

Plasma-based comprehensive epigenomic profiling enables multiplexed prediction of target gene expression and detection of resistance mechanisms

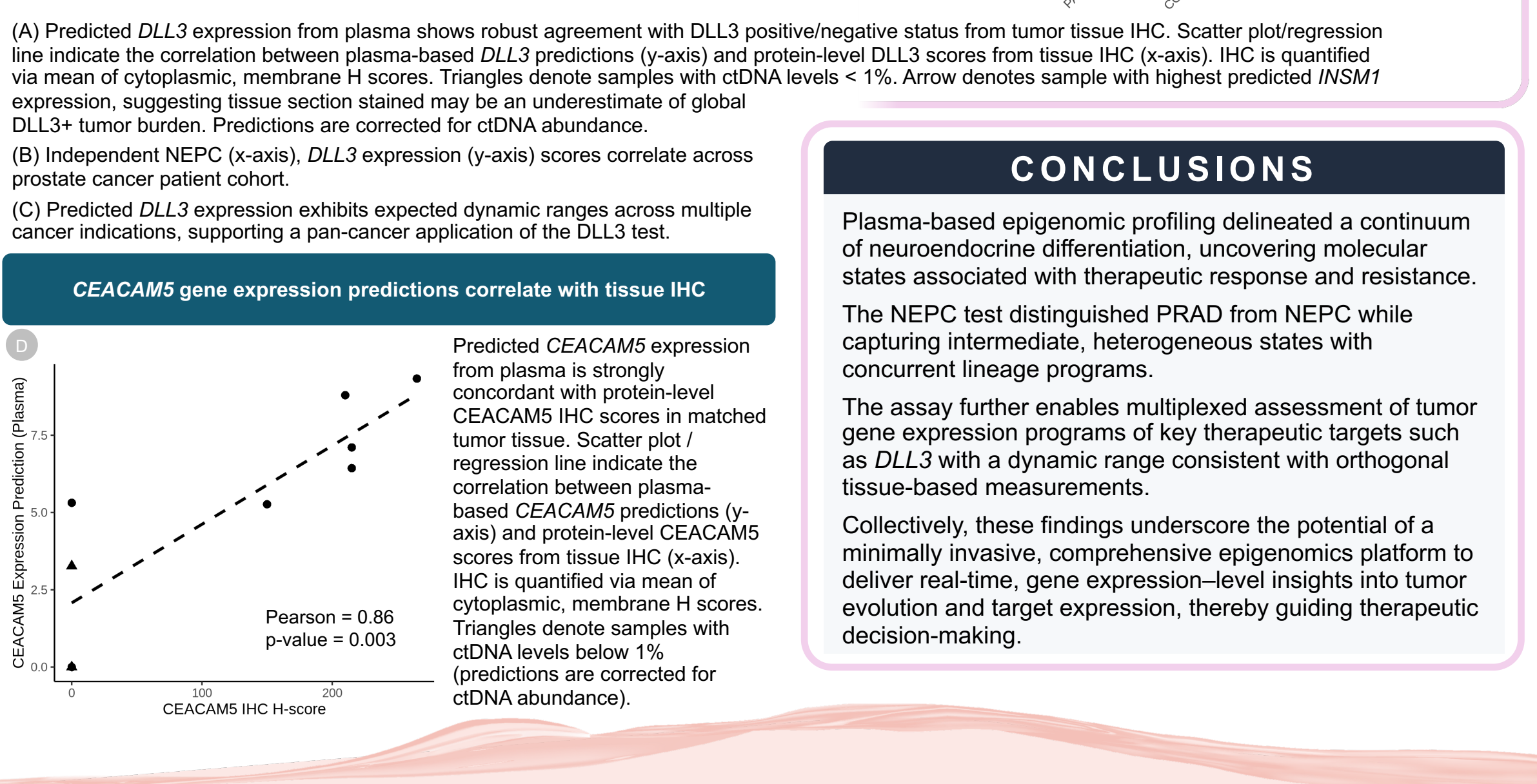
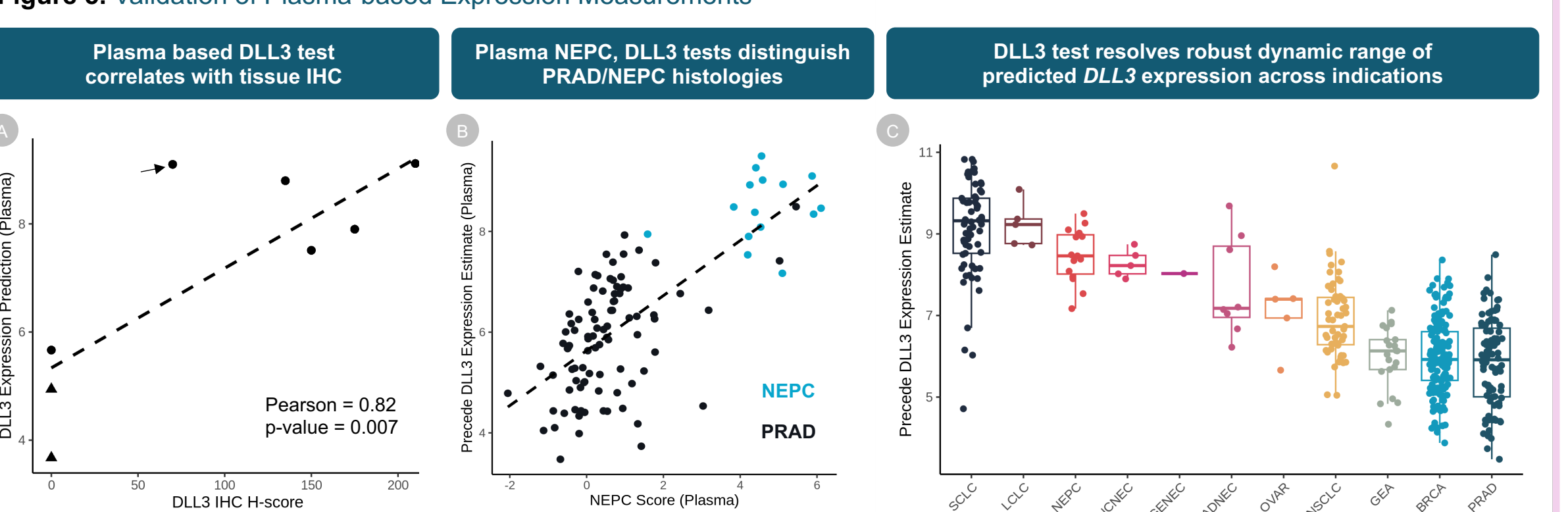
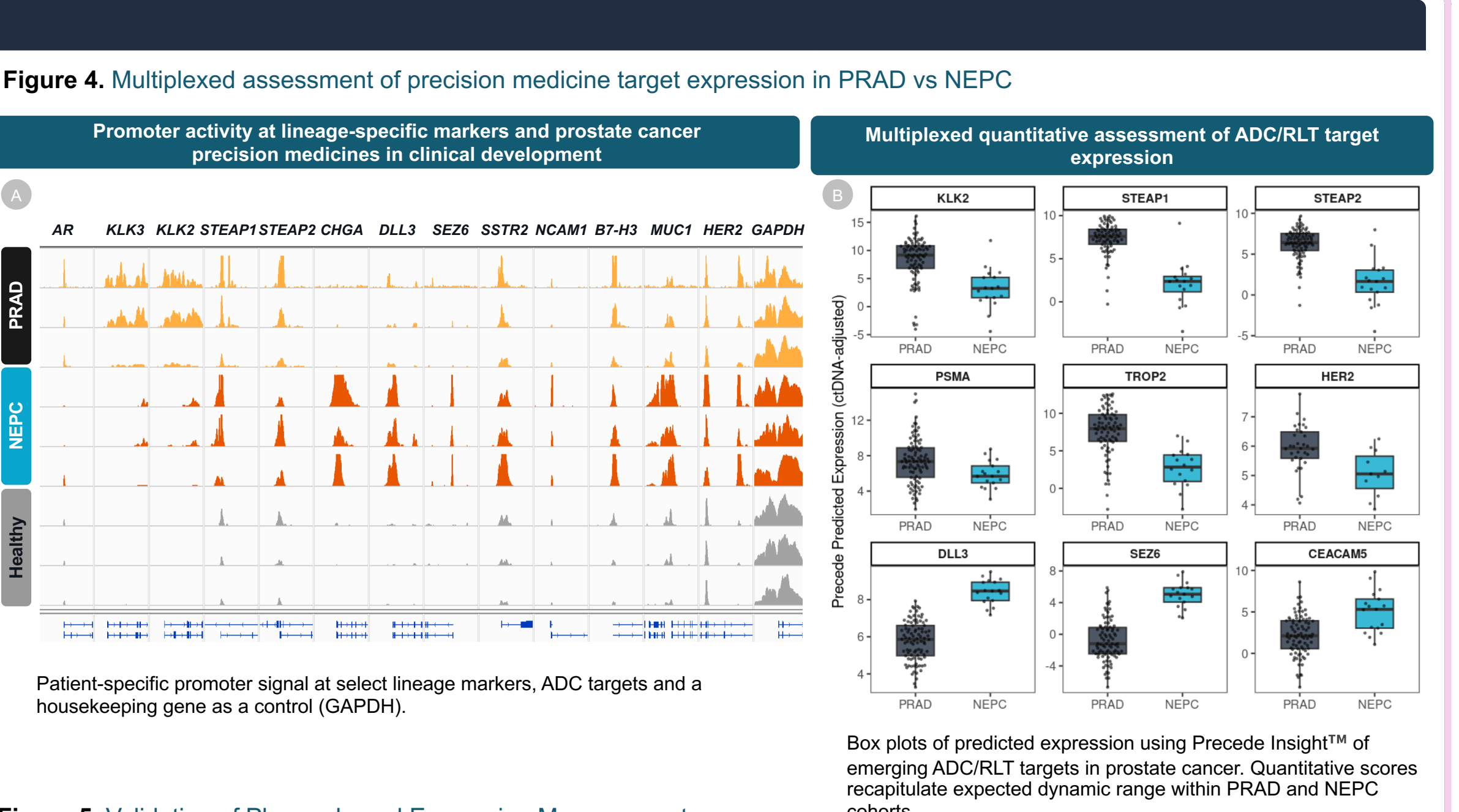
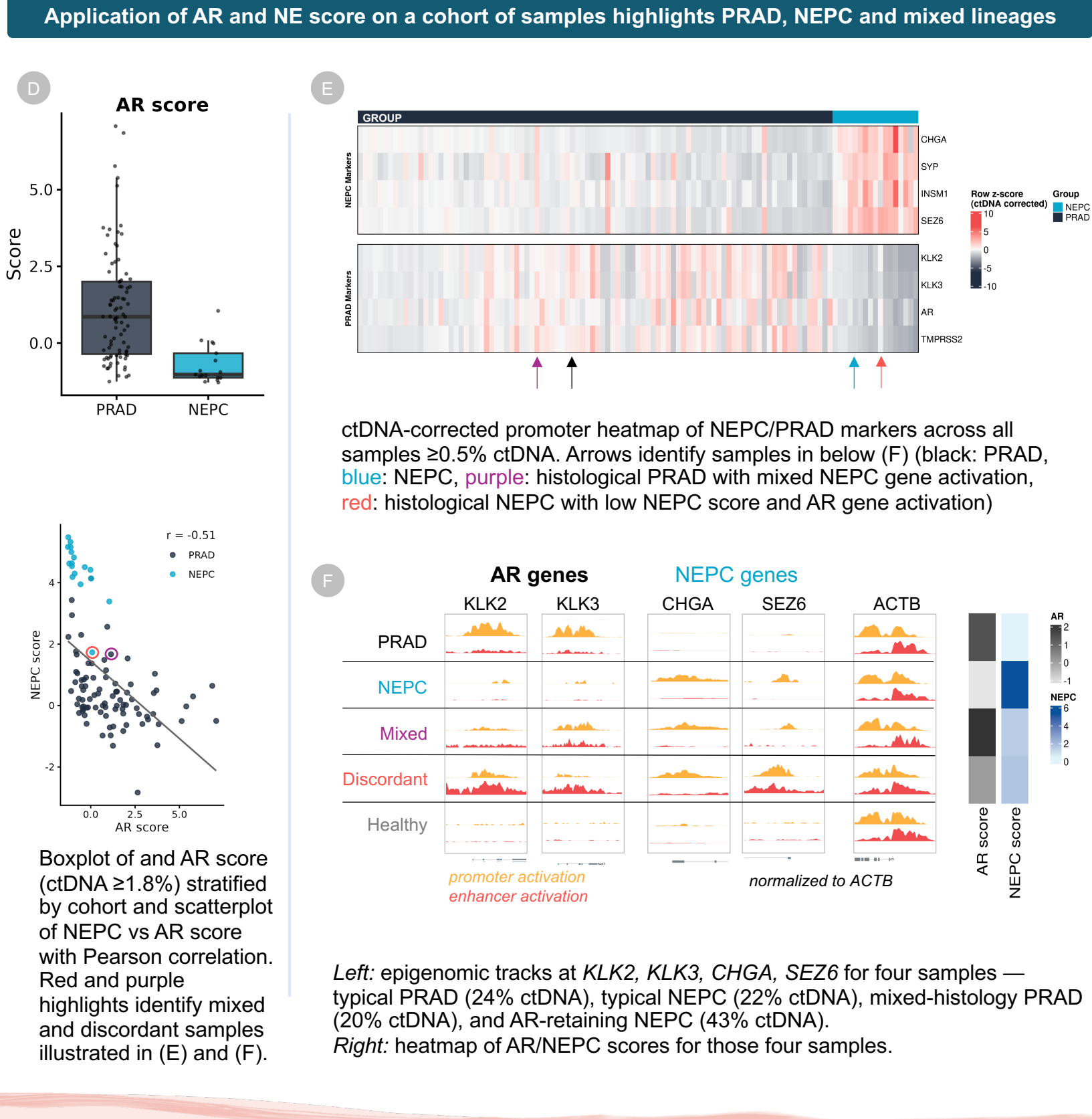
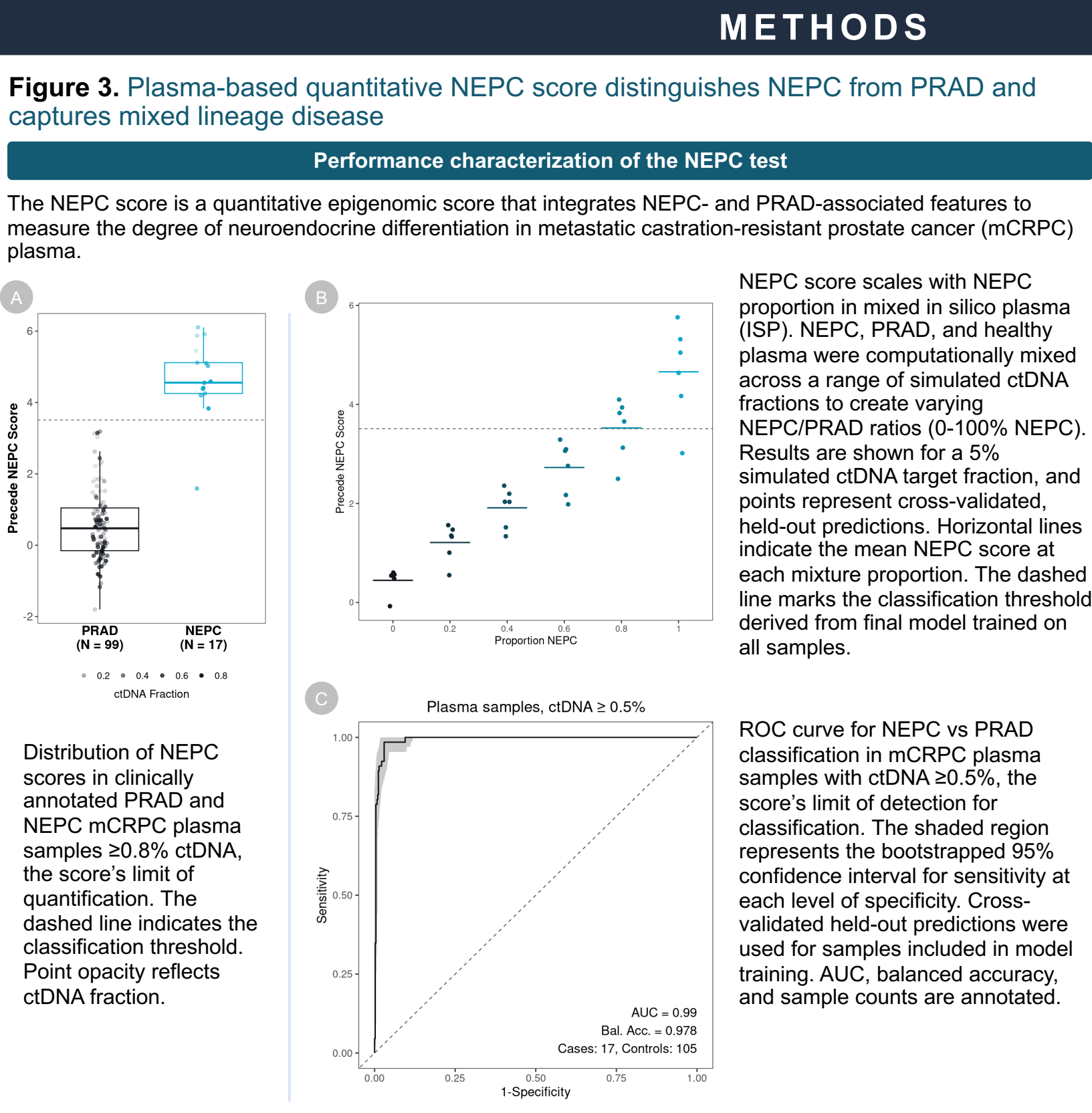
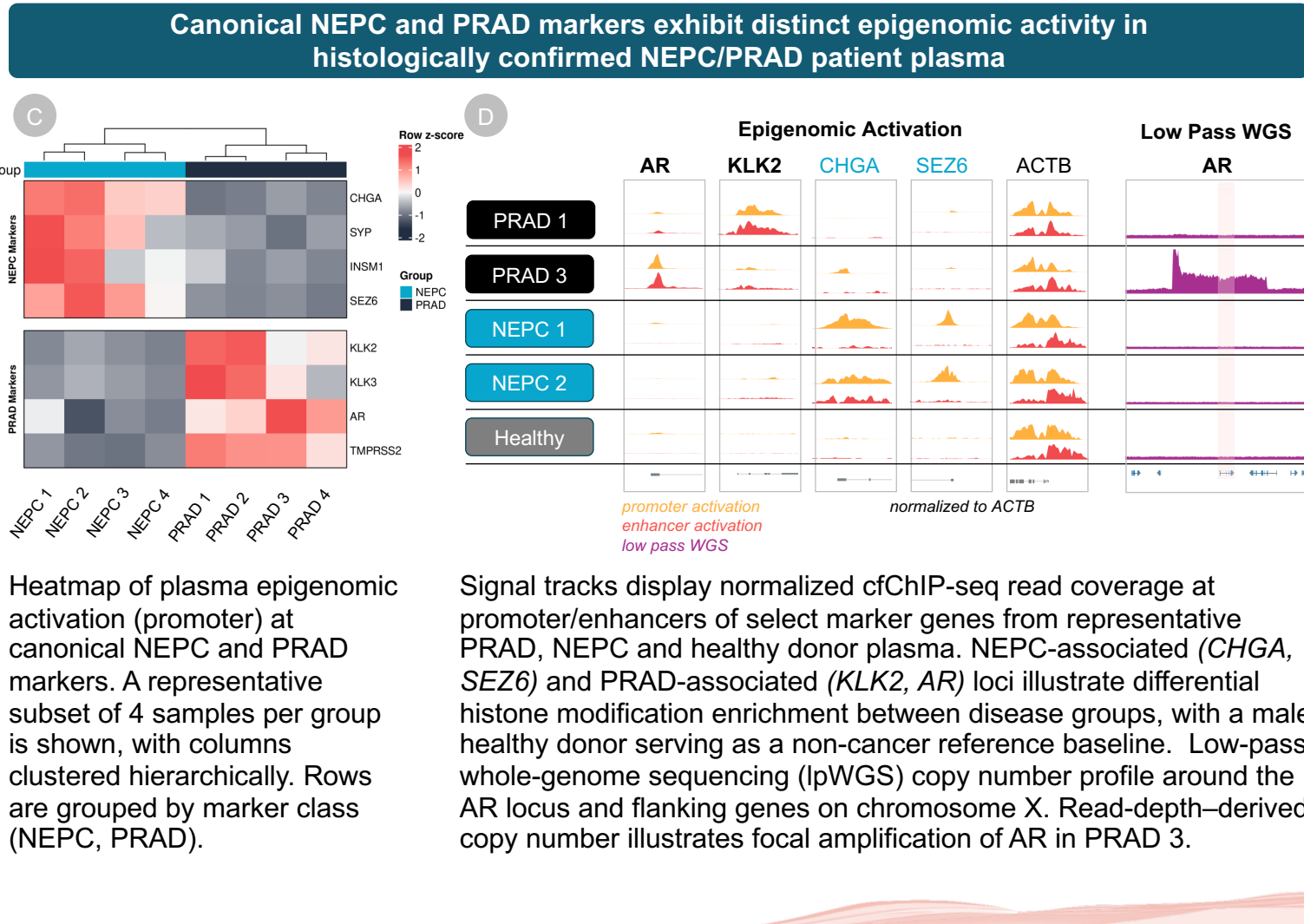
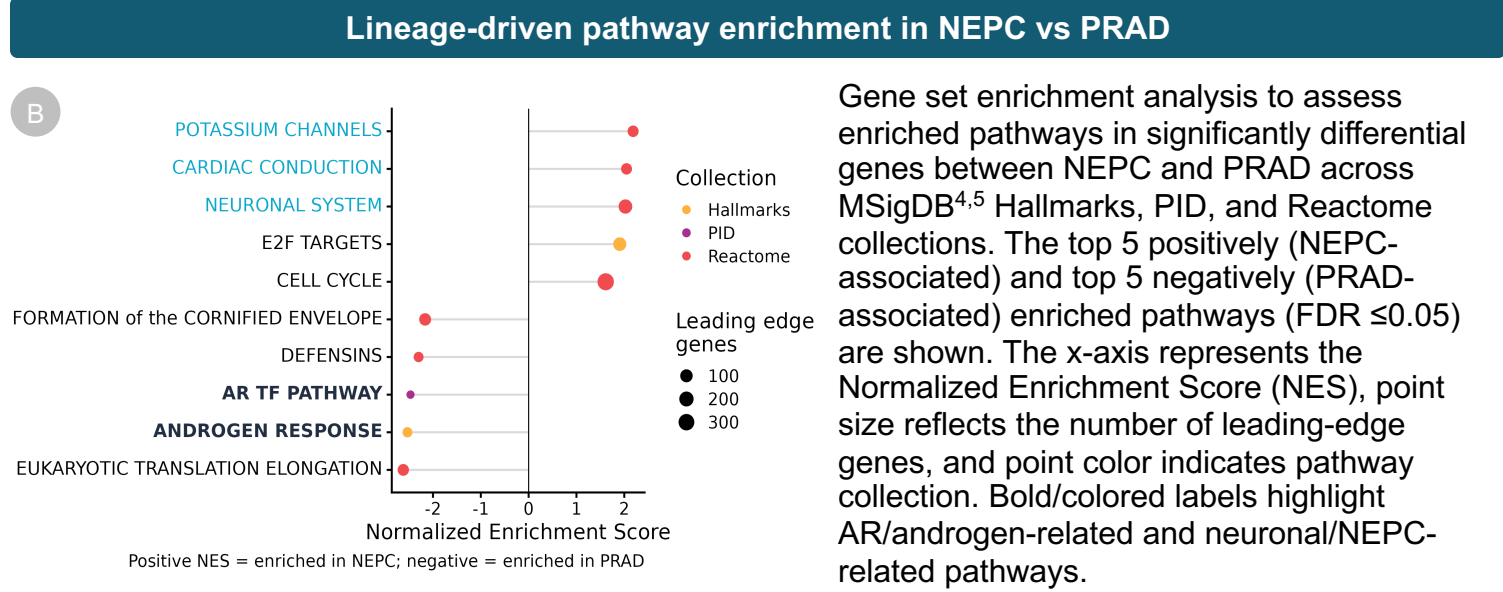
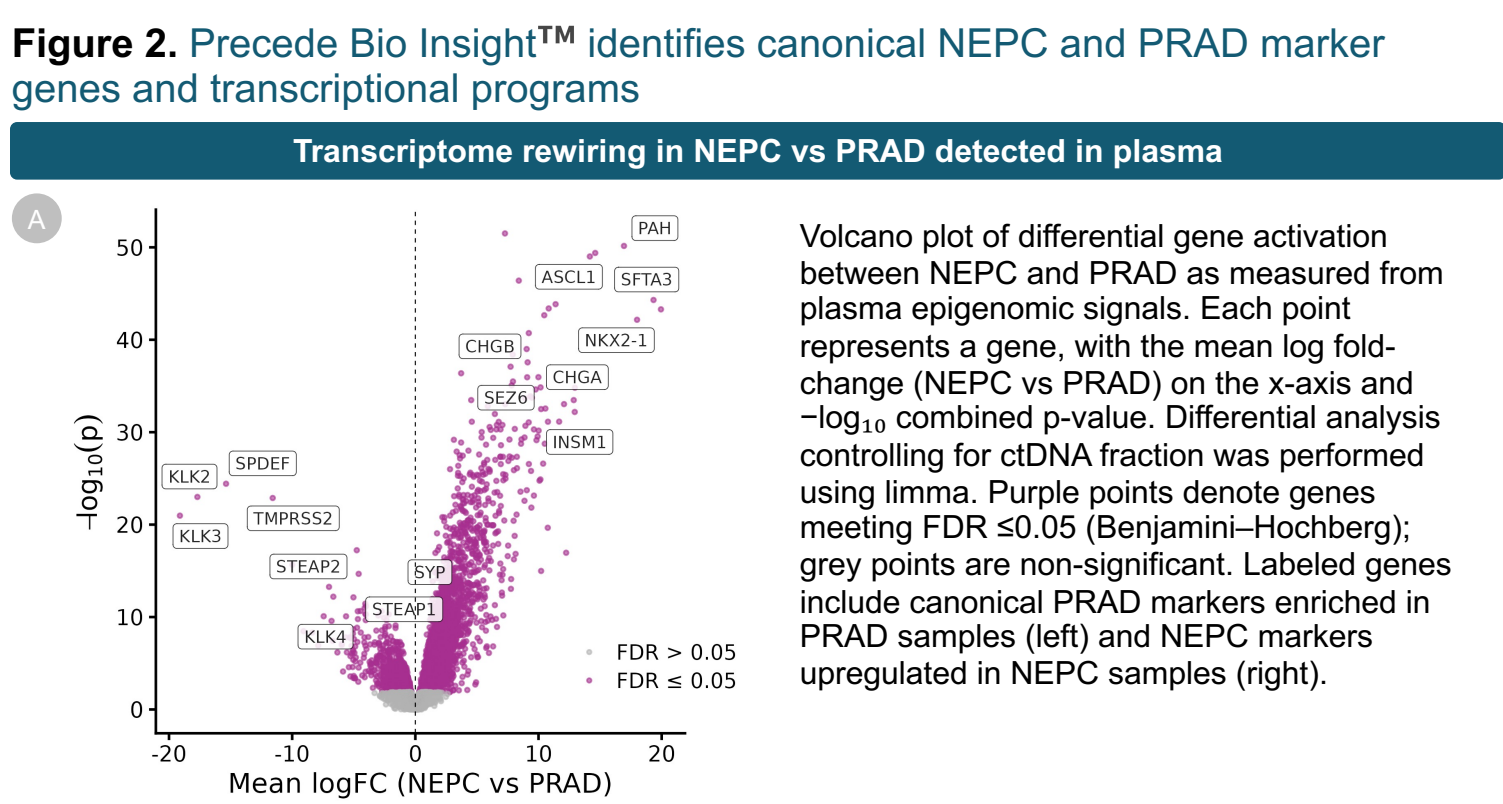
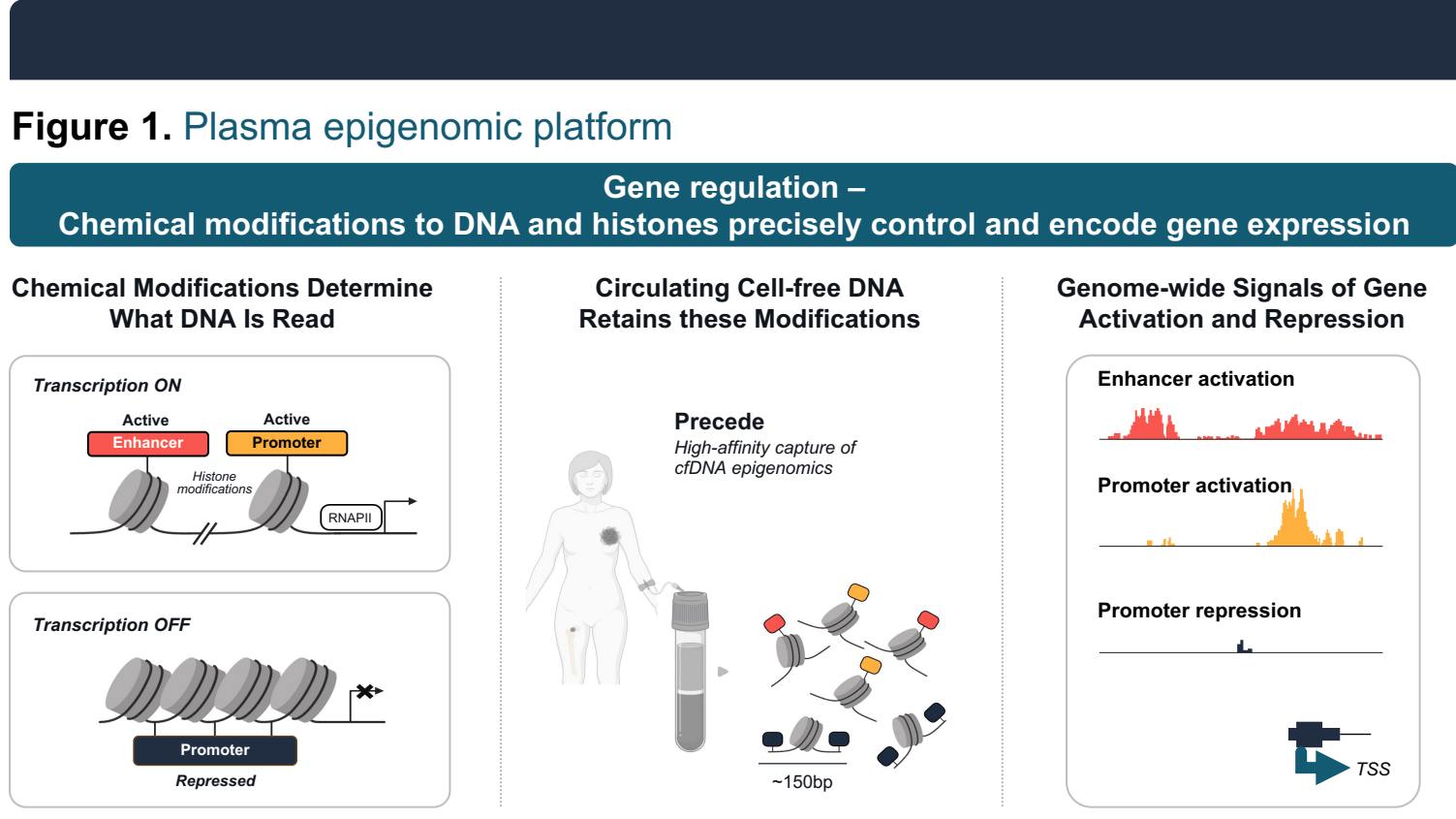
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BACKGROUND

Prostate cancer progression to metastatic castration-resistant disease (mCRPC) and treatment-emergent neuroendocrine prostate cancer (NEPC) represents a critical clinical challenge marked by lineage plasticity, therapeutic resistance, and poor prognosis. As novel targeted therapies, including drug, radio-, and immune-conjugates, advance toward broad clinical implementation, there is an urgent need for scalable, minimally invasive diagnostics capable of resolving gene expression programs to guide patient selection and therapeutic monitoring. Conventional diagnostic platforms are limited by restricted access to contemporaneous tissue, tumor heterogeneity, limited multiplexing capacity, and challenges in longitudinal profiling. To address these limitations, we applied a comprehensive epigenomics liquid biopsy¹ and machine learning platform to infer tumor gene expression, delineate lineage plasticity, and reveal therapeutically relevant molecular programs and resistance mechanisms from only 1 mL of plasma.

METHODS

1 mL of plasma from a pan-cancer cohort of patients (94 prostate adenocarcinoma [PRAD], 17 neuroendocrine prostate cancer [NEPC], 55 non-small cell lung cancer [NSCLC], 65 small cell lung cancer [SCLC], 2 large cell lung cancer [LCLC], 150 breast cancer [BRCA], 21 gastroesophageal cancer [GEA], 17 additional neuroendocrine carcinomas (8 colorectal [COADNEC], 5 pancreatic [PANCNEC], 3 lung [LCLC], 1 gastroesophageal [GENEC]), and 5 ovarian cancer [OVAR]) was profiled using Precede Biosciences liquid biopsy platform. All samples were assessed for the expression of therapeutically relevant targets using models to predict gene expression from plasma epigenomic signals^{2,3}. In prostate cancer, samples were further evaluated for the extent of neuroendocrine (NE) transformation, a key mechanism of lineage plasticity and therapeutic resistance. Immunohistochemistry (IHC) for DLL3 (Ventana SP347) and CEACAM5 (Thermo ZR370) was performed according to manufacturers' protocols and scored by a board-certified pathologist using established criteria.



CONCLUSIONS

Plasma-based epigenomic profiling delineated a continuum of neuroendocrine differentiation, uncovering molecular states associated with therapeutic response and resistance. The NEPC test distinguished PRAD from NEPC while capturing intermediate, heterogeneous states with concurrent lineage programs. The assay further enables multiplexed assessment of tumor gene expression programs of key therapeutic targets such as *DLL3* with a dynamic range consistent with orthogonal tissue-based measurements. Collectively, these findings underscore the potential of a minimally invasive, comprehensive epigenomics platform to deliver real-time, gene expression-level insights into tumor evolution and target expression, thereby guiding therapeutic decision-making.