



Annual

**Advances and Innovations in Endoscopic Oncology
and Multidisciplinary Gastrointestinal Cancer Care**

Multimodal TME Assessment in the Era of AI and Precision

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Disclosures

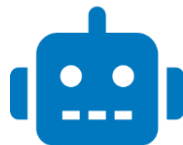
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This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Objectives

1. Understand the foundational AI/ML concepts relevant to GI pathology.
2. Evaluate published evidence on AI-driven diagnostic accuracy improvements.
3. Discuss AI's role in molecular & biomarker prediction from histopathology.
4. Present some of the recent AI Projects

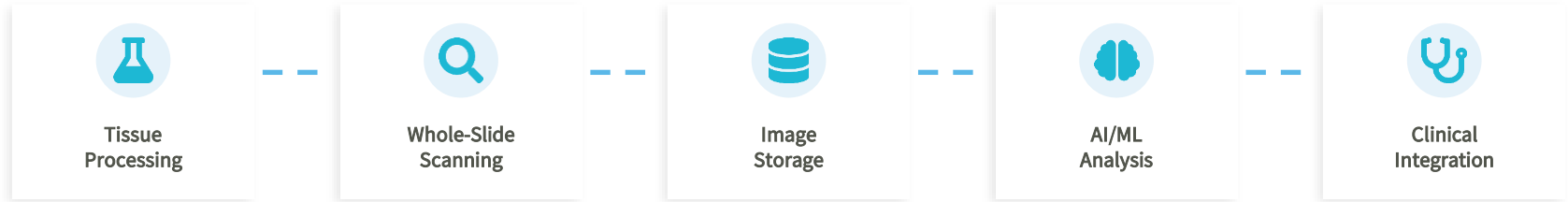
PART I



Foundations of AI in Pathology

Key concepts, terminology, and the digital pathology ecosystem

The Digital Pathology Ecosystem



Whole-Slide Imaging (WSI)

High-resolution digitization of glass slides at 40× magnification, generating multi-gigapixel images. Essential infrastructure for digital pathology. Modern scanners achieve throughput of 80-120 slides/hour.

Computational Pathology

Applies quantitative image analysis, ML/DL algorithms to WSIs for automated diagnosis, grading, biomarker prediction, and outcome prognostication.

Gao et al. J Transl Med 2025; Yilmaz et al. Lab Invest 2024

Major Key Concepts for AI in Medicine & Pathology



Artificial Intelligence (AI)

Broad discipline enabling machines to simulate human cognitive functions—reasoning, pattern recognition, decision-making.



Machine Learning (ML)

Subset of AI where algorithms learn from data without explicit programming; includes supervised, unsupervised, and reinforcement learning.



Deep Learning (DL)

Multi-layered neural networks that automatically extract hierarchical features from raw data—the backbone of modern computational pathology.

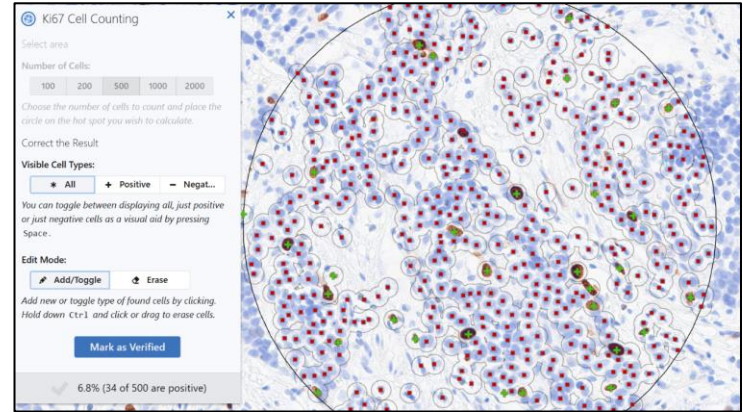
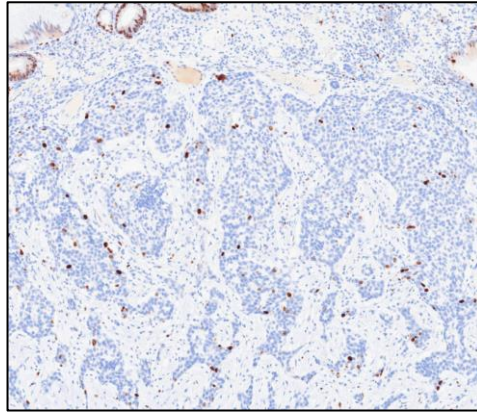
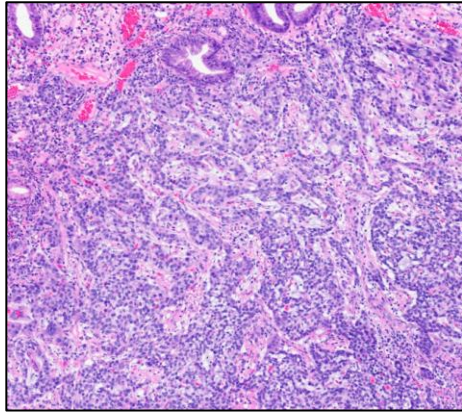


Convolutional Neural Networks (CNNs)

Specialized DL architecture for image analysis; excels at detecting morphological patterns in whole-slide images (WSI).

Yilmaz et al. Lab Invest 2024; Kather et al. Nat Med 2019; Campanella et al. Nat Med 2019

AI Applications in GI Pathology



Yilmaz et al. Lab Invest 2024; Kather et al. Nat Med 2019; Campanella et al. Nat Med 2019

Machine Learning Approaches in GI Pathology

Supervised Learning

Models trained on labeled data (pathologist annotations). Used for classification (cancer vs. benign), grading (dysplasia), and segmentation (glands, crypts). Requires extensive annotation effort.

Examples: CNN for polyp classification, Residual network (ResNet) for tumor detection

Weakly Supervised / MIL

Multiple Instance Learning (MIL) uses slide-level labels only, avoiding pixel-level annotation. Attention-based models identify diagnostically relevant regions automatically.

Examples: CLAM, TransMIL for WSI classification, MSI prediction

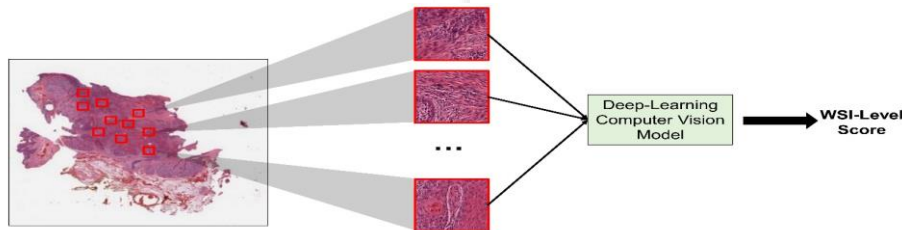
Self-Supervised / Foundation

Pre-trained on massive unlabeled datasets. Foundation models (UNI, CONCH, Virchow) learn universal histological representations, then fine-tuned for specific tasks.

Examples: UNI for multi-organ pathology, PathChat multimodal assistant

Key consideration: All approaches require robust validation on external, multi-institutional datasets before clinical deployment.

Abbr: CONtrastive learning from Captions for Histopathology (CONCH)



Campanella et al. Nat Med 2019; Lu et al. Nature 2024; Chen et al. Nat Med 2024

Foundation Models for Pathology

Model	Organization	Training Data	Key Features
UNI	Harvard/BWH	100K+ WSIs, 20+ organs	ViT-L (Vision Transformer - Large) - 34 tasks
CONCH	Harvard/BWH	1.17M image-caption pairs	Vision-language; zero-shot capability
Virchow / Virchow 2	Paige AI	1.5M+ WSIs	Largest pathology FM; clinical deployment
PathChat	Harvard/BWH	456K+ instructions	Multimodal LLM for pathology Q&A; 78-89% accuracy
Prov-GigaPath	Microsoft/Prov	170K WSIs	1.3B parameters; whole-slide analysis

Why Foundation Models Matter for GI Path

1. Pre-trained on millions of images → require minimal task-specific data
2. Generalize across organs, stains, and scanner types
3. Enable zero/few-shot learning for rare GI entities
4. Capture morphological features invisible to conventional models
5. Accelerate deployment: fine-tune in days vs. months of de novo training

Lu et al. Nature 2024; Chen et al. Nat Med 2024; Vorontsov et al. Nat Med 2024

PART II



AI Application in GI Pathology

Why GI Pathology Needs AI

4.8M

New GI cancer cases globally
per year (GLOBOCAN 2022)

27%

Adenomas missed during
standard colonoscopy

40%+

Interobserver variability in
Barrett's dysplasia grading

≤50%

Pathologist agreement on
NASH activity score

Critical Unmet Needs in GI Pathology

- Global pathologist shortage: 10× deficit in low-income countries
- Rising specimen volumes (↑ screening programs, ↑ biopsies)
- Complex reporting: IHC, molecular testing, PD-L1, MSI, TMB
- Quantitative tasks: eosinophil counting, Ki-67, fibrosis staging
- Need for standardized, reproducible diagnostics

Sung et al. CA Cancer J Clin 2021; Yilmaz et al. Lab Invest 2024; Gastroenterology 2017;152:564-570

AI-Based CRC Histological Classification

Deep learning models can classify CRC tissue into histological subtypes and predict molecular features directly from H&E-stained whole-slide images.

Tumor Epithelium:

CNN accuracy >95% for tumor vs. normal classification

Lymphocyte Infiltrate

TIL density quantification for immune scoring

Stroma (Desmoplastic)

Stromal features predict prognosis (Beck et al.)

Mucin / Mucinous

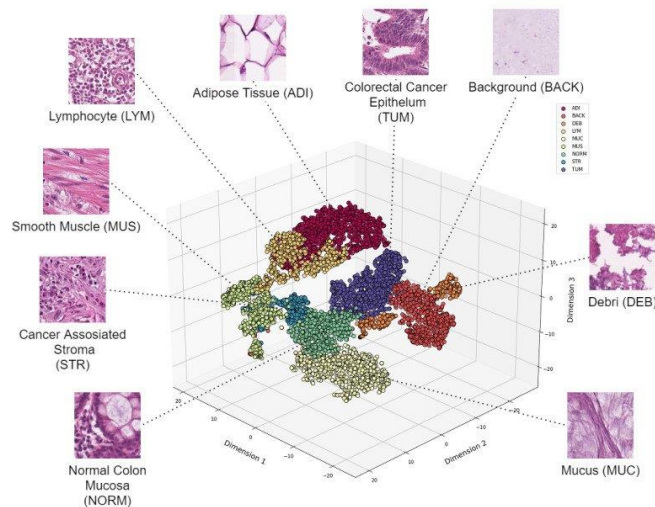
Linked to MSI-H phenotype detection

Necrosis

"Dirty necrosis" absence correlates with MSI

Normal Mucosa

Automated exclusion from diagnostic ROIs



Kather et al. PLOS Med 2019; Wulczyn et al. NPJ Digit Med 2021; L'Imperio et al. JAMA Netw Open 2023

Predicting MSI Status from H&E Slides

Deep learning can predict microsatellite instability (MSI) directly from routine H&E-stained slides, potentially serving as a pre-screening tool before IHC/PCR confirmatory testing.

Model/ Study	Training N	AUROC	Sensitivity	Specificity
Kather et al. Nat Med 2019	360 WSIs	0.77-0.84	—	—
Yamashita (MSINet) Lancet Oncol 2021	100 WSIs	0.87-0.93	76%	67%
Echle et al. ESMO Open 2022	Multi-center	0.83	—	—
Deepath-MSI 2025	5,070 WSIs	0.98	95%	91-92%
MSIntuit (validated) Nat Commun 2023	Multi-center	0.90+	—	—

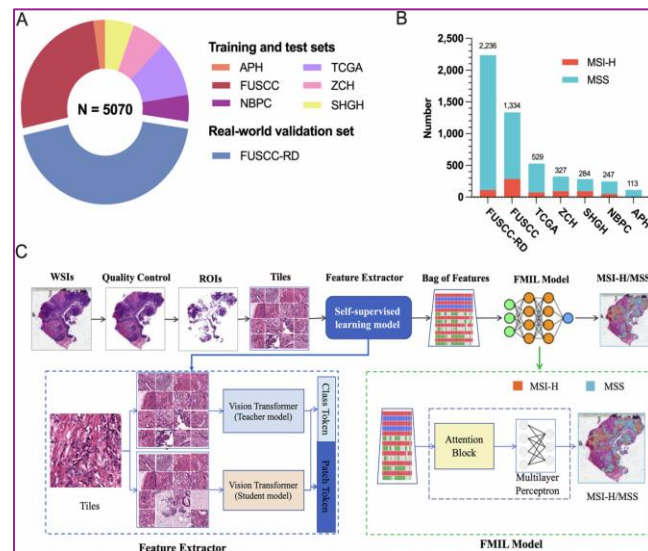
Clinical Workflow Impact

Deepath-MSI screening of all CRC H&E slides → only predicted MSI-H cases (14.4%) proceed to IHC/PCR → potentially excludes ~90.7% of MSS patients from ancillary testing → significant cost and labor savings.

Morphologic Features

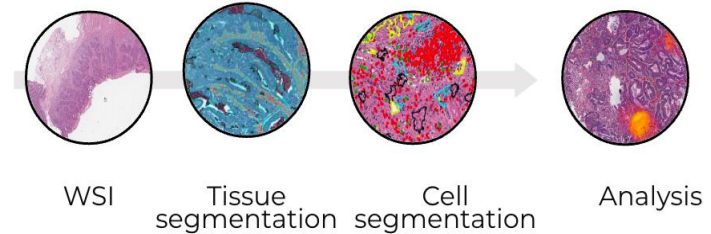
AI models identify: ↑ TILs, mucinous differentiation, absence of dirty necrosis, Crohn-like reaction, medullary pattern—features associated with MSI-H phenotype.

Kather et al. Nat Med 2019; Yamashita et al. Lancet Oncol 2021; npj Precis Oncol 2025



Self-Supervised ML for MMR Status Prediction in CRC

- 154 treatment-naïve CRC diagnosed on biopsies (20 dMMR, 134 pMMR) digitized at 40×
- Modified ResNet-50 encoder trained via contrastive self-supervised learning (SSL)
- ~1.6 million normalized patches (256×256 px) with random augmentation
- 512-dimensional embeddings per slide → MLP classifier for binary MMR prediction
- 66 of 512 deep features contributed significantly to model performance
- Framework for annotation-free biomarker prediction — no IHC input required
- Sensitivity = 97.5%; Specificity = 95.5%



Our current study...

Beyond MSI: Molecular Prediction from Histology

BRAF Mutation Prediction

- Deep learning models predict BRAF V600E mutation status from H&E
- BRAF-mutant CRC exhibits distinct morphological features (serrated architecture, mucinous differentiation) that CNNs learn to identify.

KRAS/NRAS Status

- AI models predict RAS mutation status
- Lower performance reflects more subtle morphological correlates.
- Ongoing improvements with foundation models and multi-modal data integration.

Consensus Molecular Subtypes (CMS)

- DL models can classify CRC into CMS1-4 directly from histology
- CMS classification has prognostic and therapeutic implications for targeted therapy selection.

Tumor Mutational Burden (TMB)

- Emerging models predict TMB-high status from H&E, relevant for immunotherapy eligibility beyond MSI-H tumors.
- Foundation model-based approaches show promising improvements over first-generation CNNs.

Bilal et al. Lancet Digit Health 2023; Niehues et al. Cell Rep Med 2023; Gustav et al. NPJ Precis Oncol 2024

AI-Driven CRC Prognostication



Survival Prediction

Wulczyn et al. (NPJ Digit Med 2021): interpretable DL model predicting disease-specific survival from H&E WSIs, identifying novel prognostic morphological features including tumor-adjacent stroma characteristics.



Immune Microenvironment Scoring

Automated quantification of tumor-infiltrating lymphocytes, immune contexture scoring (Immunoscore®-like), and spatial immune cell distribution—all from routine H&E slides without IHC.



Risk Stratification

L'Imperio et al. (JAMA Netw Open 2023): pathologist-validated ML feature for Stage II colon cancer risk stratification, demonstrating AI-derived biomarkers can match or exceed traditional clinicopathologic parameters.



Treatment Response Prediction

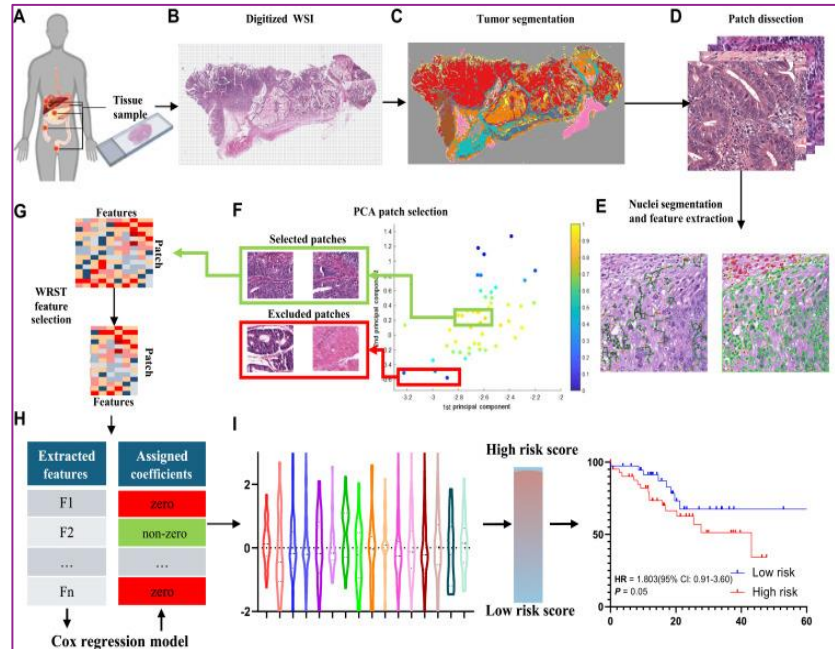
Emerging models predict response to adjuvant chemotherapy (5-FU, oxaliplatin) and immunotherapy (anti-PD-1/PD-L1) using pre-treatment biopsy WSIs, enabling personalized treatment selection.

Wulczyn et al. NPJ Digit Med 2021; L'Imperio et al. JAMA Netw Open 2023; Bilal et al. Lancet Digit Health 2023

AI Defines TIL Spatial Patterns Across Pan-GI Cancers

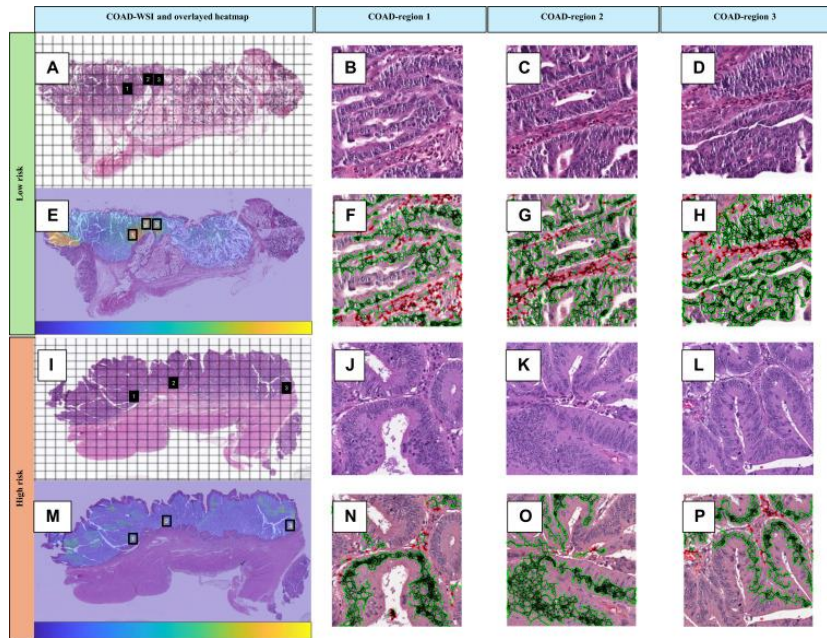
- Computer vision via CNN and ML evaluated the spatial arrangement of TILs and cancer nuclei
- Cancer type: Stomach, CRC, PDAC, HCC
- Microsatellite stable (MSS)
- >1,700 patients
- 2,236 pathomic features extracted from H&E WSIs; top 9 selected by LASSO-Cox model

Reference: Chen C, Mejbel H et al. ESMO Open 2025;10(10):105757.



Methodology: Modified Cell Cluster Graphs (CCG)

- Unlike standard CCG, the modified version includes only TILs and tumor nuclei — capturing direct immune-tumor interactions
- Top feature: Skewness-CCG: Number of Edges — measures how unevenly TILs and cancer cells interact spatially



Reference: Chen C, Mejbøl H et al. ESMO Open 2025;10(10):105757.

TIL–Tumor Spatial Architecture

Favorable features

- Higher density of epithelial TILs embedded within cancer cell regions
- Greater connectivity to tumor nuclei in local cell network diagrams; more connected TIL clusters — suggesting active immune targeting
- Structured, interconnected TIL–tumor architecture

Poor prognostic features

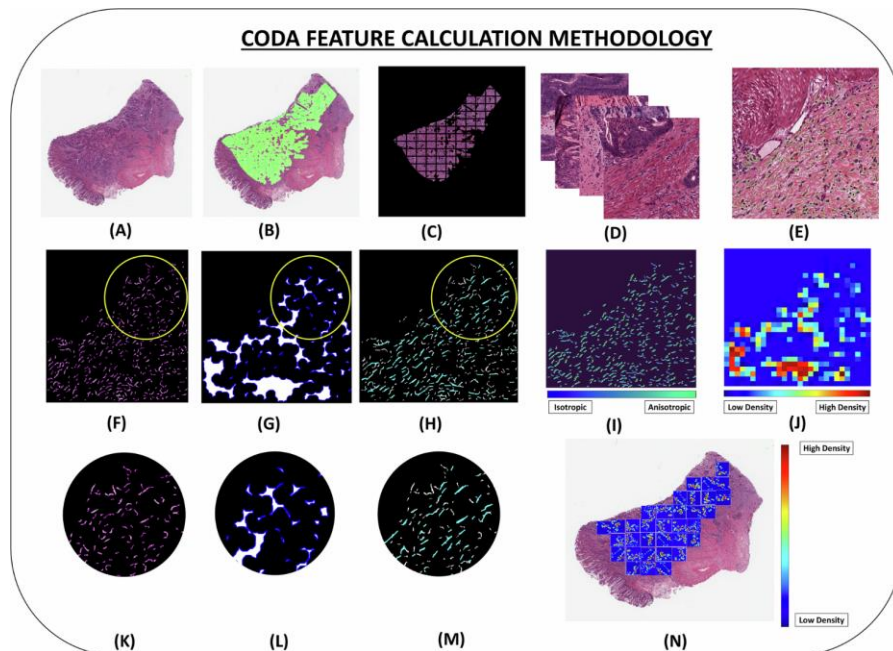
- Sparse epithelial TILs with fragmented TIL clusters
- Fewer connections between TILs and tumor nuclei; suggests weaker immune defense and immune exclusion
- Disorganized TIL spatial arrangement — correlates with recurrence

Reference: Chen C, Mejbøl H et al. ESMO Open 2025;10(10):105757.

Collagen Disorder Architecture (CoDA) in Colon Cancer

- Computational pathology pipeline to extract collagen disorder architecture (CoDA) features from H&E WSIs
- 2,212 colon cancer patients
- Five CoDA features: collagen fragmentation, bundling, anisotropy, density, and rigidity
- Evaluated against clinical variables (TNM stage), molecular classifications (CMS1–4), and genetic mutations (KRAS, BRAF, etc)

Reference: Nag R, Mejbhel H. et al. npj Precision Oncology 2025;9:304.



CoDA Feature Definitions and Biological Significance

CF Fragmentation

Ratio of collagen fiber fragments to total fiber length — reflects ECM degradation by matrix metalloproteinases (MMPs) during tumor invasion

CF Bundling

Percentage of collagen fibers organized into thick aligned bundles — dense bundling facilitates collective tumor cell migration along tracks

CF Anisotropy

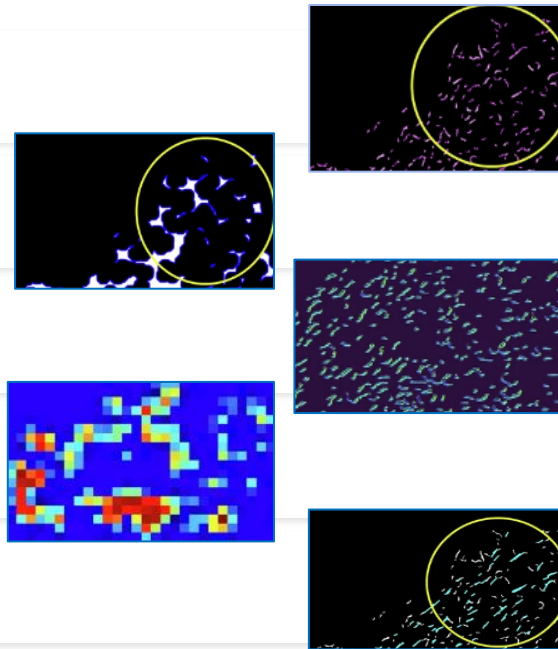
Directional preference of collagen fiber alignment — highly anisotropic fibers create migration highways for invasive cancer cells

CF Density

Area occupied by collagen in stroma — high density increases tissue stiffness, promotes integrin signaling and mechanotransduction

CF Rigidity

Product of fiber thickness $\times$ orientation — rigid, straight fibers correlate with desmoplastic response and poor prognosis



Reference: Nag R, Mejbelt H et al. npj Precision Oncology 2025;9:304.

CoDA Multivariable Prognostic Analysis

HR 1.45

OS: CoDA High vs Low Risk
 $p = 0.008$
Independent of stage or mutations

HR 1.65

DFS: CoDA High vs Low Risk
 $p = 0.0006$
Independent of stage or mutations

Key Findings from Multivariable Cox Regression

- CoDA risk score remained significant after adjusting for age, gender, race, stage, and KRAS/BRAF/NRAS mutations

Reference: Nag R, Mejbøl H, et al. npj Precision Oncology 2025;9:304.

Key Takeaways

- ✓ AI significantly improves adenoma detection during colonoscopy, with robust RCT evidence across 50,000+ patients.
- ✓ Deep learning predicts MSI, BRAF, and CMS from H&E slides, enabling molecular triage without ancillary testing.
- ✓ Foundation models (UNI, CONCH, Virchow) are transforming computational pathology with generalizable representations.
- ✓ Multimodal fusion integrating pathology, radiology, genomics, and clinical data outperforms single-modality approaches.
- ⚠ Significant challenges remain: generalizability, bias, regulatory frameworks, and cost of implementation.
- ⚠ Prospective outcome-based evidence and diverse, multi-institutional validation are critical next steps.

Work in progress

Study	Venue/Publication	Year
Pan-GI TIL Spatial Patterns (Chen, Mejbél et al.)	ESMO 2026	2025
CoDA Features in Colon Cancer (Nag, Chen, Mejbél et al.)	npj Precision Oncology 2026	2025
Machine Learning Models in Risk Stratification of Barrett's Dysplasia	ASCO	2026
Prediction of Mismatch Repair (MMR) Status in Colorectal Carcinoma	UASCAP	2026
BiliX: AI Biliary Stricture Enhancement	USCAP	2026
Cellular Signatures Of Disease Activity in IBD	CAP	2026
AI Signature of Post Transplant Liver Biopsy	In Progress	--
AI Prediction Score of Treatment Response in PDAC	In Progress	--

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Acknowledgment



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