

Transcriptome Differences Revealed by High-plex Digital Spatial Profiling Associates with Endocrine Sensitivity in hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) early breast cancer (EBC)

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Background

- Endocrine resistance occurs in nearly all patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) early breast cancer (EBC), which can develop local and distant recurrence. The situation highlights the need to explore biomarkers for the efficacy of endocrine therapy (ET).
- The study aims to explore the spatial and transcriptome differences associated with endocrine sensitivity in HR+/HER2- EBC.

Methods

Study Design

- Postoperative formalin-fixed, paraffin-embedded (FFPE) tumor samples of patients with HR+/HER2- EBC were collected.
- Designated panel was composed of 235 ET-associated genes, which were collected from over 5,000 published articles.
- All patients received adjuvant tamoxifen after surgery. The follow-up period was ten years.
- Based on disease-free survival (DFS), patients were stratified into the ET-resistant and ET-sensitive groups.
- A total of 111 spatially resolved regions in three tissue compartments defined by morphology markers [tumor (PANCK+), leucocytes (CD45+), and nonimmune stroma (CD45-/PANCK-)] were assessed based on GeoMx digital spatial profiling.
- Study design is shown in **Figure 1**.

Statistical analysis

- The t-test was used to compare mRNA expression levels across groups and identify differentially expressed genes (DEGs).
- Gene Ontology (GO) annotation analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were performed using the clusterProfiler package in R.
- The SpatialDecon tool was developed to quantify diverse cell populations using normalized mRNA expression data for each segment within each ROI. The tool used a constrained log-normal regression algorithm, which was better suited to the long-tailed distribution of mRNA expression.
- All statistical analysis was performed using SPSS (version 29.0) and R (version 4.3.2) software
- P-value of <0.05 indicated statistical significance.

Results

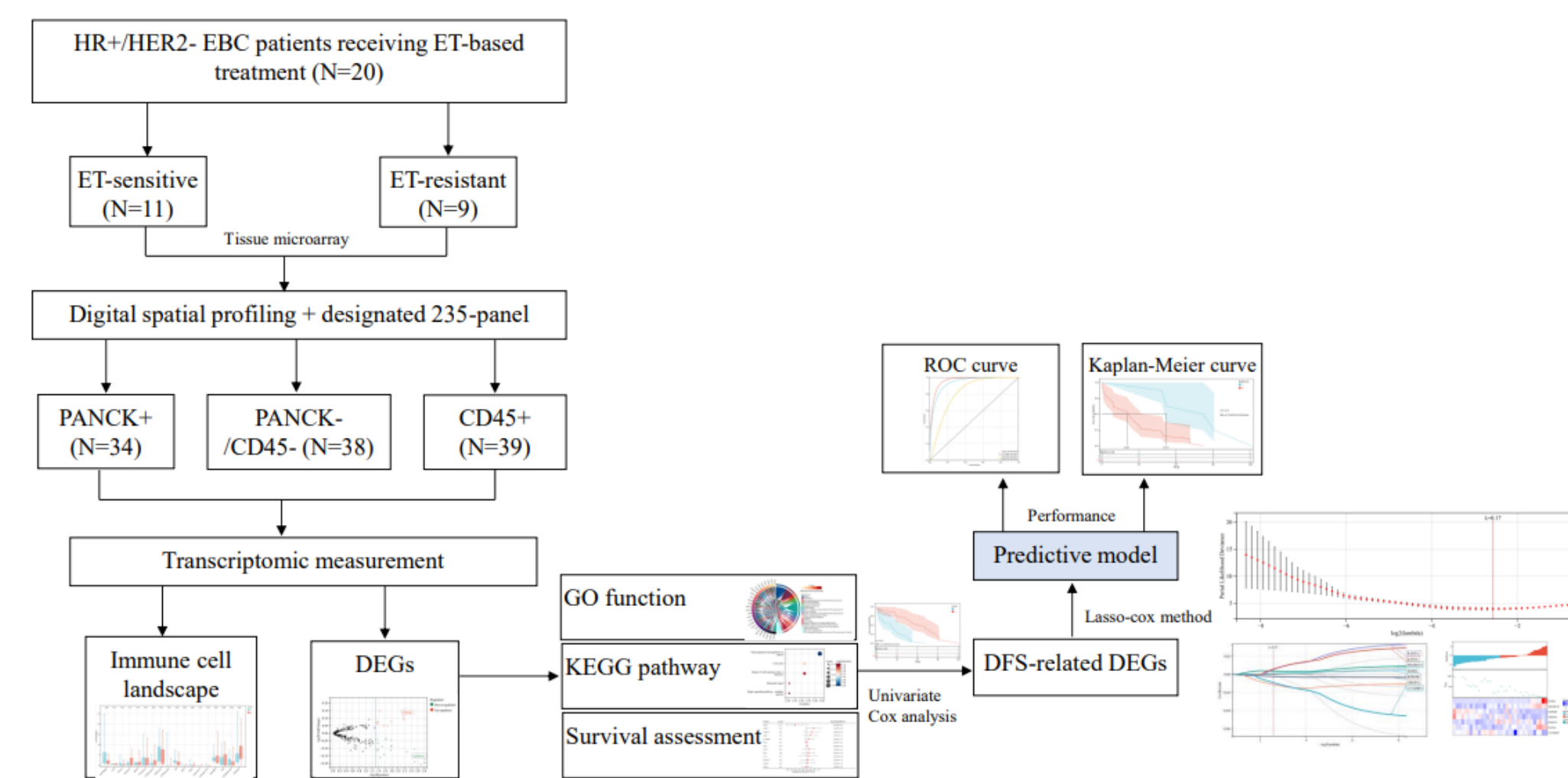


Figure 1. Study design of the study.

Baseline characteristics

- A total of 20 patients with HR+/HER2- EBC were eligible for TMA construction. They received radical surgery for primary breast tumors and adjuvant tamoxifen therapy. The pathology was confirmed as invasive ductal carcinoma (IDC), ER+/PR+/HER2- (**Table 1**).
- 9 patients were categorized as the ET-resistant group, and the other 11 as the ET-sensitive group.

Identification of differentially expressed genes (DEGs)

- In PANCK+ regions, 27 differentially expressed genes (DEGs) were identified (**Figure 2A**). They included 9 upregulated DEGs and 18 downregulated DEGs, among which the downregulated DEG GREB1L had the highest significance ($P=0.0015$) (**Figure 2B**).
- In CD45+ regions, two downregulated and eleven upregulated DEGs were identified (**Figure 2C**). The downregulated MLH3 ($P=0.013$) displayed the most tremendous significance in differential expression, followed by the upregulated RUNX1T1 ($P=0.020$) (**Figure 2D**).
- In the CD45-/PANCK- regions, 5 DEGs were selected via the screening criterion (**Figure 2E**). KDM4B, the downregulated DEG, showed the highest significance ($P=0.0026$) (**Figure 2F**).

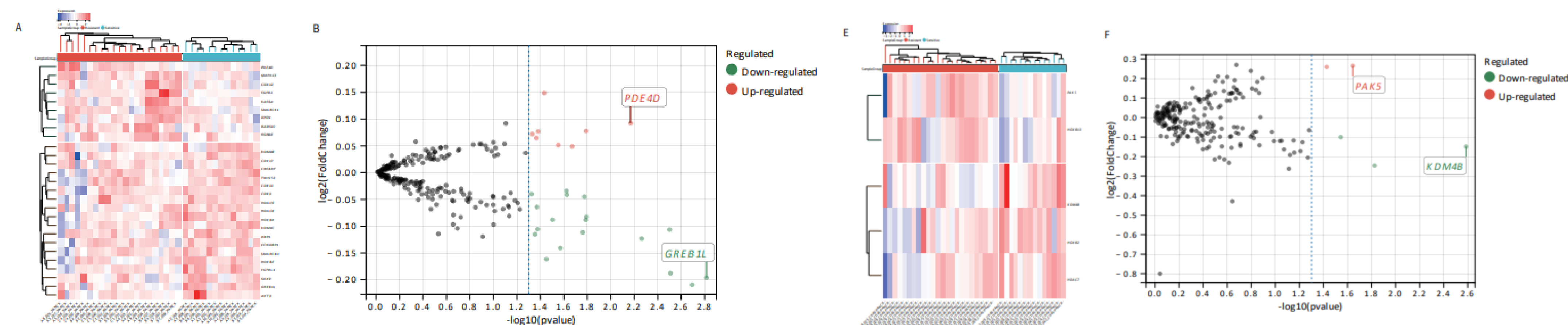


Figure 2. Identification of DEGs in spatially resolved regions from patients who showed different responses to ET-based treatment. Heat map and volcano plots of DEGs in the PANCK+ (A,B), CD45+ (C,D), and CD45-/PANCK- (E,F) regions from patients in the ET-sensitive group vs. those in the ET-resistant group were shown.

Results

Table 1. Baseline characteristics of HR+/HER2- EBC patients from ET-resistant and ET-sensitive groups

Characteristics	n (%)			P
	ET-sensitive (N=11)	ET-resistant (N=9)	Total (N=20)	
Age (year)			45.5	0.90
Median (range)	45.0 (33.0-49.0)	48.0 (33.0-55.0)	(33.0-55.0)	
Pathological grade ^a				0.21
I	1 (9.1)	0 (0)	1 (5.0)	
II	8 (72.7)	6 (66.7)	14 (70.0)	
III	0 (0)	3 (33.3)	3 (15.0)	
ECOG PS				1.00
0	3 (27.3)	2 (22.2)	5 (25.0)	
1	8 (72.7)	7 (77.8)	15 (75.0)	
Menopausal status				1.00
Premenopausal	11 (100)	9 (100)	20 (100)	
T stage				0.34
T1	9 (81.8)	5 (55.6)	14 (70.0)	
T2	2 (18.2)	4 (44.4)	6 (30.0)	
N stage				0.79
N0	2 (18.2)	3 (33.3)	5 (25.0)	
N1	5 (45.5)	2 (22.2)	7 (35.0)	
N2	3 (27.3)	3 (33.3)	6 (30.0)	
N3	1 (9.1)	1 (11.1)	2 (10.0)	

Enrichment analysis of DEGs

- In PANCK+ regions, DEGs were primarily involved in nuclear activities and cell cycle (**Figure 3A**). KEGG pathways revealed significant enrichment in pluripotency of stem cells, proteoglycans in cancer, and thermogenesis (**Figure 3B**).
- In the CD45+ regions, the dominant cellular activities were associated with the nucleus and cell cycle (**Figure 3C**). KEGG pathways are mainly enriched for transcriptional misregulation in cancer, cell cycle, and mismatch repair (**Figure 3D**).
- In the CD45-/PANCK- regions, no KEGG pathways were significantly enriched. Histone activities were highly enriched, with the histone methyltransferase complex showing significant statistical significance (**Figure 3E**).

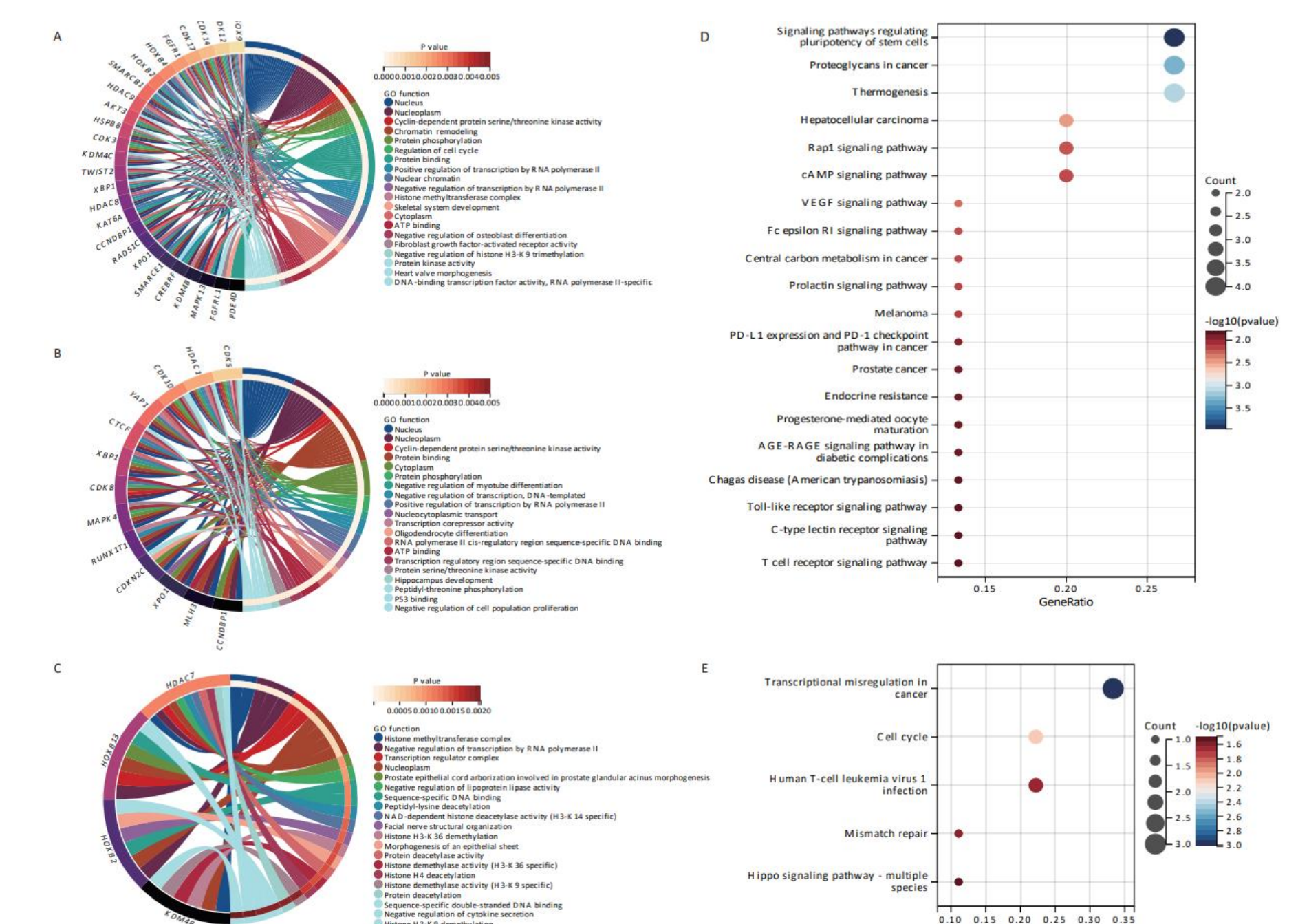


Figure 3. GO function and KEGG (B) of DEGs in different spatially defined regions. Top 20 GO function ranked by statistical significance in PANCK+ (A), CD45+ (B), and CD45-/PANCK- (C) regions were illustrated; Top 20 KEGG pathway enriched in PANCK+ regions (D), and all pathways in CD45+ (E) regions were showed.

Conclusions

- Our study identifies the transcriptomic landscapes between ET-sensitive and ET-resistant patients using a combination of DSP and a designated 235-gene panel.
- This may provide references for exploring molecular mechanisms of endocrine resistance, and stratifying patients who may derive survival benefits from ET.

DISCLOSURE: There is no conflict of interest.

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