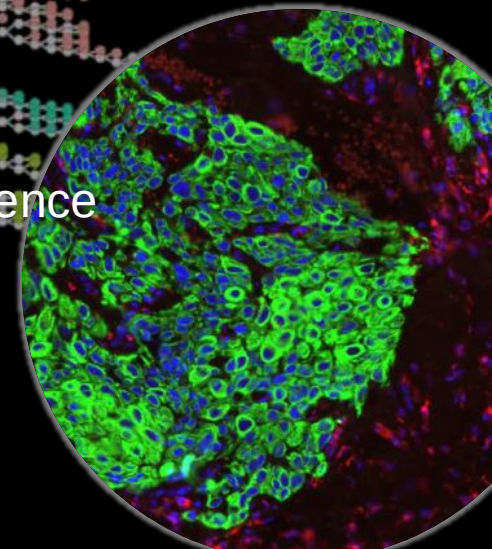
Stanford MEDICINE

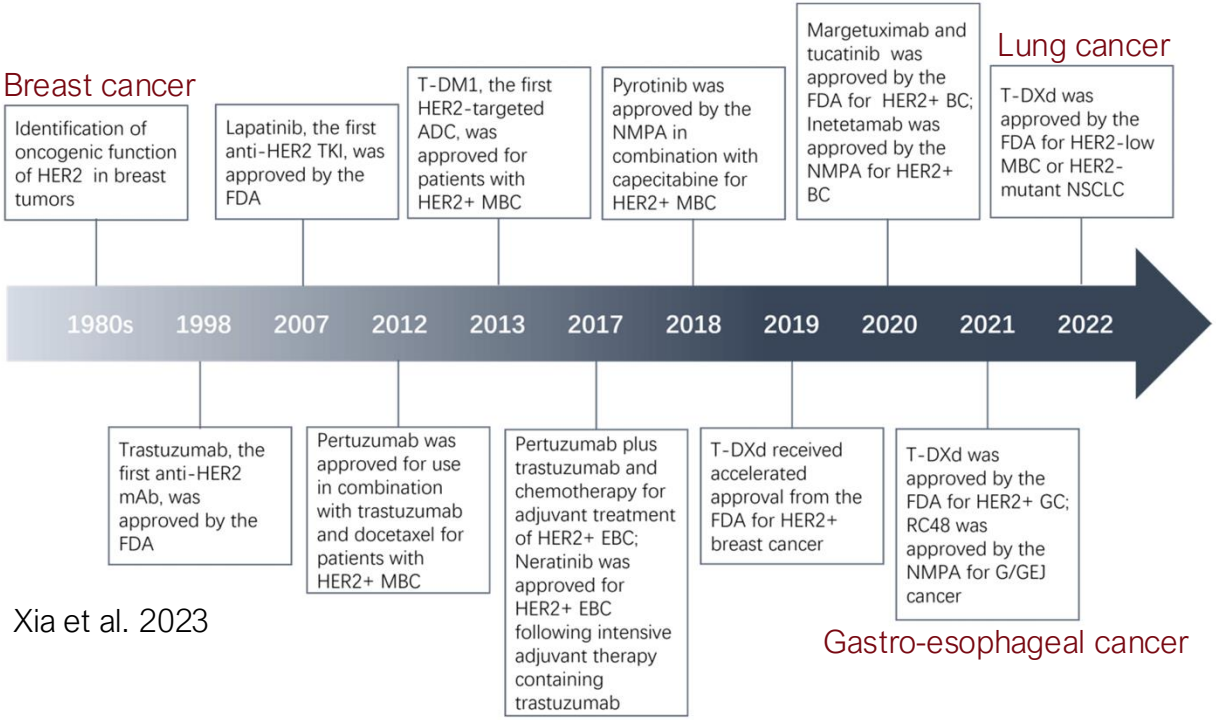
The integrative breast cancer subtypes: from relapse prediction to new targets



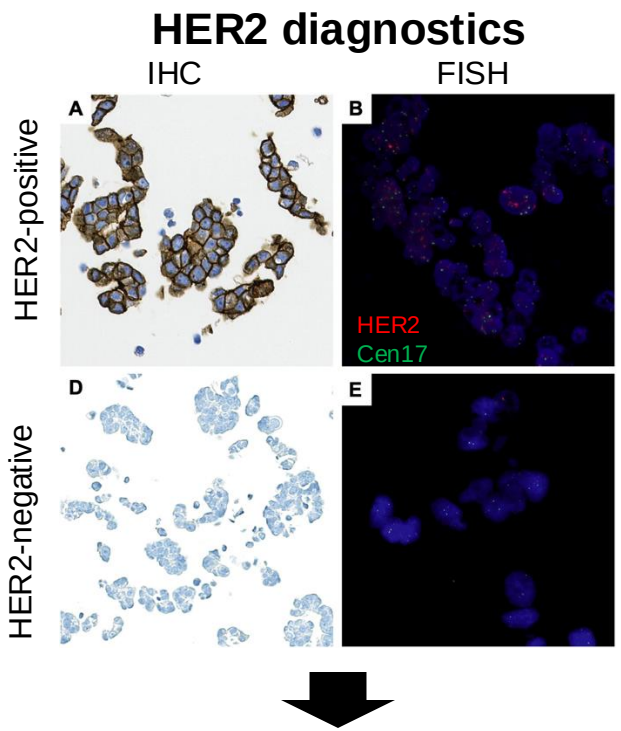
Christina Curtis, PhD, MSc
RZ Cao Professor of Medicine, Genetics & Biomedical Data Science
Stanford University
Director, Artificial Intelligence and Cancer Genomics
Director, Breast Cancer Translational Research
Investigator, Chan Zuckerberg Biohub

An archetype for precision oncology:

HER2 gene amplification as a biomarker and therapeutic target



Xia et al. 2023



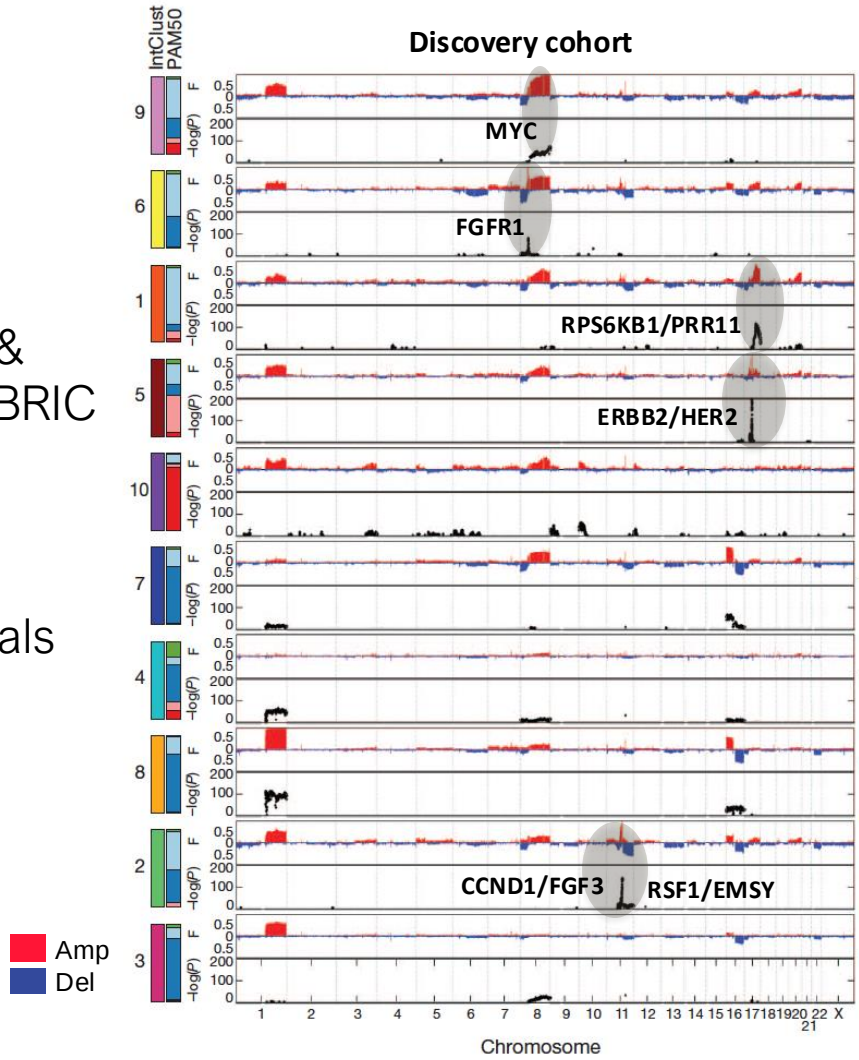
Treatment selection

~10-15% of breast cancers

Can we replicate the HER2 success story?

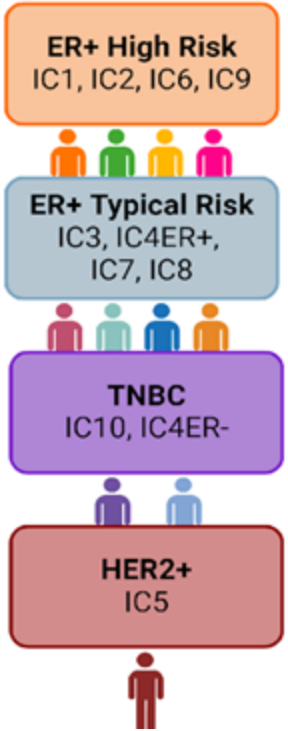
The molecular map of breast cancer redefined

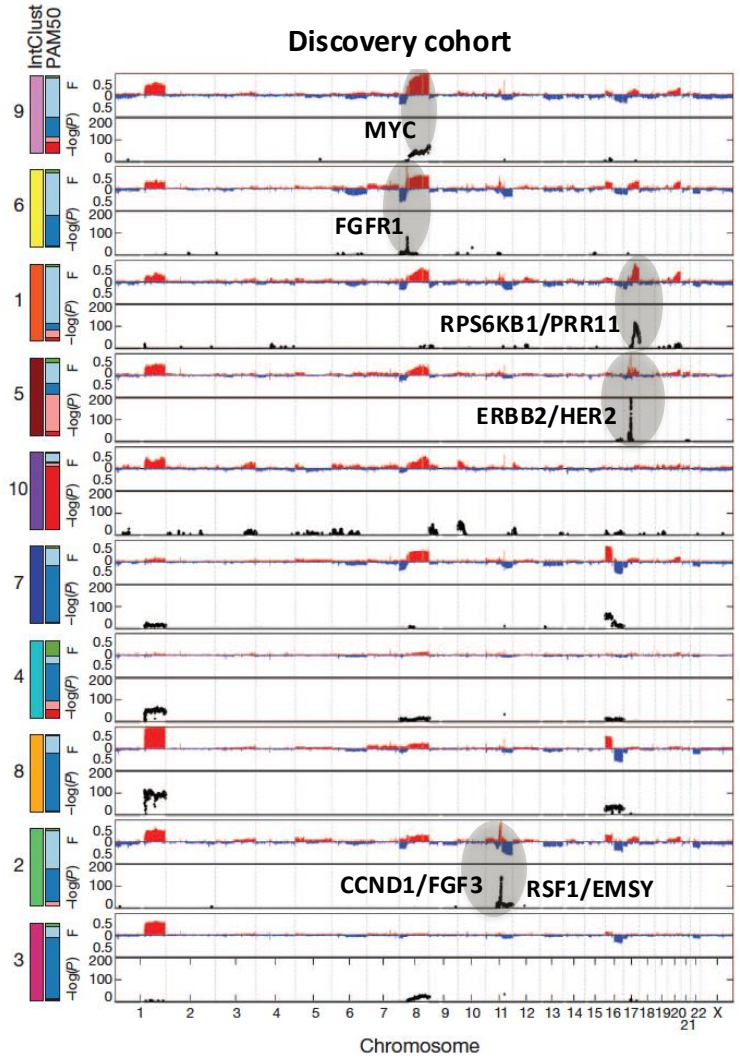
- Integrative clusters (ICs) based on genomic & transcriptomic data from 1k tumors in METABRIC
- Validated in >10,000 early-stage tumors
- ICs resolve the heterogeneity amongst luminals
- Different genomic drivers; four with amplified oncogenes, similar to HER2



Curtis et al. *Nature* 2012

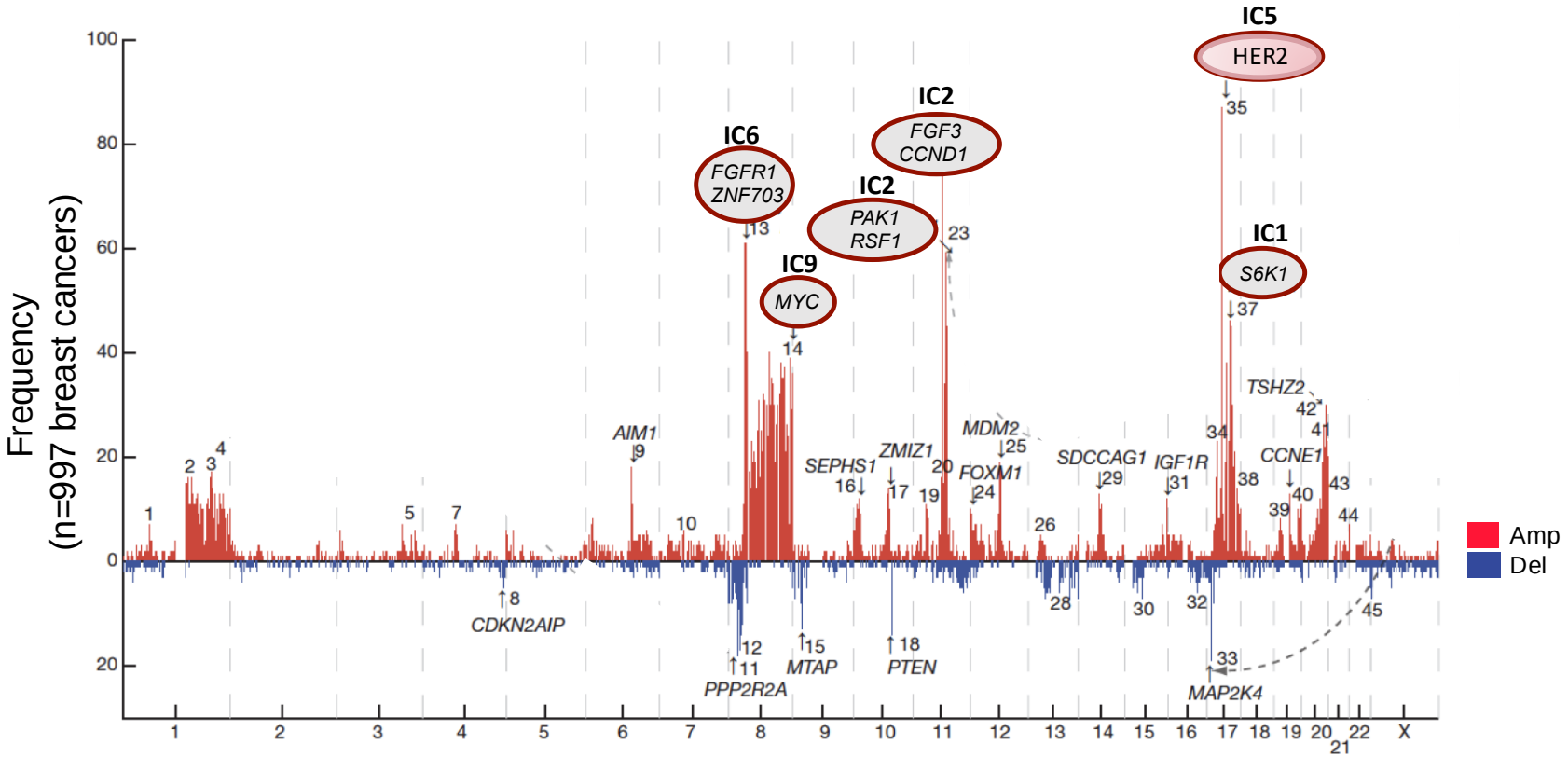
The molecular map of breast cancer redefined





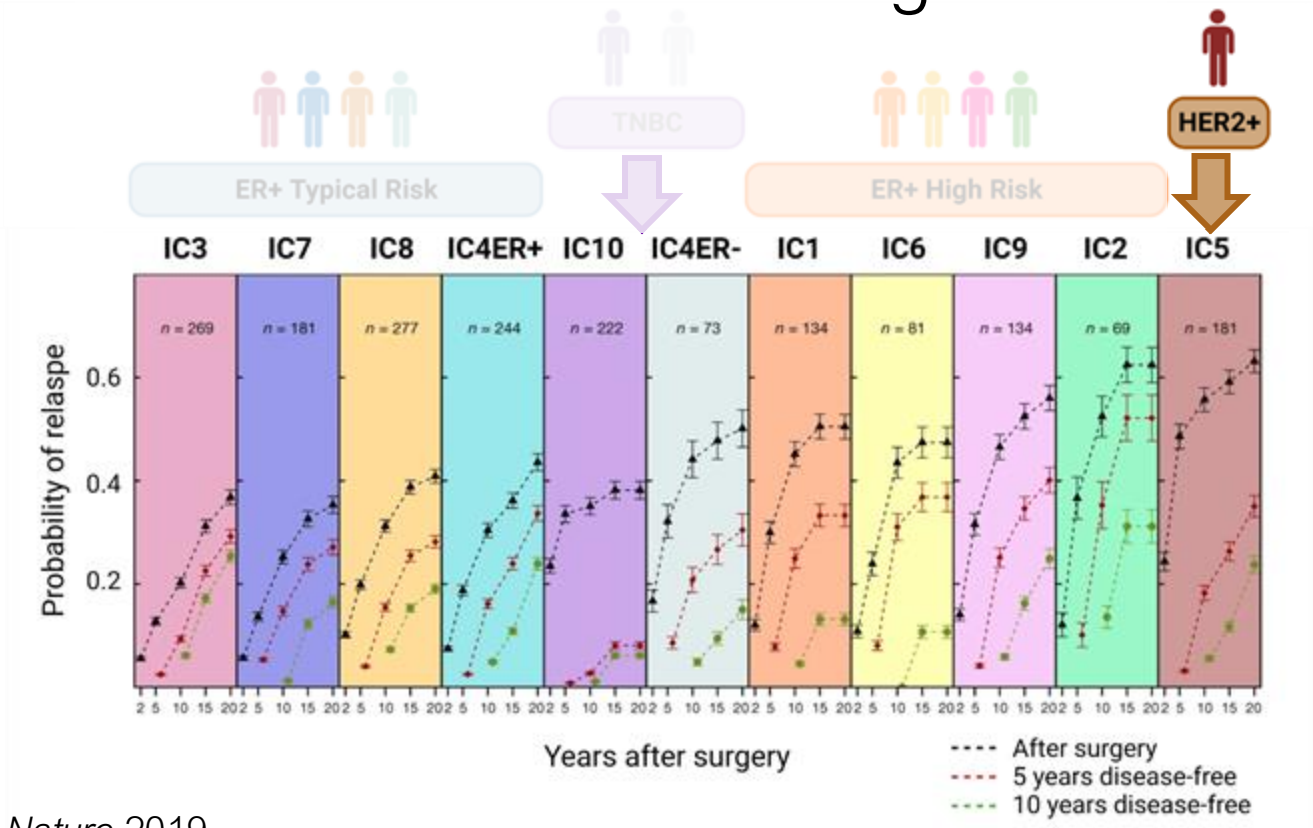
Curtis et al. *Nature* 2012

HER2 is an exemplar but not unique; amplified oncogenes define breast cancer subgroups



Curtis et al. *Nature* 2012

The integrative clusters (ICs) predict relapse two decades after diagnosis



Rueda et al. *Nature* 2019

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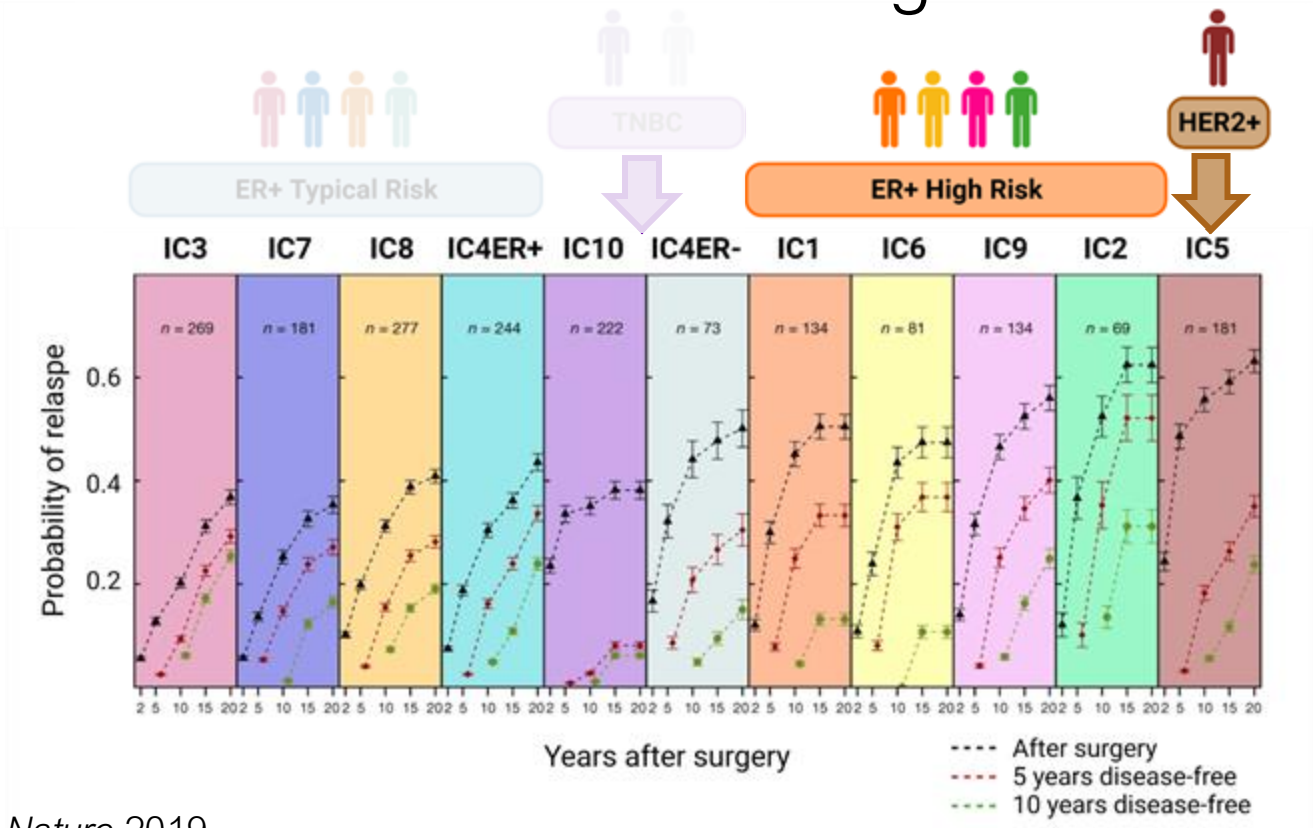
The integrative clusters (ICs) predict relapse two decades after diagnosis



Rueda et al. *Nature* 2019

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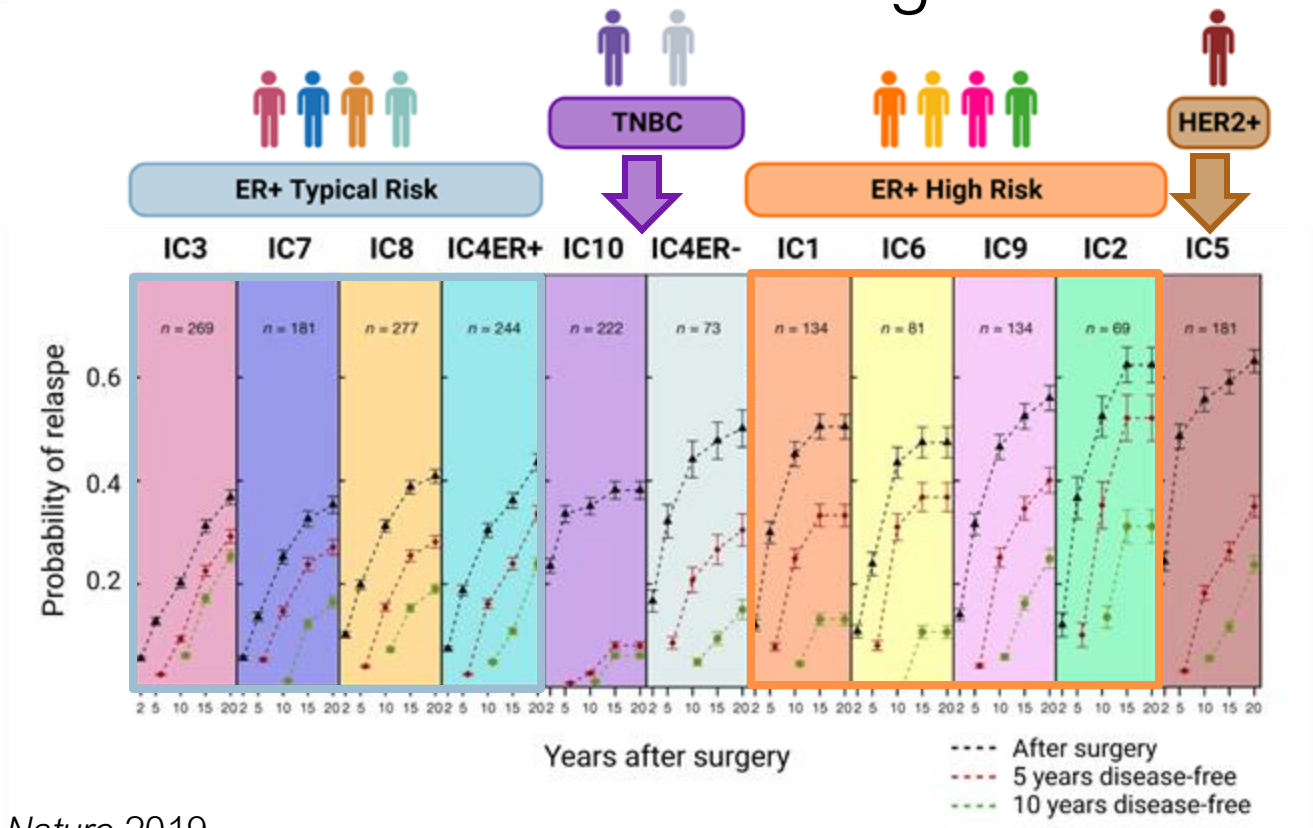
The integrative clusters (ICs) predict relapse two decades after diagnosis



Rueda et al. *Nature* 2019

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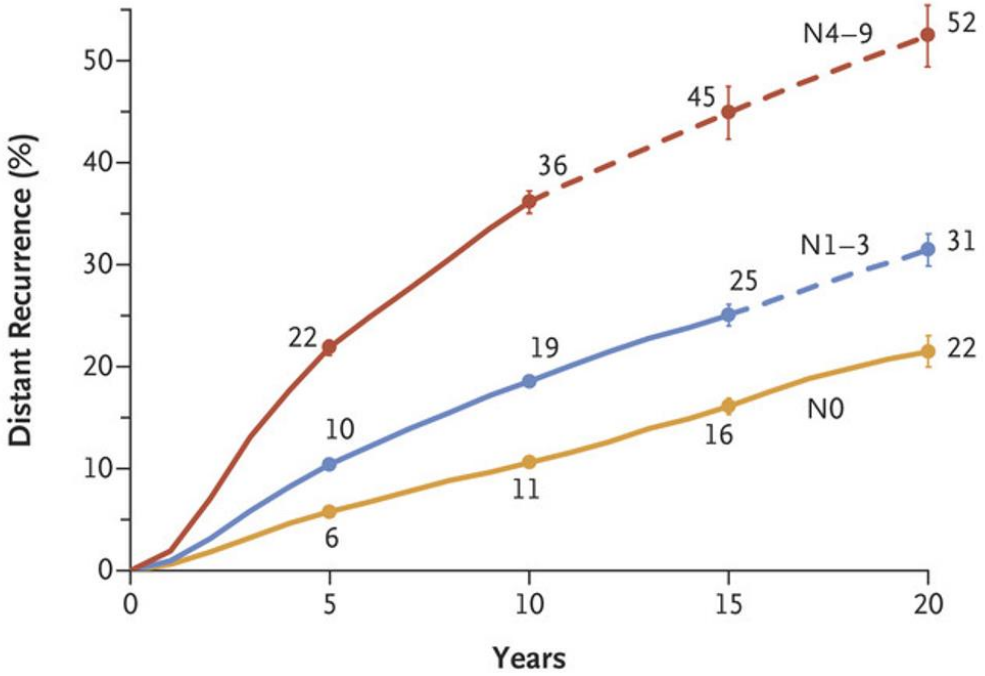
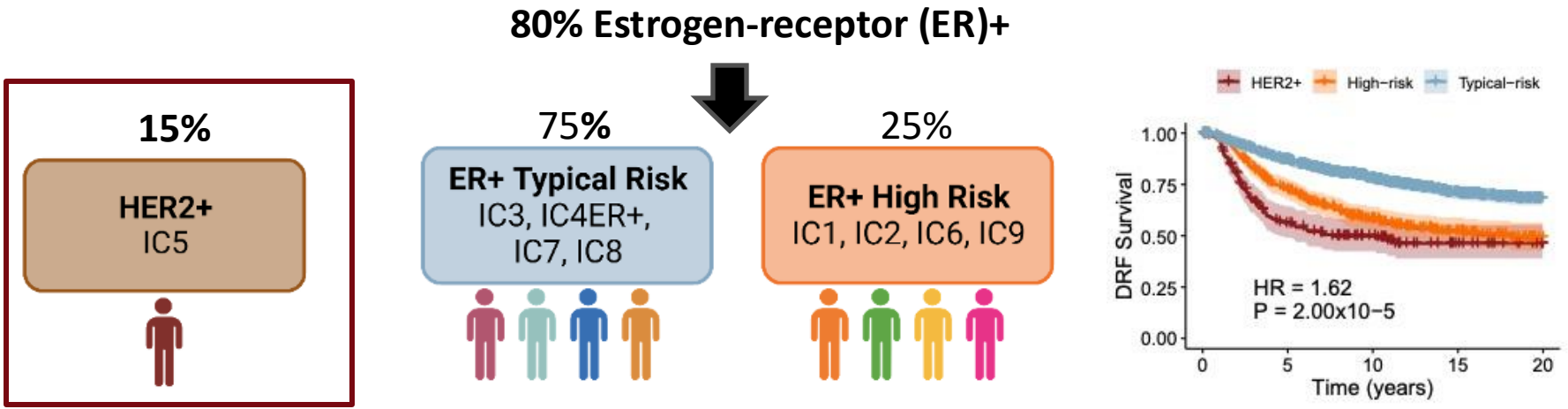
A pressing clinical challenge:
Late distant recurrence in ER+/Her2- breast cancer

- Meta analysis of 75k women with early-stage ER+ BC who received ET
- Even node-negative women have a persistent risk of recurrence & death
- Critical need to identify biomarkers to stratify risk



Pan et al. *NEJM* 2017

The four high-risk subgroups account for one quarter of ER-positive tumors and most distant metastases



Curtis et al. *Nature* 2012
Rueda et al. *Nature* 2019
Houlahan, Mangiante et al. *Nature* 2025

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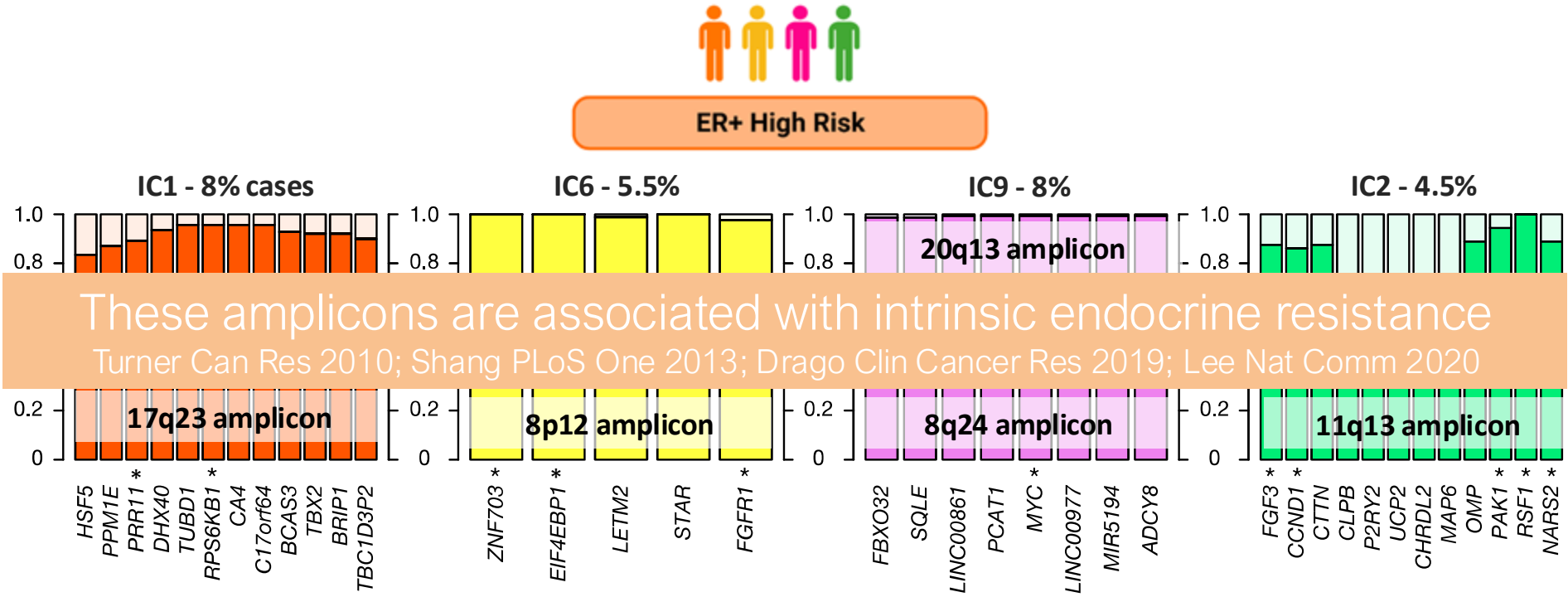
The four high-risk subgroups harbor characteristic genomic amplifications spanning oncogenic drivers



These amplicons are associated with intrinsic endocrine resistance

Turner Can Res 2010; Shang PLoS One 2013; Drago Clin Cancer Res 2019; Lee Nat Comm 2020

PI3K/Akt/mTOR pathway overactivation

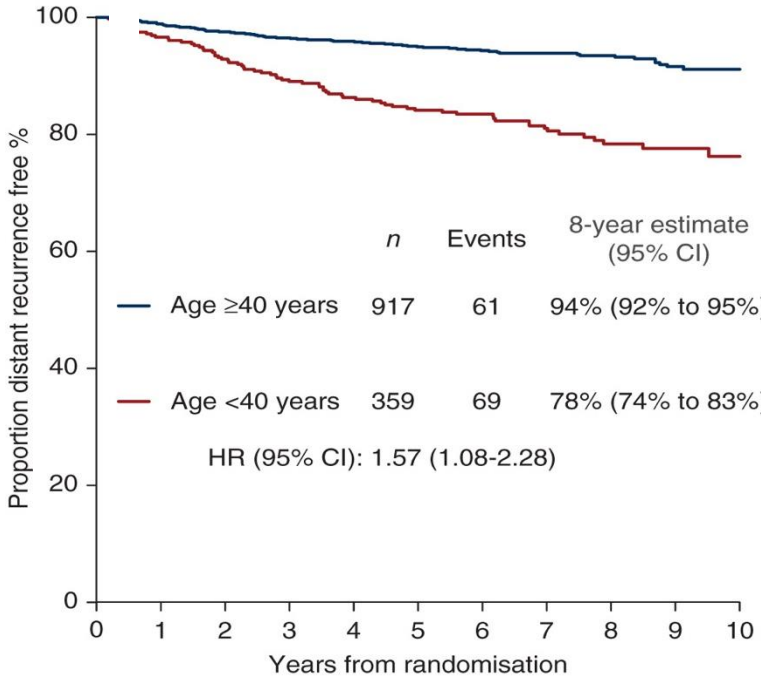
FGFR1 signaling

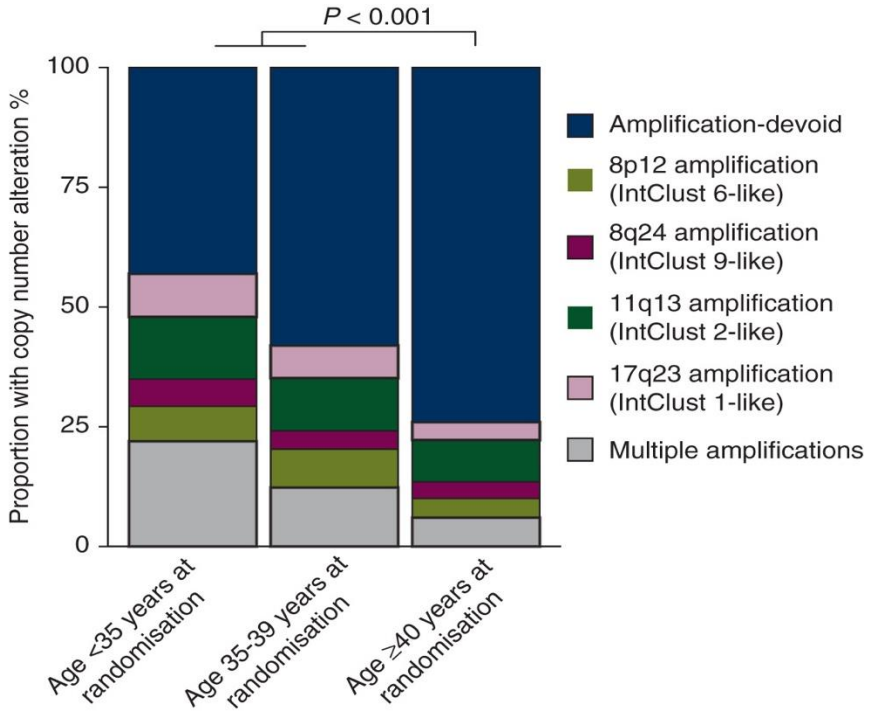
MYC/ER signaling

FGF/CCND1 activation

Rueda et al. *Nature* 2019

The high-risk ER+ ICs are enriched amongst young women: SOFT trial





Luen et al. *Annals Onc* 2023 (Sherene Loi)

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Biomarker-driven clinical trials in early-stage high-risk ER+ breast cancer

Jennifer Caswell-Jin, MD

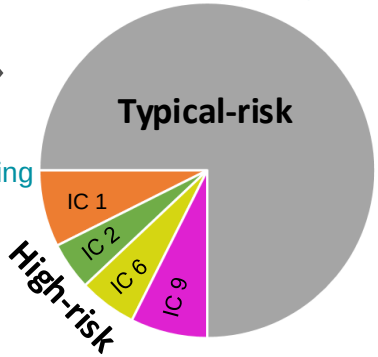
TERPSICHORE: Targeting Estrogen Receptor-Positive Selected Integrative Clusters at High-risk Of Relapse (NCT05101564)

Newly diagnosed ER+ patients

Screen for biomarker

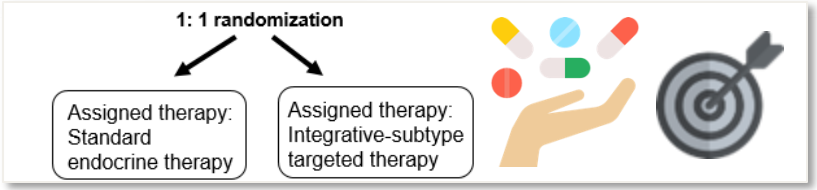
sequencing

Integrative subtyping



Biomarker-defined groups

Cohort 1	Cohort 2	Cohort 4	Cohort 3
IC 1	IC 2 & 6	IC 9	*Typical-risk*



CARIS

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Accelerating evidence: lab and clinic in the loop

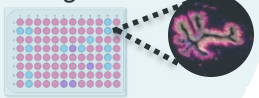
Functional and correlative studies in patient-derived organoids (avatars) and tissue

Surrogate endpoints

Response to therapy?

Mode of action? Target discovery

Screens in patient derived organoids



Tumor-immune co-culture

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How do the Integrative Subtypes distribute across stage?

What are the mutational processes that fuel the Integrative Subtypes?

Does the tumor-immune microenvironment vary?

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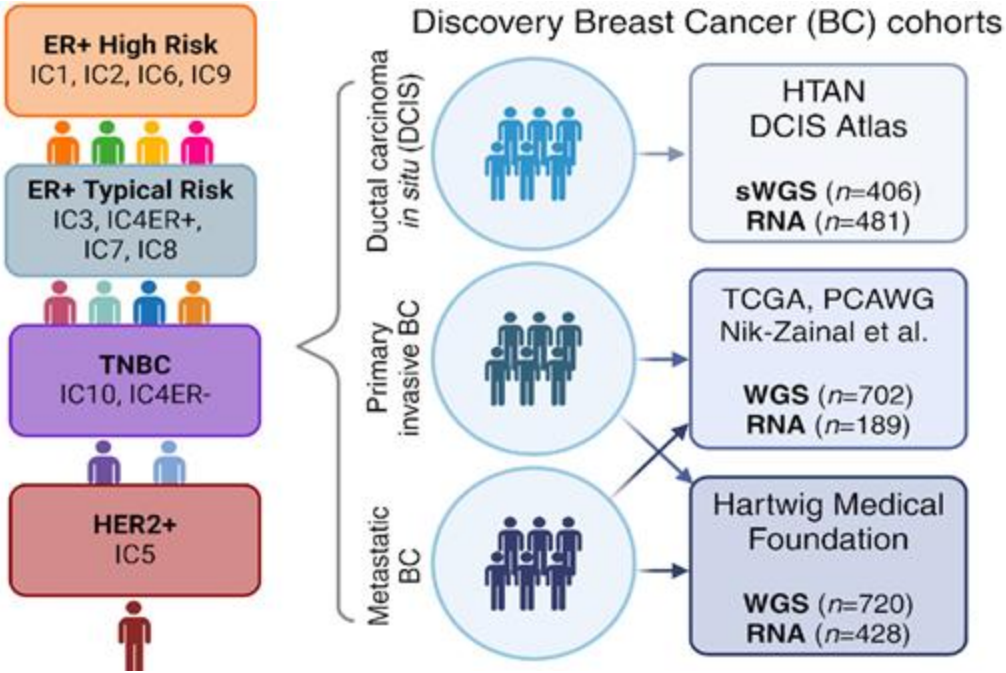
What are the mutational processes that drive progression across disease stage and subtype?



Houlahan, Mangiante et al. *Nature* 2025

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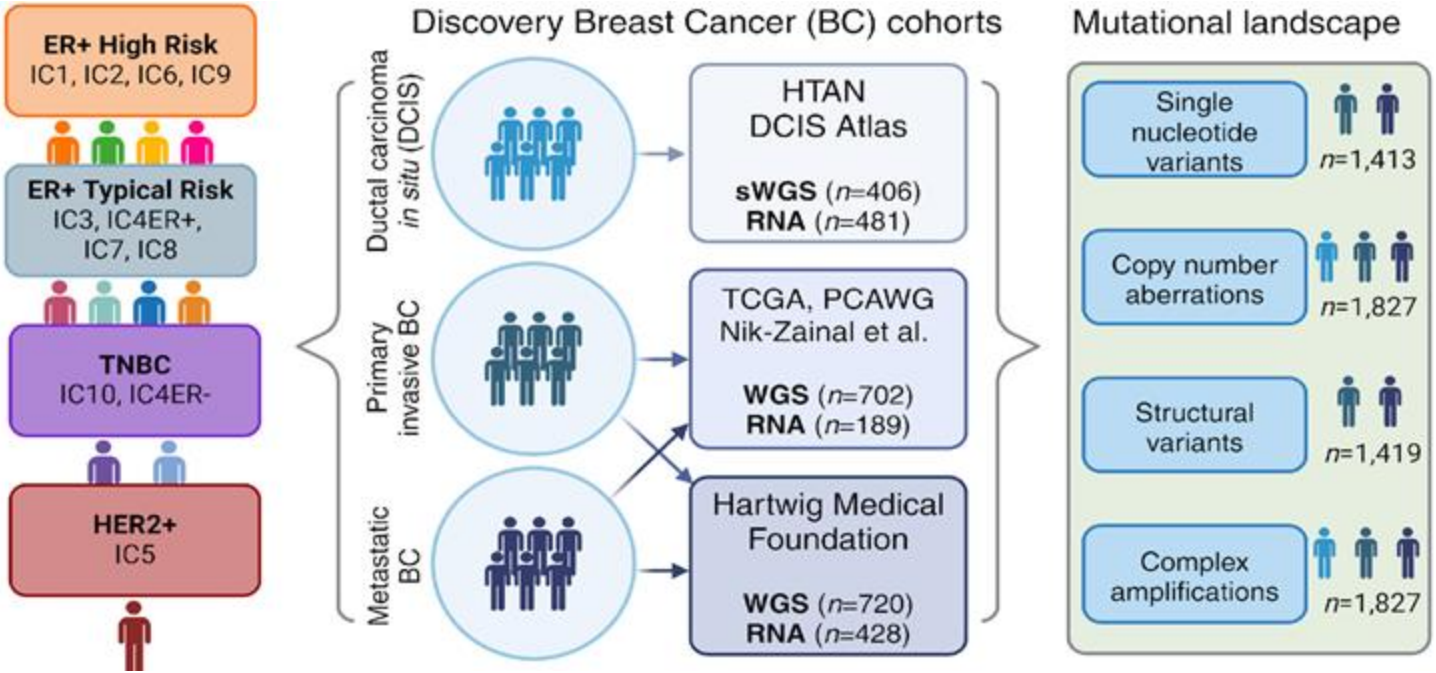

Houlahan, Mangiante et al. *Nature* 2025

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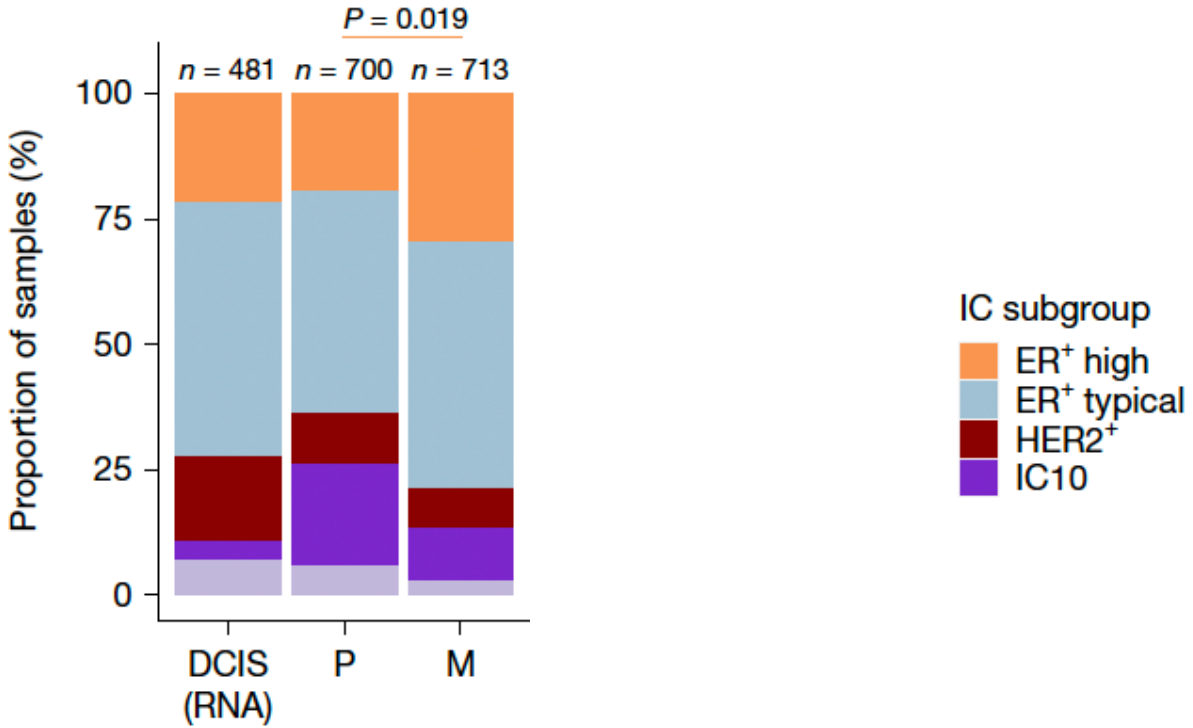
The high-risk ER+ subgroups are detectable in DCIS and enriched in metastases



Houlahan, Mangiante et al. *Nature* 2025

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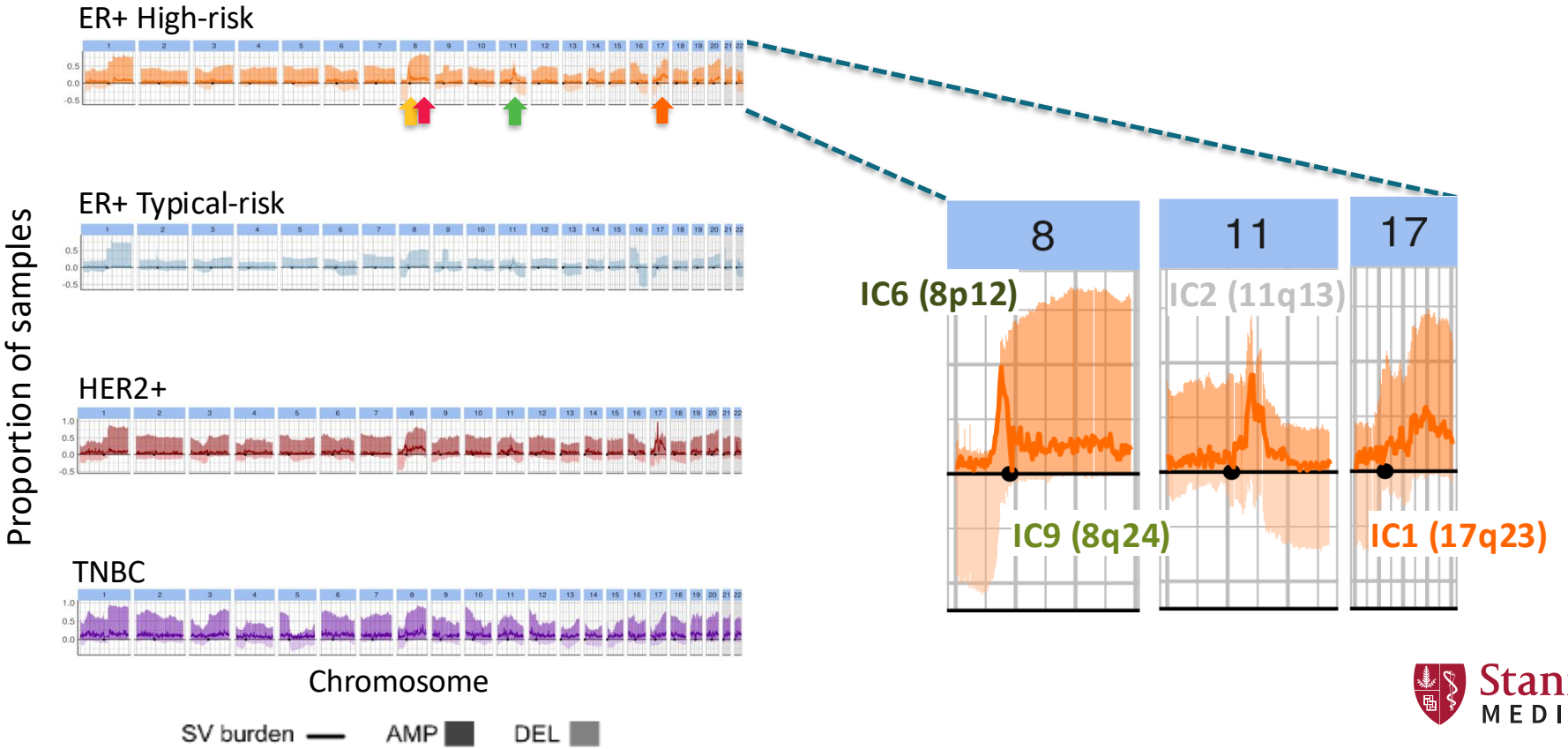
Structural variants are coincident with recurrent amplifications in ER+ High-risk tumors



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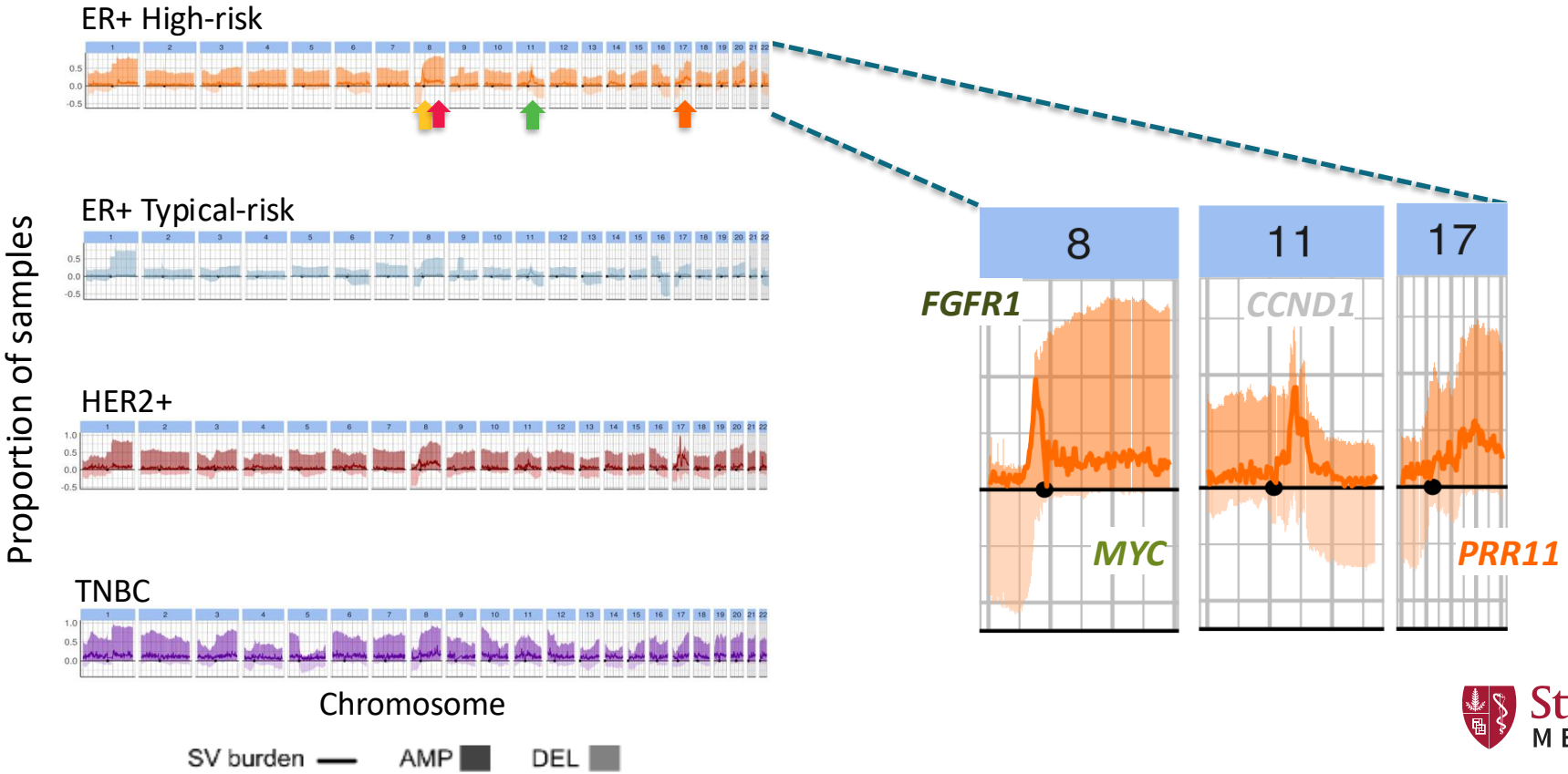

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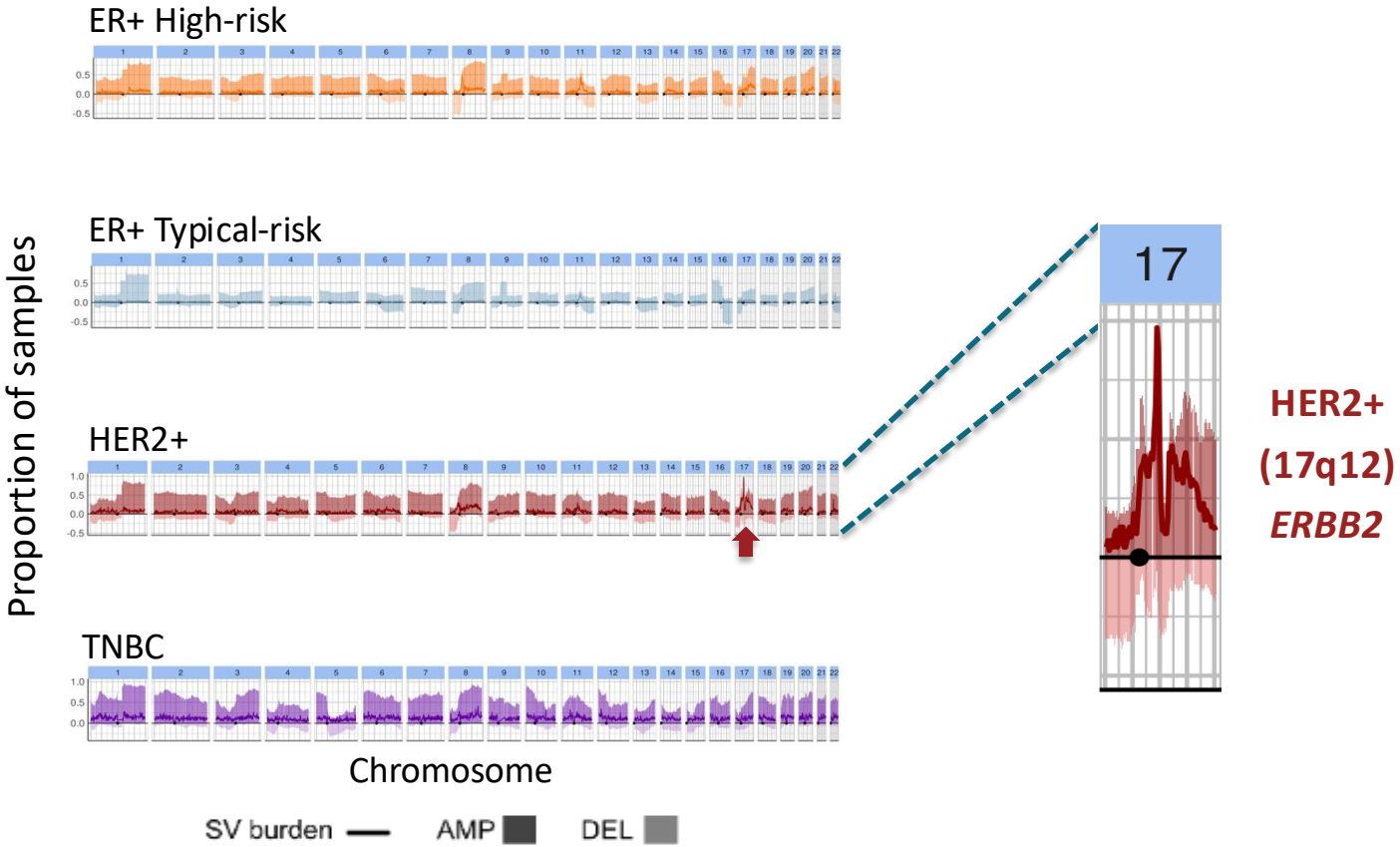
Structural variants are coincident with recurrent amplifications in HER2+ tumors



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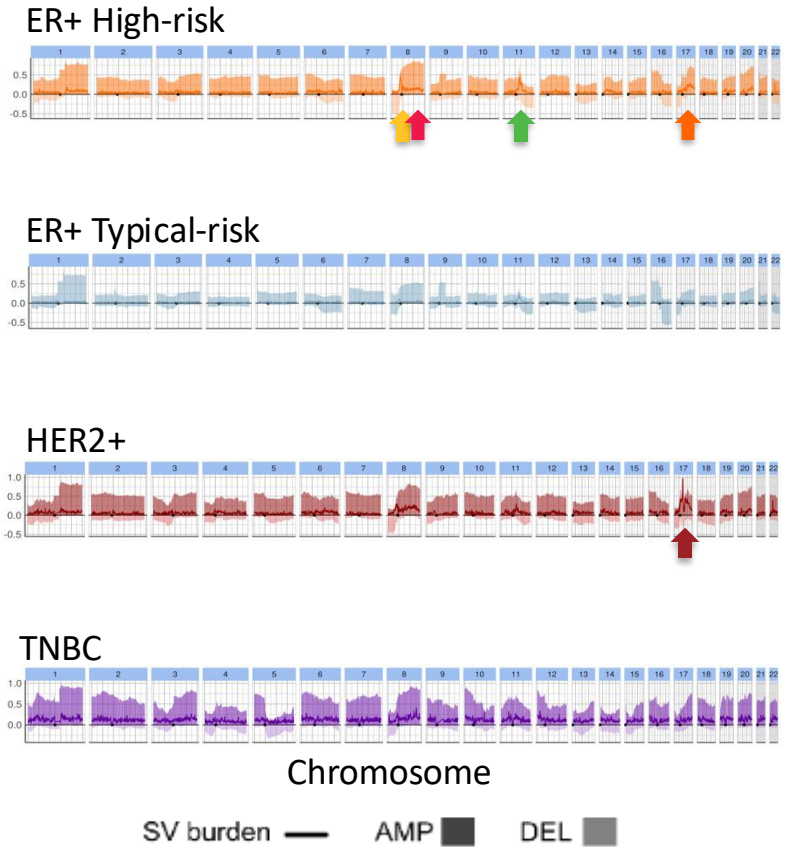
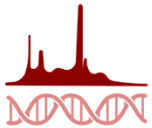
ER+ Typical-risk tumors have quiet genomes while TNBC have nonspecific alterations



Specific (IC) amplification

Lower overall burden



Specific (IC) amplification

Nonspecific alterations

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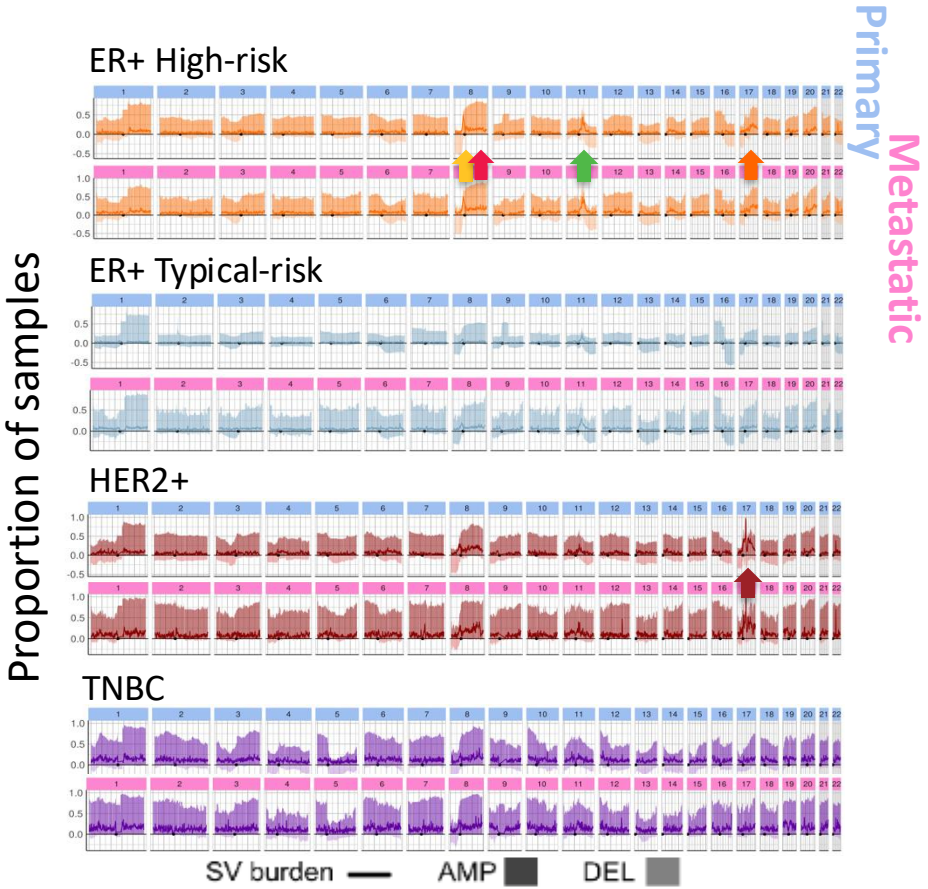
These patterns are largely conserved in metastasis



Specific (IC) amplification

Lower overall burden

Specific (IC) amplification

Nonspecific alterations

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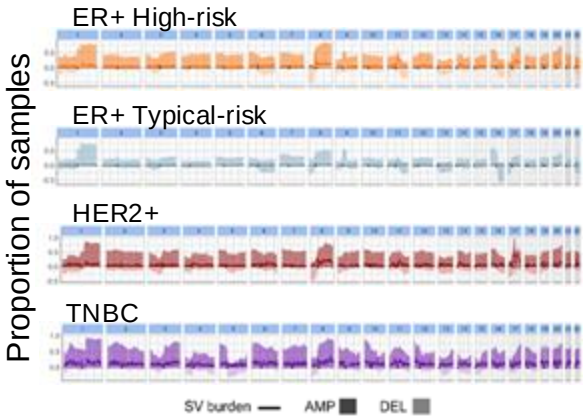
Integration of copy number and structural variant signatures



Genome-wide landscape

Copy number (CN) and structural variant (SV)

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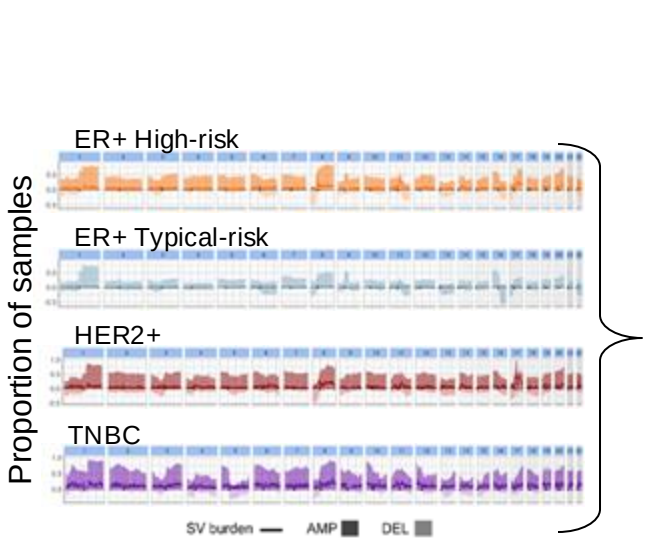
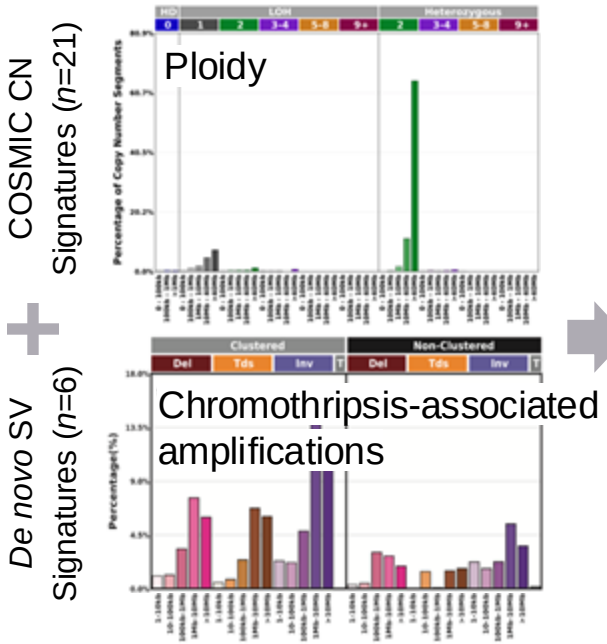
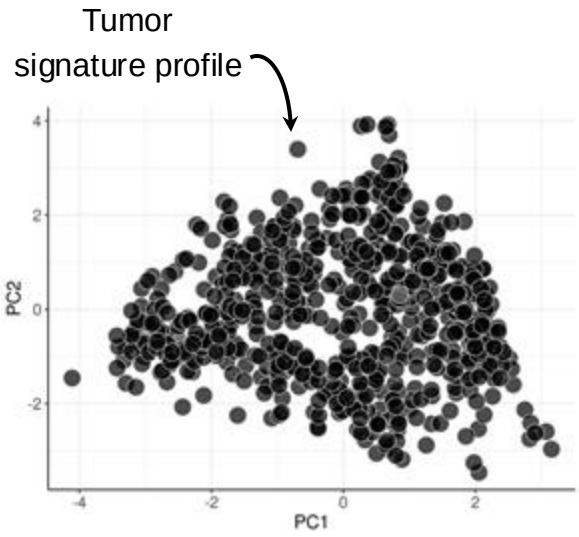
Integration of copy number and structural variant signatures







Genome-wide landscape

Copy number (CN) and structural variant (SV)

Mutational signatures

Architectural PCA

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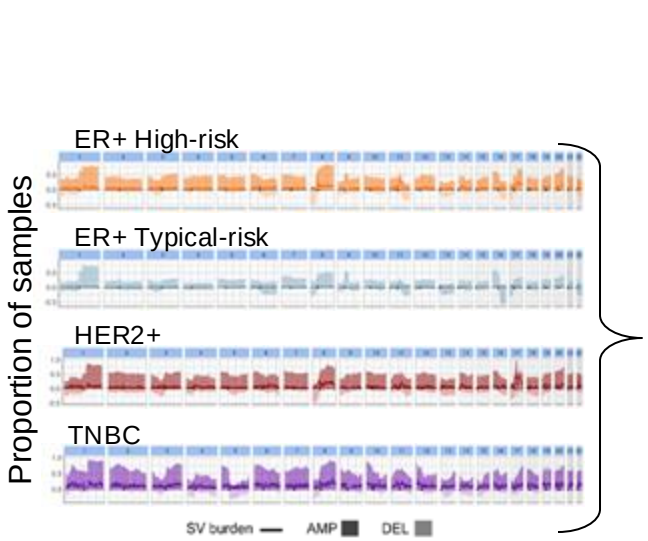
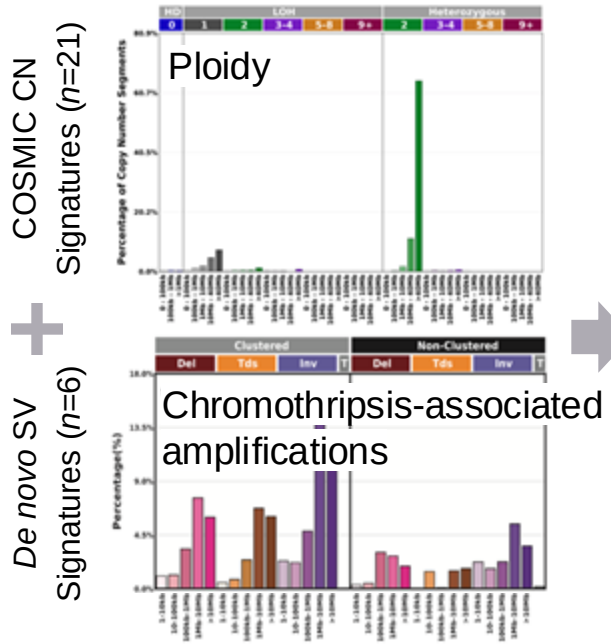
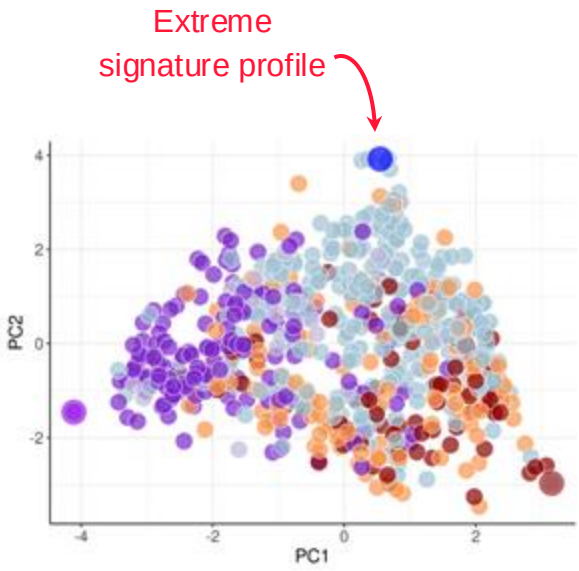
Integration of copy number and structural variant signatures







Genome-wide landscape

Copy number (CN) and structural variant (SV)

Mutational signatures

Architectural PCA

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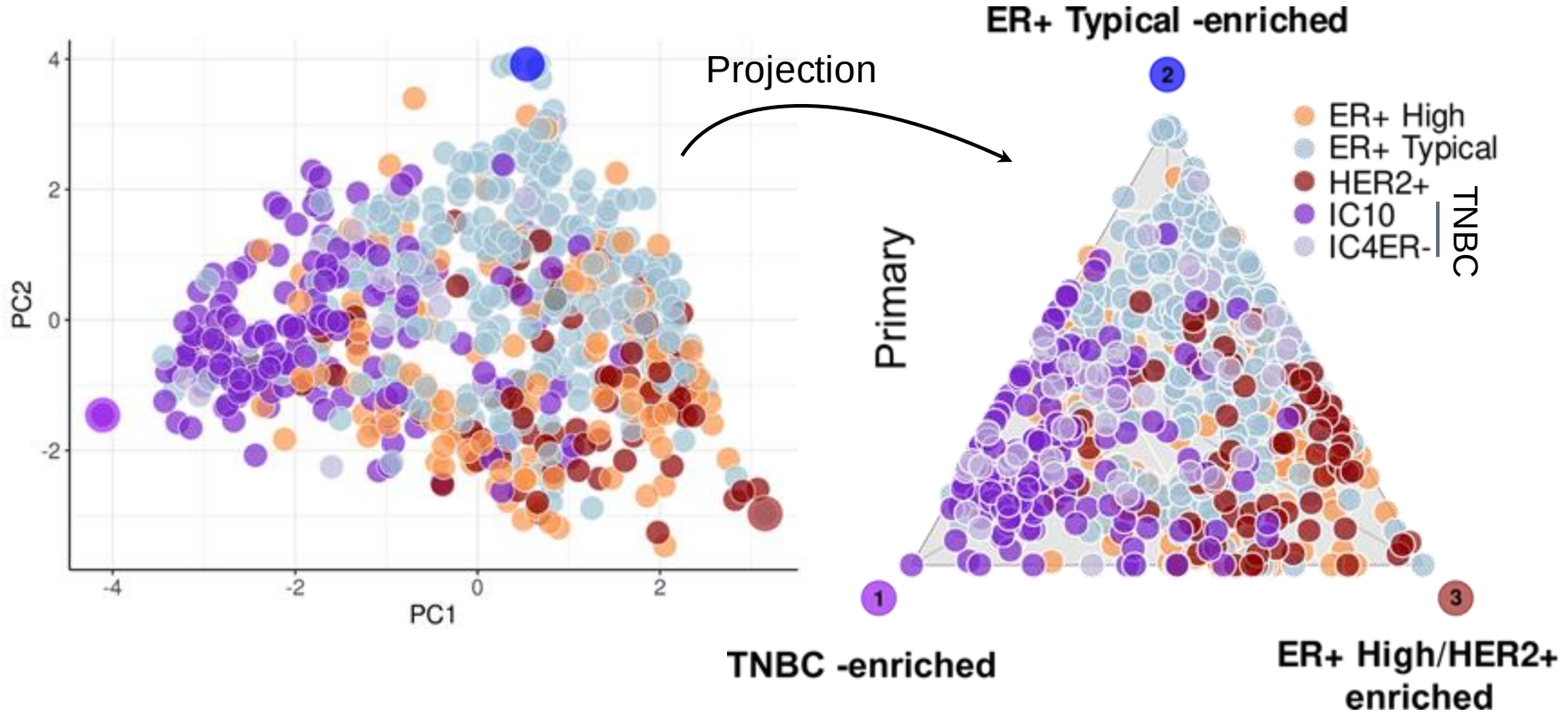
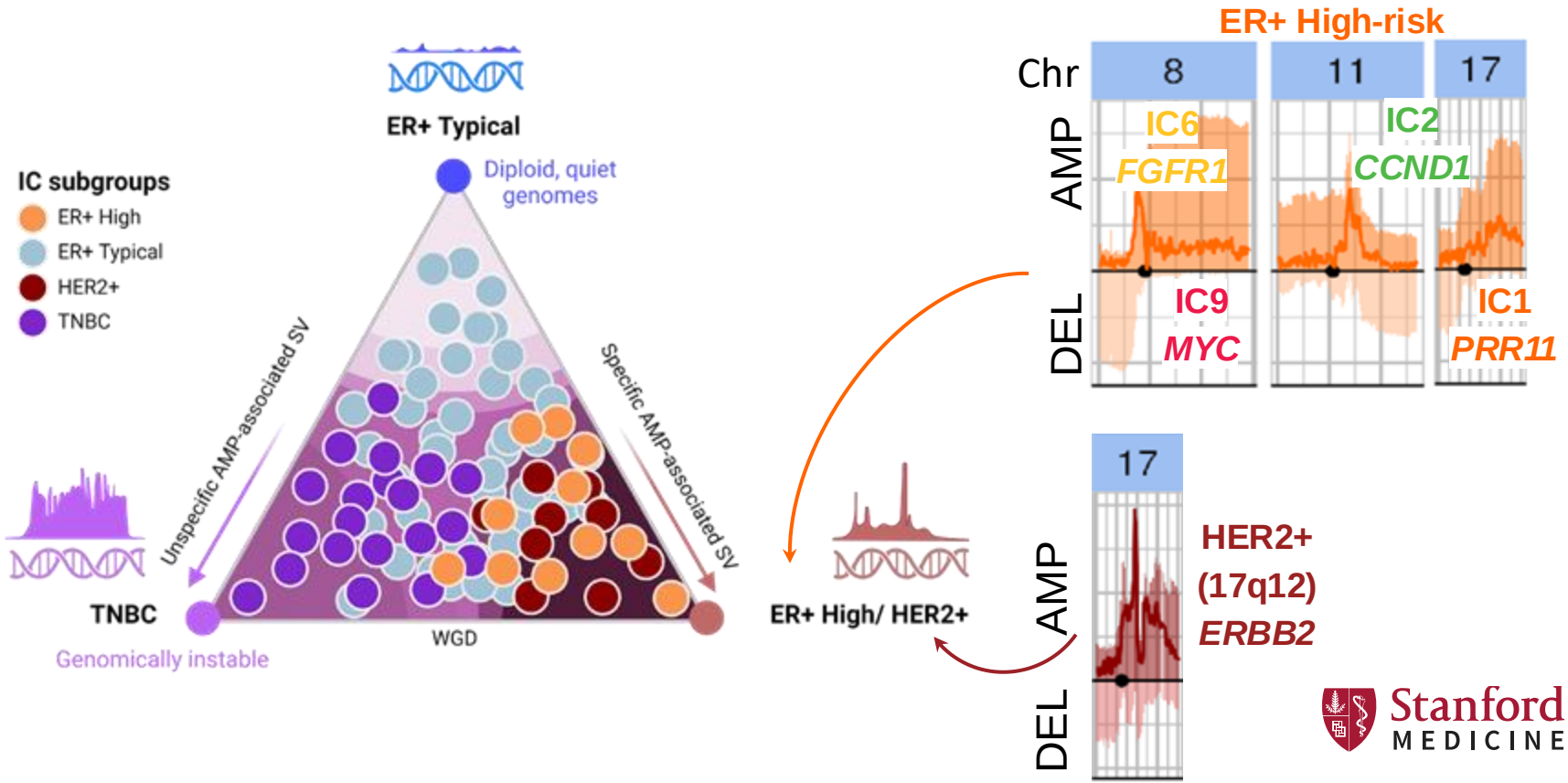
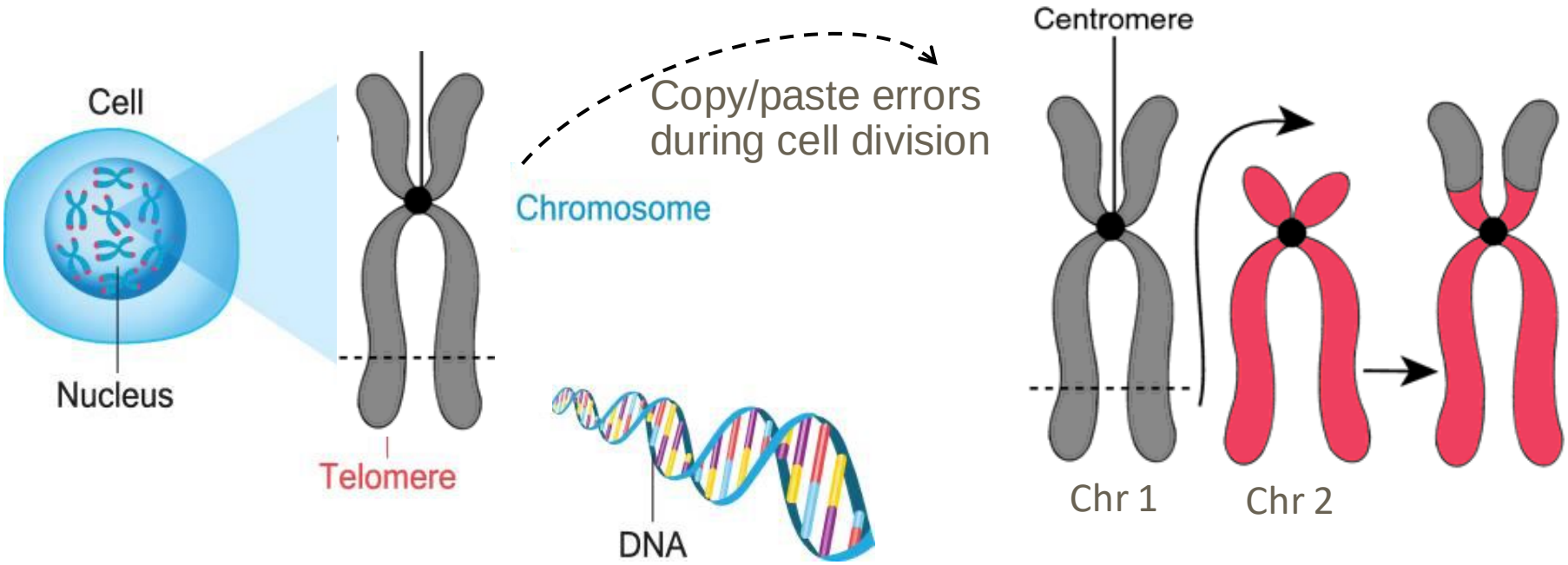
ER+ High-risk and HER2+ tumors have highly concordant profiles



ER+ High-risk and HER2+ tumors have highly concordant profiles involving distinct oncogenes



Genomic rearrangements scramble breast cancer genomes



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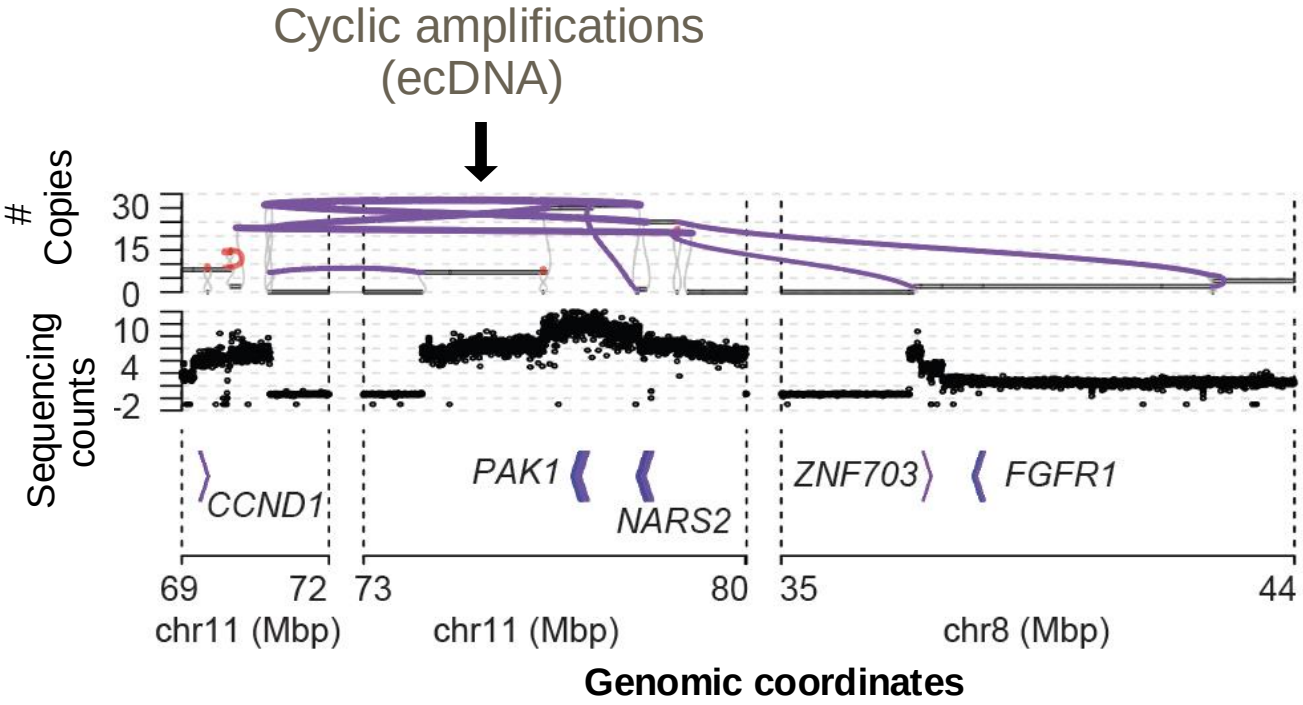
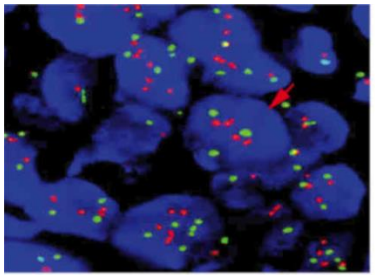
Genomic rearrangements co-occur with extrachromosomal DNA (ecDNA)





HER2 double minutes
(ecDNA)

Houlahan, Mangiante et al. *Nature* 2025

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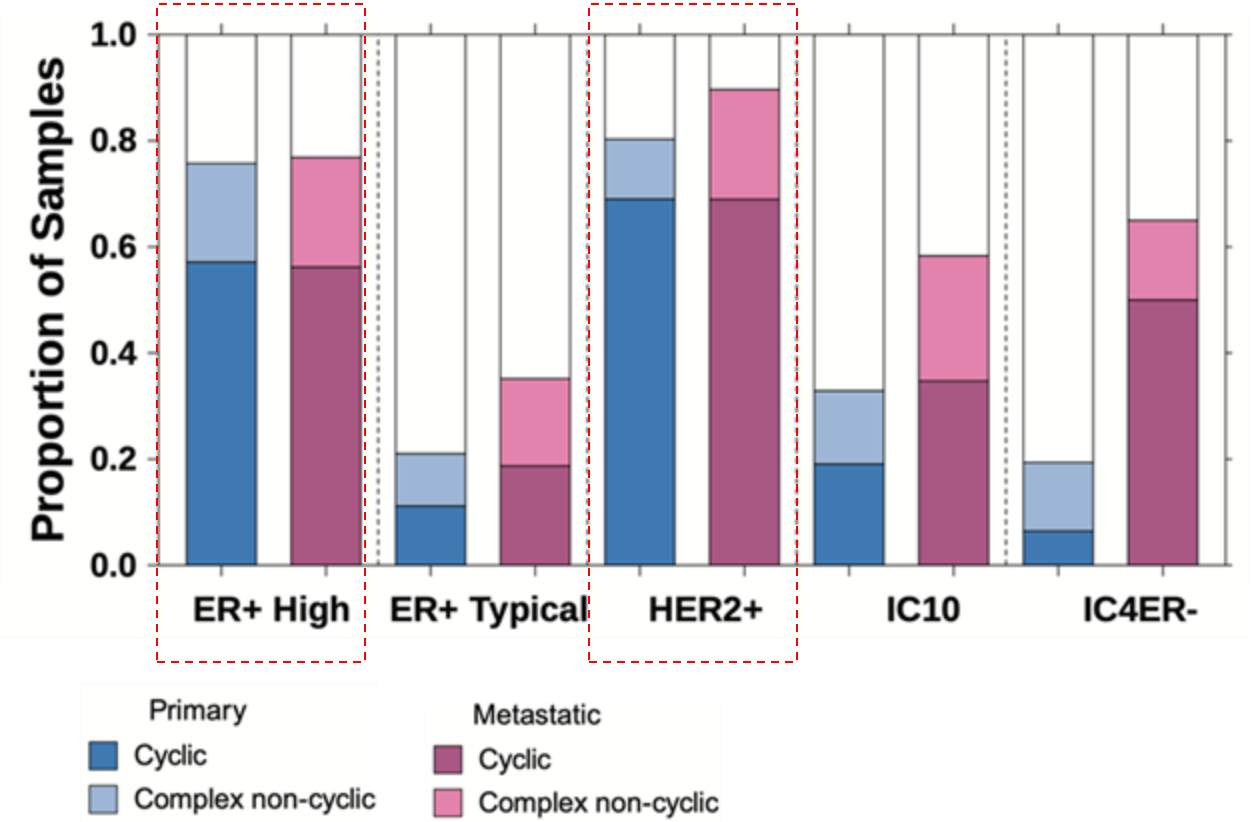
ER+ High-risk and HER2+ tumors are enriched for extrachromosomal DNA (ecDNA)



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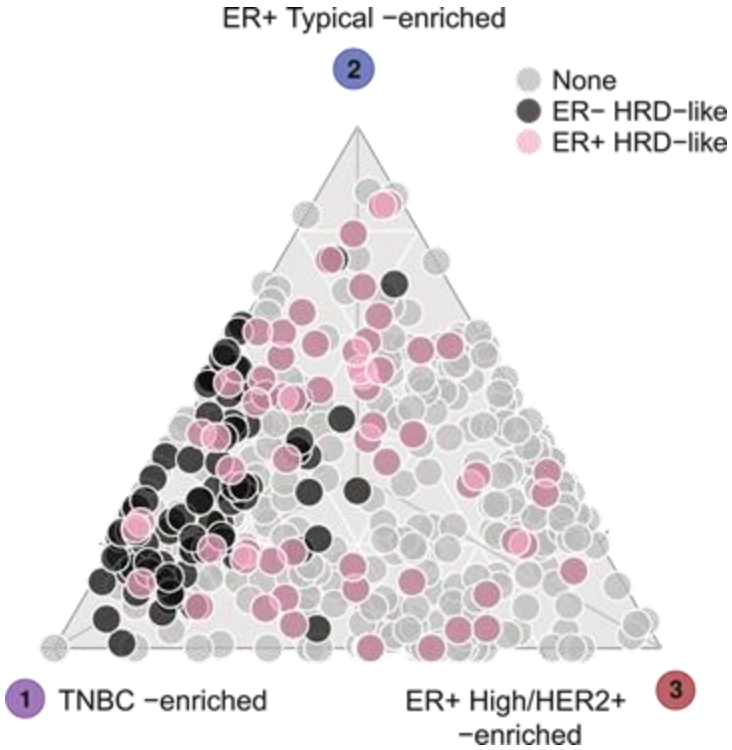
High-risk ER+ tumors exhibit BRCA2-like homologous recombination deficiency



Houlahan, Mangiante et al. *Nature* 2025

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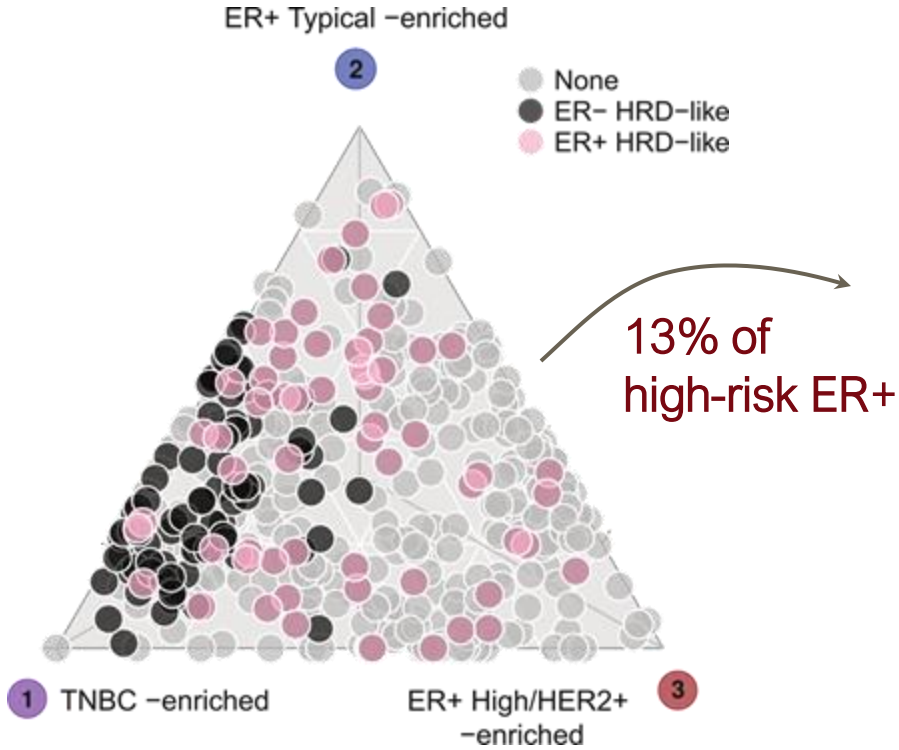
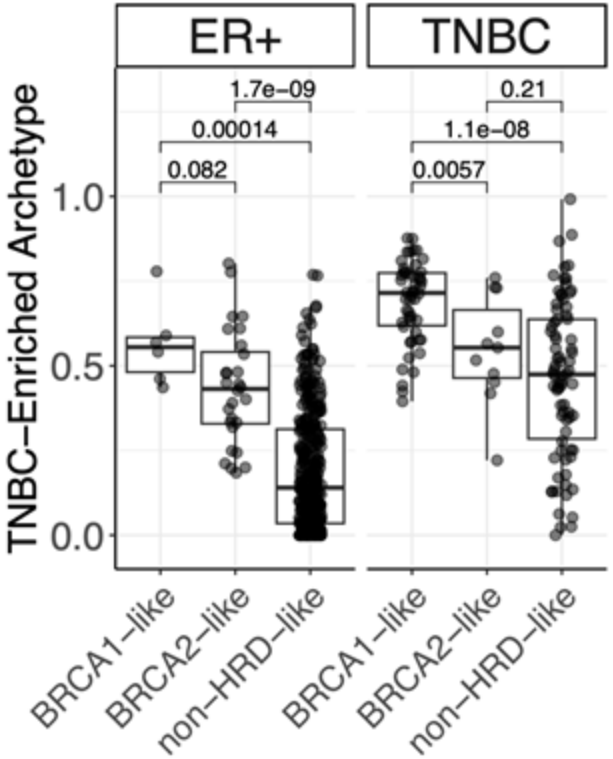


13% of high-risk ER+



Houlahan, Mangiante et al. *Nature* 2025

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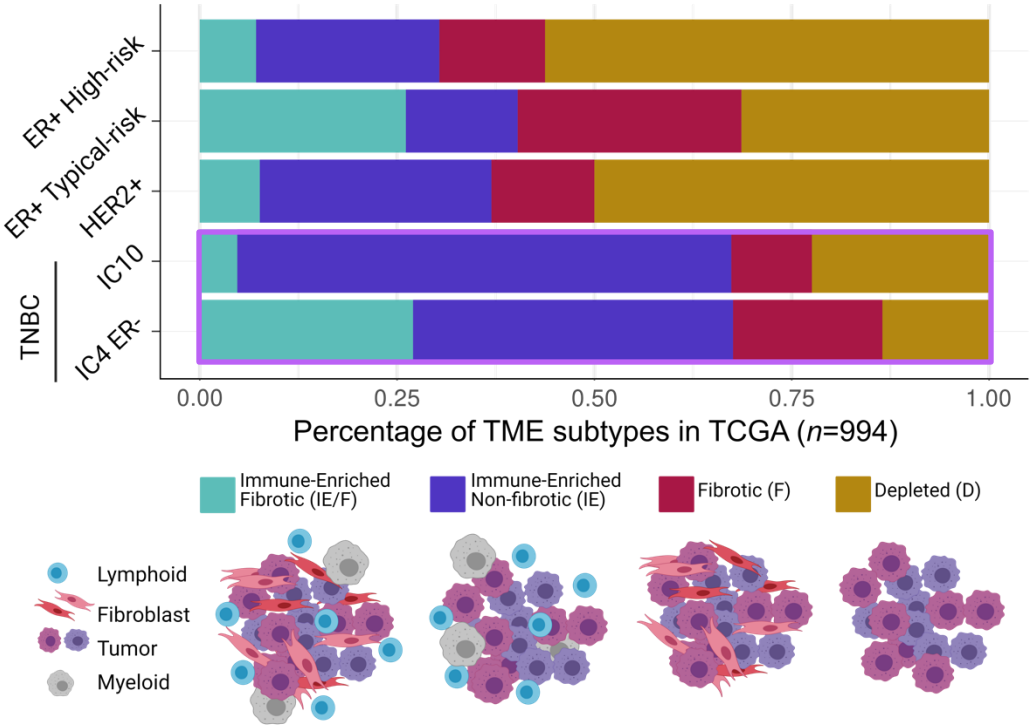
Breast cancer genomic archetypes exhibit distinct tumor microenvironments



Houlahan, Mangiante et al. *Nature* 2025

Houlahan et al. Science 2024

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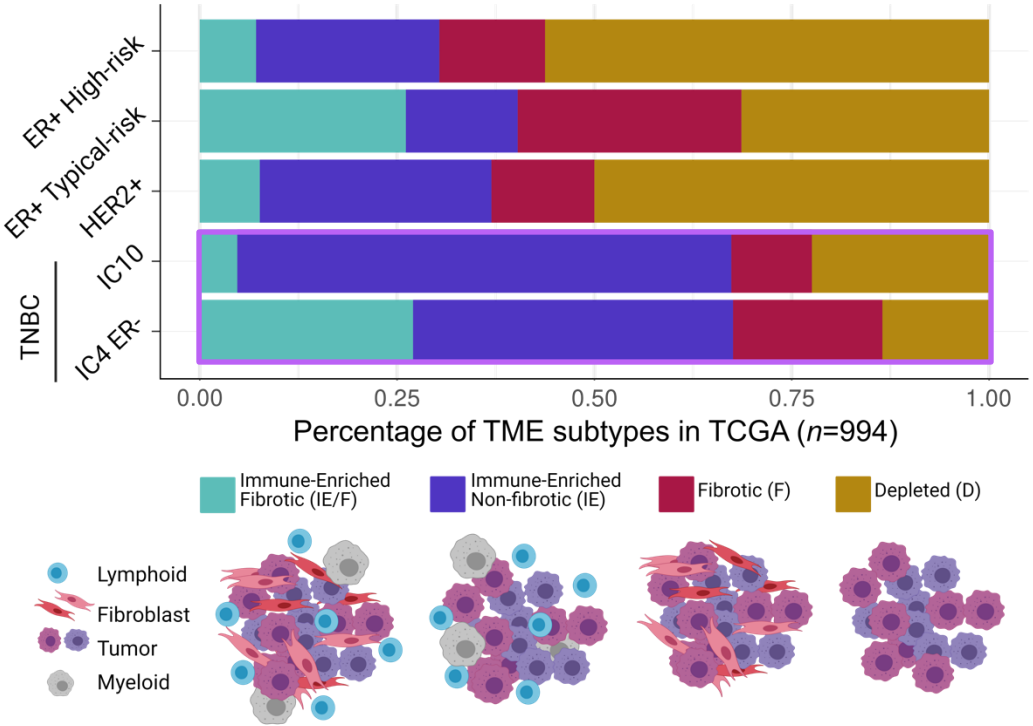

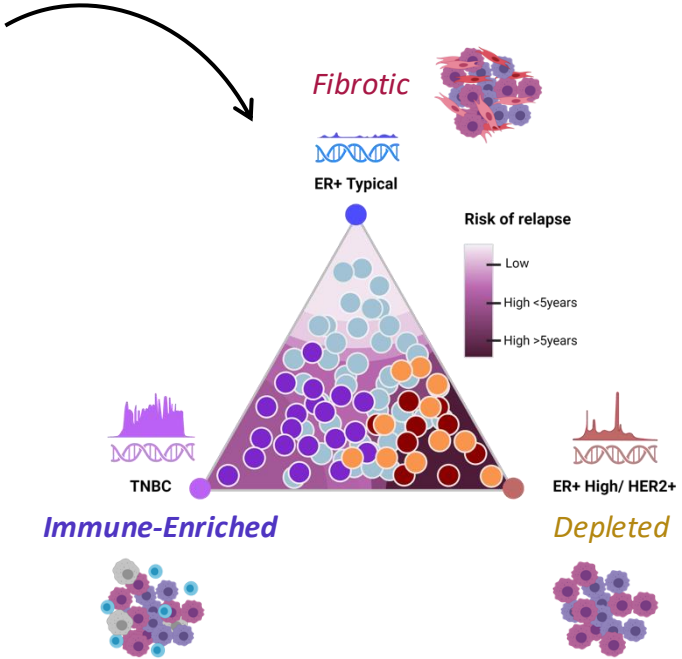

Houlahan, Mangiante et al. *Nature* 2025

Houlahan et al. Science 2024

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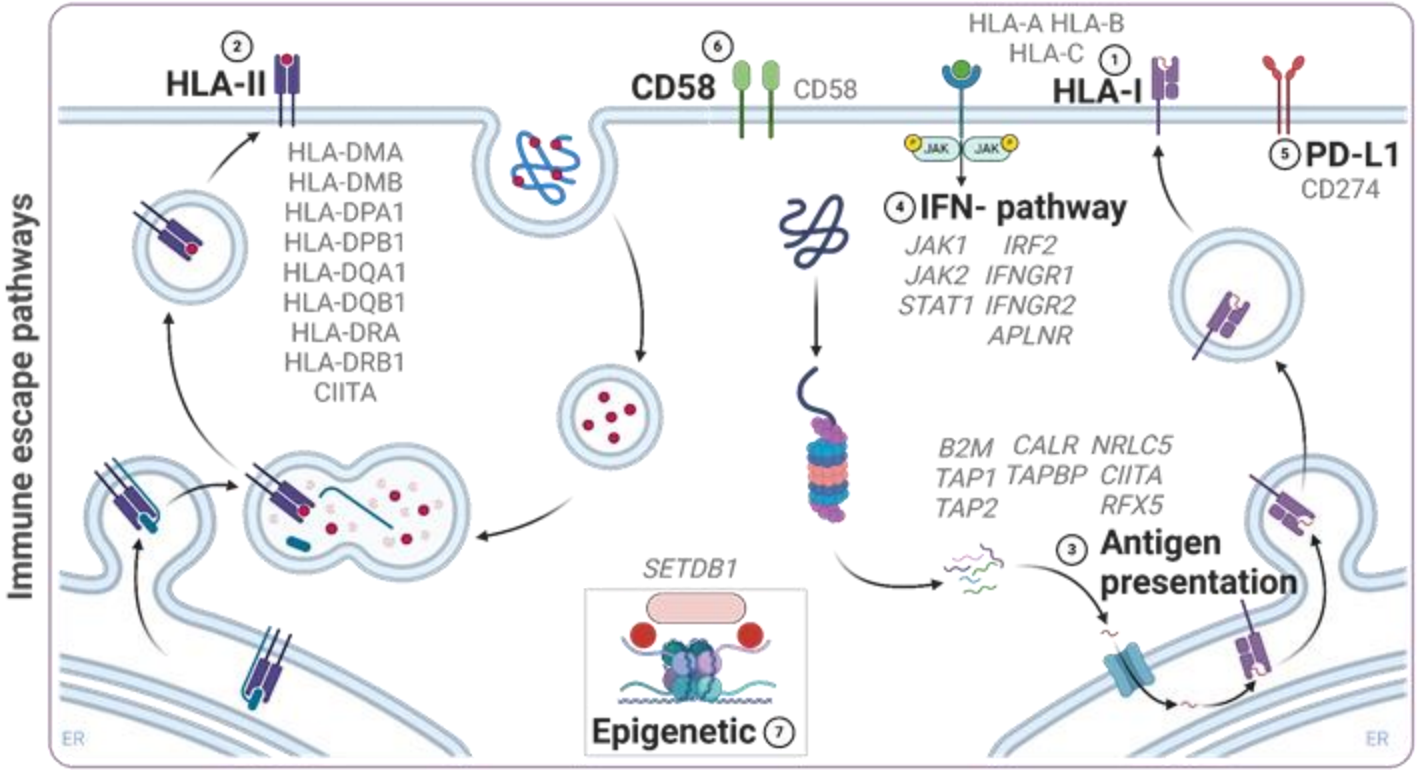
How do tumor intrinsic factors influence immune evasion?



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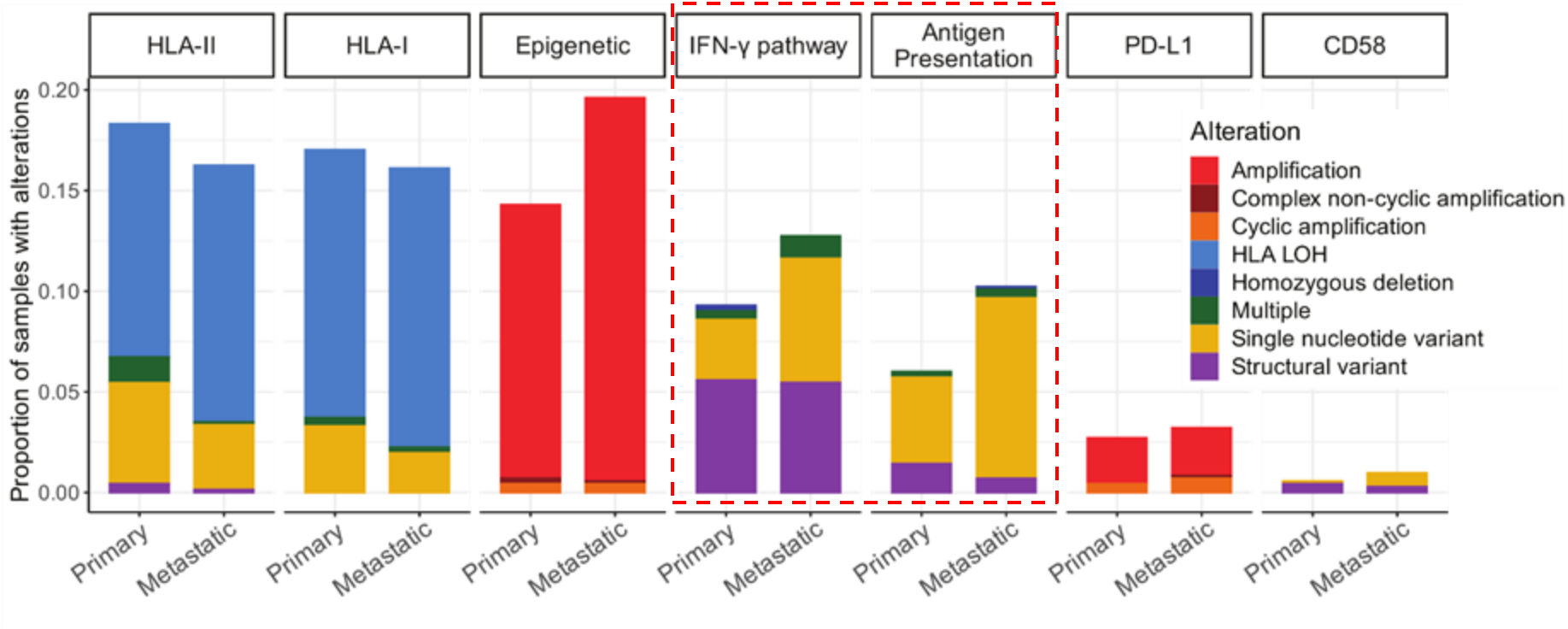
Structural variants damage the IFN-γ pathway and antigen presentation genes



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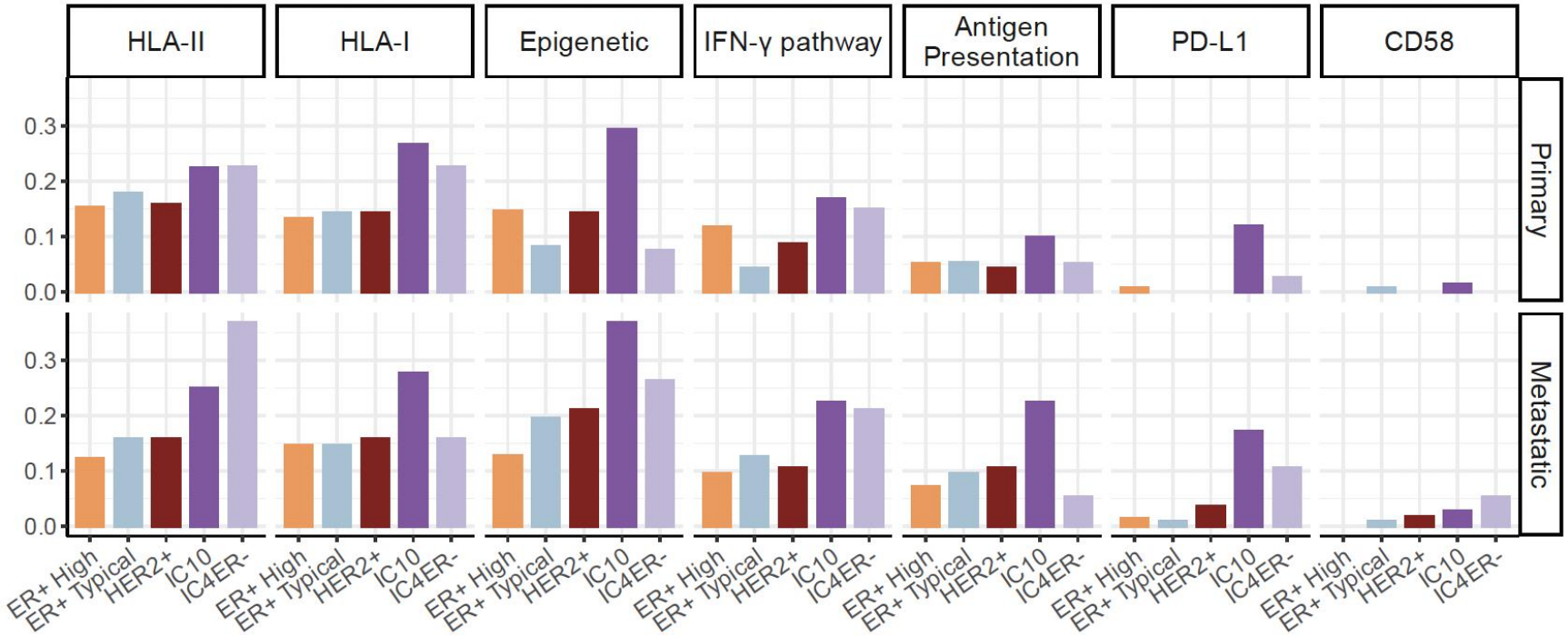
Preferred genetic immune-escape pathways across the Integrative Subtypes



- PD-L1 alterations exclusive to IC10 and IC4ER-
- IDO1 amp unique to IC2/IC6

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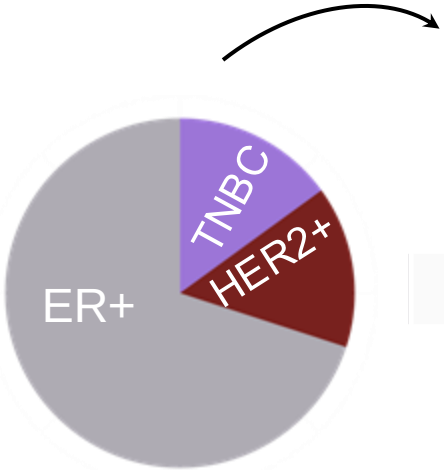
Genomic archetypes capture the continuum of risk

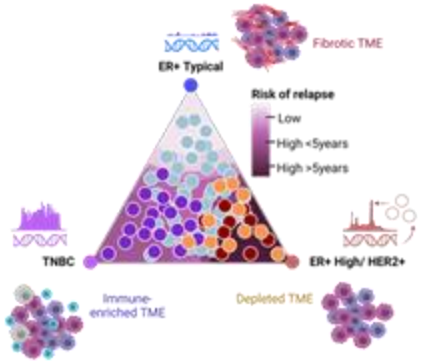


Current receptor-based classification

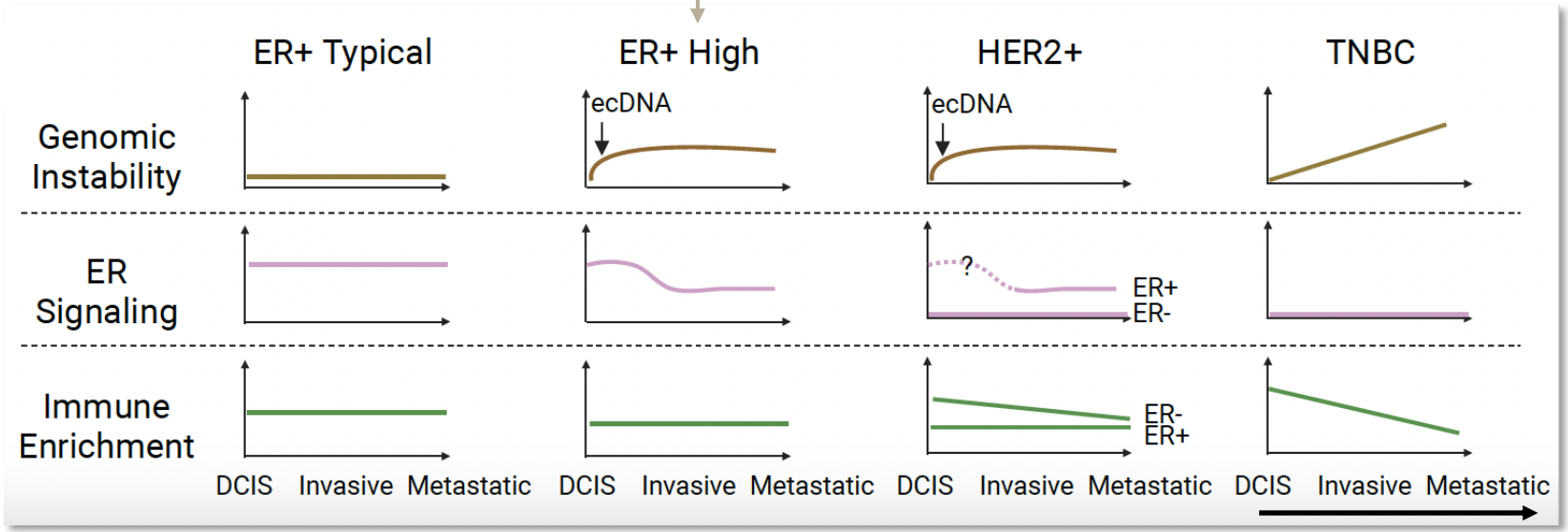
Houlahan, Mangiante et al. *Nature* 2025

ER+ High-risk & **HER2+**
Share mutational processes

Summary: Three genomic archetypes with distinct vulnerabilities and TMEs



Replication stress, HRD, APOBEC3b



Houlahan, Mangiante et al. *Nature* 2025

Summary

- The integrative subtypes define high-risk of relapse ER+ tumors with distinct vulnerabilities
- High-risk ER+ and HER2 disease are driven by focal oncogene amplification coincident with structural variation and ecDNAs
- 13% of High-risk ER+ tumors exhibit BRCA2-like signatures
- Genetic and non-genetic mechanisms contribute to immune escape

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CTD² Cancer Target Discovery and Development

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NIH National Human Genome Research Institute

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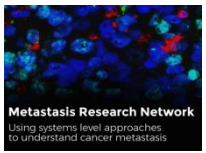

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