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Clinical subtyping of cancer from plasma based on comprehensive epigenomic profiling

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Speaker: Sylvan C. Baca, M.D., Ph.D.

Dana-Farber Cancer Institute, Boston, USA

DECLARATION OF INTERESTS

Stock / consulting fees:

- Precede Biosciences

Research funding:

- US Department of Defense
- American Society of Clinical Oncology
- Damon Runyon Cancer Research Foundation
- Fund for Innovation in Cancer Informatics
- American Society of Clinical Investigation
- PhRMA Foundation

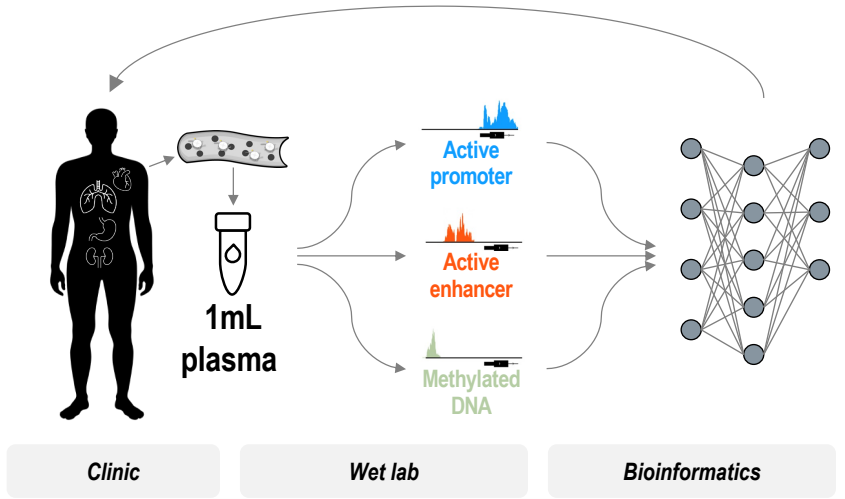
Industry collaboration:

- Defiant Technologies
- BMS

New liquid biopsy technologies could advance cancer care

- Liquid biopsies address issues of biopsy morbidity, tissue insufficiency, and inter-tumoral heterogeneity
- Current assays focus mainly on somatic genomic alterations
- **Epigenomic re-programming of gene regulation** is a hallmark of cancer[1]
- Blood-based measurements of **gene regulation** could aid **clinical diagnoses, therapeutic decision-making,** and **drug development**

We developed a **plasma-based epigenomic assay** that measures **dynamic gene regulation**

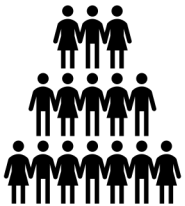


1) Hanahan et al., *Cancer Discovery* 2022

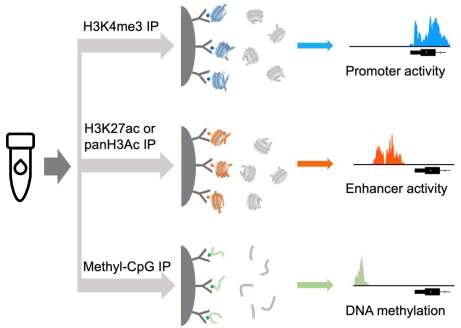
Methods

- 1,268 plasma-based epigenomic profiles from 1mL of plasma
  - 433 individuals
  - 15 advanced cancers including breast, colorectal, lung, and prostate
  - Active enhancers, active promoters, and DNA methylation

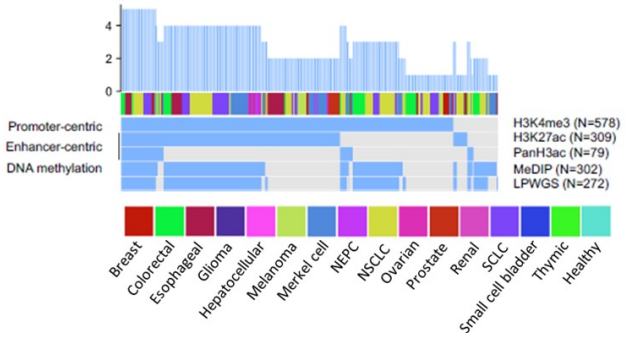
433 individuals



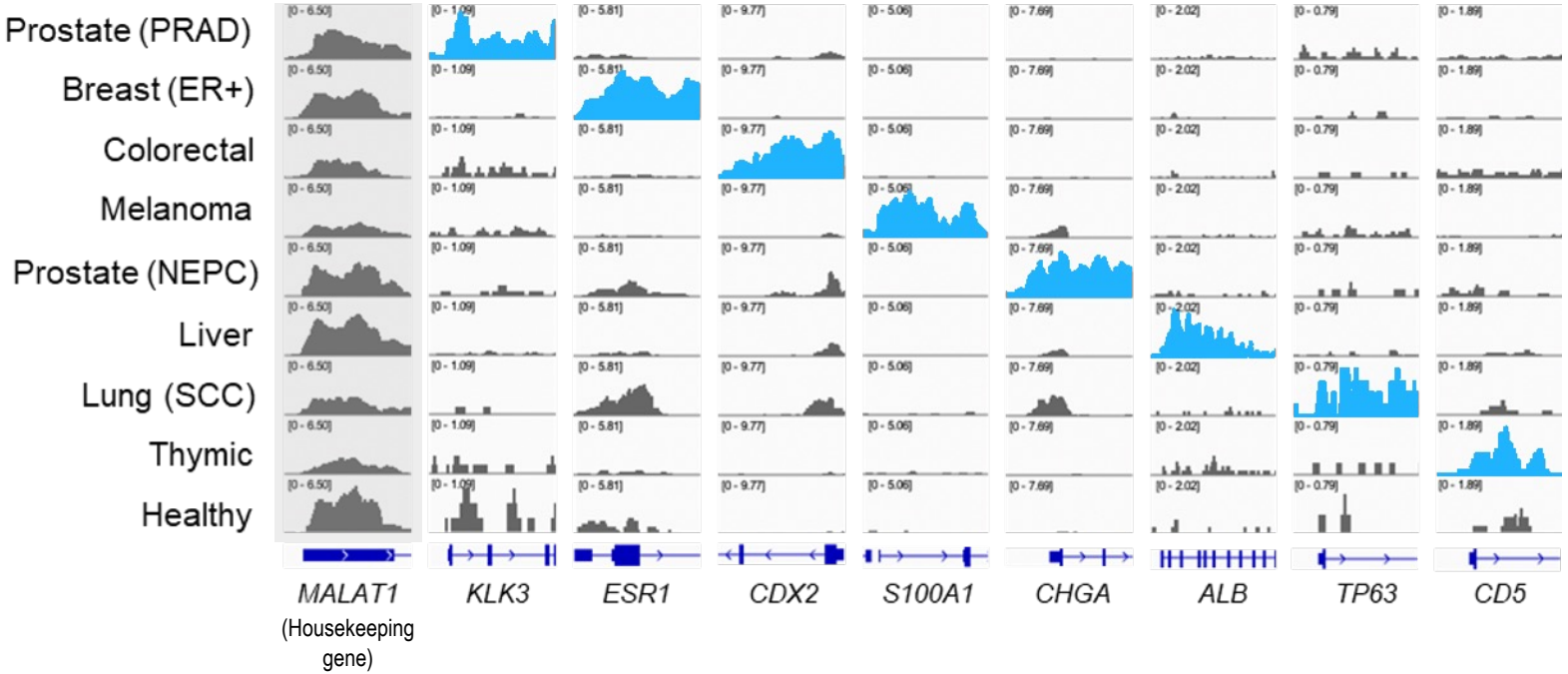
1mL of plasma



1,268 plasma-based epigenomic profiles

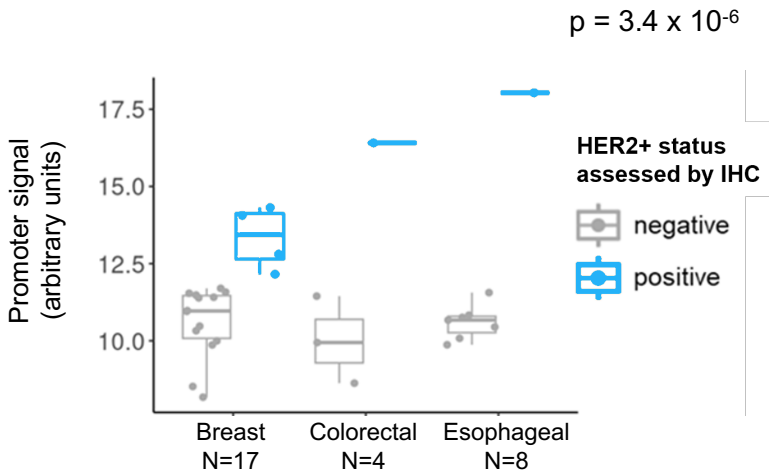


Plasma Promoter profiling captures tissue-specific diagnostic markers



Plasma Promoter profiling identifies patients with therapeutically targetable HER2+ cancer

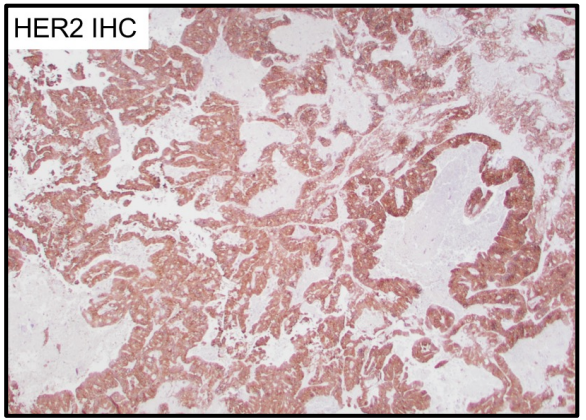
Promoter signal at *ERBB2*



HER2-	HER2+
23	6

48F with metastatic colorectal cancer

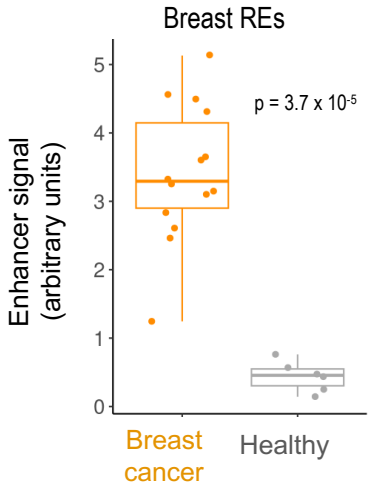
- Detected elevated *ERBB2* promoter signal in plasma
- HER2 expression **subsequently** confirmed by IHC on biopsied tissue from liver and brain metastases



Enhancer profiling measures activity of cancer regulatory elements and targetable transcription factors

- Enhancers are regulatory elements that are often highly specific to a cell type or state[1]
- Genome-wide, there are ~1M enhancers *vs.* ~20k promoters
- An *in vivo* functional readout of enhancers provides a deep, feature-rich space

Plasma enhancer signal at cancer regulatory elements (REs) defined from TCGA[1]



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1. Corces *et al.*, Science 2018

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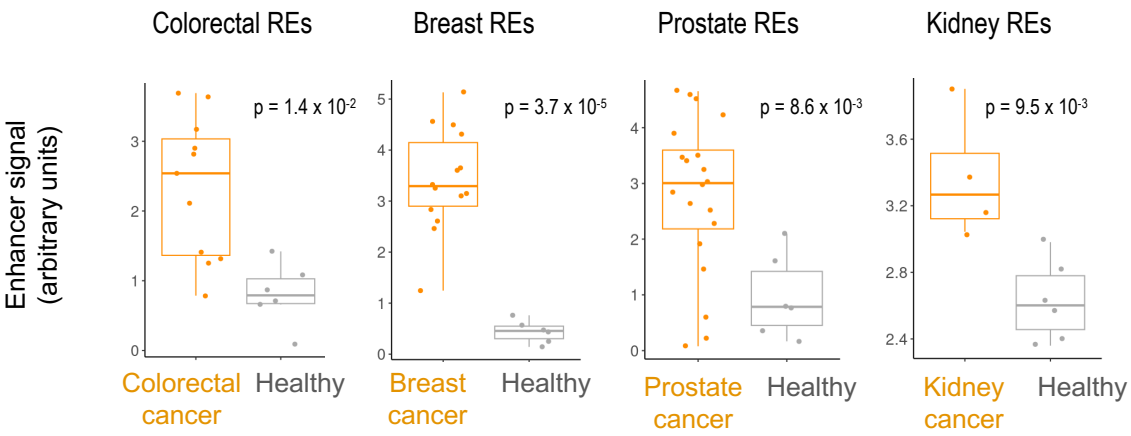

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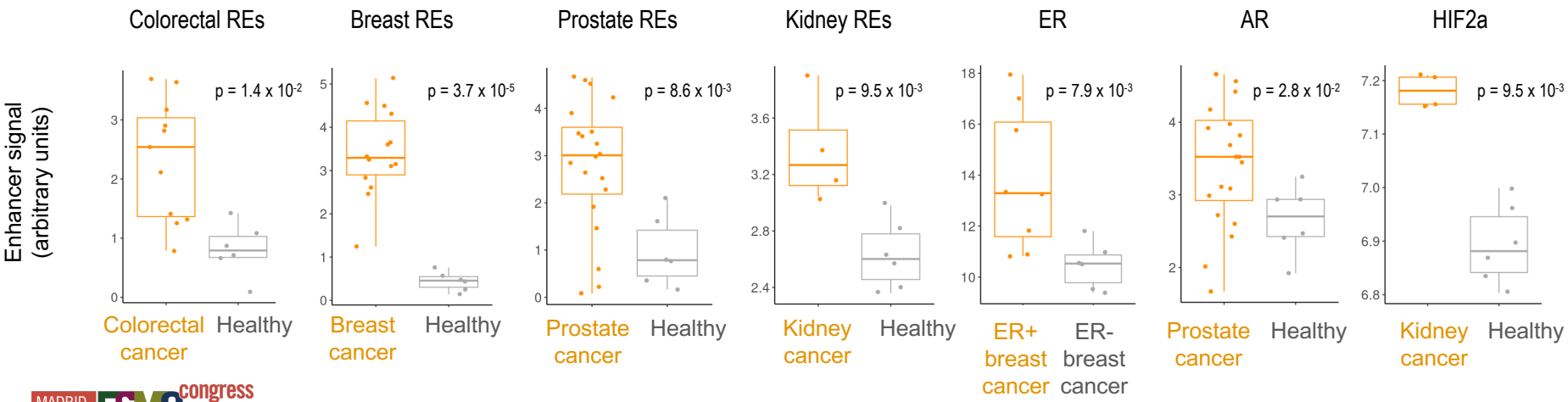
Therapeutically targetable transcription factors



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1. Corces *et al.*, Science 2018

Plasma detection of Enhancer-driven resistance in prostate cancer

Activation of AR enhancer drives treatment-resistant CRPC[1,2]

Article

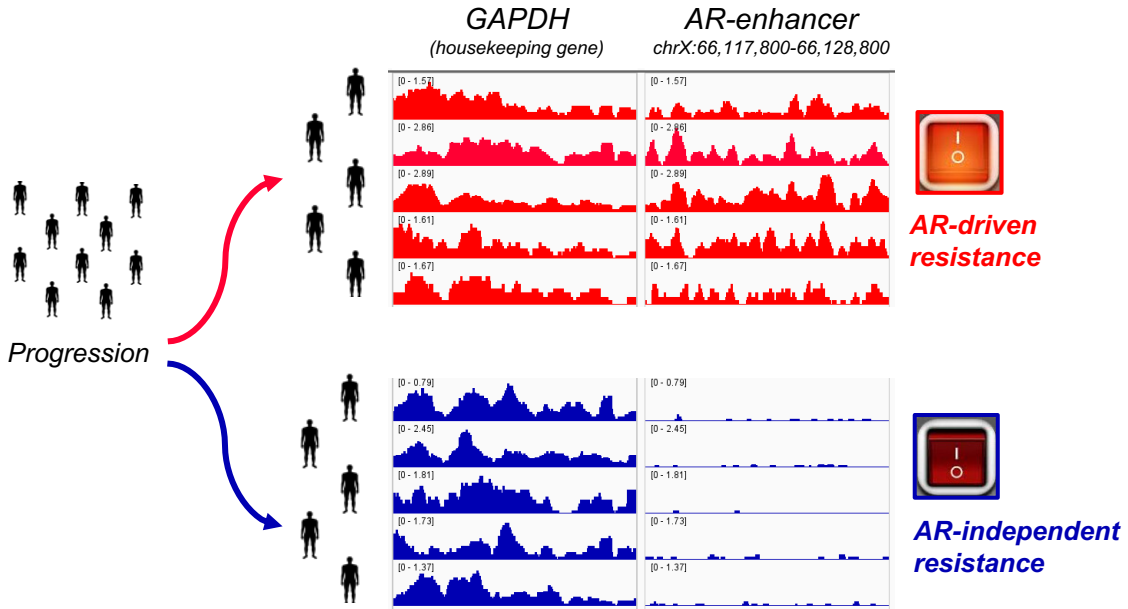
Cell

A Somatically Acquired Enhancer of the Androgen Receptor Is a Noncoding Driver in Advanced Prostate Cancer

David Y. Takeda,[1,2,13] Sándor Spisák,[1,3,13] Ji-Heui Seo,[1,3] Connor Bell,[1] Edward O'Connor,[1] Keegan Korthauer,[4,5] Dezső Ribli,[6] István Csabai,[6] Norbert Solymosi,[7] Zoltán Szállási,[8,9,10] David R. Stillman,[1] Paloma Cejas,[3] Xintao Qiu,[3] Henry W. Long,[1,3] Viktória Tisza,[1,8] Pier Vitale Nuzzo,[1,11] Mersedeh Rohanizadegan,[1,12] Mark M. Pomerantz,[1] William C. Hahn,[1,2] and Matthew L. Freedman[1,2,3,14,*]

- AR activation is not detectable by mutational profiling or DNA methylation

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



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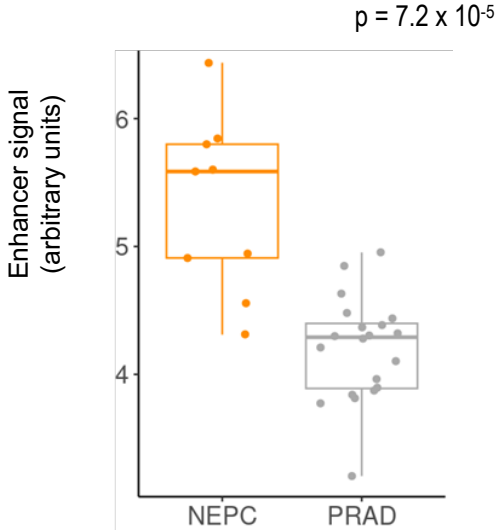
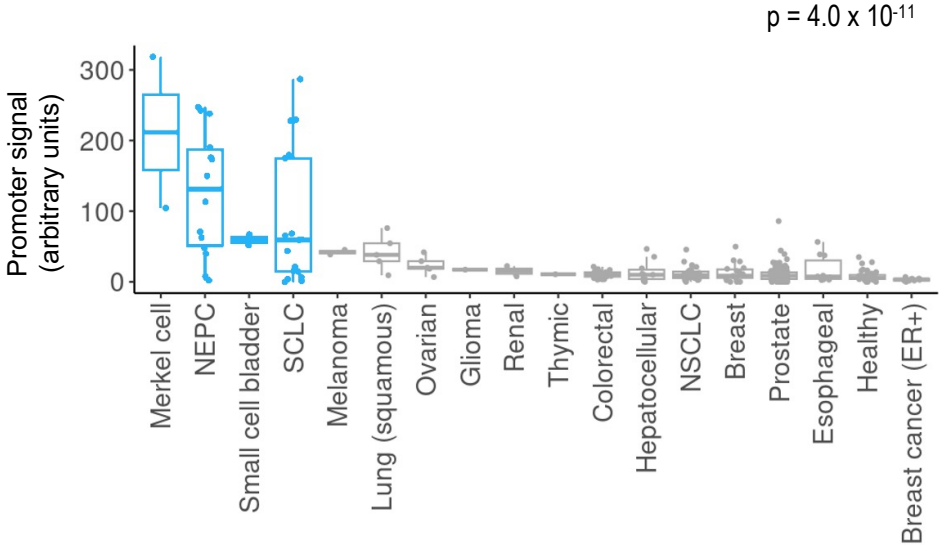
1. Takeda et al., Cell 2018
2. Image from Epstein, *Modern Pathology 2004*

Enhancer and Promoter profiling distinguish neuroendocrine cancers

Enhancer signal at master TF (*ASCL1*) binding sites

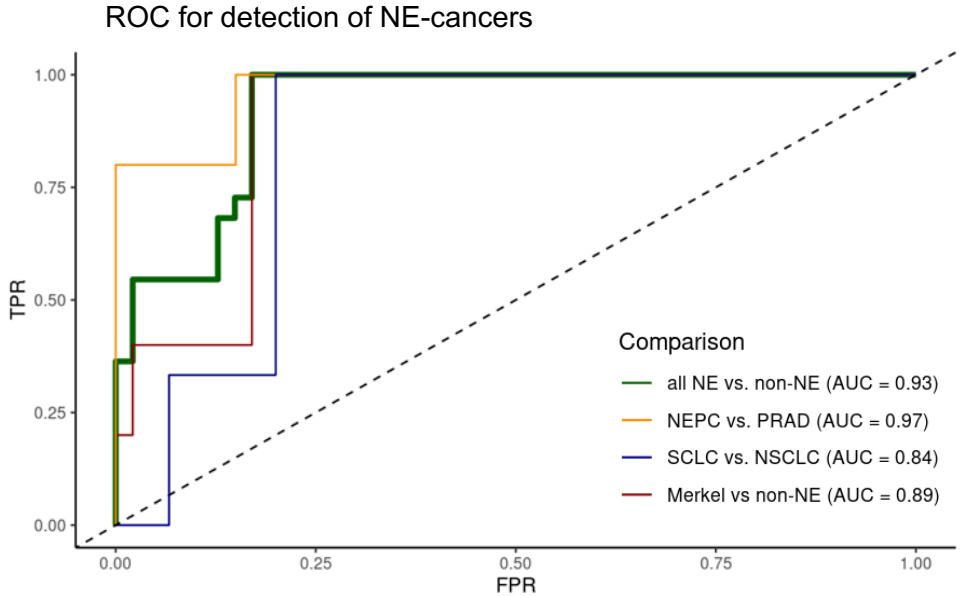


Promoter signal at *Chromogranin A*



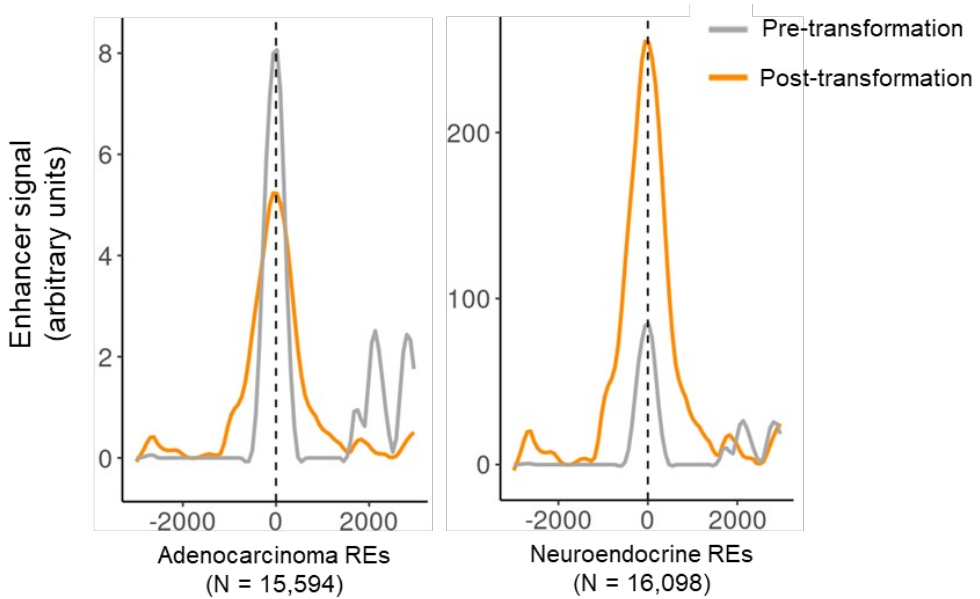
Plasma Enhancer profiling achieves robust classification of neuroendocrine cancers

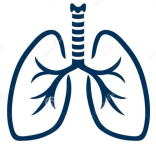
NE vs non-NE (N=70; 23 NE vs 47 non-NE)



Plasma Enhancer profiling identifies treatment-emergent SCLC in a patient with EGFRm lung adenocarcinoma

Adenocarcinoma and neuroendocrine enhancer signal pre- and post-transformation

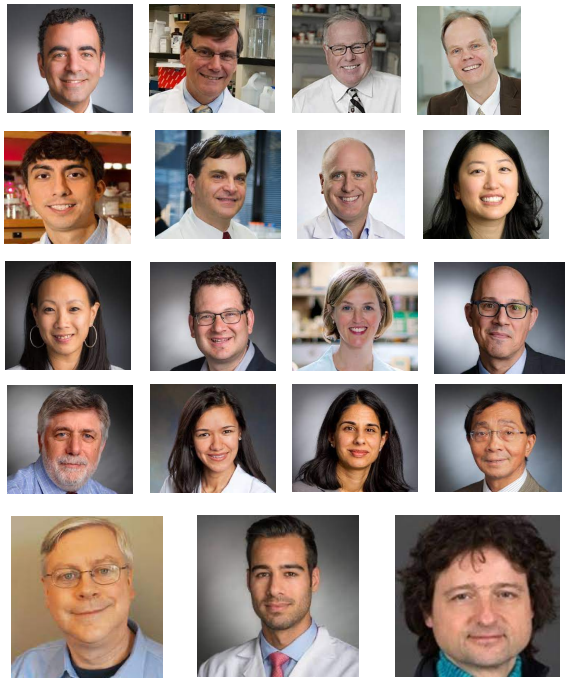




Conclusion

- We demonstrate a proof-of-concept for **comprehensive epigenomic profiling of gene regulation from plasma** to inform diagnosis, therapy selection, and resistance monitoring
- This assay provides **biological interpretability** and **longitudinal dynamic profiling**
- This method **requires only ~1mL of plasma** from standard clinical collection tubes
- Work is ongoing to further demonstrate clinical utility and discover epigenetic resistance mechanisms
- This approach is **extensible across oncology and to non-oncologic conditions**

Acknowledgements



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