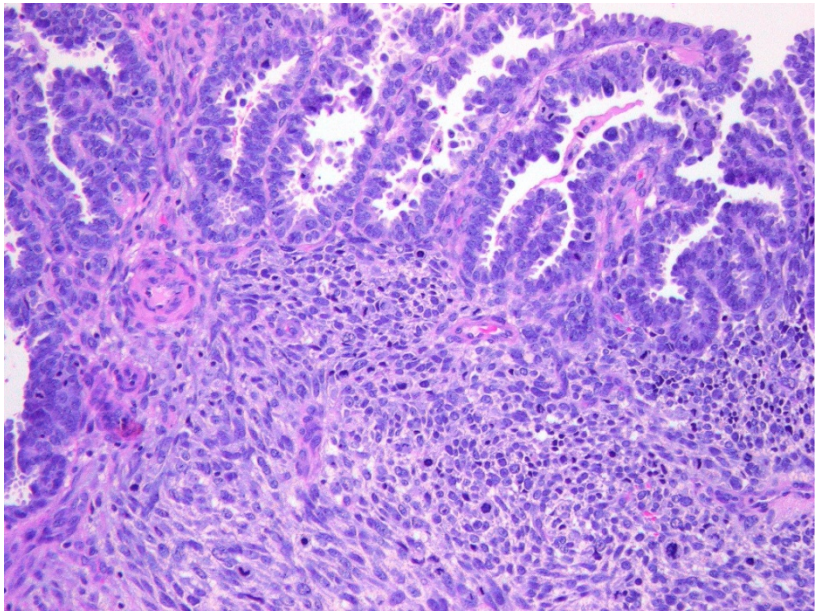
Integrated Molecular Characterization of Uterine Carcinosarcoma (UCS)

TCGA Research Network
Co-chairs:
Rehan Akbani (MD Anderson) (presenter)
Douglas A. Levine (MSKCC)

Background

- UCS contains an admixture of carcinoma (epithelial component) and sarcoma (mesenchymal component)
- Rare, aggressive tumor, found in <5% of all uterine cancers
- 5 year survival rate is about 35%
- Median survival of 24 months, compared to 60 months for endometrial cancer (UCEC)
- Median age of patients is 65 years, mostly occurring in post-menopausal women
- Symptoms include vaginal bleeding, abdominal pain, and polyps
- TCGA collected 57 samples for the UCS project

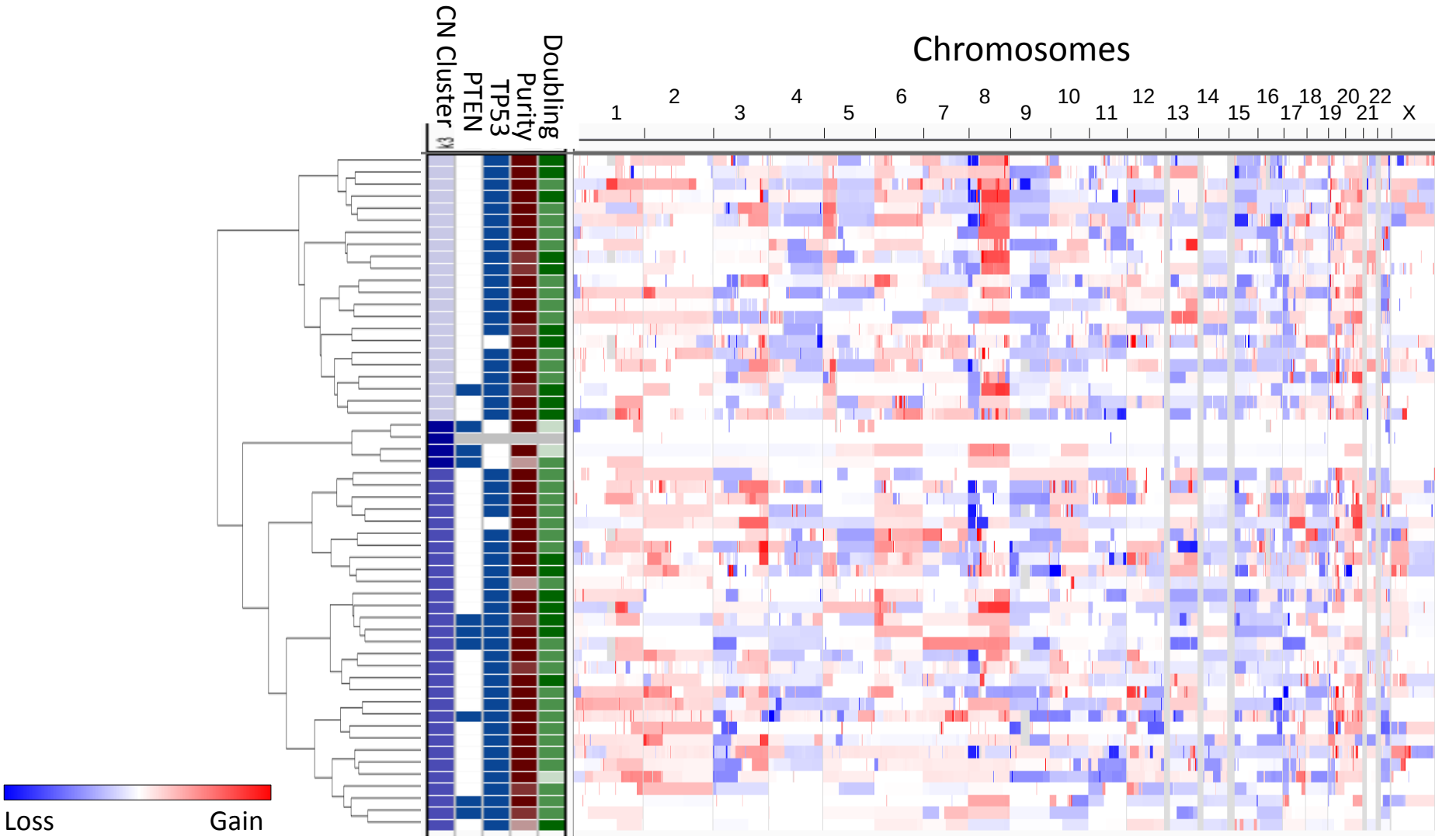
Carcinosarcoma histologic classification



- Sarcomatous components are classified as homologous or heterologous based on whether they reflect tissue types normally found within the uterus.
  - Homologous (found in the uterus), commonly, undifferentiated stromal sarcoma; associated with more favorable prognosis than heterologous
  - Heterologous (found external to the uterus), commonly, rhabdomyosarcoma

Ack: Rob Soslow

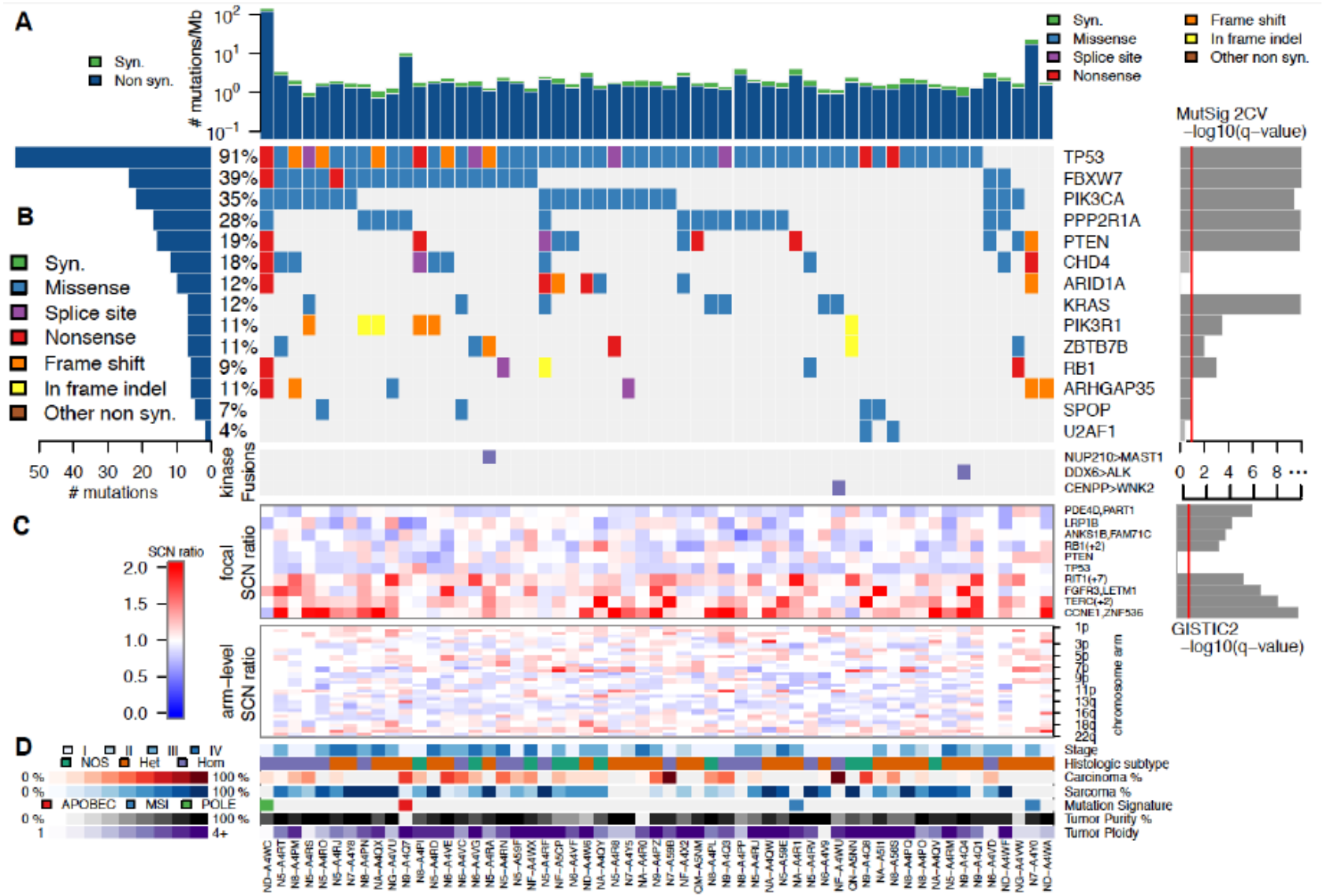
Heterogeneous disease – no robust clusters found



Copy number aberrations unsupervised clustering

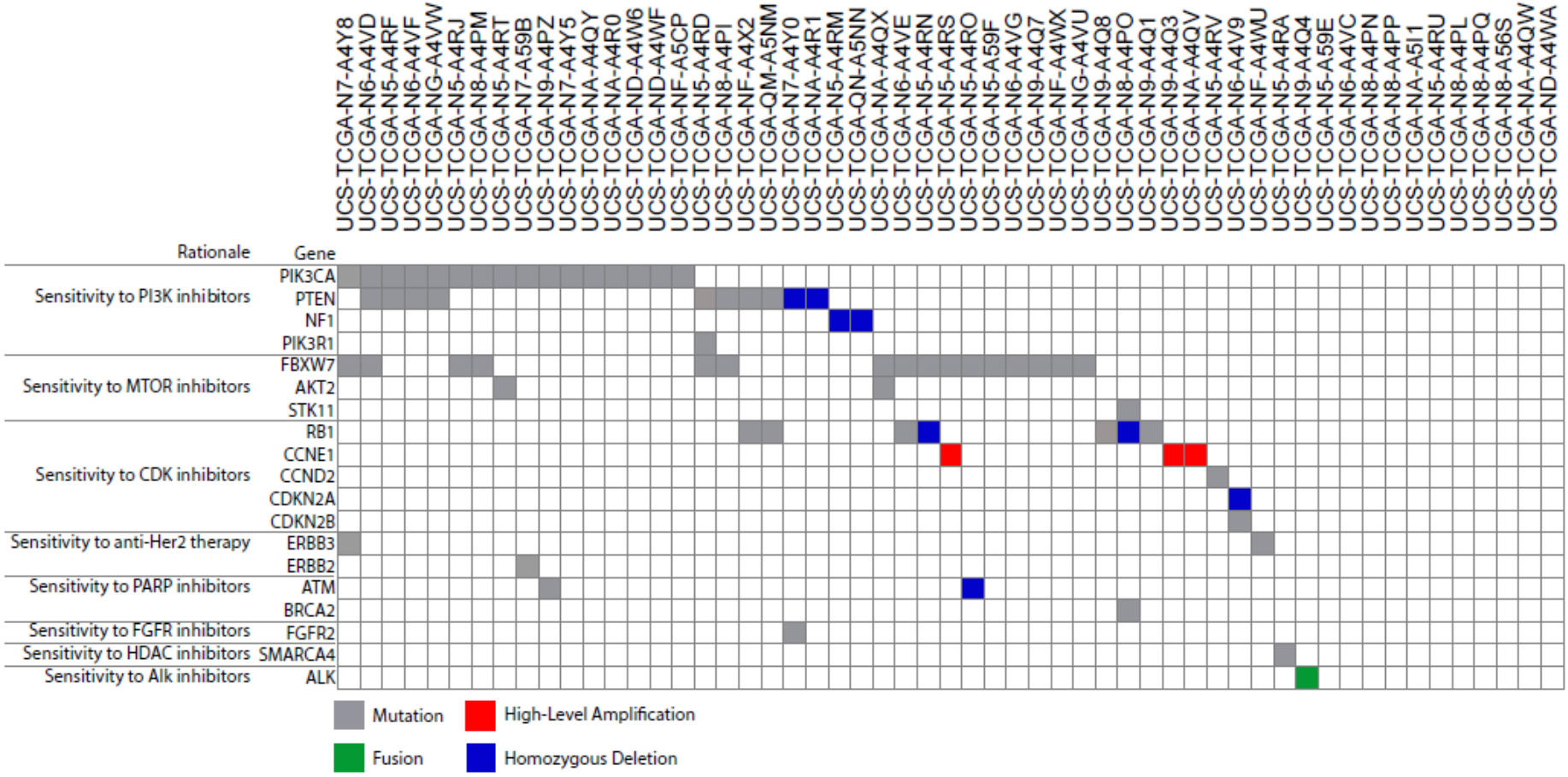
Ack: Chip Stewart, Andrew Cherniack

Landscape of DNA aberrations in UCS



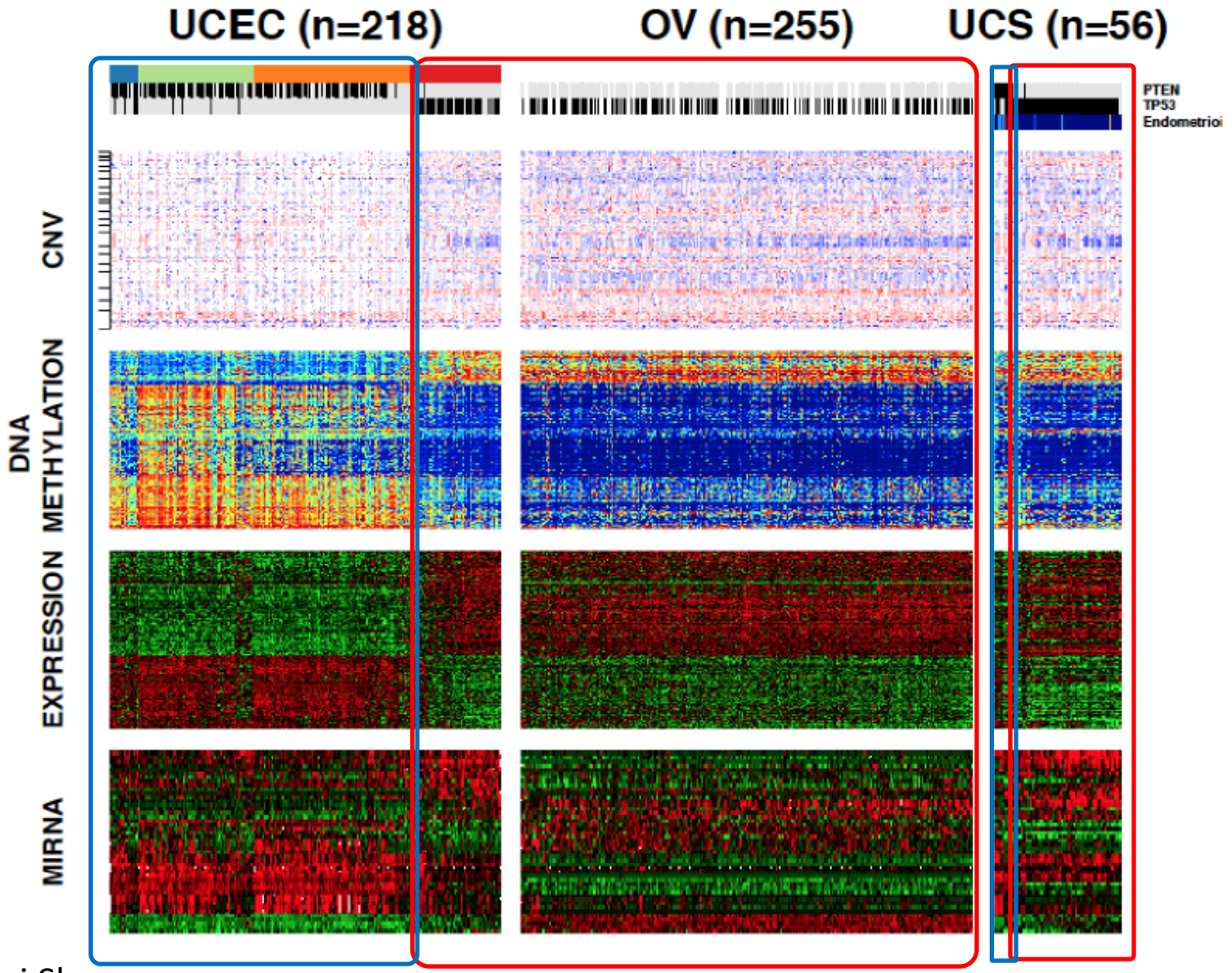
Ack: Chip Stewart, Andrew Cherniack

Potential therapeutic opportunities in UCS



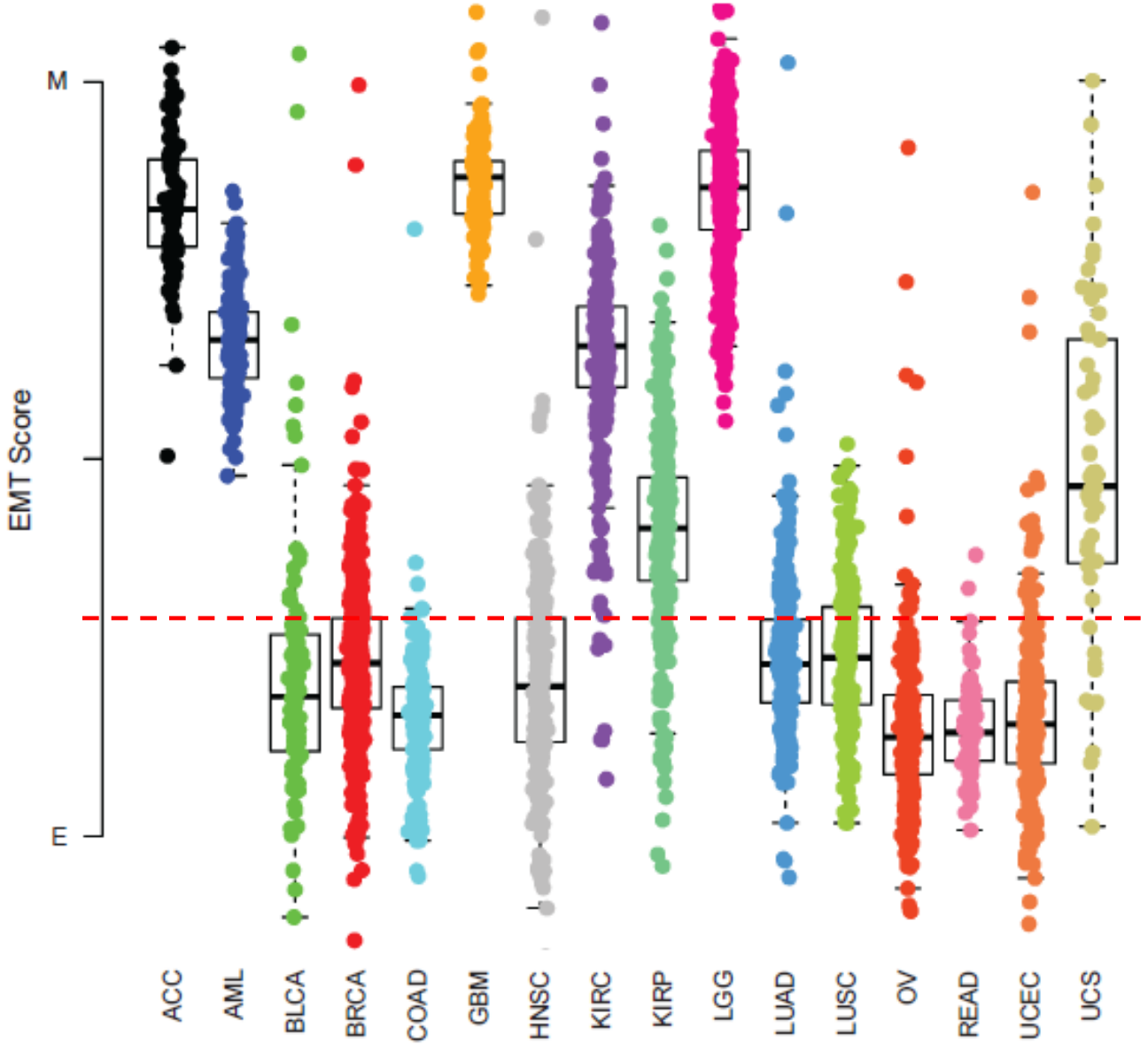
Ack: Brad Murray

UCS vs. endometrial (UCEC) and ovarian (OV) cancers



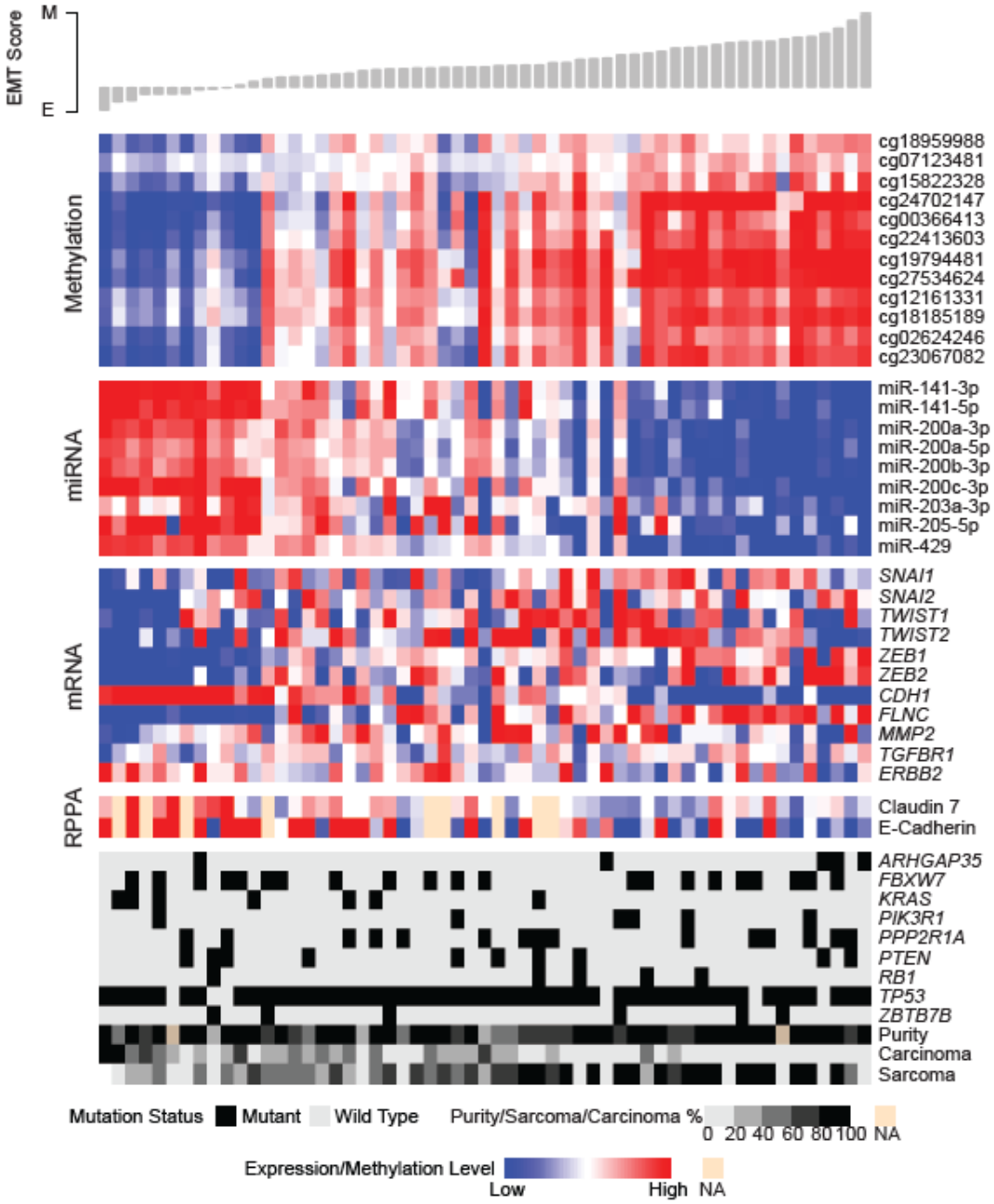
Ack: Hui Shen

Pan-Cancer EMT scores – UCS has the largest range of values



Ack: Lauren Byers, Vonn Walter

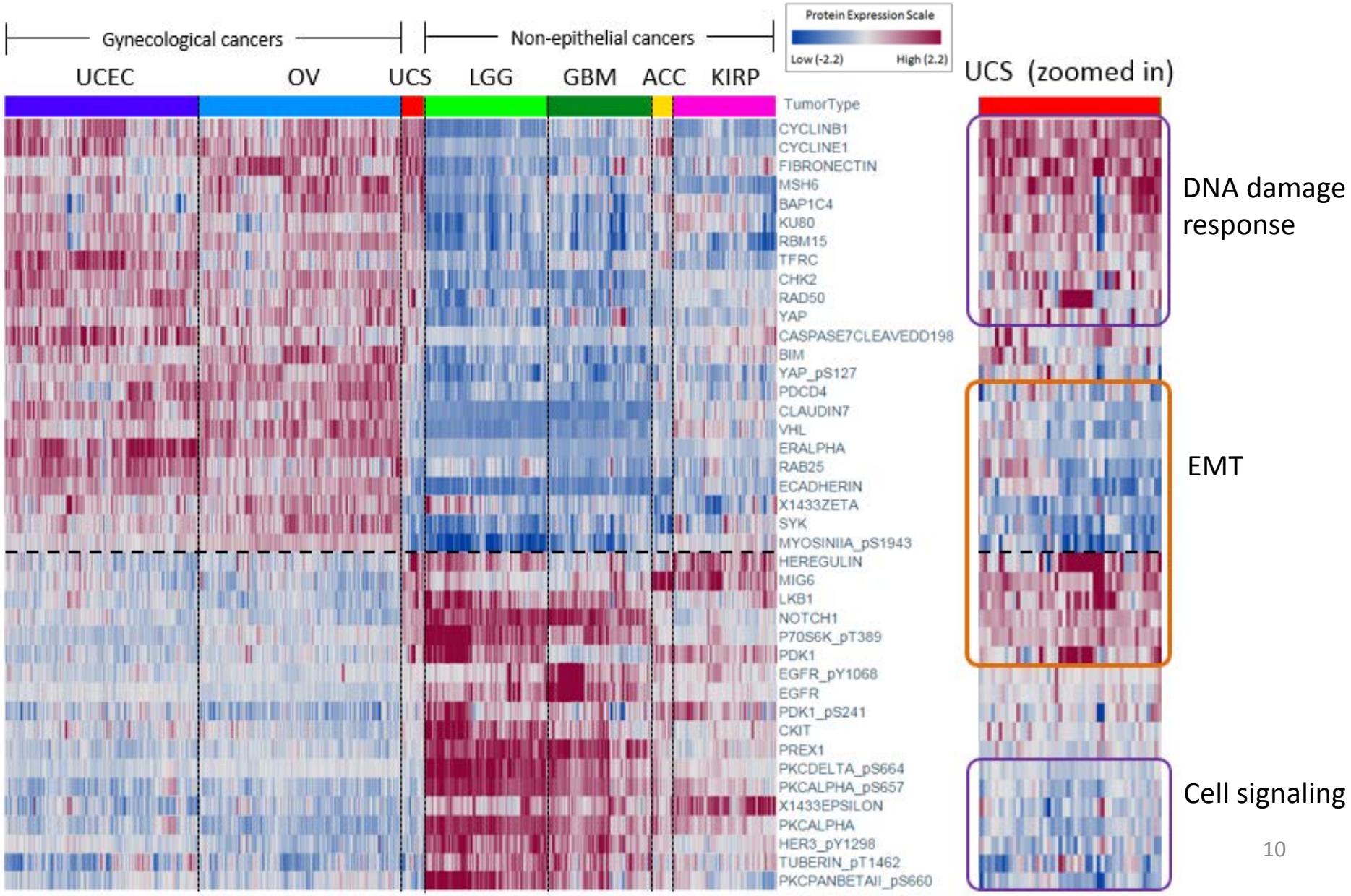
Epithelial to mesenchymal transition (EMT) in UCS



Promoters for miR-200 family

Ack: Vonn Walter et al.

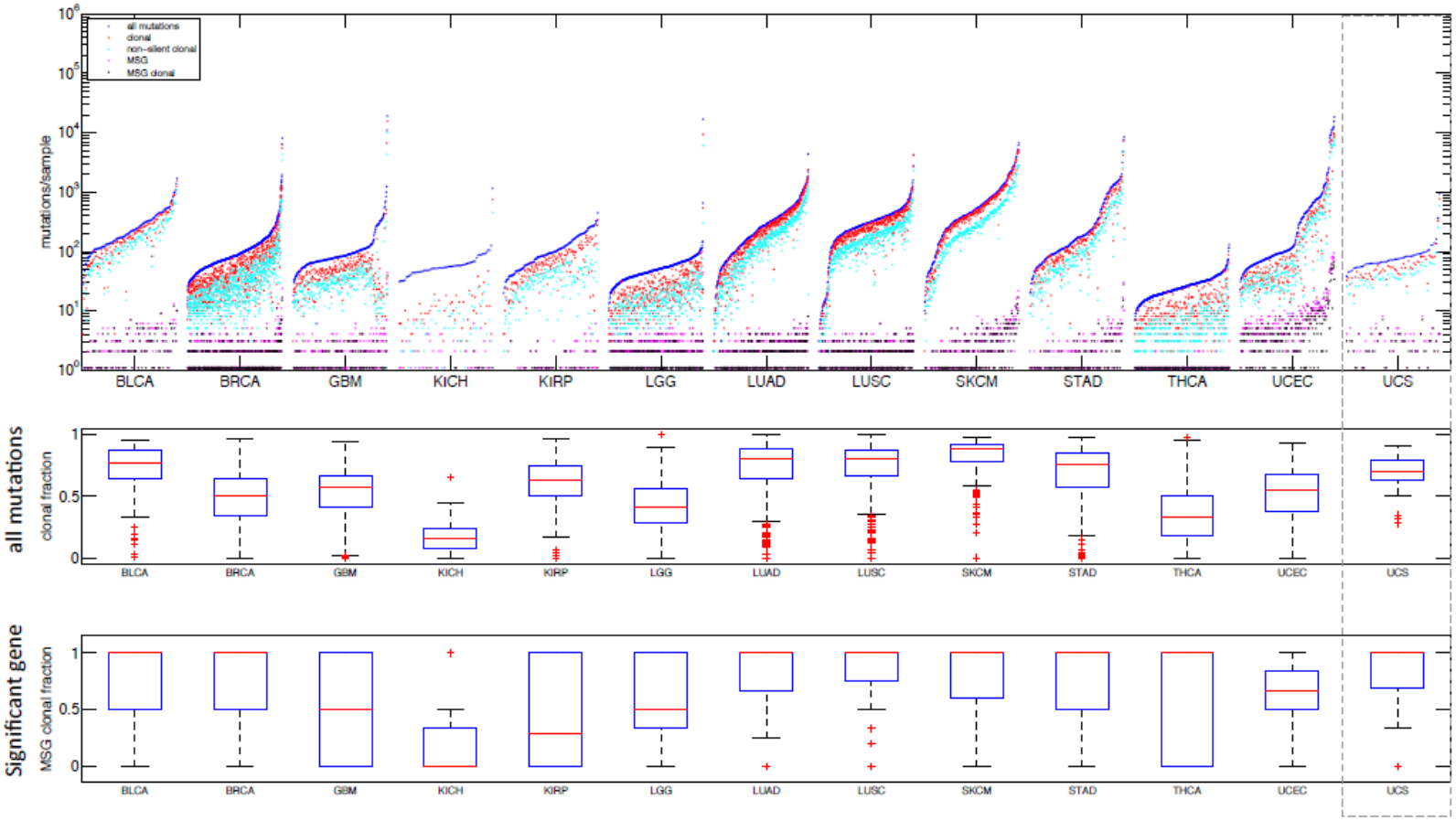
Pan-cancer proteomics comparison of UCS



Competing theories of development of UCS

1. Collision theory: A collision between adjacent, independent carcinomas and sarcomas
2. Combination theory: A combination of cellular masses that diverged early from a common precursor stem cell
3. Conversion theory: Monoclonal origin with late divergence of the carcinoma into the sarcoma

Pan-cancer comparison of mutation clonality in UCS



- 73% of all mutations, 82% in SMGs are clonal in UCS
- Similar to most other tumor types
- <u>Supports the conversion theory</u>

Ack: Chip Stewart, Andrew Cherniack

Summary

- UCS is a rare, aggressive tumor, found in <5% of uterine cancers
- Median survival of 24 months, compared to 60 months for endometrial cancer (UCEC)
- Very heterogeneous disease with poor clusters
- Extensive CNVs and recurrent mutations in TP53 (91%), FBXW7 (39%), PIK3CA (35%), PPP2R1A (28%), PTEN (19%)
- Identified DNA aberrations with potential therapeutic relevance
- Most UCS samples resemble serous endometrial and ovarian cancer samples, with TP53 mutations and high CNVs, but a few samples resemble endometrioids with PTEN mutations and low CNVs
- UCS spans a large range of EMT scores compared to other tumors
- Promoters of miR-200 family are methylated in samples with high EMT scores, with correspondingly low miR-200 expression
- UCS shares DNA damage response and cell signaling proteomic features with gynecological tumors, but EMT features with non-epithelial tumors
- Most of the mutations are clonal, supporting the conversion theory of UCS tumor development

Acknowledgements

Co-chair

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UCS writing committee

Andrew Cherniack (Broad)
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Hui Shen (Van Andel)
Julia Zhang (NCI)

Review committee

Raju Kucherlapati (Harvard)
John N. Weinstein (MD Anderson)
Gordon B. Mills (MD Anderson)

Pathologists

Rosemary Zuna (OUHSC)
Russell Broadus (MD Anderson)
Rob Soslow (MSKCC)

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