Characterizing *T*umor *M*icro *E*nvironment (TME) Using H&E Images

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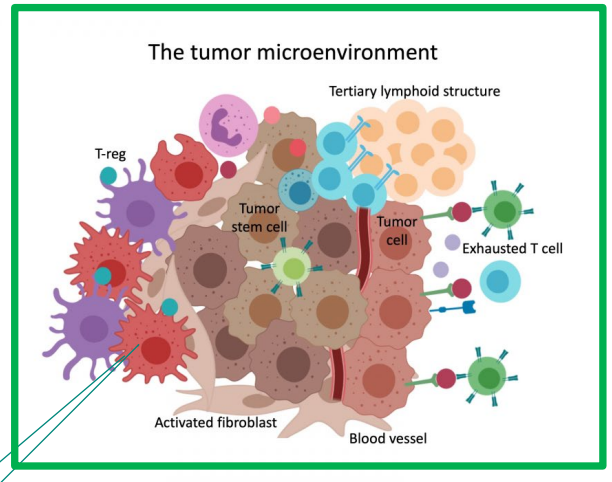
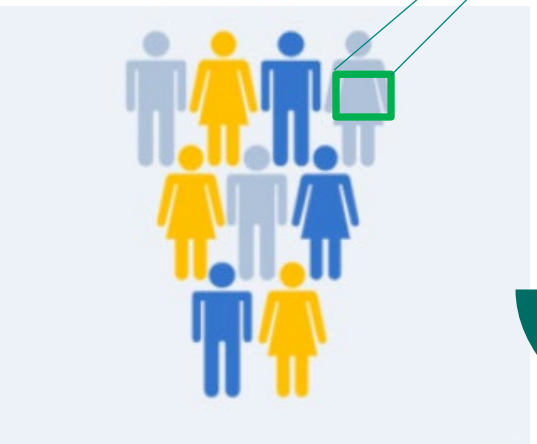
Outline

- Motivation and Background of Patho-mics/Digital Pathology in Translational Oncology
- Overview of the Internal Analytic Workflow
- Case Studies
- Future direction
- Summary and Conclusion

Motivation – Tumor Micro-Environment (TME) is Associated with Clinical Response to ICIs



- Tumors are spatially organized ecosystems that are comprised of distinct cell types, each of which can play a different role in treatment response.
- TME is generally defined as the composition, phenotype, organization, and interactions between tumor cells, immune cells stroma, and other cell types.
- Emerging evidence that TME is important in driving patient treatment response.



Responder to ICI

Responder to SOC

PROPRIETARY ICONS HERE

https://www.weizmann.ac.il/mcb/Keren/research-activities/tumor-microenvironment

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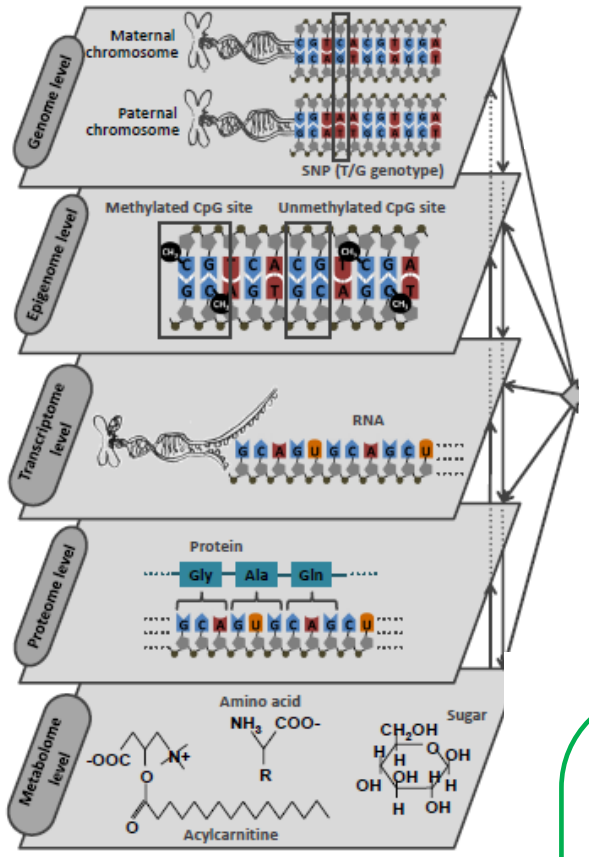
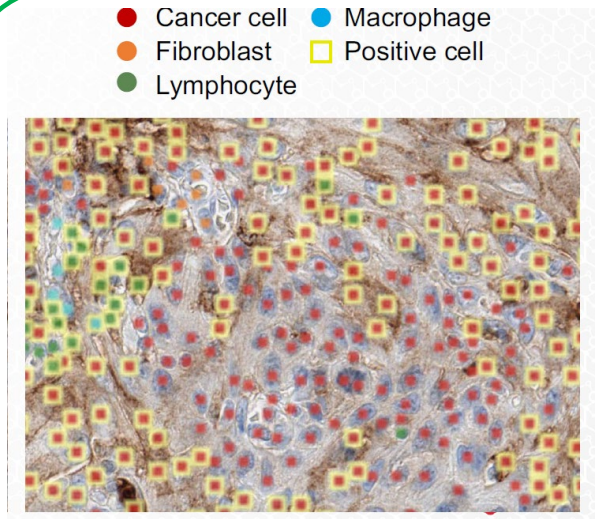
New Player in the Multi-Omics Characterization of TME : *Patho-mics*



Traditional molecular assays, quantitation only

- Past efforts used molecular assays to quantify biomarker ***abundance***
  - e.g. higher PDL1 protein expression correlates with higher response
- Large % of response/resistance mechanisms remain unaccounted for.

- Emergence of “image-based” omics, patho-mics, containing geospatial organization of the TME.



Pathomics, architectural arrangement of TME

Growing Popularity of Digital Pathology

Adoption of digital precision medicine is supported by key underlying drivers

- Shrinking pathologist workforce → Forecasted -2.4% CAGR from 2017-2027
- Increasing workload → targeted therapies require more testing and analysis time
- Cut-offs and scores associated with IO therapies lead to create complexities that lead to variability
- COVID accelerating acceptance by providers, payers, and regulators
- The digitization of medical and pathology records is enabling AI/ML-based diagnostic aids

New players are entering into the space

OWKIN *$74M*

PathAI *$255M*

syapse *$120M*

PAIGE *$220M*

komodo HEALTH *$220M*

** Funds raised as of 7/1/21*

Established firms are expanding into the space

PHILIPS

Philips IntelliSite Pathology Solution
IVD for Diagnosis

GE Healthcare Command Centers

UPath

Roche

Large Pharma's have also engaged in the Digital Pathology

AstraZeneca

- *Trained AI system to score tumor cells and immune cells for PD-L1 biomarkers for bladder cancer*
- *Radiomics with Qura.Ai – radiomics*
- *ResApp partnership for lung cancer*

NOVARTIS

- *PathAI + Novartis: Develop AI to find patients for targeted treatment [Nov 2018]*

Bristol Myers Squibb

- *PathAI + BMS: Retrospective analysis examining PD-L1 expression on tumor cells from three trials involving Opdivo (nivolumab), finding strong correlation between AI-powered and manual quantification of PD-L1 [Nov 2019]*
- *PathAI + BMS: Image analysis used on melanoma and SCCHN samples to predict GEP signatures for stromal and parenchymal CD8+ T cells [Jun 2019]*

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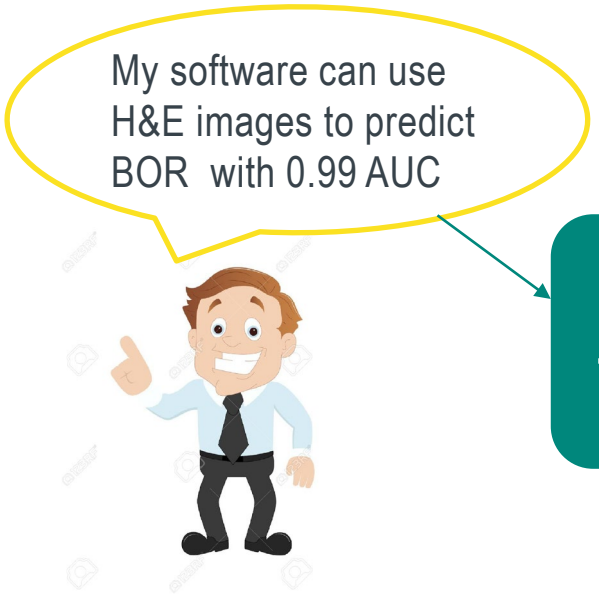
Rigorous Evaluation of the Utility of Path-omics in Drug Discovery/Development



CEO of AI Company XYZ

Technology Triage Team

Pilot? Yes

Pilot Study Phase

Planning

Execution

Validation

Role of Biostatisticians

Study design, power assessment, statistical analysis plan

Implementation of internal pipeline parallel to vendor's pipeline in data generation

Go/No-Go decision using a Bayesian framework that incorporates inter-human pathologist variability

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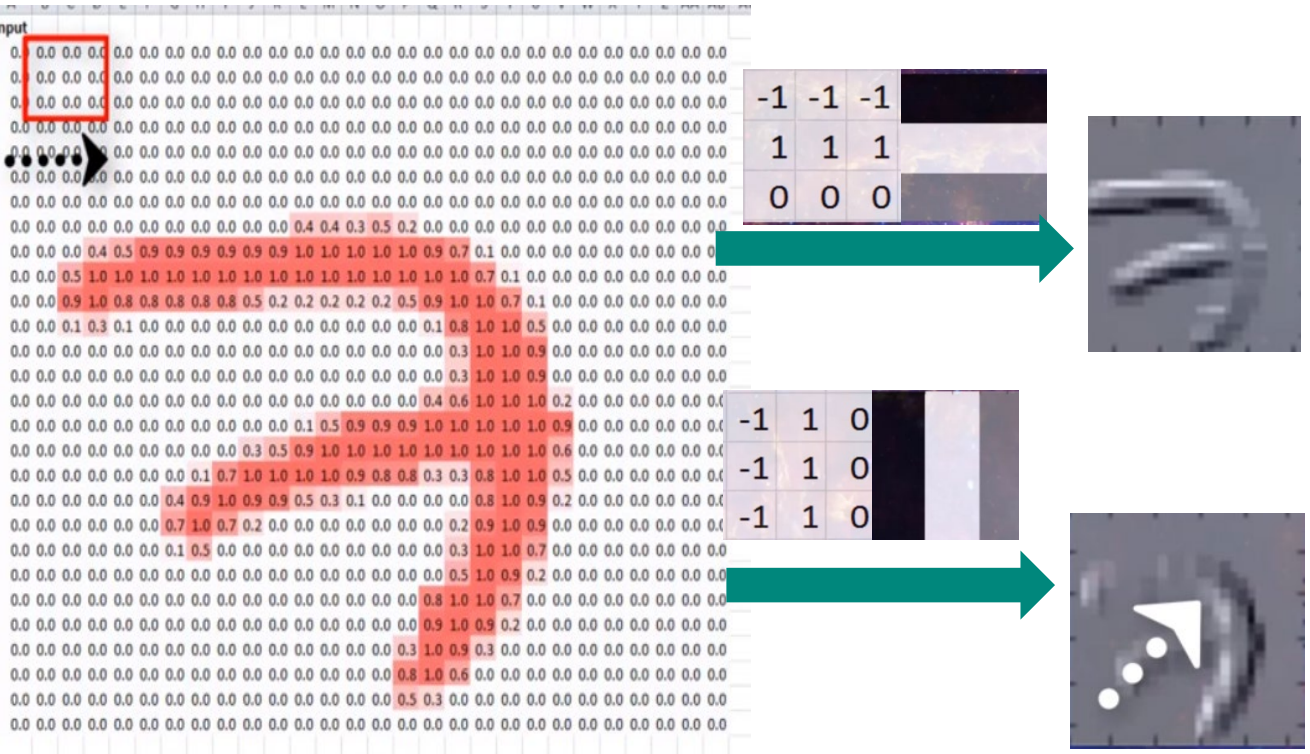
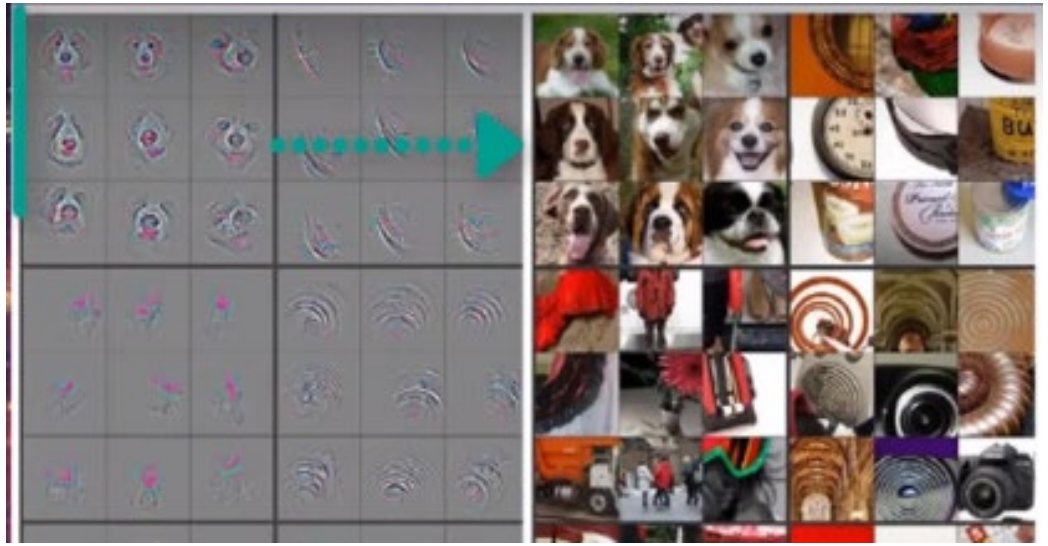
Path-omics Data Analysis Requires Advanced Machine Learning Techniques

Input data: ~10^4 x 10^4 pixel WSI
2D, 3 channel, p>>n



Toy example: edge detector using CNN



"Deeper" network allows extraction of more complicated features

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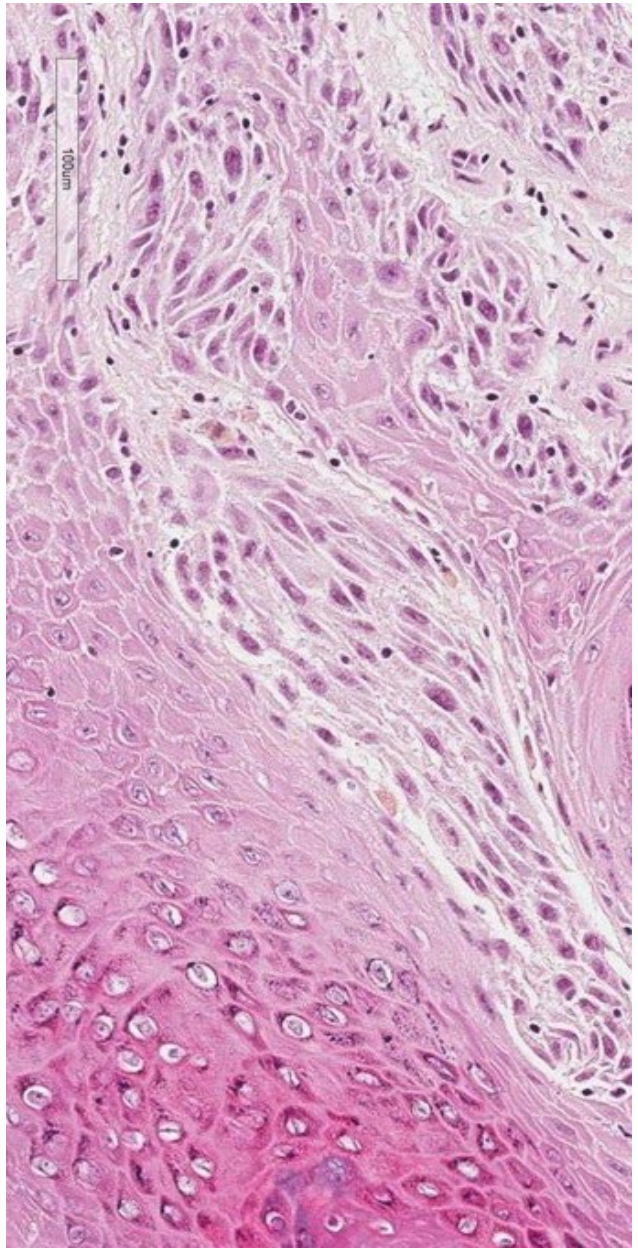
H&E Images are Commonly Used in Path-omics Analyses

- H = *H*ematoxylin,purple stain for nucleus , E= *E*osin, pink stain for ECM and cytoplasm
- Routine collection for diagnostic purposes
- Inexpensive, with low assay complexity
- Provides detailed representation of tumor architecture with high levels of cytologic, morphologic, and structural detail
  - Tumor cells, stroma, vasculature, immune infiltrate, etc
- Can readily be digitized into high resolution whole slide images for sophisticated quantitative analysis

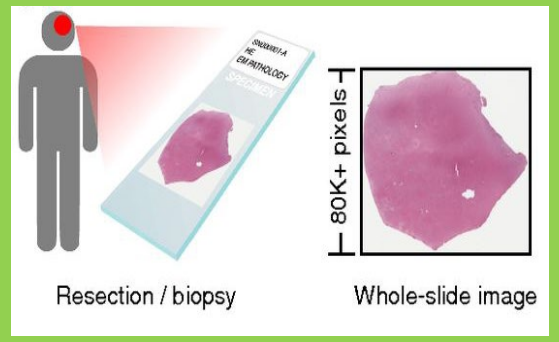


Why is Pharma interested ?

- Target discovery
- Patient stratification
- Digital CDx

Workflow: Characterize Tumor Micro Environment (TME) Features using H&E Images

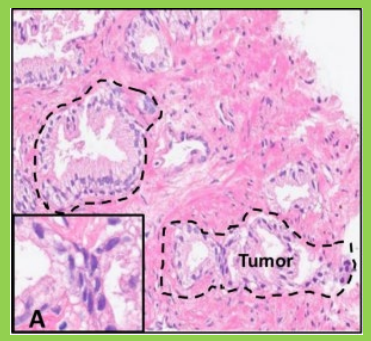
Pre - Analytics



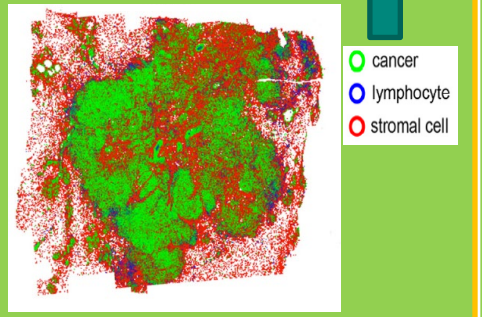
Collection of Whole Slide Images (WSI)

QC – I

Region Identification

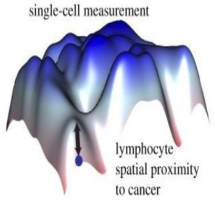


ROI & QC Region Prediction



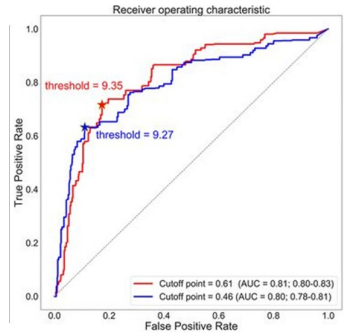
Cell Type Prediction

Engineering of Human Interpretable Features (HIF)

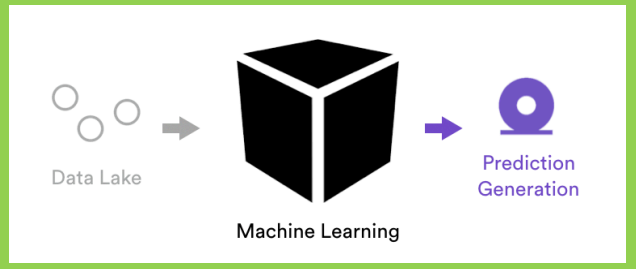


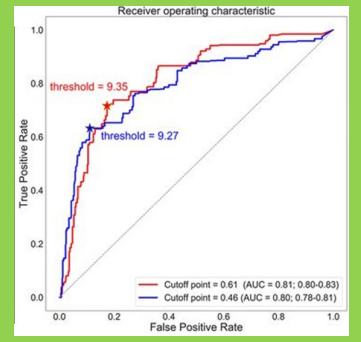
Lymphocyte/Plasma -tumor proximity analysis (% DTL, %ATL, %ITL, ITLR)

Prediction



Black Box Approach





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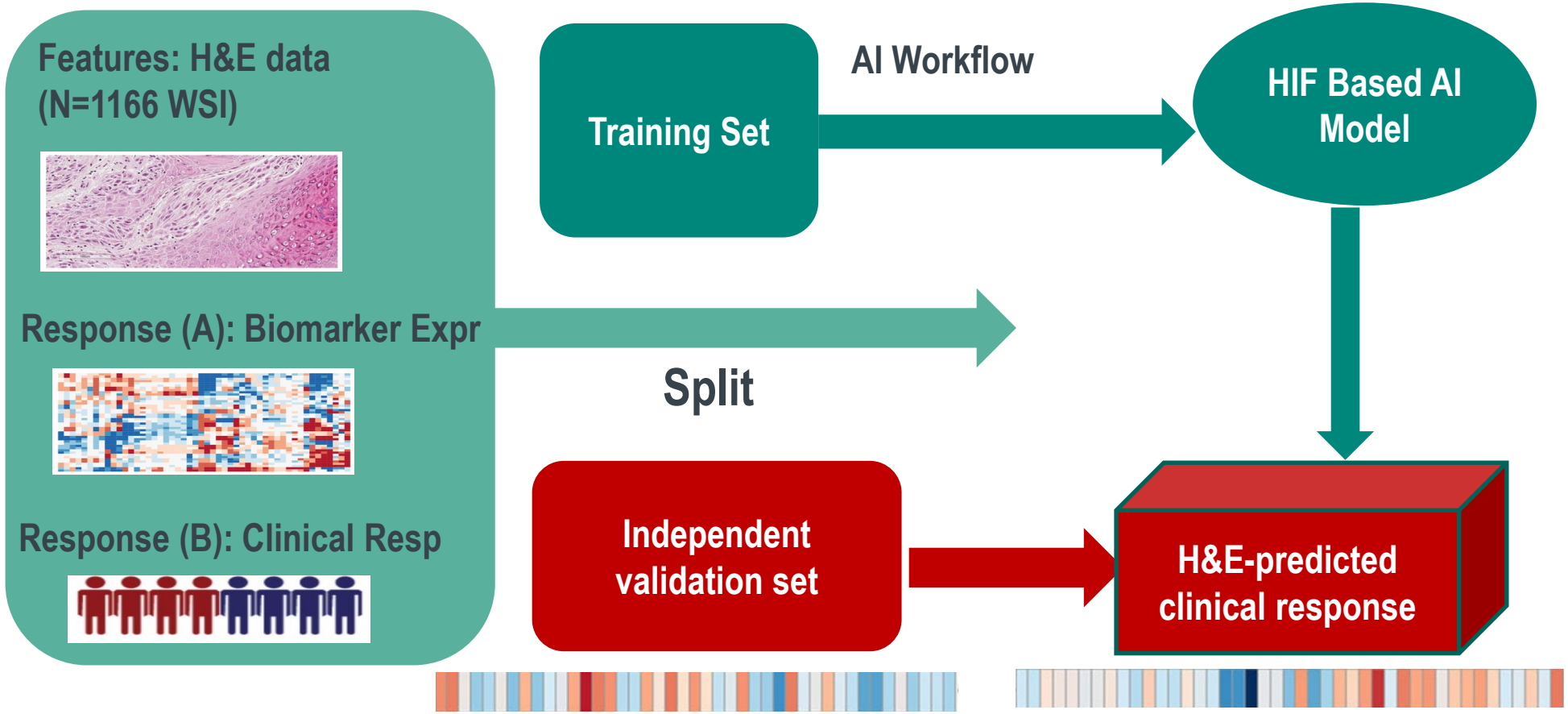
Case Study I: Can H&E Predict Cancer Treatment Response?

Pilot: Associating HIFs with Treatment Response



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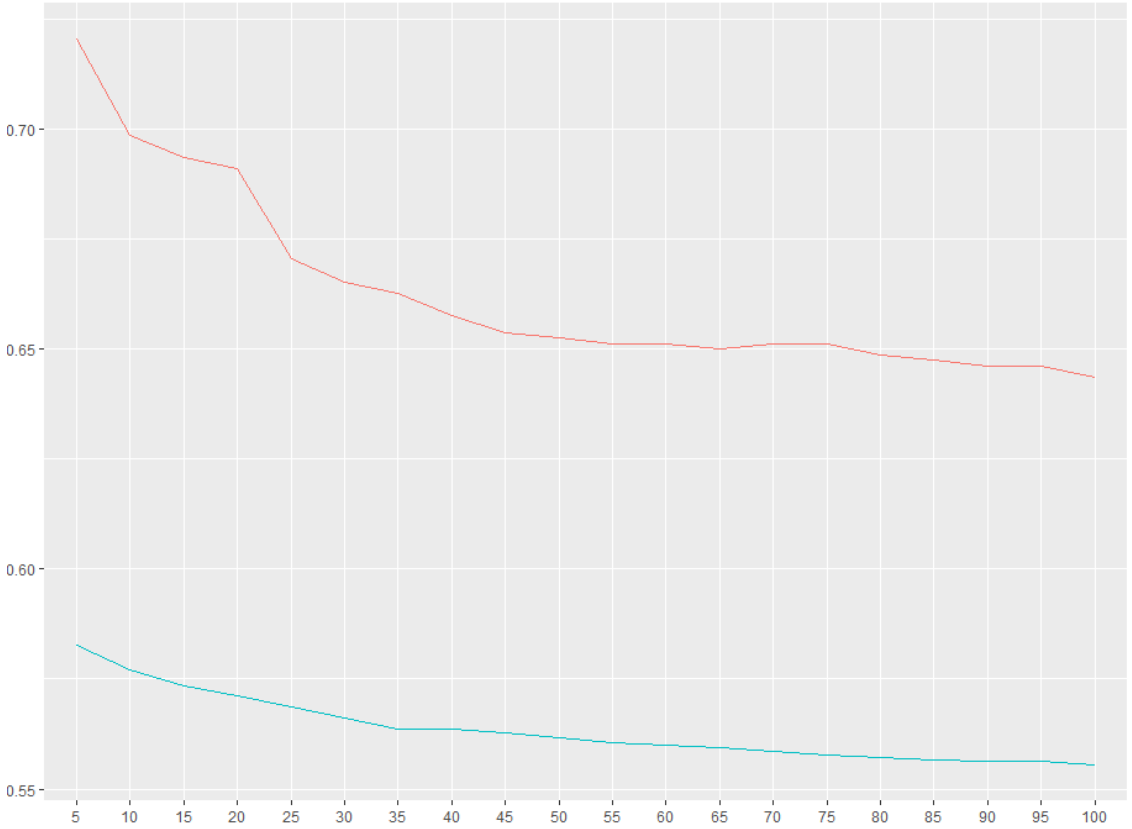
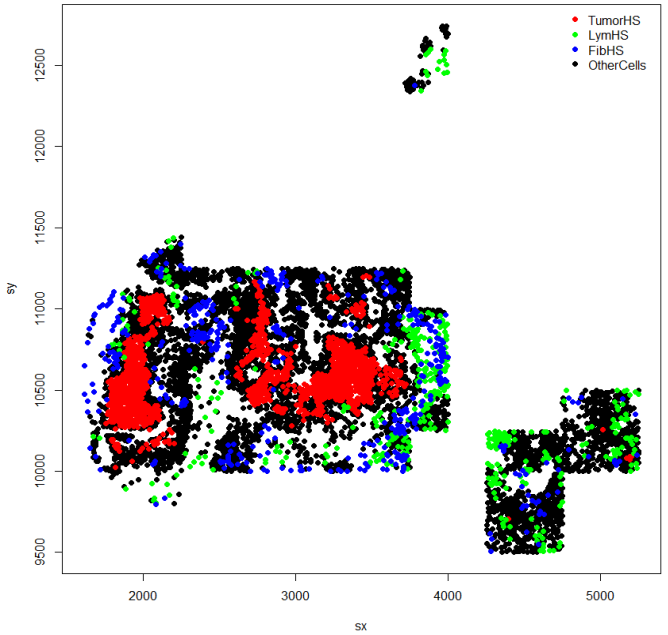
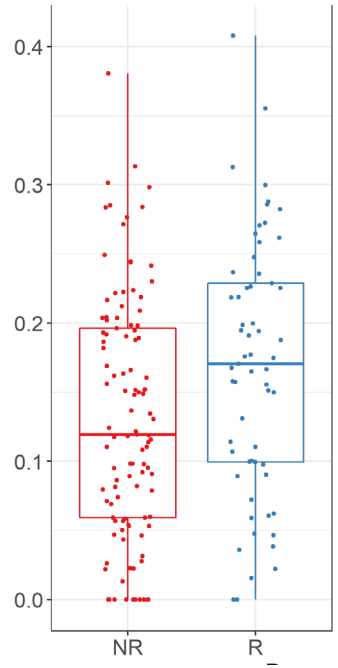
Key Findings from Pilot

(a) Distance between immune cells and tumor cells is associated with treatment response



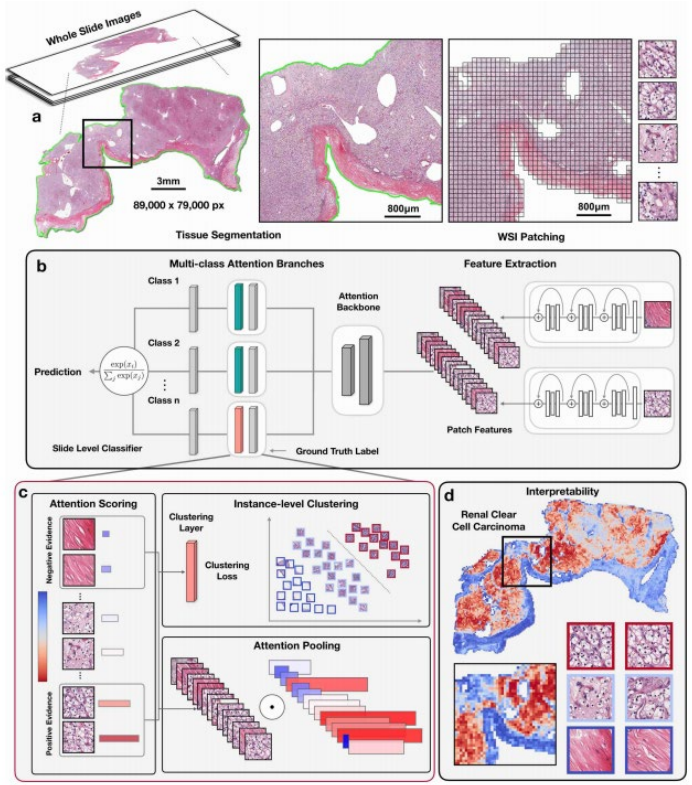
(b) Co-localization of immune cell and tumor cells clusters is associated with treatment response.





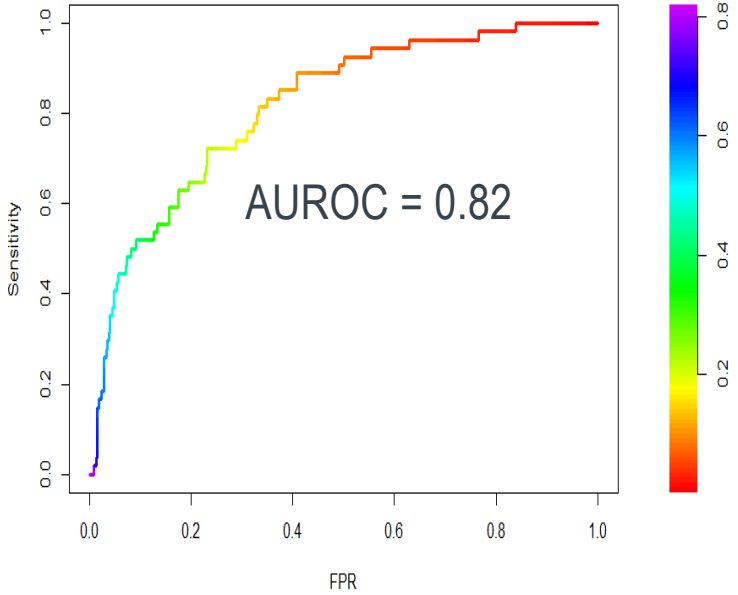
Case Study II: Can H&E Predict Tumor Mutation Burden (TMB)?

- TMB is an FDA approved pillar biomarker for ICI.
- Profiling of TMB requires Next Generation Sequencing (NGS), which is expensive and may not be available for all patients.
- Objective: evaluate if H&E can serve as a cheaper alternative to molecular TMB assay

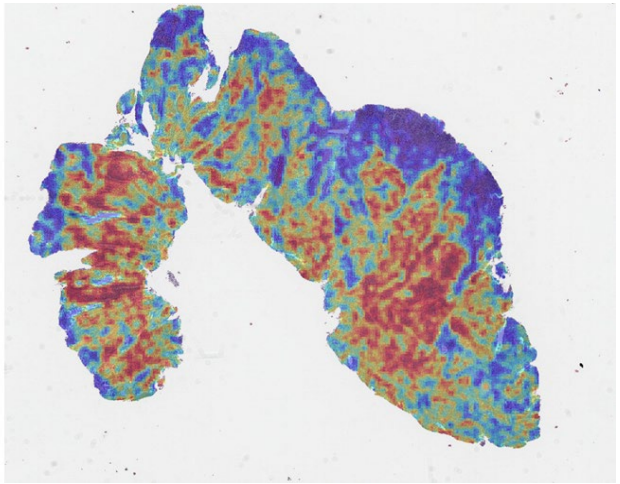


Attention based MIL

- Attention weight based multiple instance learning (MIL) framework was applied to the TCGA Heck & Neck dataset.



ROC Curve in Predicting TMB-H/ Non TMB-H

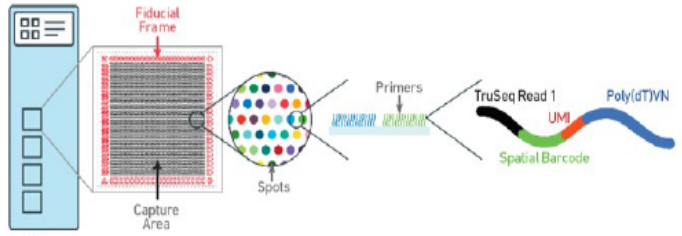


Heatmap of Attention Weights

Going Beyond H&E Images

- H&E images suffer from some major limitations
  - Detection of certain cell types based on H&E stains alone is challenging (e.g. myeloid cells)
  - Immune cell subtypes might share the same morphology on H&E, but carry opposite functions (e.g. macrophage M1 vs M2, Treg vs. T killer cell)
  - Lacks single gene resolution for immediate “usable” target nomination

Next step:
Develop data integration strategies for H&E images and “lower throughput” spatial transcriptomics data (and/or multi-plex IHC images).



- Unbiased, whole transcriptome

Visium Spatial Transcriptomics

Summary and Conclusion

- Compared to traditional omics layers which focus on quantifying “abundance”, path-omics provides orthogonal geospatial information about TME.

- Advanced machine learning techniques such as deep learning are often required for path-omics data analyses.

- There are both internal and external studies that demonstrated PoC that path-omics could be powerful in certain translational oncology applications.

- Integration between H&E images and other cutting-edge technologies such as spatial transcriptomics is likely required to obtain a more accurate depiction of the TME architecture.

Thank you!