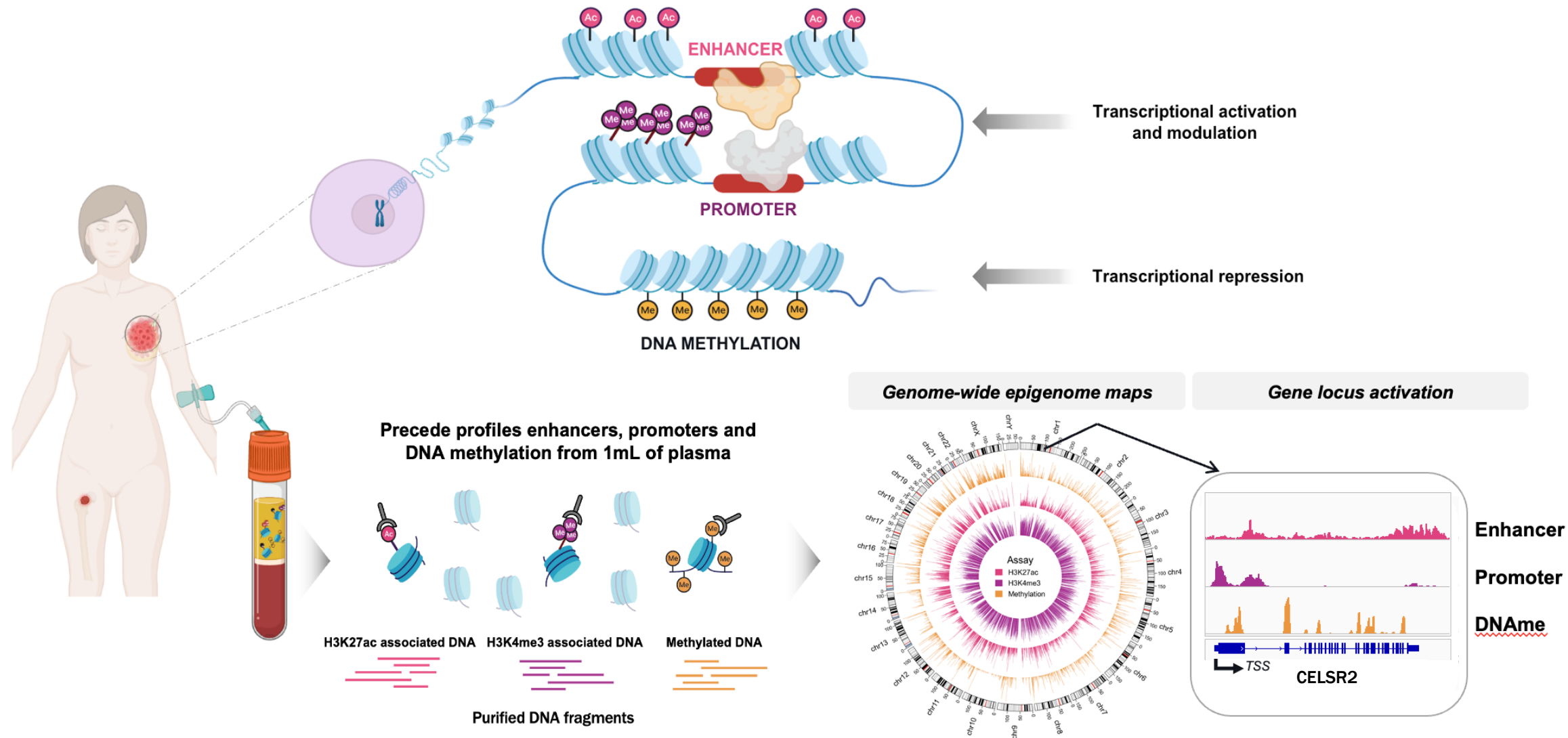


Comprehensive Epigenomic Profiling from Plasma to Inform Drug Development, Cancer Biology, and Therapy Selection

J. Carl Barrett, CSO, Precede Biosciences

Comprehensive epigenomic platform offers dynamic resolution into target and pathway biology from 1mL of plasma



Developing a menu of actionable tests to inform drug development and impact therapeutic decision-making

Core elements of Precede developed tests

- **ctDNA fraction assessment** using Precede proprietary epigenomic based method
- Resolution into **activation status of genes of interest**



Breast

- ER-positivity
- ER pathway activation
- HER2-positivity
- Other high-value targets such as TROP2...



Prostate

- AR pathway activation
- Neuroendocrine transformation
- Other high-value targets such as PSMA...



Lung

- SCLC transformation
- SCLC subtyping
- Other high-value targets such as MET...

Emerging...

- **Oncology:** CRC; select others based on academic interest and target relevance
- **Autoimmune:** Lupus, Multiple sclerosis



ASCO

naturemedicine ESM ASCO

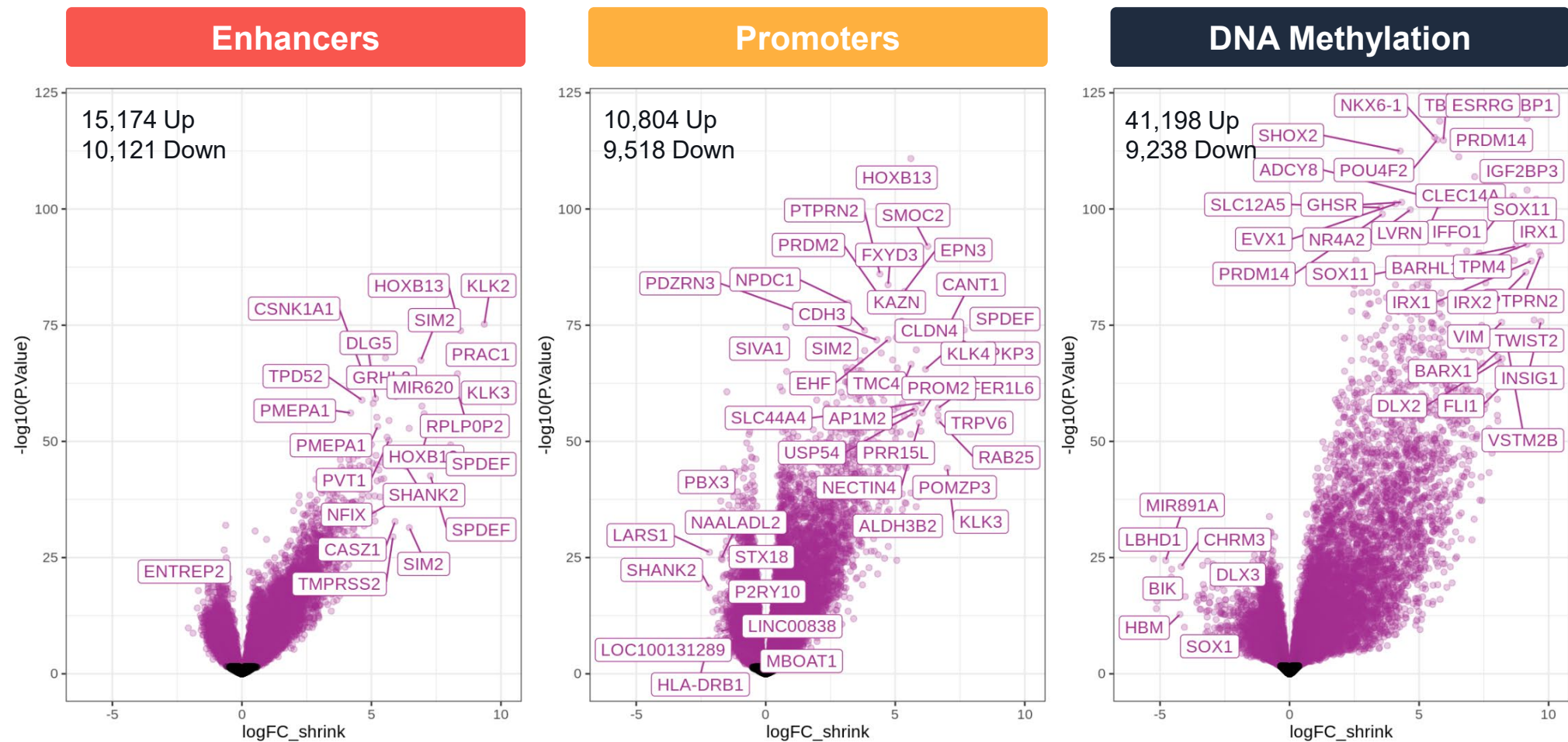
AACR

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT
AND RESEARCH IN MULTIPLE SCLEROSIS

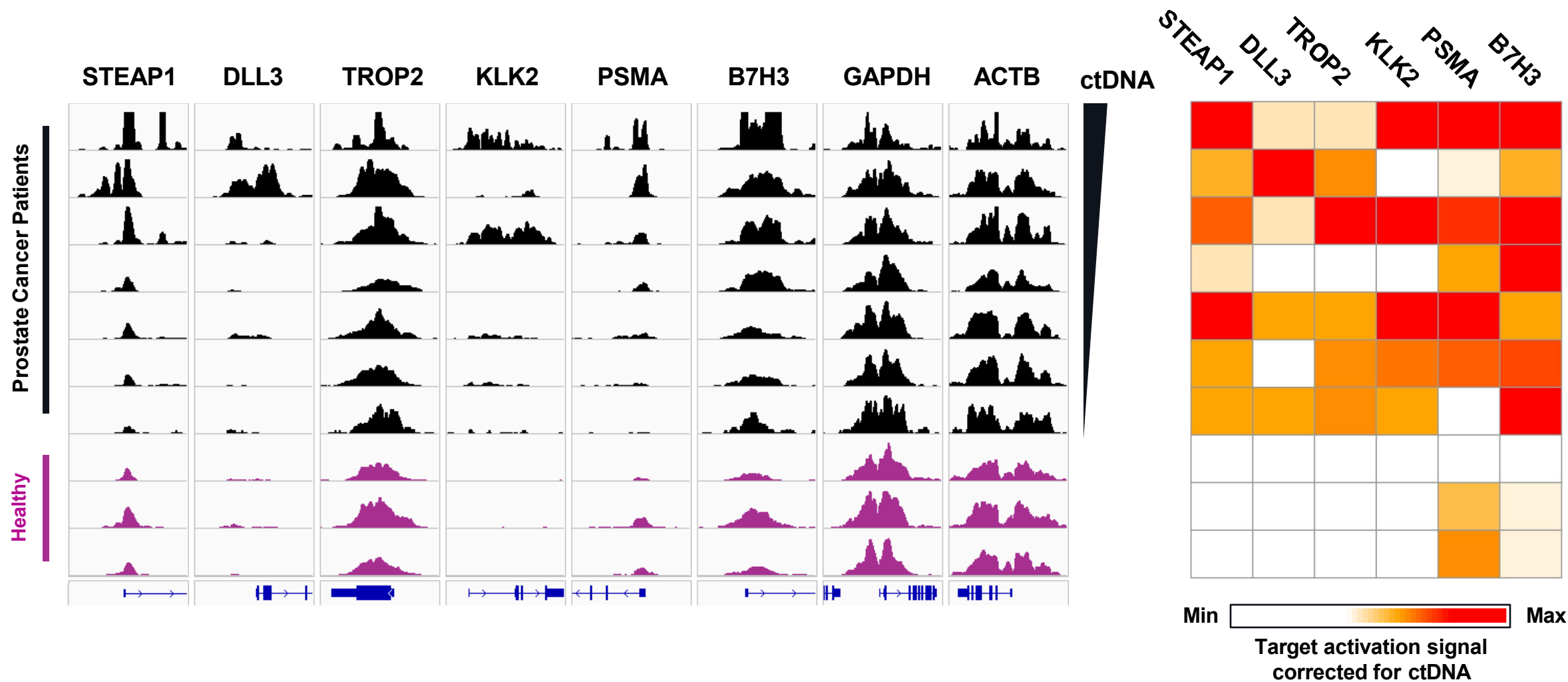
Prostate Cancer

*Multiple targets in one genome-wide assay
provides insights into cancer biology*

Prostate cancer biology revealed from comprehensive epigenomic analysis of mCRPC patients

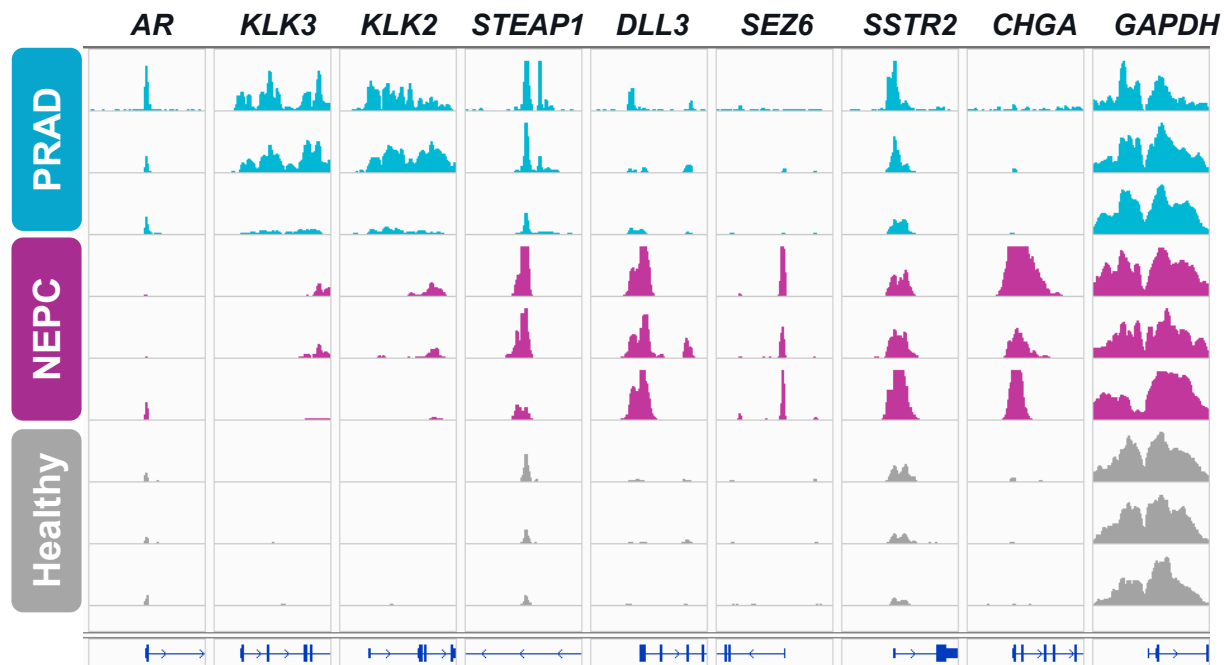


Identifying therapeutically relevant targets in prostate cancer from 1mL of plasma

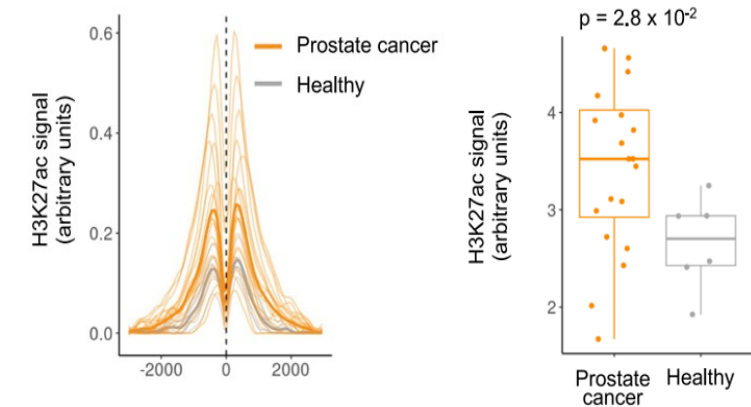


Identification of neuroendocrine transition biomarkers and target expression for new therapies in the same assay

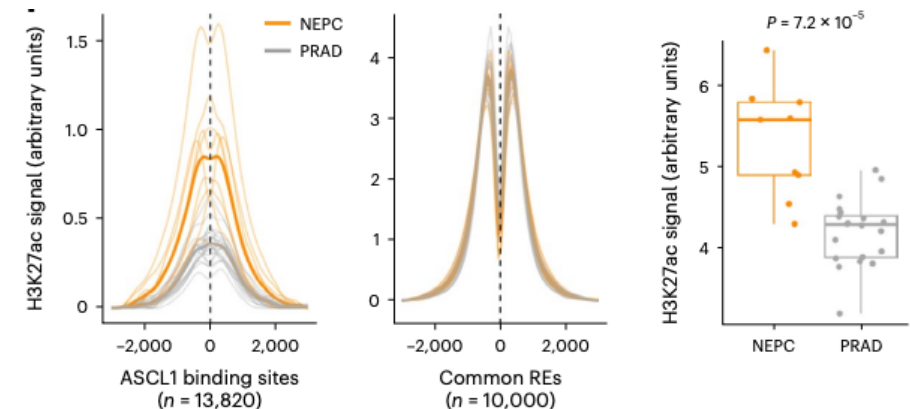
Lineage plasticity underlies tumor heterogeneity and drug resistance



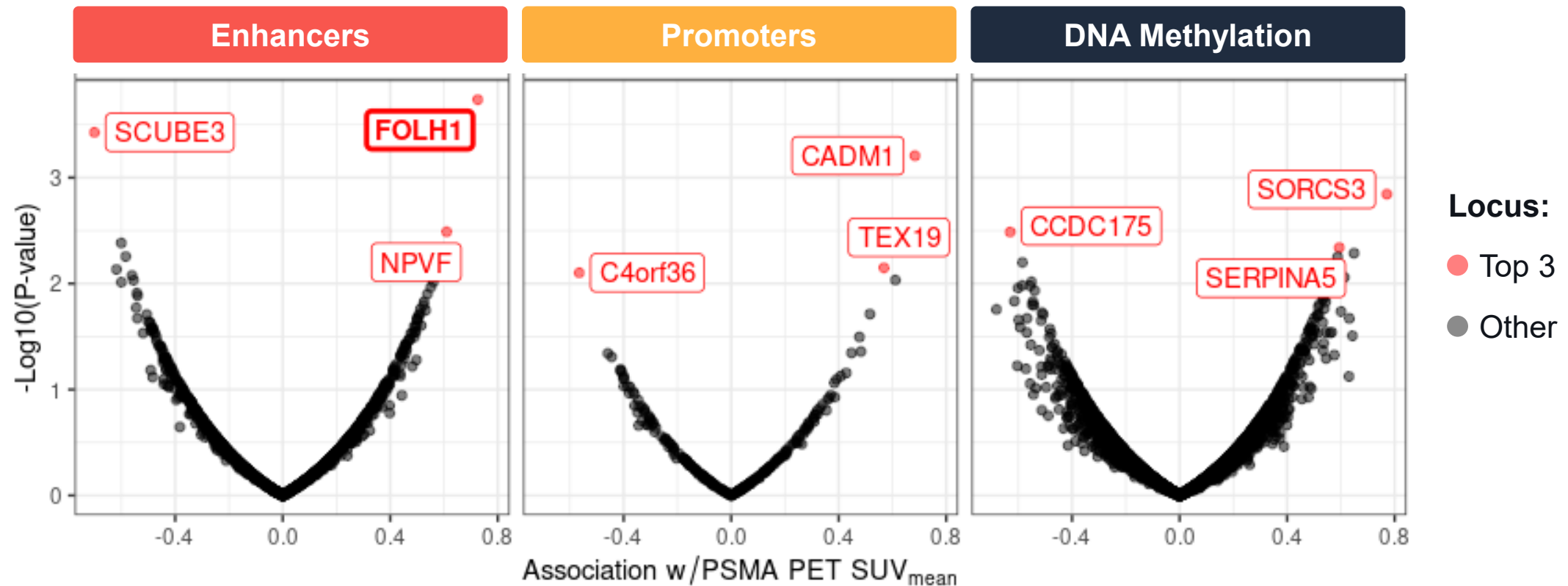
AR-scores for patients with AR+/NE- PRAD



Relevant therapy in NE+ tumors



Genome wide analysis of epigenomic signal associated with PSMA PET SUV_{mean} confirms *FOLH1* enhancer signal as a top correlate



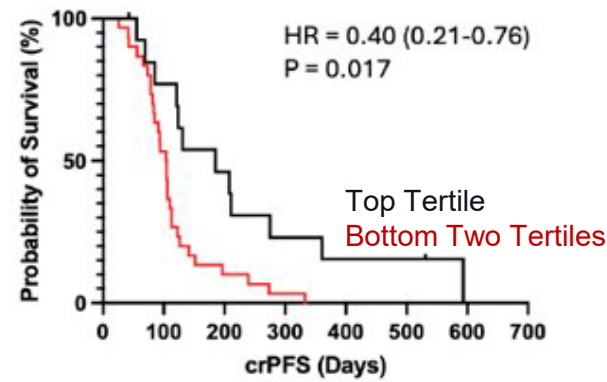
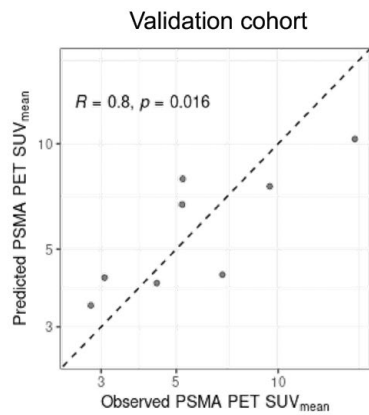
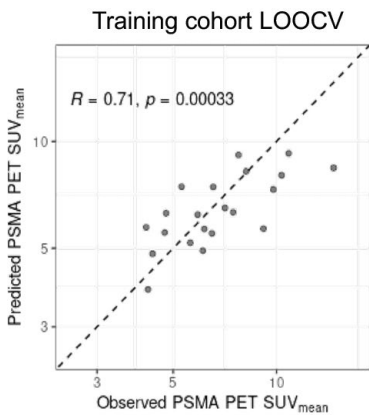
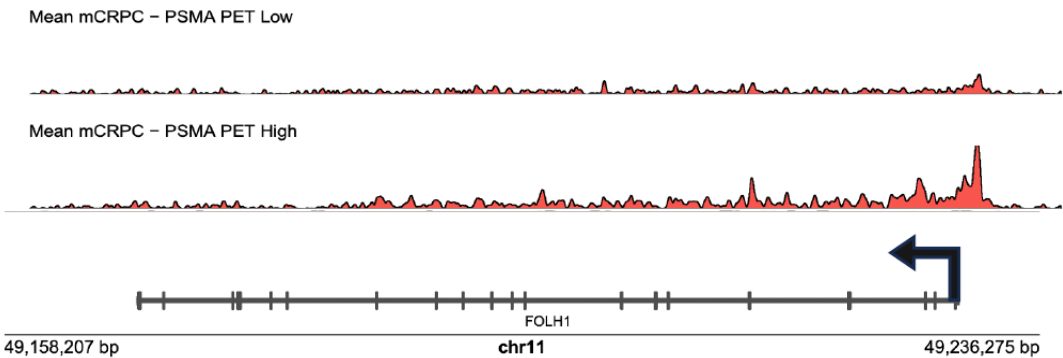
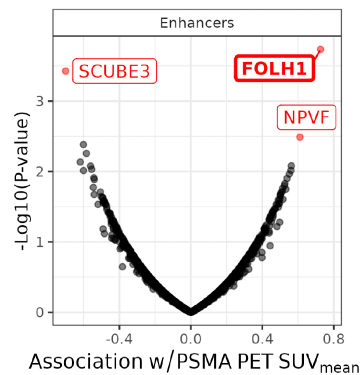
Determination of tumor PSMA expression and predicting Pluvicto response in mCRPC

PSMA is the target of the FDA-approved RLT Pluvicto

Precede platform identifies signature in PSMA-high expressors that correlates with PSMA-PET and predicts response to Pluvicto



Men with metastatic prostate cancer who underwent PSMA PET scan



Breast Cancer

ER and HER2 classification - receptor switching examples

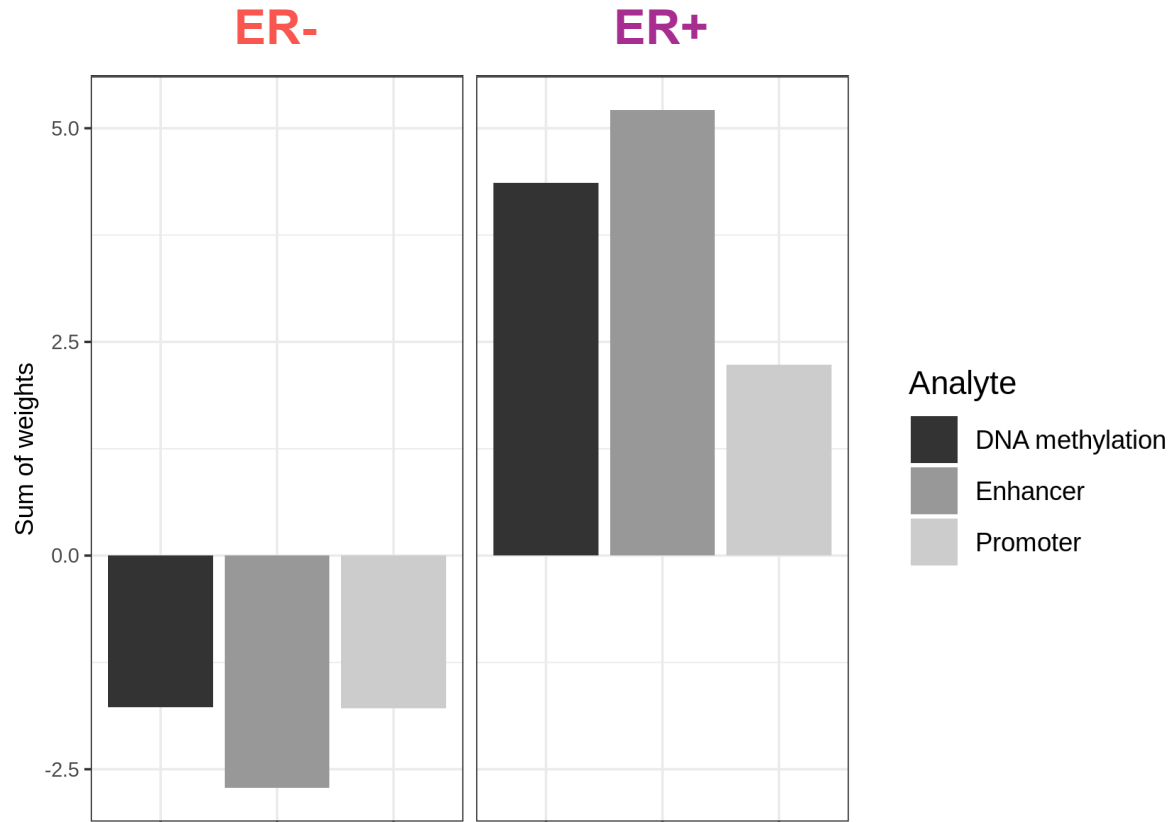
ER activation score

Breast cancer outcome predictor (coming at SABCS)

ER classifier based on chromatin regions near biologically relevant genes and multiple epigenomic features

ER classifier utilizes 116 loci genome-wide

Loci are associated with known biology



ER-

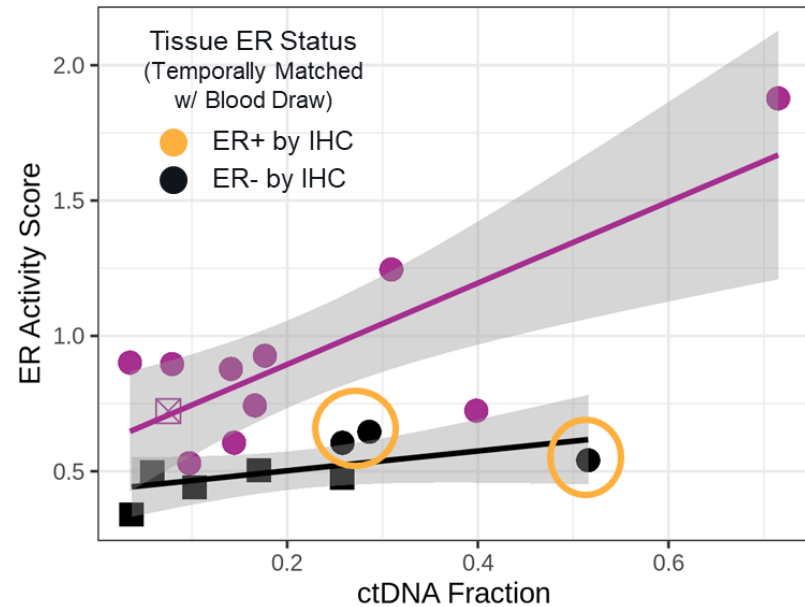
Genes associated with TNBC
e.g. RRM2, EN1, TNK2, NCOA7

ER+

Genes associated with ER signaling
e.g. ZNF703, RDH16, DCK17, PCGF2, BCAS3

Detecting ER & HER2 receptor switching: insights into tumor dynamics from LBx

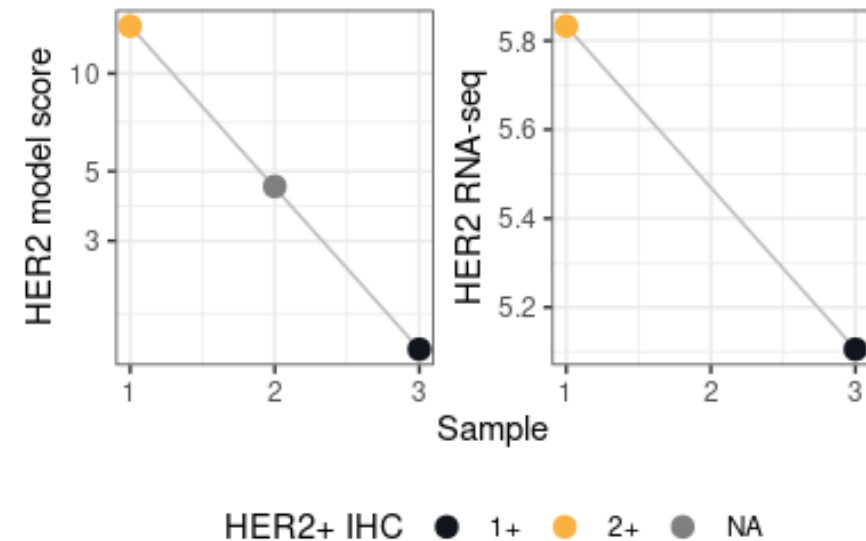
ER switching (plasma ER classifier)



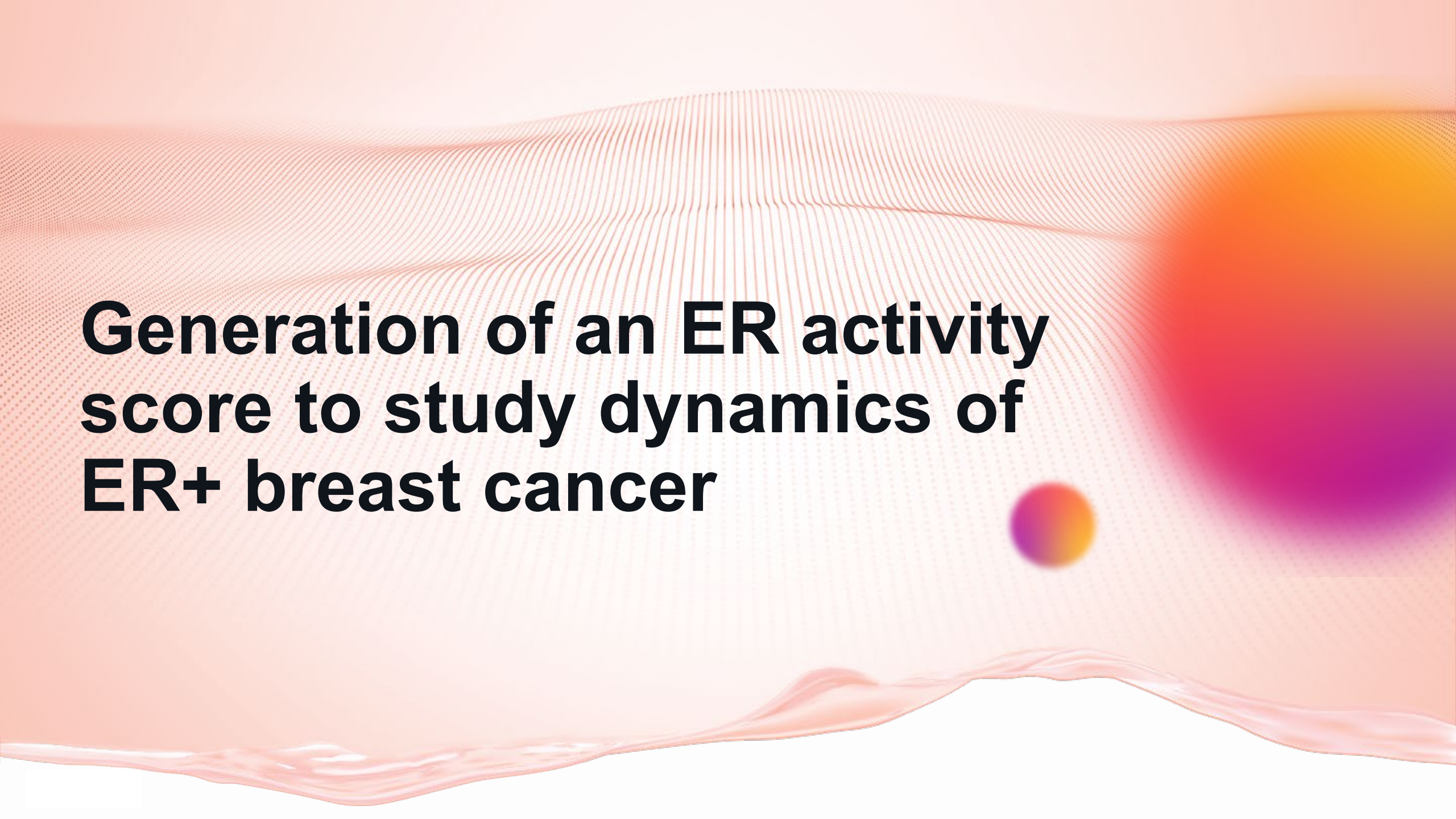
Primary ER Status: ● Positive ☒ Not Done ■ Negative

- 3 samples initially ER+
- Subsequent tissue Bx confirmed ER-
- Temporally matched LBx confirmed ER-

HER2 switching (plasma HER2 classifier)

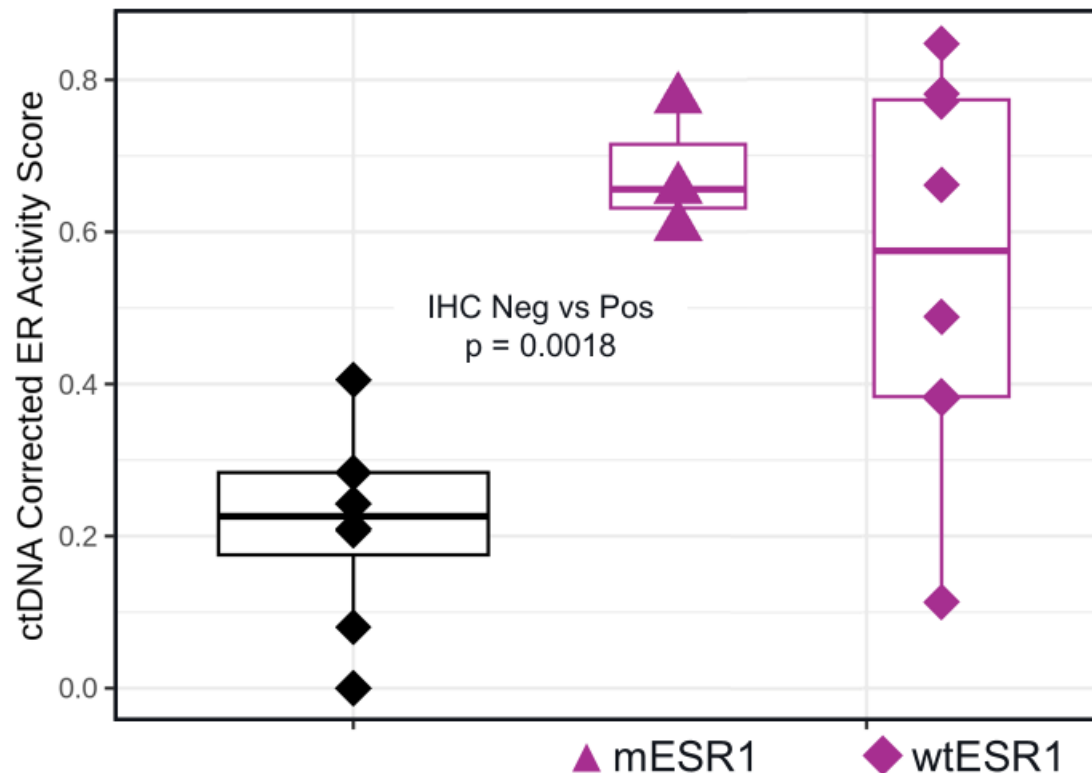


- 3 longitudinal samples from 1 patient
 - Time point 1 = HER2 2+ (IHC)
 - Time point 3 = HER2 1+ (IHC)
- HER2 plasma-classifier and matched tissue RNAseq indicate a **decreasing HER2 signal**, reflecting receptor switching



Generation of an ER activity score to study dynamics of ER+ breast cancer

ER activity score tracks with ESR1 mutation status



- ER activity score segregates ER positive from negative samples
- mESR1 patients display consistently higher scores than the wider range of wtESR1 patients.

ER- by IHC

ER+ by IHC

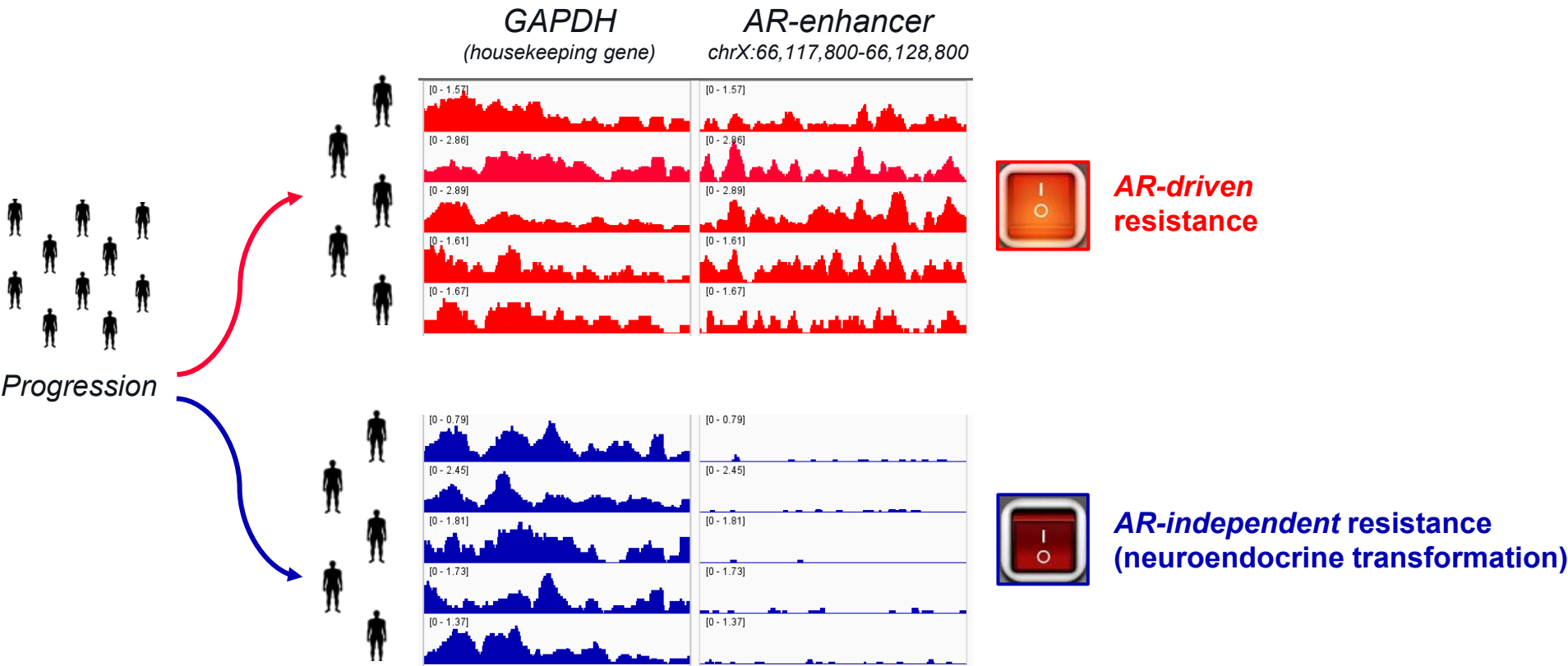
Tissue & plasma temporally matched



Monitoring and discovering resistance mechanisms

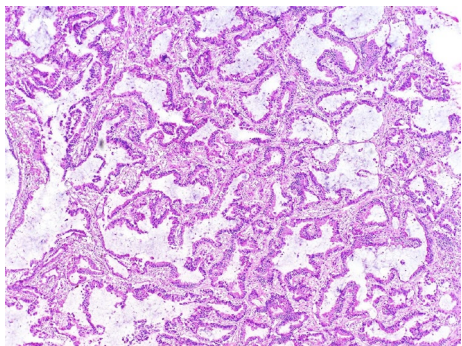
Detection of enhancer-driven resistance in prostate cancer plasma

Activation of *AR* enhancer in plasma of patients with AR-dependent resistance

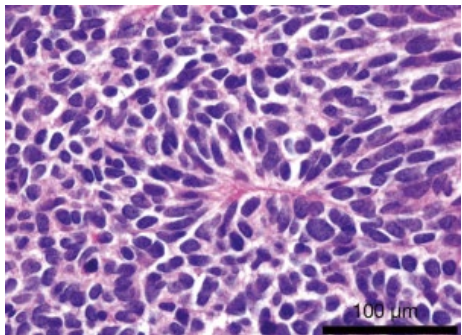


Plasma epigenomic profiling to detect histologic transformation from *EGFR* mutant lung adenocarcinoma to small cell lung cancer

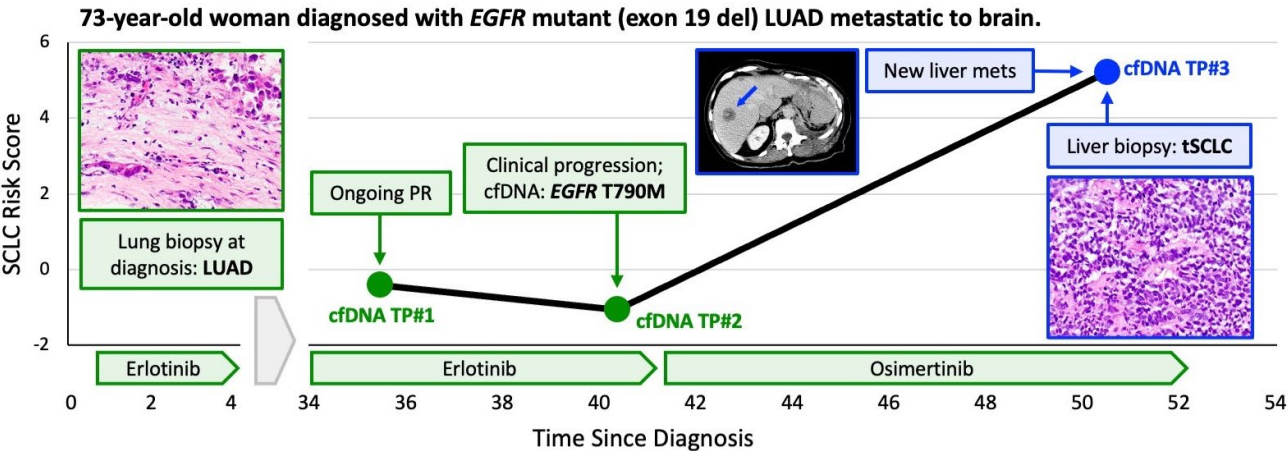
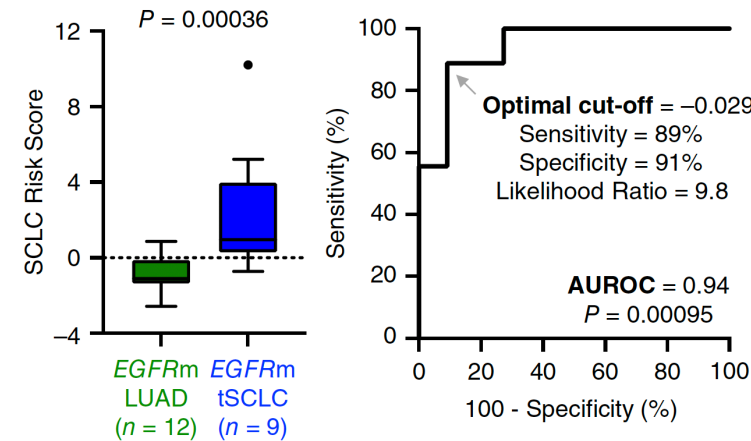
EGFR mutant lung adenocarcinoma



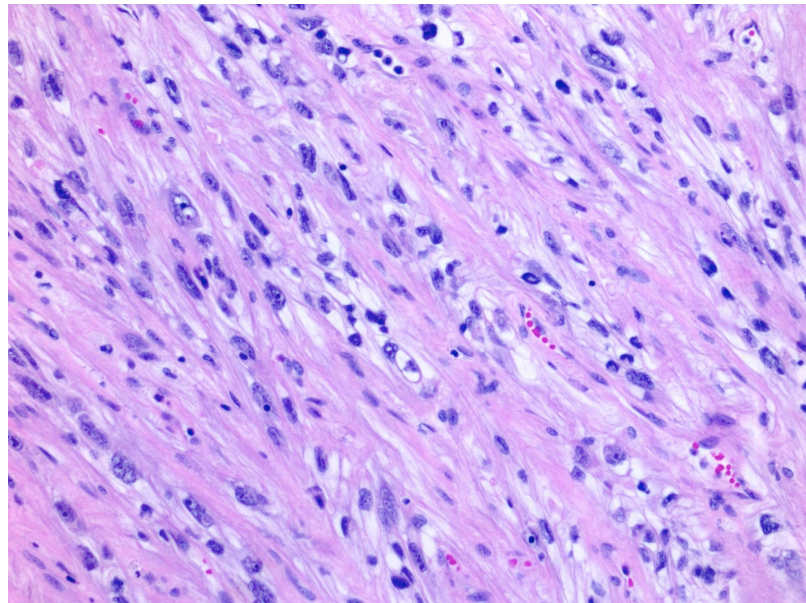
Small cell lung cancer



Integrated plasma epigenomic-based classifier to detect transformation¹



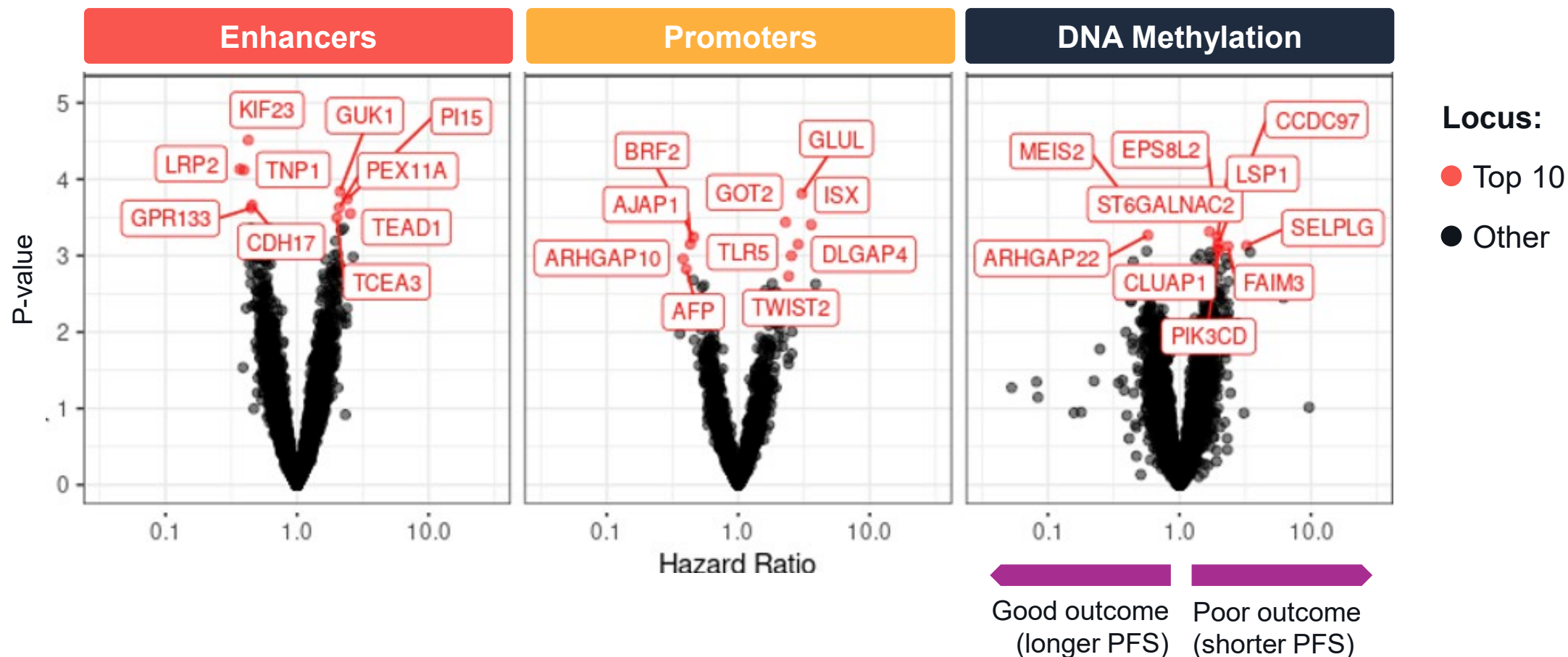
EMT phenotype observed with sarcomatoid differentiation of RCC



- Aggressive
- Associated with EMT-like changes in gene expression
- Poor response to VEGF TKI
- High response to immunotherapy
- Pathologic diagnosis is complicated by spatial heterogeneity

ADC resistance: Epigenome-wide analysis of features that predict PFS better than baseline ctDNA

Enrichment of EMT features associated with poor outcome (shorter PFS)



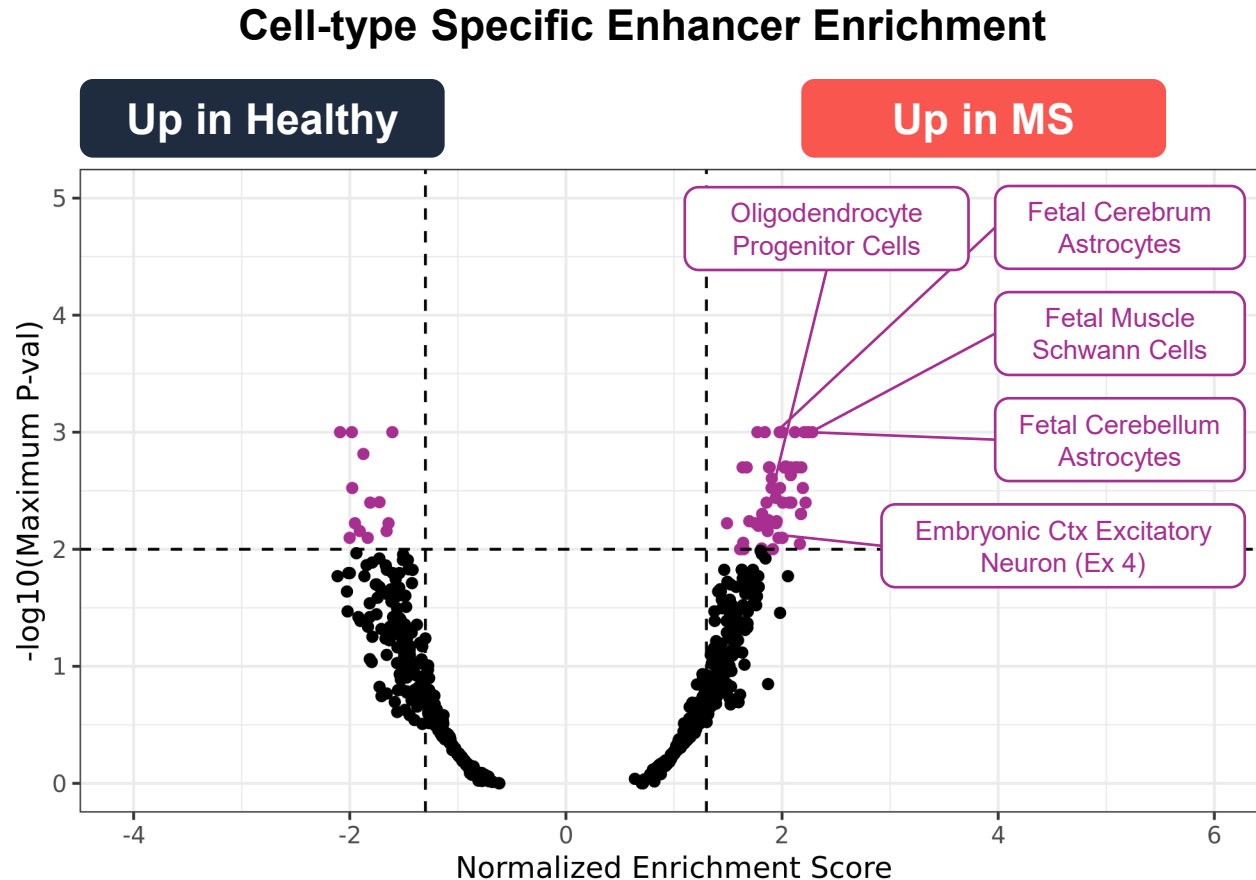
Top 10 features for each analyte/arm are annotated with their closest gene (TSS).
HR > 1, poor prognosis and lower PFS; HR < 1 better prognosis and higher PFS

Non-oncology applications of epigenomic profiling by liquid biopsy:

Multiple Sclerosis

Blood based measures correlates with imaging

MS-enriched enhancer signal is associated with neural cell types



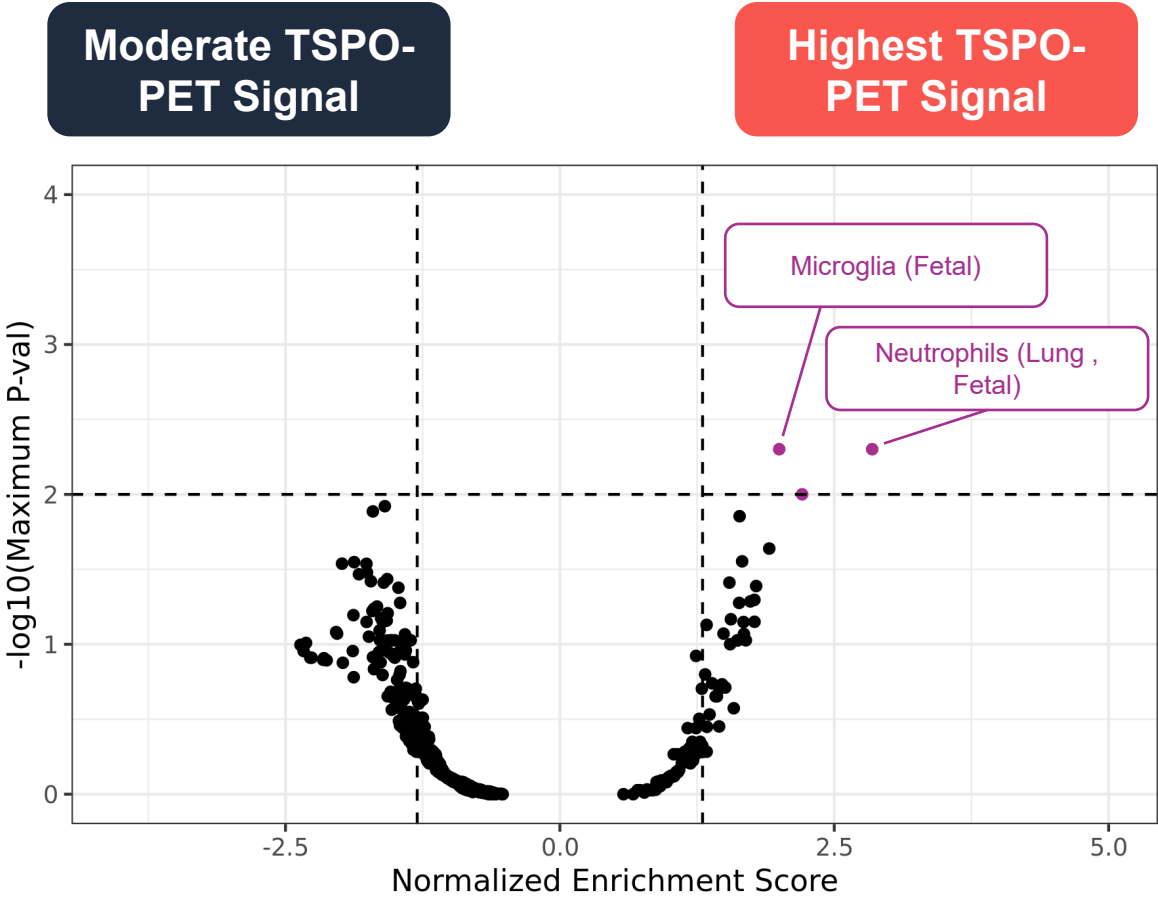
Enriched *cell types* likely indicating preferential cell damage/death

Enriched MS biological processes:

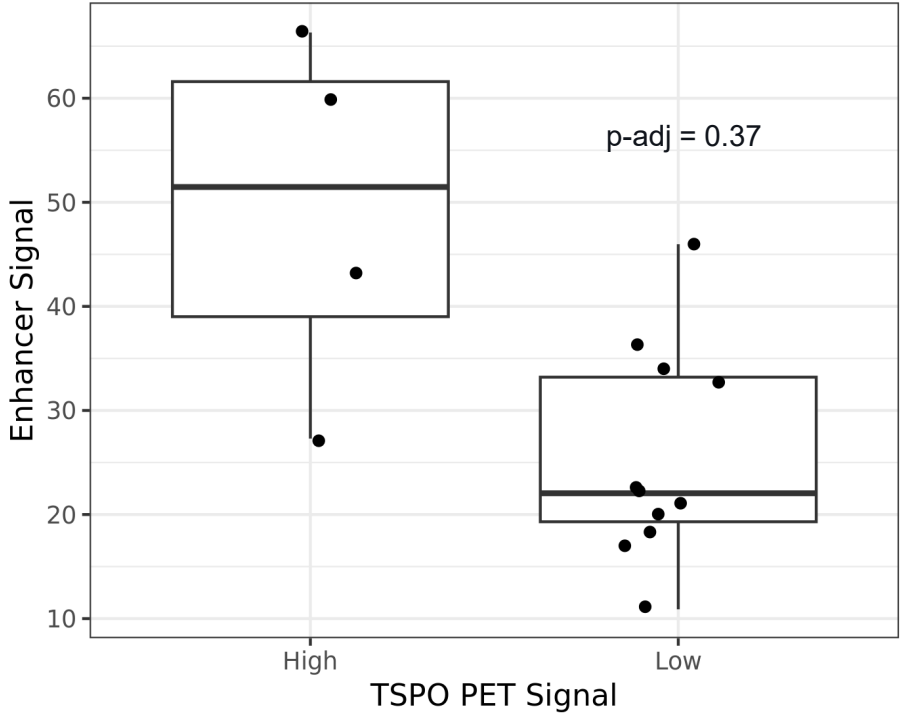
- Oligodendrocyte differentiation
- Neurogenesis
- Spinal Cord Development
- Neuron Projection Development
- Glial Cell Differentiation
- + non neural pathways

Genome-wide enrichment reveals increased microglial enhancer signature in high PET samples

Cell-type Specific Enhancer Enrichment

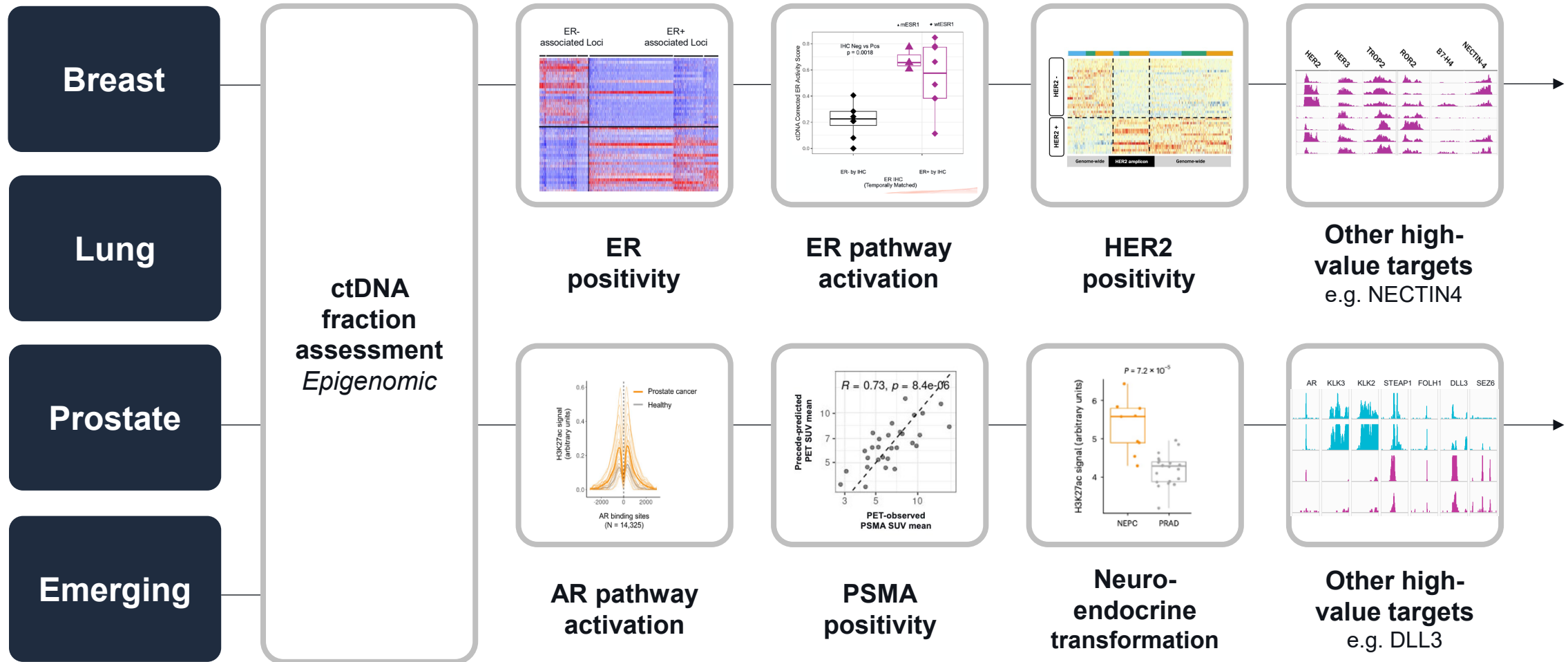


MAP4K4, Microglial Marker



TSPO-PET imaging using [¹¹C]PK11195- ligand and blood sampling were conducted concurrently.

Precede resolves disease biology and plasticity and enables tests to inform drug development and treatment from 1mL plasma



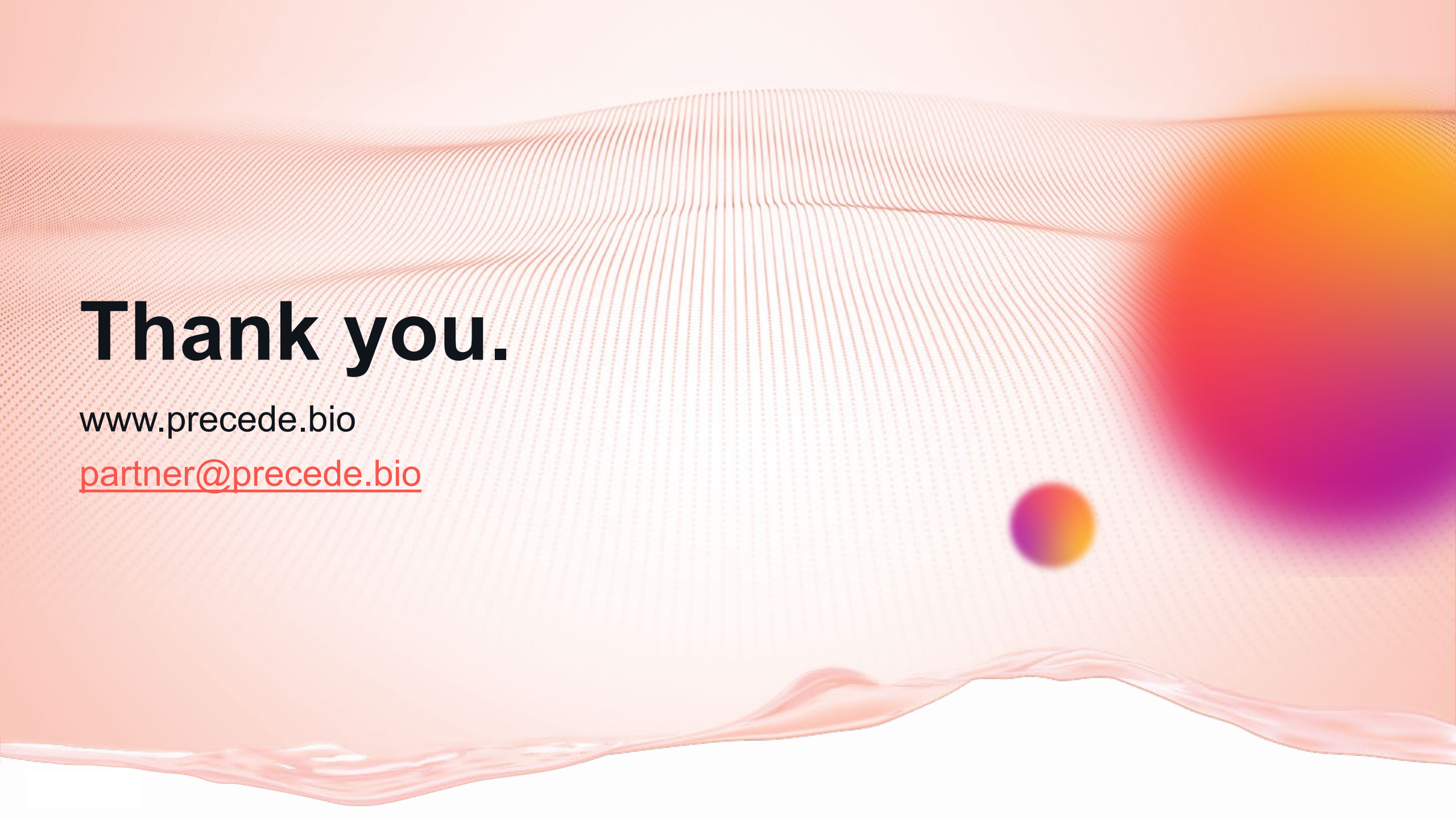
Acknowledgements

Precede team

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Toni Choueiri
Sylvan Baca
Rehan Verjee
Heather Parsons
Ana Garrido-Castro
Jacob Berchuck
Donald McDonnell
Samuel Klempner
Gordon Mills

The background features a series of thin, wavy, reddish-pink lines that create a sense of depth and movement. On the right side, there is a large, out-of-focus sphere with a gradient from orange to purple. A smaller, similar sphere is visible in the lower right quadrant.

Thank you.

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partner@precede.bio