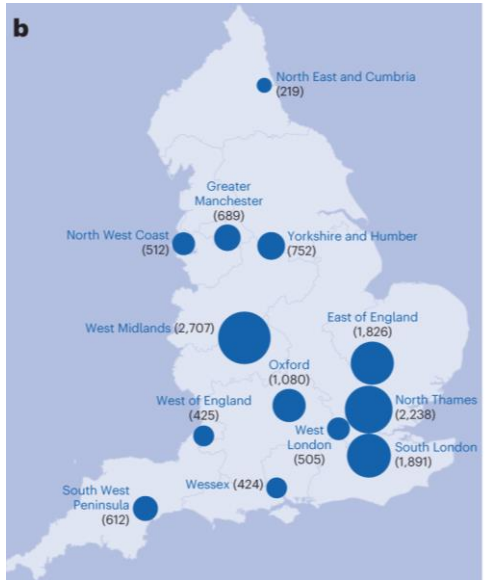
Progress in clinical translation of whole genome sequencing

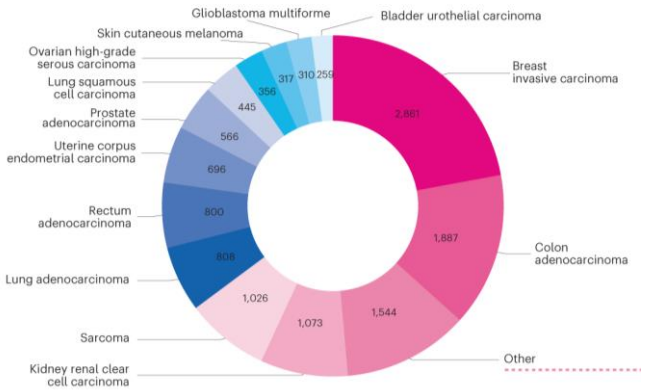
WGS captures more information on genomic structure than targeted NGS



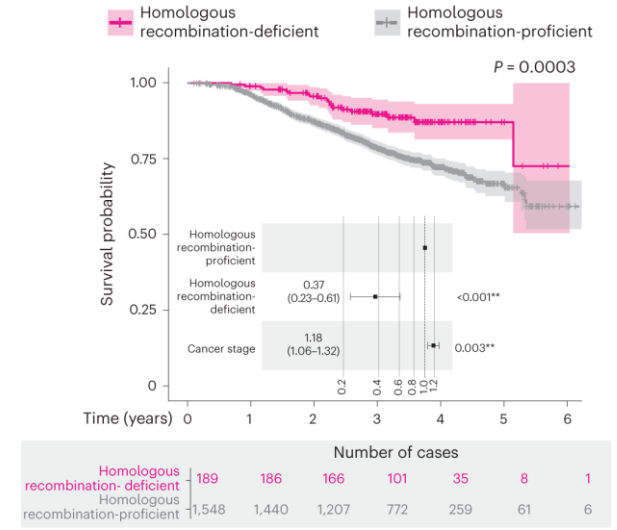
Akhoundova and Rubin, Nat Med 2024
PMID 38200256

100,000 Genomes Project (data from >13,000 WGS-analyzed tumors)





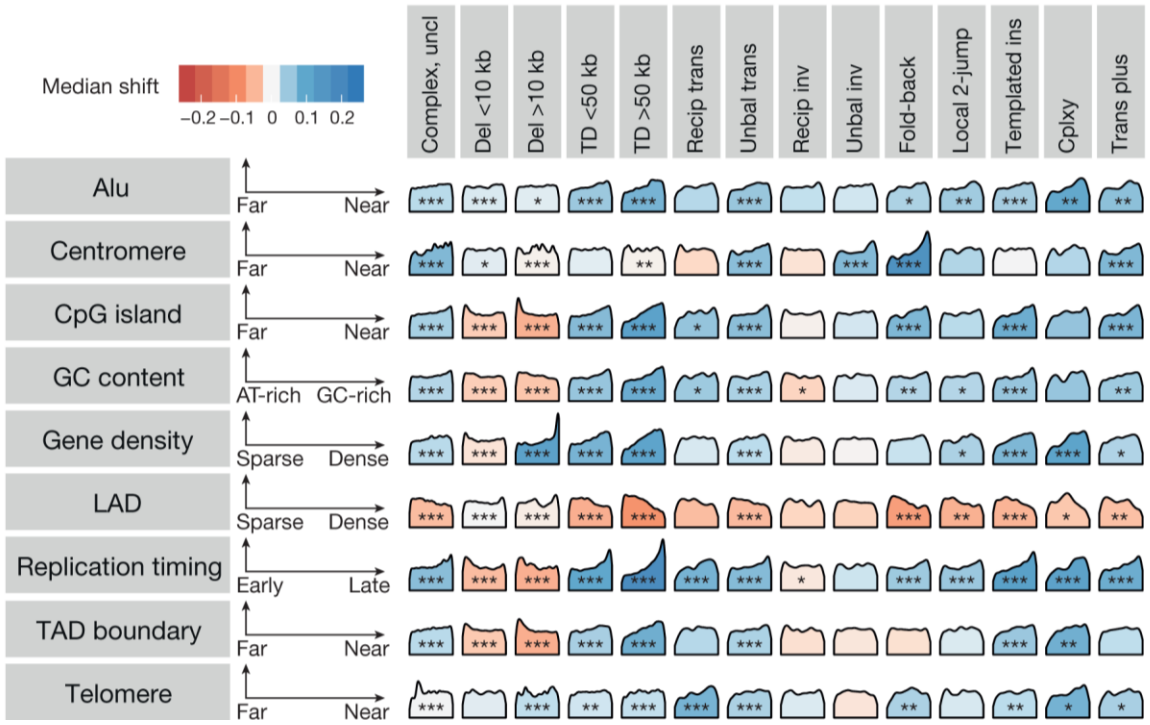
Clinical implications of genomic scar signatures

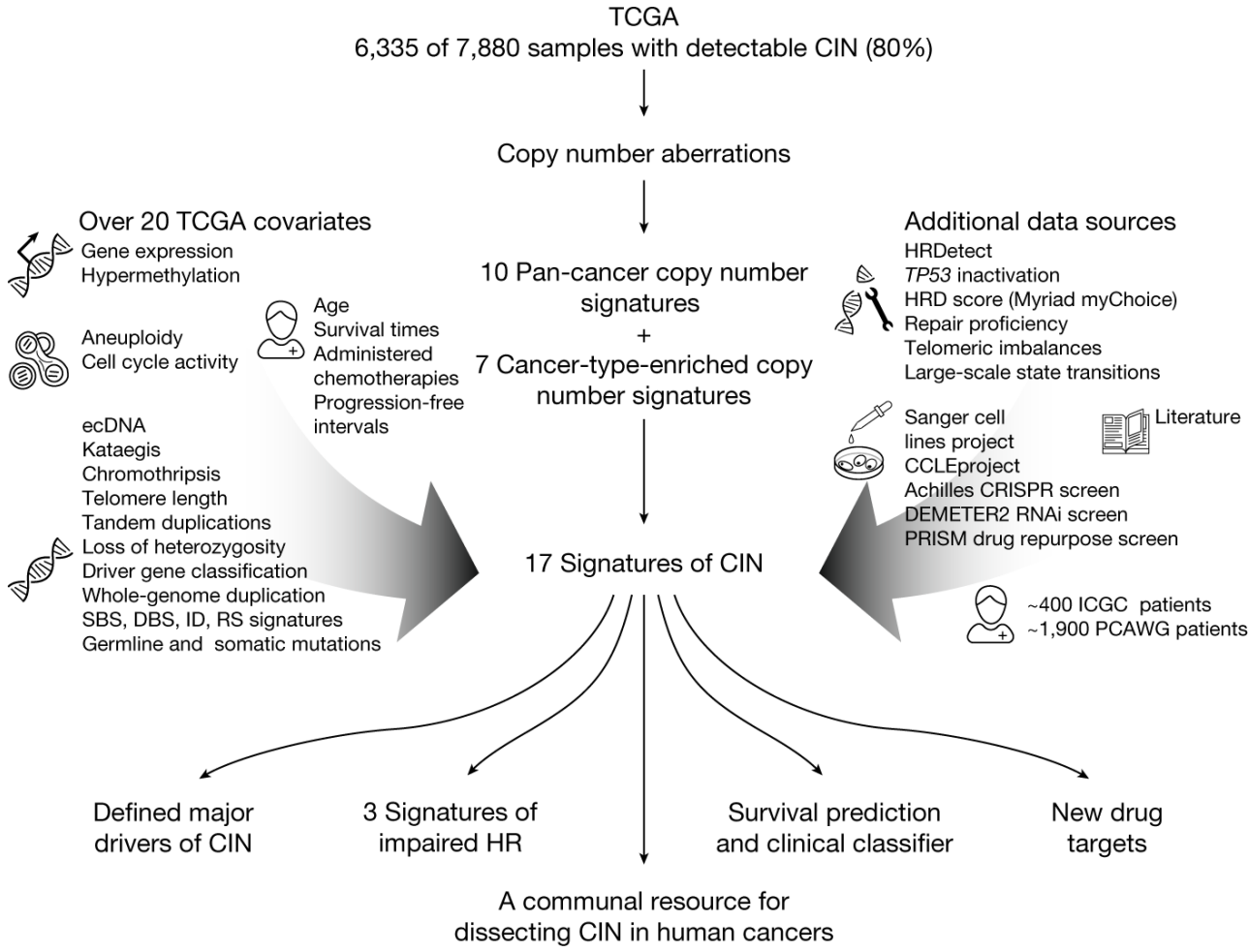


Sosinksi et al, Nat Med 2024
PMCID PMC10803271

Patterns of chromosomal rearrangement are emerging

PCAWG has analyzed thousands of cancer genomes with WGS and multi-omics to define CIN signatures

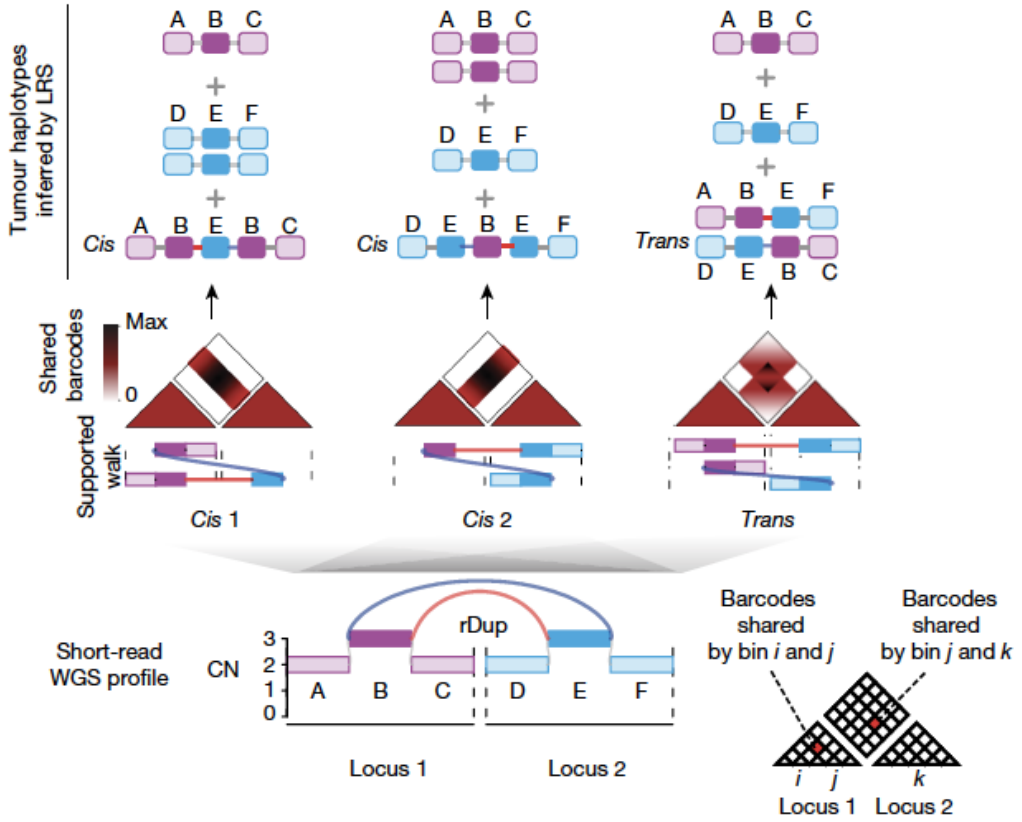




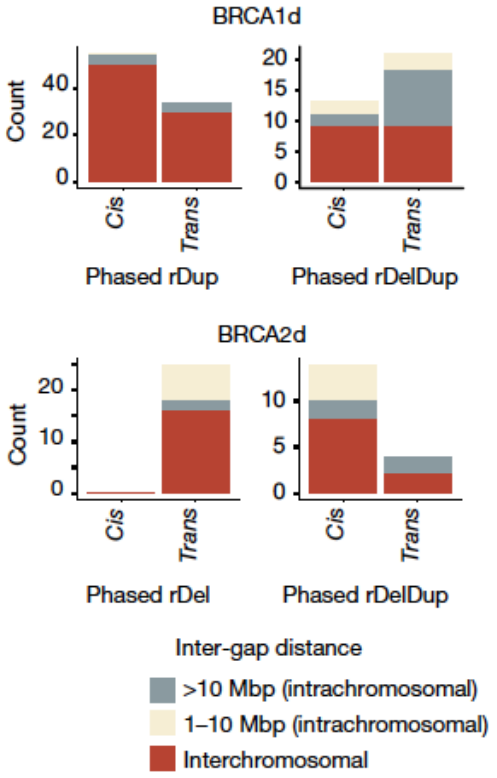
Li, et al, Nature 2020 PMCID PMC7025897
Drews, et al, Nature 2022 PMCID PMC7613102

Knowledge gap 1: Improved/optimized methods for characterizing genomes

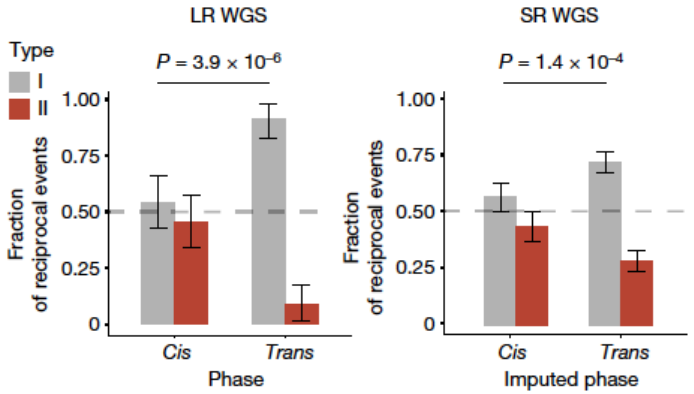
short-read sequencing can miss structural rearrangement signals



Reciprocal pair rearrangement profiles distinguish BRCA1/2 mutant cancer genomes



Knowledge of these missing signals can improve imputation of short-read sequencing data

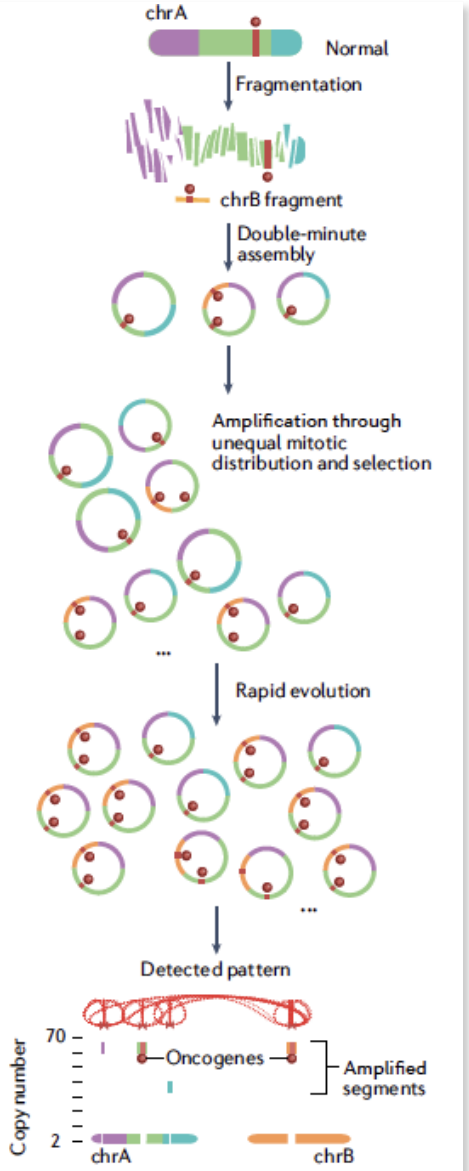


More accurate identification of HR-deficiency may broaden the impact of PARP inhibitors and other therapies more active in HRD cancers

Setton, et al, Nature 2023 PMCID PMC10482687

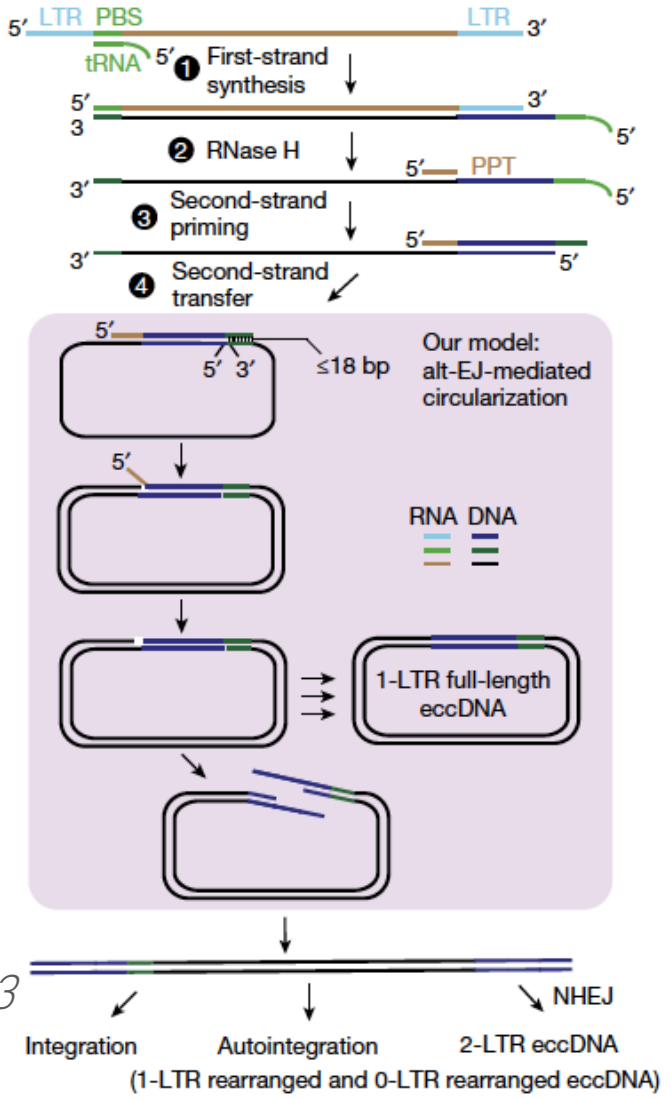
Knowledge gap 2: DNA repair processes that drive rearrangement profiles

Extrachromosomal circular DNA **(eccDNA)** can promote rapid evolution of treatment resistance through tunable oncogene amplification



Dubois, et al, Nature Rev. Cancer 2022 PMCID PMC10423586

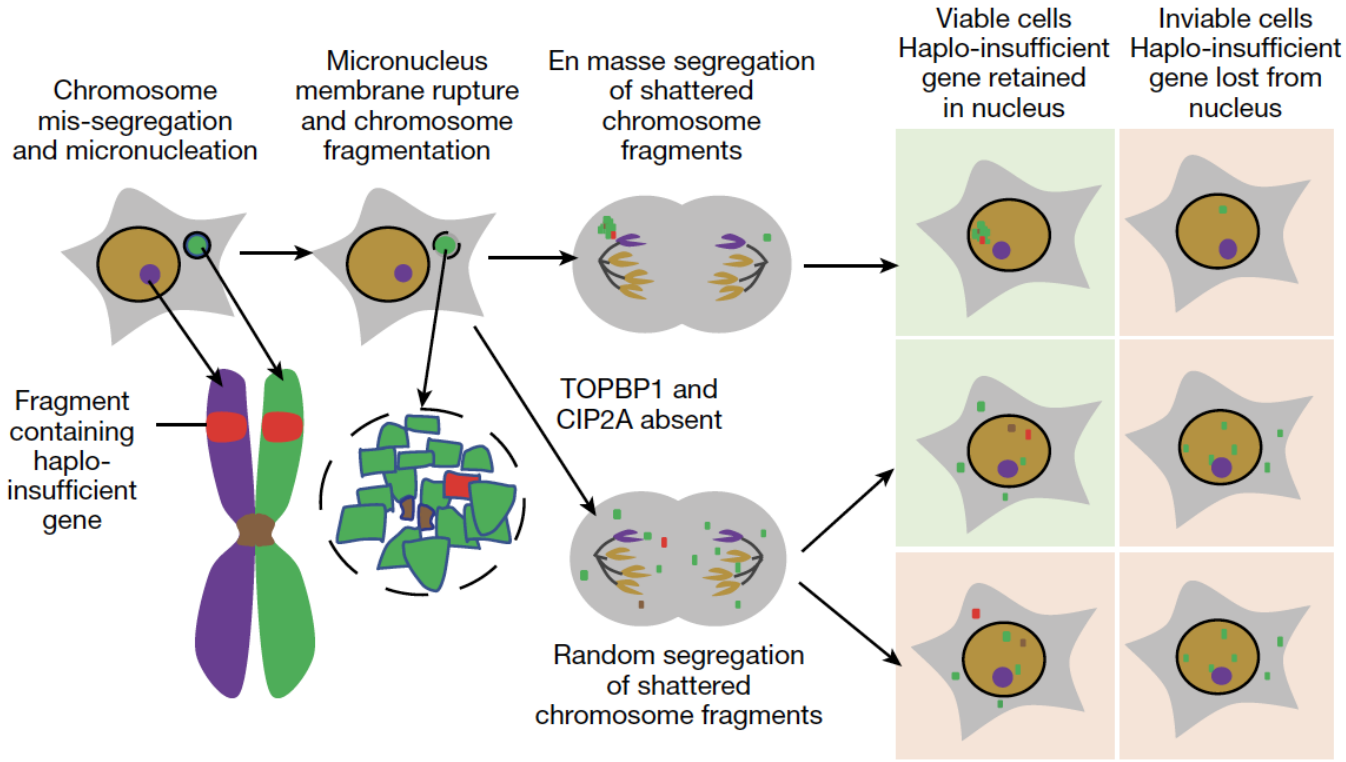
Pol θ/alt-EJ may be required for the circularization step of eccDNA generation -> *a potentially druggable target?*



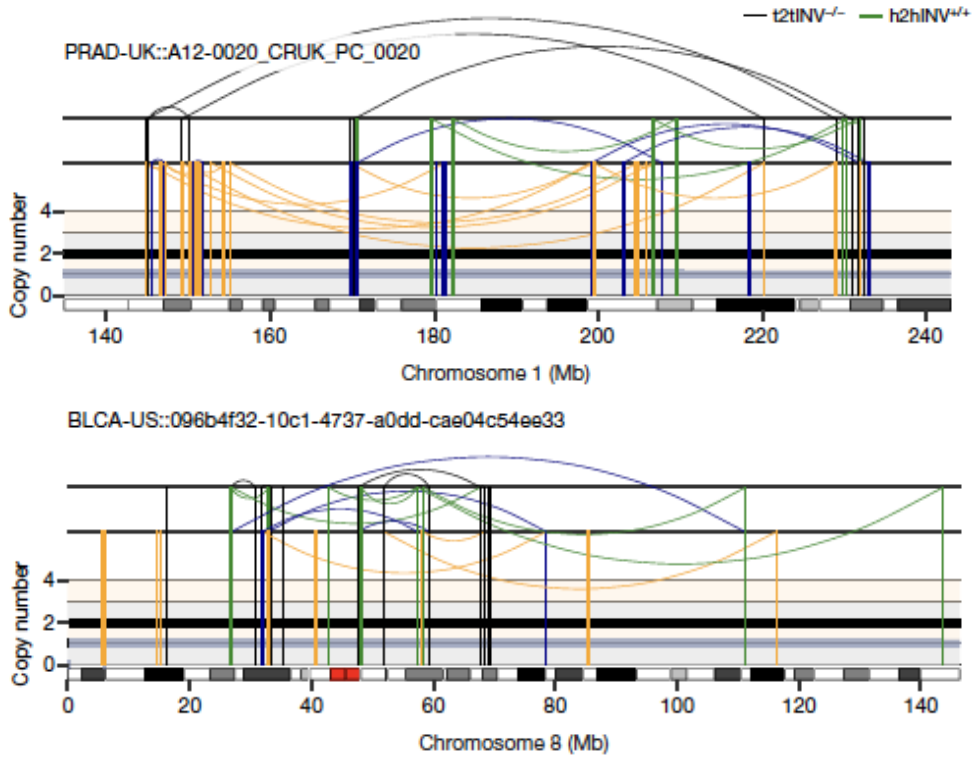
Yang, et al, Nature 2023 PMCID PMC10691919

Knowledge gap 3: Pathways dictating cellular fates after errors in mitosis

Novel TOPBP1-CIP2A pathway promotes clustering and preservation of chromosome fragments arising in mitosis



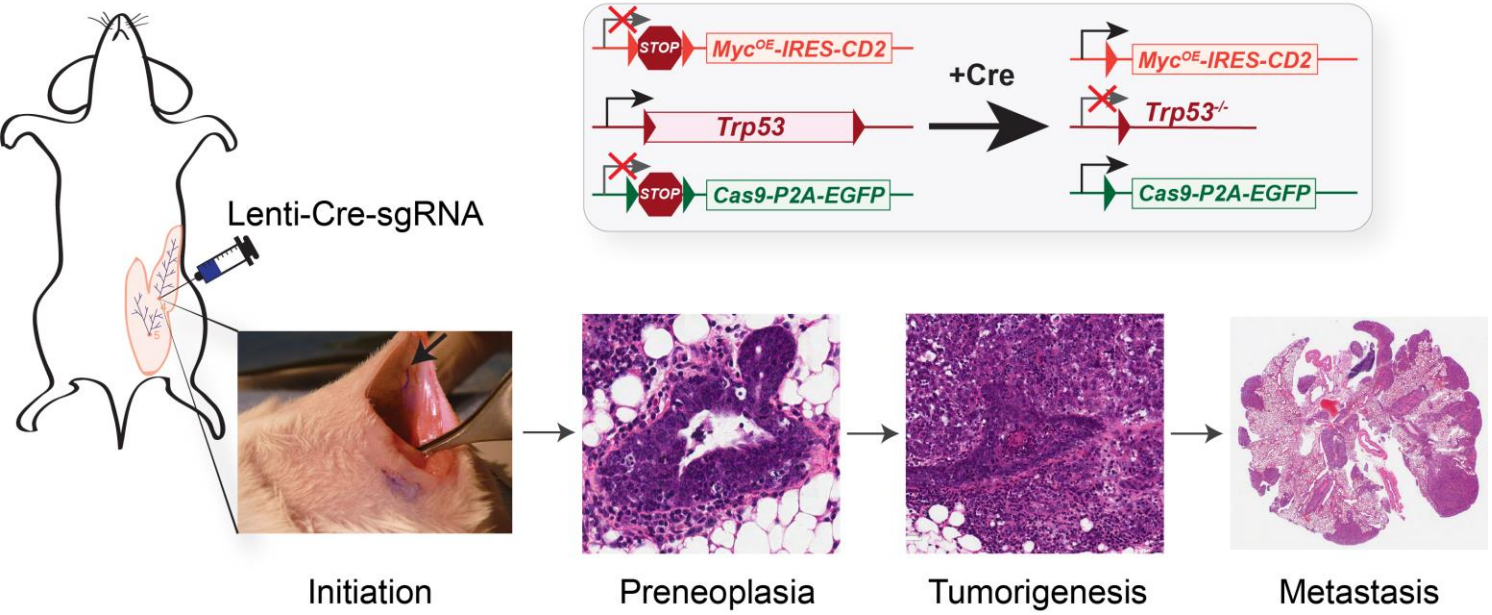
Upregulation of TOPB1-CIP2A is associated with a "balanced chromothripsis signature" in human cancers



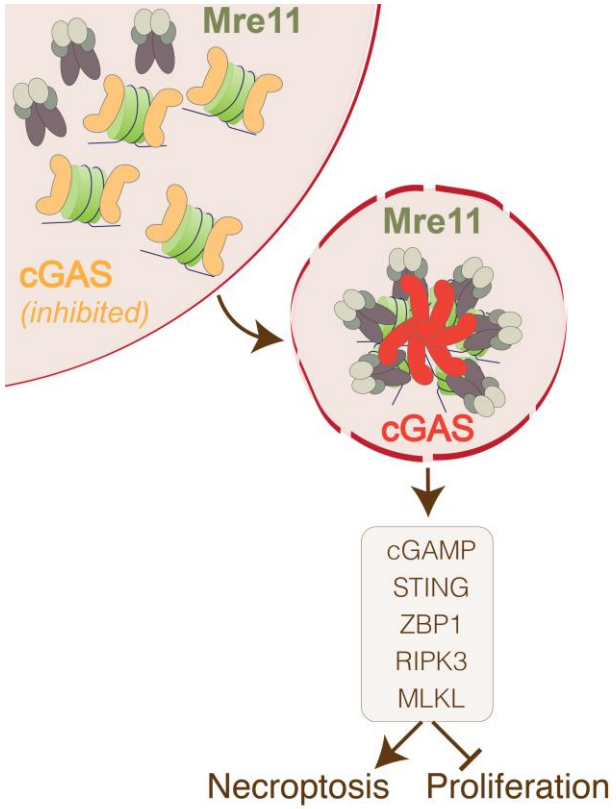
Lin, et al, Nature 2023 PMCID PMC10307639
Trivedi, et al, Nature 2023 PMCID PMC10424572

Knowledge gap 4: Interplay between genome rearrangement and immune surveillance pathways

In vivo CRISPR screen for regulators of preneoplasia -> carcinoma transition in TNBC mouse model



DNA damage sensing directly linked to innate immune activation and tumor suppression



Cho, et al, Nature 2024 PMCID PMC10794148

Genome Rearrangements: A Roadmap for Precision Oncology

- Develop optimized methods for genome characterization, and evaluate strategies/feasibility for clinical translation
- Conduct mechanistic studies to uncover etiology of different genome rearrangement signatures and evaluate implications for cancer prevention
- Interrogate the interplay between genome rearrangement pathways and the immune system in cancer development, progression, and therapeutic response
- Identify targetable vulnerabilities of cancers with distinguishable signatures of genome rearrangement and/or instability