DLBCL Prognostic Gene Signatures

Genome-Wide Survival Analysis by Cell of Origin

HMRN/Lacy Cohort Analysis

2026-01-19

Section 1

Introduction

Study Overview

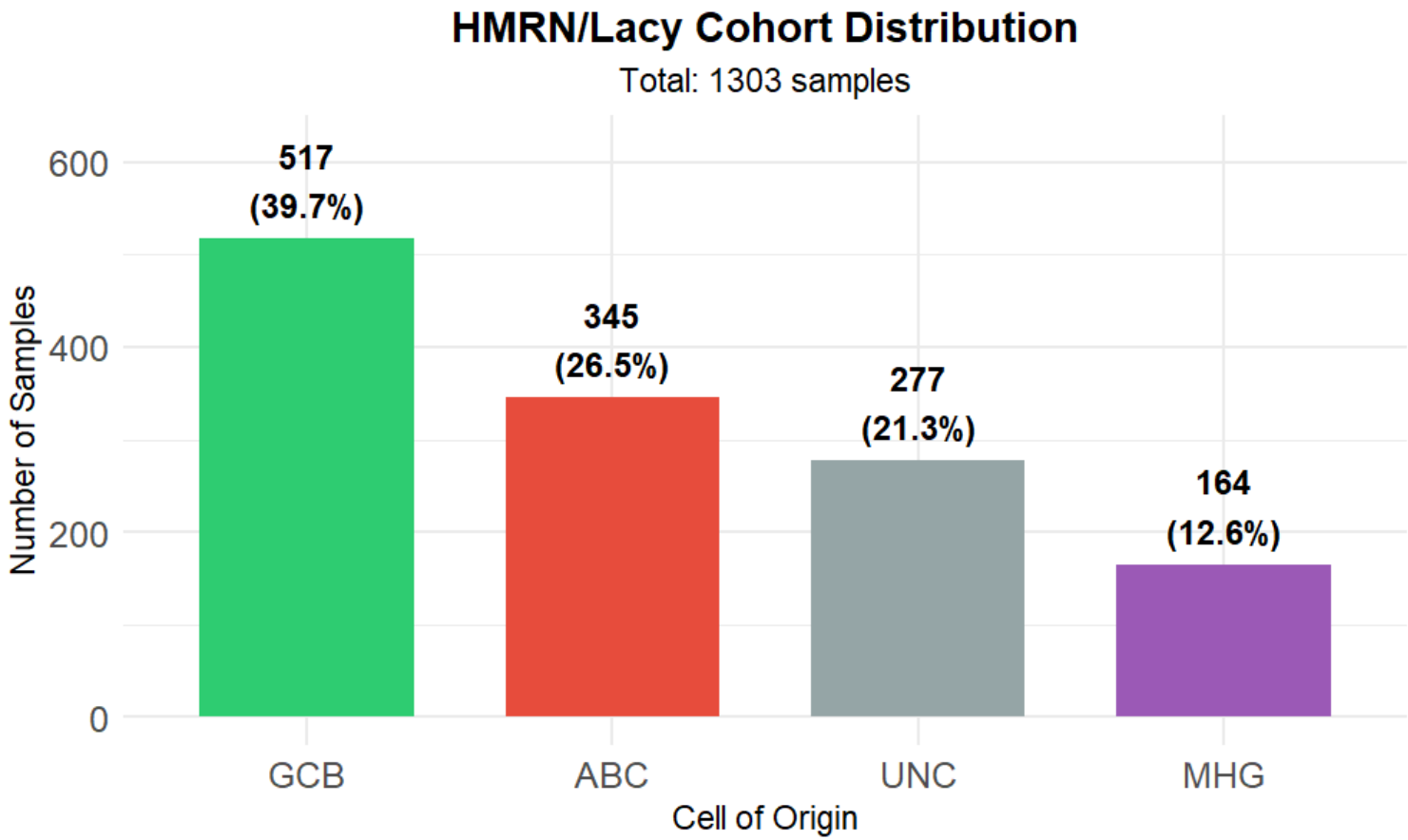
Objective:

- Identify prognostic gene signatures in DLBCL
- Compare across Cell of Origin (COO) subtypes
- Test independence from IPI

Key Questions:

- Which genes predict survival?
- Are signatures COO-specific?
- Do they add value beyond IPI?

Study Cohort

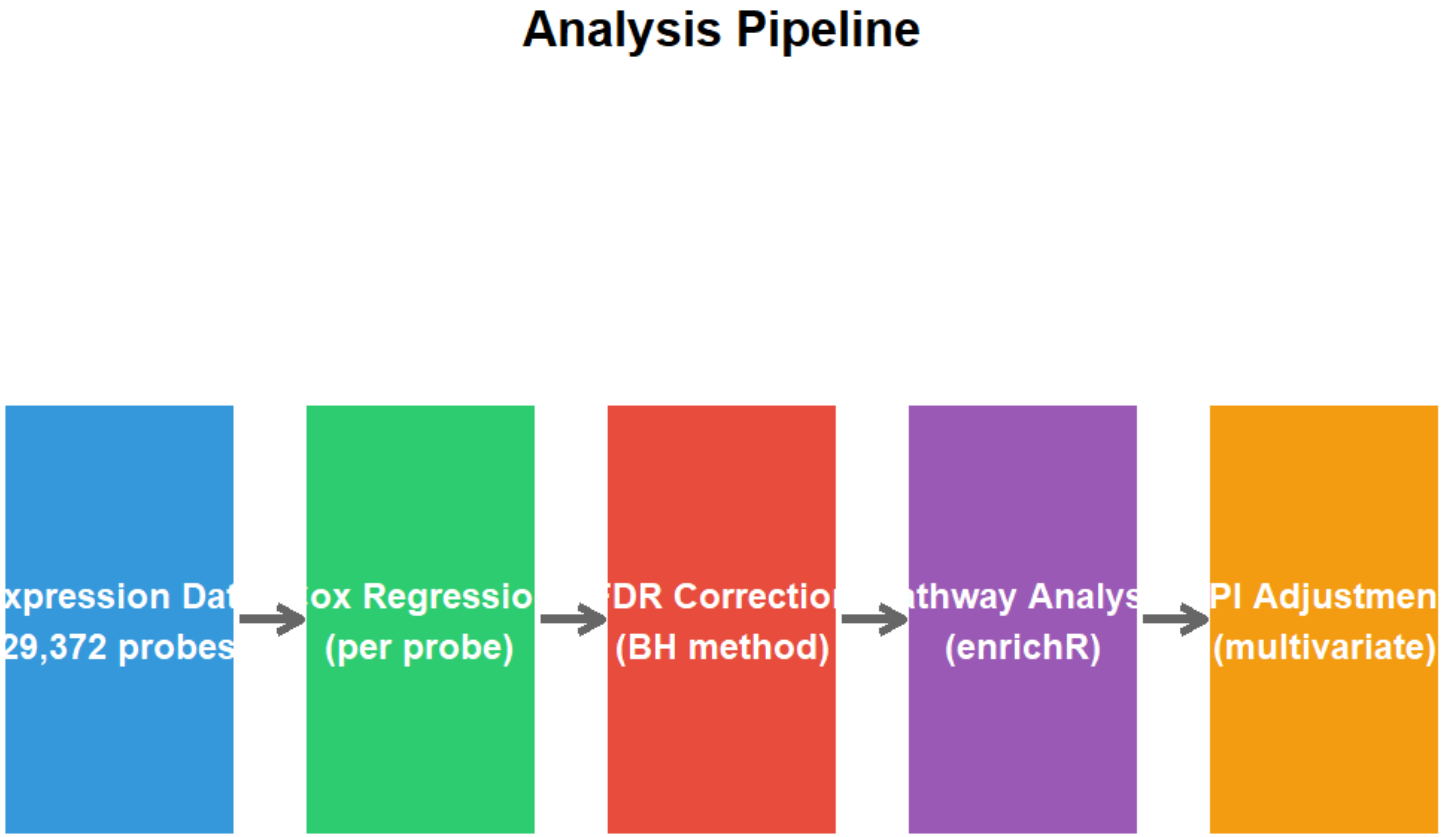


- **HMRN/Lacy Cohort** (GSE181063): 1,303 samples with survival data
- **Platform**: Illumina HumanHT-12 V4 BeadChip (29,372 probes)

Section 2

Methodology

Analysis Pipeline



Statistical Methods

Univariate Analysis:

$$h(t|x) = h_0(t) \cdot e^{\beta x}$$

- Cox proportional hazards
- Per-probe regression
- Z-score normalized expression

Multiple Testing:

- Benjamini-Hochberg FDR
- Significance: FDR < 0.05

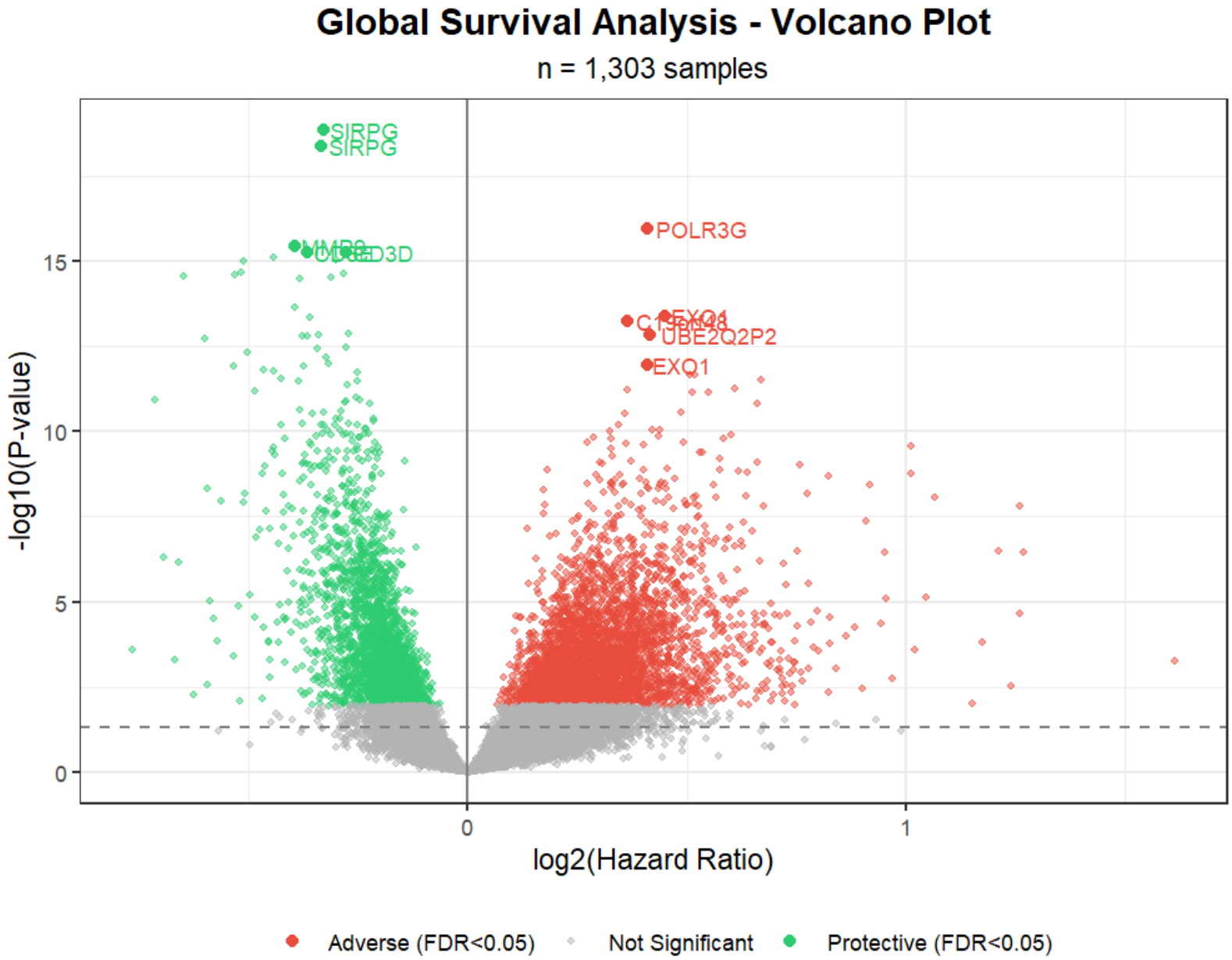
IPI Adjustment:

$$h(t|x, IPI) = h_0(t) \cdot e^{\beta_1 x + \beta_2 IPI}$$

Section 3

Results: Global Analysis

Volcano Plot - Global Survival Analysis



Key Findings - Global

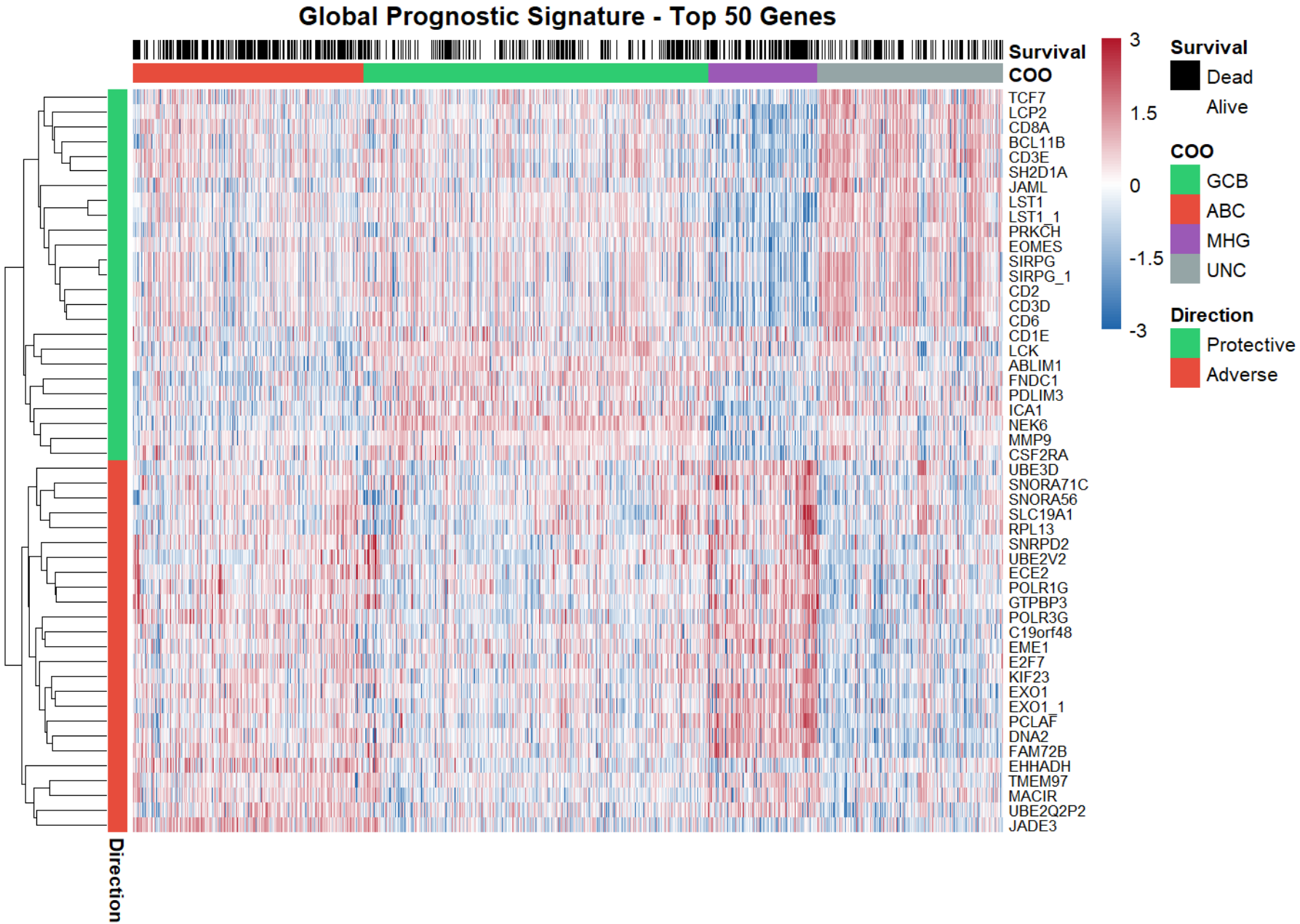
Significant Probes:

- **6,748** FDR < 0.05
- **3,243** Protective (HR < 1)
- **3,505** Adverse (HR > 1)

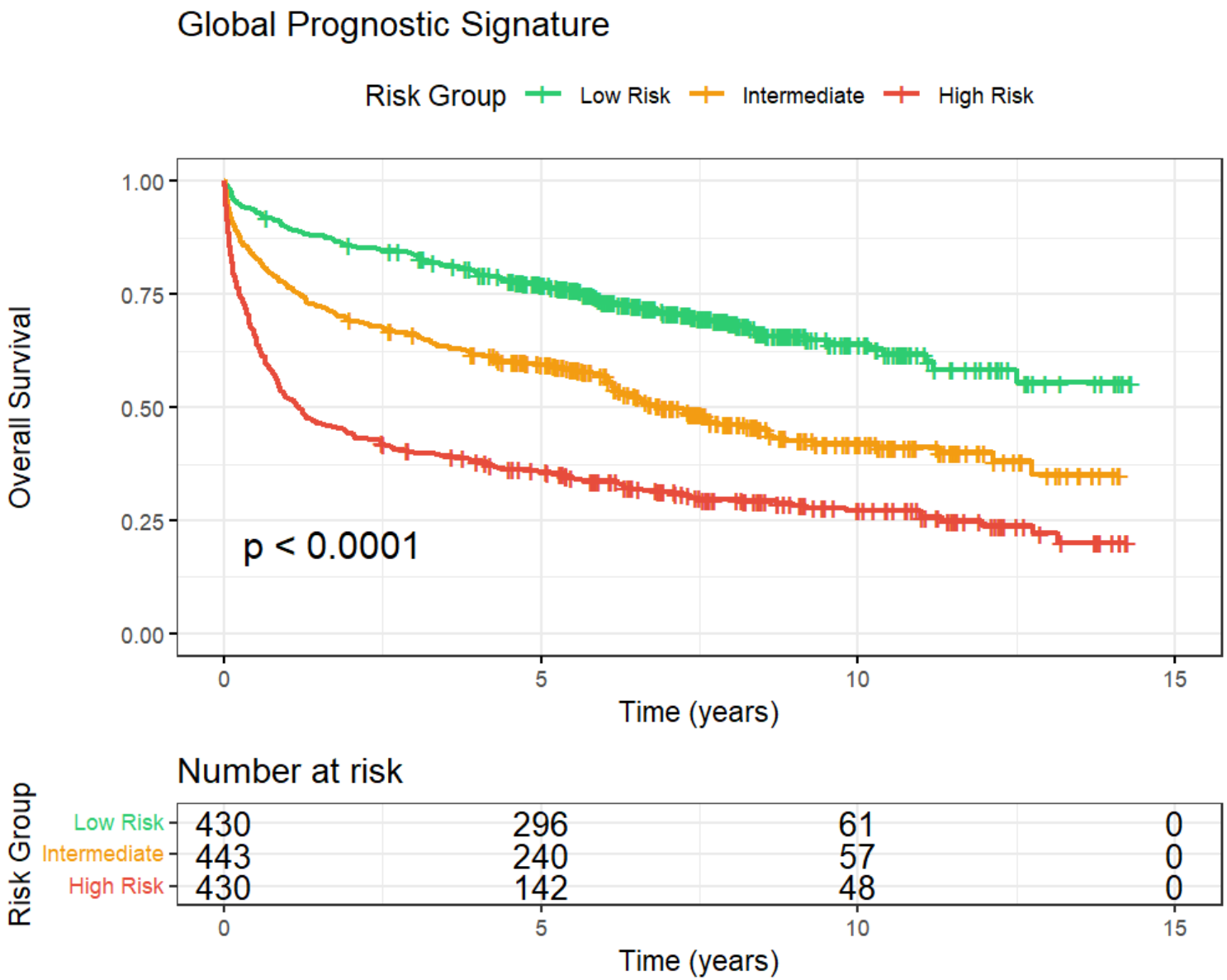
Top Genes:

Protective	Adverse
SIRPG	POLR3G
CD3D, CD3E	EXO1
MMP9	C19orf48
BCL11B	UBE2Q2P2
LCK, CD2	SHCBP1

Prognostic Signature Heatmap



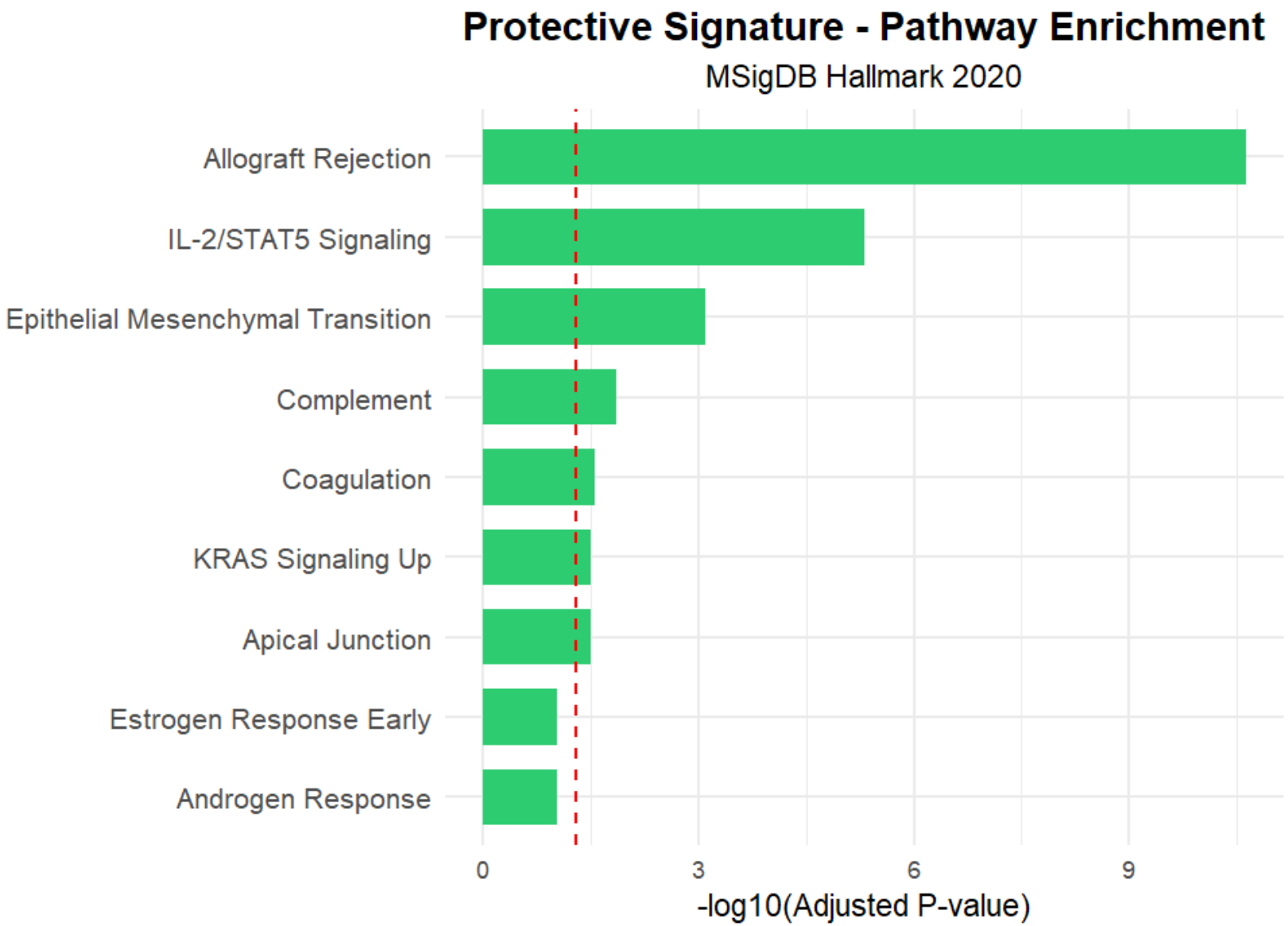
Kaplan-Meier: Global Signature



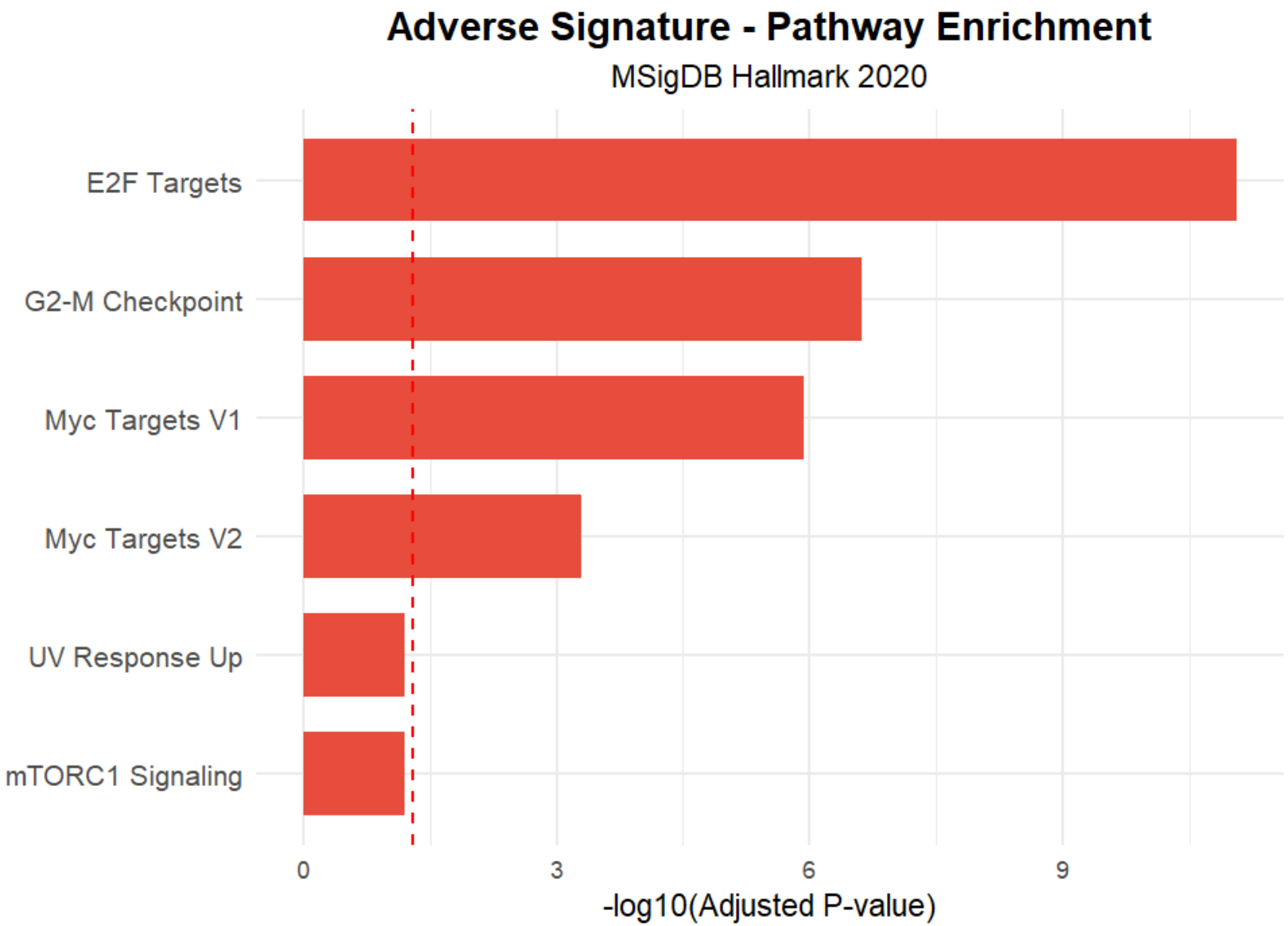
Section 4

Pathway Enrichment (GSEA)

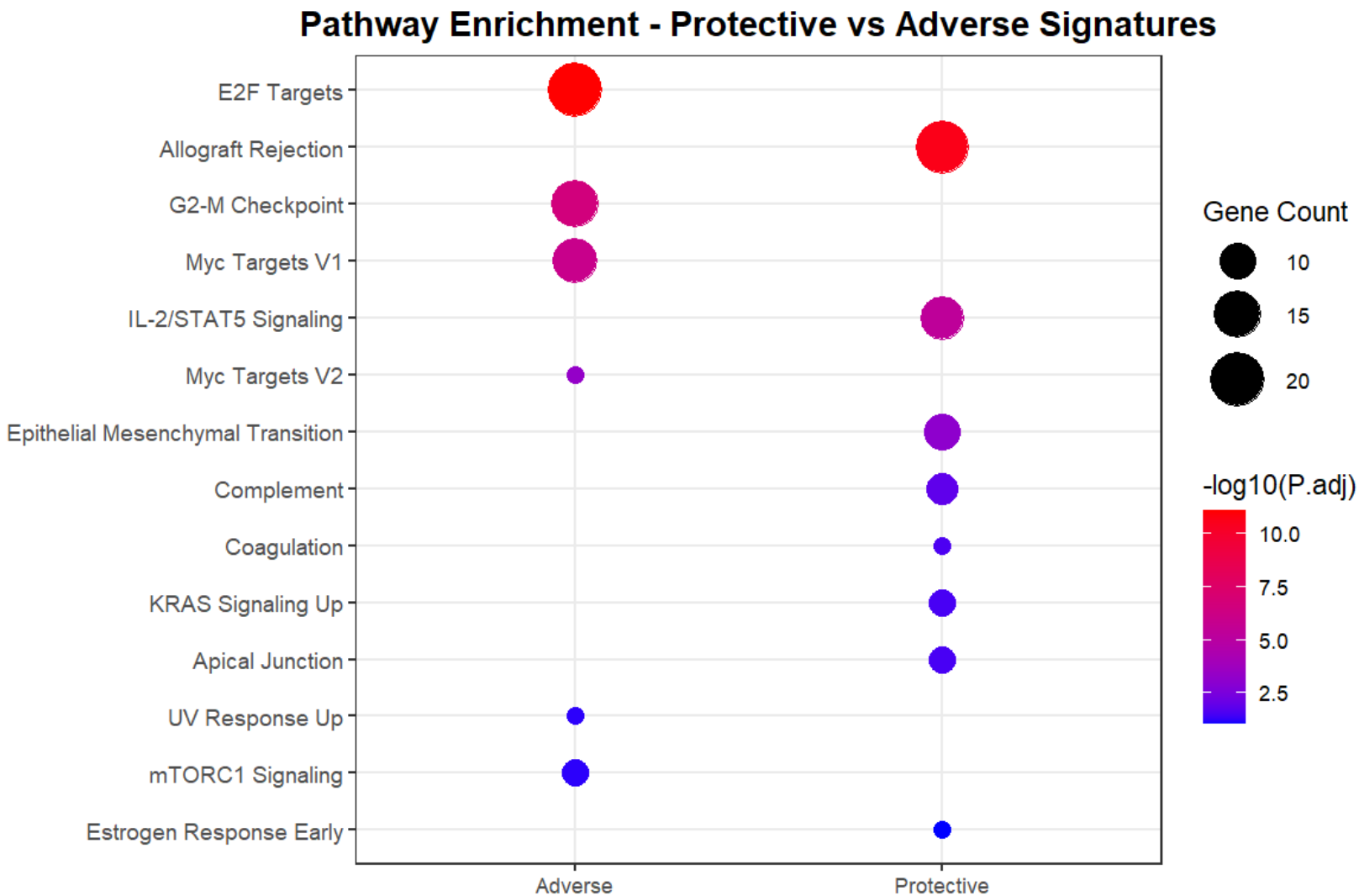
Protective Pathways



Adverse Pathways



Combined Pathway Analysis



Pathway Summary

Protective Pathways:

- Allograft Rejection
- IL-2/STAT5 Signaling
- T-cell Activation
- Immune Surveillance

$\Rightarrow$ T-cell infiltration = Good prognosis

Adverse Pathways:

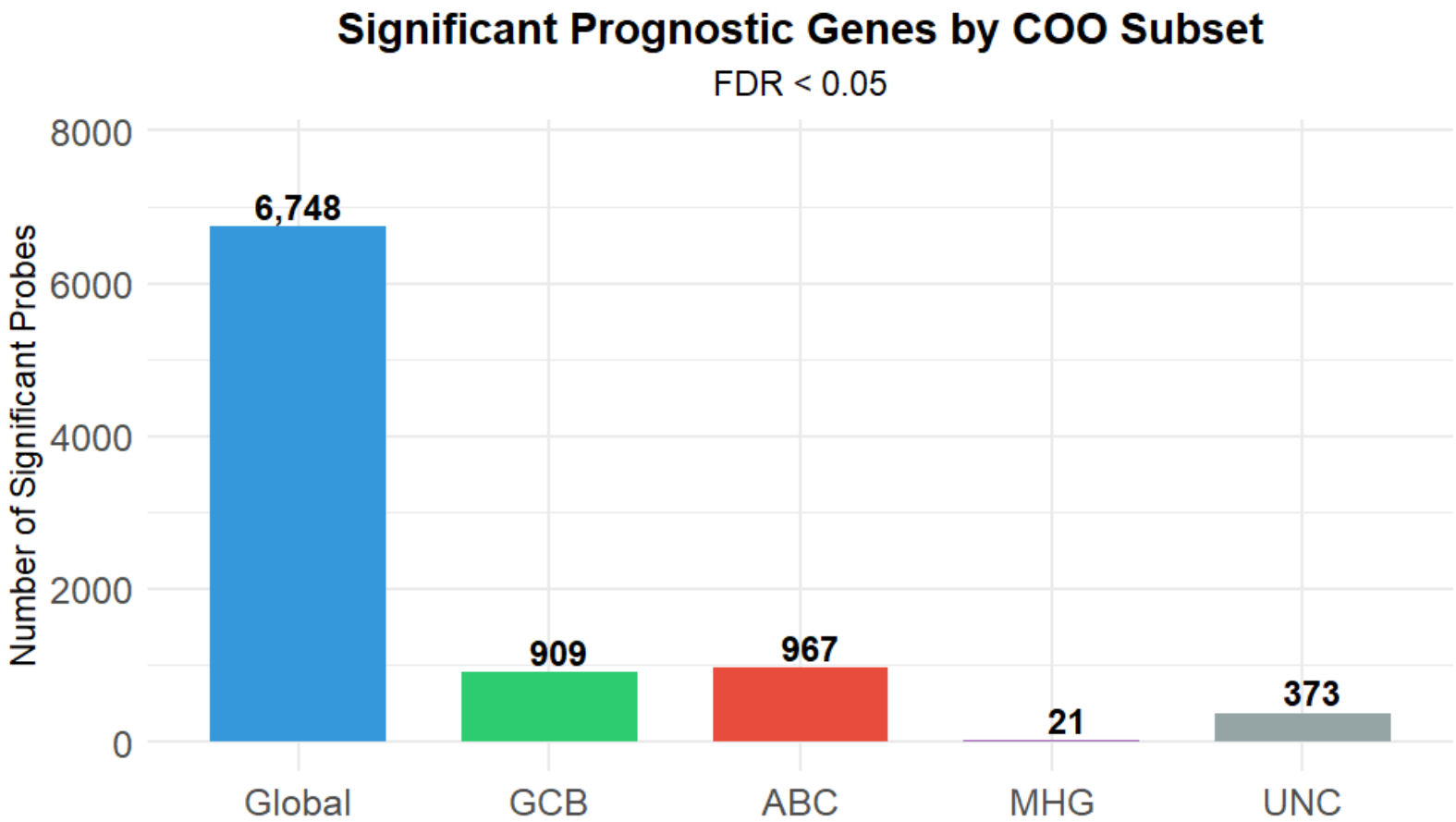
- E2F Targets
- G2M Checkpoint
- DNA Repair/HDR
- MYC Targets

$\Rightarrow$ Proliferation = Poor prognosis

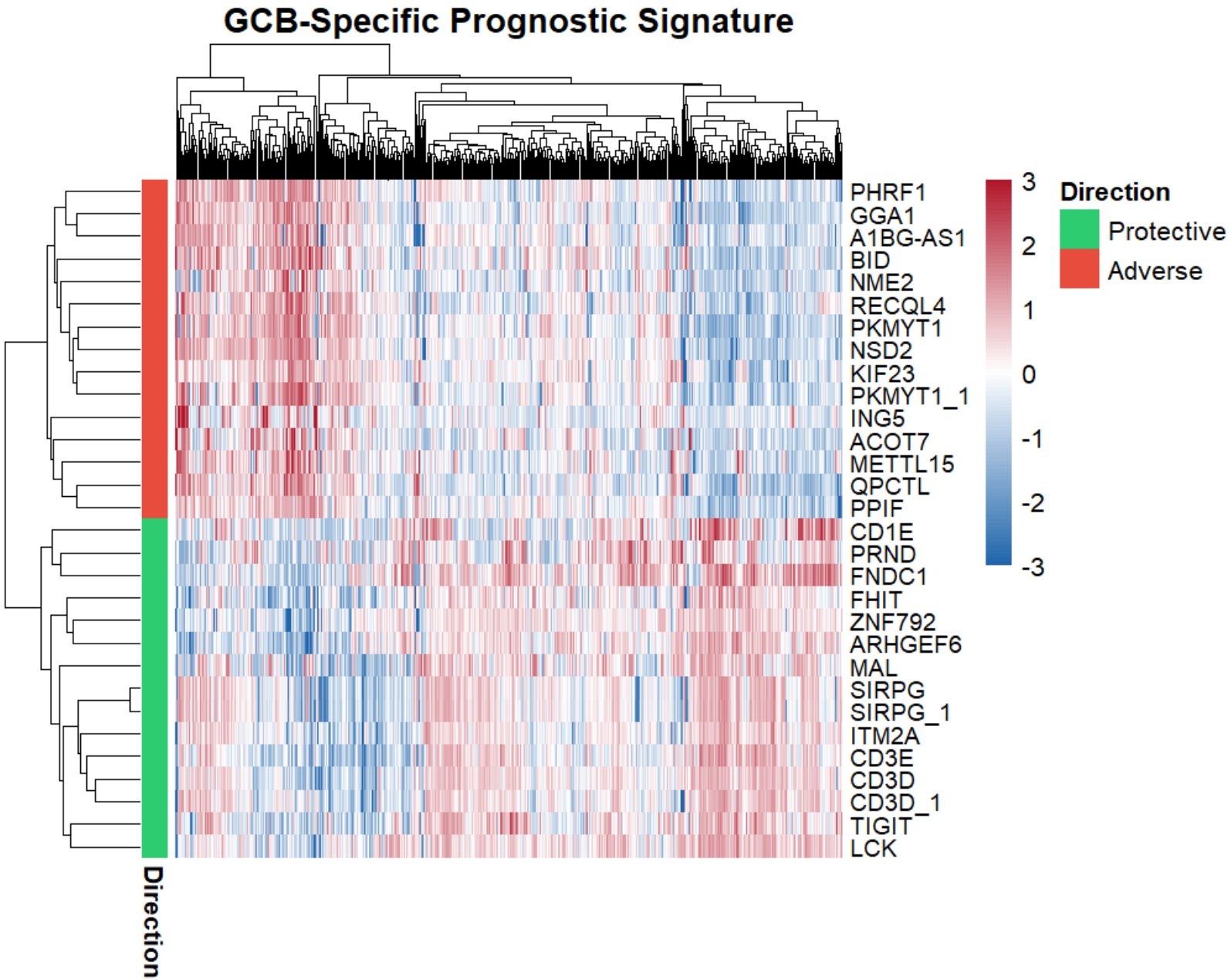
Section 5

COO-Specific Signatures

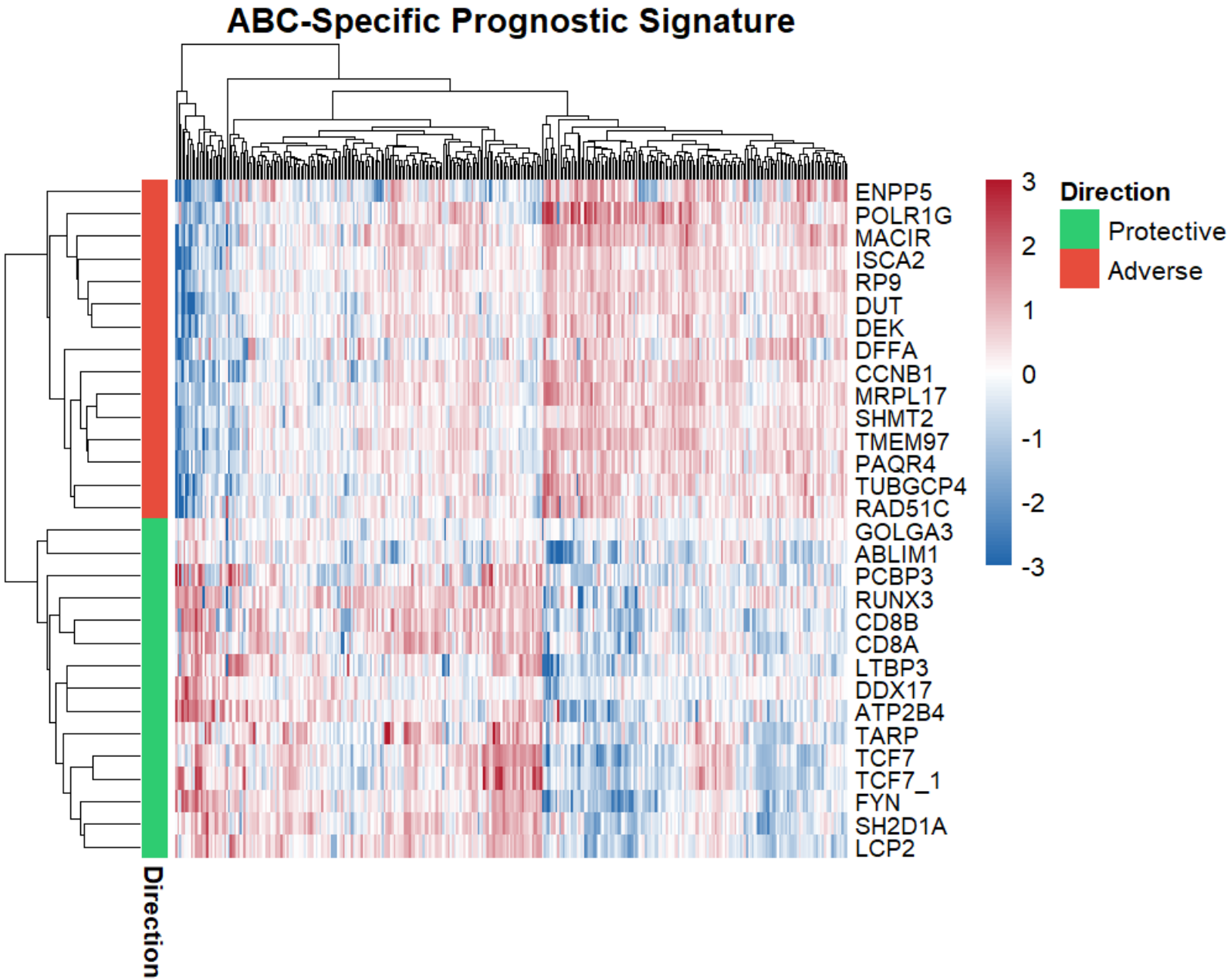
Significant Genes by COO Subset



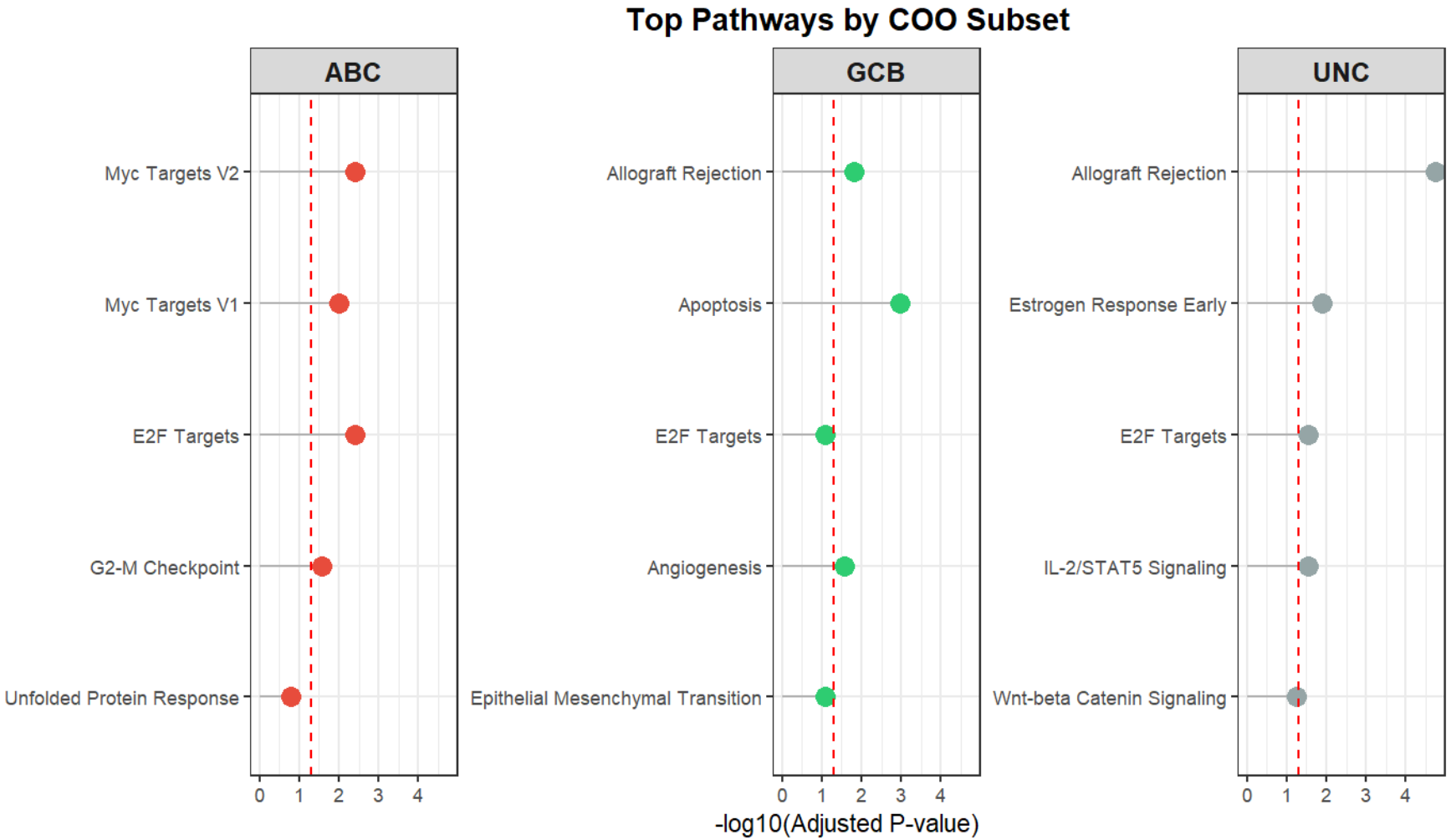
GCB-Specific Signature



ABC-Specific Signature



COO Pathway Comparison



COO Signature Overlap

Minimal overlap between COO-specific signatures

GCB ∩ ABC	**GCB ∩ MHG**	**ABC ∩ MHG**
4 genes	0 genes	0 genes

$\Rightarrow$ **Each COO subtype has distinct prognostic biology**

Section 6

IPI Independence Analysis

IPI Independence - Methodology

Analysis Design:

- 317 GCB samples with IPI data
- Compare univariate vs multivariate
- Test if genes remain significant after IPI adjustment

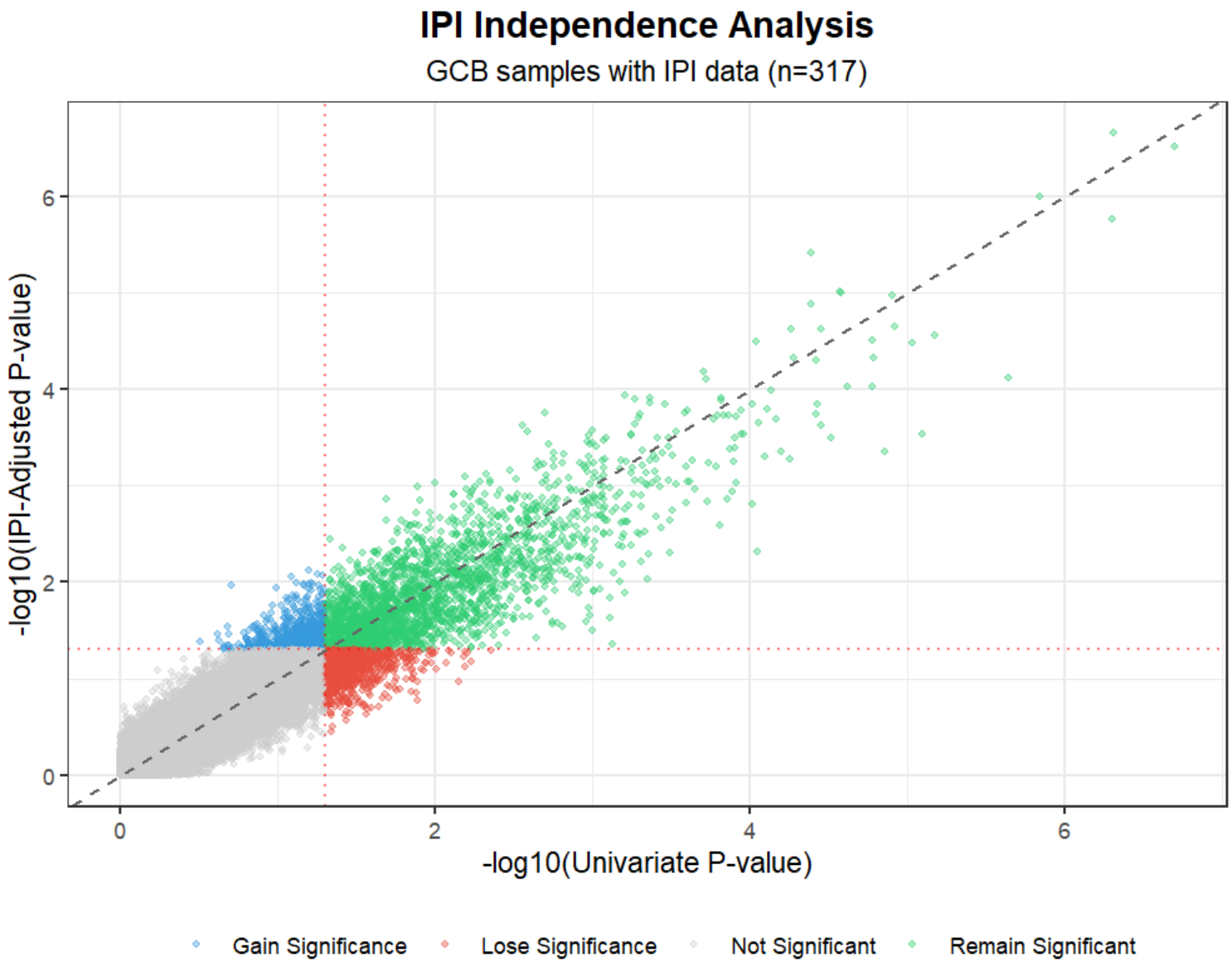
Multivariate Model:

$$h(t) = h_0(t) \cdot e^{\beta_1 \cdot Gene + \beta_2 \cdot IPI}$$

IPI-independent if:

$p_{adjusted} < 0.05$

IPI Independence Results



IPI Independence Summary

The prognostic genes are largely IPI-INDEPENDENT

- **3,037** univariate significant
- **2,839** remain after IPI adjustment
- Only **701** lose significance

- **93%** of genes retain significance
- Gene expression adds prognostic value beyond IPI

Section 7

Conclusions

Key Findings

1. **Strong Prognostic Signatures**
   - 6,748 significant probes (FDR < 0.05)
   - Clear separation by risk score
2. **COO-Specific Biology**
   - Minimal overlap between subsets
   - Each has distinct prognostic determinants
3. **Biological Themes**
   - Protective: T-cell infiltration/immune activation
   - Adverse: Proliferation/cell cycle
4. **IPI Independence**
   - 93% genes remain significant after IPI adjustment
   - Signatures provide additional prognostic information

Clinical Implications

Risk Stratification:

- Refine beyond IPI
- Identify high-risk patients within IPI groups
- COO-specific prognostication

Therapeutic Targets:

- T-cell function enhancement
- Cell cycle inhibition
- Immunotherapy selection

Gene expression signatures could complement clinical staging for personalized treatment decisions

Acknowledgments

Data Source
HMRN/Lacy Cohort (GSE181063)

Methods
R packages: survival, survminer, enrichR, pheatmap

Analysis Pipeline
Cox regression $\rightarrow$ FDR correction $\rightarrow$ Pathway enrichment $\rightarrow$ IPI adjustment

Thank You

Questions?

Analysis code and data available upon request