

PDOmics: Systems-Level Insights from a Multi-Omic Landscape of 111 Breast Cancer Patient-Derived Organoids

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INTRODUCTION

Conventional breast cancer models fail to capture patient-level molecular diversity. Patient-Derived Organoids (PDOs) are generally thought preserve this diversity at scale, but comprehensive credentialing is lacking. We present **PDOmics**, the largest multi-omic breast cancer PDO atlas to date: 111 PDOs across NST, ILC, and mixed subtypes, profiled by scRNA-seq, bulk RNA-seq, WES, CNA, and structural variant calling.

THE IPM PDO BIOBANK

111

patient-derived organoids*

97 14

primary tumors metastatic sites

metastatic sites: bone · LN · ovary · ascites · peritoneum

histological subtypes

NST (59)

Invasive Ductal
(No Special Type)

ILC (37)

Invasive Lobular
Carcinoma

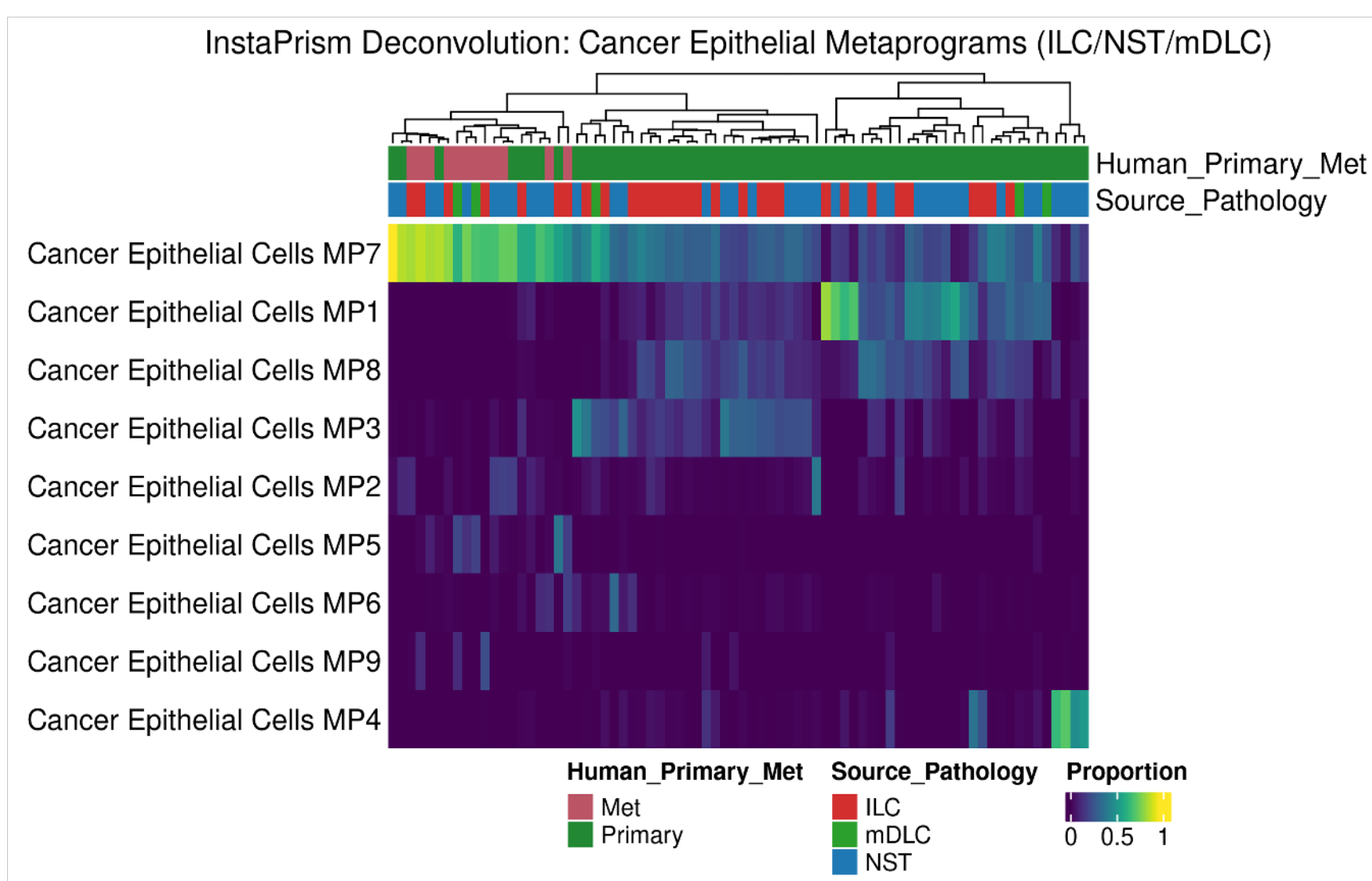
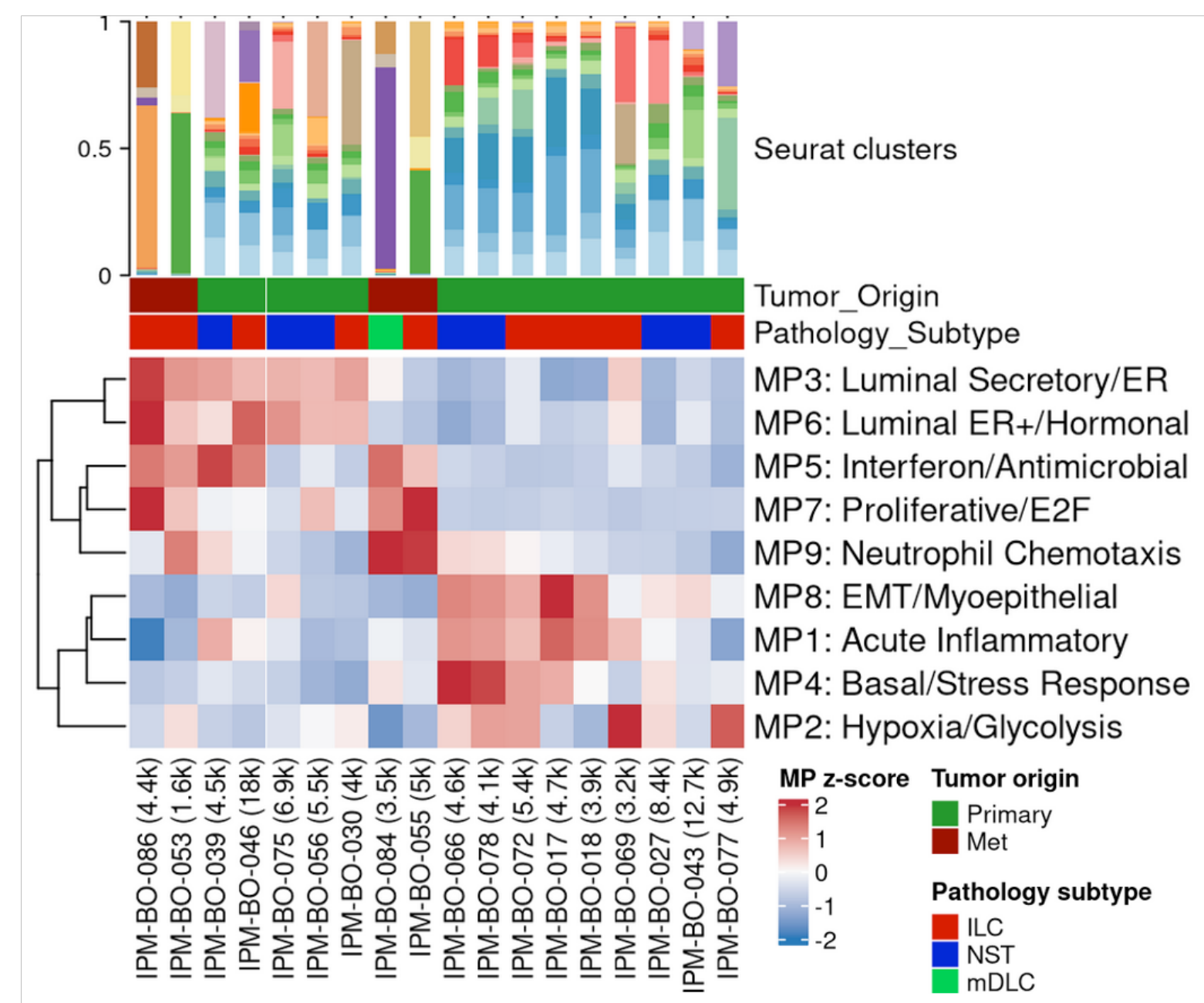
Other (15)

Mixed Ductal/Lobular,
Ductal & Lobular *in situ*

OBJECTIVES

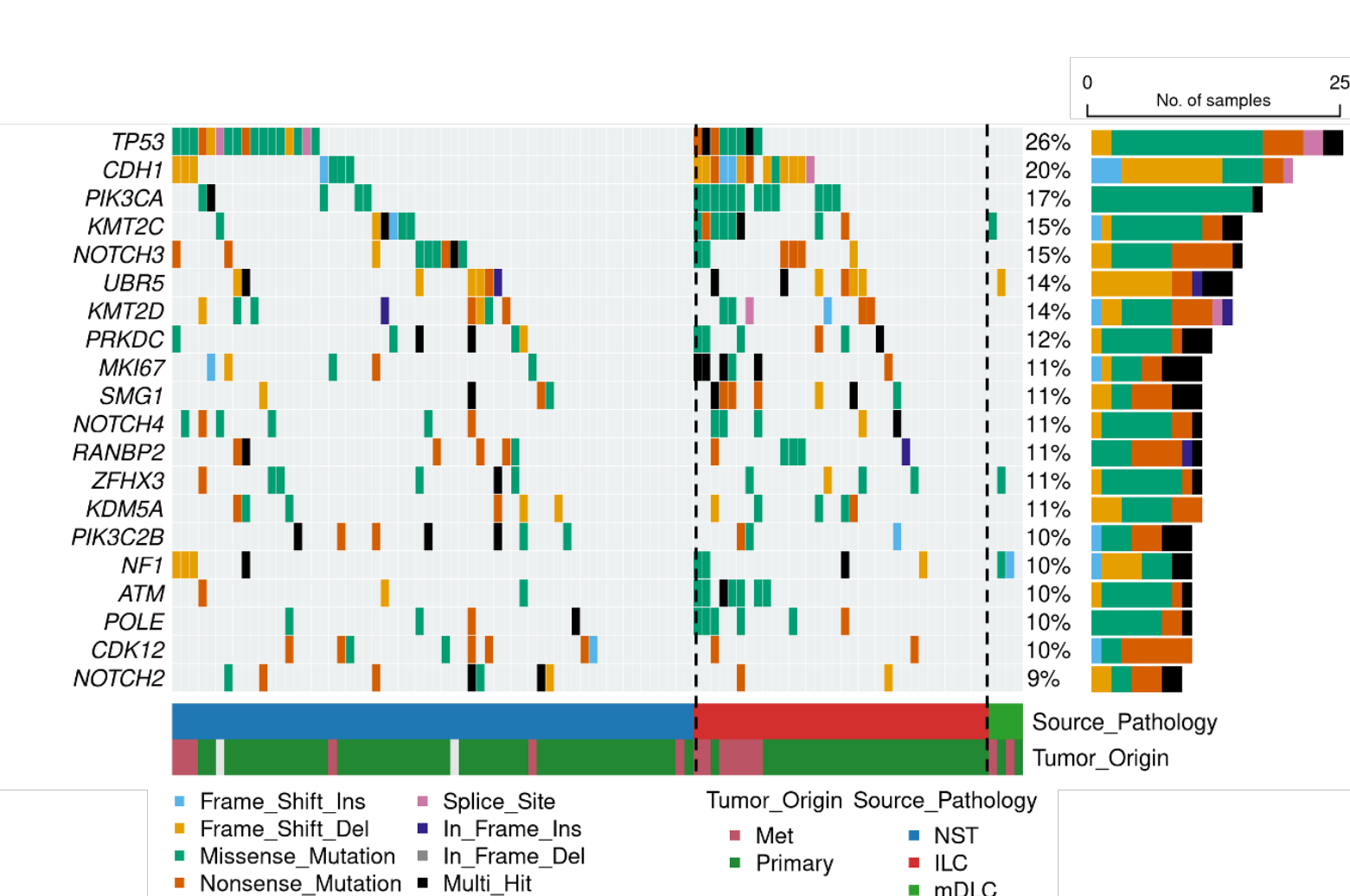
- Construct and characterize** a multi-omic atlas of 111 breast cancer PDOs spanning NST, ILC, and mixed ductal/lobular subtypes
- Identify** conserved transcriptomic programs using consensus non-negative matrix factorization (cNMF)
- Assess** genomic and transcriptomic fidelity of PDOs across serial passages
- Integrate** across omic layers to uncover molecular axes of variation beyond histological classification (MOFA2)

TRANSCRIPTOMIC HETEROGENEITY



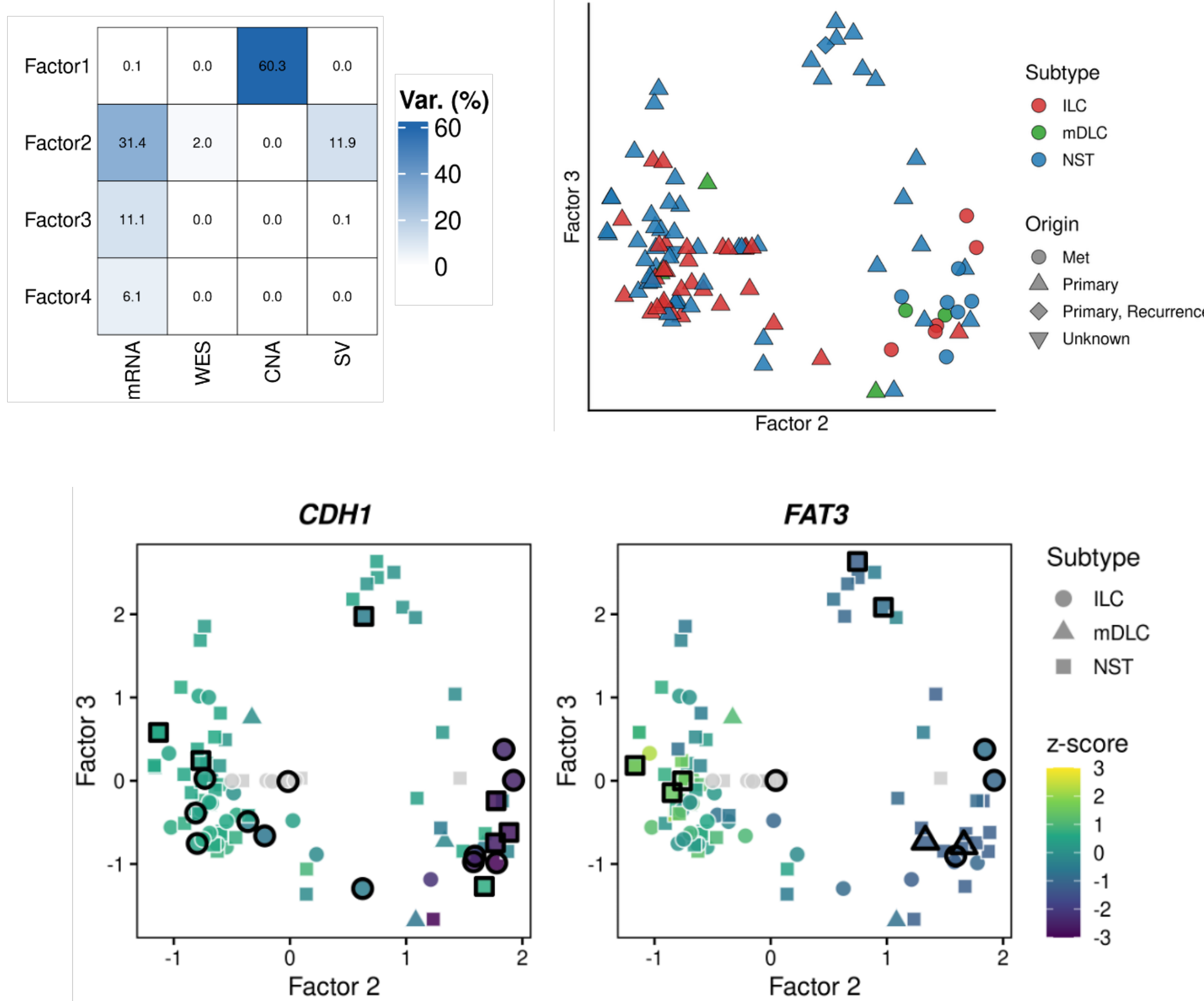
scRNA-seq of 18 PDOs identified **9 conserved meta-programs** via cNMF (**top**) spanning luminal/ER signaling, proliferation, hypoxia, EMT, and immune response. These programs are recoverable from bulk RNA-seq across all 95 profiled PDOs via InstaPrism deconvolution (**bottom**). PDOs demonstrate considerable **inter and intra-organoid heterogeneity**, recapitulating the heterogeneity of the originating tumor tissue.

GENOMIC LANDSCAPE



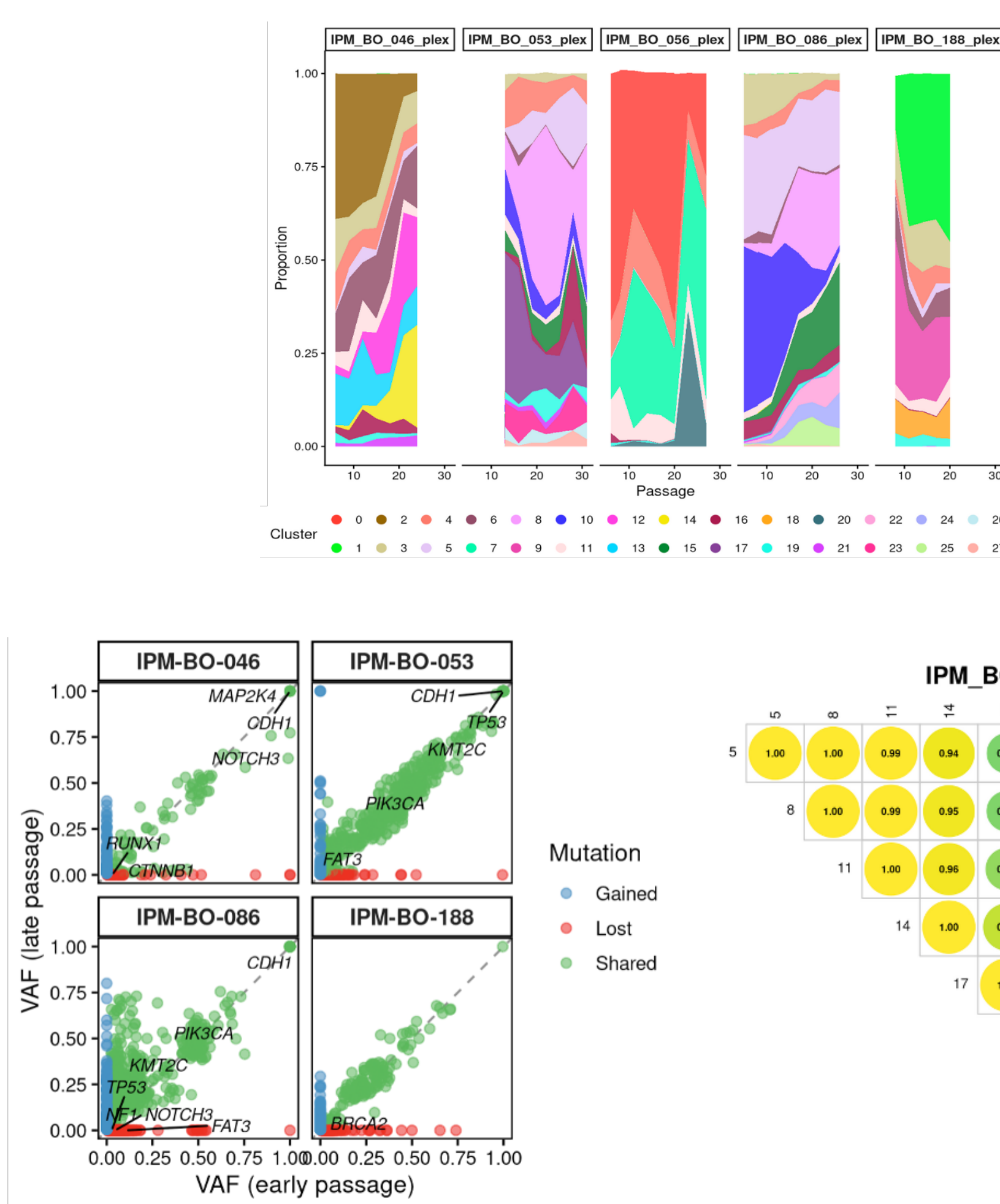
WES of 98 PDOs identified **recurrent drivers**: TP53 (26%), CDH1 (20%), PIK3CA (17%), with expected subtype enrichment and sub-clonal heterogeneity

MULTI-OMIC INTEGRATION



MOFA2 across 4 views (mRNA, WES, CNA, SV; 109 PDOs) resolved **4 latent factors**: CNA burden (F1), basal/luminal + TP53/CDH1 axis (F2), luminal identity (F3), squamous differentiation (F4). Novelly, FAT3 expression loss and mutation co-localize on F2 alongside CDH1

LONGITUDINAL FIDELITY



Across passages 5–31, scRNA-seq and paired WES confirm PDOs retain transcriptomic programs and clonal driver mutations. Subclonal variants show expected drift. **Core molecular identity is stable.**

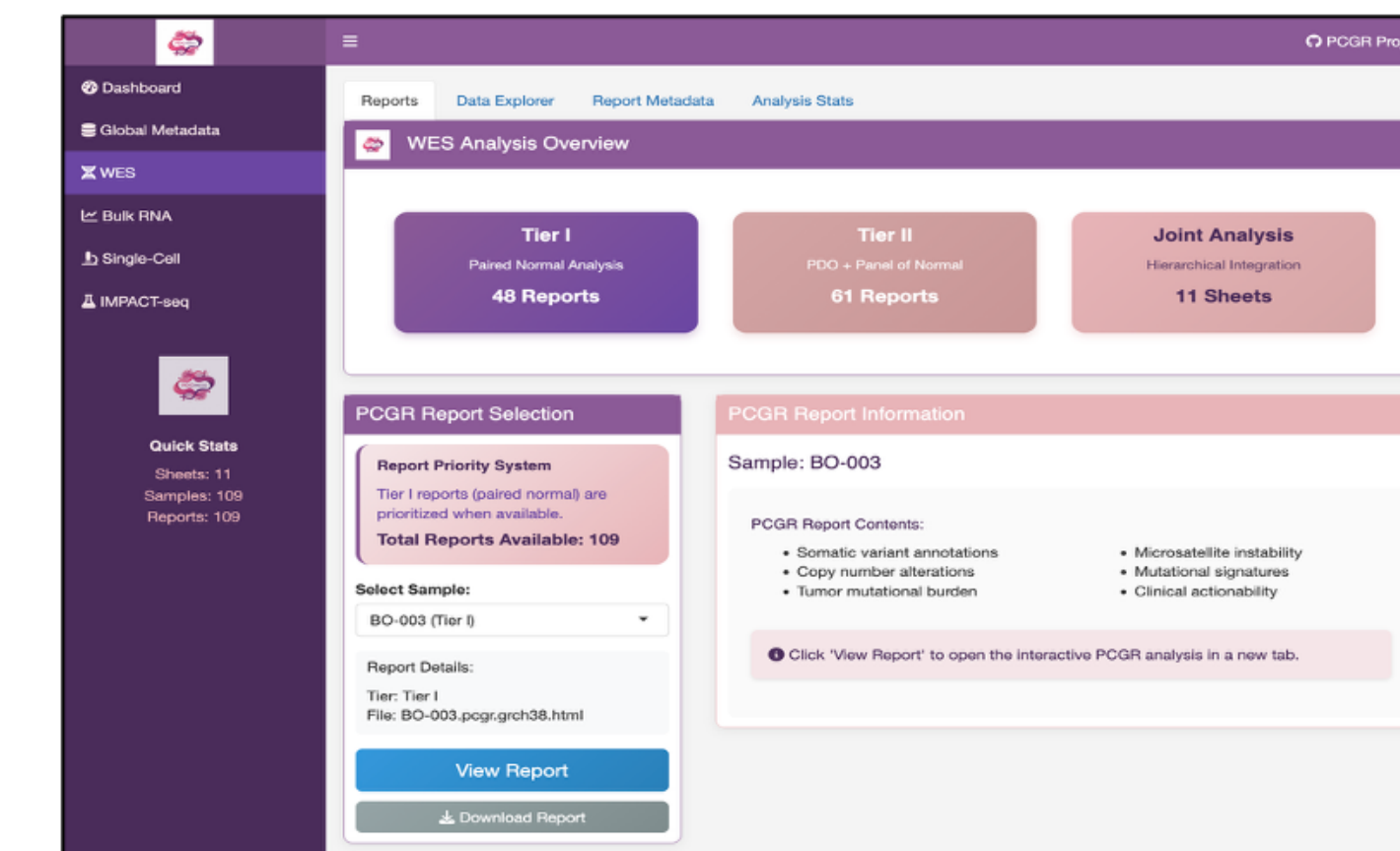
CONCLUSIONS

- PDOs faithfully preserve molecular identity across passage and histological subtype
- 9 conserved meta-programs** underlie bulk and single-cell transcriptomic heterogeneity
- FAT3** emerges as a novel, multi-omic feature of breast cancer heterogeneity

FUTURE DIRECTIONS

Matched patient tumor-tissue validation and IMPACT sequencing analysis of tissue are underway to confirm PDO fidelity at the genomic level. FAT3 loss in ILC is being further characterized to establish functional and clinical relevance, with the broader goal of linking multi-omic signals identified here to patient outcomes.

COMMUNITY RESOURCE



PDOmics multi-omic profiles are being made available through a dedicated R-Shiny web atlas (in development). PDOs from the biobank are available for purchase through the IPM, providing the community access to a characterized, clinically-annotated breast cancer PDO resource.

ACKNOWLEDGEMENTS

Funded in part by the Breast Cancer Research Foundation. PDOs were developed and maintained by Dr. Daniel Brown at the IPM. Research was supported in part by the University of Pittsburgh Organoid Research Core Facility (RRID:SCR_025698) and Center for Research Computing and Data (RRID:SCR_022735). Sequencing data was collected over several years by members of the Lee/Oesterreich and IPM teams. We thank Jian Chen and Dr. Fresia Pareja for their invaluable contributions to sample preparation and sequencing.