

Genomic Approaches to the Tumor Microenvironment

Alexandra Snyder, MD



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#SITC2018

Presenter Disclosure Information

Alexandra Snyder

The following relationships exist related to this presentation:

Merck – current employee, stock ownership

Adaptive Biotechnologies – former employee

BMS – prior research funding

Genentech – prior consulting

MSKCC – prior employee and research funding

Topics for Discussion

- Background: genomic and tumor microenvironment (TME) heterogeneity
- Application of molecular techniques to measure tumor microenvironment heterogeneity in ovarian cancer
- Correlations between molecular and radiomics assessments of the TME



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Diversity of Methods with which to Evaluate the Tumor Microenvironment (TME)

- Multiplex IHC or IF
- RNAseq with pathway analysis or deconvolution
- Radiomics
- High-dimensional flow cytometry
- Quantitative and Spatially Resolved Imaging Mass Cytometry
- Single cell RNA sequencing



Diversity of Methods with which to Evaluate the Tumor Microenvironment (TME)

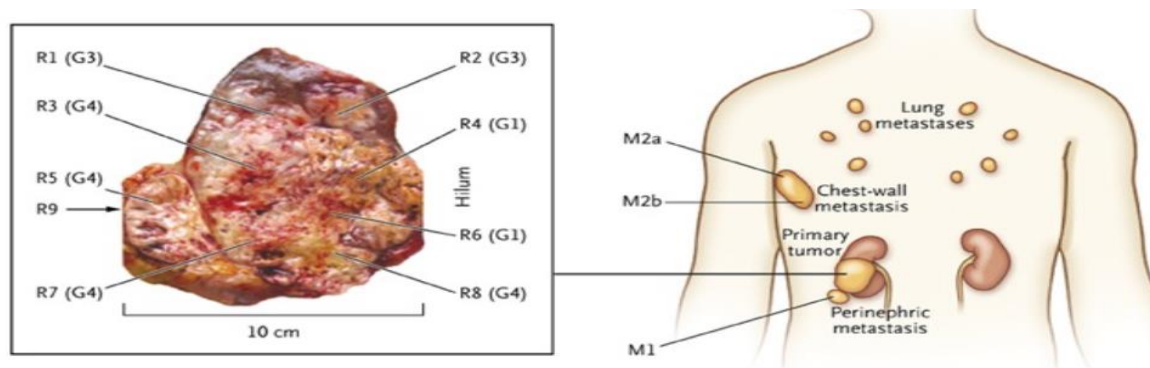
- **Multiplex IHC or IF**
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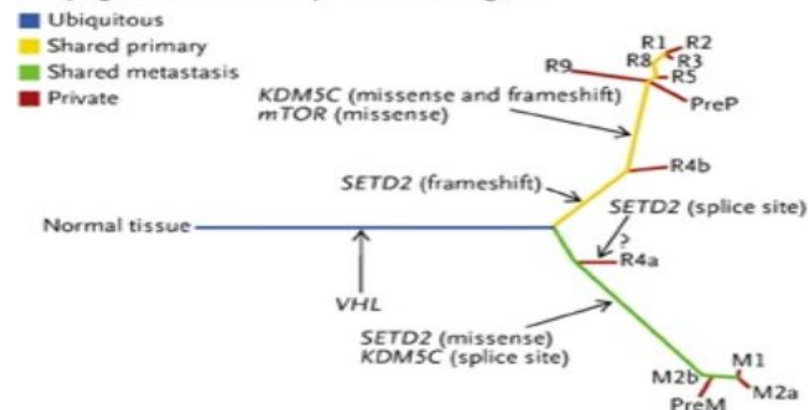
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Multi-Region Sequencing Demonstrated Heterogeneity & Convergent Evolution in RCC



Is this phenomenon seen in other cancers?

Phylogenetic Relationships of Tumor Regions



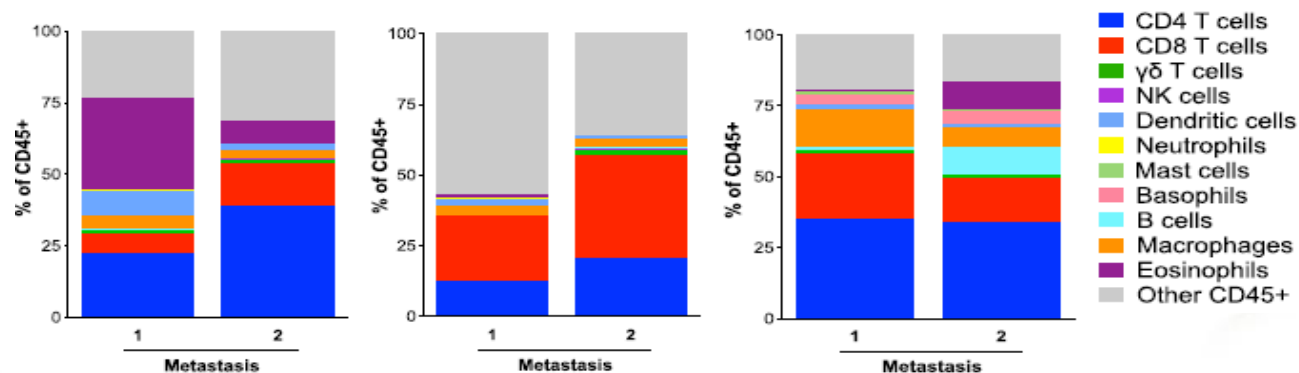
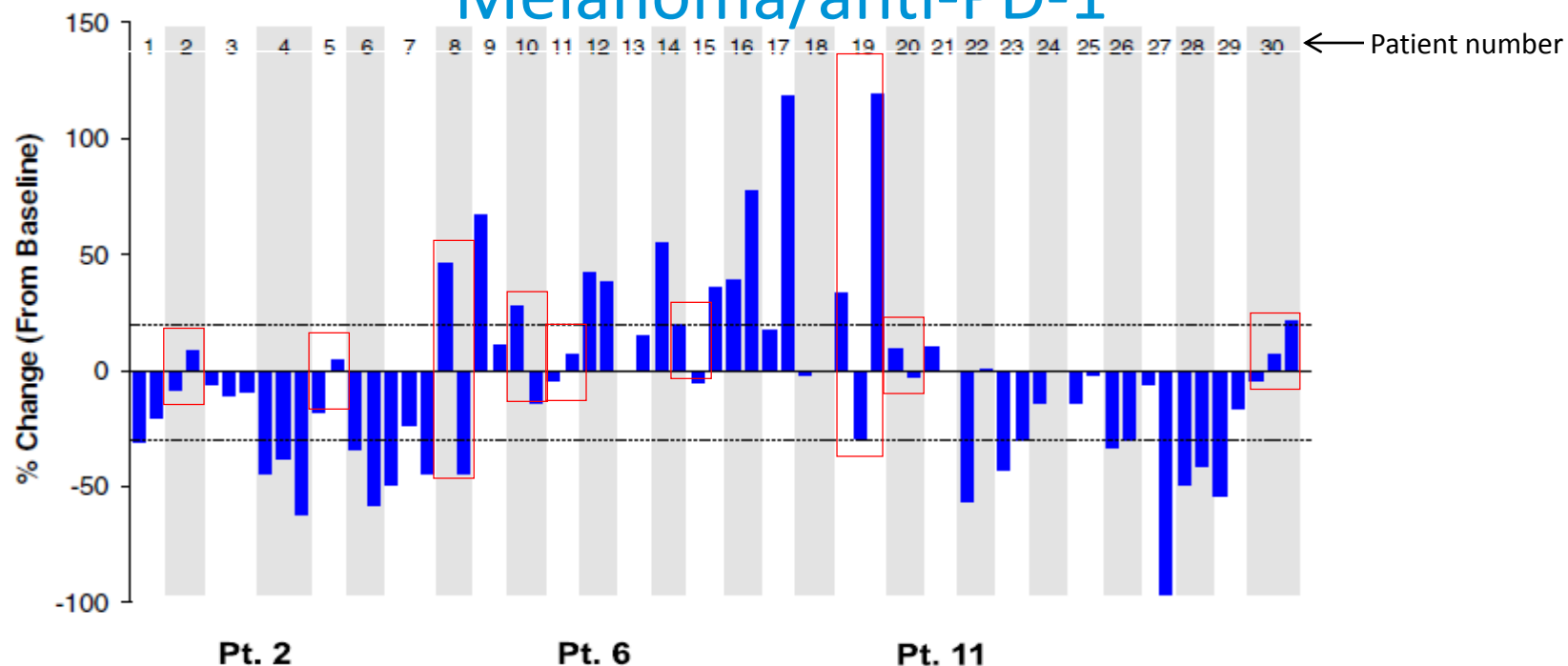
Genetic & Tumor Microenvironment Heterogeneity: Melanoma/anti-PD-1



Alex Reuben
MDACC



Jen Wargo
MDACC



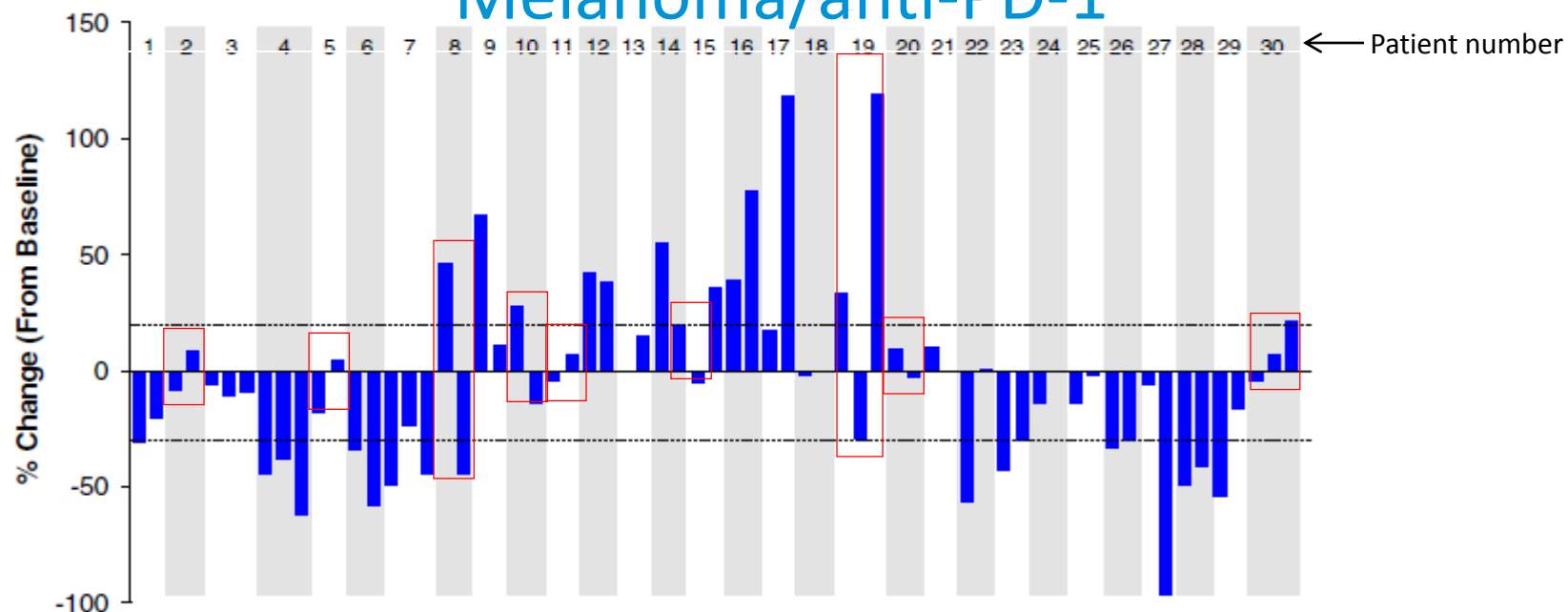
Genetic & Tumor Microenvironment Heterogeneity: Melanoma/anti-PD-1



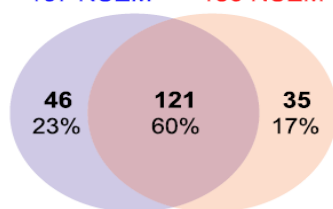
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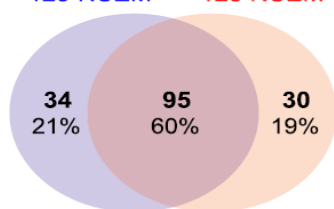


Metastasis 1 **Metastasis 2**
167 NSEM 156 NSEM



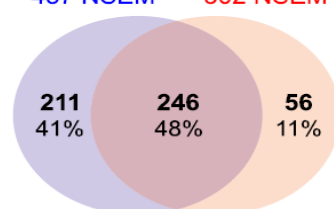
Pt. 3

Metastasis 1 **Metastasis 2**
129 NSEM 125 NSEM



Pt. 7

Metastasis 1 **Metastasis 2**
457 NSEM 302 NSEM



Pt. 12

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Topics for Discussion

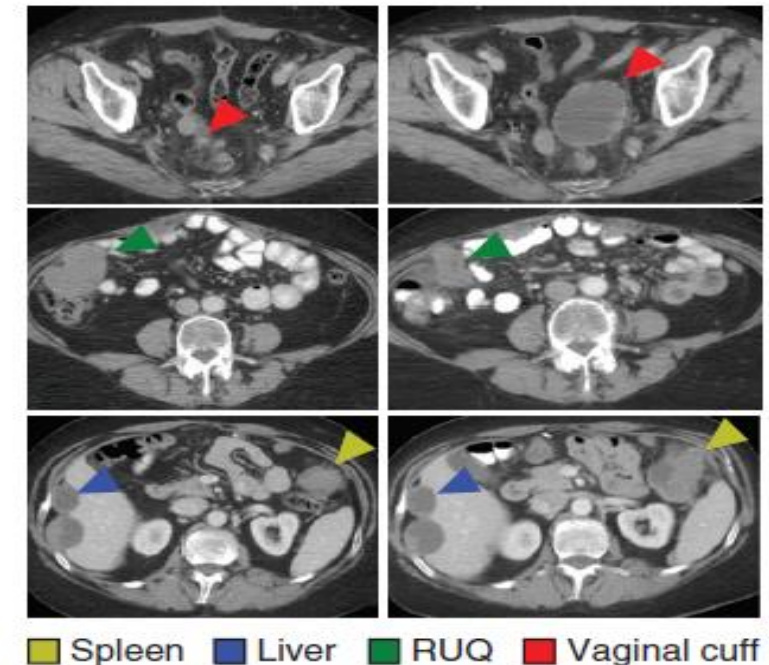
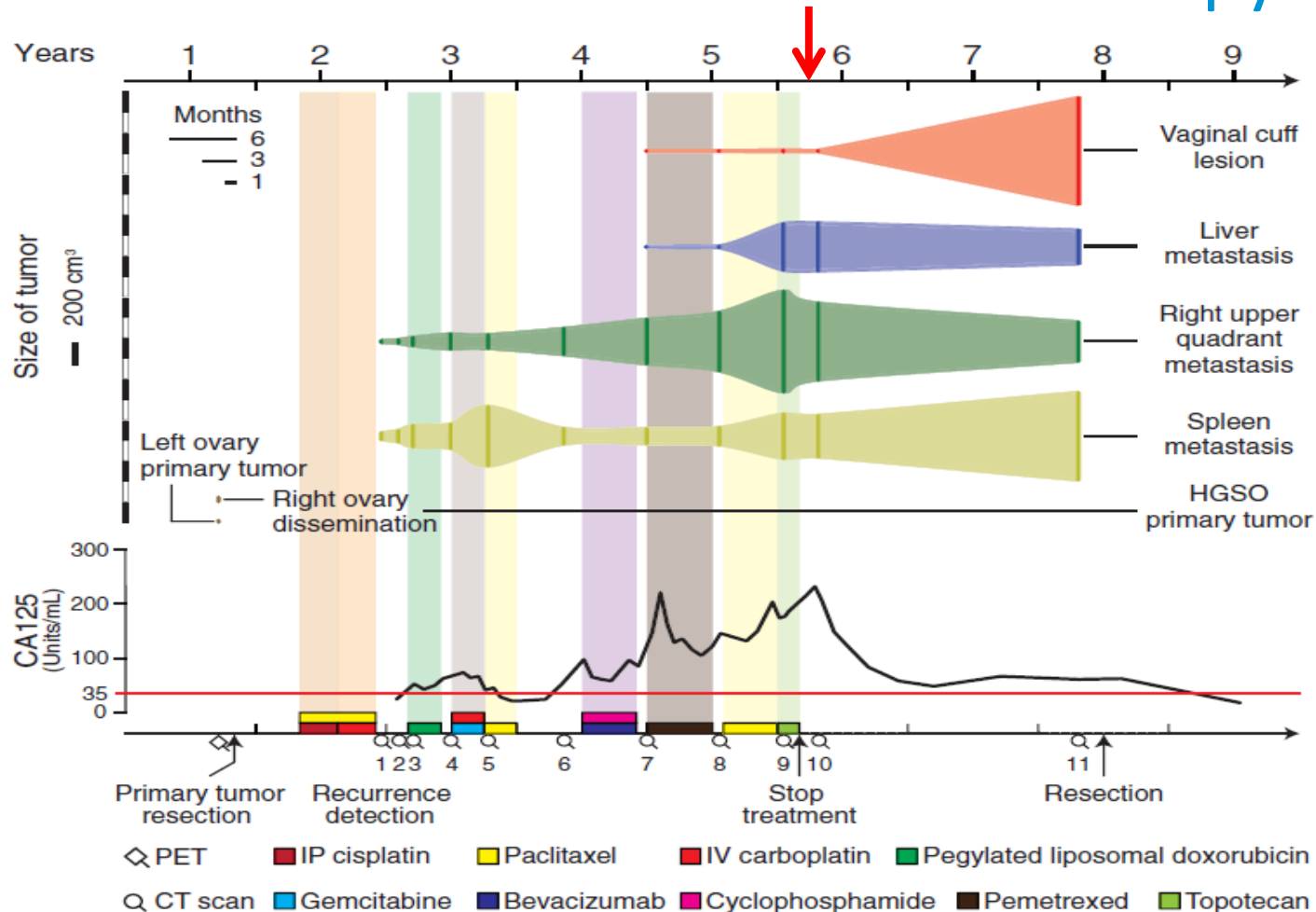
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Contrasting Fates of Tumors in a Patient with Recurrent Advanced Ovarian Cancer Off Therapy



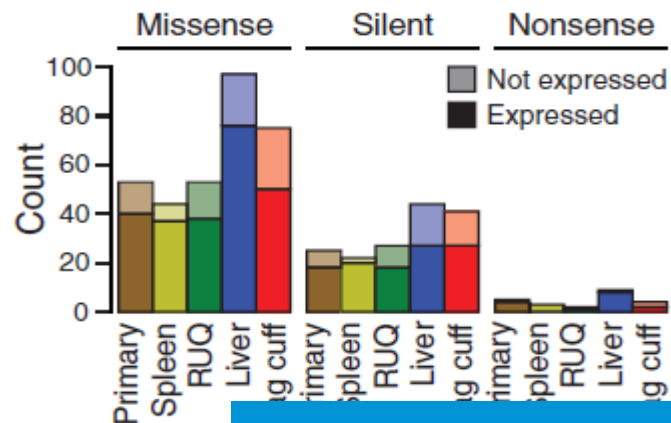
Genomic and Tumor Microenvironment Heterogeneity in a Patient with HGSOc



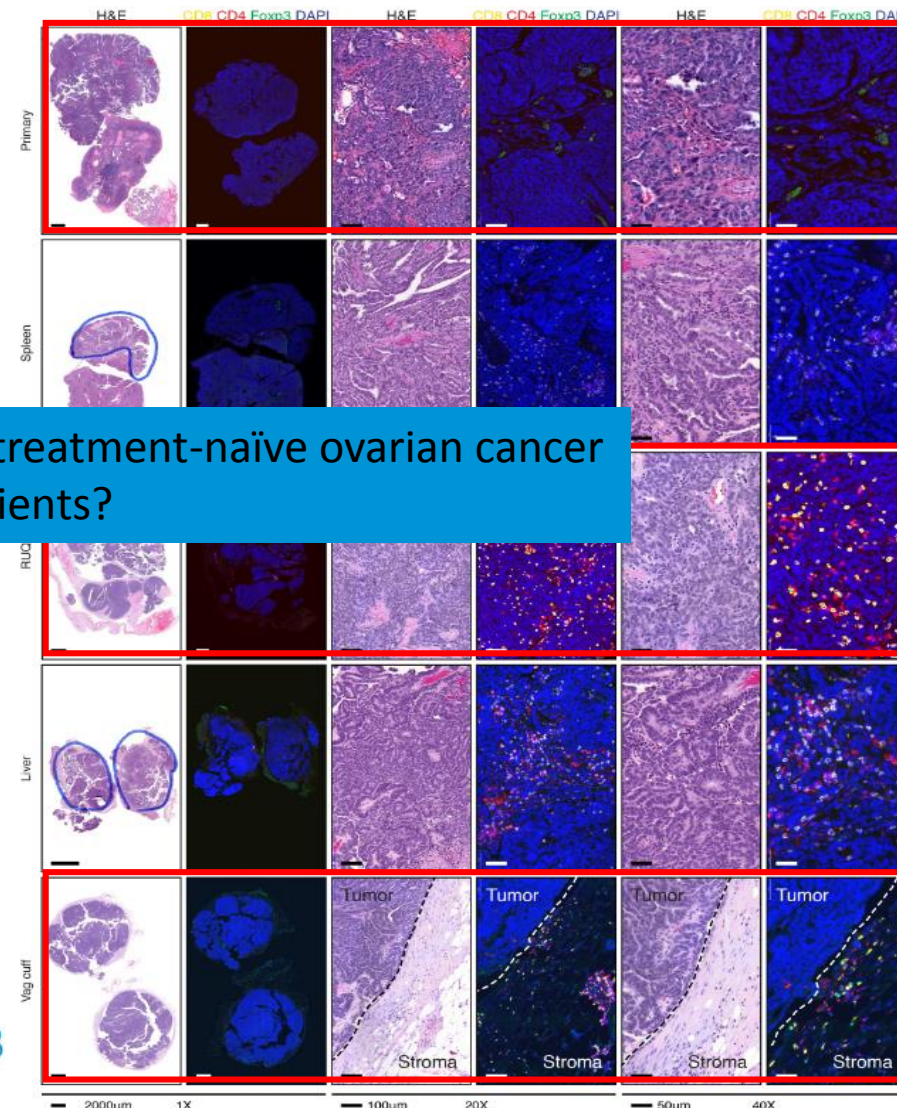
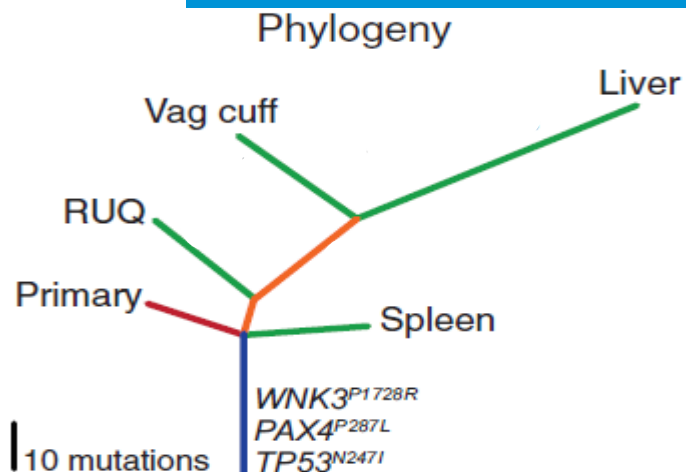
Martin Miller
CRUK Cambridge



Alejandro Jimenez Sanchez
CRUK Cambridge



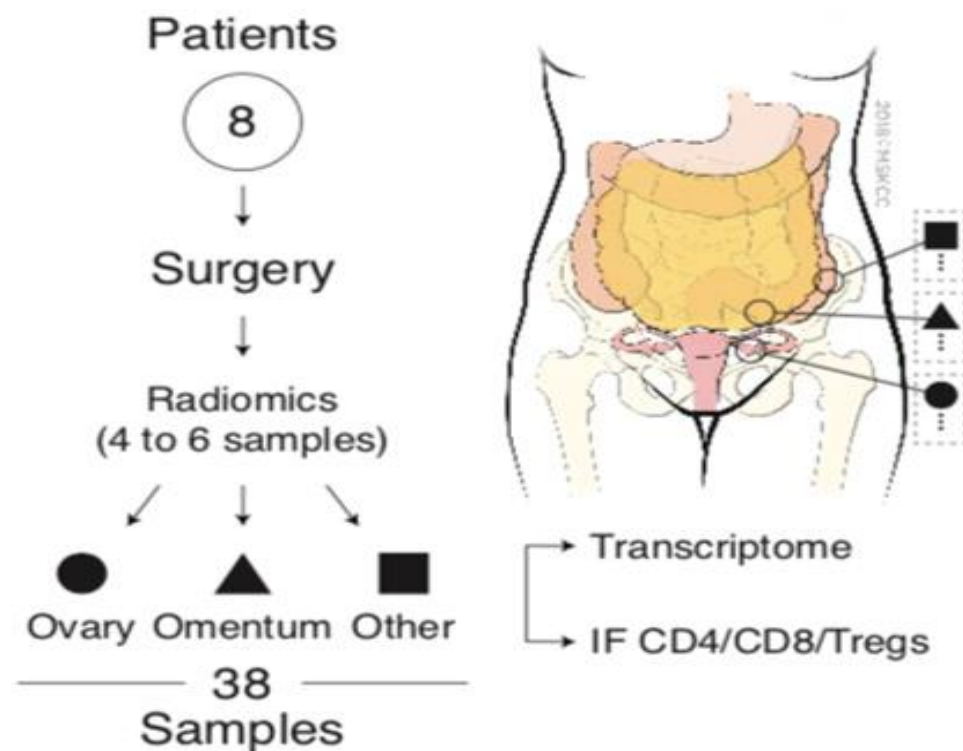
Is this phenomenon seen in treatment-naïve ovarian cancer patients?





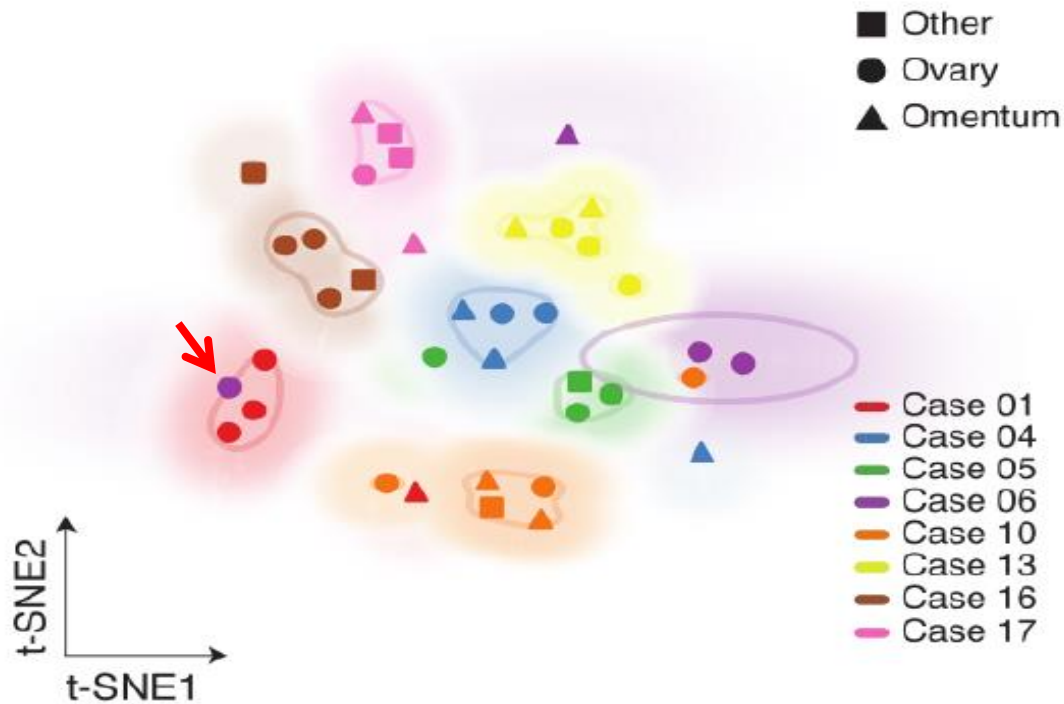
Evis Sala
CRUK Cambridge

Multi-Site and Intra-Site Sub-Sampling of 8 Patients with HGSOC

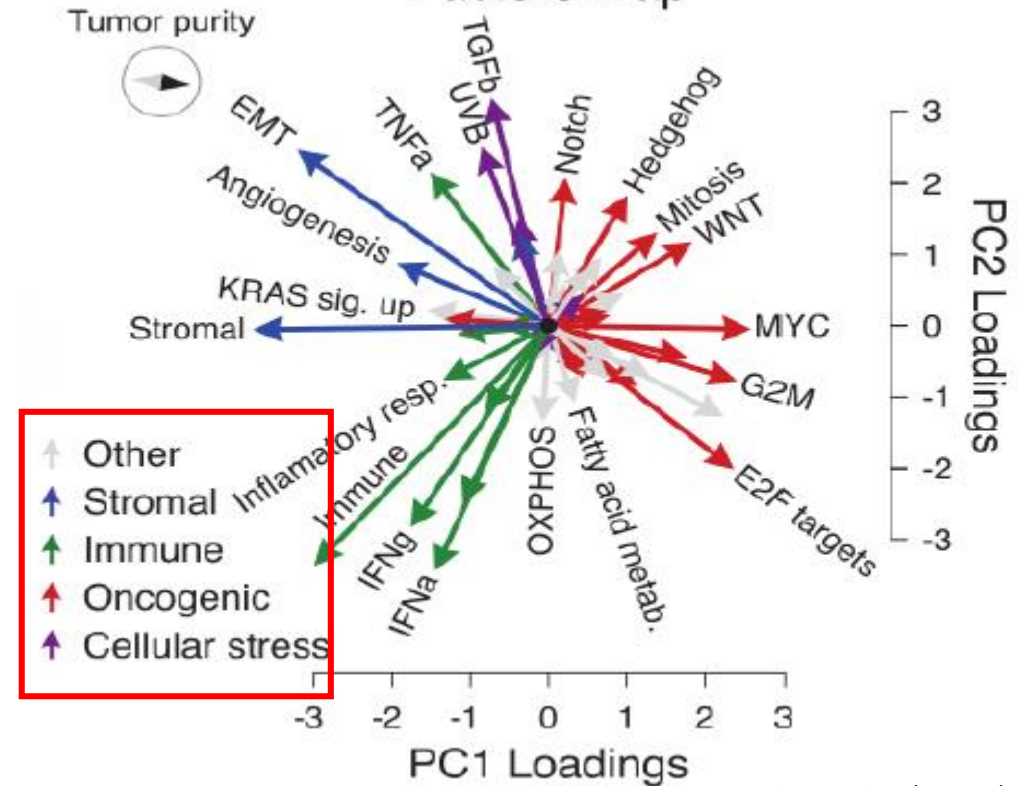


Immune Signaling Contributes to Majority of Transcriptional Variance

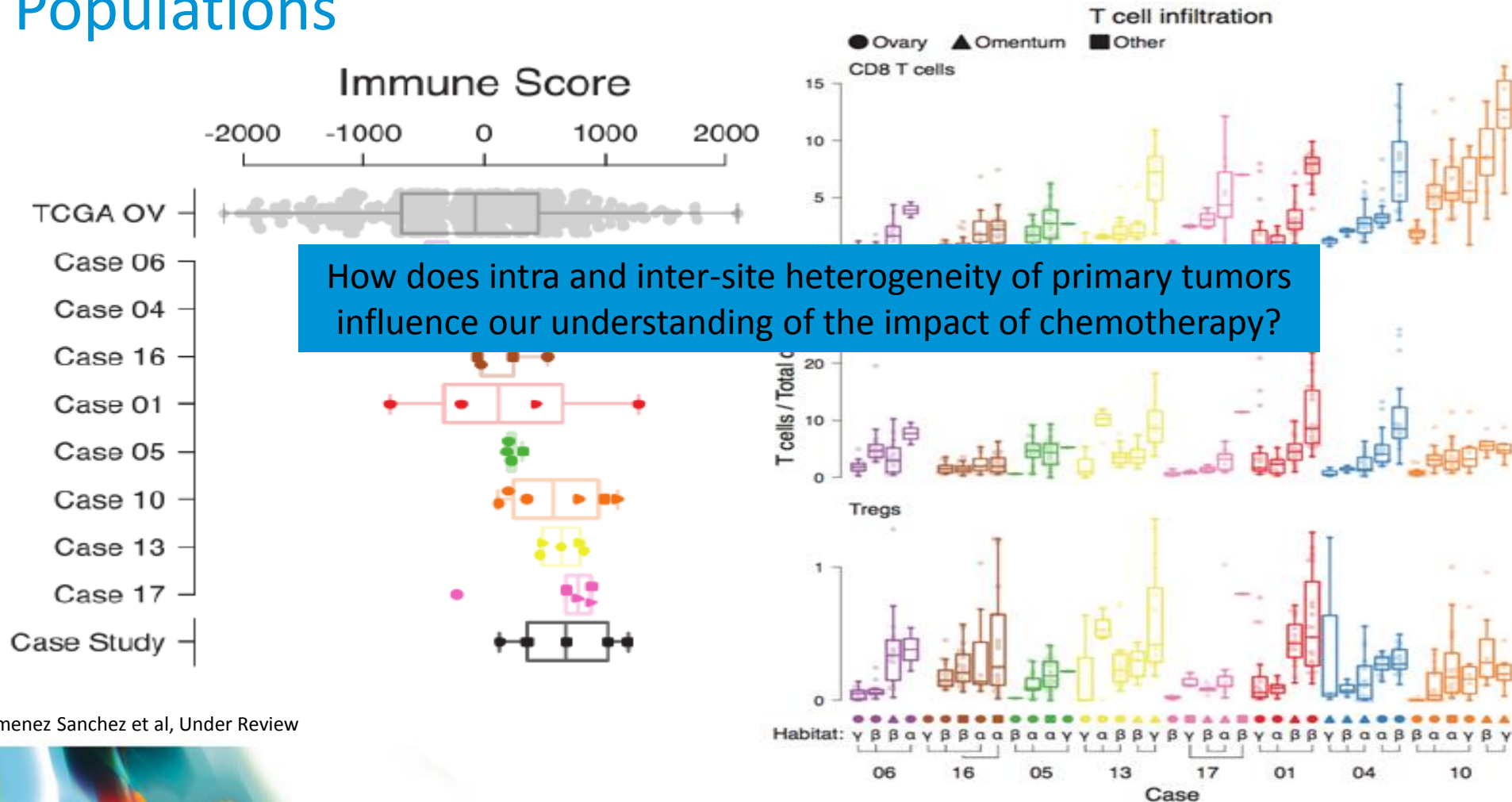
t-SNE analysis of transcriptomes



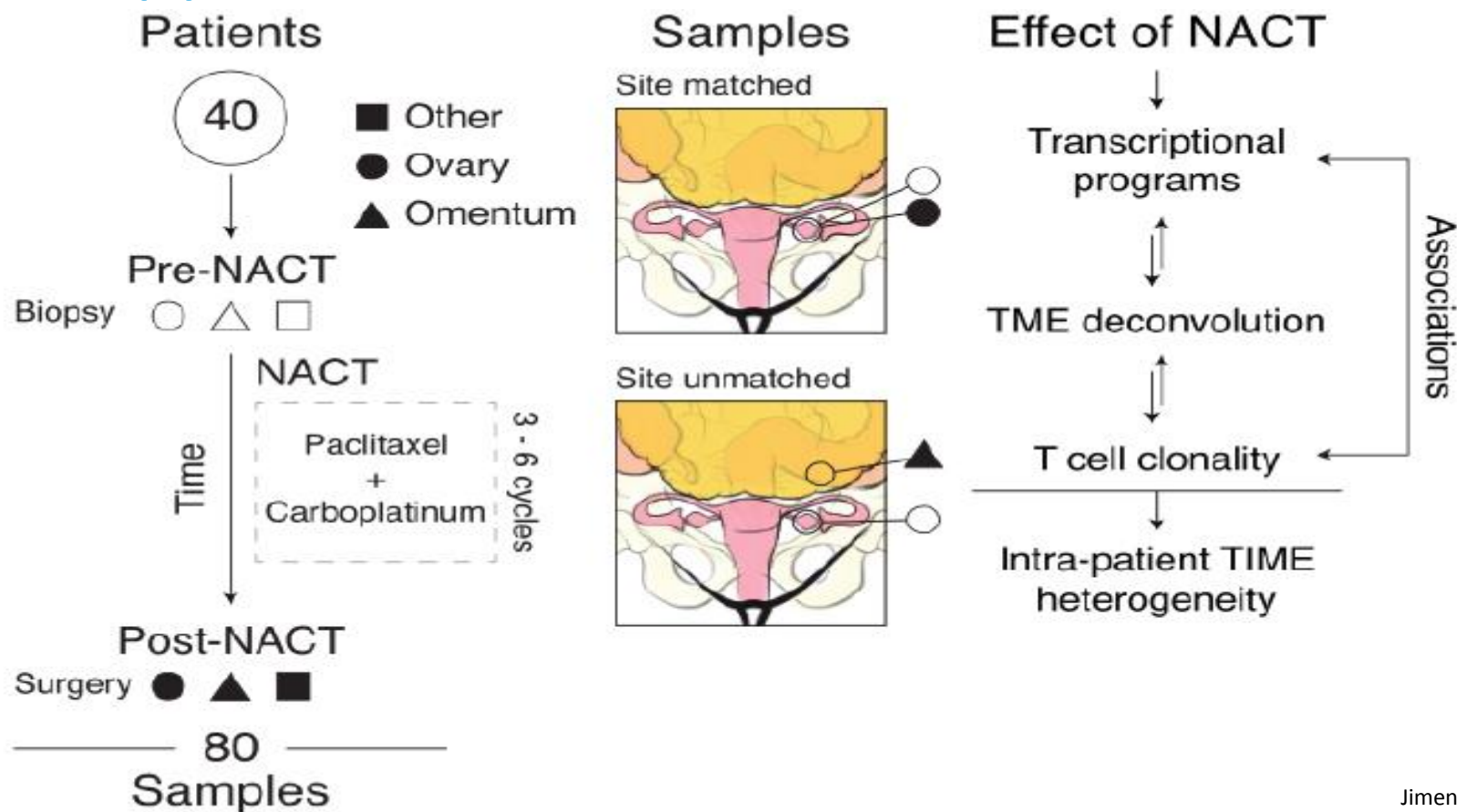
Factors map



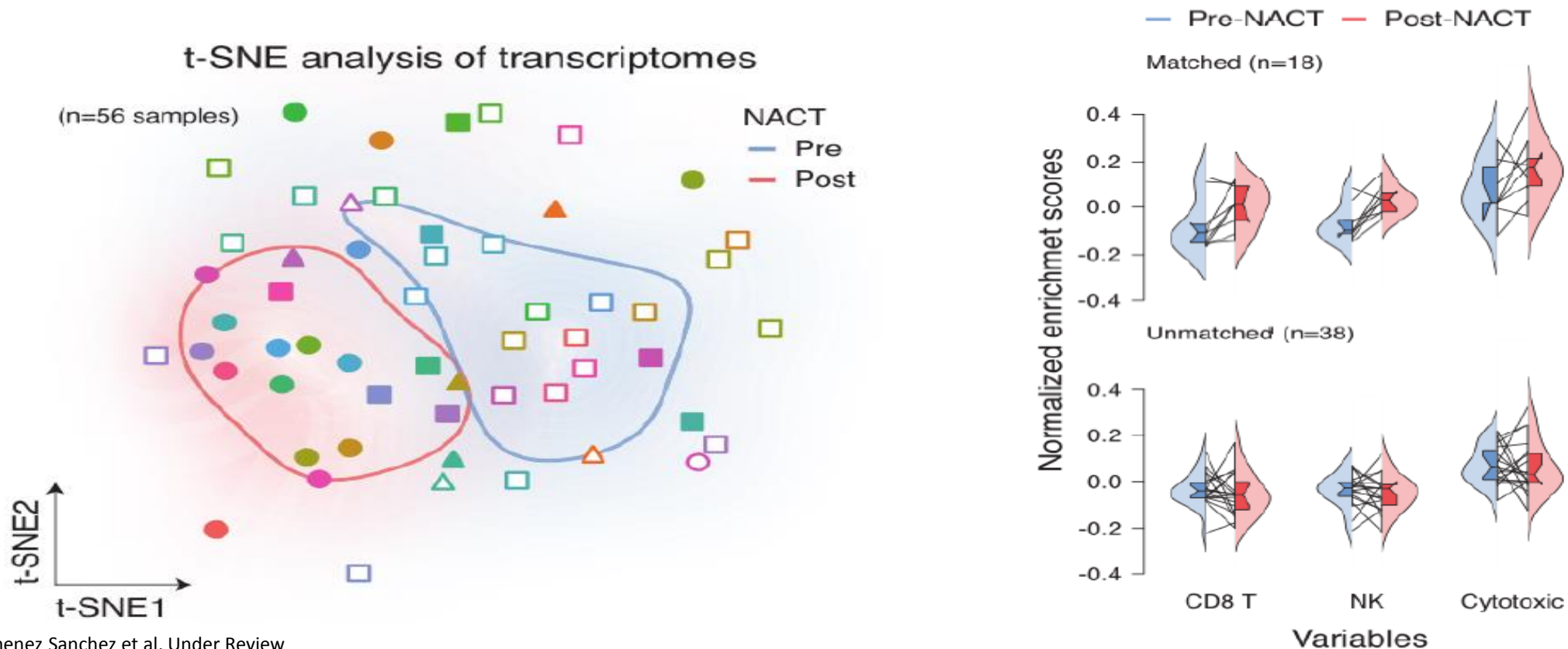
Inter- and Intra-Site Variability of Infiltrating Lymphocyte Populations



Evaluation of Site Matched and Unmatched Tumors after Chemotherapy

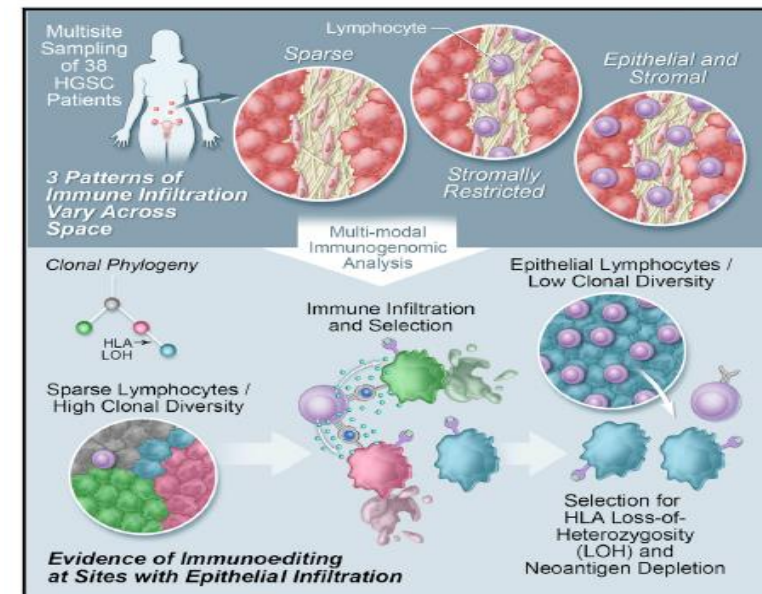
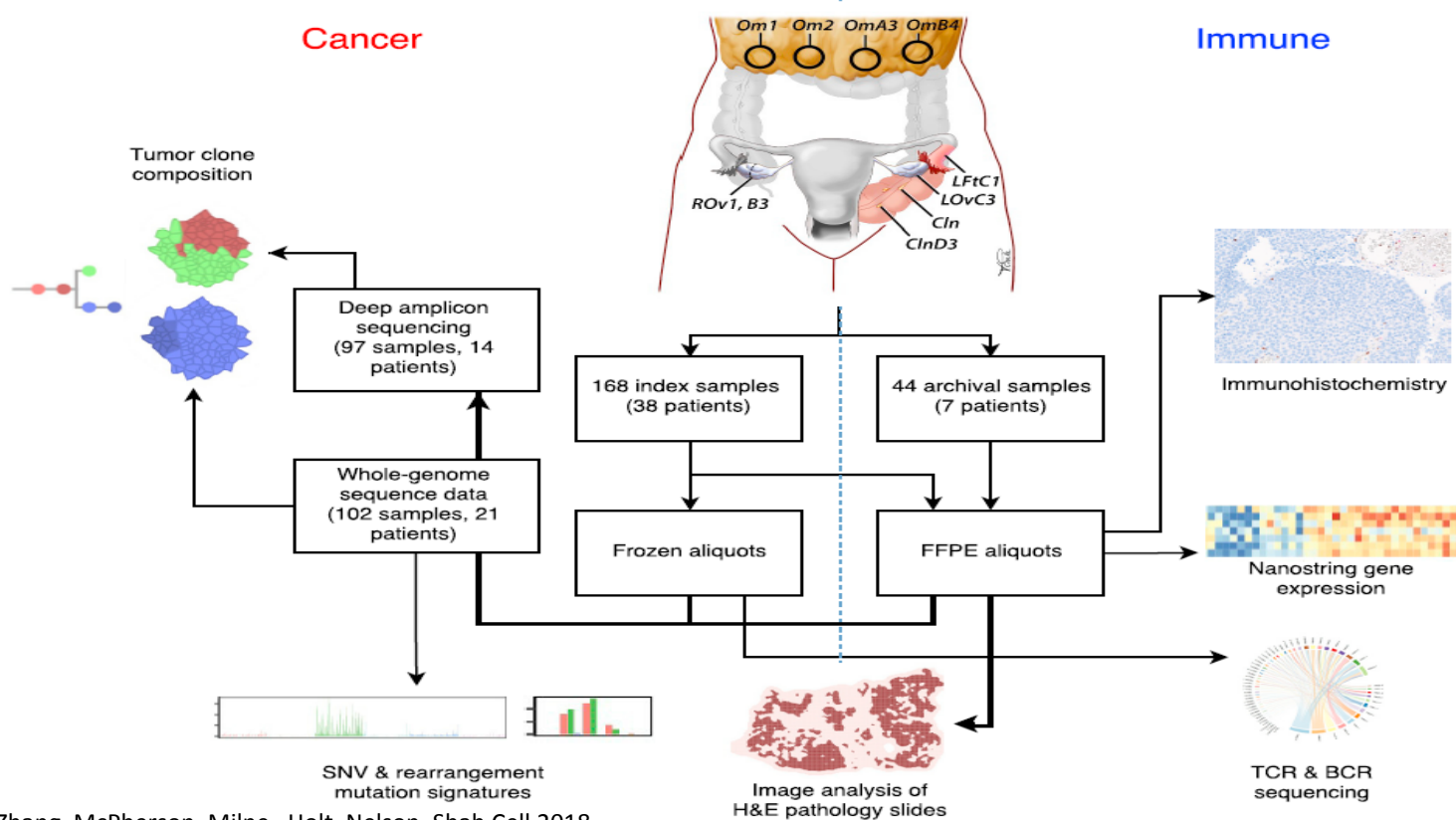


Site-Matched Deconvolution Reveals Increase in Cytotoxic Immune Populations After Chemotherapy



Jimenez Sanchez et al, Under Review

Concurrent Genomic and Tumor Immune Microenvironment Heterogeneity in Ovarian Cancer



Highlights

- Immune infiltrates vary across space within patients at the time of diagnosis
- Immune infiltration shapes malignant cell evolutionary trajectories
- T cell clones track with tumor clones across spatial sites within patients
- Immune infiltrates and mutational processes show prognostic interactions

Topics for Discussion

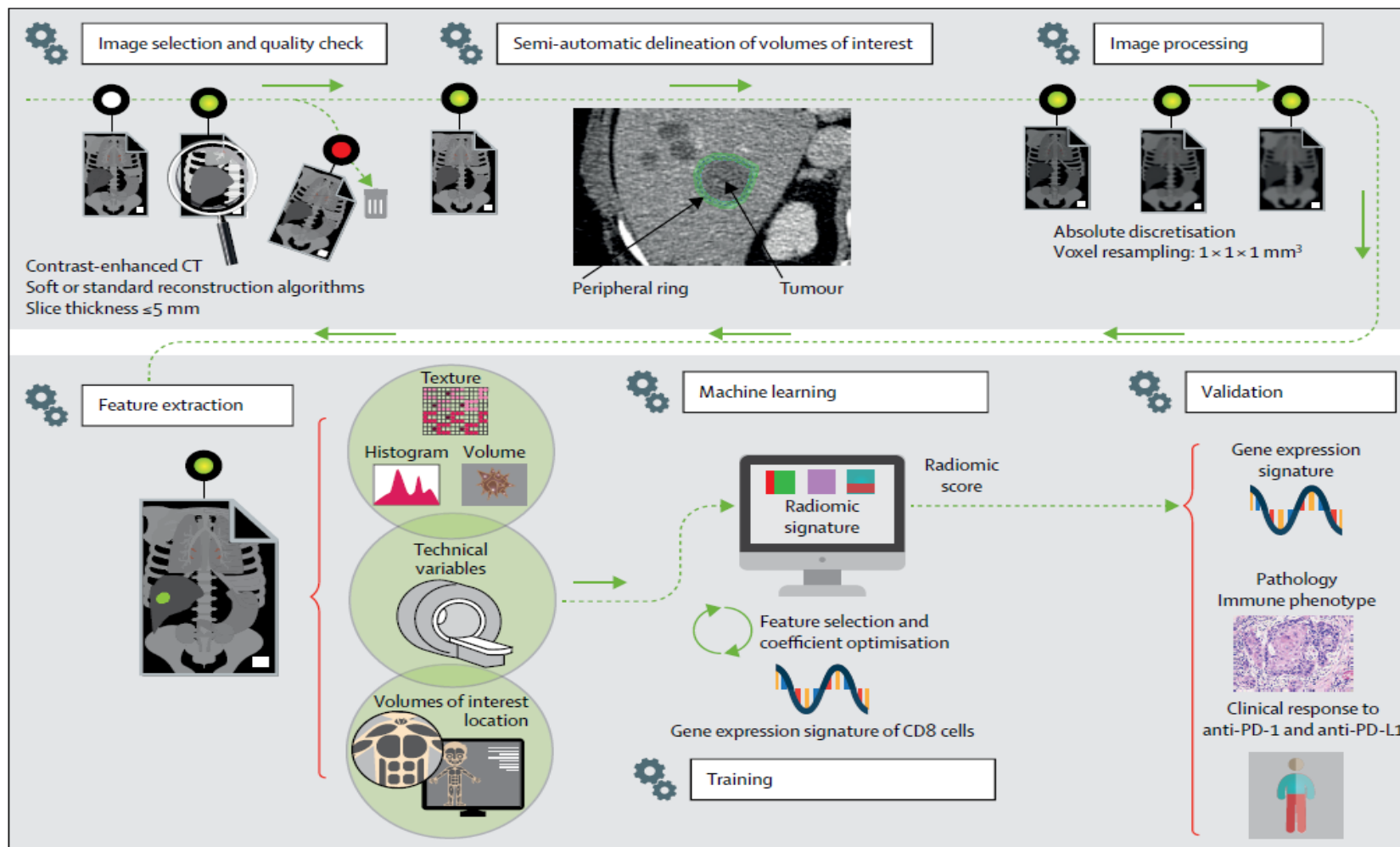
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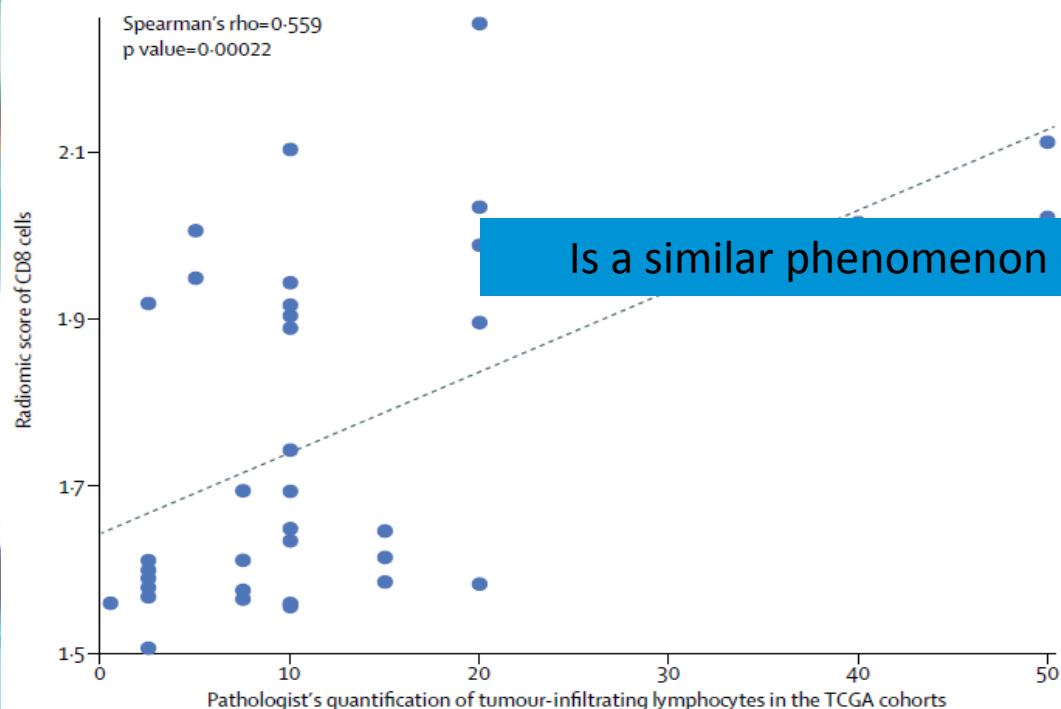
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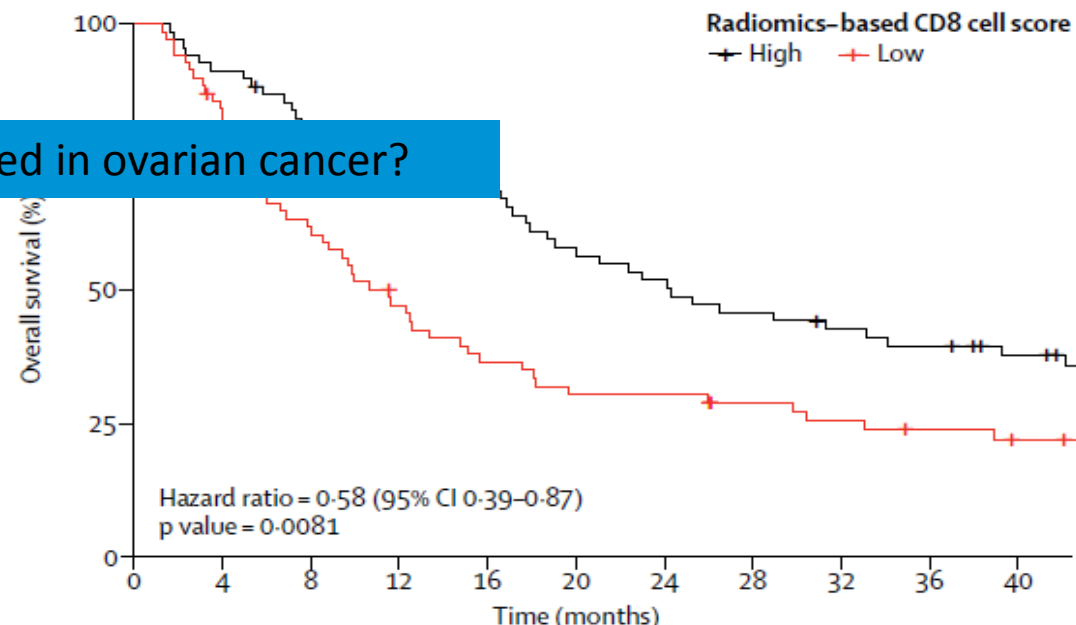
Radiomics to Non-Invasively Evaluate the TME



Despite Modest Correlation with Pathologically-Defined TIL, Radiomics-Based CD8 Count Correlates with OS

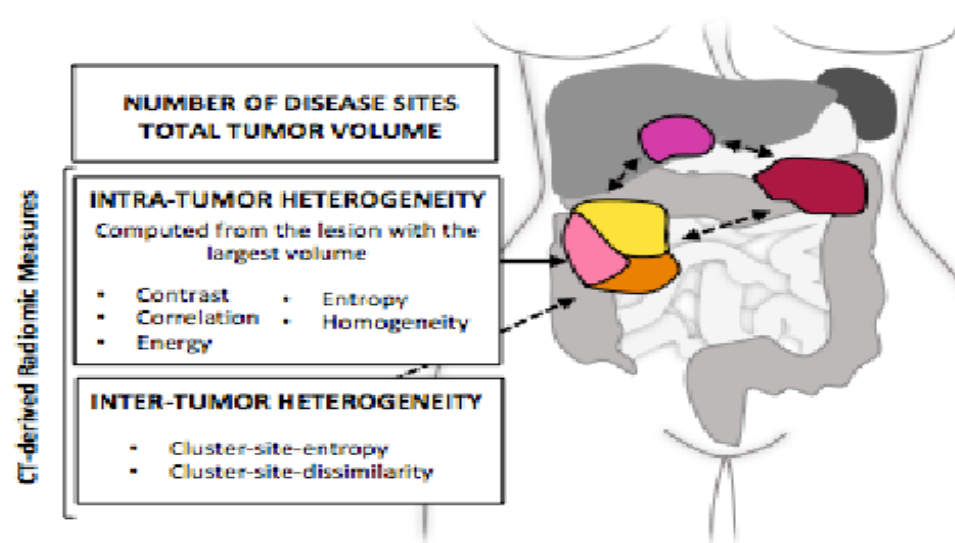


Is a similar phenomenon observed in ovarian cancer?



Radiomics in HGSOC Patients: Indirect Measure of TME Heterogeneity

*Quantitative Imaging And Radiomic Measures
From The Baseline Contrast-enhanced CT*



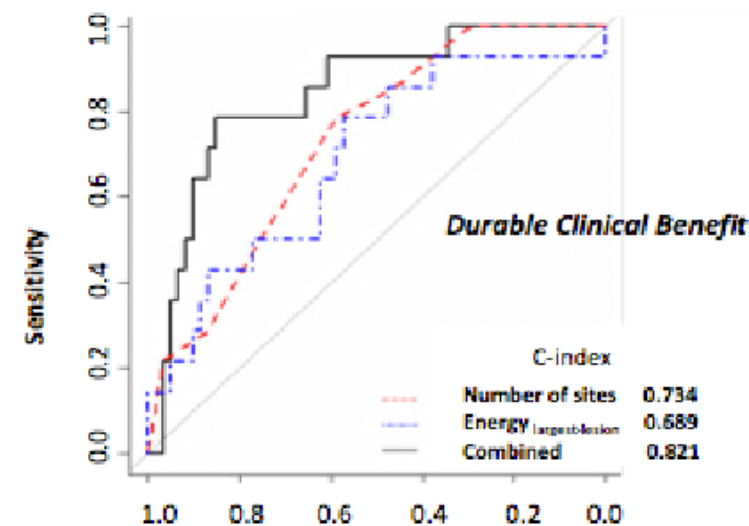
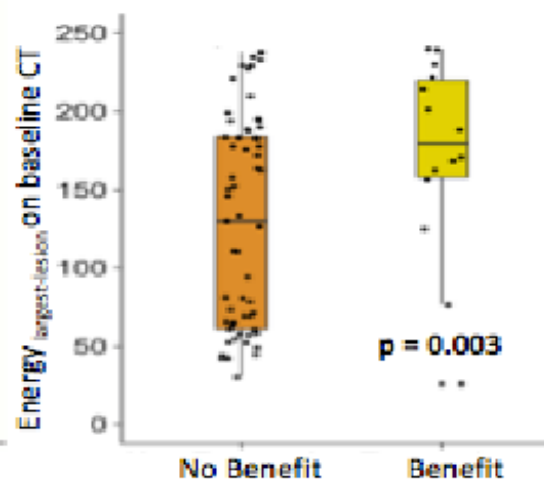
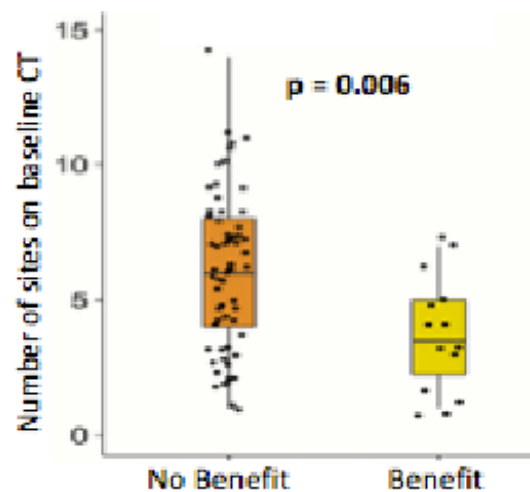
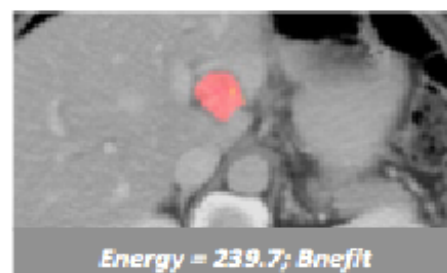
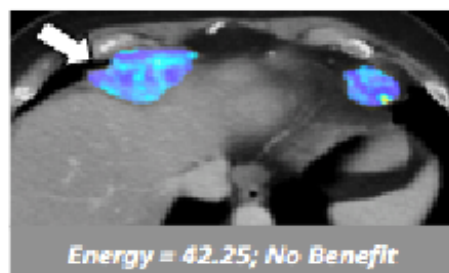
Evis Sala
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Yuliya Lakhman
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Himoto et al, Under Review

Number of Sites and Radiomic Heterogeneity Associate with Clinical Benefit in Ovarian Cancer



Conclusions and Future Directions

- Diverse molecular assessments of the tumor microenvironment demonstrate intra- and inter-site heterogeneity in ovarian cancer and other malignancies
- Non-invasive methods of assessing such heterogeneity, including radiomics, are being developed
- Genomic and TME heterogeneity may impact clinical responses to therapeutic interventions



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CRUK Cambridge

Evis Sala
Martin Miller
Alejandro Jimenez Sanchez

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