Agenda

- Why AI-powered pathology for UC?

- Tissue and cell model quantification of UC histological features

- Evaluation of model-generated human interpretable features

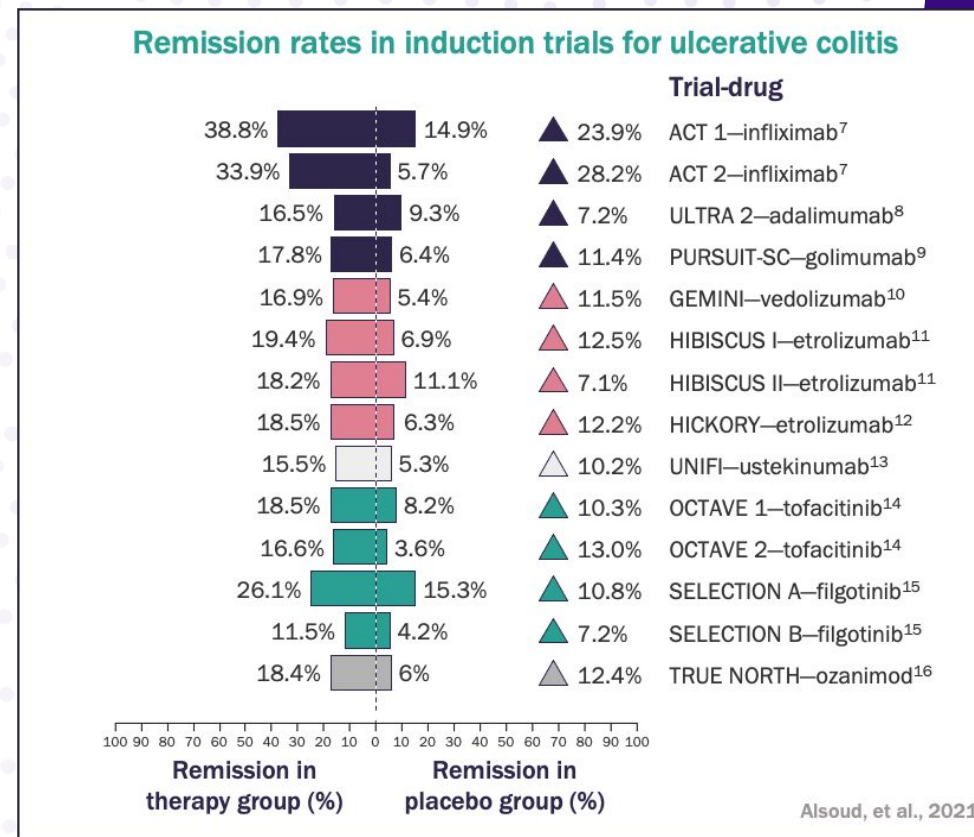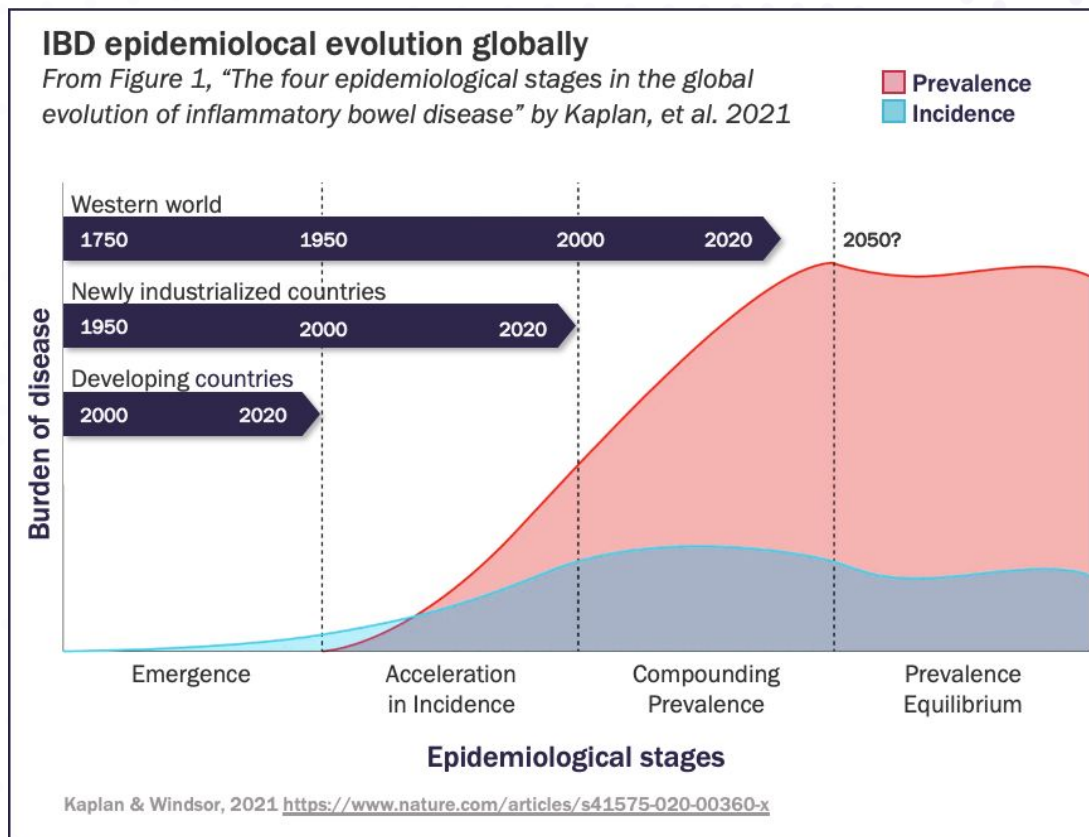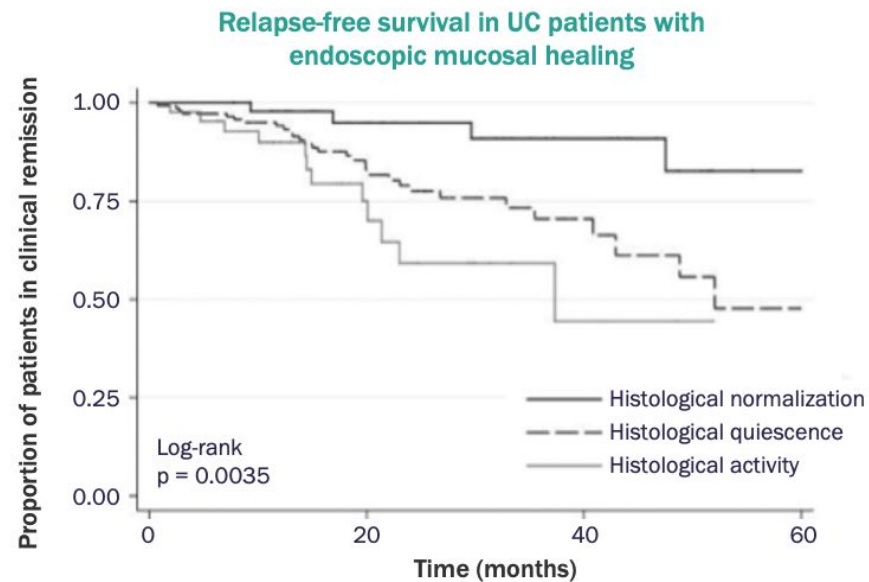- HIF-based prediction of disease severity scores and histologic remission

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Artificial Intelligence Applications in Inflammatory Bowel Disease: Quantifying the Mucosal Microenvironment of Ulcerative Colitis

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The prevalence of ulcerative colitis continues to rise, but few long-term treatment options exist

IBD epidemiolocal evolution globally

From Figure 1, "The four epidemiological stages in the global evolution of inflammatory bowel disease" by Kaplan, et al. 2021

Kaplan & Windsor, 2021 https://www.nature.com/articles/s41575-020-00360-x

Remission rates in induction trials for ulcerative colitis

Alsoud, et al., 2021

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Histological activity has been recognized as an important prognostic factor and potential target for more efficacious treatments in ulcerative colitis

A more predictive indicator of treatment response

Histologic measurement in UC patients demonstrated stronger association with relapse-free survival compared to endoscopic mucosal healing
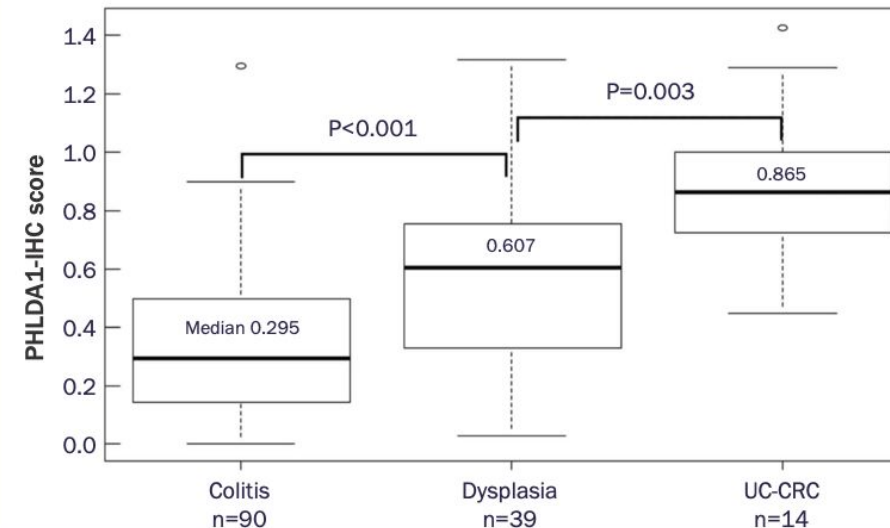
Relapse-free survival in UC patients with endoscopic mucosal healing

- Histological normalization
- Histological quiescence
- Histological activity

Log-rank
p = 0.0035

Source: Christensen, B. et al. 2017. *Clin Gastroenterol Hepatol.*

Unlocking new insights on disease, drug activity, and patients

Characterization of the microscopic inflammatory environment of UC patients provides insights for biomarkers that may be predictive of outcomes

IHC for PHLDA1 and finds associations of PHLDA1 levels with dysplasia and CRC in UC patients

P<0.001

P=0.003

Median 0.295

0.607

0.865

Colitis
n=90

Dysplasia
n=39

UC-CRC
n=14

Source: Orita, et al. 2021. https://www.spandidos-publications.com/10.3892/mco.2021.2354

Artificial Intelligence Applications in Inflammatory Bowel Disease:
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Challenges inherent to histological evaluation and interpretation can pose risks to UC research and clinical development

Histological Remission

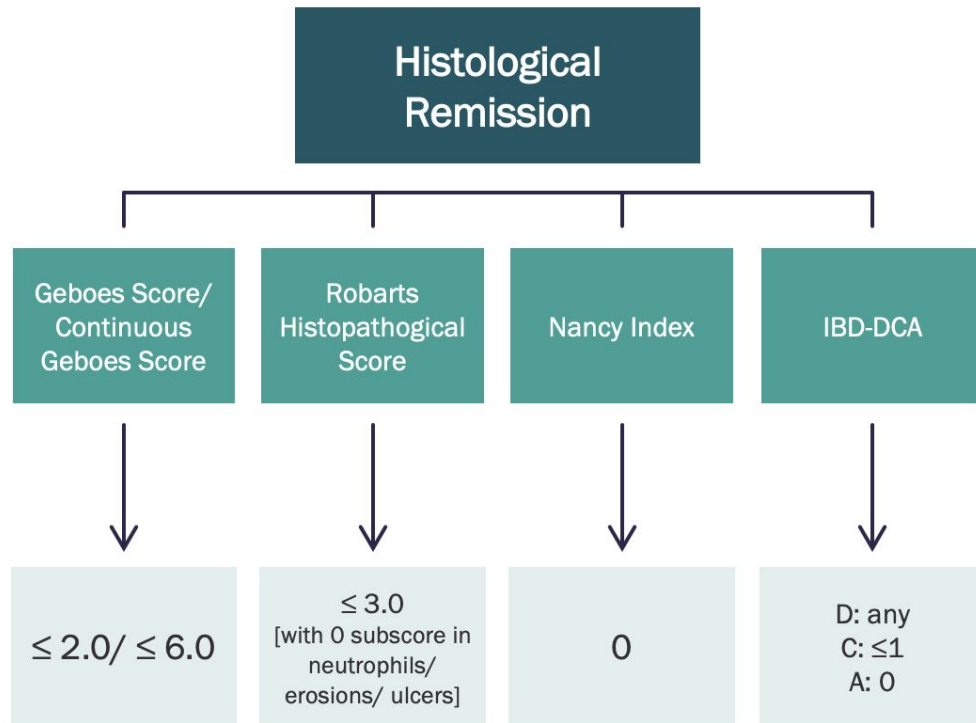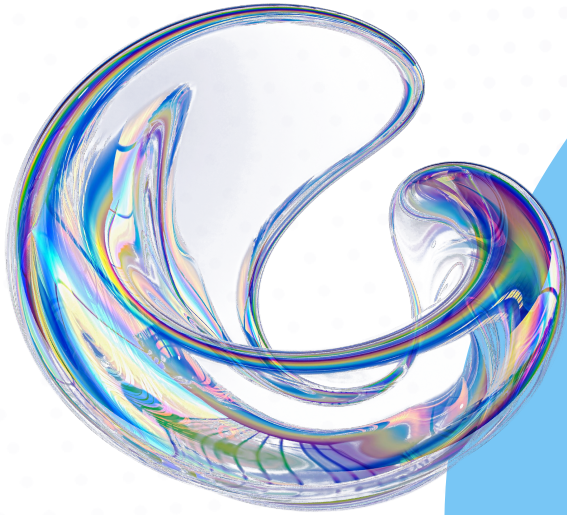| Geboes Score/ Continuous Geboes Score	Robarts Histopathogical Score	Nancy Index	IBD-DCA
≤ 2.0/ ≤ 6.0	≤ 3.0 [with 0 subscore in neutrophils/ erosions/ ulcers]	0	D: any C: ≤1 A: 0

Image redesigned from Vespa et al. Histological Scores in Patients with Inflammatory Bowel Diseases: The State of the Art. Journal Clin Med. 2022

- Lack of standardization in histology scoring systems

- Intra- and inter-rater variability

- Complex quantitative and spatial insights and markers are indiscernible to human pathologists and analysis

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Artificial Intelligence Applications in Inflammatory Bowel Disease: Quantifying the Mucosal Microenvironment of Ulcerative Colitis

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Tissue and cell model predictions of UC histological features

Patient and image characteristics of datasets used in model development and evaluation

- Data set split between train/validation/test was performed with the aim to balance the distribution of these characteristics

		Lab 1		Lab 2		Other commercial laboratories	
Slides		702		308		254	
Patients		376		243			
Cases		377		284		227	
Gender							
	Female	193	(51.1)	103	(41.7)		
	Male	182	(48.4)	140	(58.3)		
	Unknown	2	(0.5)				
Age							
	13-18 (%)	2	(0.5)				
	19-44 (%)	141	(37.4)	76	(30.8)		
	45-64 (%)	146	(38.7)	106	(42.9)		
	65-79 (%)	79	(21.0)	58	(23.5)		
	80+ (%)	9	(2.4)	7	(2.8)		
	Unknown (%)						
Data Split							
	Training / Validation	383				254	
	Test	319		308			
Scanners							
	Leica Aperio AT2	7		308		254	
	Leica Aperio GT450	695					
Original Diagnosis							
	Chronic inactive colitis (%)	187	(26.6)	43	(14.0)		
	Mild chronic active colitis (%)	143	(20.3)	63	(20.5)		
	Moderate chronic active colitis (%)	132	(18.8)	78	(25.3)		
	Severe chronic active colitis (%)	92	(13.1)	32	(10.4)		
	Focal Active Colitis (%)	2	(0.3)	64	(20.8)		
	Normal colon (%)	146	(20.8)	14	(4.5)		
	Unknown (%)			14	(4.5)		
Collection Site							
	Left (%)	579	(82.5)	93	(30.2)	123	(48.4)
	Right (%)			76	(24.7)		
	Rectum (%)	123	(17.6)	69	(22.4)	131	(51.6)
	Other (%)			70	(22.7)		
NHI Score							
	NHI 0 (%)	142	(32.7)	60	(19.5)		
	NHI 1 (%)	38	(8.8)	7	(2.2)		
	NHI 2 (%)	72	(16.6)	39	(12.7)		
	NHI 3 (%)	137	(31.6)	138	(44.8)		
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- Lab 1 is **PathAI Diagnostics**
  - Subspecialties in gastroenterology, urology, dermatology and women's health
  - ~2,000 samples processed daily
  - ~490,000 patient reports annually

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AI models were trained using pathologist labeling of histological features of ulcerative colitis
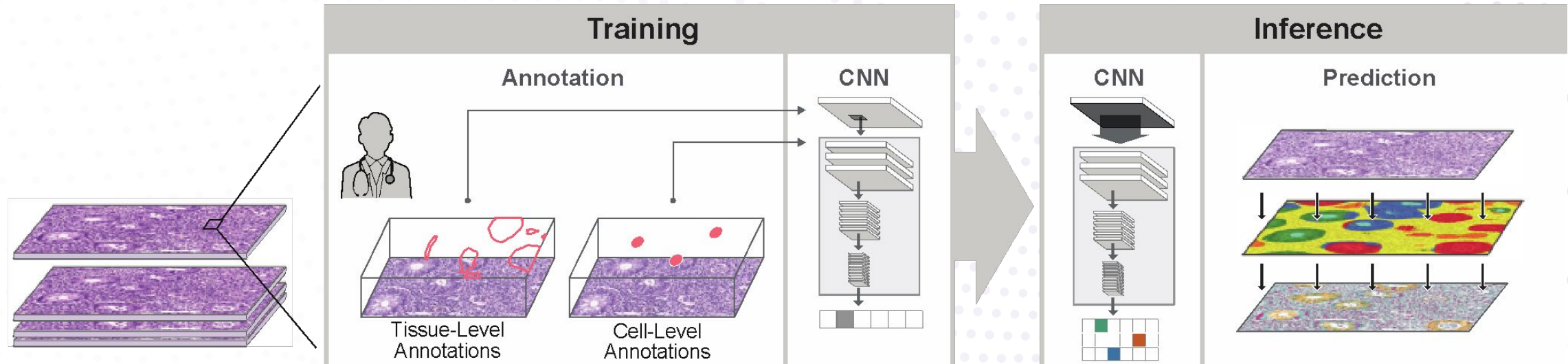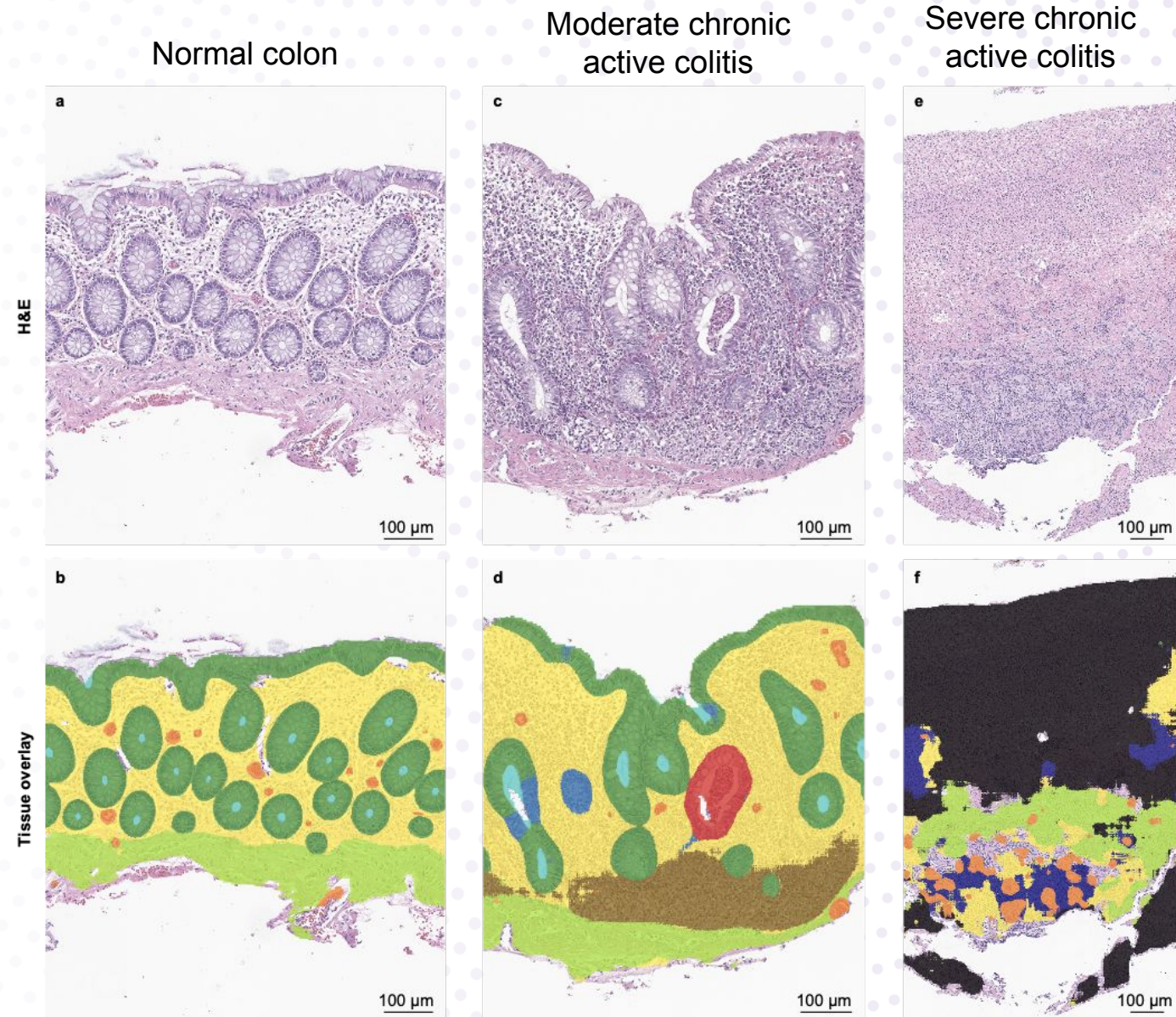

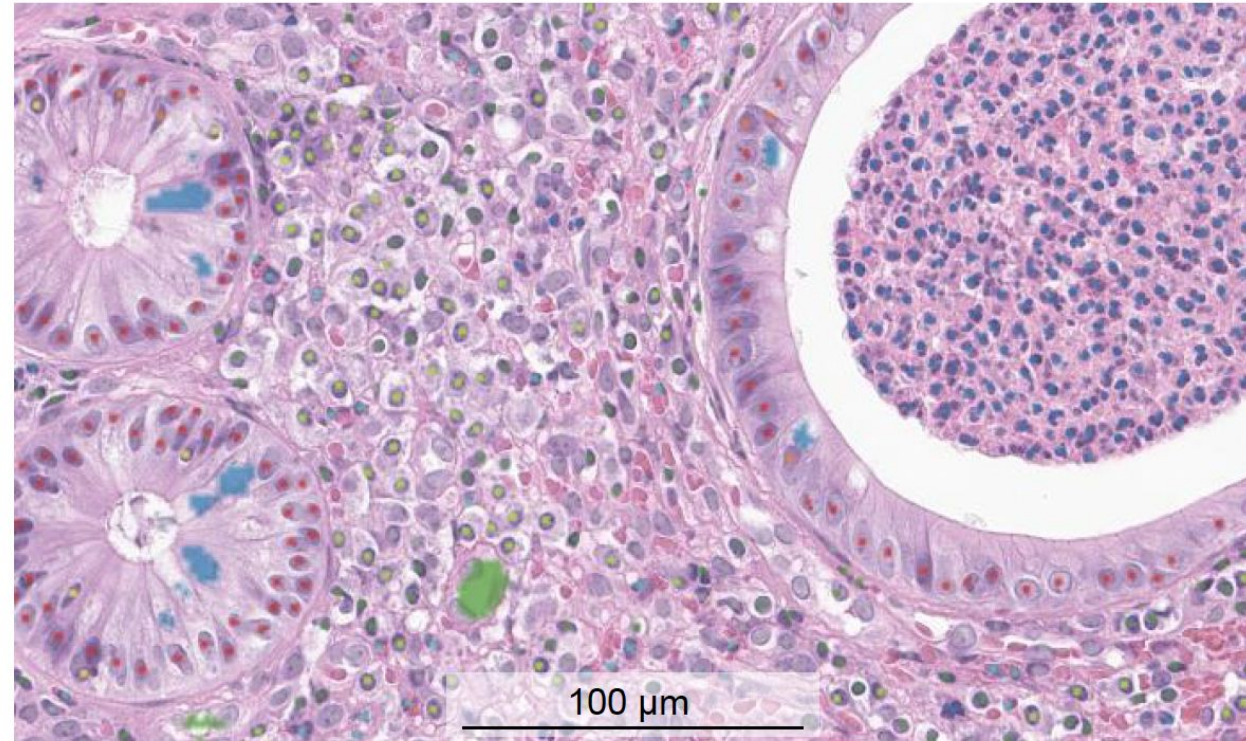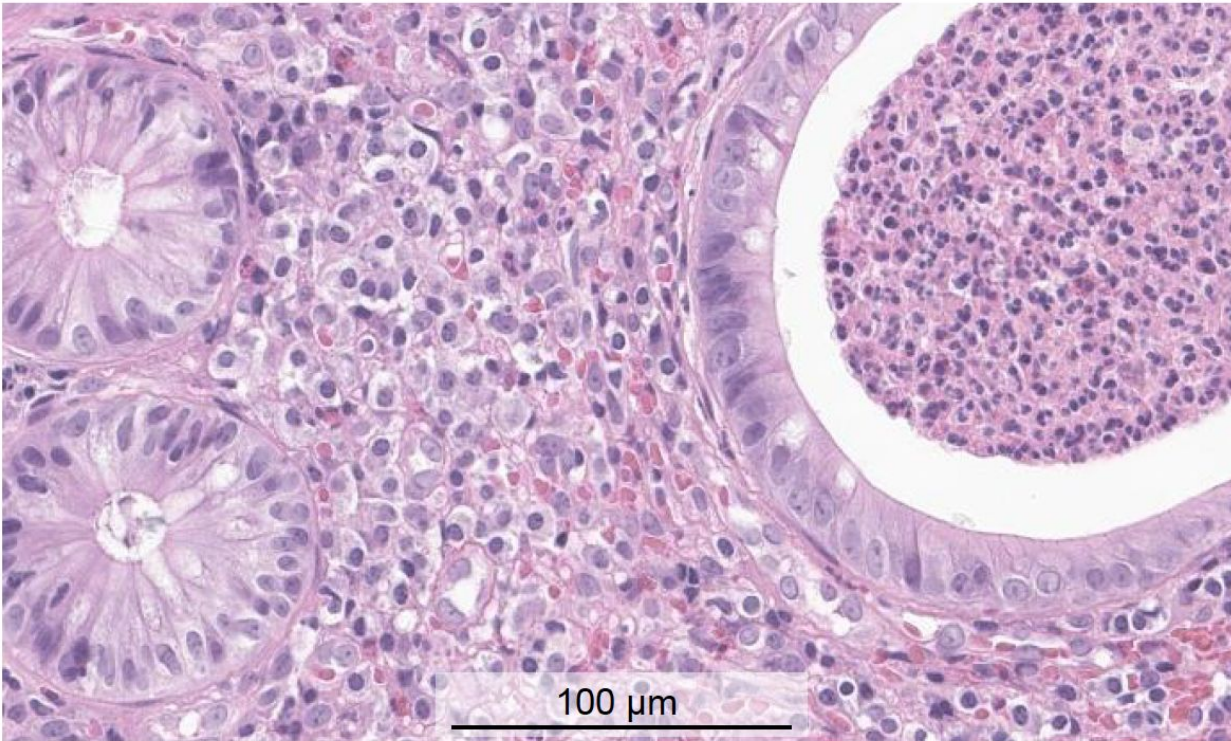We collected ~38,000 tissue-level region annotations and ~124,000 cell-level point annotations

A convolutional neural network (CNN) with over 20 layers and 8 million parameters was then trained to produce pixel-level predictions of UC histology

Tissue model predictions

Legend:
- 🟩 Normal epithelium
- 🟦 Infiltrated epithelium
- 🟦 Inter-gland lumen
- 🟥 Crypt abscess
- 🟩 Muscularis mucosa
- 🟨 Lamina propria
- ⬛ Erosion/ulceration
- 🟧 Blood vessel
- 🟦 Granulation tissue
- 🟫 Basal plasmacytosis

Normal colon — Moderate chronic active colitis — Severe chronic active colitis

Artificial Intelligence Applications in Inflammatory Bowel Disease:
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Cell model predictions

Legend:
- 🟧 Goblet cell nucleus
- 🟥 Epithelial non-goblet cell enterocyte
- 🟨 Intraepithelial lymphocyte
- 🟩 Lymphocyte non intraepithelial
- 🟩 Plasma cell
- 🟦 Eosinophil
- 🟦 Neutrophil
- 🔵 Goblet cell cytoplasm
- 🟢 Blood vessel lumen

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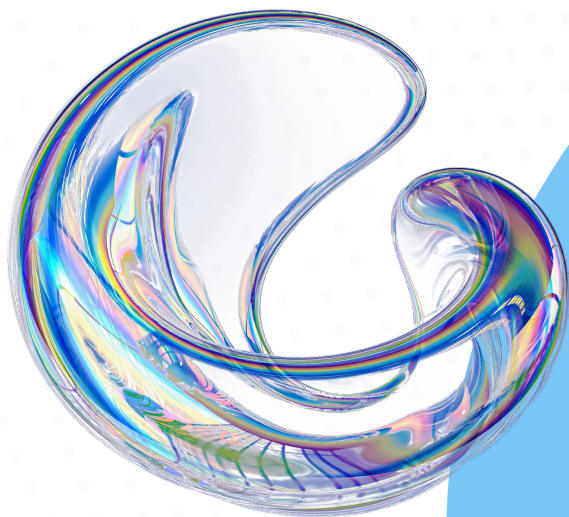
11

Cell model prediction performance evaluated against pathologist consensus

- Exhaustive cell-level point annotations were collected from 5 pathologists across a set of tissue frames

- The F1 score, which equally weights false positive and false negative errors, was calculated for the cell model predictions and for each annotator, compared to consensus
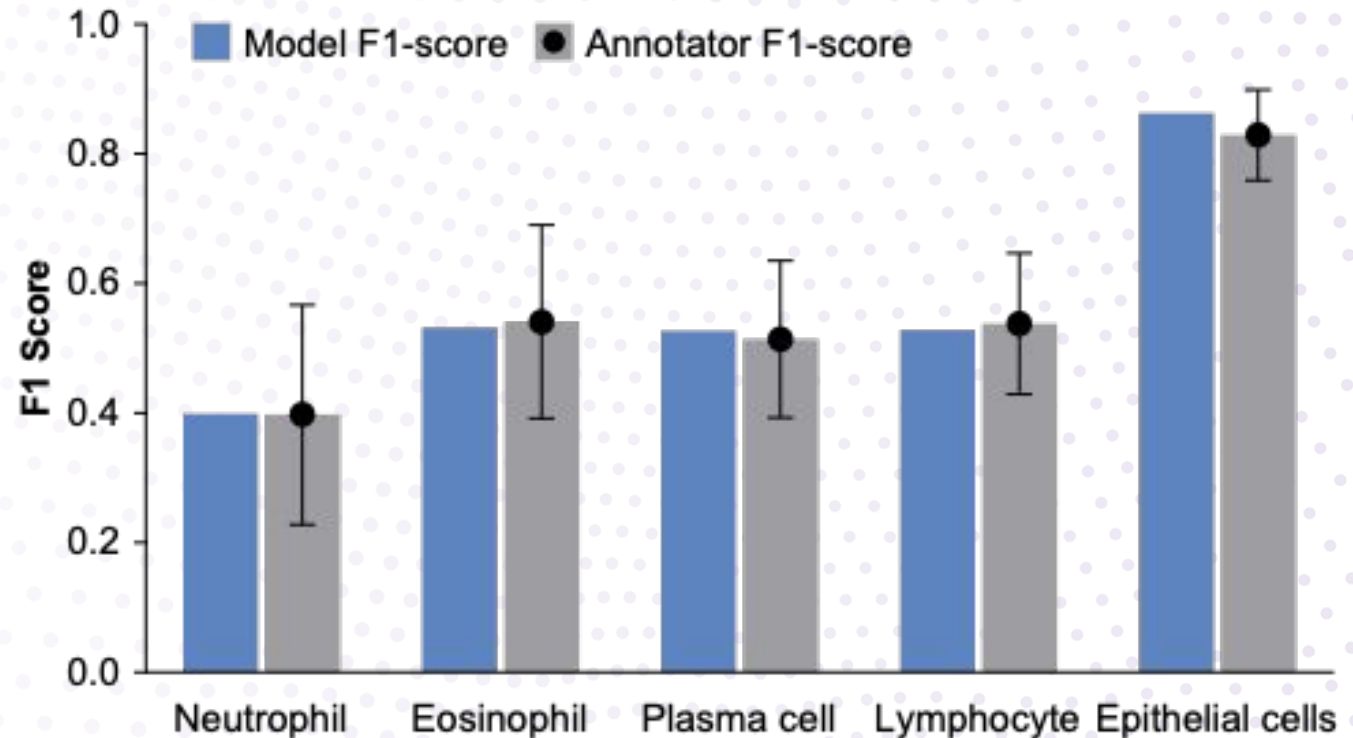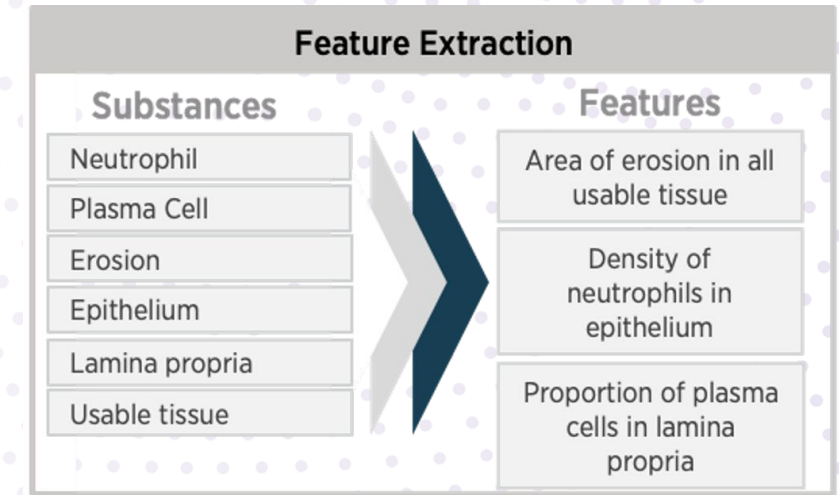

Model performance was essentially equal to or within 95% CI of the mean of individual pathologist performance
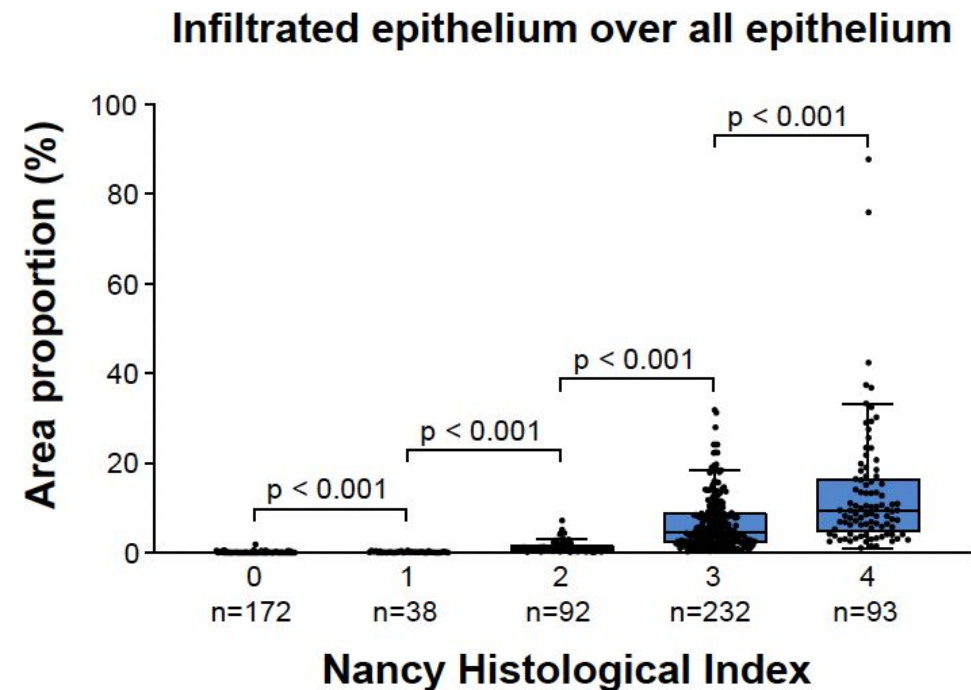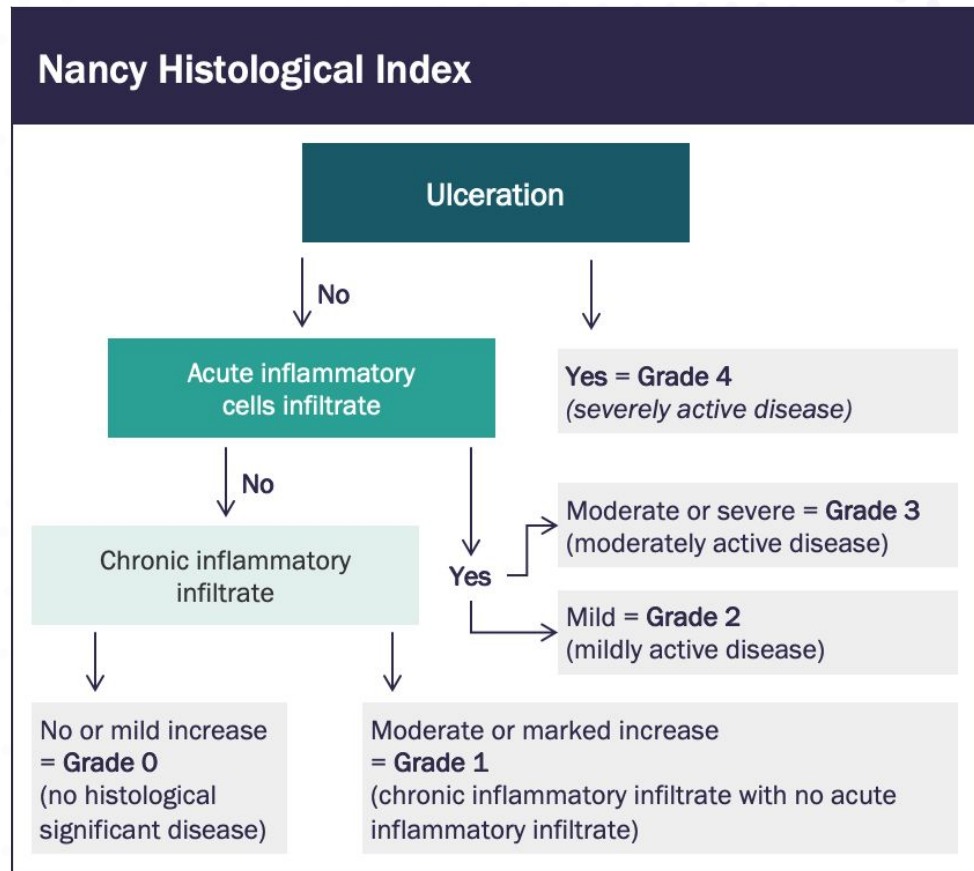
Artificial Intelligence Applications in Inflammatory Bowel Disease:
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Correlation of model-generated *human-interpretable features* with pathologist scoring

Tissue and cell model predictions are used to generate "Human Interpretable Features (HIFs)"
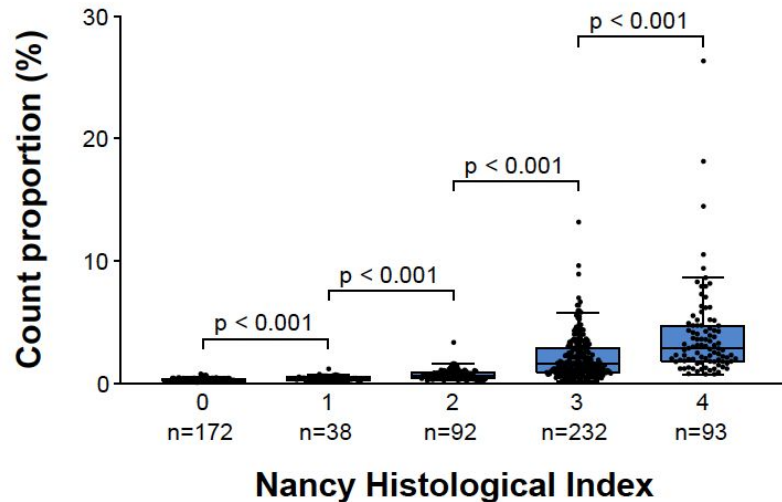
Feature Extraction

Substances	Features
Neutrophil	Area of erosion in all usable tissue
Plasma Cell	Density of neutrophils in epithelium
Erosion	Proportion of plasma cells in lamina propria
Epithelium	
Lamina propria	
Usable tissue	

ML read-out	Feature type	Rationale
[Erosion/ulceration] / [total usable tissue]	Area proportion	Feature of severely active disease
[Basal plasmacytosis] / [total usable tissue]	Area proportion	Feature of chronicity; shown to be associated with relapse
[Crypt abscess] / [all epithelium]	Area proportion	Feature of moderately active disease
[Infiltrated epithelium] / [all epithelium]	Area proportion	Feature of disease activity
[Goblet cell cytoplasm] / [all epithelium]	Area proportion	Correlate of disease activity
[Plasma cells] / [All cells] in [usable tissue]	Count proportion	Feature of chronic inflammatory infiltrate
[Neutrophils] / [Lamina propria]	Cell density	Feature of acute inflammatory infiltrate

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Features	All	Lab 1	Lab 2	Left	Right	Rectum
AREA PROPORTION OF INFILTRATED EPITHELIUM, CRYPT ABSCESS, EROSION OR ULCERATION, AND GRANULATION TISSUE OVER MUCOSA	0.896	0.897	0.86	0.897	0.856	0.882
AREA PROPORTION OF INFILTRATED EPITHELIUM, CRYPT ABSCESS, EROSION OR ULCERATION, GRANULATION TISSUE, AND BASAL PLASMACYTOSIS OVER MUCOSA	0.873	0.883	0.828	0.882	0.864	0.839
AREA PROPORTION OF ALL INFILTRATED EPITHELIUM AND CRYPT ABSCESS OVER ALL EPITHELIUM AND CRYPT ABSCESS	0.869	0.888	0.804	0.879	0.874	0.822
AREA PROPORTION OF ALL INFILTRATED EPITHELIUM OVER ALL EPITHELIUM	0.868	0.883	0.804	0.877	0.868	0.821
AREA PROPORTION OF CRYPT ABSCESS, EROSION OR ULCERATION, AND GRANULATION TISSUE OVER MUCOSA	0.855	0.841	0.846	0.832	0.803	0.855
AREA PROPORTION OF ALL INFILTRATED EPITHELIUM OVER MUCOSA	0.846	0.869	0.771	0.873	0.866	0.768
AREA PROPORTION OF ALL INFILTRATED EPITHELIUM AND CRYPT ABSCESS OVER MUCOSA	0.847	0.872	0.768	0.874	0.87	0.769
AREA PROPORTION OF EROSION OR ULCERATION AND GRANULATION TISSUE OVER MUCOSA	0.827	0.803	0.828	0.795	0.759	0.837
AREA PROPORTION OF GRANULATION TISSUE OVER MUCOSA	0.811	0.807	0.783	0.797	0.703	0.807
AREA PROPORTION OF EROSION OR ULCERATION OVER MUCOSA	0.795	0.769	0.858	0.735	0.86	0.811
AREA PROPORTION OF CRYPT ABSCESS OVER ALL EPITHELIUM AND CRYPT ABSCESS	0.777	0.809	0.7	0.776	0.849	0.724
AREA PROPORTION OF CRYPT ABSCESS OVER MUCOSA	0.759	0.799	0.667	0.767	0.833	0.695
AREA PROPORTION OF BASAL PLASMACYTOSIS OVER MUCOSA	0.635	0.692	0.525	0.684	0.641	0.472
AREA PROPORTION OF BLOOD VESSEL OVER MUCOSA	0.319	0.417	0.434	0.207	0.234*	0.434
AREA PROPORTION OF GOBLET CELL CYTOPLASM OVER ALL EPITHELIUM	-0.532	-0.557	-0.491	-0.458	-0.159*	-0.635
COUNT PROPORTION OF NEUTROPHILS OVER ALL CELLS IN ALL EPITHELIUM	0.828	0.866	0.817	0.814	0.835	0.822
COUNT PROPORTION OF LYMPHOCYTES, PLASMA CELLS, AND EOSINOPHILS OVER ALL CELLS IN MUCOSA	0.648	0.661	0.58	0.642	0.699	0.541
COUNT PROPORTION OF LYMPHOCYTES AND PLASMA CELLS OVER ALL CELLS IN MUCOSA	0.632	0.637	0.572	0.625	0.65	0.511
COUNT PROPORTION OF NEUTROPHILS OVER ALL CELLS IN MUCOSA	0.642	0.696	0.832	0.578	0.782	0.696
COUNT PROPORTION OF PLASMA CELLS OVER ALL CELLS IN BASAL PLASMACYTOSIS	0.614	0.618	0.523	0.632	0.69	0.598
COUNT PROPORTION OF PLASMA CELLS OVER ALL CELLS IN MUCOSA	0.461	0.467	0.317	0.546	0.424	0.478
COUNT PROPORTION OF NEUTROPHILS OVER ALL CELLS IN LAMINA PROPRIA	0.35	0.46	0.722	0.264	0.602	0.436
COUNT PROPORTION OF EOSINOPHIL CELLS OVER ALL CELLS IN MUCOSA	0.178	0.189	0.164*	0.263	0.457	0.281
COUNT PROPORTION OF INTRAEPITHELIAL LYMPHOCYTES OVER ALL CELLS IN EPITHELIUM	0.137	0.303	0.368	0.135*	0.23*	0.053*
COUNT PROPORTION OF NON-INTRAEPITHELIAL LYMPHOCYTES OVER ALL CELLS IN LAMINA PROPRIA	0.104*	0.186	0.095*	0.049*	-0.076*	-0.057*
COUNT PROPORTION OF EOSINOPHIL CELLS OVER ALL CELLS IN LAMINA PROPRIA	-0.09*	-0.057*	-0.117*	0.003*	0.087*	0.069*
DENSITY OF NEUTROPHILS IN INFILTRATED EPITHELIUM, CRYPT ABSCESS, EROSION OR ULCERATION, AND GRANULATION TISSUE	0.904	0.909	0.885	0.902	0.898	0.889
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DENSITY OF EOSINOPHILS IN MUCOSA	0.31	0.358	0.251	0.392	0.462	0.401

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Correlation is maintained across datasets from two independent laboratories, and across WSI from different regions of the colon, indicating generalizability of tissue and cell model predictions

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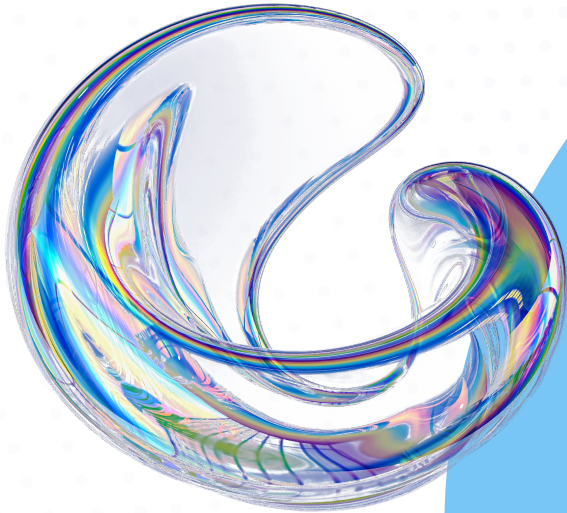| Features	All	Lab 1	Lab 2	Left	Right	Rectum
AREA PROPORTION OF INFILTRATED EPITHELIUM, CRYPT ABSCESS, EROSION OR ULCERATION, AND GRANULATION TISSUE OVER MUCOSA	0.896	0.897	0.86	0.897	0.856	0.882
AREA PROPORTION OF INFILTRATED EPITHELIUM, CRYPT ABSCESS, EROSION OR ULCERATION, GRANULATION TISSUE, AND BASAL PLASMACYTOSIS OVER MUCOSA	0.873	0.883	0.828	0.882	0.864	0.839
AREA PROPORTION OF ALL INFILTRATED EPITHELIUM AND CRYPT ABSCESS OVER ALL EPITHELIUM AND CRYPT ABSCESS	0.869	0.888	0.804	0.879	0.874	0.822
AREA PROPORTION OF ALL INFILTRATED EPITHELIUM OVER ALL EPITHELIUM	0.868	0.883	0.804	0.877	0.868	0.821
AREA PROPORTION OF CRYPT ABSCESS, EROSION OR ULCERATION, AND GRANULATION TISSUE OVER MUCOSA	0.855	0.841	0.846	0.832	0.803	0.855
AREA PROPORTION OF ALL INFILTRATED EPITHELIUM OVER MUCOSA	0.846	0.869	0.771	0.873	0.866	0.768
AREA PROPORTION OF ALL INFILTRATED EPITHELIUM AND CRYPT ABSCESS OVER MUCOSA	0.847	0.872	0.768	0.874	0.87	0.769
AREA PROPORTION OF EROSION OR ULCERATION AND GRANULATION TISSUE OVER MUCOSA	0.827	0.803	0.828	0.795	0.759	0.837
AREA PROPORTION OF GRANULATION TISSUE OVER MUCOSA	0.811	0.807	0.783	0.797	0.703	0.807
AREA PROPORTION OF EROSION OR ULCERATION OVER MUCOSA	0.795	0.769	0.858	0.735	0.86	0.811
AREA PROPORTION OF CRYPT ABSCESS OVER ALL EPITHELIUM AND CRYPT ABSCESS	0.777	0.809	0.7	0.776	0.849	0.724
AREA PROPORTION OF CRYPT ABSCESS OVER MUCOSA	0.759	0.799	0.667	0.767	0.833	0.695
AREA PROPORTION OF BASAL PLASMACYTOSIS OVER MUCOSA	0.635	0.692	0.525	0.684	0.641	0.472
AREA PROPORTION OF BLOOD VESSEL OVER MUCOSA	0.319	0.417	0.434	0.207	0.234*	0.434
AREA PROPORTION OF GOBLET CELL CYTOPLASM OVER ALL EPITHELIUM	-0.532	-0.557	-0.491	-0.458	-0.159*	-0.635
COUNT PROPORTION OF NEUTROPHILS OVER ALL CELLS IN ALL EPITHELIUM	0.828	0.866	0.817	0.814	0.835	0.822
COUNT PROPORTION OF LYMPHOCYTES, PLASMA CELLS, AND EOSINOPHILS OVER ALL CELLS IN MUCOSA	0.648	0.661	0.58	0.642	0.699	0.541
COUNT PROPORTION OF LYMPHOCYTES AND PLASMA CELLS OVER ALL CELLS IN MUCOSA	0.632	0.637	0.572	0.625	0.65	0.511
COUNT PROPORTION OF NEUTROPHILS OVER ALL CELLS IN MUCOSA	0.642	0.696	0.832	0.578	0.782	0.696
COUNT PROPORTION OF PLASMA CELLS OVER ALL CELLS IN BASAL PLASMACYTOSIS	0.614	0.618	0.523	0.632	0.69	0.598
COUNT PROPORTION OF PLASMA CELLS OVER ALL CELLS IN MUCOSA	0.461	0.467	0.317	0.546	0.424	0.478
COUNT PROPORTION OF NEUTROPHILS OVER ALL CELLS IN LAMINA PROPRIA	0.35	0.46	0.722	0.264	0.602	0.436
COUNT PROPORTION OF EOSINOPHIL CELLS OVER ALL CELLS IN MUCOSA	0.178	0.189	0.164*	0.263	0.457	0.281
COUNT PROPORTION OF INTRAEPITHELIAL LYMPHOCYTES OVER ALL CELLS IN EPITHELIUM	0.137	0.303	0.368	0.135*	0.23*	0.053*
COUNT PROPORTION OF NON-INTRAEPITHELIAL LYMPHOCYTES OVER ALL CELLS IN LAMINA PROPRIA	0.104*	0.186	0.095*	0.049*	-0.076*	-0.057*
COUNT PROPORTION OF EOSINOPHIL CELLS OVER ALL CELLS IN LAMINA PROPRIA	-0.09*	-0.057*	-0.117*	0.003*	0.087*	0.069*
DENSITY OF NEUTROPHILS IN INFILTRATED EPITHELIUM, CRYPT ABSCESS, EROSION OR ULCERATION, AND GRANULATION TISSUE	0.904	0.909	0.885	0.902	0.898	0.889
DENSITY OF NEUTROPHILS IN INFILTRATED EPITHELIUM	0.854	0.882	0.797	0.88	0.873	0.777
DENSITY OF PLASMA CELLS IN MUCOSA	0.568	0.609	0.42	0.627	0.444	0.593
DENSITY OF EOSINOPHILS IN MUCOSA	0.31	0.358	0.251	0.392	0.462	0.401

Correlation is maintained across datasets from two independent laboratories, and across WSI from different regions of the colon, indicating generalizability of tissue and cell model predictions

Artificial Intelligence Applications in Inflammatory Bowel Disease: Quantifying the Mucosal Microenvironment of Ulcerative Colitis

Model-derived HIFs correlate strongly with pathologist NHI scoring

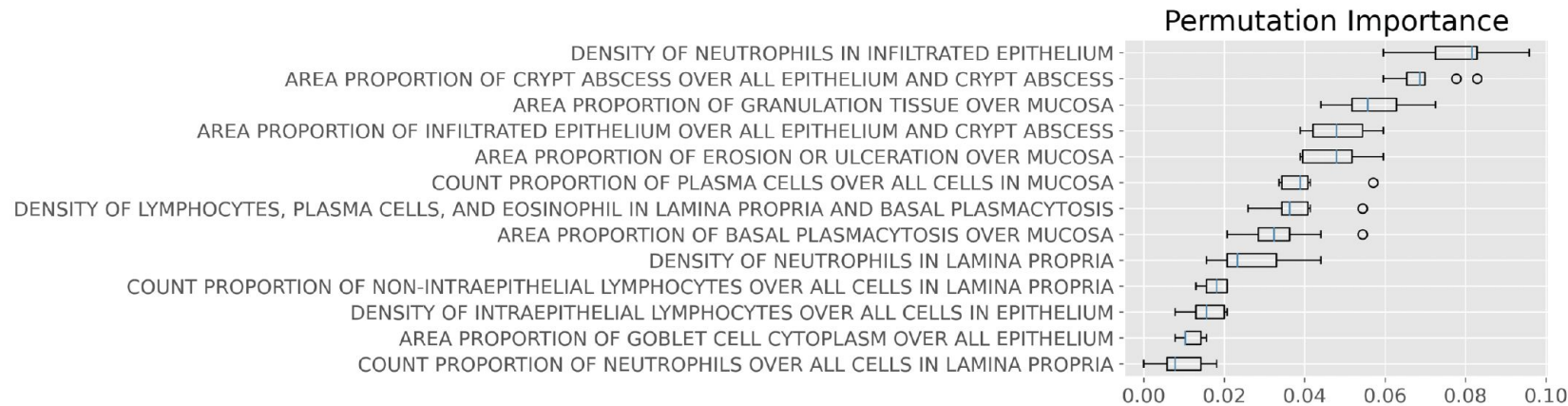| Features	All	Lab 1	Lab 2	Left	Right	Rectum
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These HIFs are also relevant to other scoring systems such as Geboes, RHI, and the recently reported PHRI score; they also capture features not part of current scoring systems
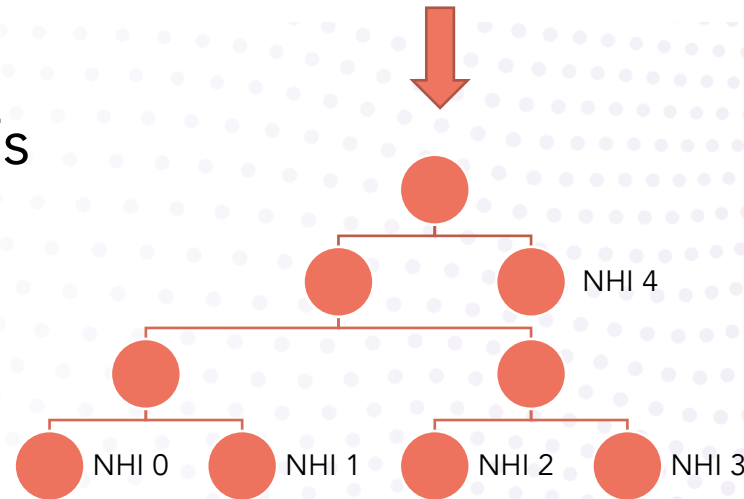
Artificial Intelligence Applications in Inflammatory Bowel Disease: Quantifying the Mucosal Microenvironment of Ulcerative Colitis

HIF-based prediction of Nancy Histological Index scores

Model-generated HIFs were used to train a random forest classifier

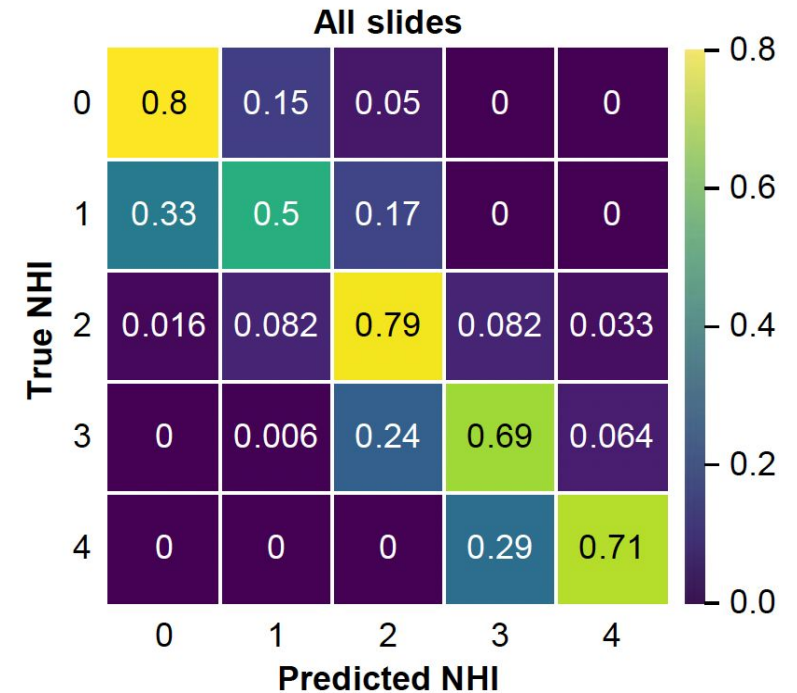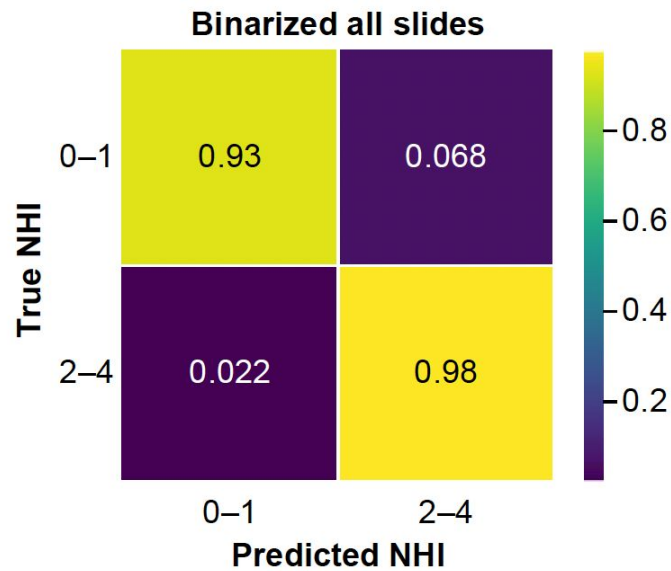Permutation Importance

- Inputs – A subset of HIFs generated from the previous step

- Outputs – NHI Score

NHI 4

NHI 0   NHI 1   NHI 2   NHI 3

Artificial Intelligence Applications in Inflammatory Bowel Disease:
Quantifying the Mucosal Microenvironment of Ulcerative Colitis

RFC predicted individual NHI scores and histologic remission with high accuracy

Binarized all slides

	Predicted NHI 0–1	Predicted NHI 2–4
True NHI 0–1	0.93	0.068
True NHI 2–4	0.022	0.98

All slides

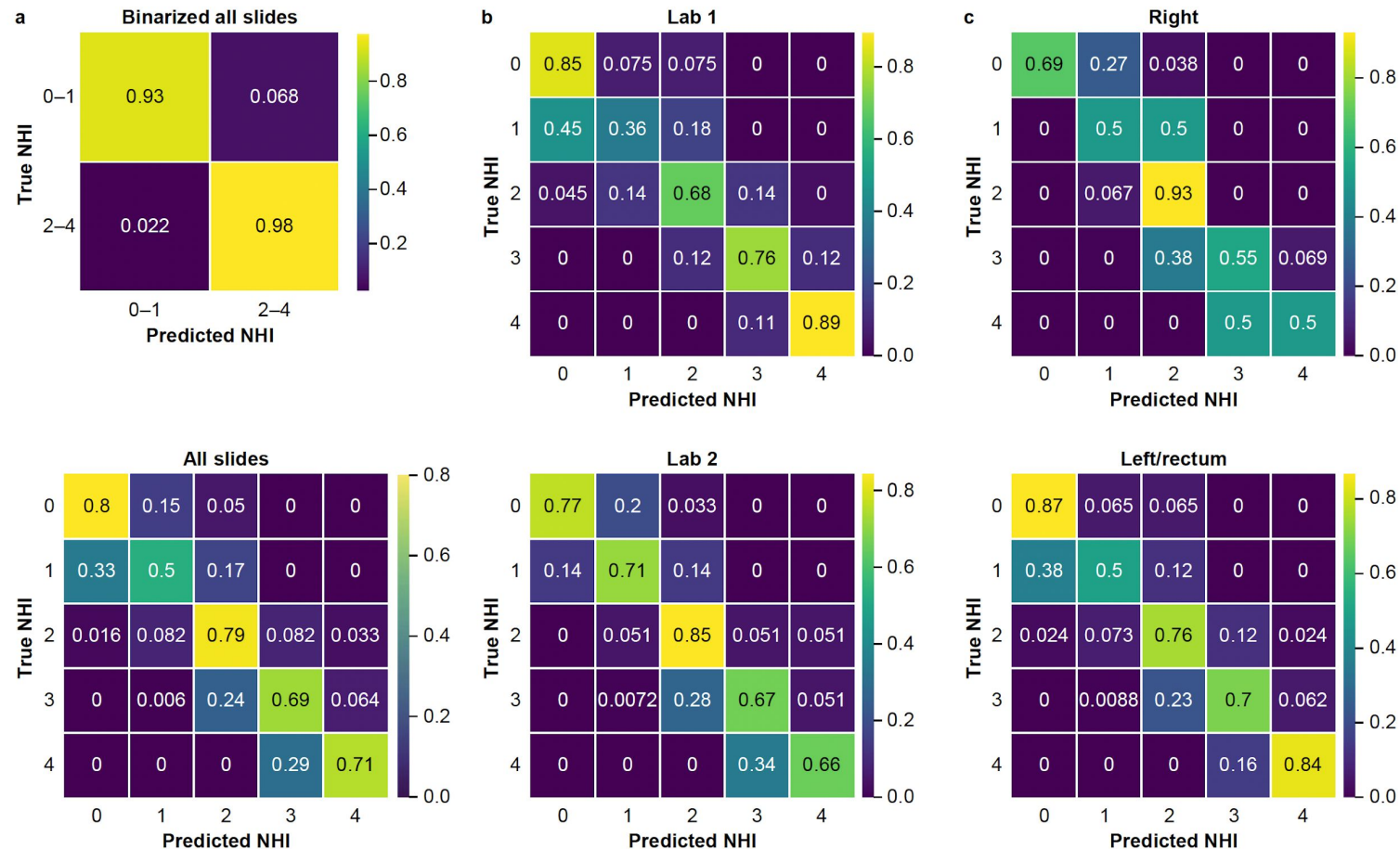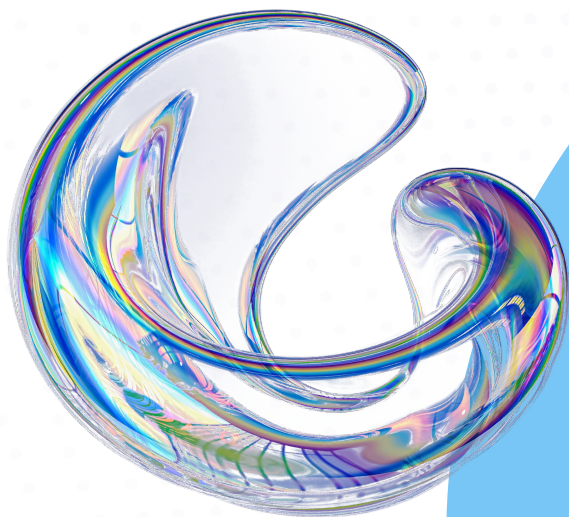| True NHI \ Predicted NHI	0	1	2	3	4
0	0.8	0.15	0.05	0	0
1	0.33	0.5	0.17	0	0
2	0.016	0.082	0.79	0.082	0.033
3	0	0.006	0.24	0.69	0.064
4	0	0	0	0.29	0.71

- Accuracy of 0.97 (weighted kappa k= 0.91 and Spearman correlation ρ=0.91, p<0.001) for prediction of histological remission

- Weighted kappa k= 0.91 and Spearman correlation ρ=0.89 (p<0.001) for prediction of individual NHI scores

Artificial Intelligence Applications in Inflammatory Bowel Disease: Quantifying the Mucosal Microenvironment of Ulcerative Colitis

RFC predictions are generalizable across different laboratories and regions of the colon

Artificial Intelligence Applications in Inflammatory Bowel Disease:
Quantifying the Mucosal Microenvironment of Ulcerative Colitis

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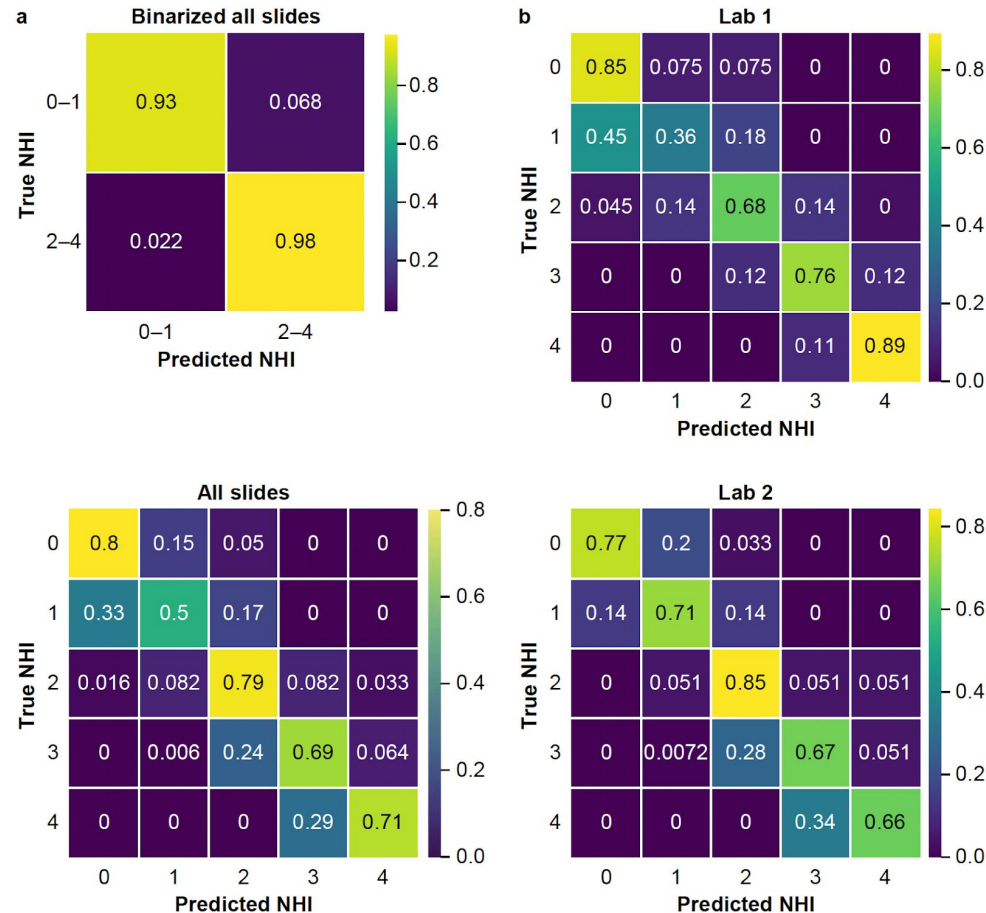
Summary and future directions

We report an AI-powered approach to quantify tissue- and cell-level histological features in ulcerative colitis

- Model-generated interpretable features can be used to predict disease activity and histologic remission using the NHI index

- This approach is interpretable, repeatable, and scalable

- Preprint published on medRxiv: Najdawi F, et al. *Artificial Intelligence Enables Quantitative Assessment of Ulcerative Colitis Histology* (2022)

Future directions include extension to other histological scoring systems (e.g. Geboes) and deployment in clinical trials through PathAI's AISight cloud-based software for WSI evaluation and scoring

PathAI IBD team

Artificial Intelligence Applications in Inflammatory Bowel Disease:
Quantifying the Mucosal Microenvironment of Ulcerative Colitis

Thank you

Archit Khosla

Director, Machine Learning

archit.khosla@pathai.com

pathai.com

Fedaa Najdawi

Director, Pathology

fedaa.najdawi@pathai.com

pathai.com

Stop by our booth, and check out our poster (#15):

"Generation of an atlas characterizing the tumor immune microenvironment via AI-based histologic mapping of multiple cancer types at scale"

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