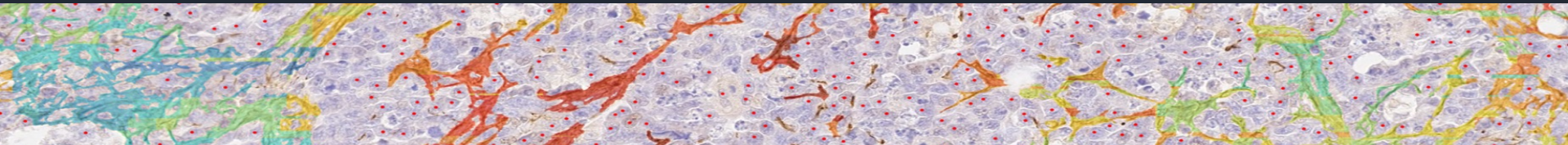
TIA Centre
Tissue Image Analytics

Computational Pathology: The Road Ahead Part II

Nasir Rajpoot
Professor of Computational Pathology
Wolfson Fellow, The Royal Society
Director, Tissue Image Analytics (TIA) Centre
University of Warwick, UK

Croucher ASI **AI for Biomedicine** (Fri 28 Nov 2025)



AI/ML can Help with Making Cellular Pathology More ‘Precise’

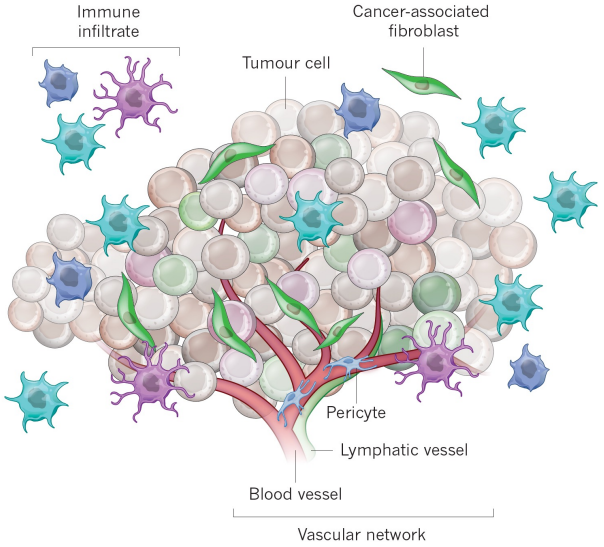
The Spatial Tumor Microenvironment (Spatial-TME)

Several important players other than the tumor cells

The **Seed & Soil** theory



Conventional approaches including chemotherapy have targeted tumor cells

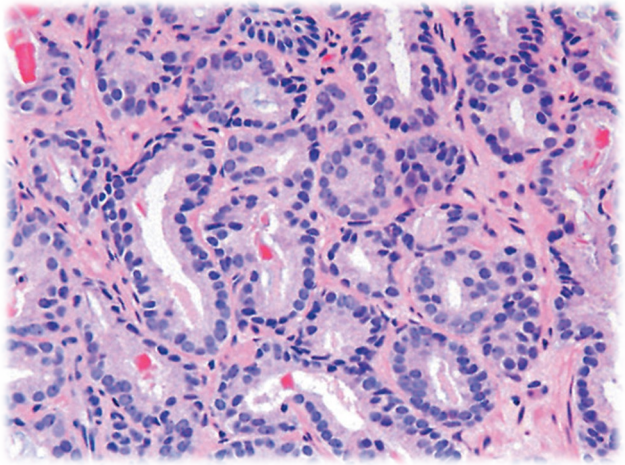


Junttila & De Suavage (Nature 2013)

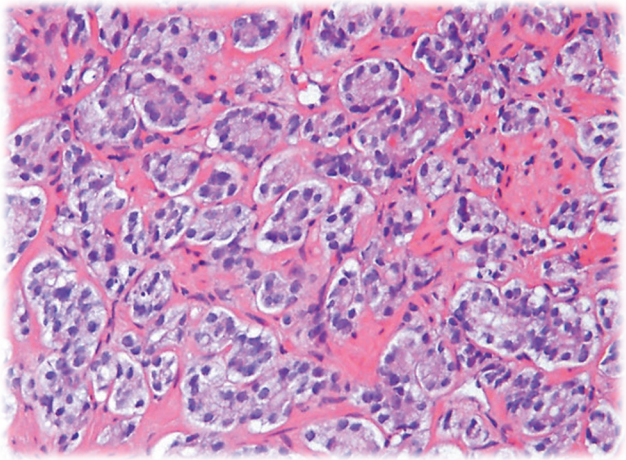
The Power of HVS



Train wreck



Gleason Pattern 3



Gleason Pattern 4

Source: Epstein *et al*. (***Eur Urol***, 2015)

HVS Limitation: Information Overload



Ground truth=1567, Proposed=1590

Image Source: CRCV@UCF

The Need for Generalizability

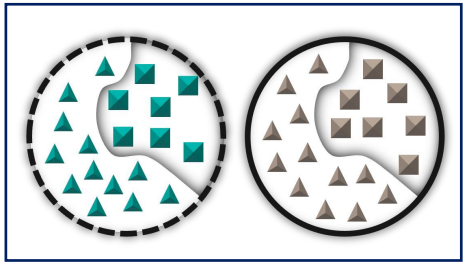
Stain Variability (*aka* **Domain Shift**)

Stain variability results from methods and protocols used to prepare the specimen:

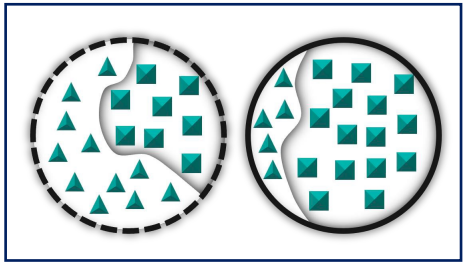
- Type and duration of fixation
- Consistency and thickness of the sections
- Room or specimen/dye temperatures
- Stain reactivity (pH, enzyme concentration) for different manufacturers/batches
- Incubation times
- Scanner equipment/settings

Types of Domain Shift in CPath

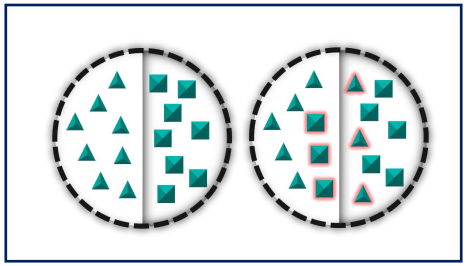
Type 1 – Covariate Shift



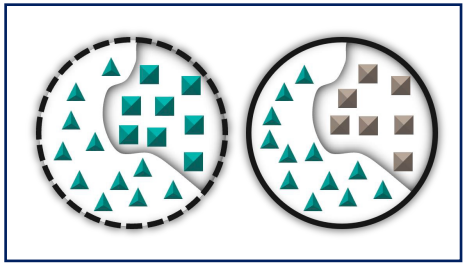
Type 2 – Prior Shift



Type 3 – Posterior Shift

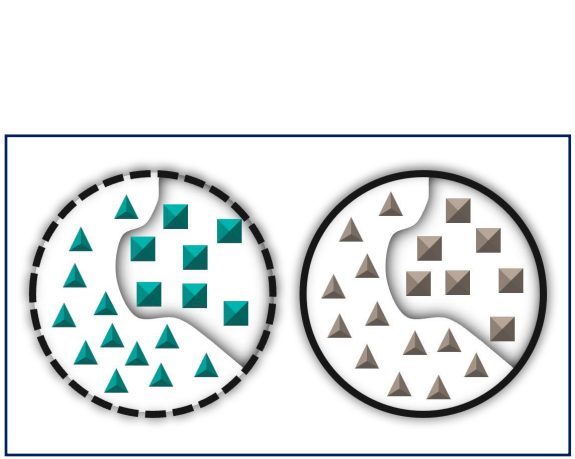


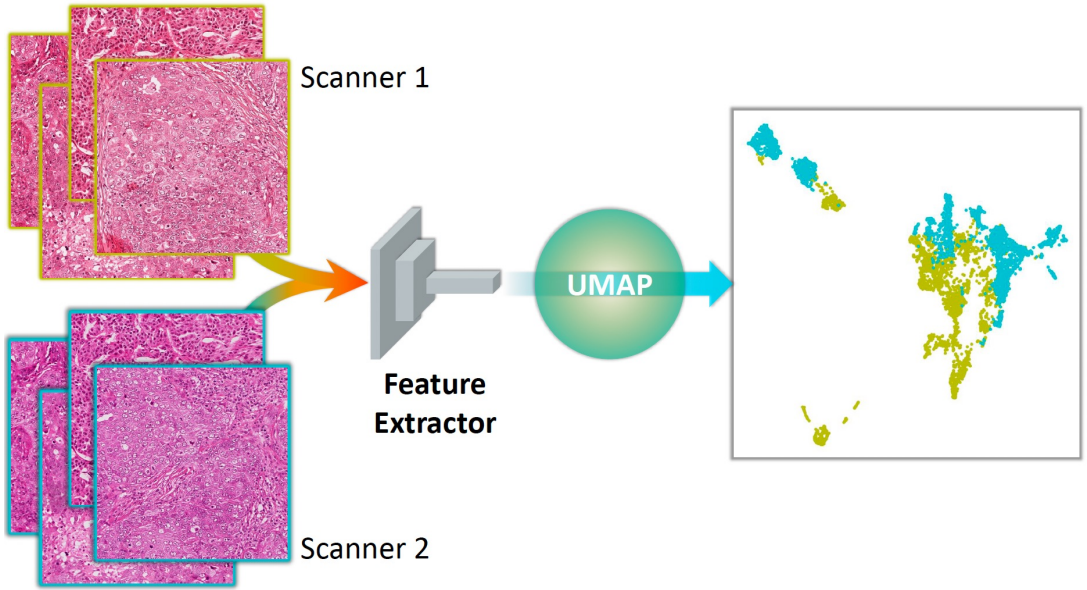
Type 4 – Class-Cond Shift



Jahanifar *et al.*, *ACM Computing Surveys* (June 2025)

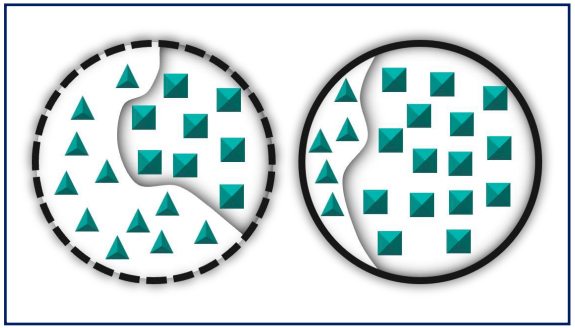
Domain Shift – Type 1 (***Covariate*** Shift)

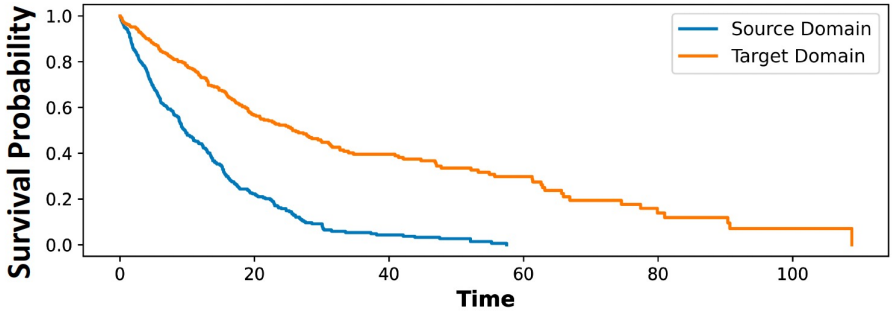


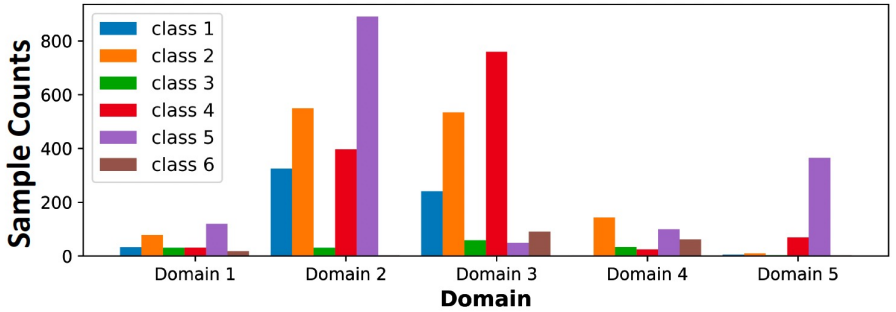


Jahanifar *et al.*, *ACM Computing Surveys* (June 2025)

Domain Shift – Type 2 (***Prior*** Shift)

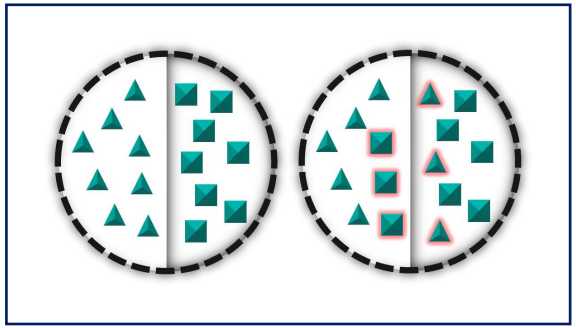


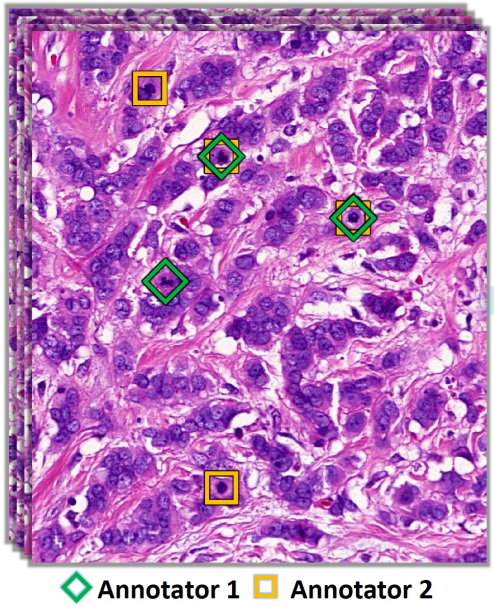


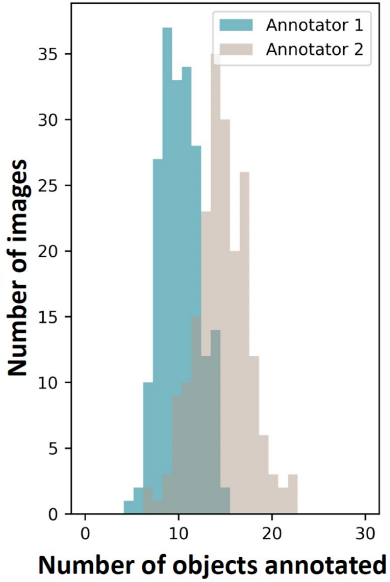


Jahanifar *et al.*, *ACM Computing Surveys* (June 2025)

Domain Shift – Type 3 (***Posterior*** Shift)

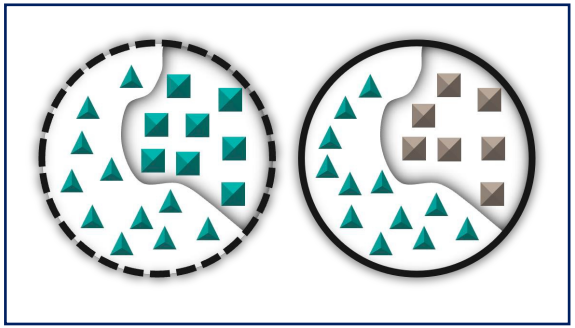


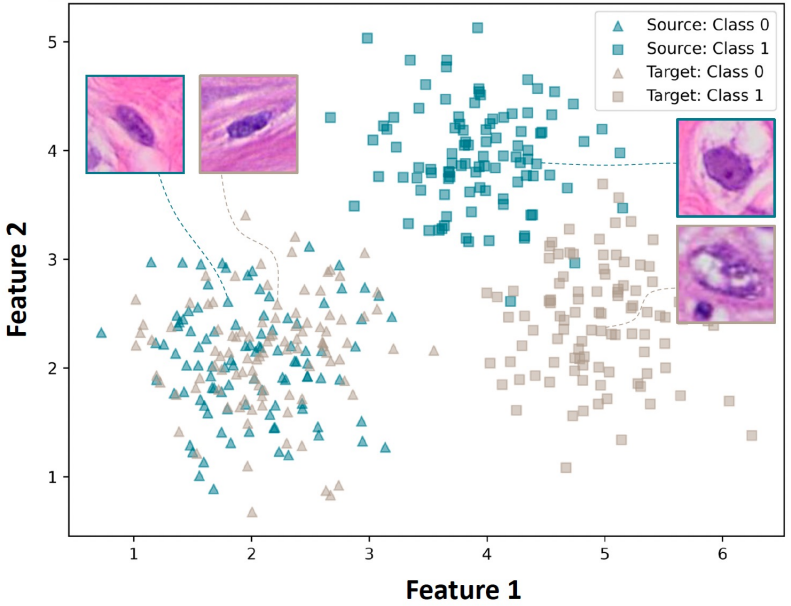




Jahanifar *et al.*, *ACM Computing Surveys* (June 2025)

Domain Shift – Type 4 (***Class-Cond*** Shift)



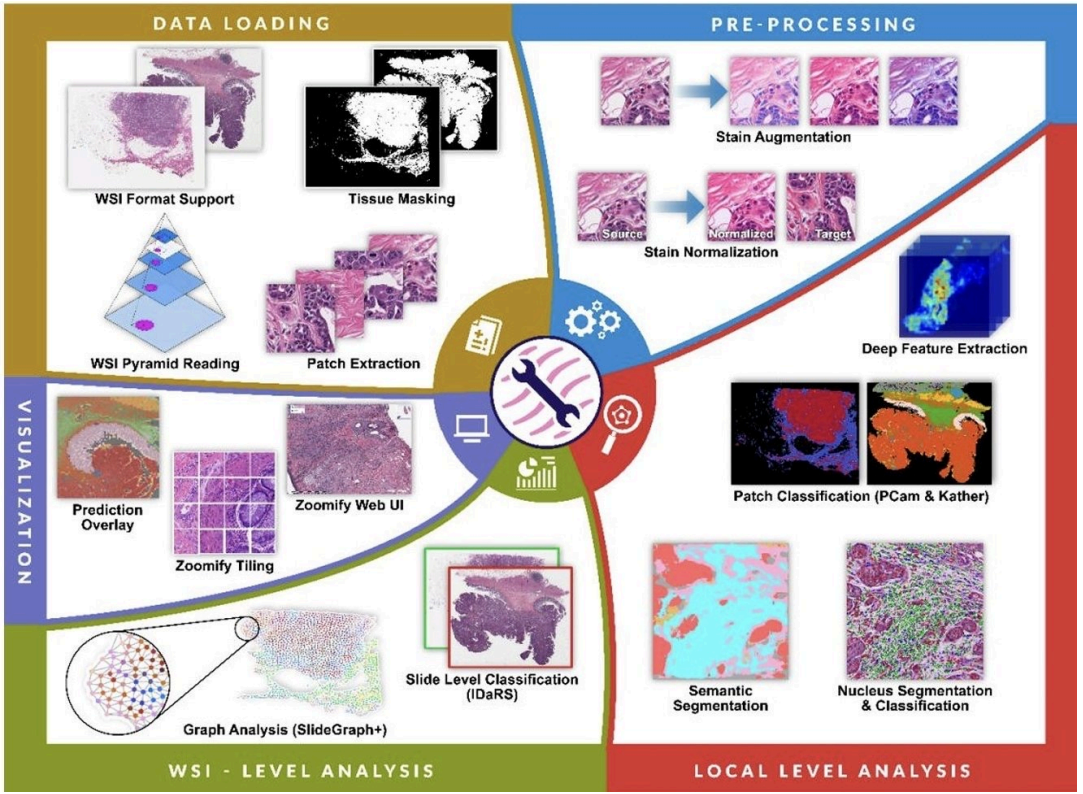


Jahanifar *et al.*, *ACM Computing Surveys* (June 2025)

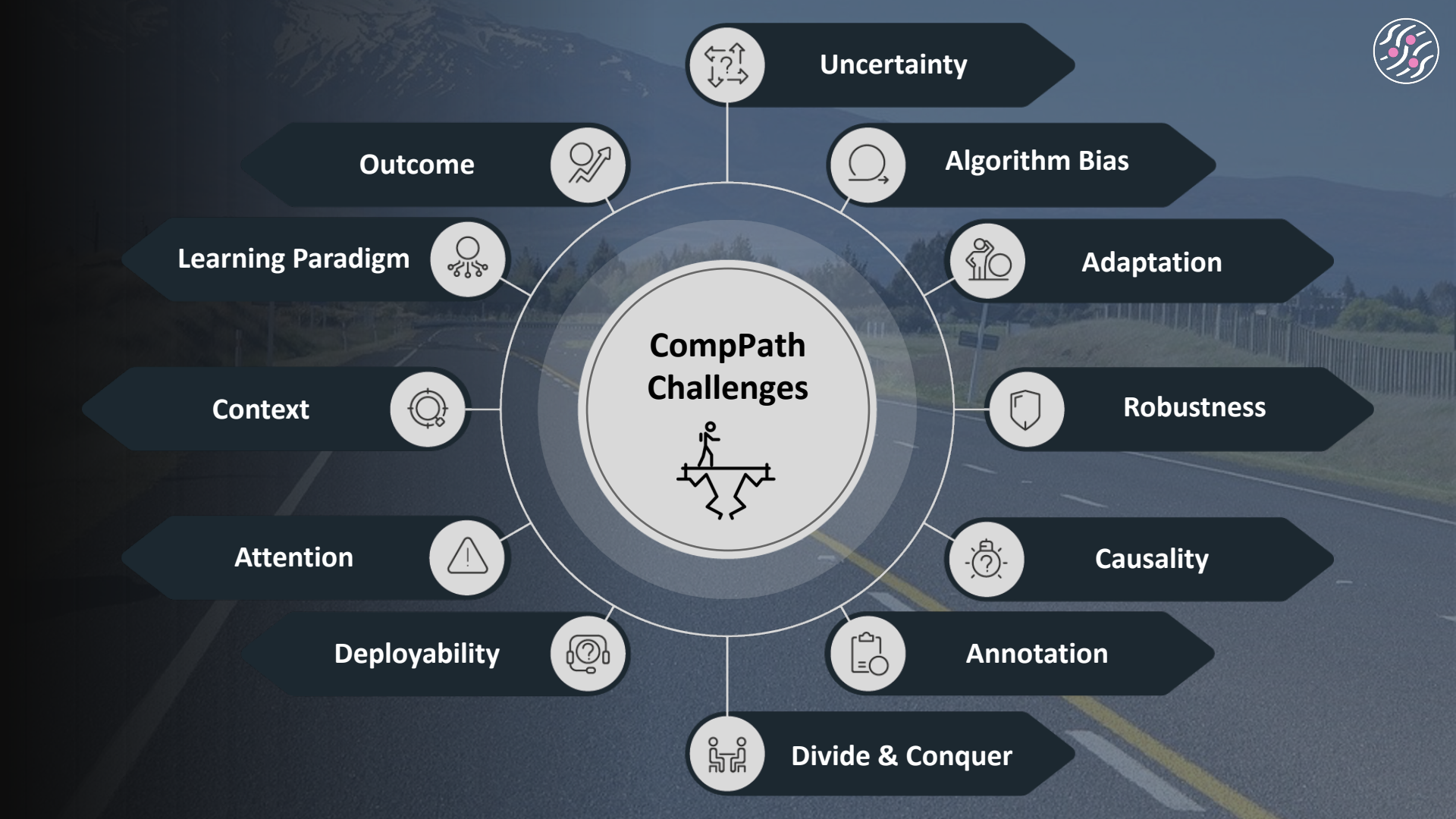
TIAToolbox



Shan Raza

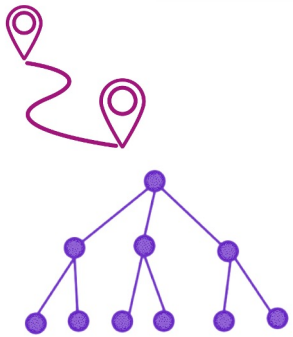


Pocock *et al*. (***Nature Comms Med***, Oct 2022)

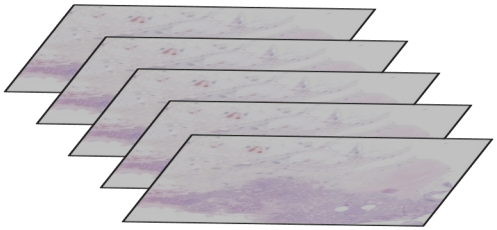

CompPath Challenges
Uncertainty
Algorithm Bias
Adaptation
Robustness
Causality
Annotation
Divide & Conquer
Deployability
Attention
Context
Learning Paradigm
Outcome


Learning Paradigm
CompPath Challenges

Learning Paradigms

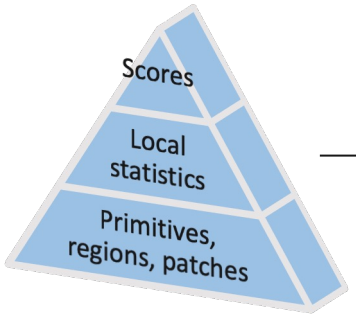


End-to-end ML
vs
Bottom-Up /
Top-Down ML



Bad Prognosis

Good Prognosis

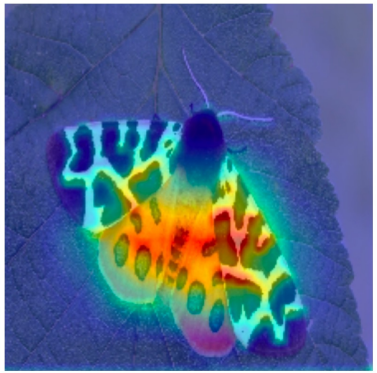


Stats and **Scores** for
Diagnosis, Prognosis
Outcome, Response etc

Top-down ML in CompPath combines the above two paradigms

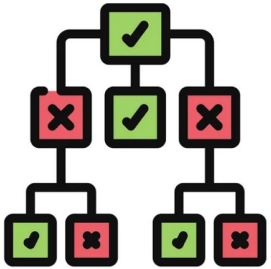
Explainable *vs* Interpretable AI

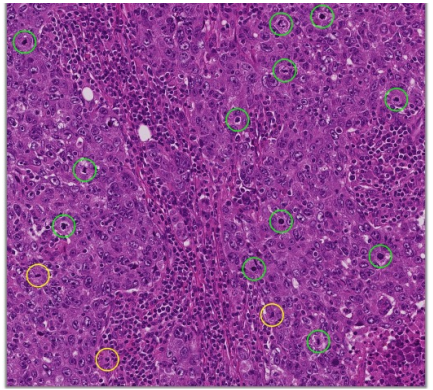
Explainable AI



‘Explains’ its predictions
(eg, by GradCAM / Attention etc)

Interpretable AI

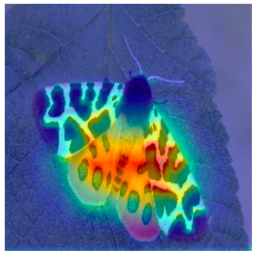




Makes its predictions based on ‘interpretable’ features
(eg, clinical features, mitotic index etc)

Transparent AI

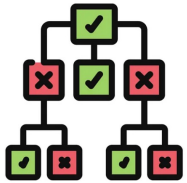
Explainable

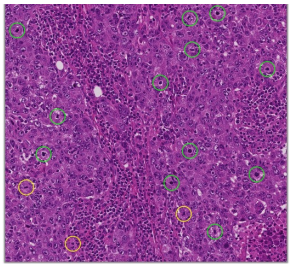


‘Explains’ its predictions
(heatmaps)

+

Interpretable

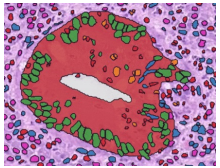




Makes its predictions based on histologically meaningful features
(often **global** features)

+

Spatial

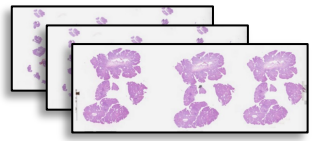


Localised features
(richer profiling)

→ **Transparent AI**

An Example of Transparent AI for Colon Biopsy Screening

Colon Biopsy Screening – The COBI Tool



Large Bowel H&E Slides

AI

Normal → Automatic Screening → Reduction in ~ 33% of slides that require examination

Abnormal → Sent to Pathologist → Triaging and decision support tool

TIA Centre
Tissue Image Analytics

NHS
University Hospitals Coventry and Warwickshire
NHS Trust

PathLAKE
Computational Pathology Excellence

Colon Biopsy Audit (2019)

Site	Histopathology requests	Large bowel biopsies (%)	Large bowel biopsies normal (%)
Coventry	41,771	4,877 (11.7)	1,680 (34.4)
Wolverhampton	52,008	9,708 (18.7)	4,140 (42.6)
Oxford	56,575	7,766 (13.7)	3,938 (50.7)
Nottingham	59,851	10,562 (17.6)	3,428 (32.4)
Newcastle	59,843	5,348 (8.9)	2,015 (37.7)
Durham	34,958	6,240 (17.8)	2,353 (37.7)
Glasgow	108,000	29,000 (13.9)	7,830 (27)
Total	**413,006**	**73,501 (17.8)**	**25,384 (34.5)**

Colon Biopsy Screening – The COBI Tool

Original research

Screening of normal endoscopic large bowel biopsies with interpretable graph learning: a retrospective study

Simon Graham [1,2] Fayyaz Minhas [1] Mohsin Bilal [1] Mahmoud Ali [3] Yee Wah Tsang,[3] Mark Eastwood [1] Noorul Wahab [1] Mostafa Jahanifar [1] Emily Hero [4] Katherine Dodd,[3] Harvir Sahota,[3] Shaobin Wu,[5] Wenqi Lu [1] Ayesha Azam [3] Ksenija Benes,[3,6] Mohammed Nimir [3] Katherine Hewitt [3] Abhir Bhalerao,[1] Andrew Robinson,[3] Hesham Eldaly,[3] Shan E Ahmed Raza [1] Kishore Gopalakrishnan [3] David Snead [2,3,7] Nasir Rajpoot [1,2,3]

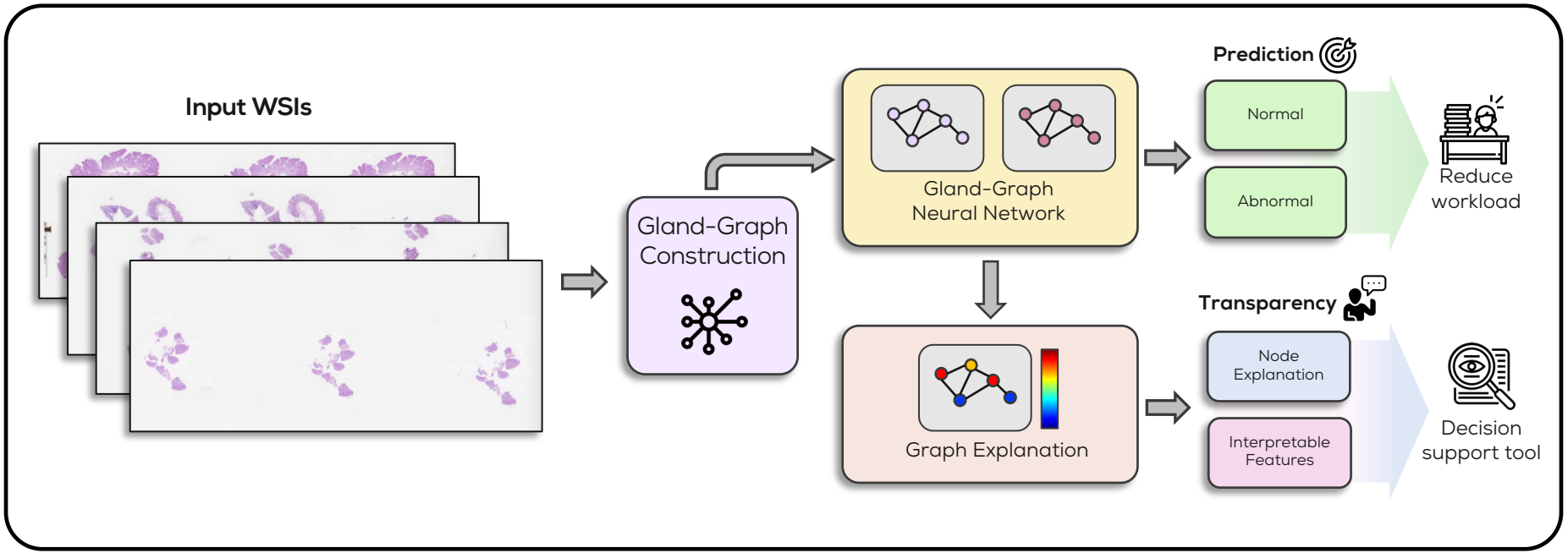
Graham *et al.*, **Gut** (May 2023)

TIA Centre
Tissue Image Analytics

NHS
University Hospitals Coventry and Warwickshire
NHS Trust

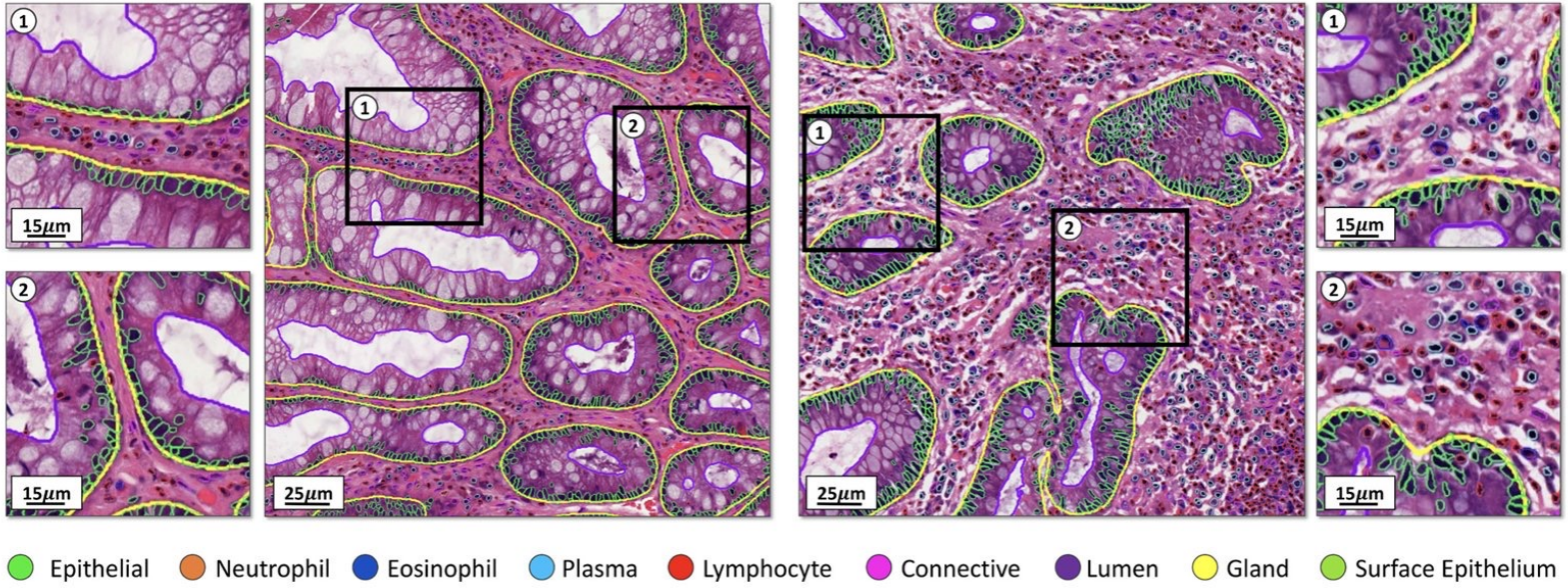
PathLAKE
Computational Pathology Excellence

IGUANA for **Colon Biopsy Screening**



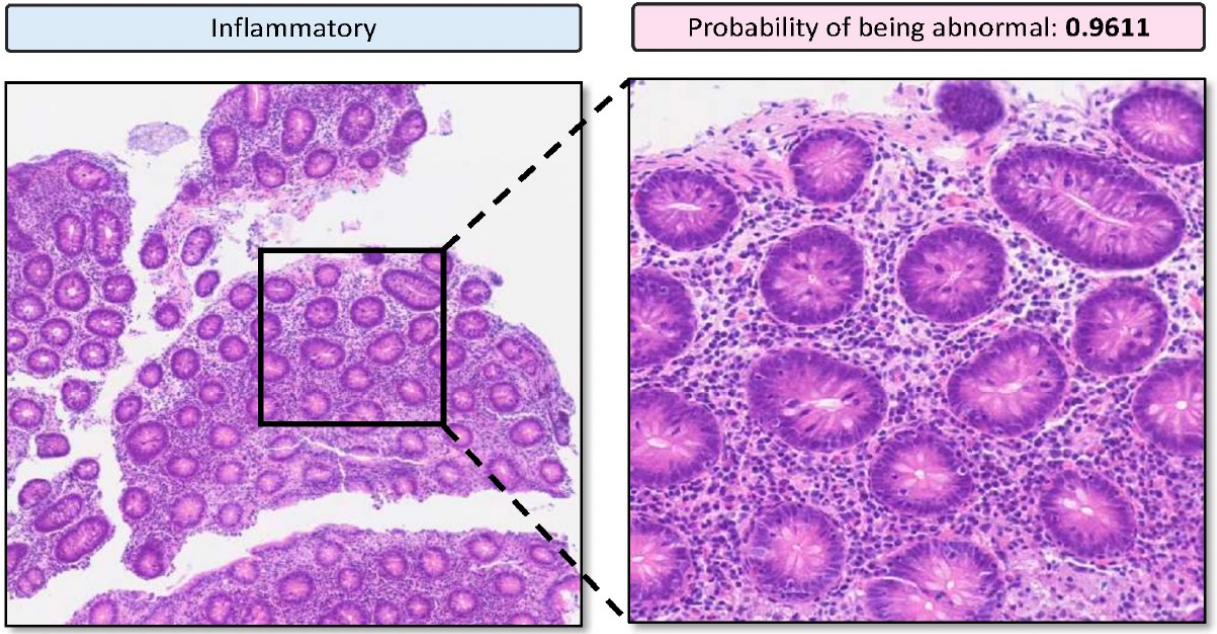
IGUANA (*patent pending*) – Graham et al., **Gut** (May 2023)

IGUANA Tissue & Nuclei Segmentation



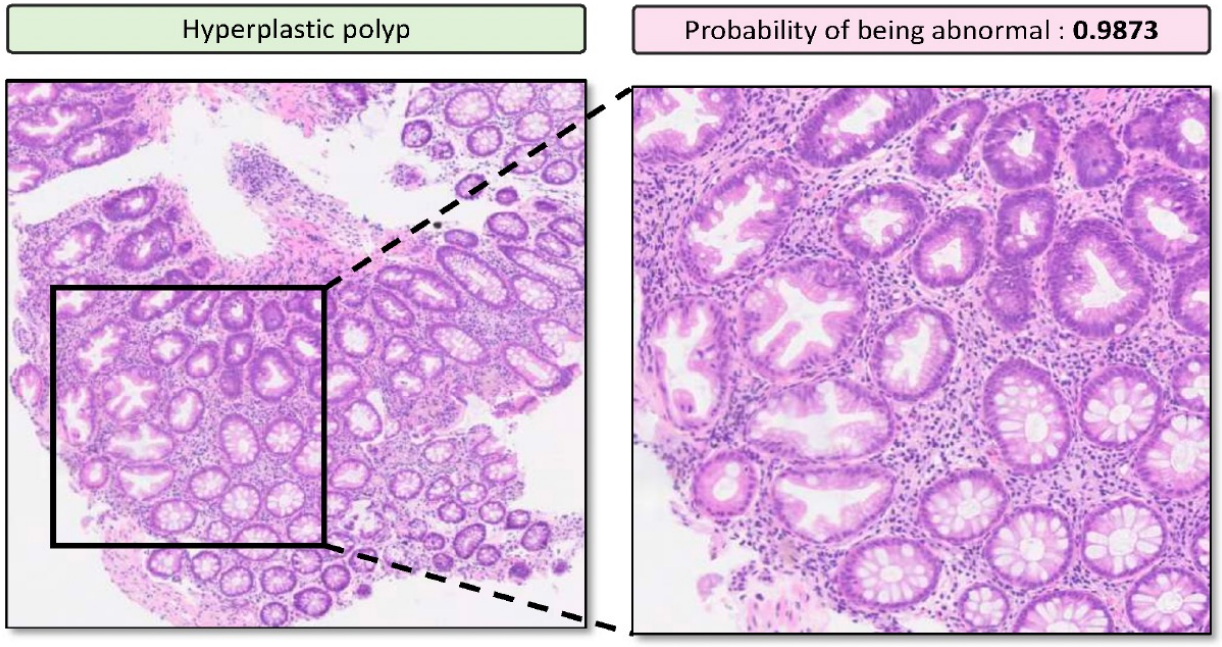
IGUANA (*patent pending*) – Graham et al., **Gut** (May 2023)

IGUANA picks up **missed** abnormalities

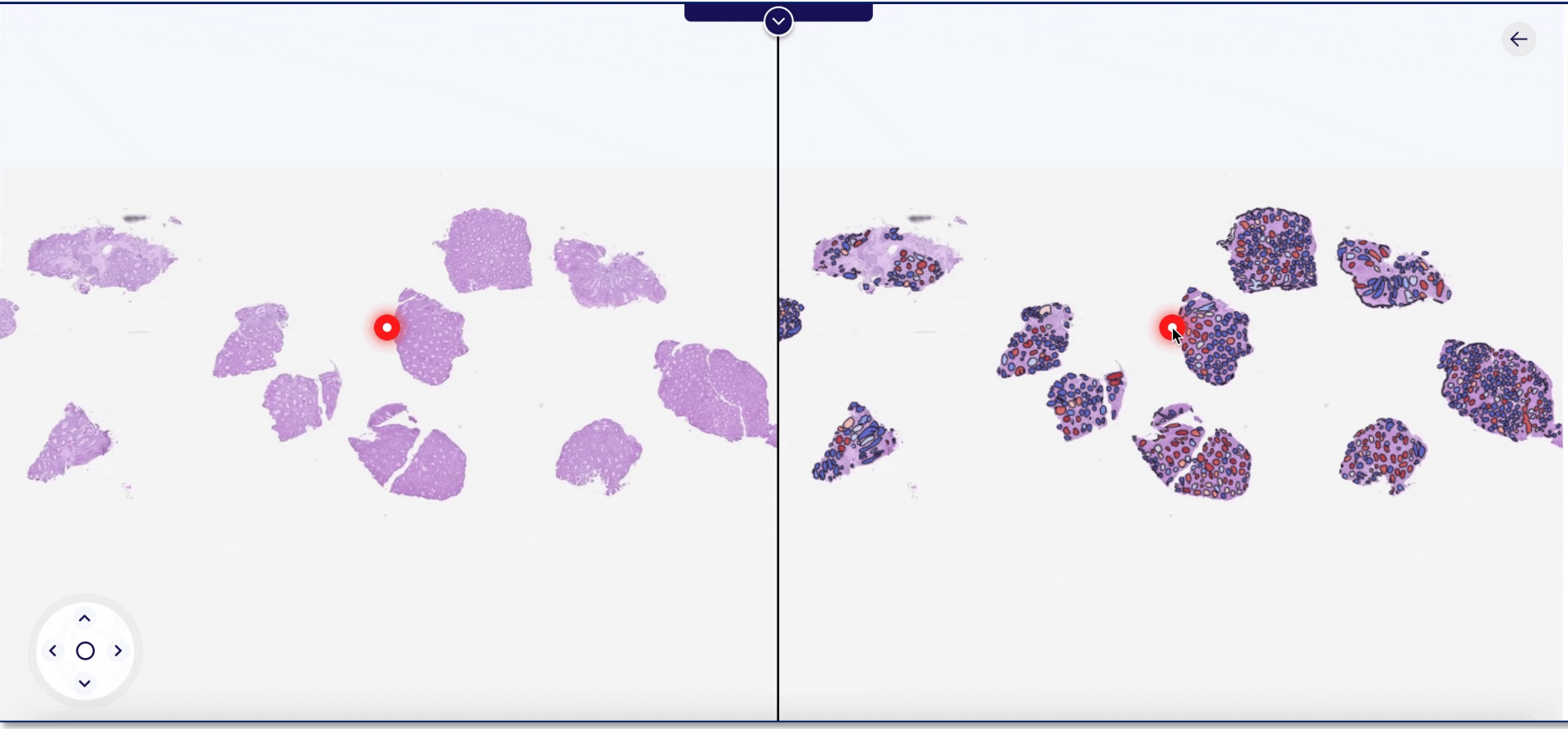


IGUANA (*patent pending*) – Graham et al., **Gut** (May 2023)

IGUANA picks up **missed** abnormalities

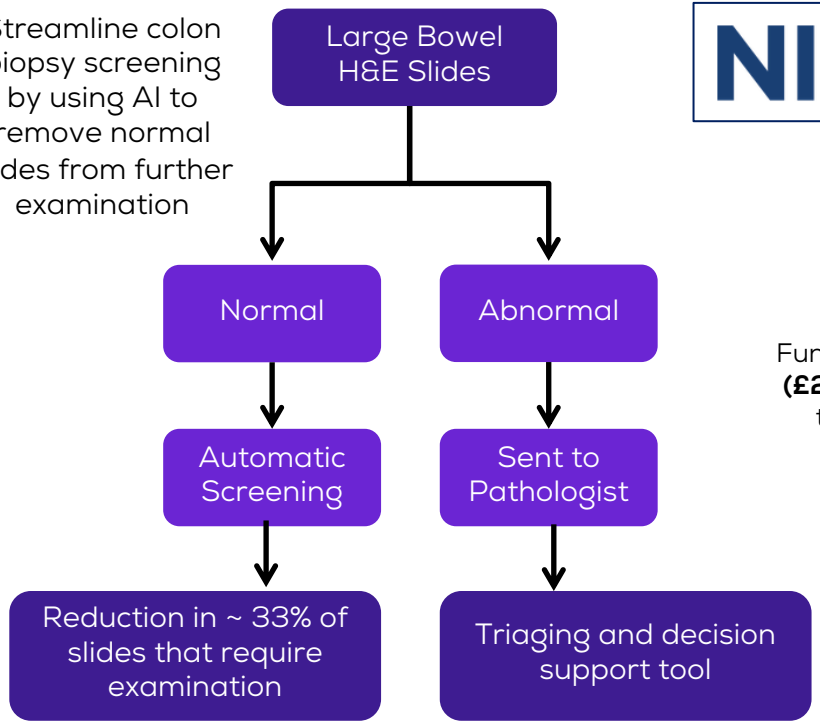


IGUANA (*patent pending*) – Graham et al., **Gut** (May 2023)



COBIx: Multi-Centric Validation of the COBI Tool

Streamline colon biopsy screening by using AI to remove normal slides from further examination

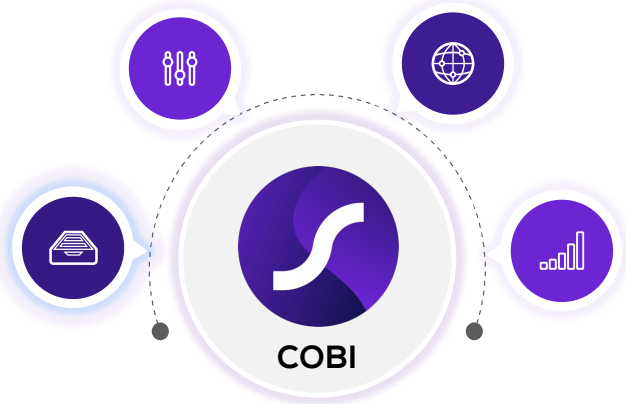


NIHR

Funded by NIHR **(£2.6M, £530K** to Histofy)

First-of-its-kind tool using transparent AI

10 NHS sites, **10K+ patients** 30K slides



No current automated reporting tool

Started 1st April 2023

Pan-Cancer Mitotic Profiling

Detecting Mitotic Figures

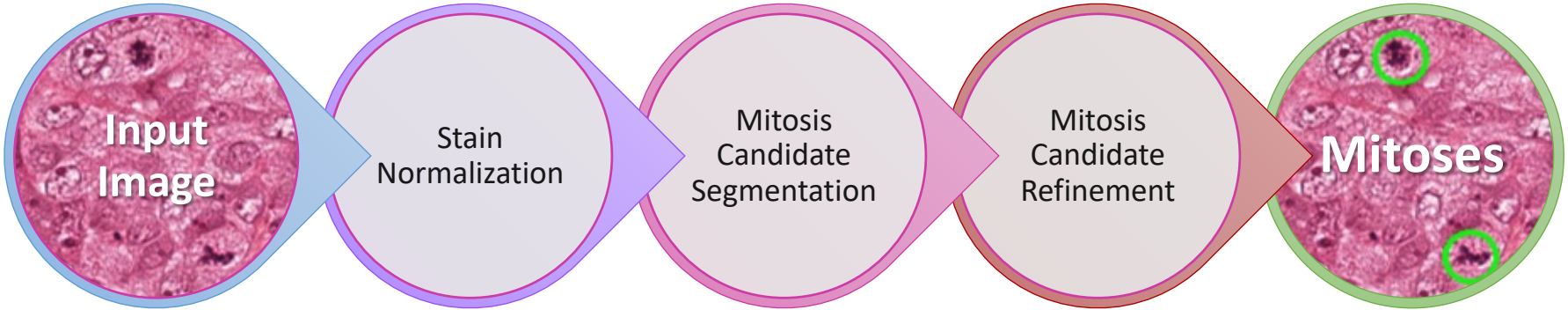


Mitosis in domain shift

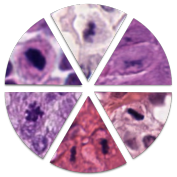


Mitosis vs. Mimicker

Detecting Mitotic Figures



The MIDOG Challenge



MIDOG 2021

Mitosis Domain Generalization

MICCAI2021

Team

TIA Centre

Mostafa Jahanifar, Adam Shephard, Neda Zamani Tajeddin, R.M. Saad Bashir, Mohsin Bilal, Syed Ali Khurram, Fayyaz Minhas, Nasir Rajpoot

University of Warwick, UK
University of Sheffield, Sheffield, UK

Team

AI_medical

Sen Yang, Feng Luo, Jun Zhang, Xiyue Wang

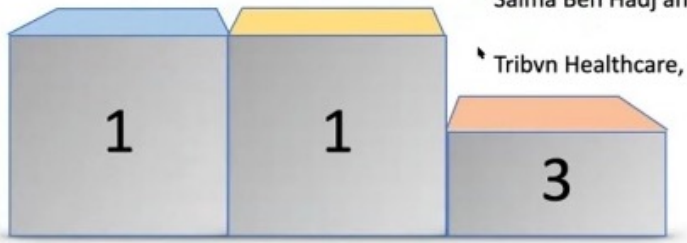
Sichuan University, Chengdu, China
Tsinghua University, Shenzhen, China

Team

serendipidy

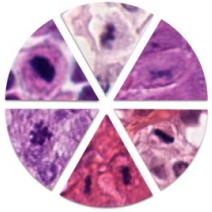
Gauthier Roy, Jules Dedieu, Capucine Bertrand, Alireza Moshayedi, Ali Mammadov, Stéphanie Petit, Saima Ben Hadj and Rutger H.J. Fick

Tribvn Healthcare, Paris, France





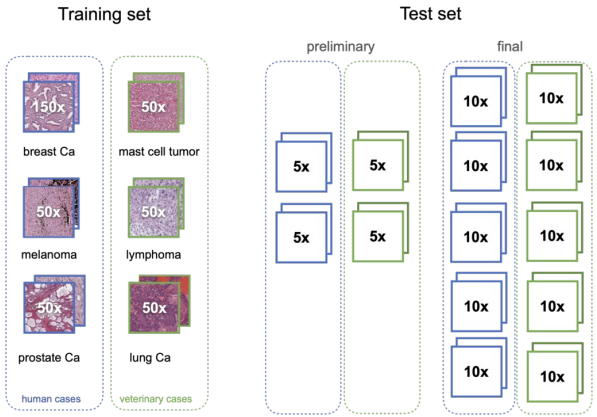
Mostafa Jahanifar

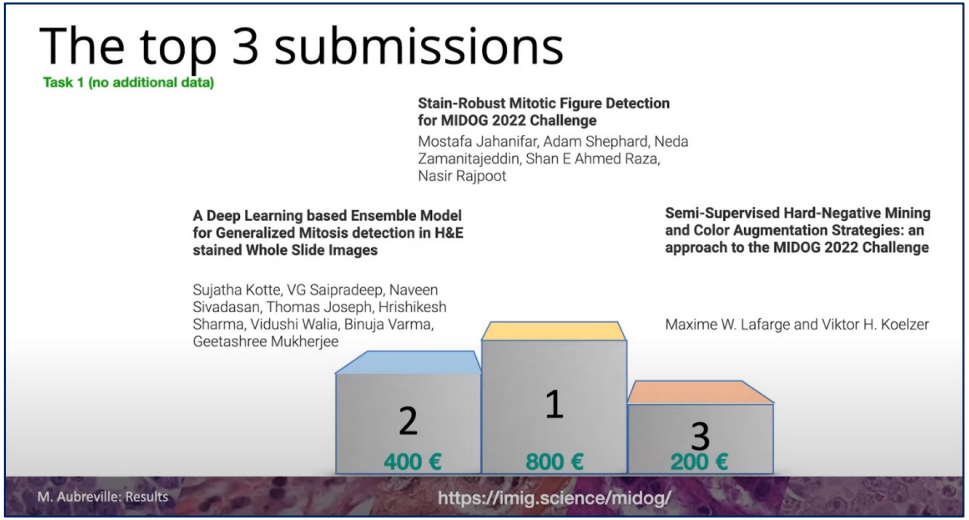


MIDOG 2022

Mitosis Domain Generalization Challenge

part of MICCAI2022 Singapore



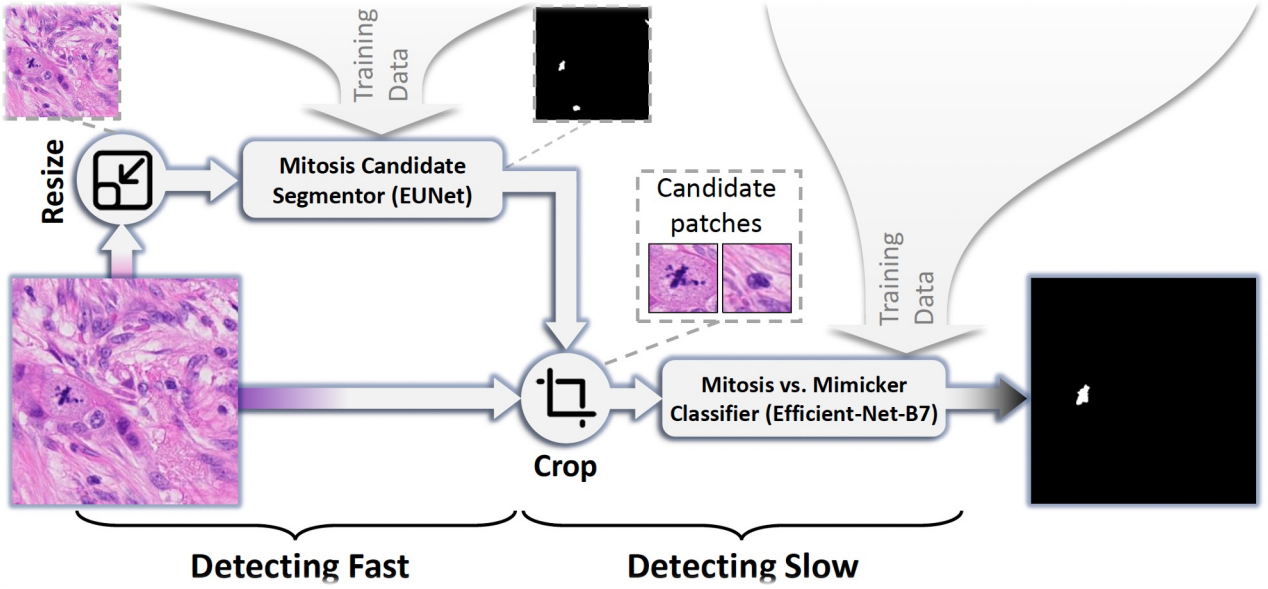




Mostafa Jahanifar

Jahanifar *et al.*, **Medical Image Analysis** (May 2024)

Mitotic Detection, Fast & Slow (MDFS)





Mostafa Jahanifar

Histofy

Jahanifar *et al.*, **Medical Image Analysis** (May 2024)

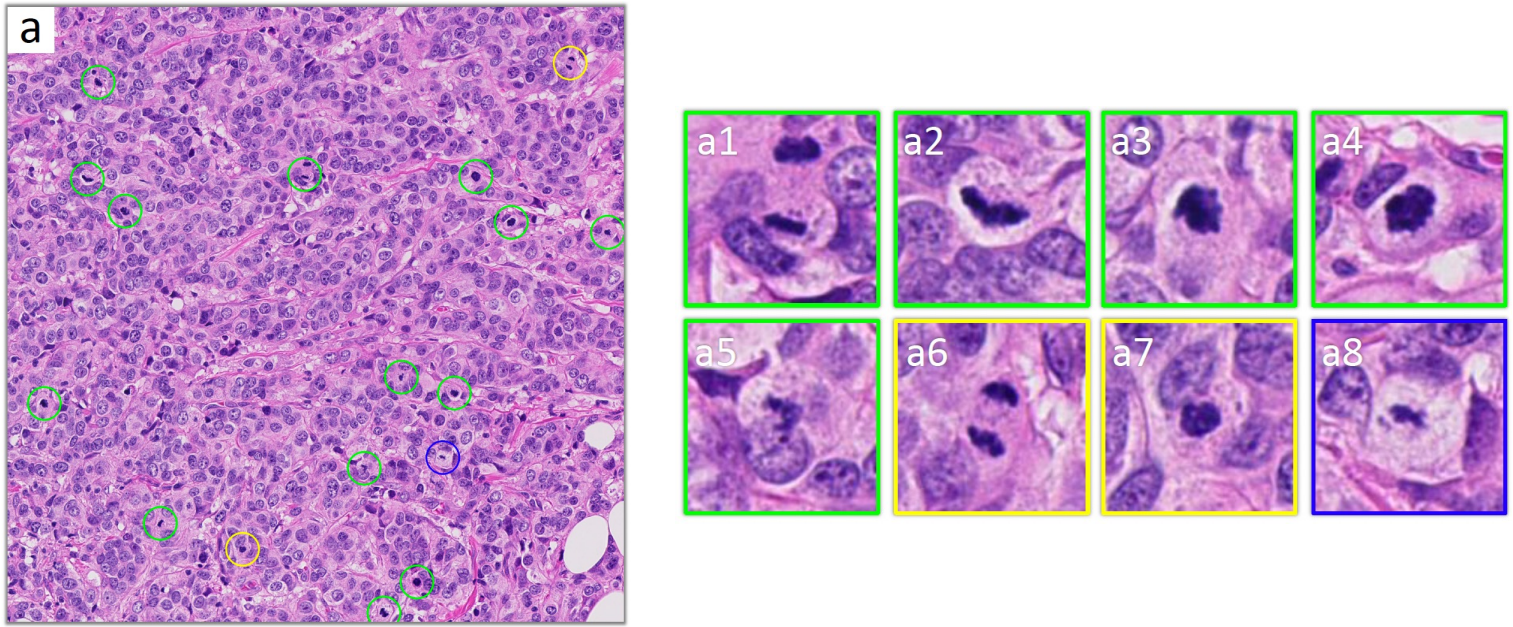


New York, 22 June 2023



London, 18 July 2023

MDFS: Sample Results

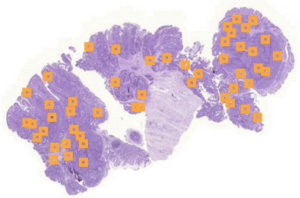


Jahanifar *et al.*, **Medical Image Analysis** (May 2024)

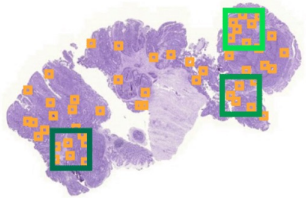
MitPro: Next-Generation Mitosis Profiling

Pathology slide is scanned

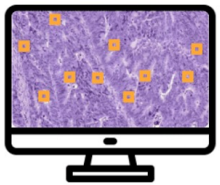
MitPro detects mitotic figures across entire slide



MitPro identifies hotspots for counting



Case opened in IMS and results are waiting

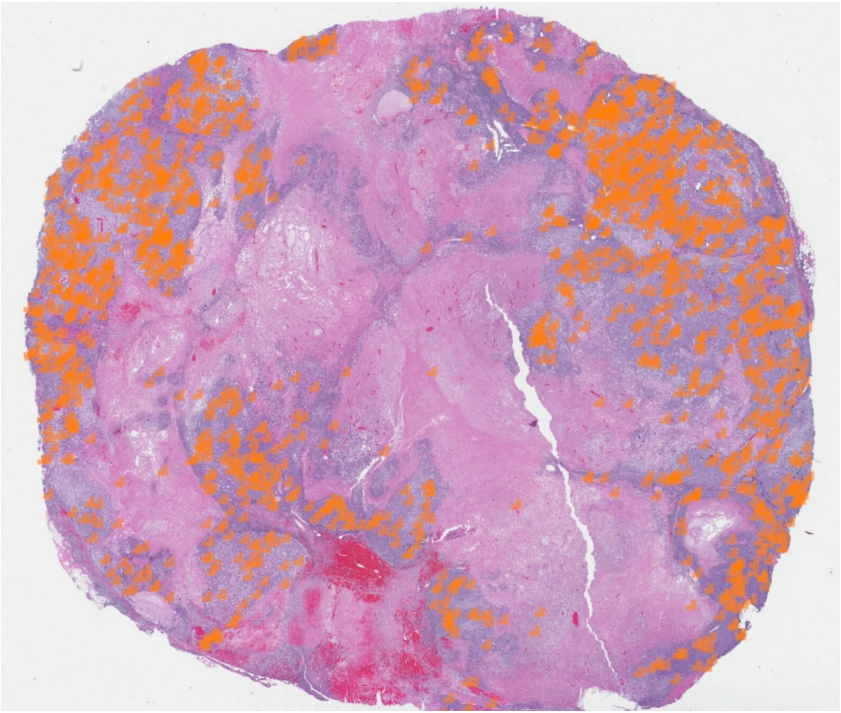


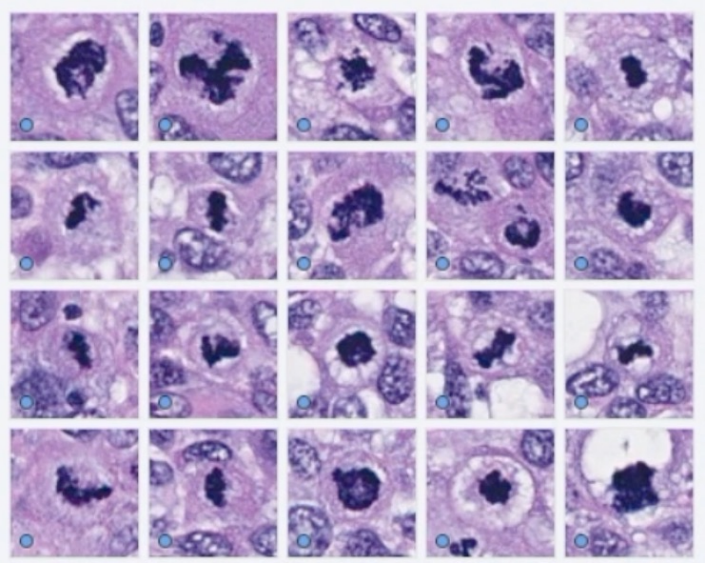
AI-assisted mitotic count reported



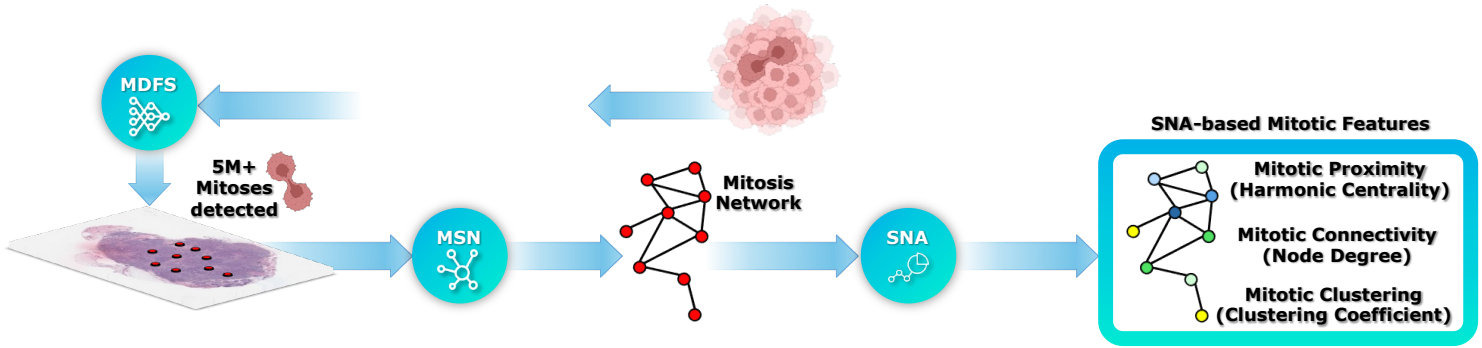
Jahanifar *et al.*, **Medical Image Analysis** (May 2024)

MitPro: Sample Results





PACMAN: Pan-Cancer Mitotic Activity Networks



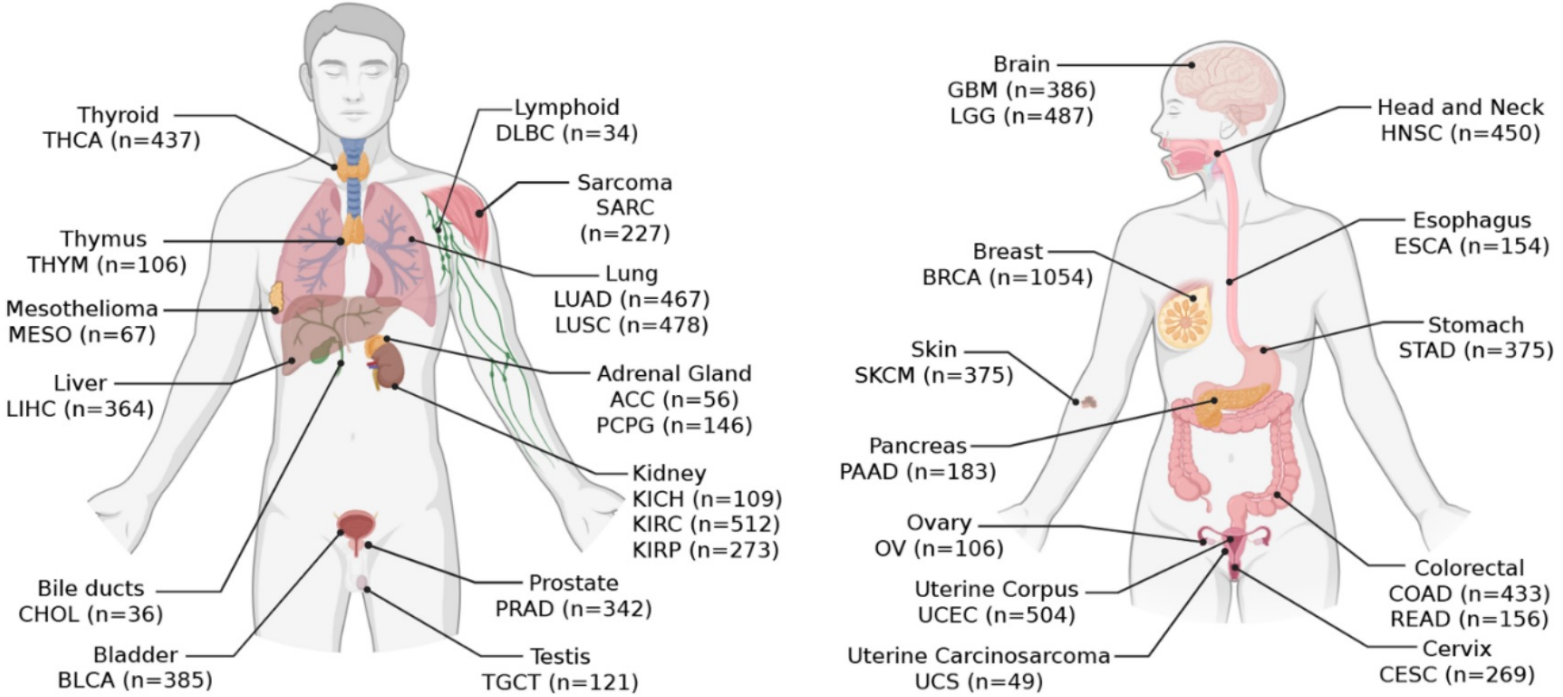


Mostafa Jahanifar

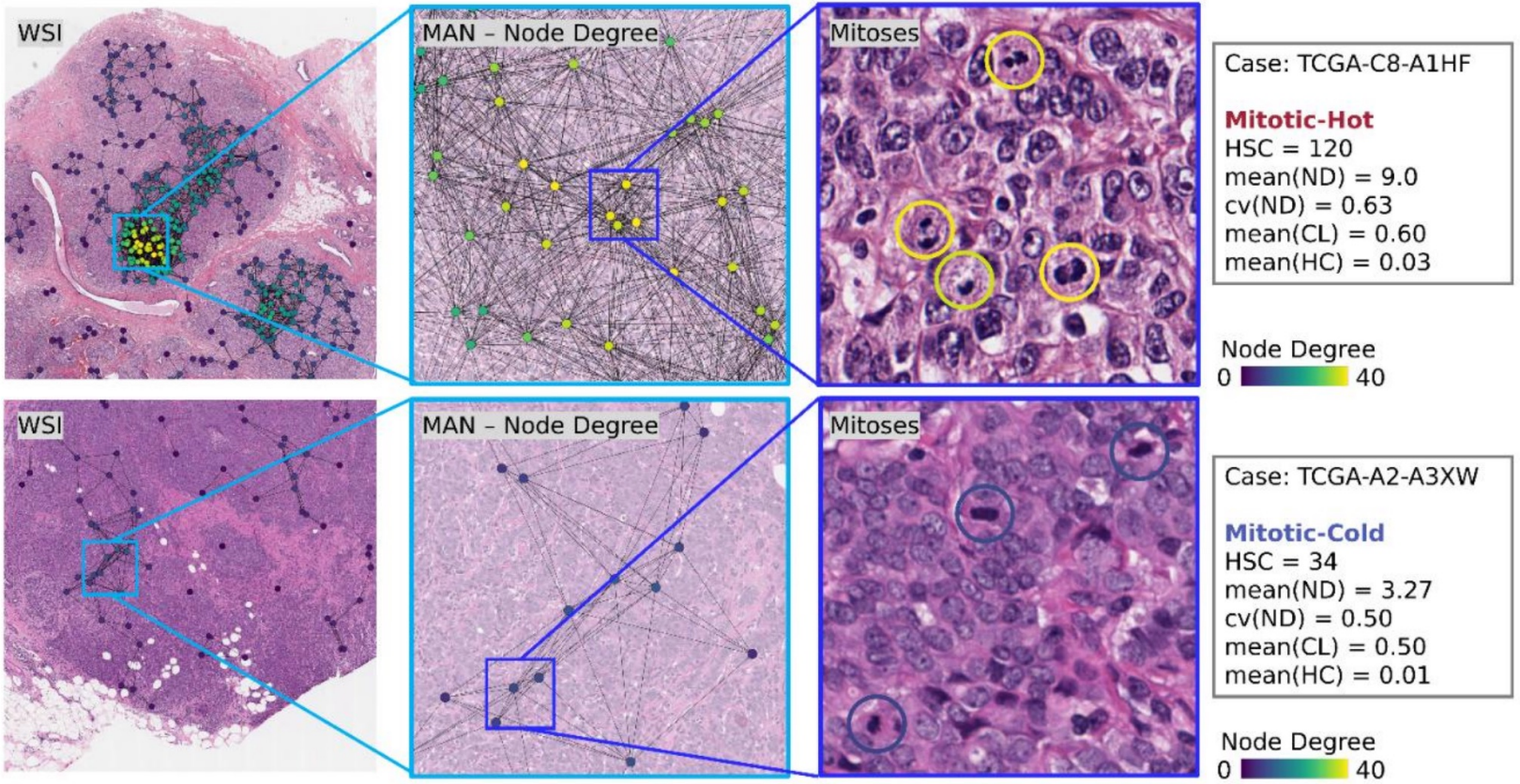
Social Network of Mitotic Figures

Jahanifar *et al., medRxiv 2025* (unpublished)

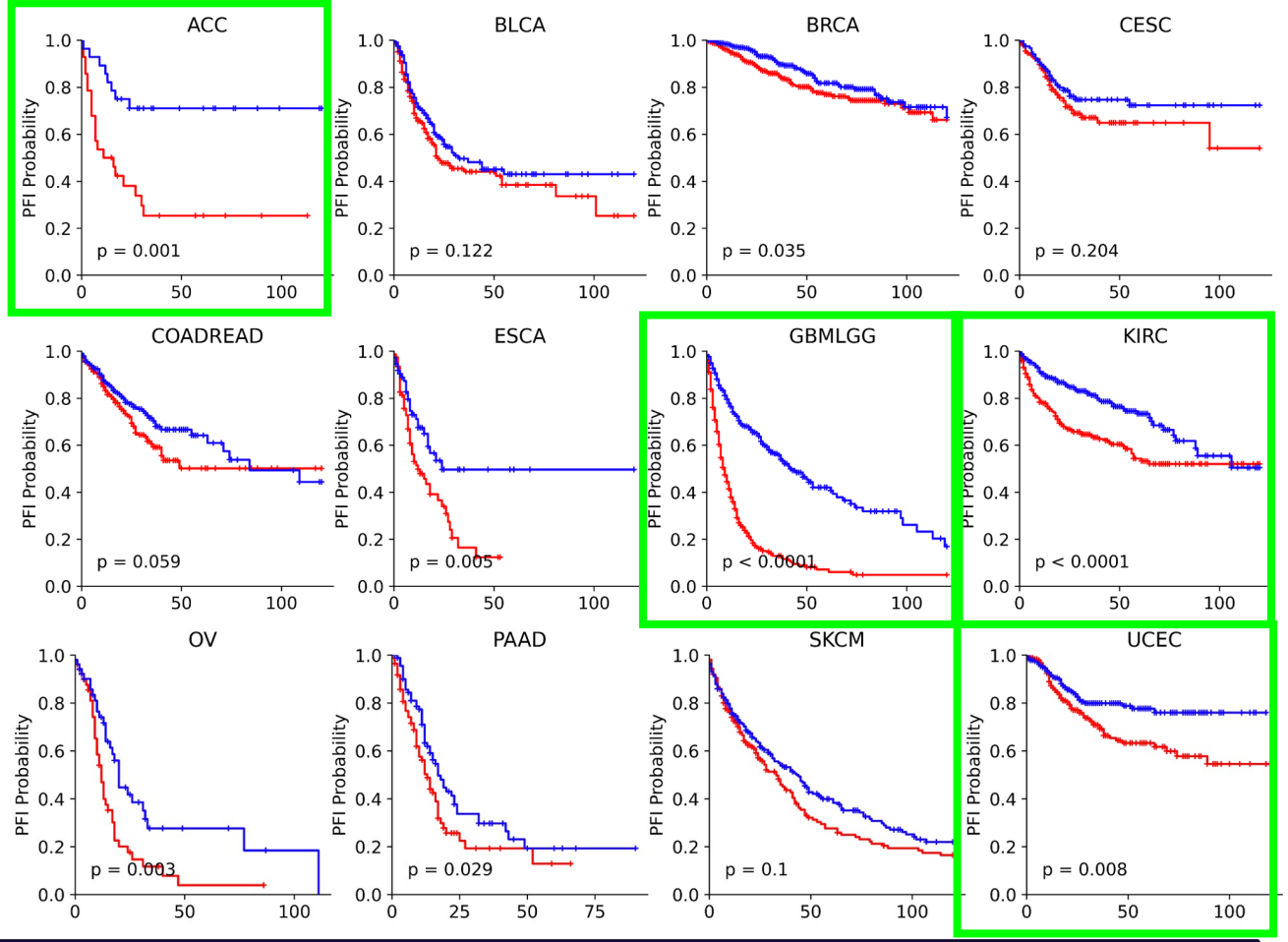
PACMAN: Pan-Cancer Mitotic Activity Networks



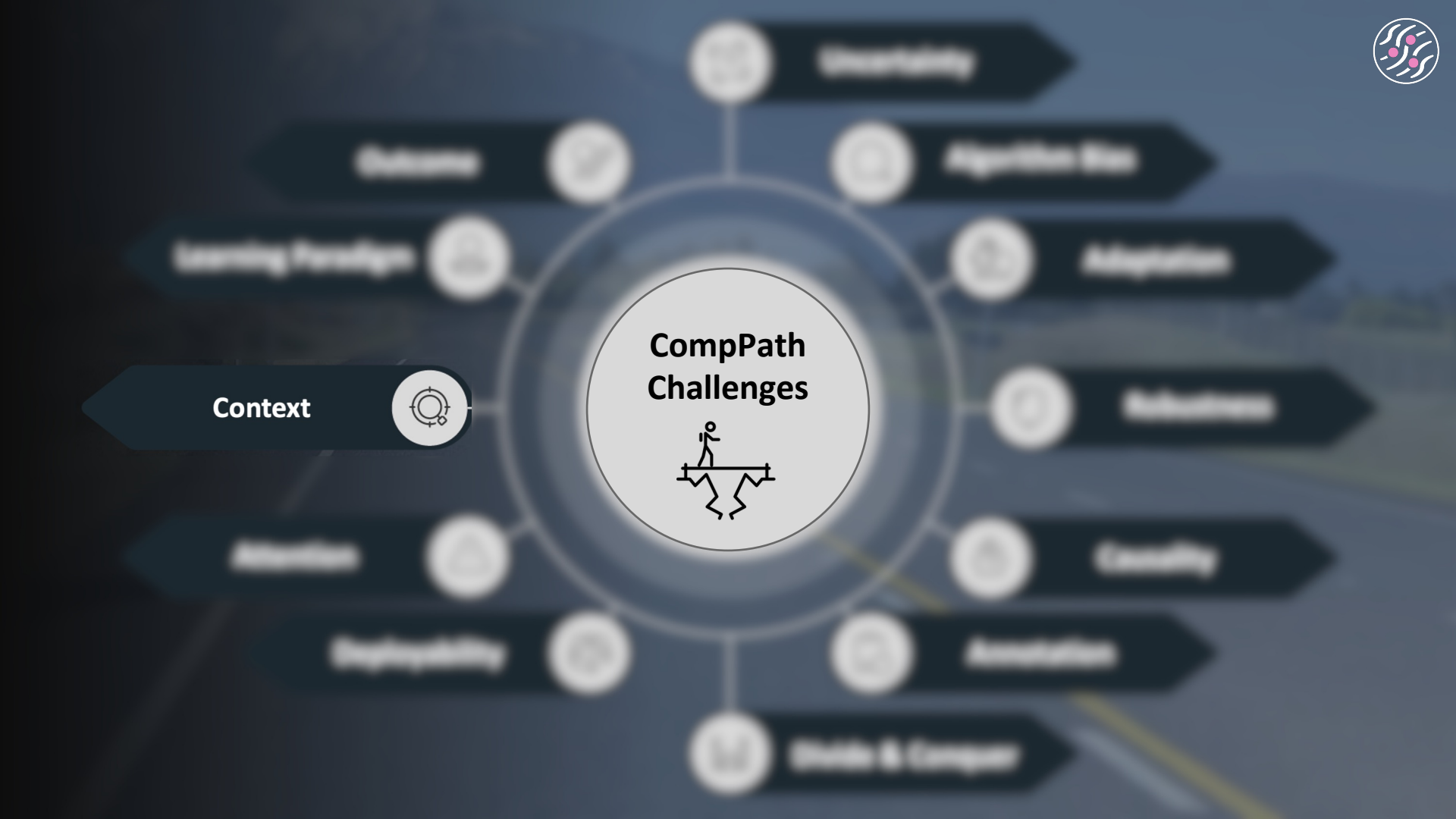
Jahanifar *et al., medRxiv 2025* (unpublished)



Jahanifar *et al., medRxiv 2025* (unpublished)



Jahanifar *et al., medRxiv 2025* (unpublished)


CompPath Challenges
Context

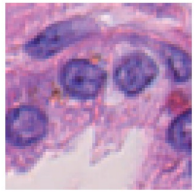
The Importance of Visual Context



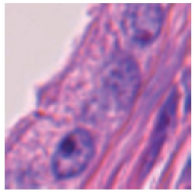
A cat

Sirinukunwattana *et al.*, MICCAI (Sep 2018)

Benign



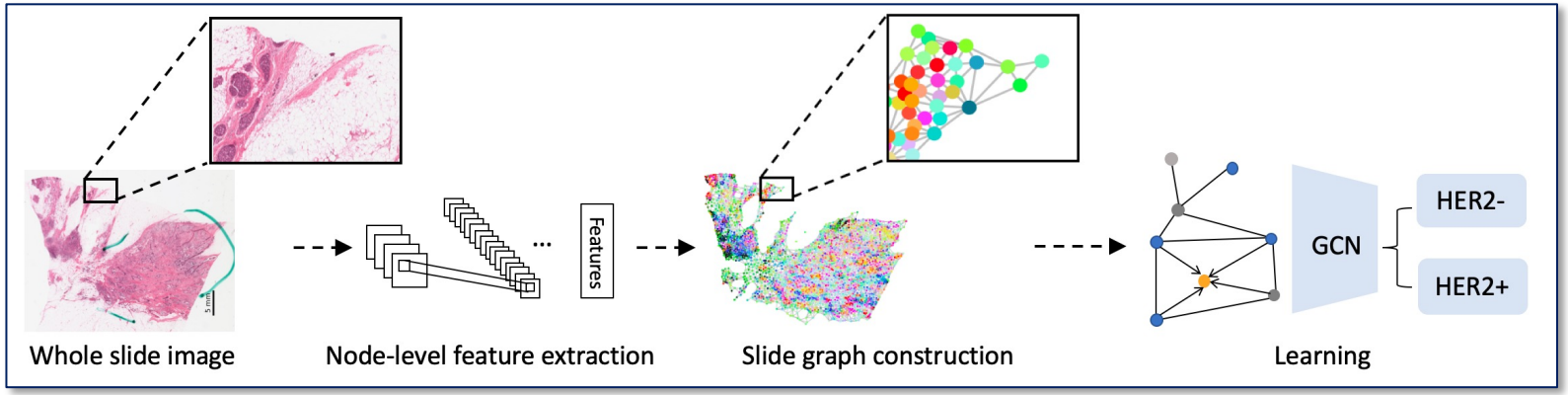
Tumour



20x

Shaban *et al.*, IEEE Trans Medical Imaging (July 2020)

SlideGraph for Prediction of **Her2** in **BCa**



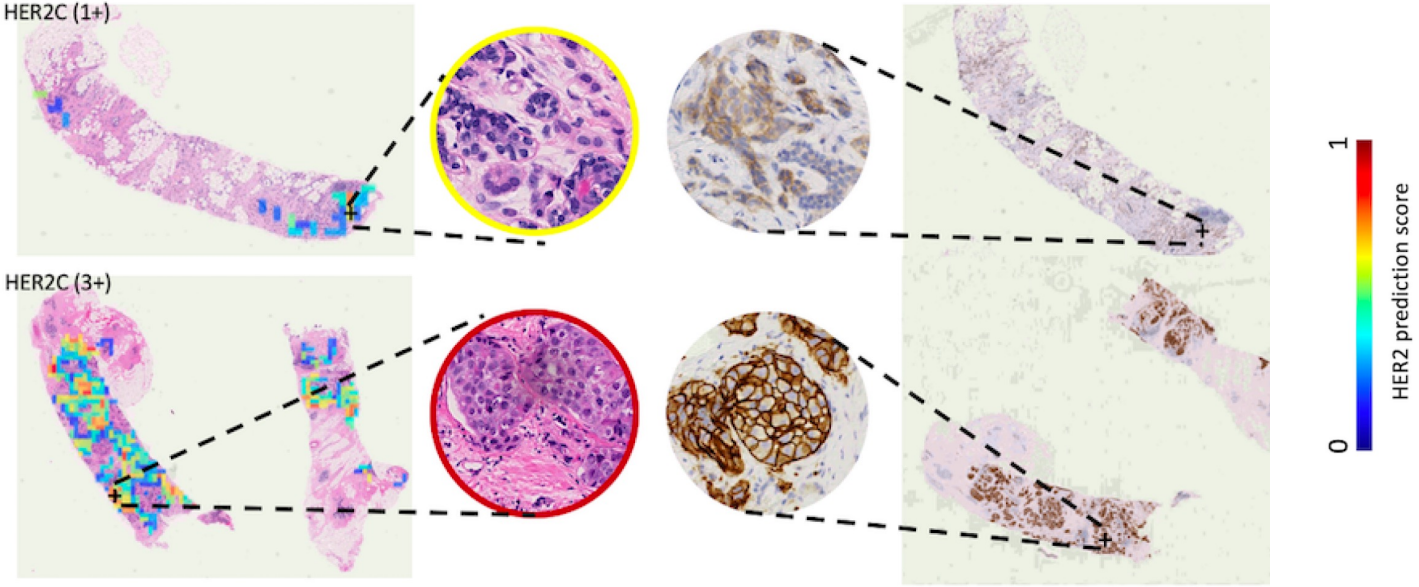
Lu *et al*. (***Medical Image Analysis***, May 2022)


Wenqi Lu


Fayyaz Minhas


Emad Rakha

SlideGraph for Prediction of **Her2** in **BCa**



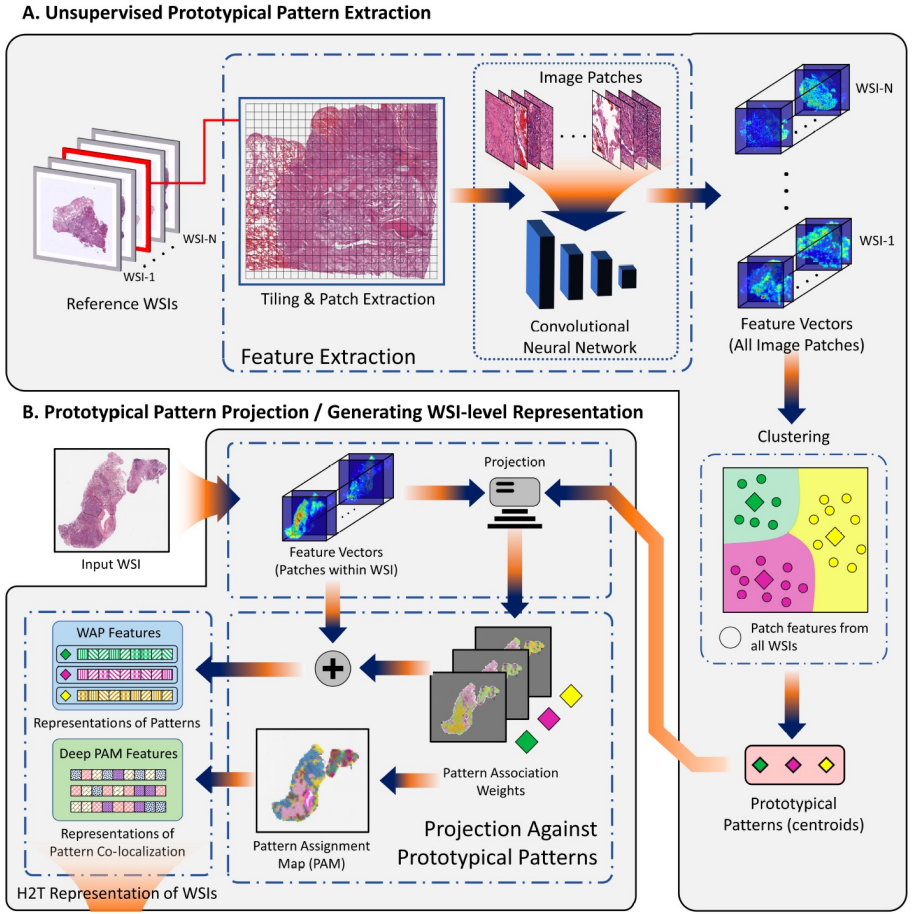
Lu *et al*. (***Medical Image Analysis,*** May 2022)

Handcrafted Histological (**H2T**) Transformers



Dang Vu

Unsupervised Learning of Prototypical Histology Patterns



Vu *et al*. (**Medical Image Analysis**, Jan 2023)


AI for Pathology Challenges
Annotation

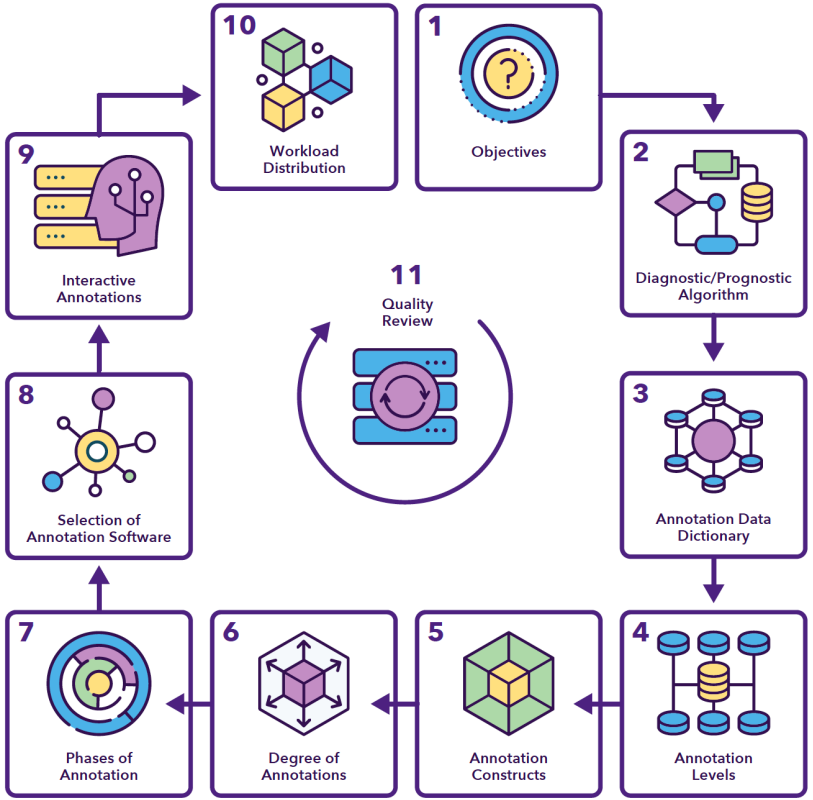
To Annotate or Not (How Much) to Annotate

- Most supervised ML algorithms require lots of annotations, often a costly and laborious process

- **Annotation protocols**
- Ways around:
  - ***Weakly* supervised learning** (requires only slide- or case-level labels)
  - **AI-assisted annotations**
  - **Self-supervised learning**
  - **Unsupervised learning**

Annotation Protocols

What to annotate?
How to annotate?
How to QC annotations?
How much to annotate?



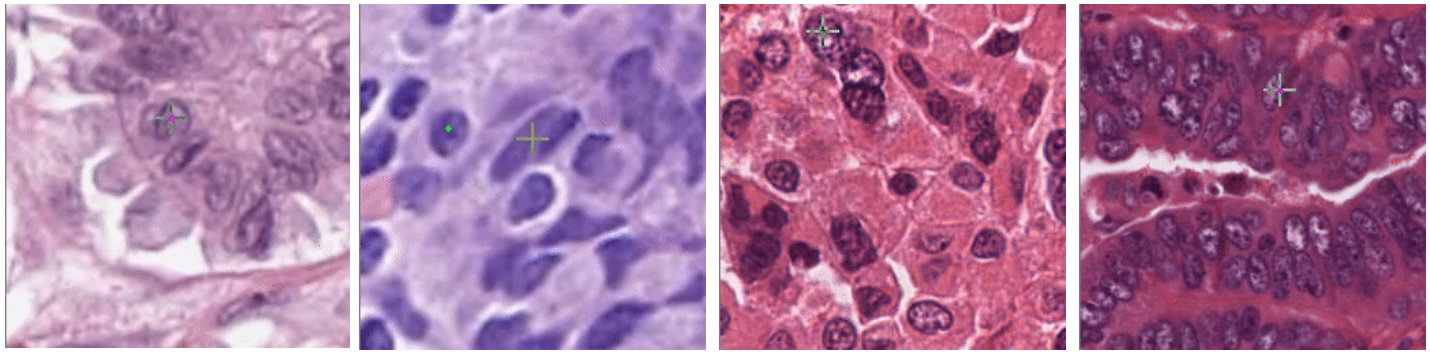


Noorul Wahab

Wahab *et al.* (***J Clinic Pathology***, Dec 2021)

PanNuke: Pan-Cancer Nuclear Dataset

PanNuke: A dataset of **200K+ pan-cancer nuclei** for nuclear segmentation and classification, where **NuClick** was used for collecting the segmentation masks



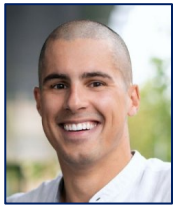
Koohbanani *et al.*, ***Medical Image Analysis*** (Oct 2020) & Gamper *et al.* (***ECDP*** 2019 & ***Arxiv*** 2020)



Navid Alemi

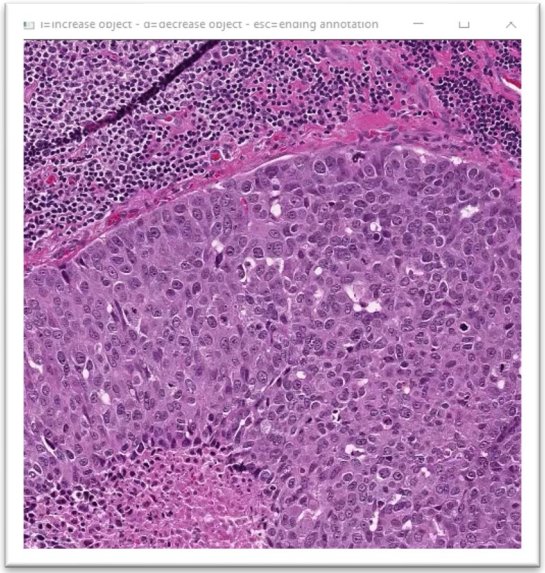


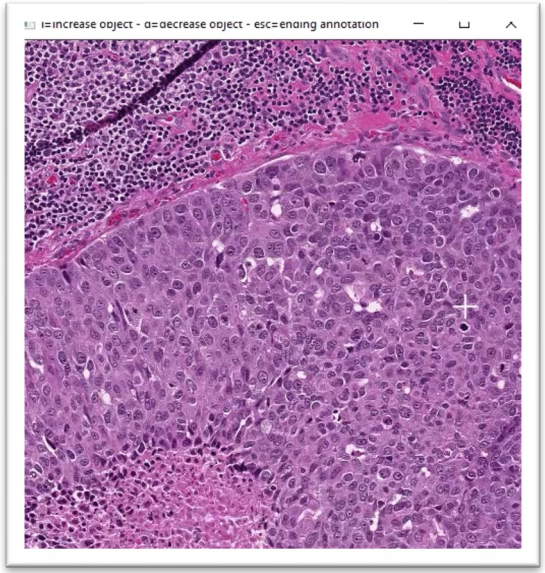
Mostafa Jahanifar



Jev Gamper

Interactive Region Segmentation



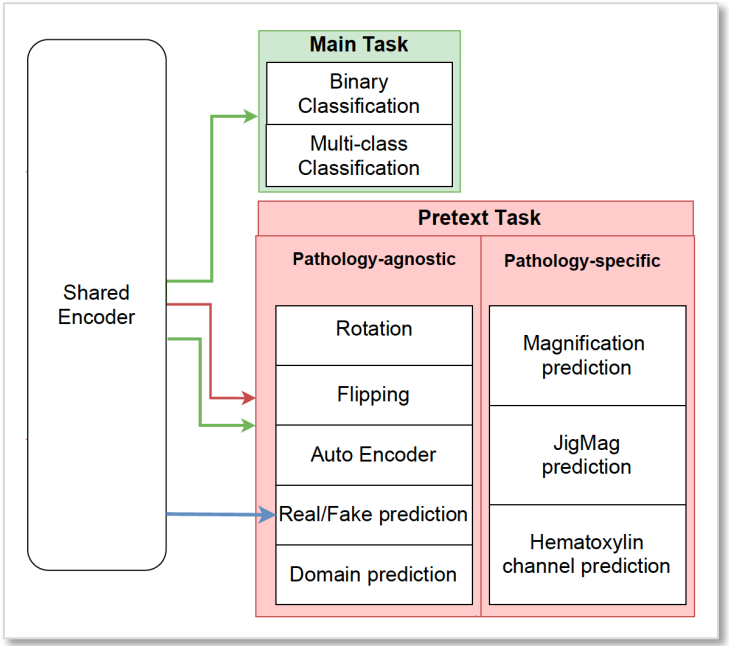


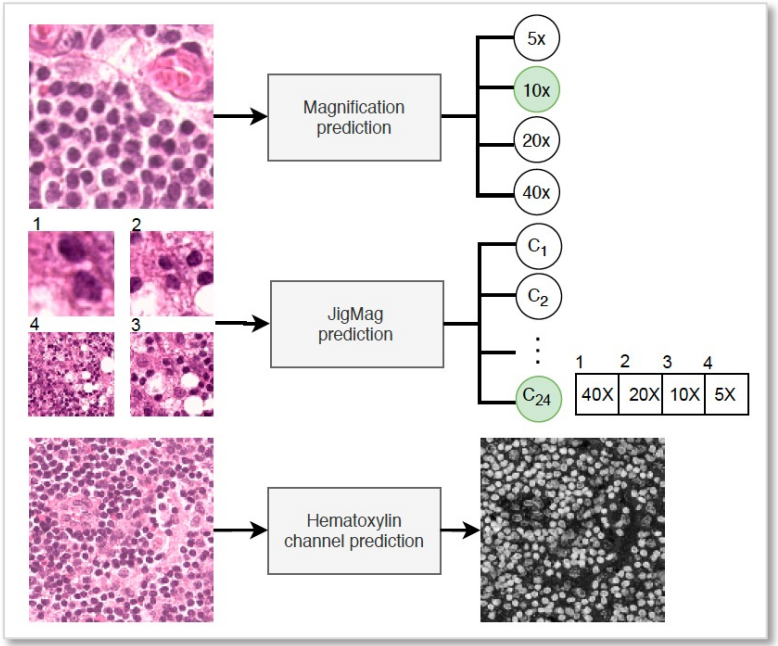


Mostafa Jahanifar

Jahanifar *et al.*, ***ICCV CDPATH***, 11 Oct 2021 **Best Paper Award**

Self-Path: Leveraging Self-Supervision







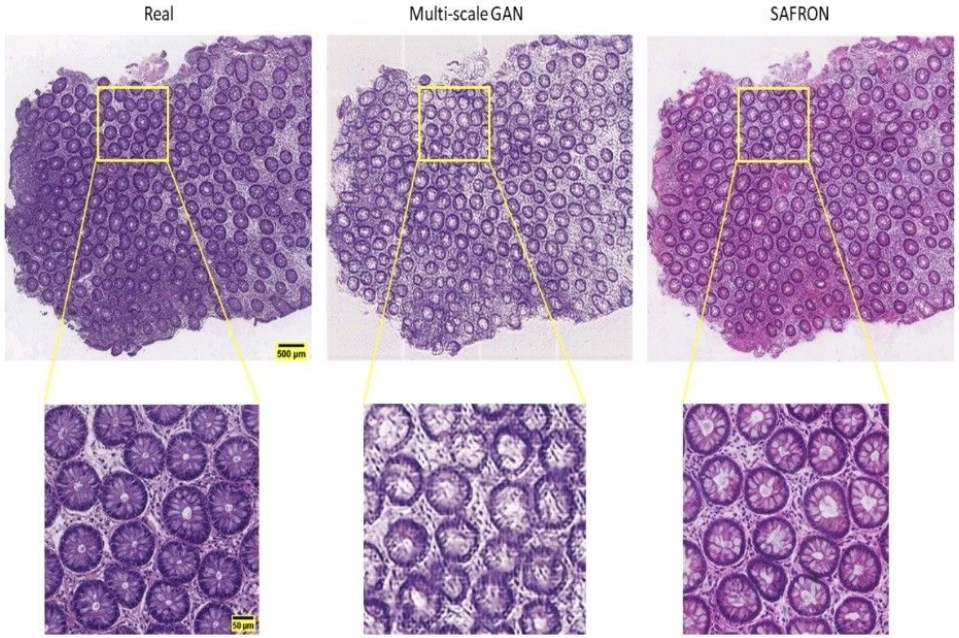
Koohbanani *et al.*, **IEEE Trans Med Imaging** (Feb 2021)

Self-Path: Leveraging Self-Supervision

Labeled WSIs (No. Patches)	1%(600)	2%(1000)	5%(2600)	10%(6400)	20%(13540)
	AUROC(%)	AUROC(%)	AUROC(%)	AUROC(%)	AUROC(%)
			Baselines		
supervised baseline	68.3 ± 5.1	74.5 ± 5.8	81.2 ± 2.5	88.4 ± 2.3	92.1 ± 0.5
Mean Teacher [2]	73.7 ± 3.8	78.5 ± 2.6	84.5 ± 2.4	92.7 ± 1.9	93.1 ± 0.9
VAT [3]	70.9 ± 5.8	77.4 ± 3.3	81.3 ± 5.2	90.3 ± 2.3	92.8 ± 1.5
TS chain [17]	74.9 ± 6.9	76.9 ± 3.2	83.8 ± 2.1	93.1 ±2.5	**93.9 ± 1.3**
			Pathology-Agnostic Self-supervised Tasks		
rotation	69.8 ± 4.8	74.5 ± 3.1	80.4 ± 2.5	90.1 ± 2.0	92.4 ± 2.5
flipping	70.2 ± 6.2	75.4 ± 3.5	81.6 ± 5.1	89.4 ± 0.6	92.3 ± 1.6
autoencoder	70.1 ± 2.4	75.6 ± 4.1	82.3 ± 4.5	90.5 ± 2.3	92.4 ± 1.1
generative	72.5 ± 5.5	77.6 ± 5.4	82.4 ± 7.2	92.6 ± 3.2	93.6 ± 1.5
			Pathology-Specific Self-Supervised Tasks		
magnification	77.5 ± 3.1	84.6 ± 5.2	85.1 ± 3.6	**93.2 ± 3.4**	93.4 ± 2.5
JigMag	**81.7 ± 3.8**	**86.3 ± 5.2**	**87.4 ± 4.5**	90.6 ± 4.6	92.8 ± 2.4
hematoxylin	72.8 ± 4.6	78.3 ± 4.5	84.6 ± 3.4	92.3 ± 4.1	**93.7 ± 2.5**
Best Self-supervised	**81.7 ± 3.8**	**86.3 ± 5.2**	**87.4 ± 4.5**	**93.2 ± 3.4**	**93.7 ± 2.5**

Koohbanani *et al.*, **IEEE Trans Med Imaging** (Feb 2021)

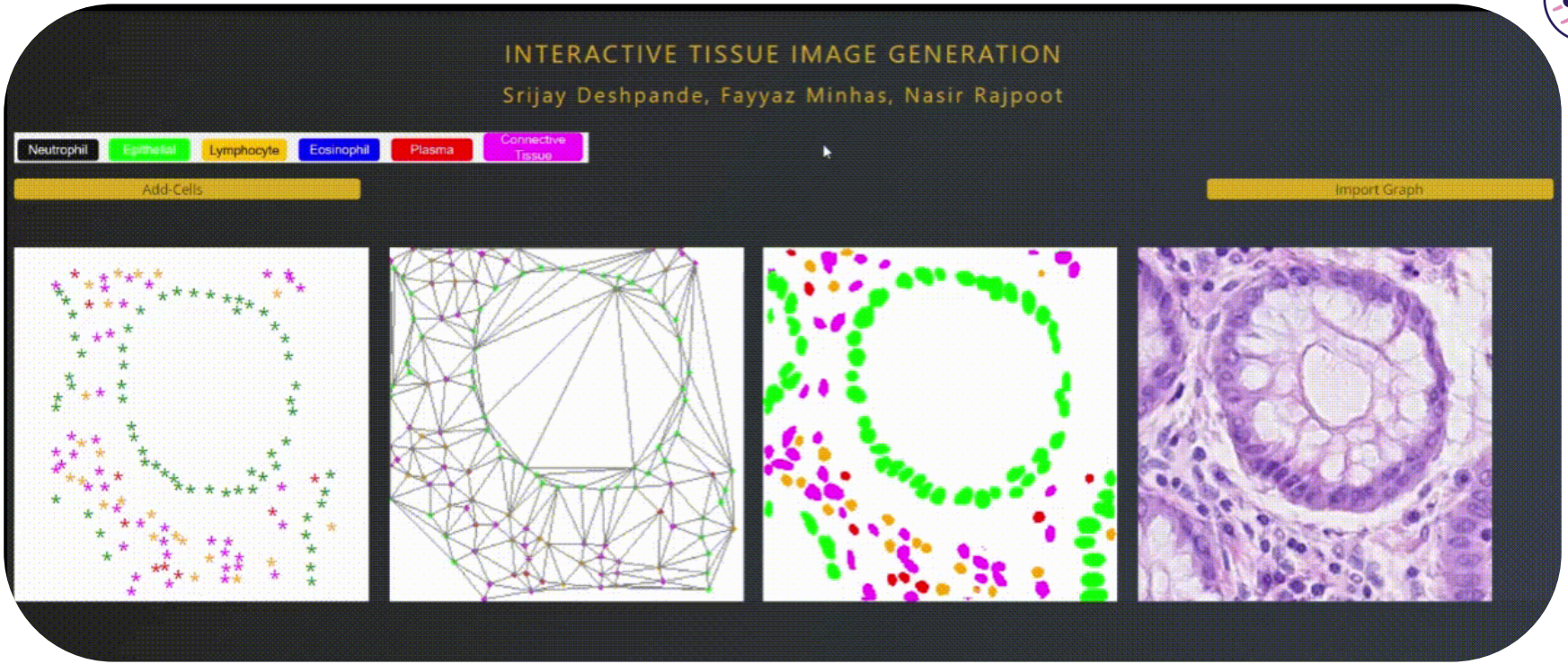
SAFRON: Synthetic Histology Images





Srijay Deshpande

Deshpande *et al.*, **Medical Image Analysis** (Feb 2022)



Deshpande *et al.*, **Medical Image Analysis** (Jan 2024)


AI4Health
Challenges
Deployability

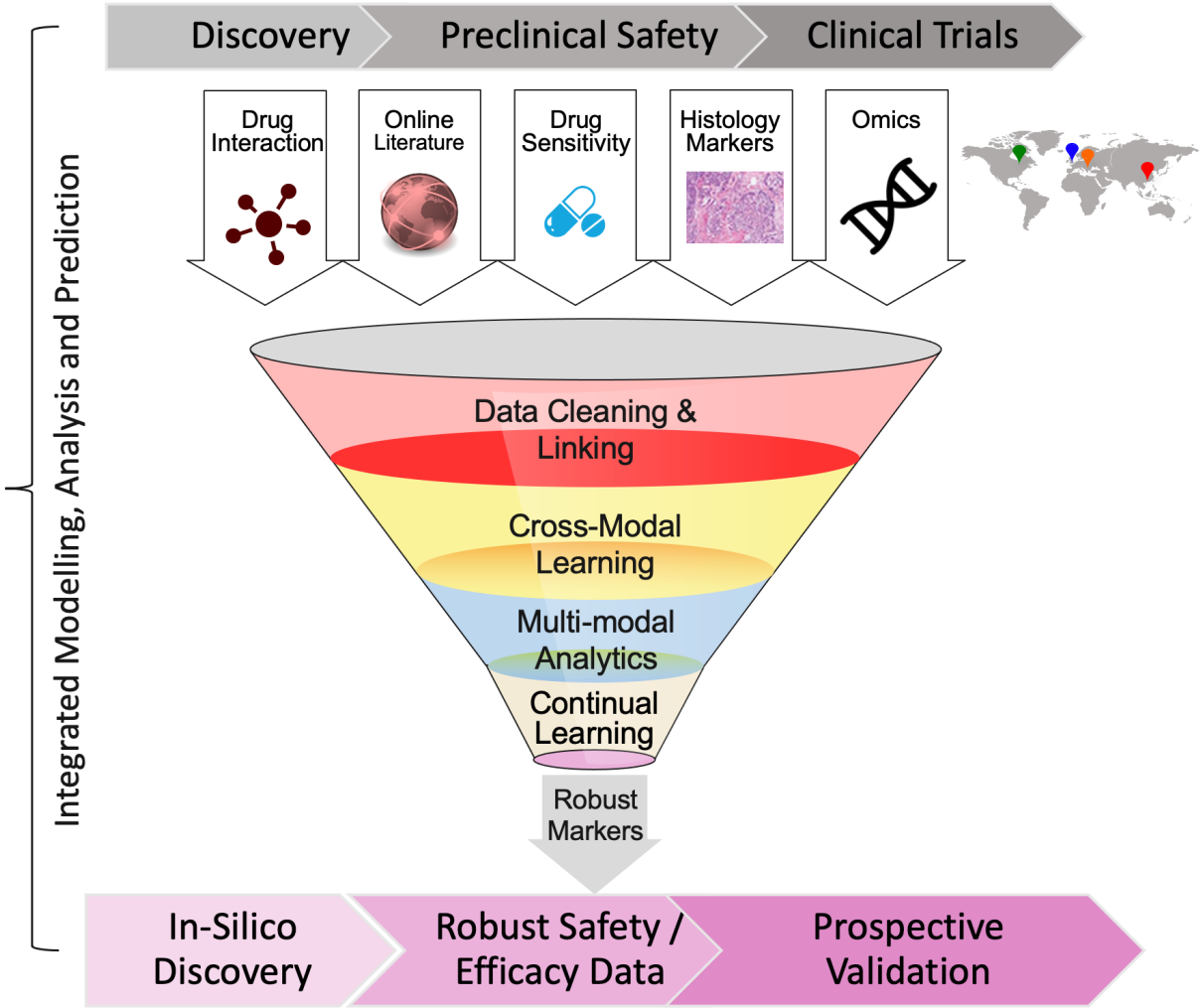
Deployability

- **Workflow integration**
- Validation and **regulatory approvals**
- Interoperability of image formats
- Cost model (e.g., pay-per use)

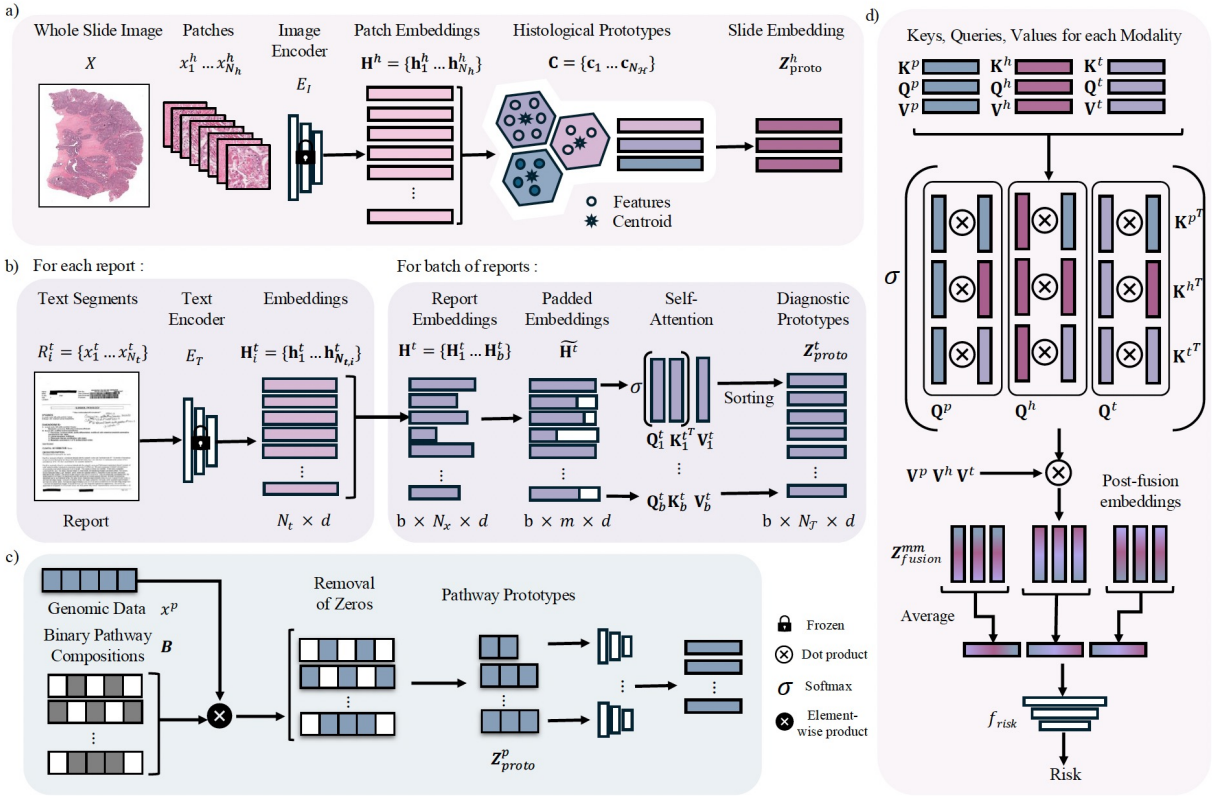
- **Usefulness** (eg, efficiency gains)
- **Interpretability**
- **Compute resources**
  - Bring-your-**compute-to-data** model (adequate for **data lakes**)
  - Bring-your-**data-to-compute** model (for **clinical use**)
  - **Federated Learning** → Learn locally, merge globally; needs local compute resources

Multimodal AI is the Future

Multimodal AI is the Future



PS3: Predicting Survival from 3 Modalities





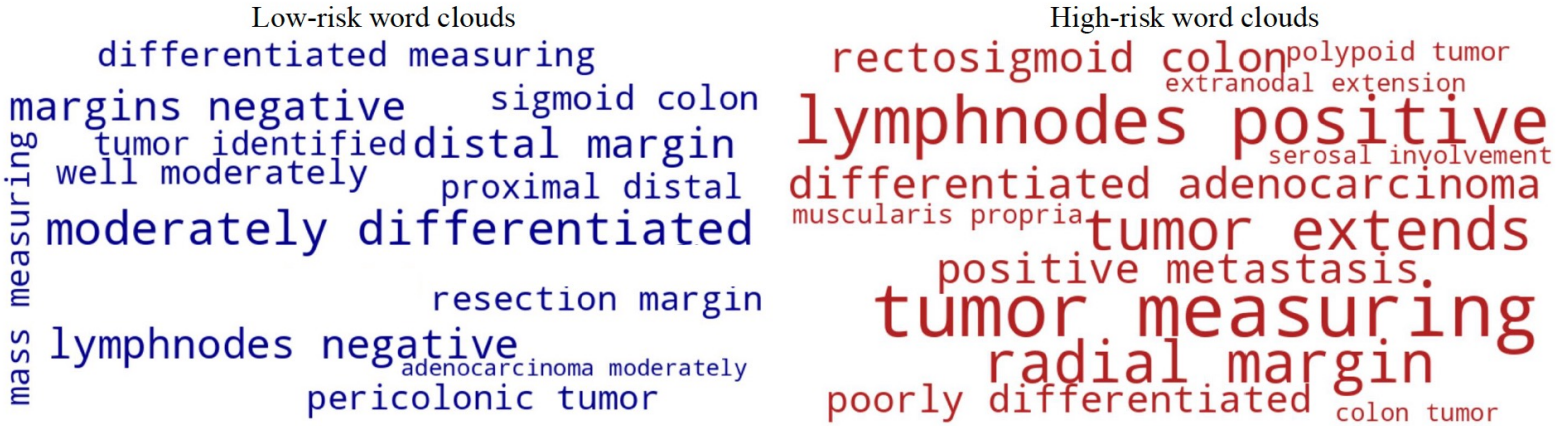
Manahil Raza

Raza *et al.*, ICCV'2025

	Model	BLCA	LUAD	KIRC	STAD	CRC	HNSC	Avg (↑)
	Clinical	0.557 ± 0.062	0.494 ± 0.093	0.723 ± 0.044	0.583 ± 0.051	0.496 ± 0.099	0.516 ± 0.090	0.561
Gene	Gene exp [20]	0.656 ± 0.047	0.508 ± 0.064	0.764 ± 0.042	0.578 ± 0.080	0.678 ± 0.069	0.595 ± 0.076	0.630
Gene	$PS3_p$	0.643 ± 0.062	0.578 ± 0.068	0.765 ± 0.040	0.614 ± 0.059	0.710 ± 0.063	0.601 ± 0.060	0.652
Text	Text ABMIL [18]	0.522 ± 0.069	0.560 ± 0.053	0.598 ± 0.079	0.594 ± 0.067	0.772 ± 0.137	0.507 ± 0.067	0.592
Text	$PS3_t$	0.629 ± 0.065	0.536 ± 0.087	0.623 ± 0.075	0.548 ± 0.078	0.805 ± 0.130	0.550 ± 0.080	0.615
Histology	CLAM [36]	0.562 ± 0.100	0.606 ± 0.104	0.684 ± 0.055	0.510 ± 0.078	0.680 ± 0.127	0.560 ± 0.075	0.600
Histology	TransMIL [48]	0.585 ± 0.049	0.594 ± 0.096	0.736 ± 0.085	0.558 ± 0.035	0.671 ± 0.120	0.594 ± 0.070	0.623
Histology	RRTMIL [57]	0.550 ± 0.065	0.557 ± 0.091	0.704 ± 0.128	0.603 ± 0.088	0.575 ± 0.035	0.556 ± 0.056	0.591
Histology	$PS3_{WSI}$	0.539 ± 0.033	0.597 ± 0.071	0.759 ± 0.102	0.542 ± 0.085	0.586 ± 0.197	0.502 ± 0.053	0.588
Multimodal	SurvivMIL [40]	0.484 ± 0.050	0.568 ± 0.048	0.654 ± 0.101	0.492 ± 0.068	0.663 ± 0.057	0.552 ± 0.086	0.569
Multimodal	SurvPath [20]	0.613 ± 0.036	0.567 ± 0.055	0.761 ± 0.054	0.608 ± 0.048	0.640 ± 0.054	0.536 ± 0.055	0.621
Multimodal	MOTCat [67]	0.636 ± 0.057	0.533 ± 0.039	0.766 ± 0.049	0.553 ± 0.082	0.677 ± 0.067	0.586 ± 0.044	0.625
Multimodal	MCAT [5]	0.636 ± 0.068	0.512 ± 0.040	0.762 ± 0.030	0.572 ± 0.074	0.661 ± 0.101	0.578 ± 0.064	0.620
Multimodal	CMTA [73]	0.637 ± 0.067	0.565 ± 0.045	0.741 ± 0.044	0.578 ± 0.065	0.659 ± 0.058	0.579 ± 0.030	0.627
Multimodal	MMP_{Trans} [51]	0.641 ± 0.053	0.606 ± 0.068	**0.776** ± 0.059	0.639 ± 0.063	0.689 ± 0.078	0.566 ± 0.075	0.653
Multimodal	MMP_{OT} [51]	0.645 ± 0.030	0.617 ± 0.058	0.774 ± 0.026	**0.660** ± 0.073	0.689 ± 0.074	0.545 ± 0.041	0.655
	PS3	**0.684** ± 0.026	**0.640** ± 0.093	**0.776** ± 0.061	0.638 ± 0.045	**0.826** ± 0.101	**0.627** ± 0.066	**0.699**

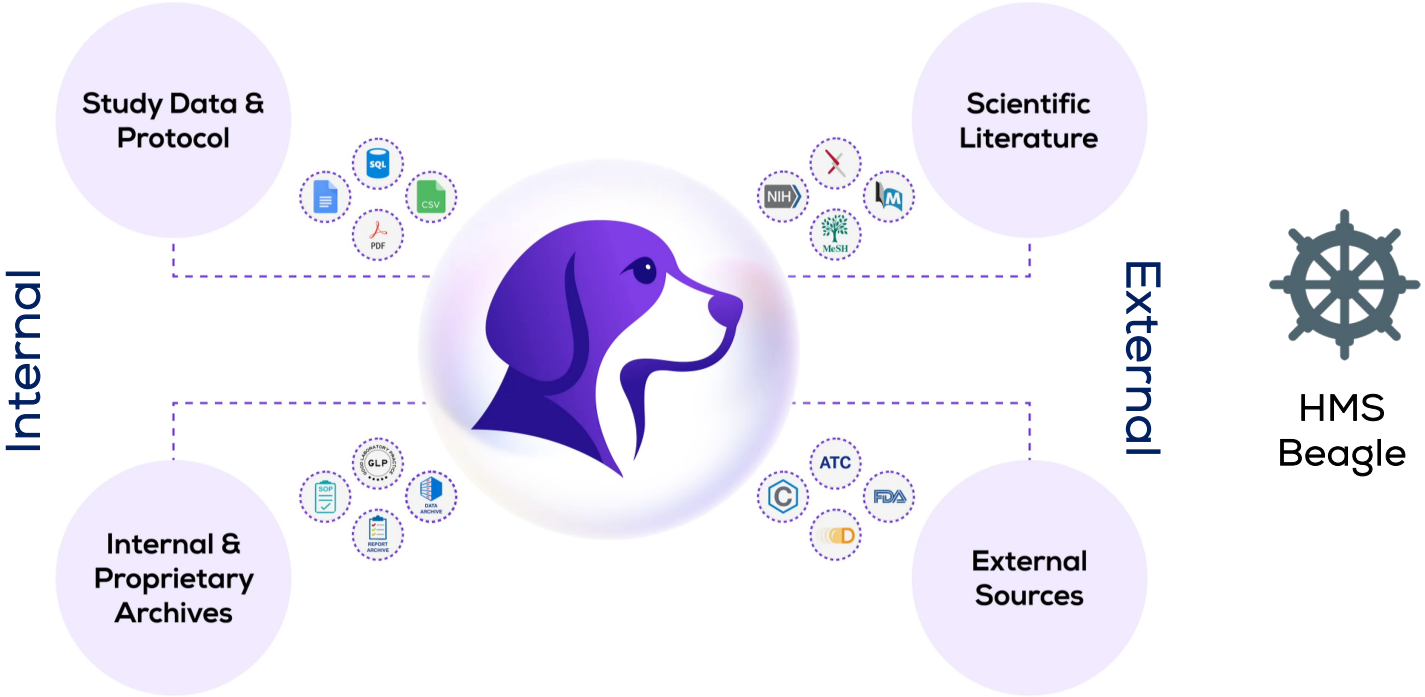
Raza *et al.*, ICCV'2025

Word Clouds for High-Risk vs Low-Risk



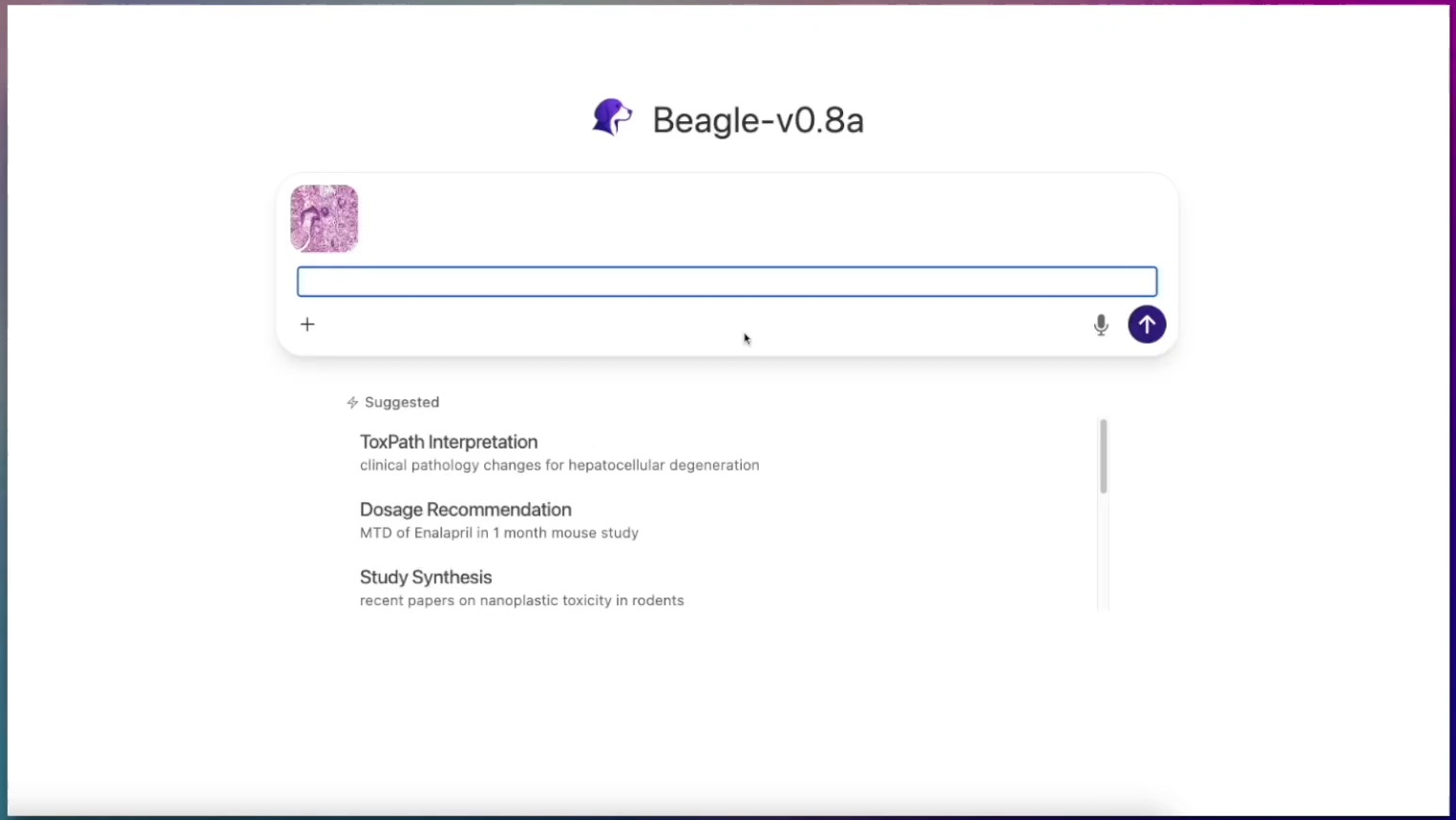
Two-phrase word clouds for high-risk group (red) and low-risk (blue) group for TCGA-CRC

Beagle: Agentic AI system for Tox Path



histofy.ai/beagle

What lesion do you see ?



Can you find images of similar lesions ?

Description: Numerous irregular, often angulated bile duct profiles embedded within dense fibrous stroma, associated with reactive fibroblasts.
Severity: Moderate (based on extent and disruption of normal architecture)
Artefacts/Uncertainty: No prominent artefacts; morphology typical for this lesion in rodents (general knowledge).

⚡ Immediate Actions
Correlate with clinical pathology (cholestasis, liver enzymes)
Review dosing and exposure history for potential causative agents (e.g., known biliary tract toxicants or test article on file)
Check background incidence in the relevant species/strain for context

🔄 What's Next
Step 2 of 2: Assess for associated lesions (e.g., cholestasis, hepatocellular changes)
Literature search for causality and background rates (if required)
Semi-quantitative grading and reporting for the pathology table

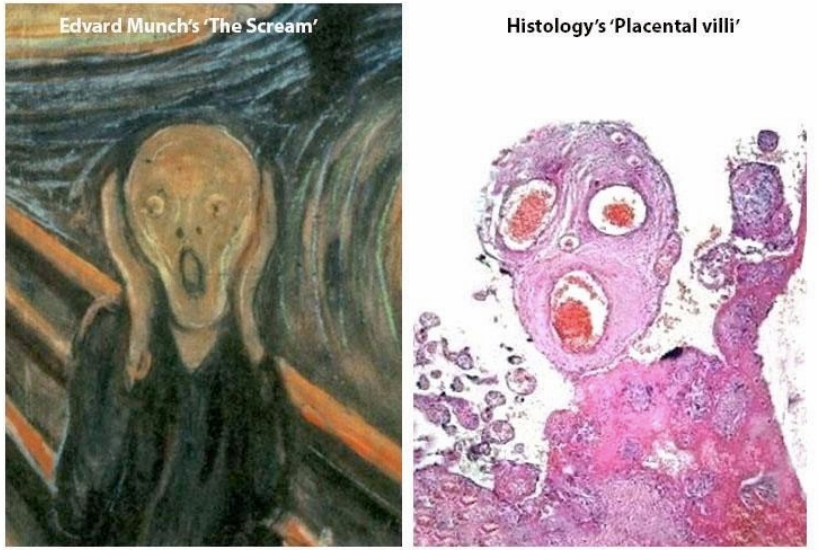
Definition (INHAND):
Cholangiofibrosis is characterised by irregular bile ductular profiles within abundant fibrous connective tissue, frequently extending into periportal regions, and typically with minimal-to-moderate inflammation.

References:
INHAND Liver Terminology [general knowledge]
Toxicologic Pathology Liver Lesion Atlas

Let me know if you wish to see published photomicrographs for comparison or require background incidence data.

1 Image Analysis

And that’s all, folks! (Part 1)



Source: I Heart Histo



https://warwick.ac.uk/TIA (photo taken at ECDP 2023, Budapest)

TIA Centre
Tissue Image Analytics

Computational Pathology: The Road Ahead Part II

Nasir Rajpoot
Professor of Computational Pathology
Wolfson Fellow, The Royal Society
Director, Tissue Image Analytics (TIA) Centre
University of Warwick, UK

Croucher ASI **AI for Biomedicine** (Fri 28 Nov 2025)

