

# Cross-linking omics and histological imaging with AI

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**Building a Sustainable UK Diagnostic Sector III: Novel approaches to cancer diagnosis – regional strengths and opportunities**

University of Manchester

1410-1430 Monday March 17, 2024

<https://warwick.ac.uk/research/priorities/health/events/bsukdsiii>



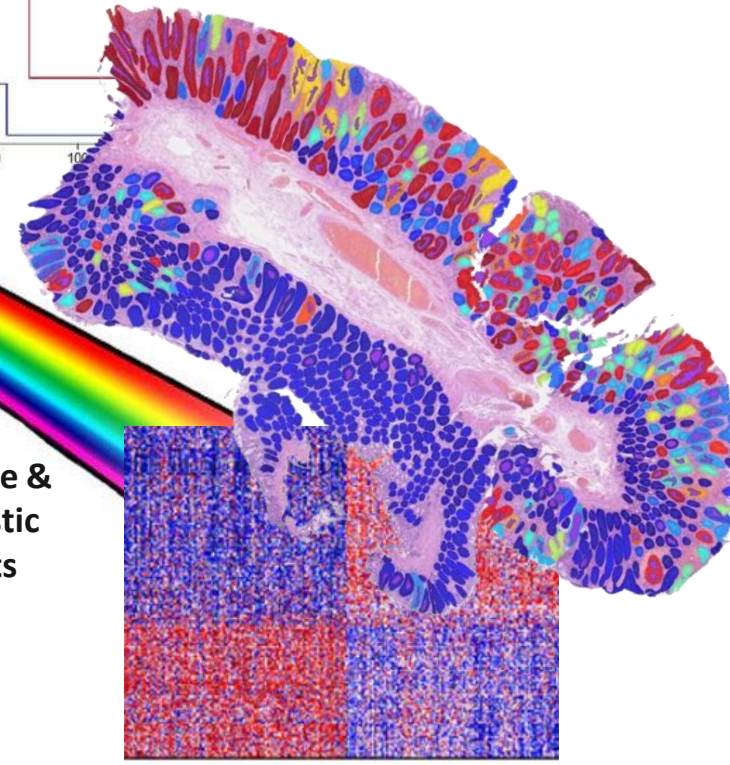
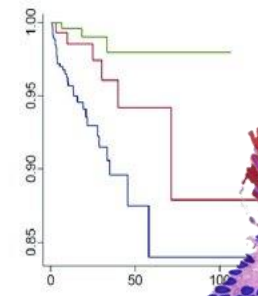
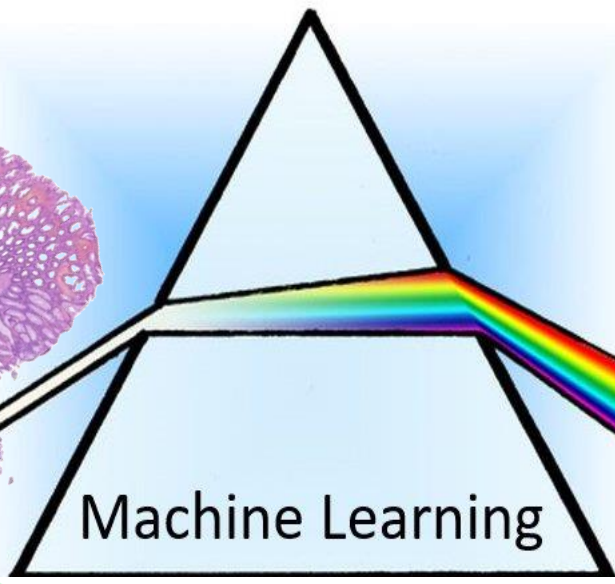
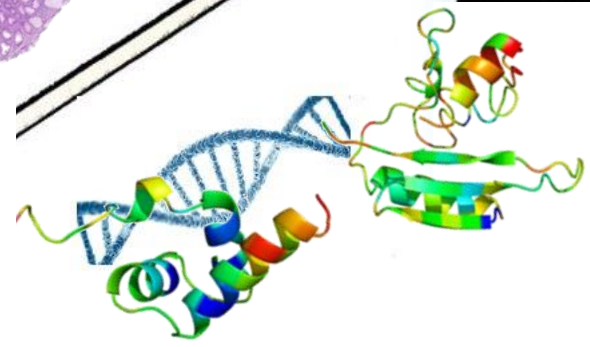
Case Number: XXXXX  
 Diagnosis:  
 A: Colon, transverse, partial colectomy  
 Tumour Histologic Type: Invasive adenocarcinoma  
 Histologic Grade: moderately differentiated (2 of 4)  
 Tumour Location: transverse colon

Depth of Invasion:  
 -Through muscularis propria and into and pericolic soft tissue MDO-3  
 Lymphovascular Invasion: not identified  
 Perineural Invasion: not identified

Margins:  
 Proximal margin: negative  
 Distal margin: negative  
 Mesenteric margin: negative  
 Distance of carcinoma from closest margin (specify): 6.6 cm to the closest distal margin of resection



**Biomedical Data**



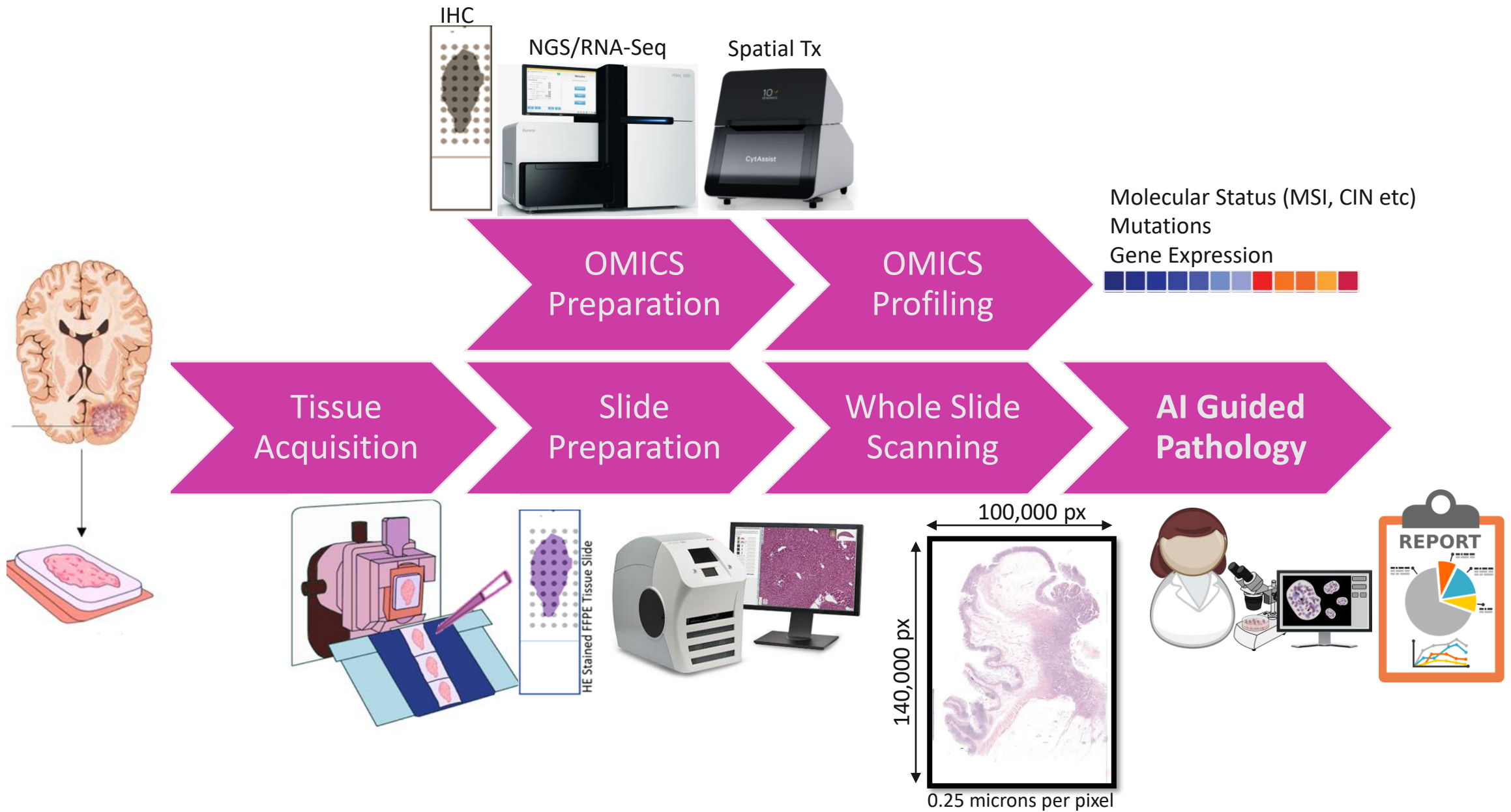
**Predictive & Prognostic Insights**

*AI and ML to help discover and understand biology and pathology*

@fayyazhere







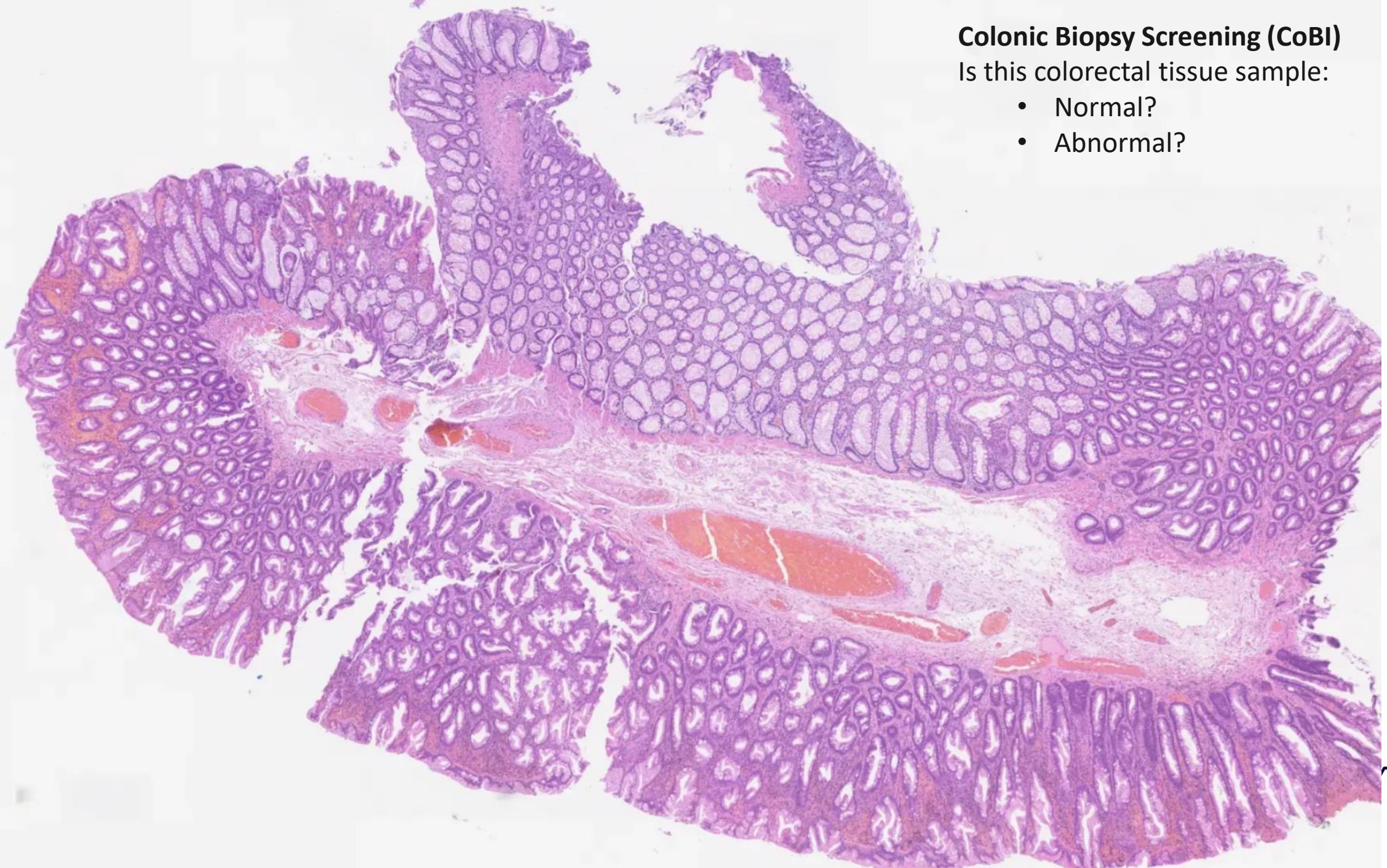
**Example Independent validation study of PAIGE Prostate:** Kanan, Christopher, Jillian Sue, Leo Grady, Thomas J. Fuchs, Sarat Chandarlapaty, Jorge S. Reis-Filho, Paulo G O Salles, Leonard Medeiros da Silva, Carlos Gil Ferreira, and Emilio Marcelo Pereira. "Independent Validation of Paige Prostate: Assessing Clinical Benefit of an Artificial Intelligence Tool within a Digital Diagnostic Pathology Laboratory Workflow." *Journal of Clinical Oncology* 38, no. 15\_suppl (May 20, 2020): e14076–e14076. [https://doi.org/10.1200/JCO.2020.38.15\\_suppl.e14076](https://doi.org/10.1200/JCO.2020.38.15_suppl.e14076).



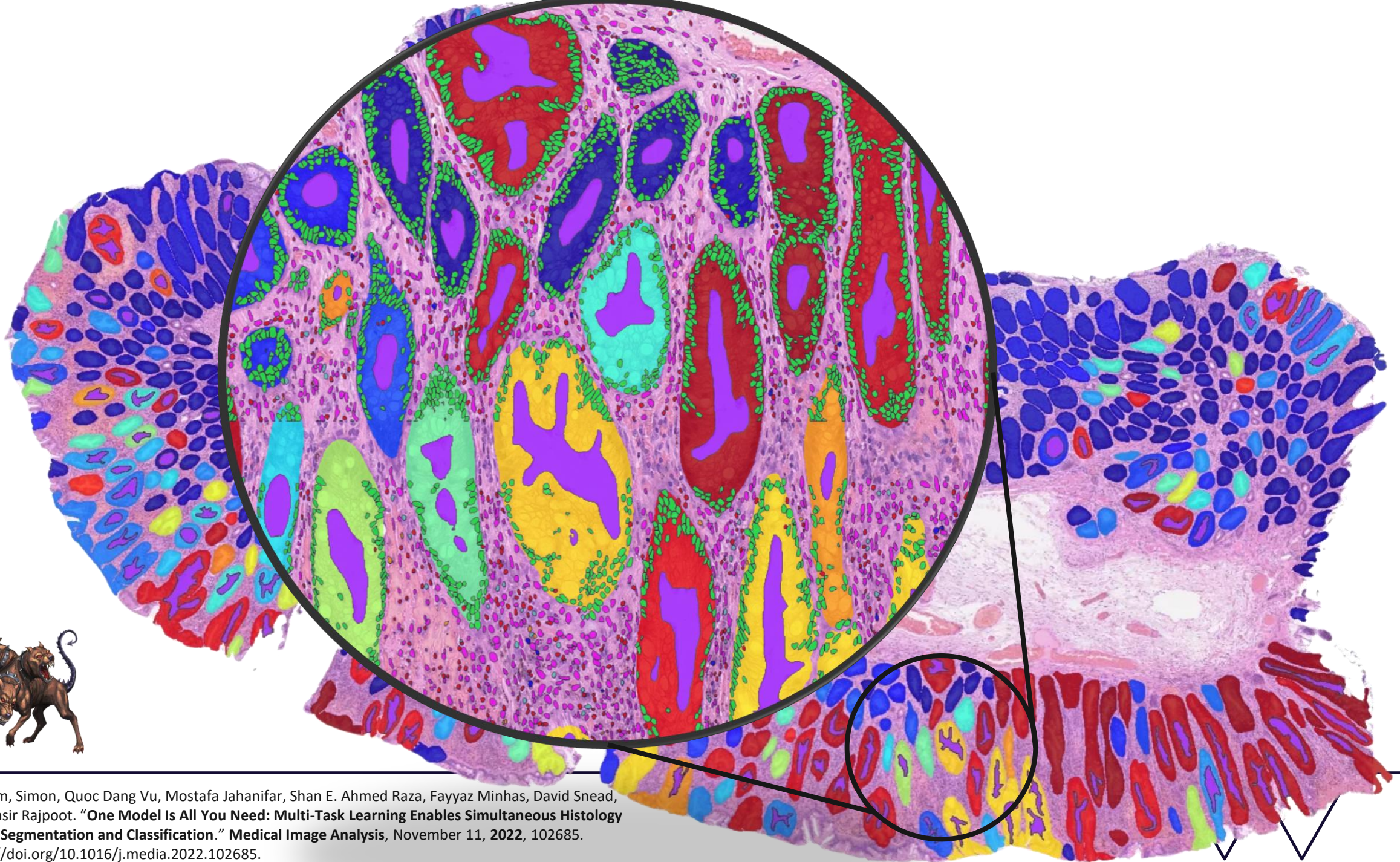
## Colonic Biopsy Screening (CoBI)

Is this colorectal tissue sample:

- Normal?
- Abnormal?



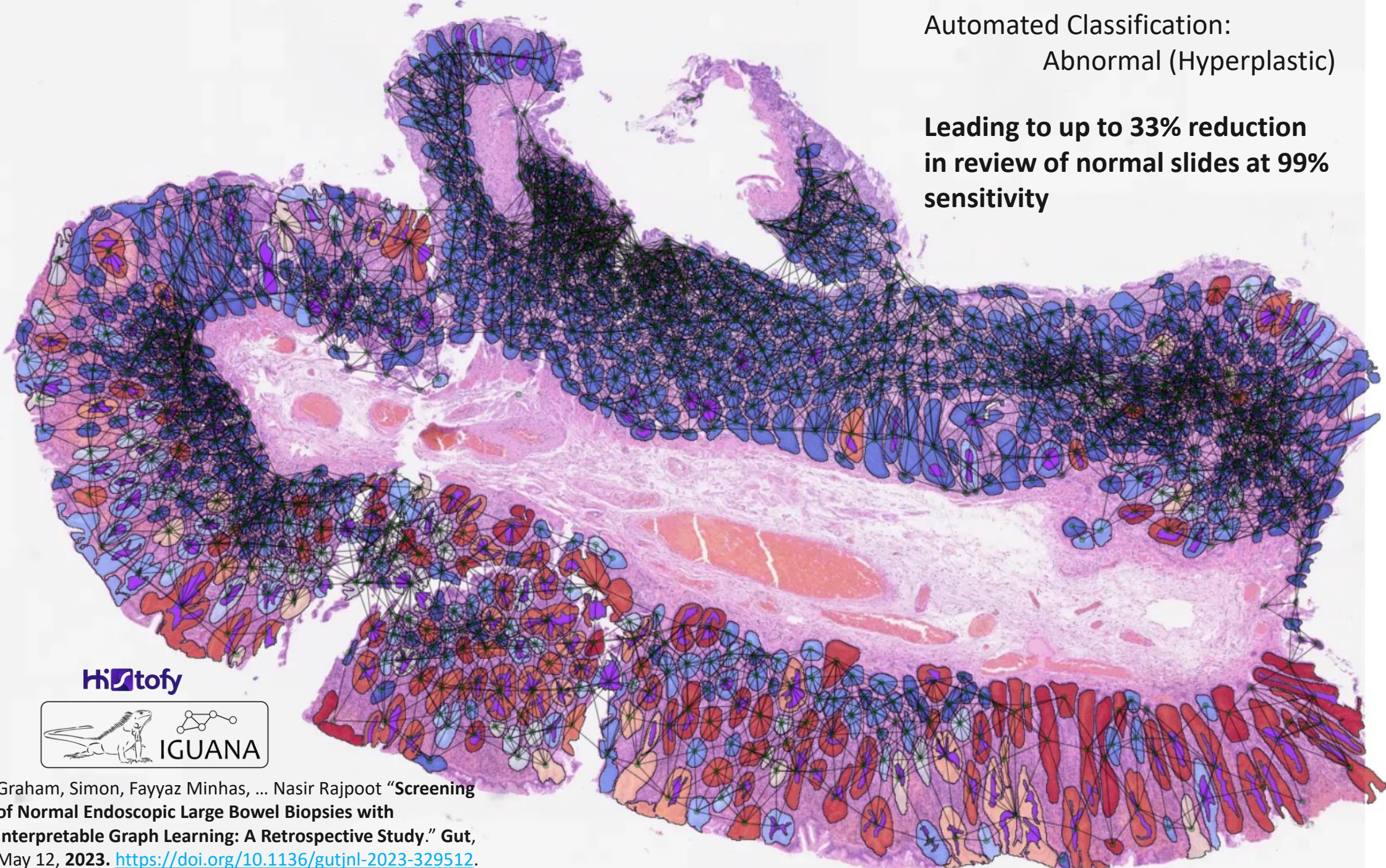






Automated Classification:  
Abnormal (Hyperplastic)

Leading to up to 33% reduction  
in review of normal slides at 99%  
sensitivity



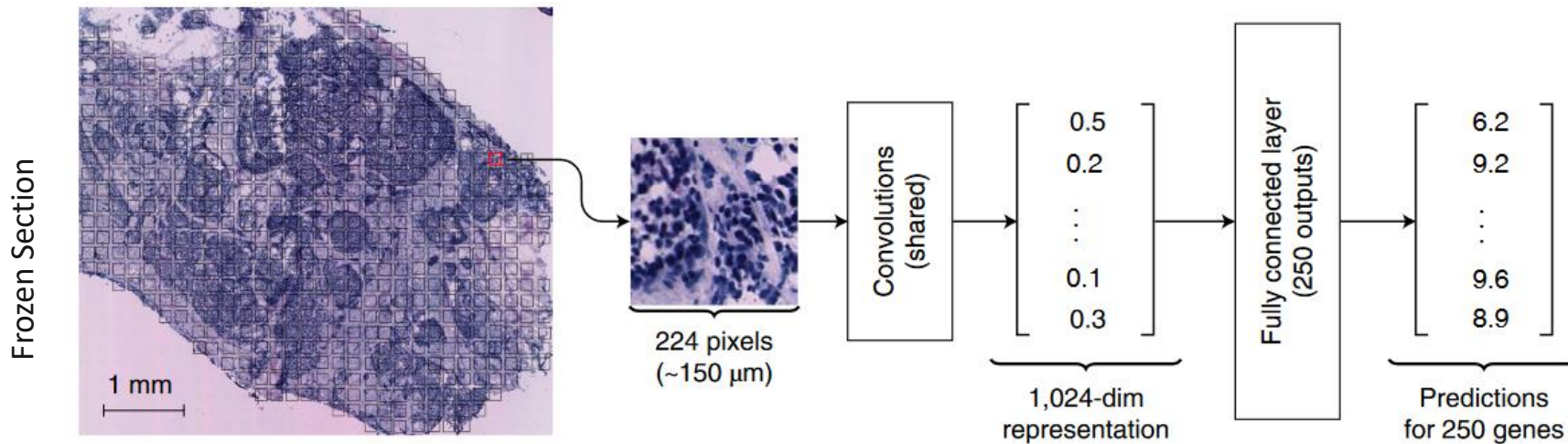
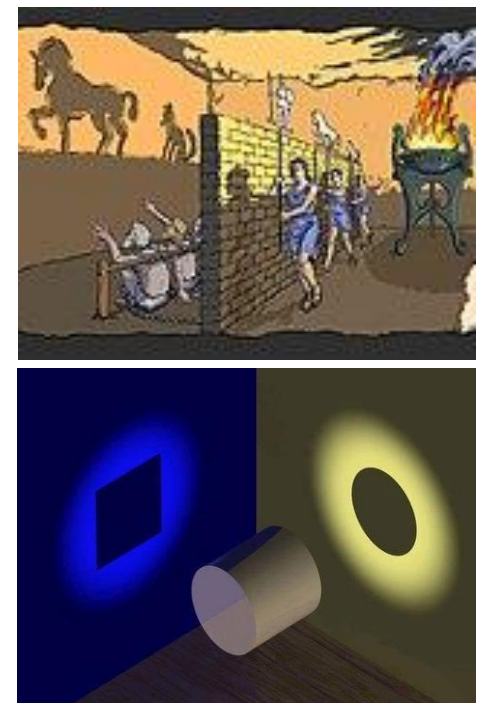
Hi tofy



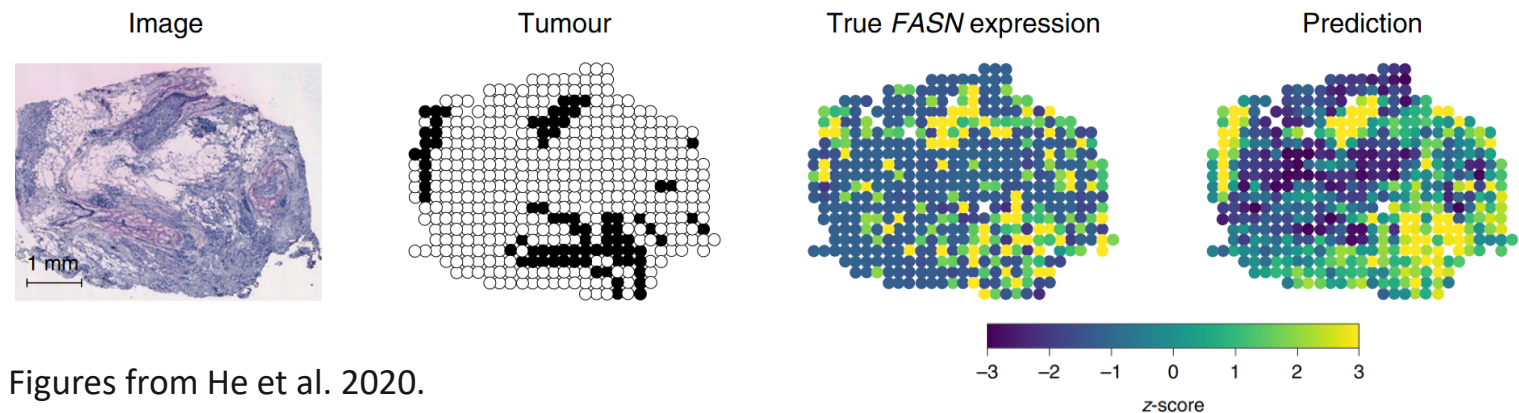
Graham, Simon, Fayyaz Minhas, ... Nasir Rajpoot "Screening of Normal Endoscopic Large Bowel Biopsies with Interpretable Graph Learning: A Retrospective Study." Gut, May 12, 2023. <https://doi.org/10.1136/gutjnl-2023-329512>.



# Predicting Spatial Transcriptomic Profiles from Imaging?



Gene	No. of consistent patients	Median correlation	Median correlation (smooth)	10x Correlation
<i>GNAS</i>	23	0.34	0.49	0.43
<i>ACTG1</i>	22	0.33	0.50	0.47
<i>FASN</i>	23	0.31	0.50	0.46
<i>DDX5</i>	22	0.30	0.52	0.51
<i>XBP1</i>	21	0.29	0.43	0.54

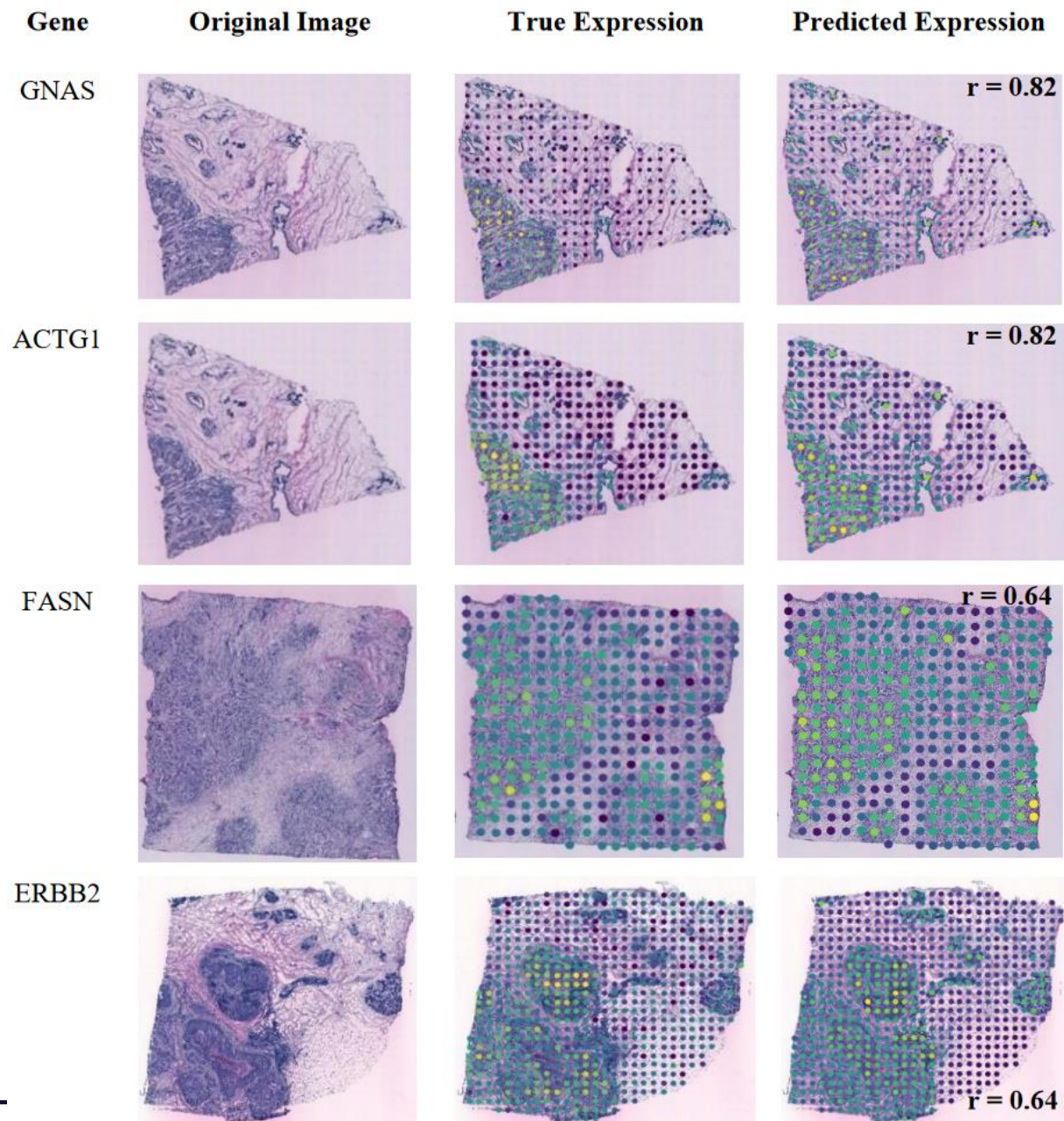
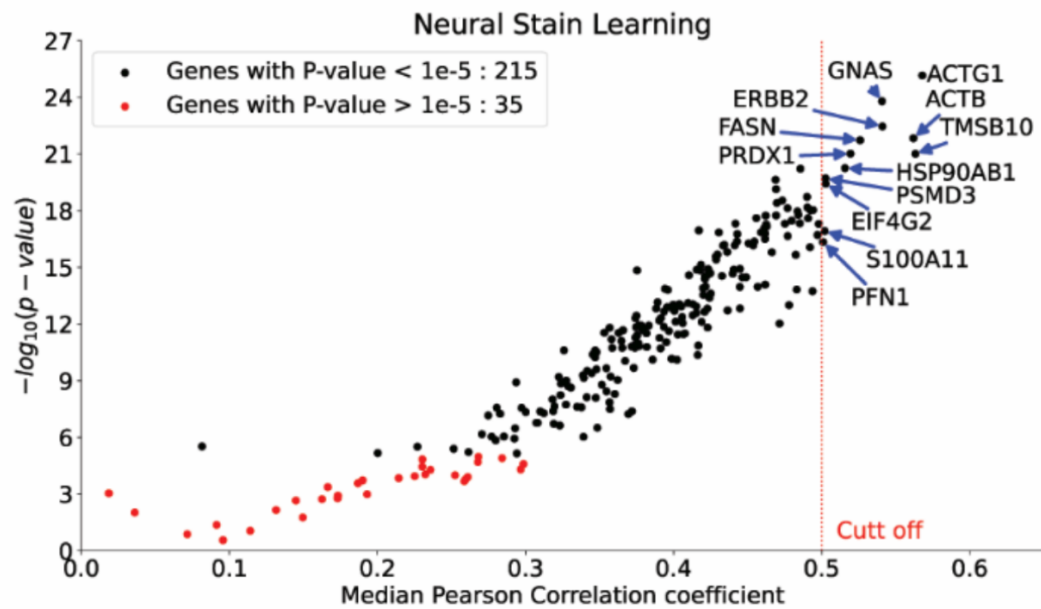


Figures from He et al. 2020.

# • Critical Questions

- Can color variations in whole slide image patches predict spatial expression of genes?
- Do we really need deep neural networks for this?

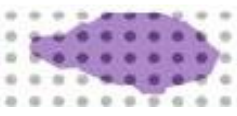
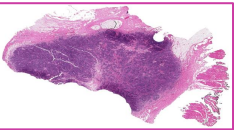
• Answer: **All you need is color**





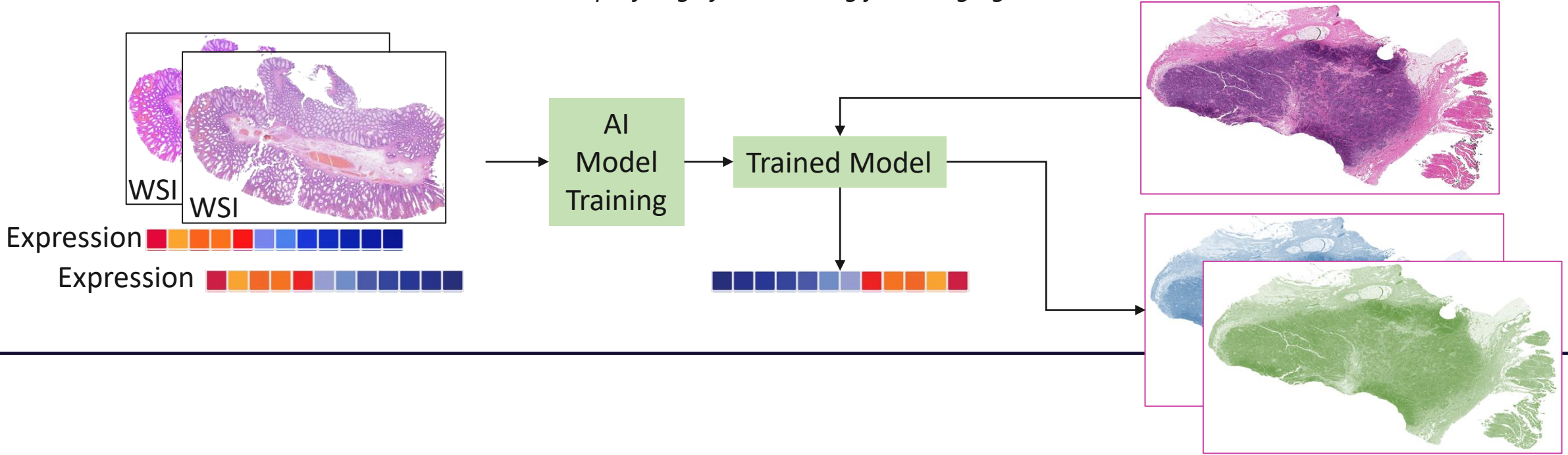
Can we do spatial-OMICs profiling  
without spatial-OMICs profiling?

# Making OMICs Spatial at Scale?



Modality / Features	H&E WSIs	“Bulk” OMICs	Spatial OMICs technologies
Cost	Low (\$2)	Medium	High
Spatial Resolution	Very High (subcellular)	N/A	Medium (spot)-High (cell)
Gene/Protein Expression Measurement	Not Direct Measurement	Direct	Direct
Primary Use-Case	Clinical	Clinical/Research	Research
Available Data	Very Large datasets	Large datasets	Limited

Wouldn't it be great if we could utilize Bulk sequencing data and machine learning to allow meaningful spatial profiling of tissue using just imaging?

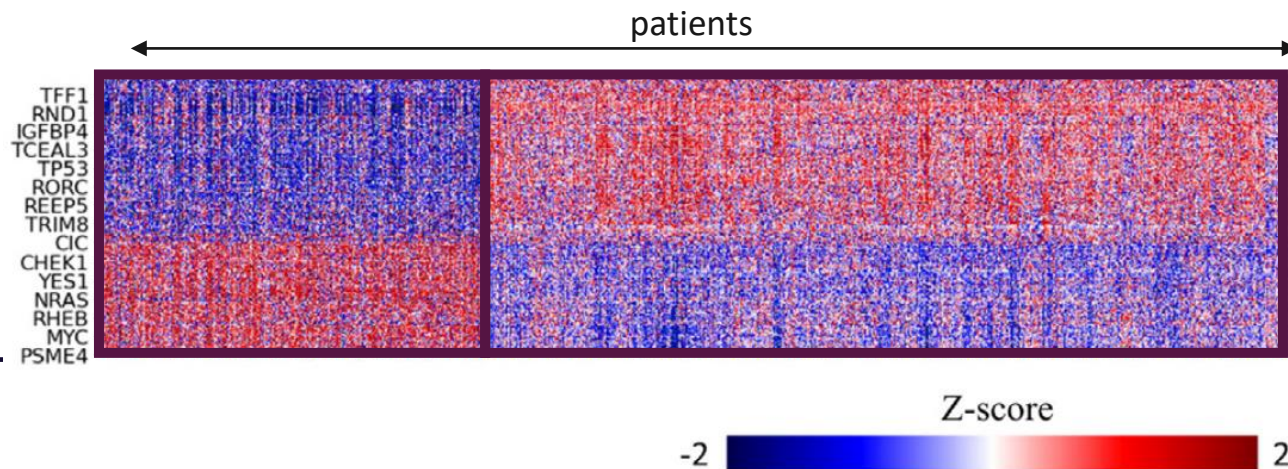




# Previous Work : Bulk Transcriptomics

## Biases

1. Association between expression of different genes
2. Phenotypic effects captured by Image-based predictor might be associated with the expression profile of set of genes not a single gene.
3. Disentanglement of phenotypic effects might be challenging, and it may be better to predict expression of "groups of genes"



CONVERGENCE AND TECHNOLOGIES | OCTOBER 01 2021

## Predicting Molecular Phenotypes from Histopathology Images: A Transcriptome-Wide Expression-Morphology Analysis in Breast Cancer

Yinxin Wang ; Kimmo Kartasalo ; Philippe Weitz ; Balázs Ács ; Masi Valkonen; Christer Larsson; Pekka Ruusuvoori ; Johan Hartman ; Mattias Rantalainen

## A deep learning model to predict RNA-Seq expression of tumours from whole slide images

Benoît Schmauch ; Alberto Romagnoni, Elodie Pronier, Charlie Saillard, Pascale Maillé, Julien Calderaro, Aurélie Kamoun, Meriem Sefta, Sylvain Toldo, Mikhail Zaslavskiy, Thomas Clozel, Matahi Moarii, Pierre Courtiol & Gilles Wainrib

*Nature Communications* 11, Article number: 3877 (2020) | [Cite this article](#)

43k Accesses | 95 Citations | 71 Altmetric | [Metrics](#)

## Learning to predict RNA sequence expressions from whole slide images with applications for search and classification

Areej Alsaafin, Amir Safarpour, Milad Sikaroudi, Jason D. Hipp & H. R. Tizhoosh

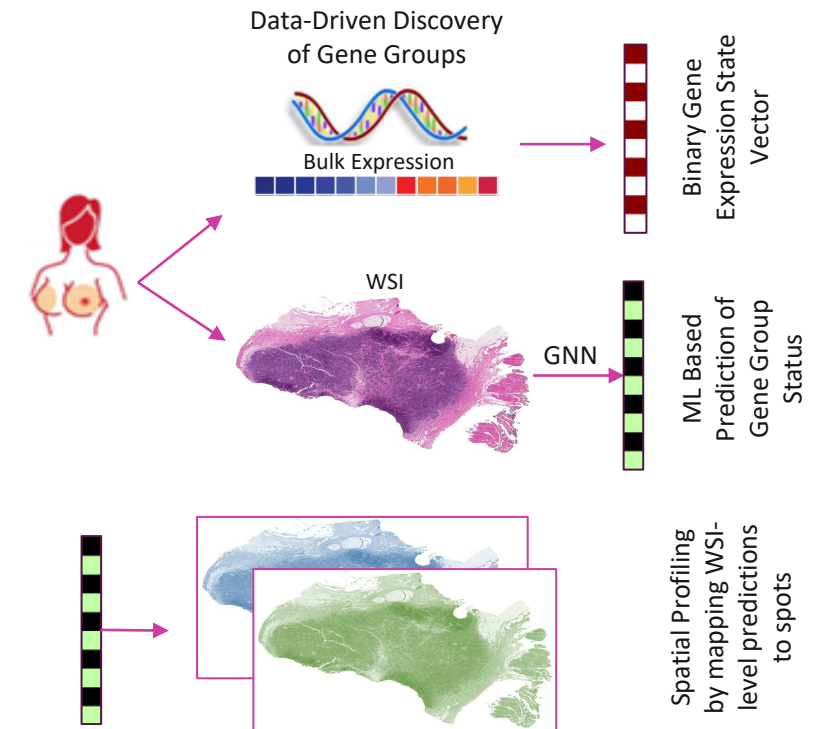
*Communications Biology* 6, Article number: 304 (2023) | [Cite this article](#)

# Cross-linking cancer transcriptomic states with histology imaging

- **Can we achieve spatial transcriptomics without spatial transcriptomics?**

- **Solution:**

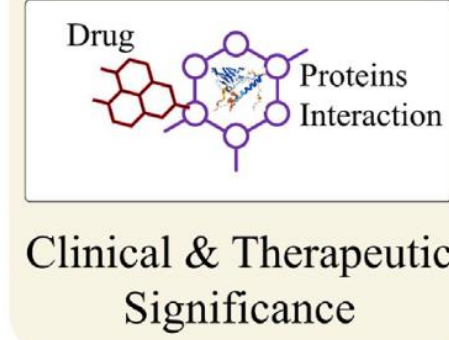
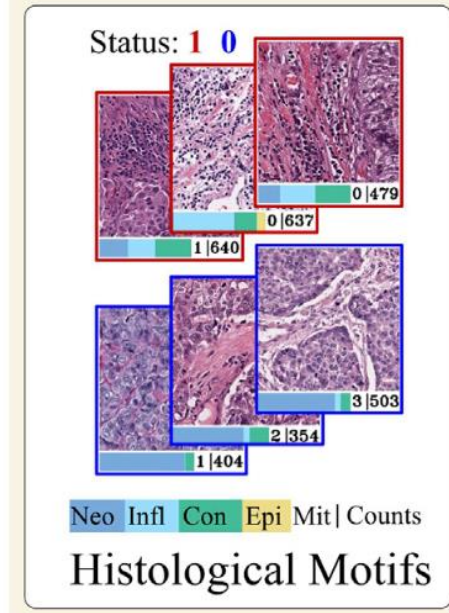
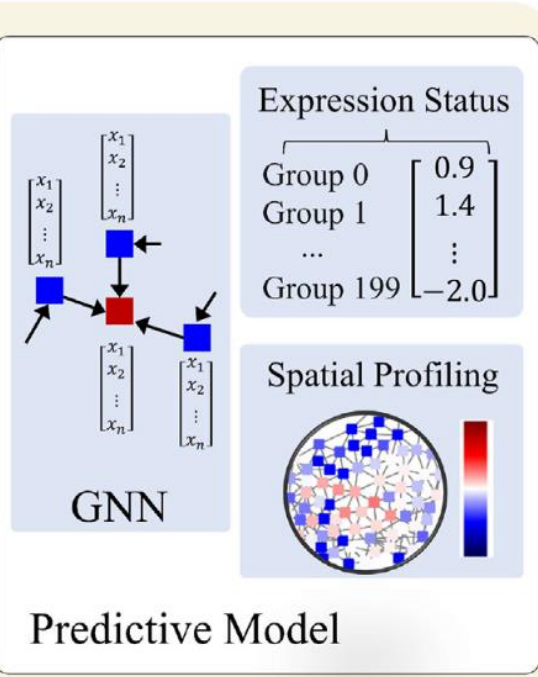
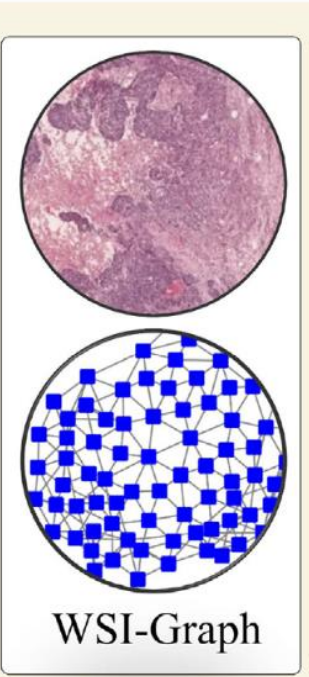
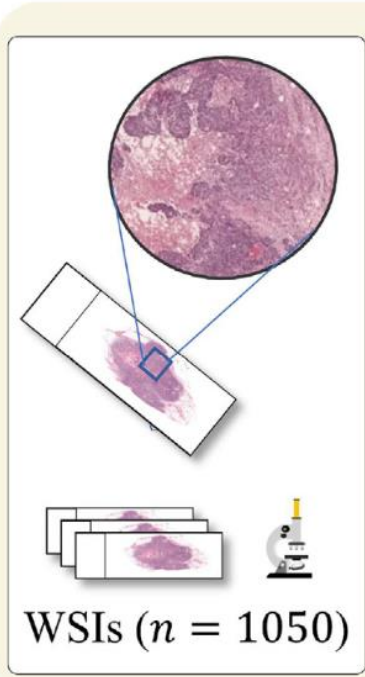
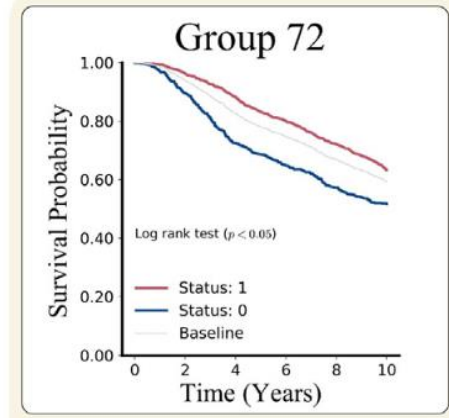
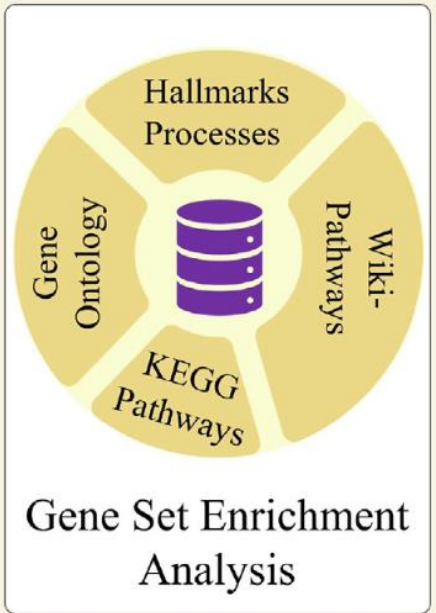
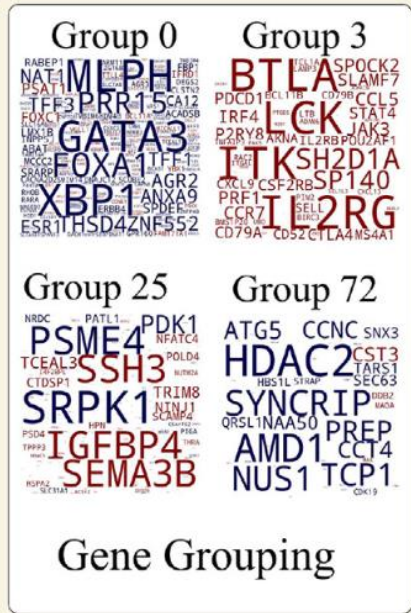
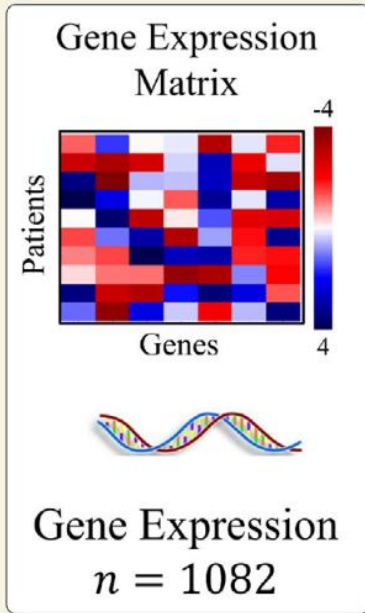
1. Represent the expression profile of a patient in terms of (200) binary gene group statuses
  - *Capture association in expression of genes*
2. Predict these statuses from WSIs
3. Map the WSI level predictions back onto tissue regions
  - *What is the association between consistent patterns of gene expression patterns with image patterns*





# Breast Cancer Patient Data

- Training/ Discovery
  - TCGA (n = 1082)
- Test/Validation Cohorts
  - METABRIC (n = 1980)
  - ABCTB (n = 178)
  - CPTAC (n = 2303)





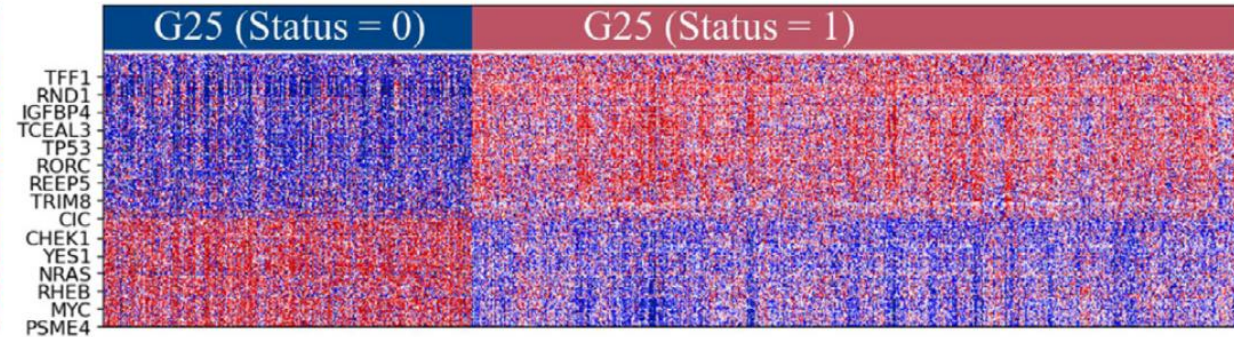
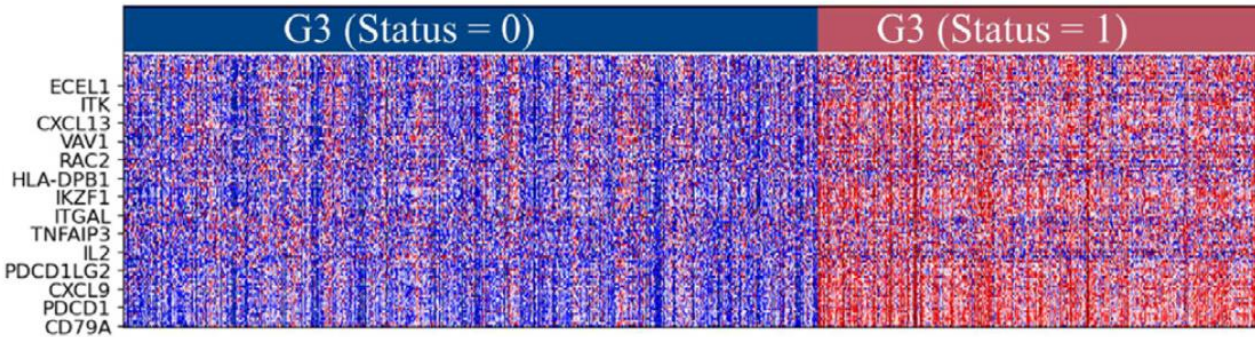
# Defining binary transcriptomic state

- Model each patient's transcriptomic profile in 200 binary gene group statuses
  - Each gene group indicates consistent gene expression patterns across patients for a set of genes
  - Purely data driven and shows the association between expression of different genes across patients

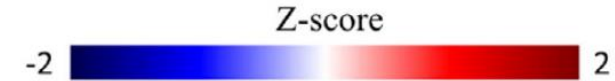
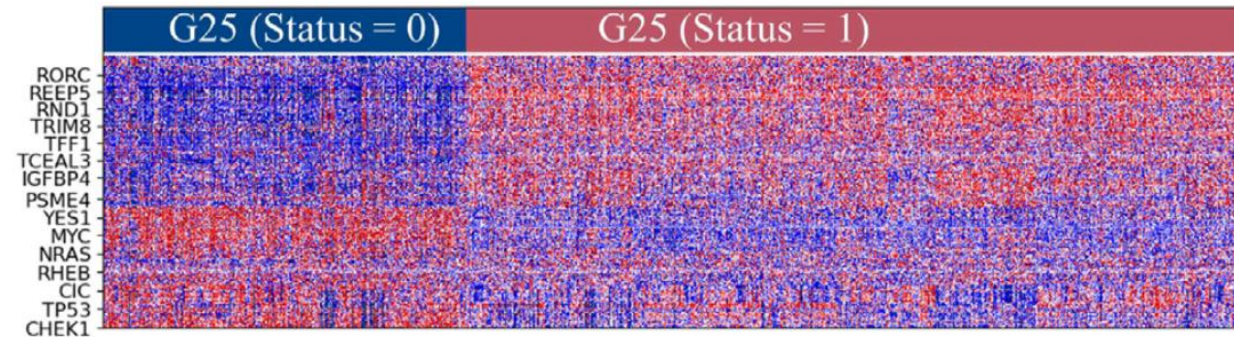
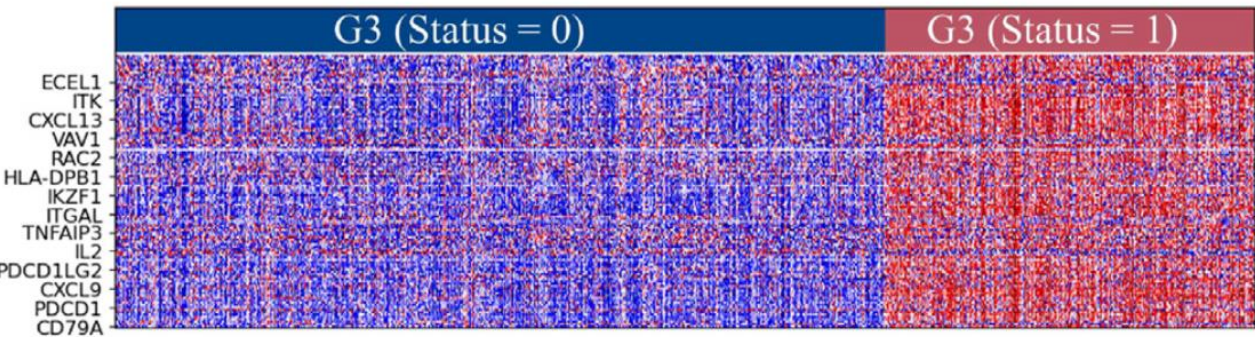
Data-Driven Discovery  
of Gene Groups



## Discovery Cohort (TCGA BRCA)

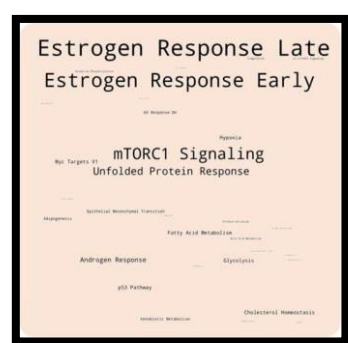
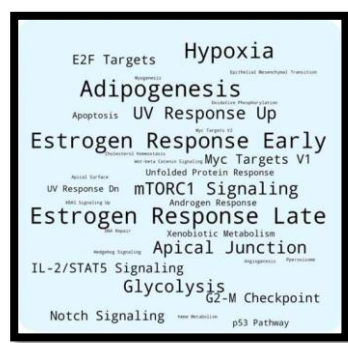


## Independent Validation (METABRIC)



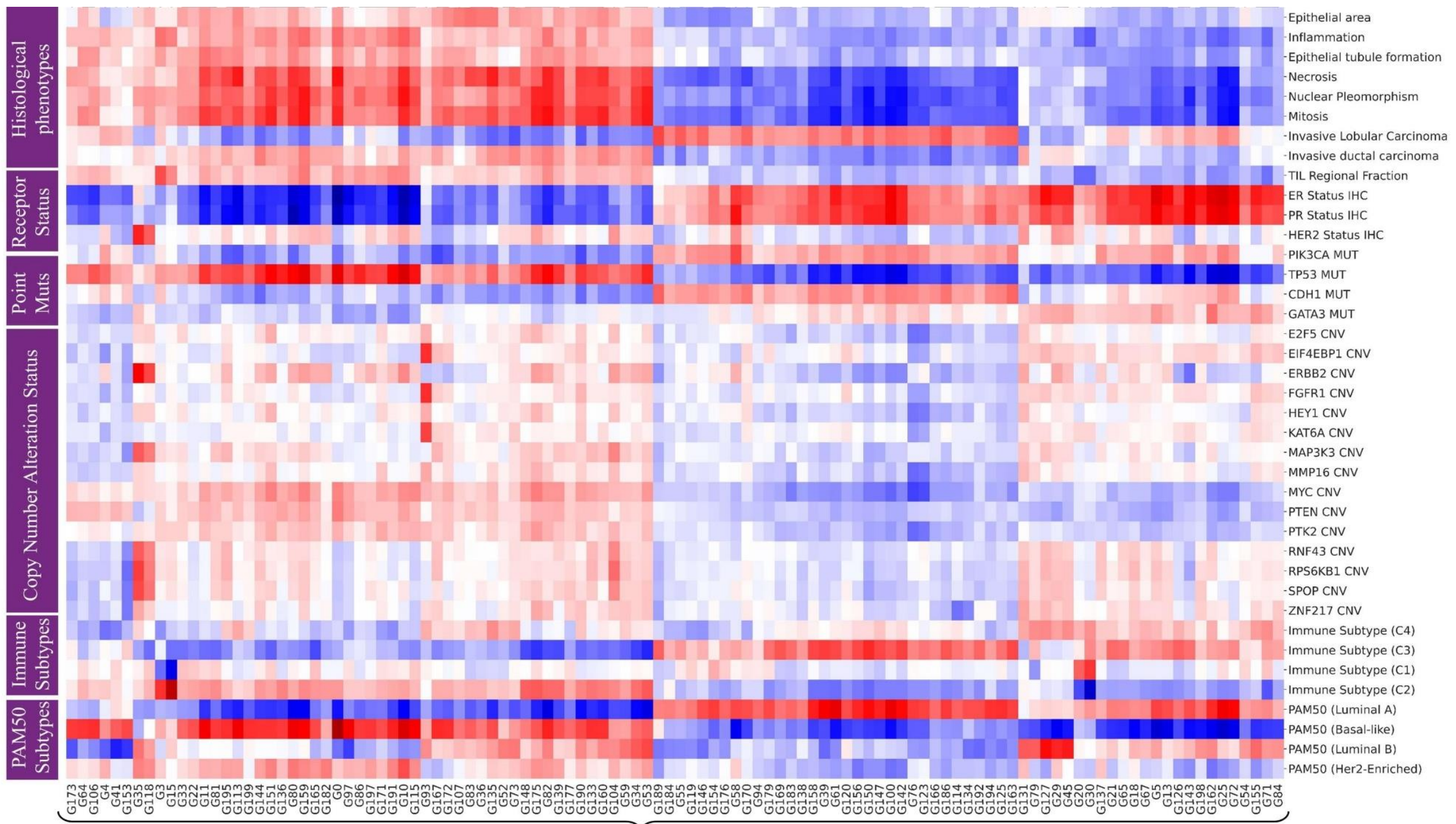
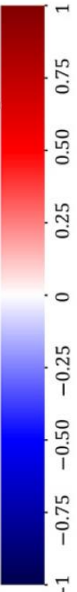


# Role of Gene Groups





Kendal's Tau Correlation with Gene Group Status



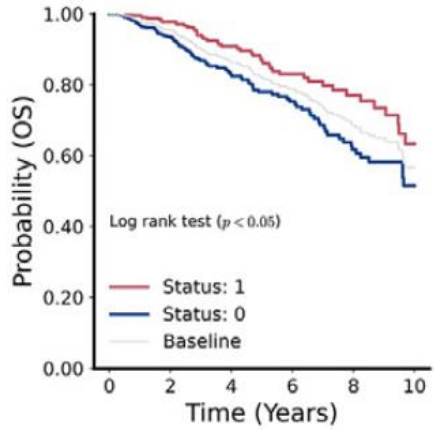
Gene Groups

G173 G164 G106 G4 G41 G353 G35 G118 G3 G15 G33 G22 G11 G81 G95 G113 G199 G144 G151 G136 G80 G159 G165 G182 G0 G97 G86 G197 G171 G191 G10 G115 G93 G167 G172 G107 G83 G36 G35 G32 G73 G48 G175 G82 G139 G177 G190 G123 G59 G104 G34 G53 G189 G84 G55 G119 G46 G154 G176 G58 G170 G94 G179 G169 G83 G38 G158 G39 G61 G20 G156 G150 G47 G100 G142 G76 G123 G166 G186 G14 G34 G92 G94 G25 G163 G131 G179 G27 G20 G45 G20 G30 G37 G21 G65 G18 G67 G5 G13 G26 G143 G198 G162 G25 G72 G54 G35 G71 G84

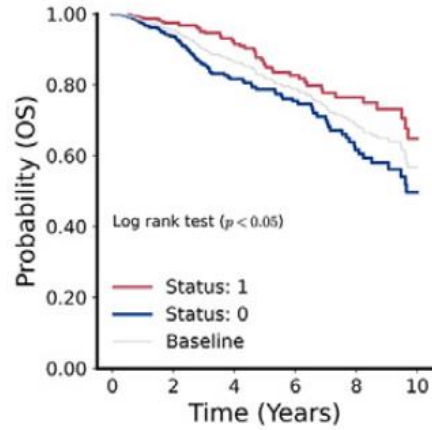


## Discovery Cohort (TCGA BRCA)

G163

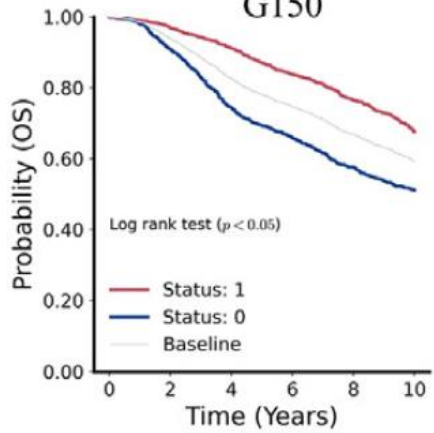


G194

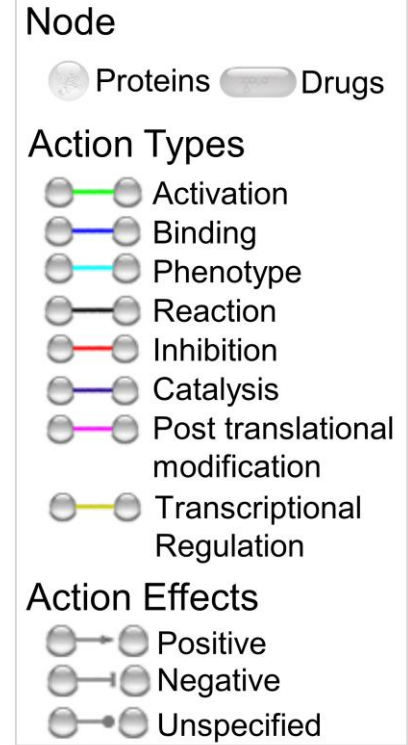
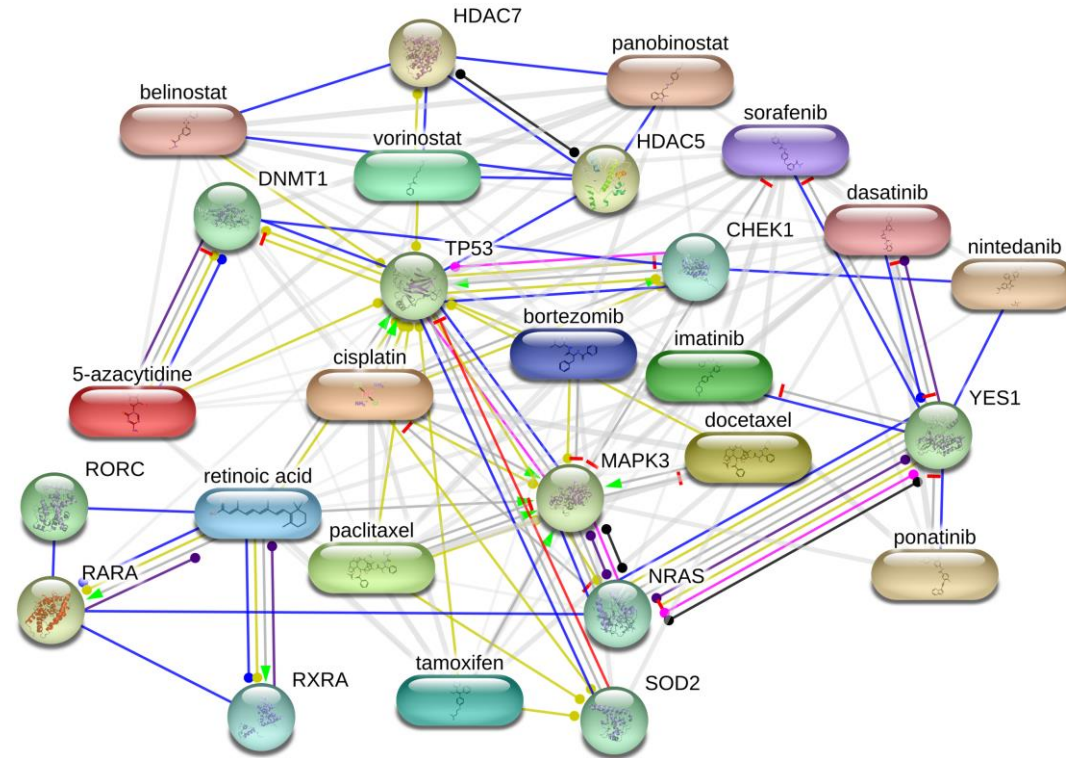
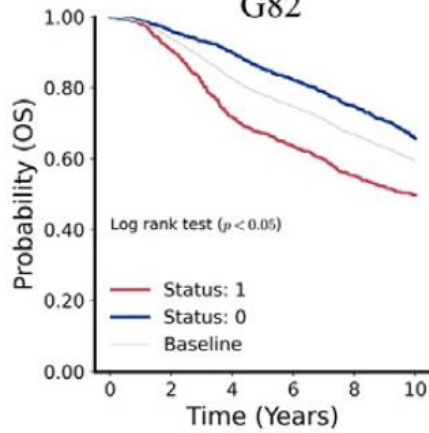


## Independent Validation (METABRIC)

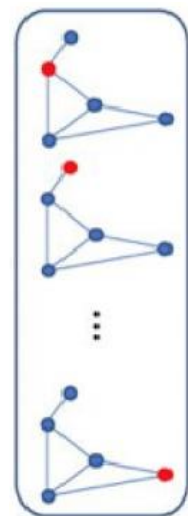
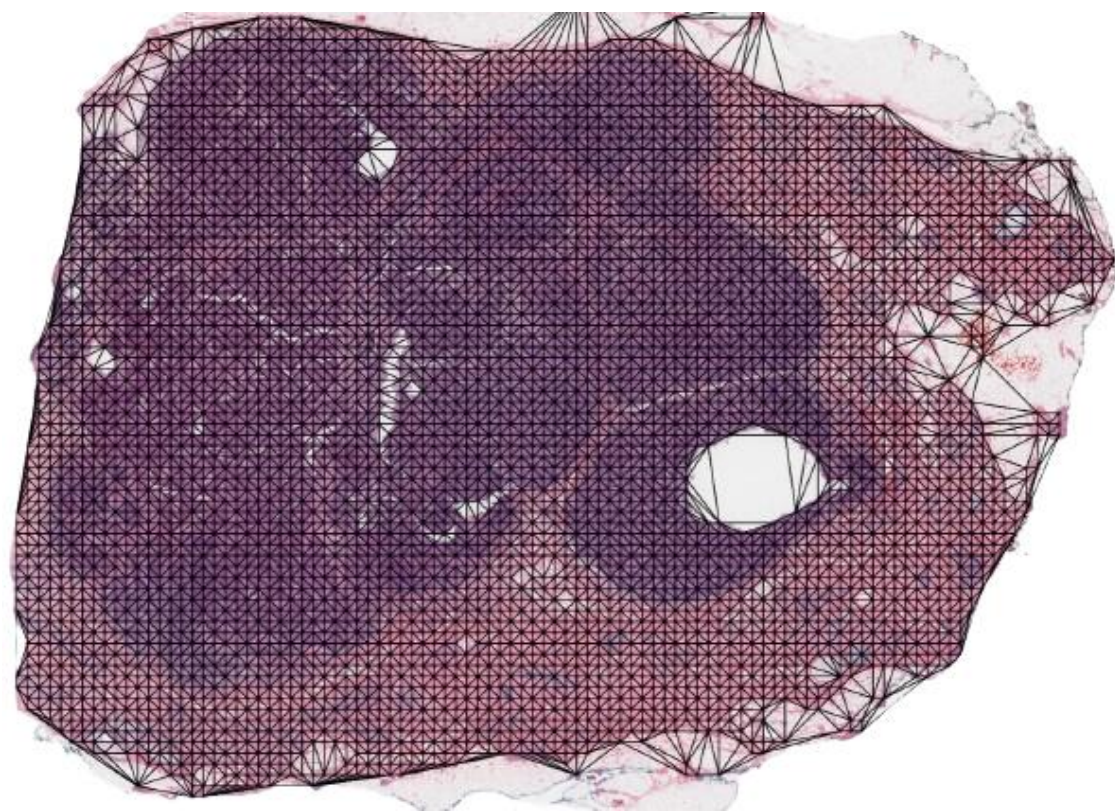
G150



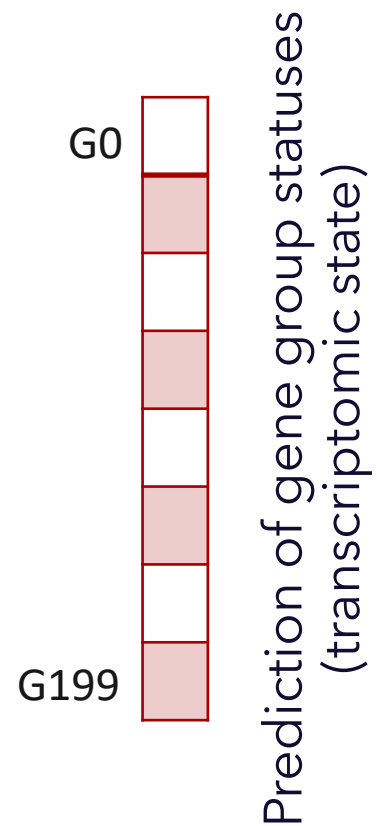
G82



# WSI Based Prediction of Transcriptomic State

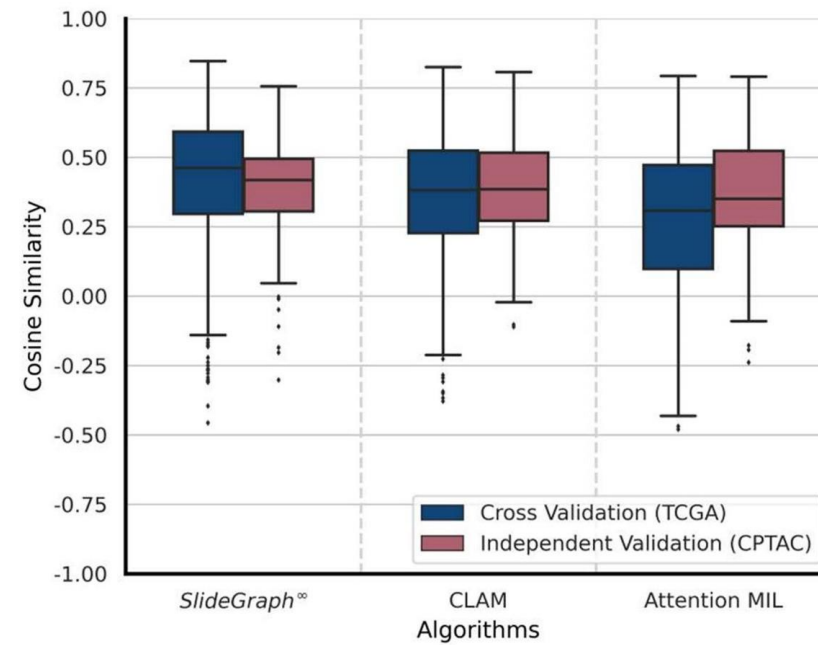
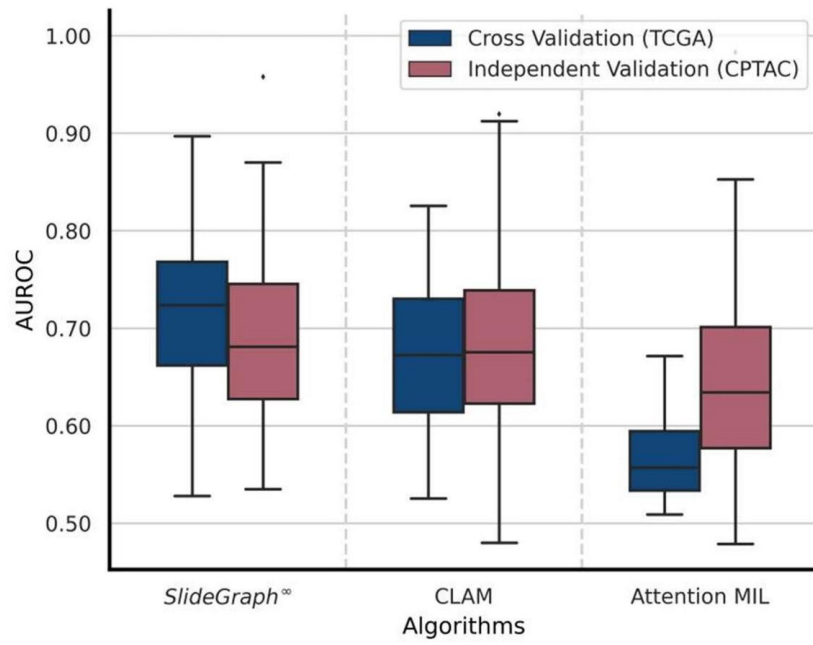


Graph  
Neural  
Network

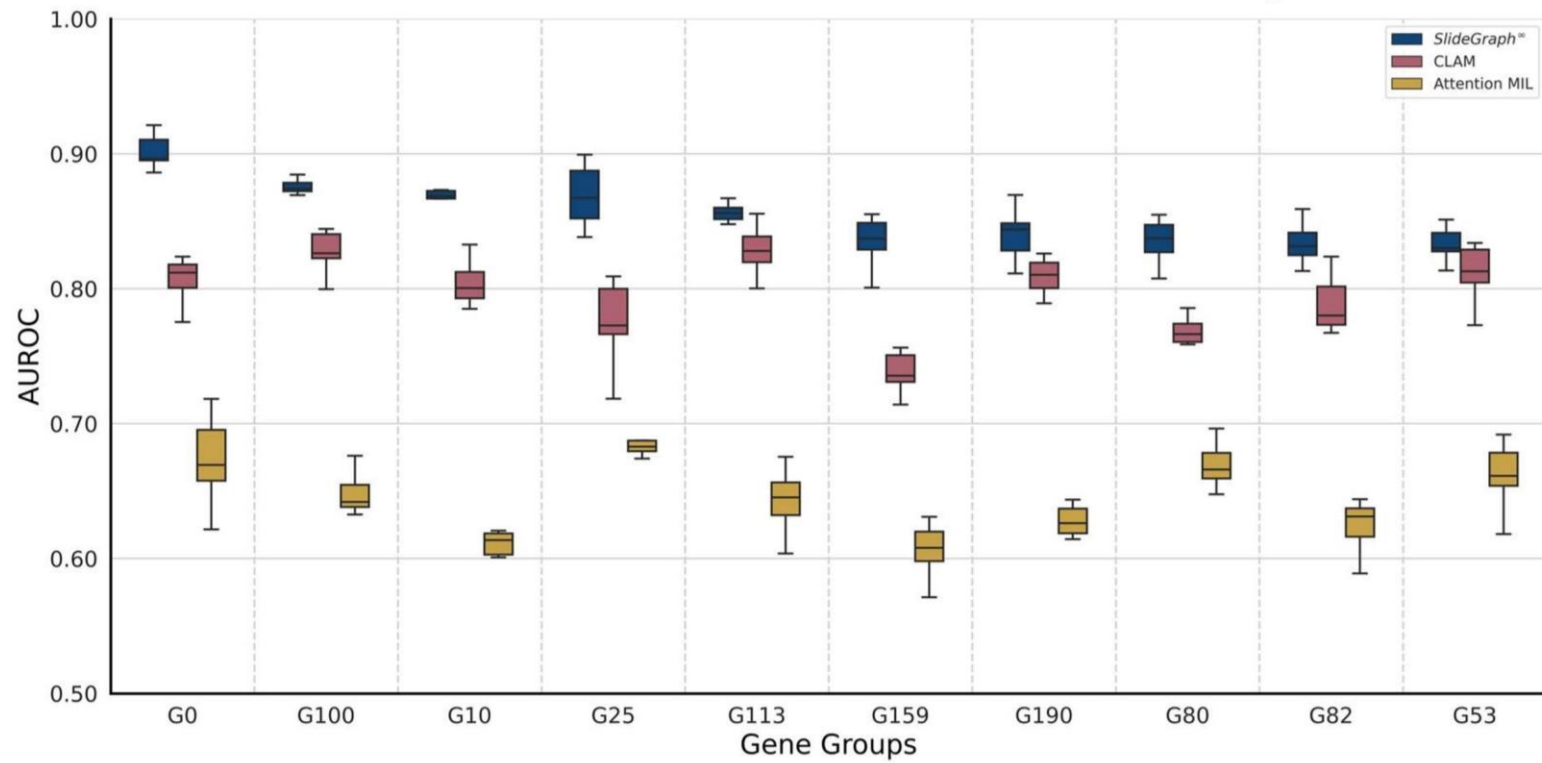




Predicting Status of Gene Expression Groups



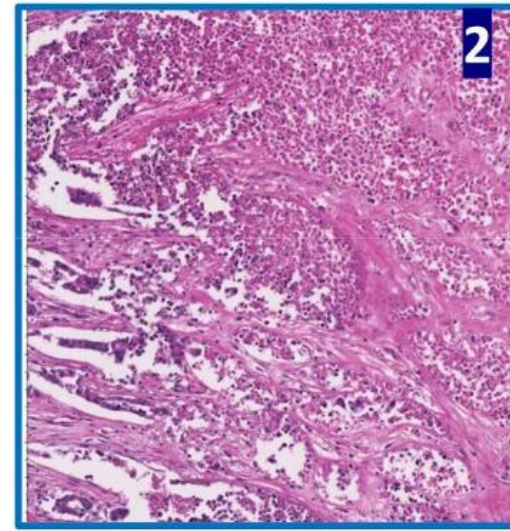
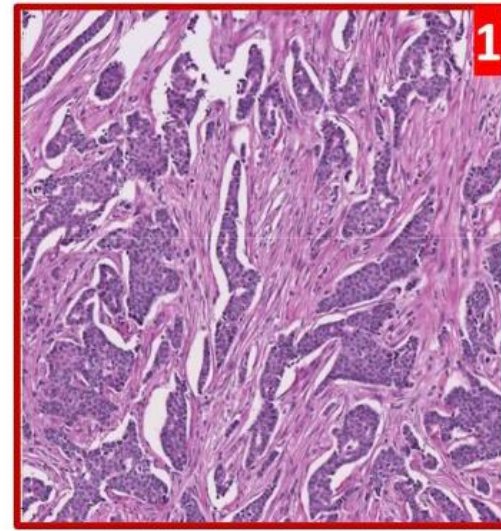
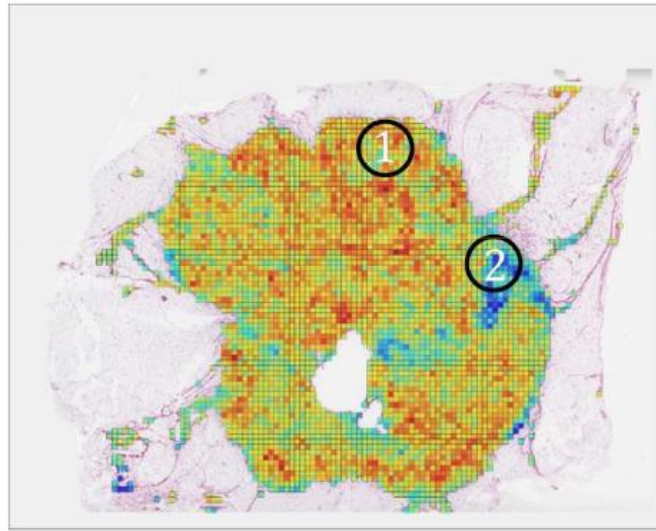
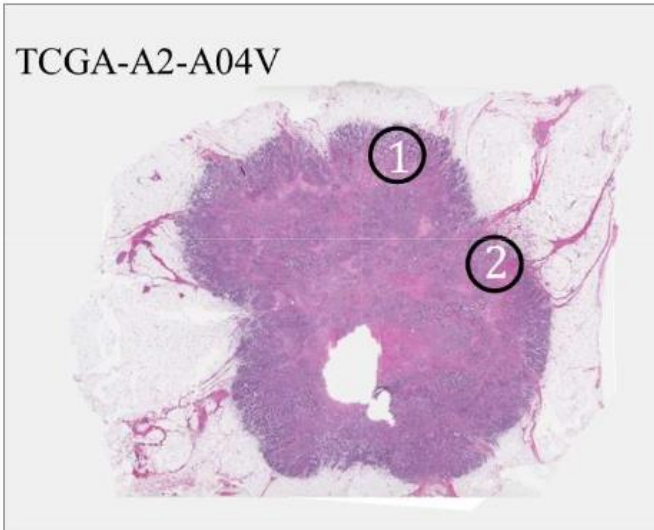
Predicting Transcriptomic State of Patients



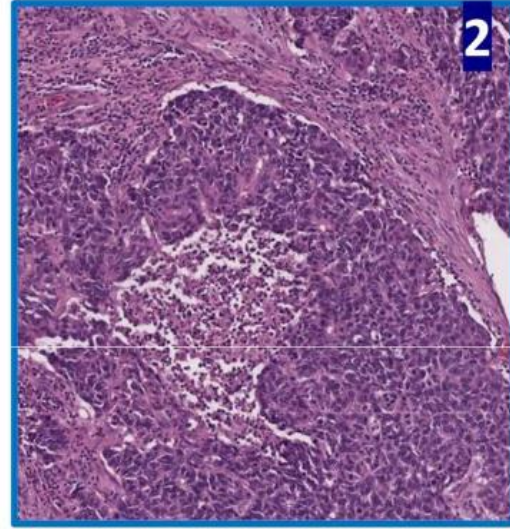
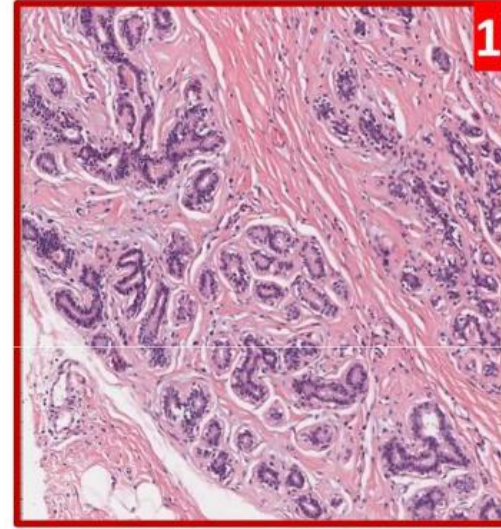
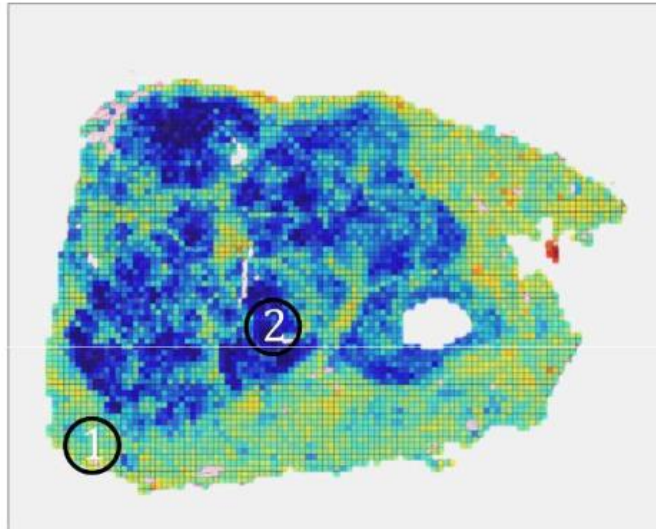
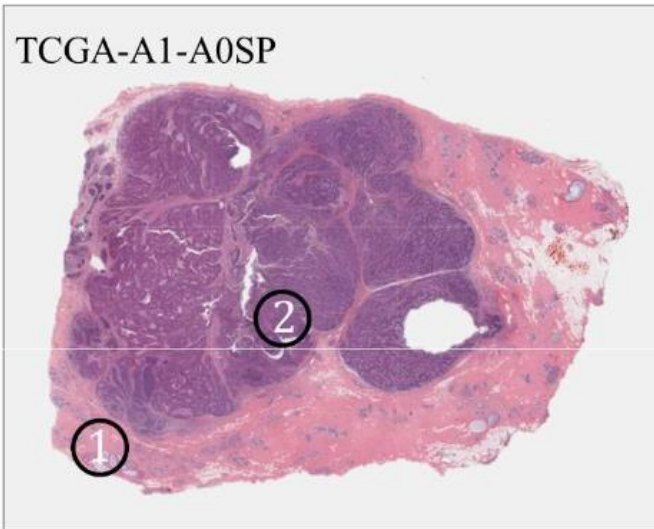


# Spatial Gene Group Profiling

G25 (Status = 1)



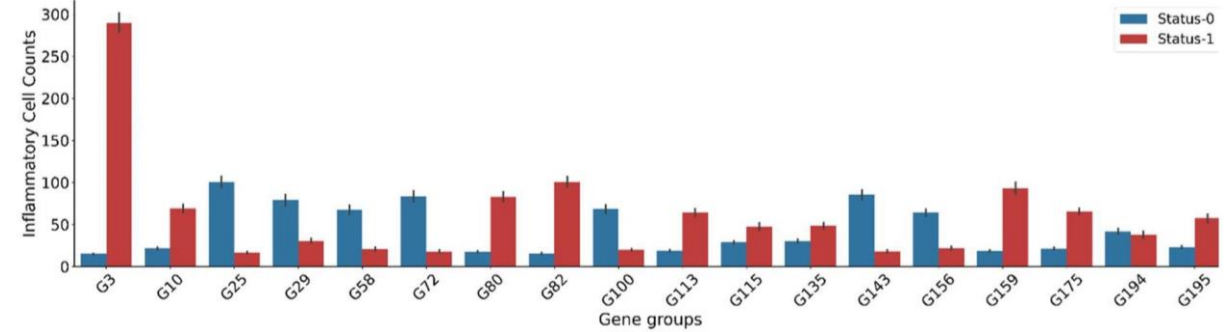
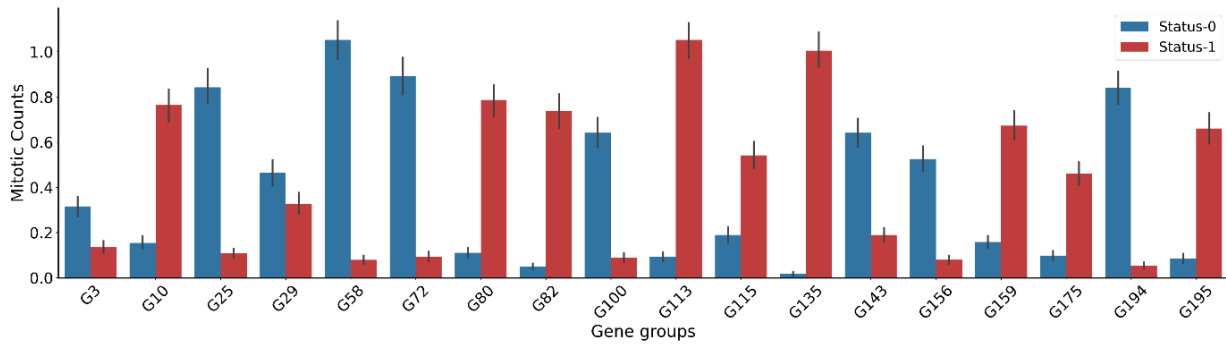
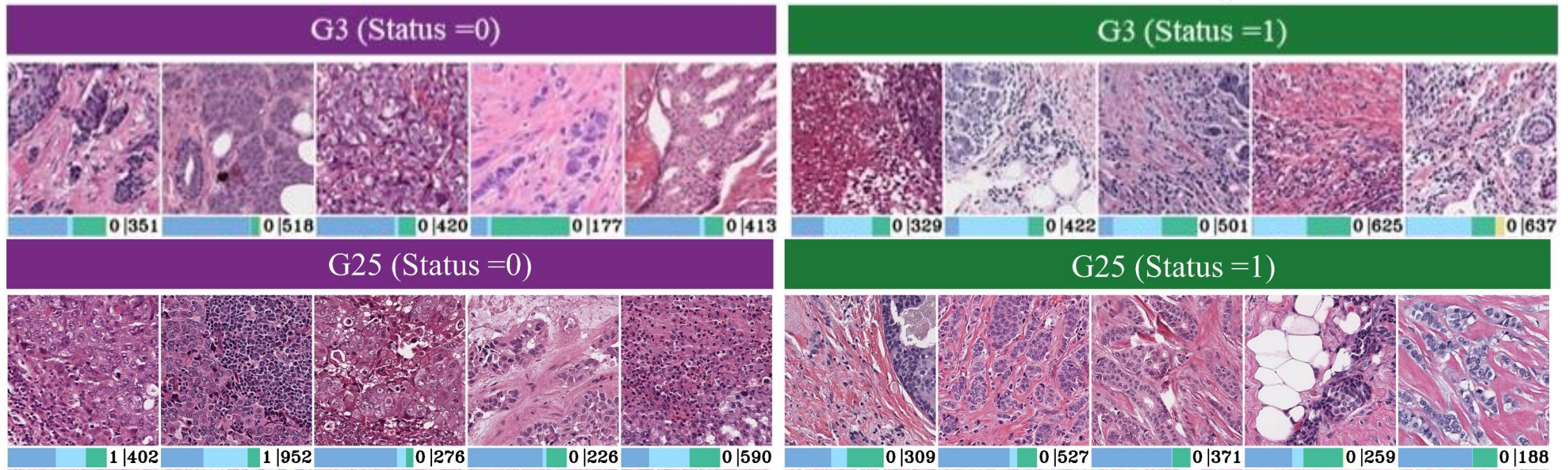
G25 (Status = 0)





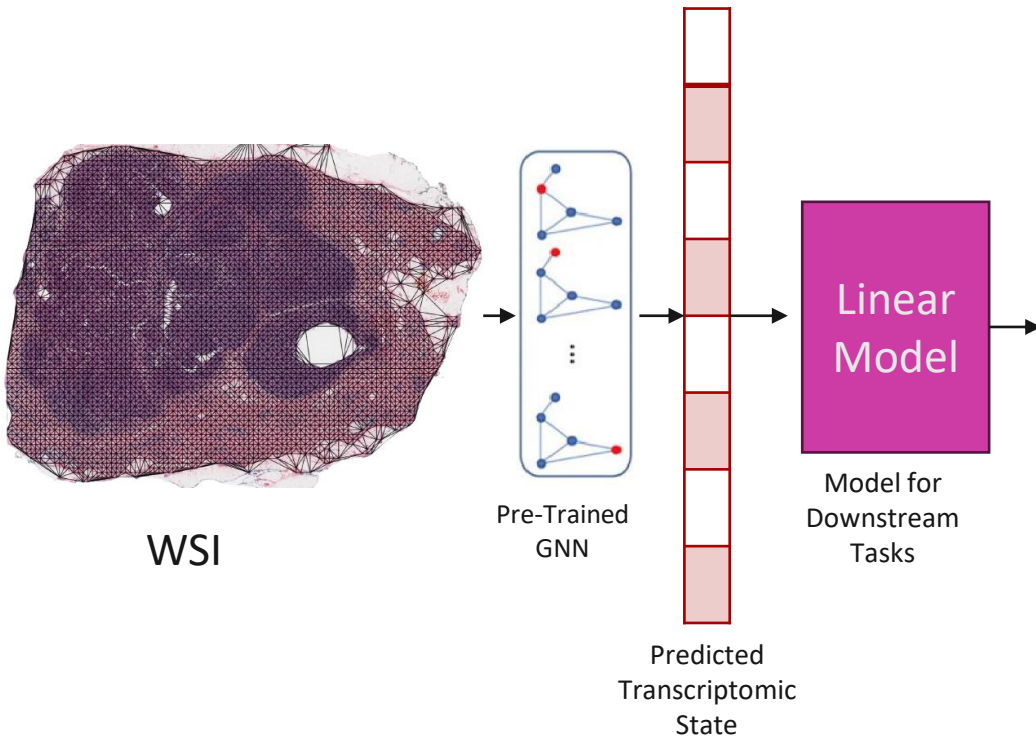
# Differences in Cellular Composition

Neoplastic Inflammatory Connective Epithelial Mitotic Count | Cellularity

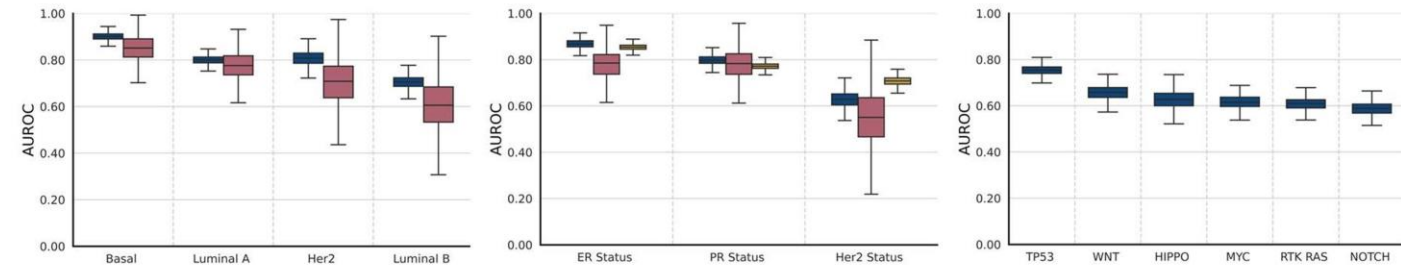




# Downstream tasks



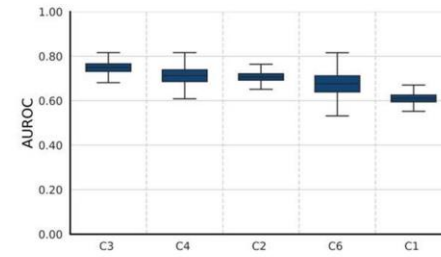
- Use the embeddings generated by the transcriptomic state predictor to predict multiple downstream variables



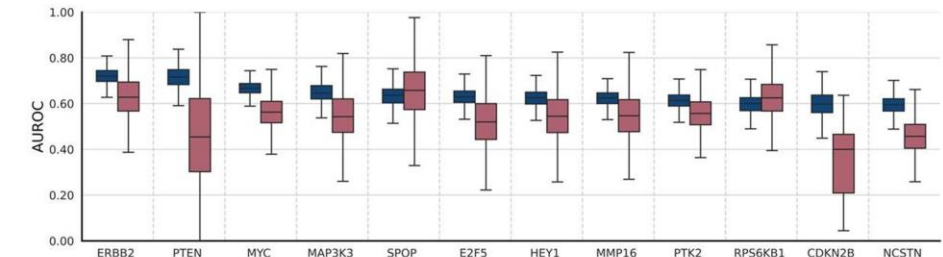
**A: PAM50 subtypes**

**B: Receptor status**

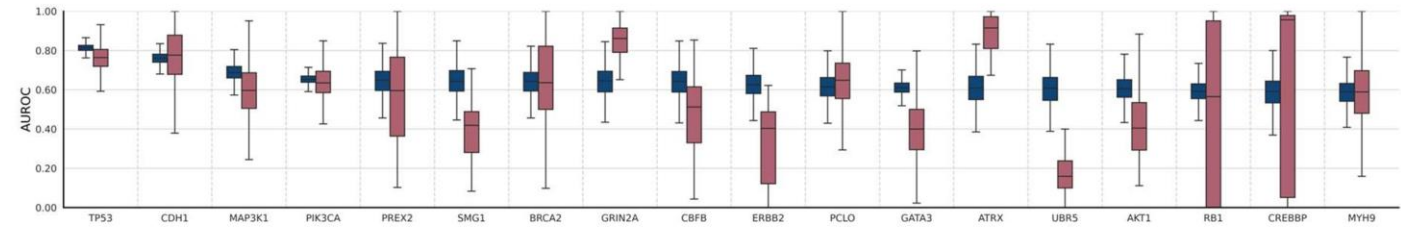
**C: Pathways alteration status**



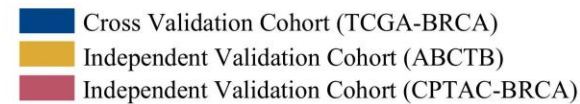
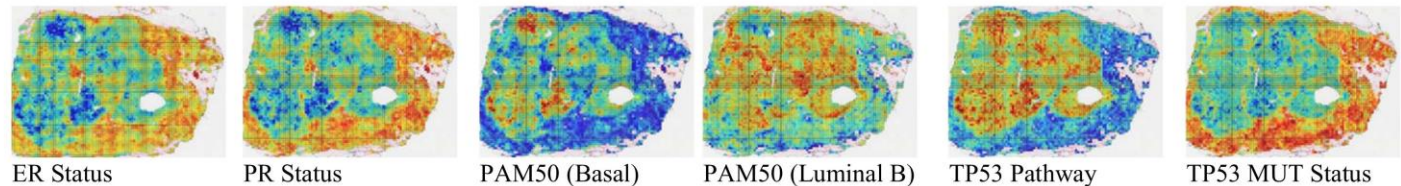
**D: Immune Subtypes**



**E: Copy number alteration status**



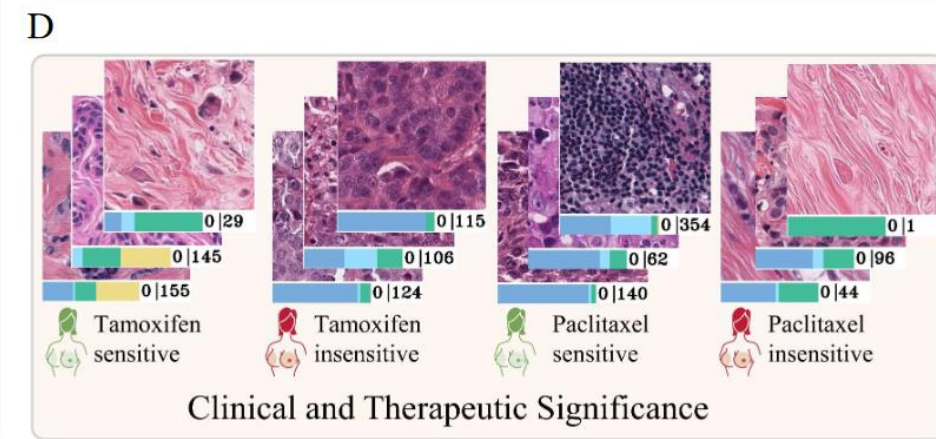
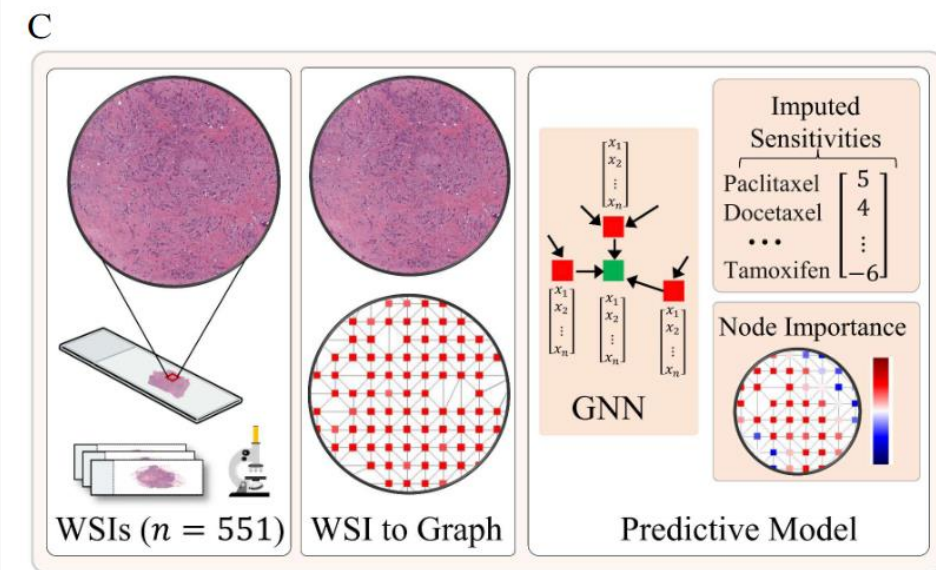
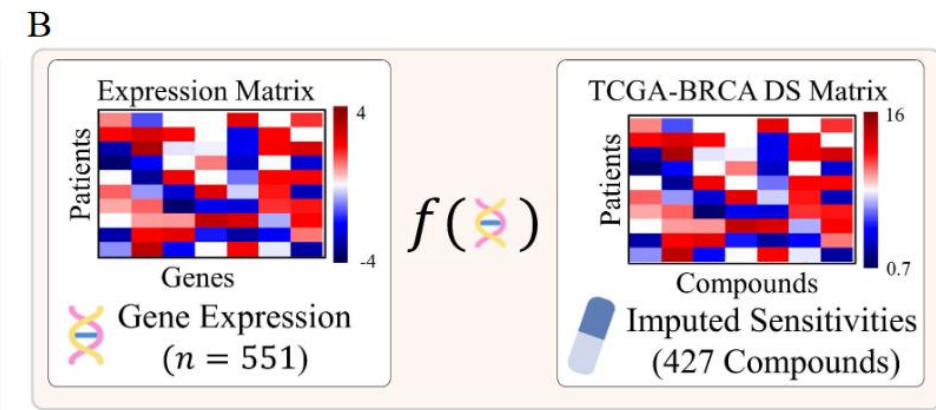
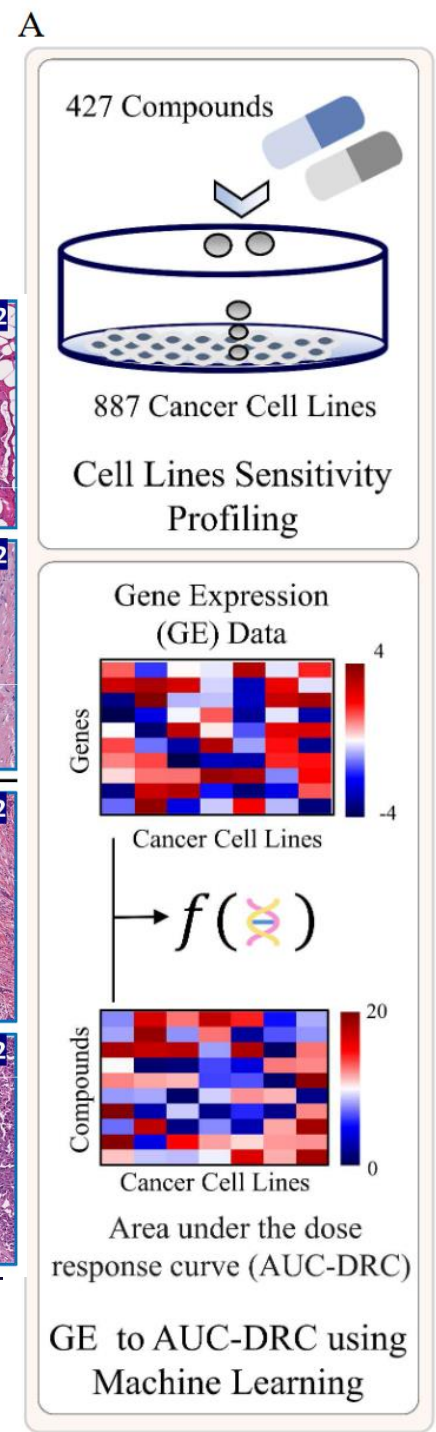
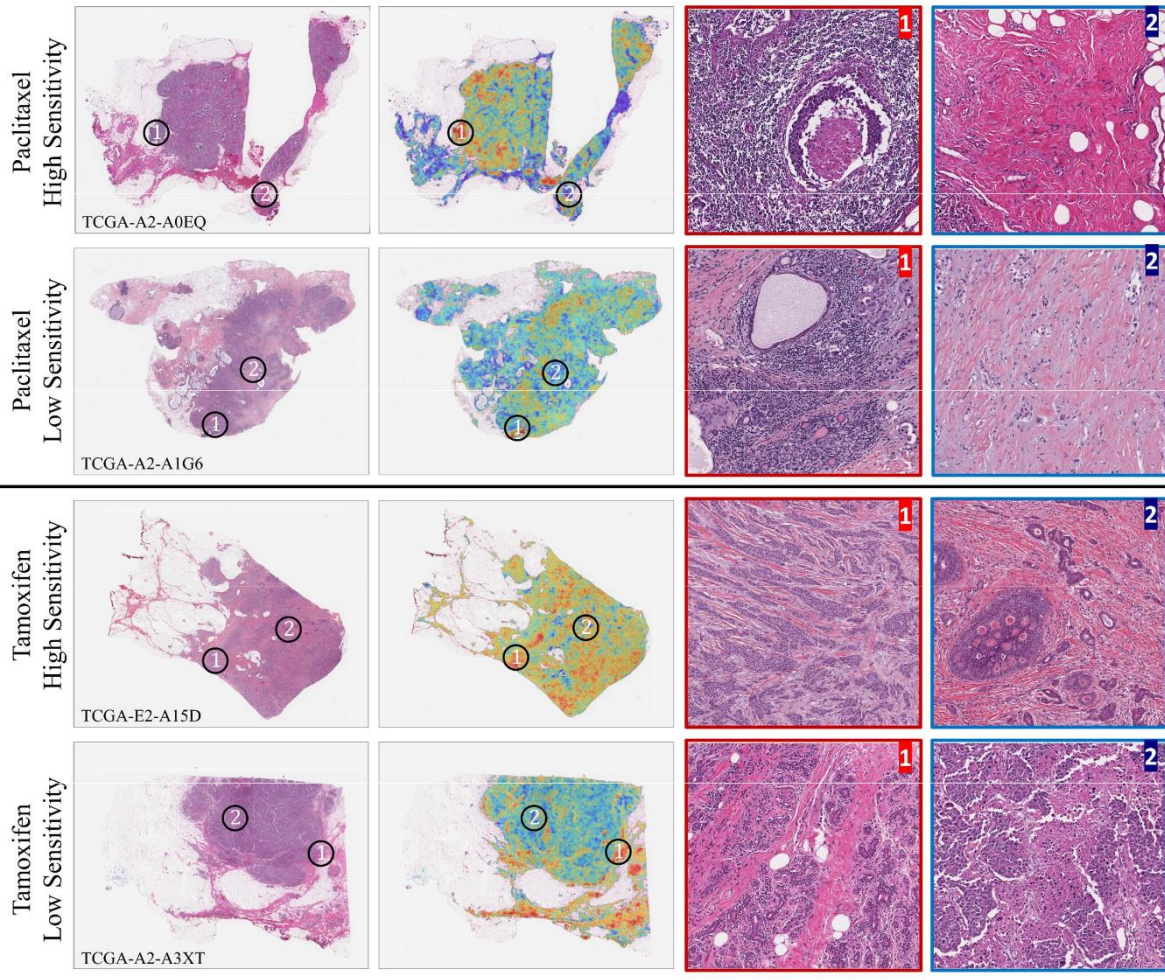
**F: Point mutation status**



**G: Spatial profiling of clinical variables**



# WSI graphs to predict drug sensitivities

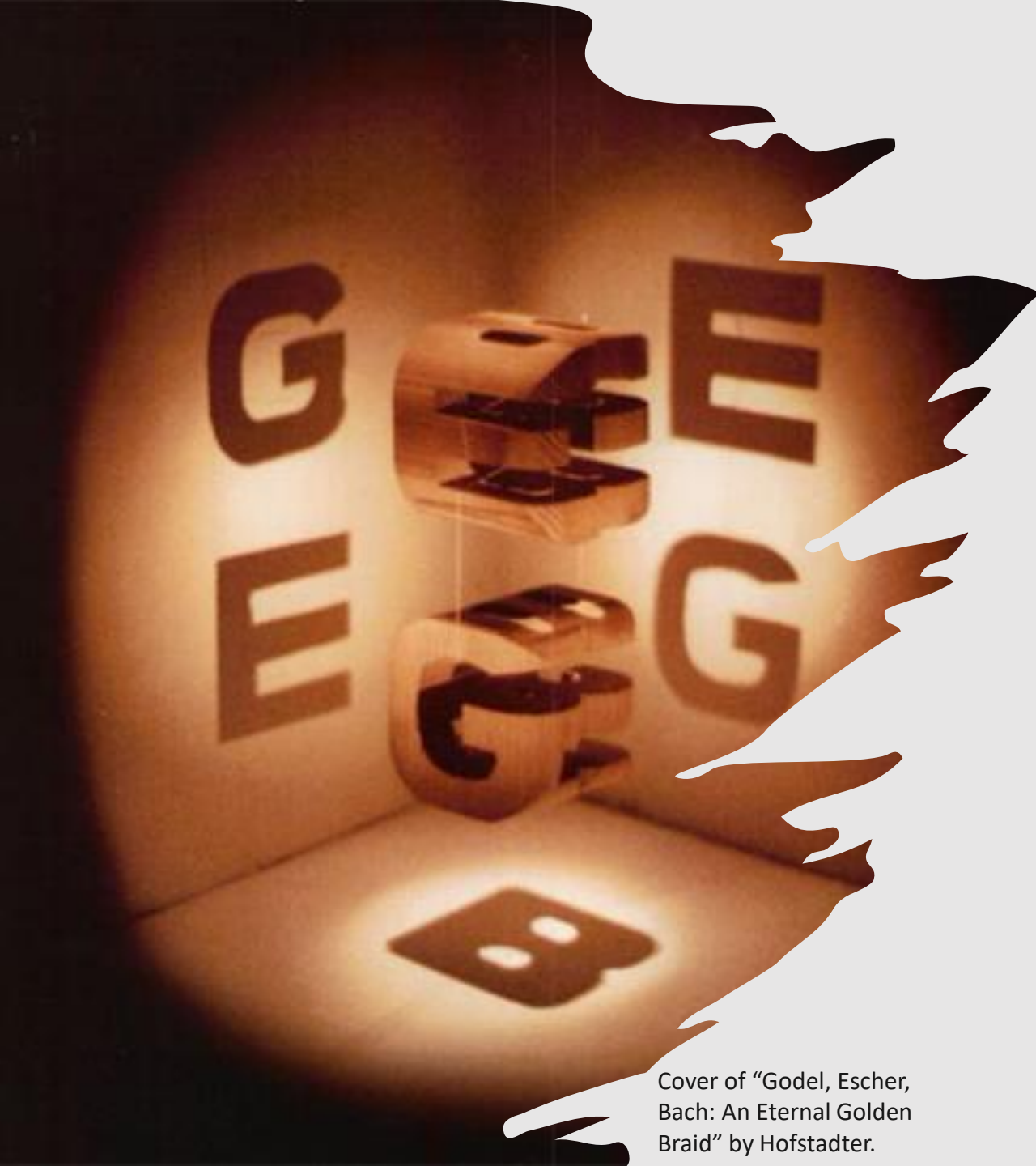


Dawood, Muhammad, Quoc Dang Vu, Lawrence S. Young, Kim Branson, Louise Jones, Nasir Rajpoot, and Fayyaz ul Amir Afsar Minhas. "Cancer Drug Sensitivity Prediction from Routine Histology Images." *Npj Precision Oncology* 8, no. 1 (January 6, 2024): 1–13. <https://doi.org/10.1038/s41698-023-00491-9>.



# Limitations and Conclusions

- It is possible to find associations between patterns observed in spatial OMICs and routine whole slide imaging
- Generative approaches hold a lot of potential
- We need to consider the effects of confounding factors and biases in cross-linking histological imaging and spatial omics as well as causality
  - Cross-linking with methylation, chromatin organization and protein expression?



Cover of "Godel, Escher, Bach: An Eternal Golden Braid" by Hofstadter.





<https://warwick.ac.uk/TIA>



@fayyazhere







Order 66: when certain clones disobeyed orders to kill the Jedi. These clones are the bad batch (cancer)



Omega joins the bad batch (Oncogenesis.)

Crosshair leaves the bad batch to join the empire (Cancer cell treated)



Echo leaves the bad batch to join Captain Rex and help "liberate" clones from prisons like Tantiss. (Cancer spreading)



Tech dies because of the empire (cancer cell death)



Clone assassin (white blood cell) along with Commander Wolffe try to deal with the bad batch and others



Omega, Crosshair, and Batcher escape the imperial base Tantiss. (Oncogenesis)



Omega gets captured because Cid ratted the bad batch out. (cancer cell treated)

**"So essentially you'll present about the bad batch".**

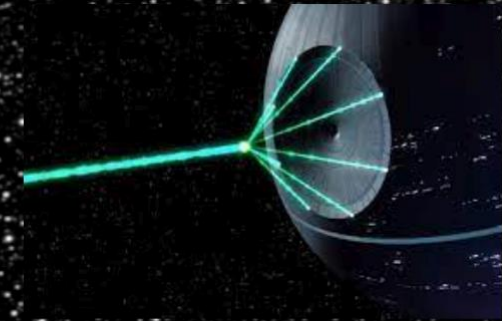
**Credits and with permission of Haider Afsar:**

Information based on last episode (s3 e7) of The Bad Batch which was released on 13th of March 2024.





Giant kyber crystals are used as the main power of the death star. The kyber crystals transfers the energy stored in power cells(organic compounds)to the giant laser(molecules of ATP). (Mitochondria)



The giant laser contains a green pigment. The green laser takes the energy of the sun into fuel(food) for the laser. (chloroplast)

The hangar regulates the passage of transport shuttles, fighters and lambda class shuttles. The hangar are behind the wall and close off the death star. (cell membrane)

The rigid outer wall of the death star is used to support it from rebel attacks. It provides more support than the hangar. (cell wall)



The trash compactor has strong enzymes used for the digestion of proteins, carbs and lipids and nucleic acids. It rids the deathstar of trash and dead people. (Lysosome)



The cantina stores the food and water of the death star. In the cantina there are bathrooms that store the metabolic waste. (Vacuole)

***"So essentially you'll present about clone wars".***



Transport shuttles may or may not have storm troopers( ribosomes). Transport shuttles move things from one part of the death star to another.( Endoplasmic reticulum)



Stormtroopers may be found in the death stars extra space and in transport shuttles. Stormtroopers are the most numerous in the death star. Stormtroopers translate members to officers(mRNA) and carry out building. Stormtroopers are the site of fighting (protein synthesis). (Ribosome)