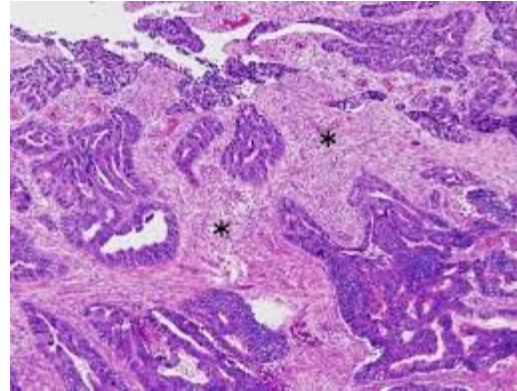


Clinical Context : Companion Test for Immunotherapy

Cost : 3 000 up to 20 000 euros every three weeks



Efficacy : Only a subgroup of patients can benefit + side effects

CRC
ColoRectal
Cancer
(Colon)

HCC
HepatoCellular
Carcinoma
(Liver)

Phase 2 clinical trial

High Chance of success so far
+ Patent France and US

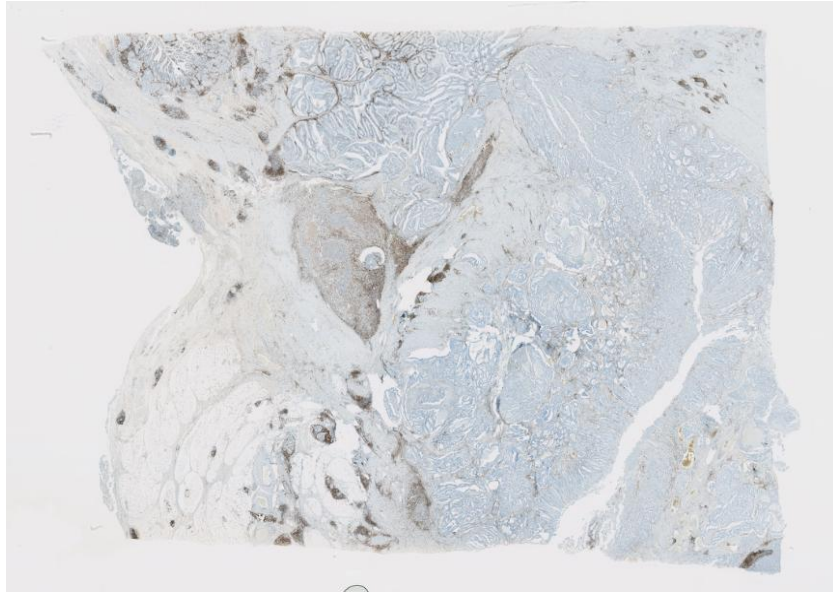
Our team :
AI-based tool for
Efficient Immuno

Multi-centric study

Published in Lancet Oncology 2023

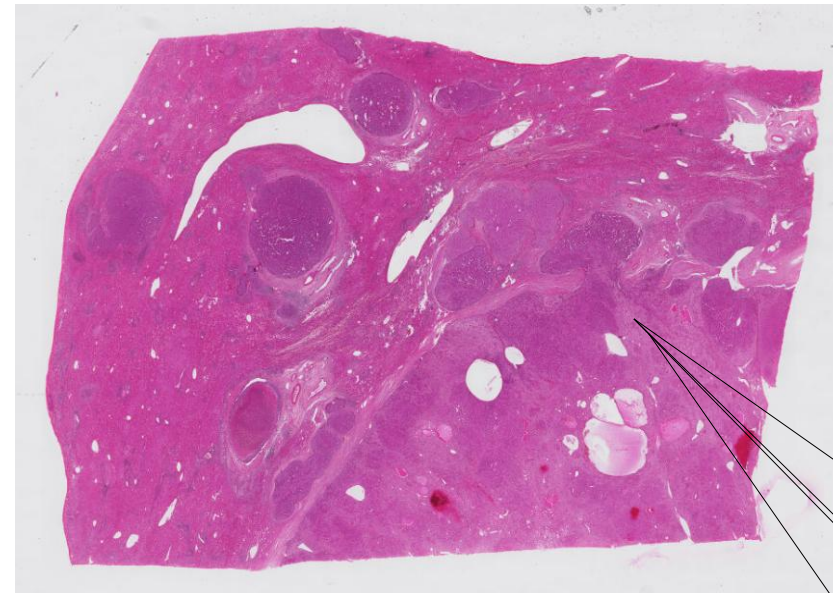
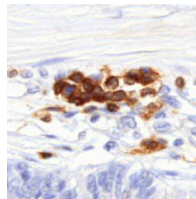
Context : the Whole Slide Images (WSI)

WSI : Whole Slide Image : digital version of a tissue specimen (x5, x20, x40)



Immunohistochemistry staining
70k pixels x 50k pixels, 9.41 GB uncompressed

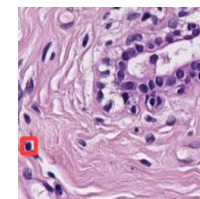
IHC



Stained with hematoxylin and eosin (H&E)
60k pixels x 40k pixels, 6.85 GB uncompressed

H&E

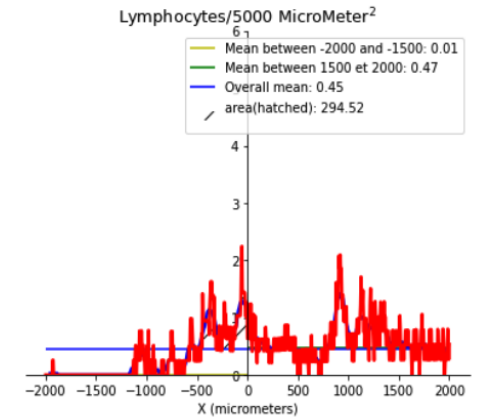
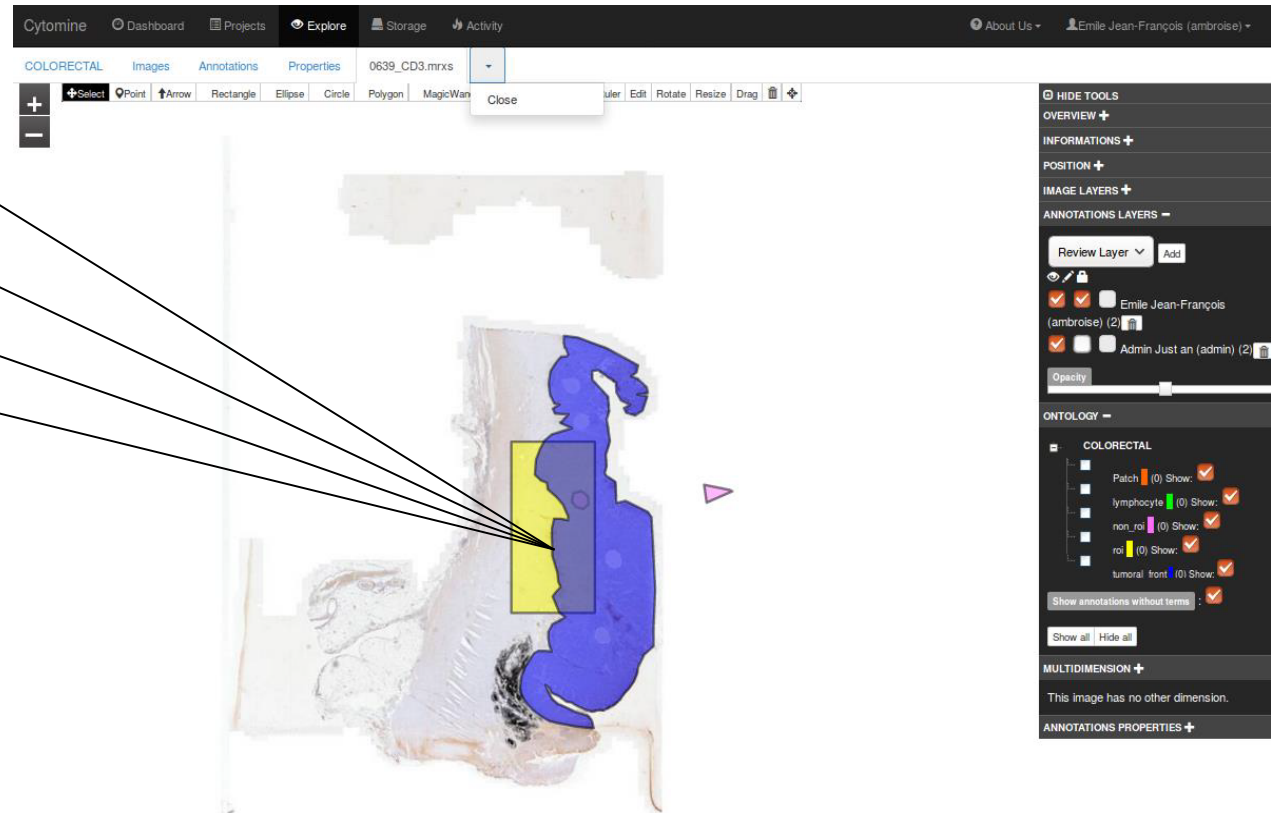
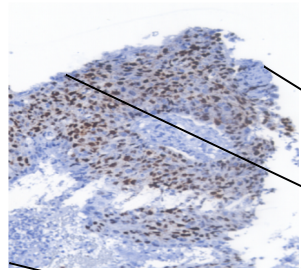
256
pixels



Translational project : a companion test

Lymphoid infiltration assessment in CRC

POCHI Project - Collaboration avec PUPH JF. Emile – Hôpital Ambroise Paré.



**ColoRectal Cancer
CRC**

IHC Coloration

Phase 2 clinical trial

Semi-automatic (IVD
Certification ?)



Translational projects : the TULIS test



Digestive and Liver Disease

Available online 30 June 2021

In Press, Corrected Proof



Progress Report

Pembrolizumab with Capox Bevacizumab in patients with microsatellite stable metastatic colorectal cancer and a high immune infiltrate: The FFCD 1703-POCHI trial

Claire Gallois ^a, Jean-François Emile ^b, Stefano Kim ^c, Carole Monterymard ^d, Marine Gilibert ^e, Jérémie Bez ^d, Astrid Lièvre ^f, Laetitia Dahan ^g, Pierre Laurent-Puig ^h, Laurent Mineur ⁱ, Romain Coriat ^j, Jean-Louis Legoux ^k, Vincent Hautefeuille ^l, Jean-Marc Phelip ^m, Thierry Lecomte ⁿ, Harry Sokol ^o, Claude Capron ^p, Violaine Randrian ^q, Come Lepage ^r, Nicolas Lomenie ^s, Camille Kurtz ^s, Julien Taieb ^a, David Tougeron ^{q, r, s}

^a Service de Gastroentérologie et d'Oncologie Digestive, Hôpital Européen George Pompidou, Université de Paris, AP-HP, Paris, France

^b Service d'Anatomie et Cytologie Pathologique, Hôpital Ambroise Paré, AP-HP, Paris, France

^c Service d'Oncologie Médicale, CHRU Jean Minjoz, Besançon, France

^d FFCD EPICAD INSERM LNC-UMR 1231, Université Bourgogne Franche-Comté, Dijon, France

^e Service d'Oncologie Médicale, Institut Paoli-Calmettes, Marseille, France

^f Service des Maladies de l'Appareil Digestif, CHU Pontchaillou, Université de Rennes 1, INSERM U1242, Rennes, France

^g Service d'Oncologie Digestive, AP-HM, Hôpital La Timone, Aix-Marseille Université, Marseille, France

^h INSERM U1138, Centre de Recherche des Cordeliers, Université Paris, Paris, France

10-15% MSI

So far 35 patients MSS treated.

Positive ++ results

Room for improvement :

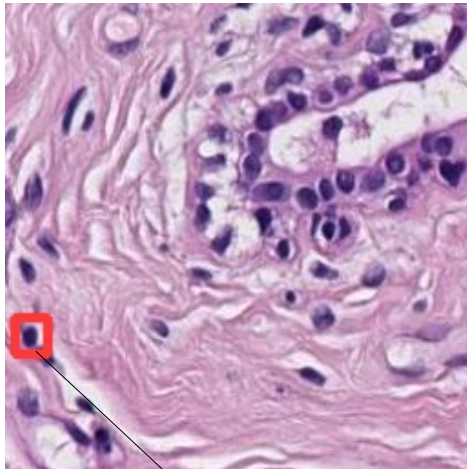
- H&E based test (Amine MARZOUKI)
- Tumoral Area detection (Zhuxian GUO)
- Gene signature prediction (Qinghe ZENG)
- Foundation Models (Yanis KOUADRI)

Translational projects : can we skip IHC ?

Translational projects : can we skip IHC ?

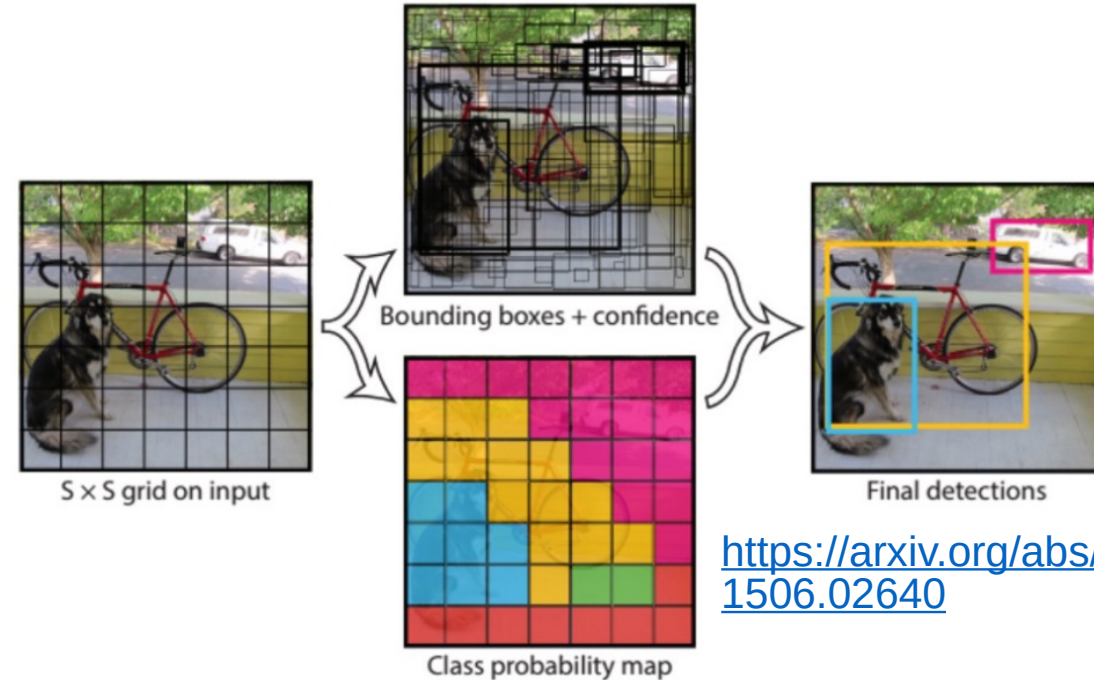
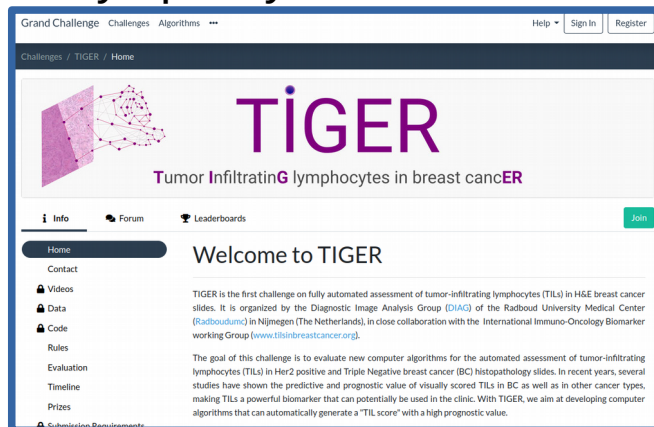


PRT-K project (currently ARC project extension) : Artificial intelligence to estimate the prognostic of colorectal cancer (CRC) in adjuvant setting using hematoxylin eosin safran histological slides



YOLO Architecture
←
You Only Look Once
For **object detection**

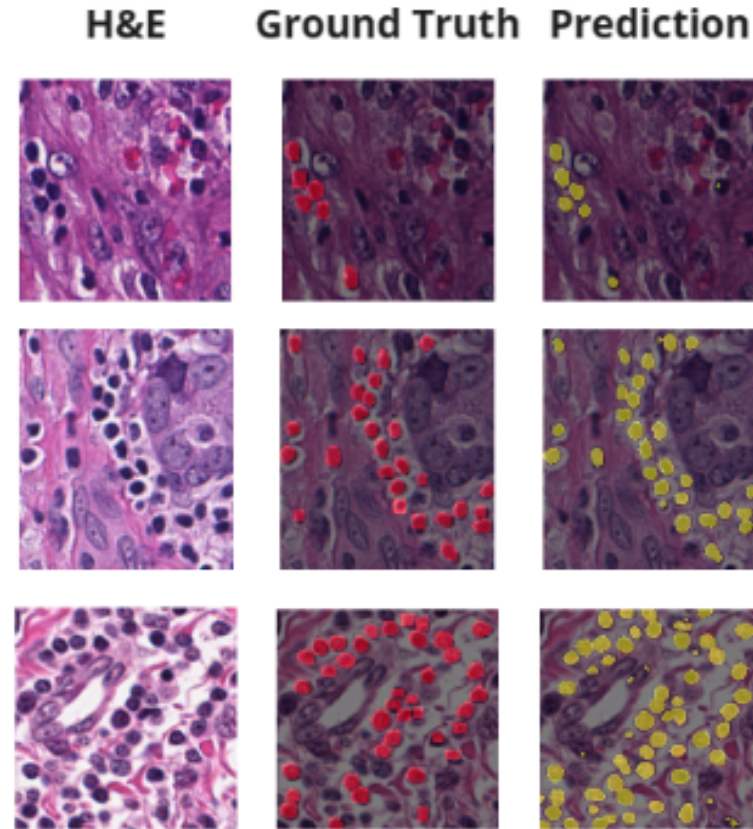
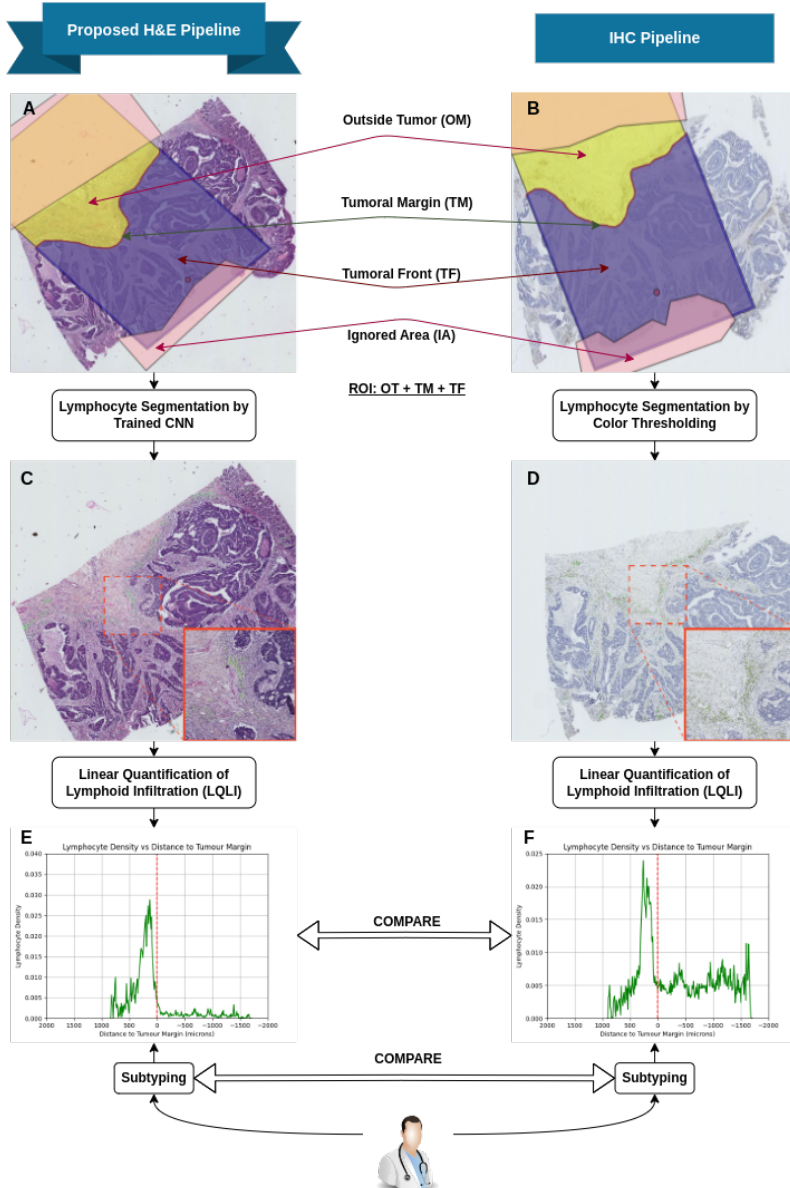
Fine tuned for lymphocyte detection



<https://arxiv.org/abs/1506.02640>



Translational projects : can we skip IHC ?



NuCLS dataset

Translational project : can we skip IHC ?

Some
Issues

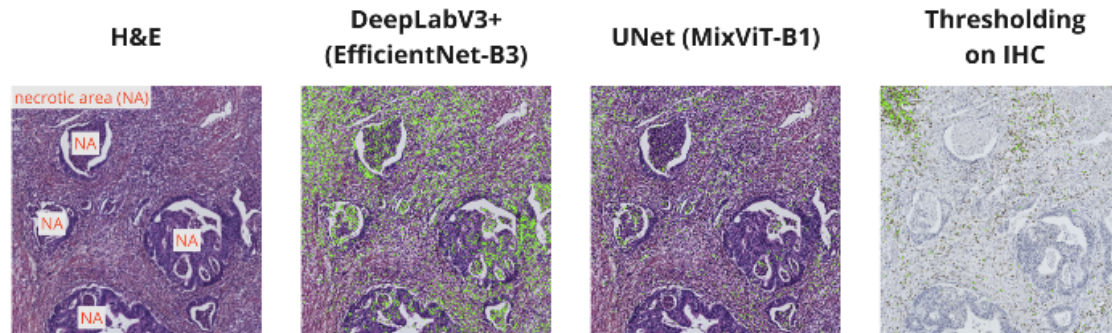
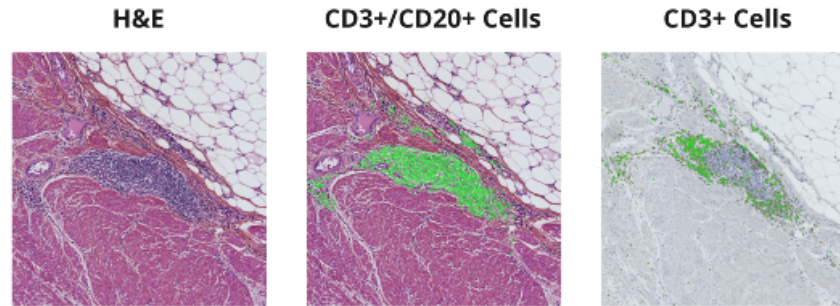


Fig. 4. Tumor cell in necrotic areas within large tumor glands and lymphocytes appear similar. Using a contextual aware neural network, a U-Net architecture with frozen Mix Vision Transformer encoder (UNet (MixViT-B1)), has better performance in distinguishing necrotic cells and lymphocytes.

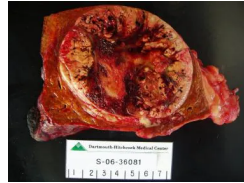
From MICCAI'24 Conference
Medical Image Computing and
Computer-Assisted Intervention

Oct. 2024

Translational project : can we skip genomic analysis based on H&E WSI ?

Translational project : can we skip genomic analysis based on H&E WSI ?

Liver Cancer (HCC) but same kind of data and challenges



Artificial intelligence based pathology as a biomarker of sensitivity to atezolizumab-bevacizumab in patients with hepatocellular carcinoma: a multicentric, retrospective study

Lancet Oncology
Nov. 2023

| | CXCL9 | STAT1 | CXCL10 | IDO1 | CD8A | HLA-DRA | IFNG | CD274 (PD-L1) | LAG3 | CCL2 | CCL4 | GZMK | HLA-DMA | HLA-DMB | HLA-DOA | HLA-DOB | ICOS | IRF1 | CCL5 | CD27 | CXCR6 | CCR5 | CXCL11 | GZMA | PRF1 | CD276 | PDCD1LG2 | TIGIT | |
|--|--------|--------|--------|--------|--------|---------|--------|---------------|--------|--------|--------|--------|---------|---------|---------|---------|--------|--------|--------|--------|--------|--------|--------|--------|------|--------|----------|--------|--|
| 6-Gene Interferon Gamma p(ORR) = 0.05, p(OS) = 0.009 | Orange | Orange | Orange | Orange | Orange | Orange | Orange | | | | | | | | | | | | | | | | | | | | | | |
| Gajewski 13-Gene Inflammatory p(ORR) = 0.04, p(OS) = 0.05 | Orange | | Orange | | Orange | | | | | Orange | Orange | Orange | Orange | Orange | Orange | Orange | Orange | Orange | | | | | | | | | | | |
| Inflammatory p(ORR) = 0.05, p(OS) = 0.01 | | Orange | | | Orange | | | Orange | Orange | | | | | | | | | | | | | | | | | | | | |
| Interferon Gamma Biology p(ORR) = 0.07, p(OS) = 0.008 | Orange | Orange | | Orange | | | | | | | | | | | | | | | Orange | Orange | | | | | | | | | |
| Ribas 10-Gene Interferon Gamma p(ORR) = 0.07, p(OS) = 0.02 | Orange | Orange | Orange | Orange | Orange | Orange | | | | | | | | | | | | | | | Orange | Orange | Orange | Orange | | | | | |
| T-cell Exhaustion p(ORR) = 0.03, p(OS) = 0.04 | | | | | Orange | | | Orange | Orange | | | | | | | | | | | | | | | | | Orange | Orange | Orange | |

¹Sangro, Bruno, et al. "Association of inflammatory biomarkers with clinical outcomes in nivolumab-treated patients with advanced hepatocellular carcinoma." Journal of Hepatology 73.6 (2020): 1460-1469.

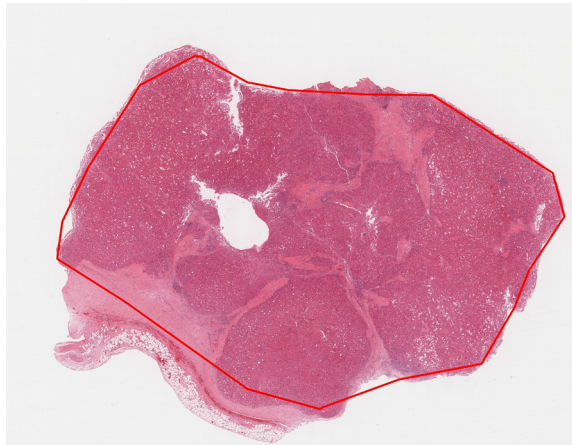


Image Data

Discovery series: TCGA (n=336 cases)

<https://portal.gdc.cancer.gov/>

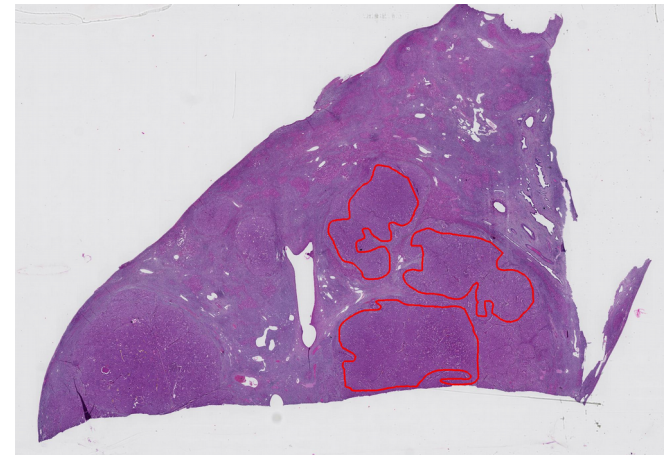
- Gene expression data: RNA sequencing
- WSIs: n=349
 - a) Scanner: Aperio scanner
 - b) Magnification (20X): $\sim 128 \times 128 \mu\text{m}^2$, $\sim 0.5 \mu\text{m}/\text{pixel}$
 - c) Staining: Hematein-eosin (H&E)



— Tumor annotation

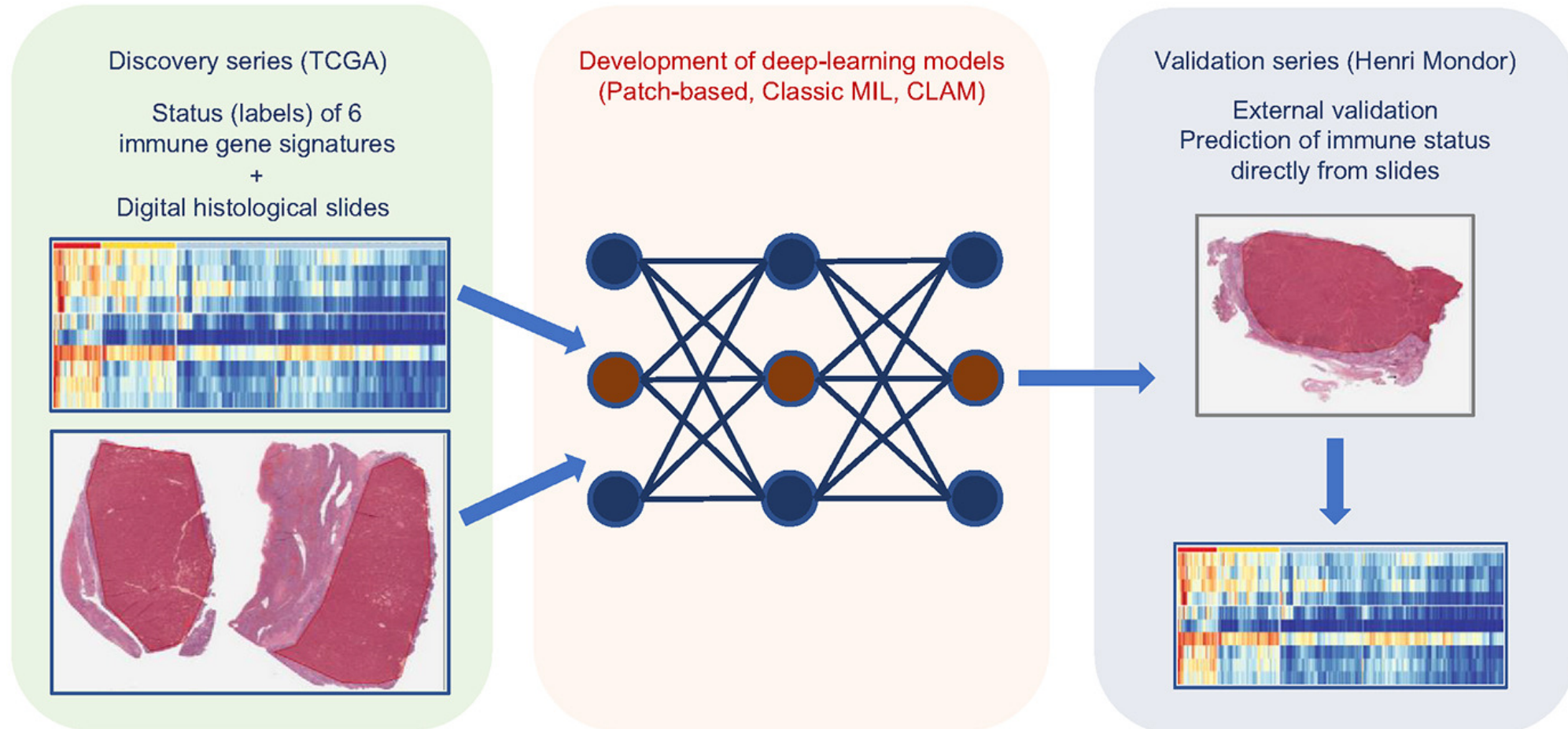
External validation series: Hospital Henri Mondor (n=139 cases)

- Gene expression data: Nanostring (Panel IO360)
- WSIs: n=139 resections + 7 pre-operative biopsies
 - a) Scanner: Hamamatsu
 - b) Magnification (20X): $\sim 115 \times 115 \mu\text{m}^2$, $\sim 0.45 \mu\text{m}/\text{pixel}$
 - c) Staining: Hematein-eosin-saffron (HES)



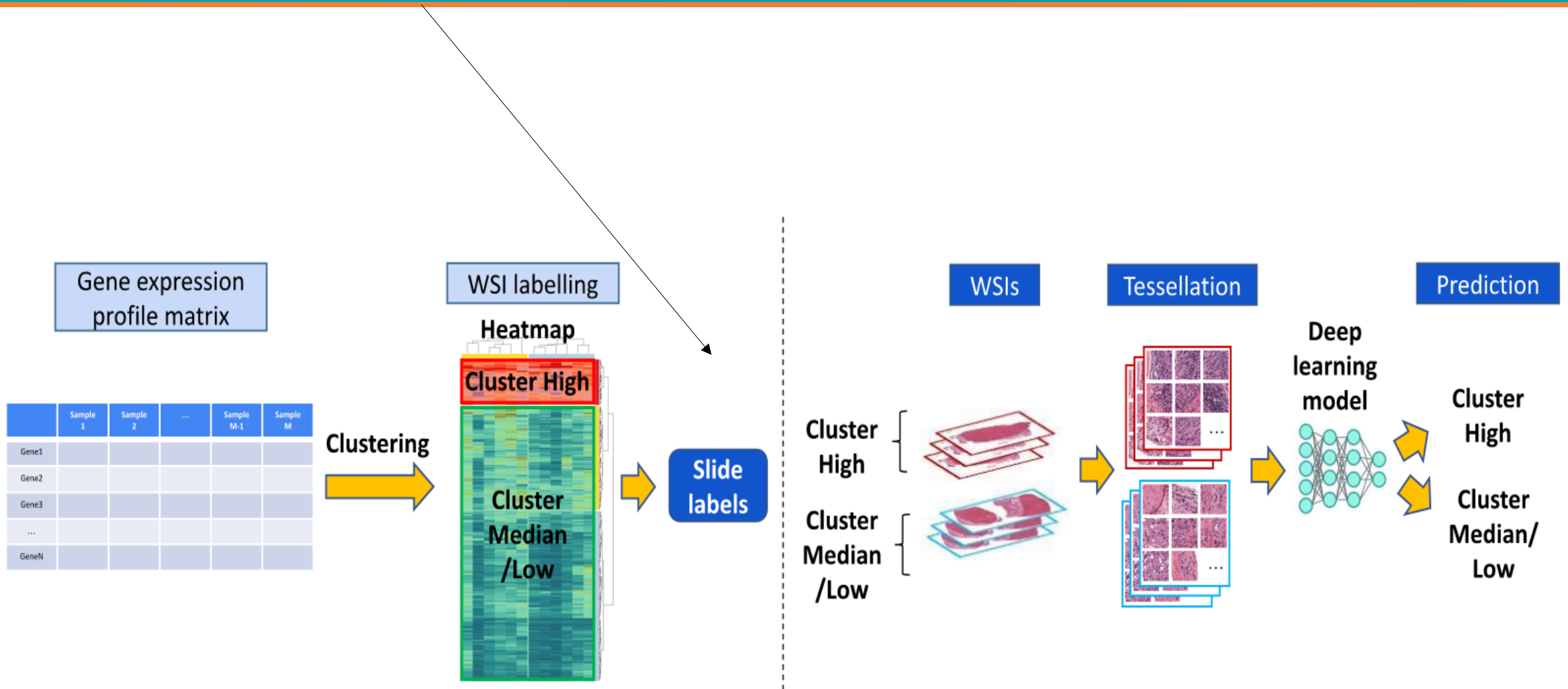
— Tumor annotation

AI methodology



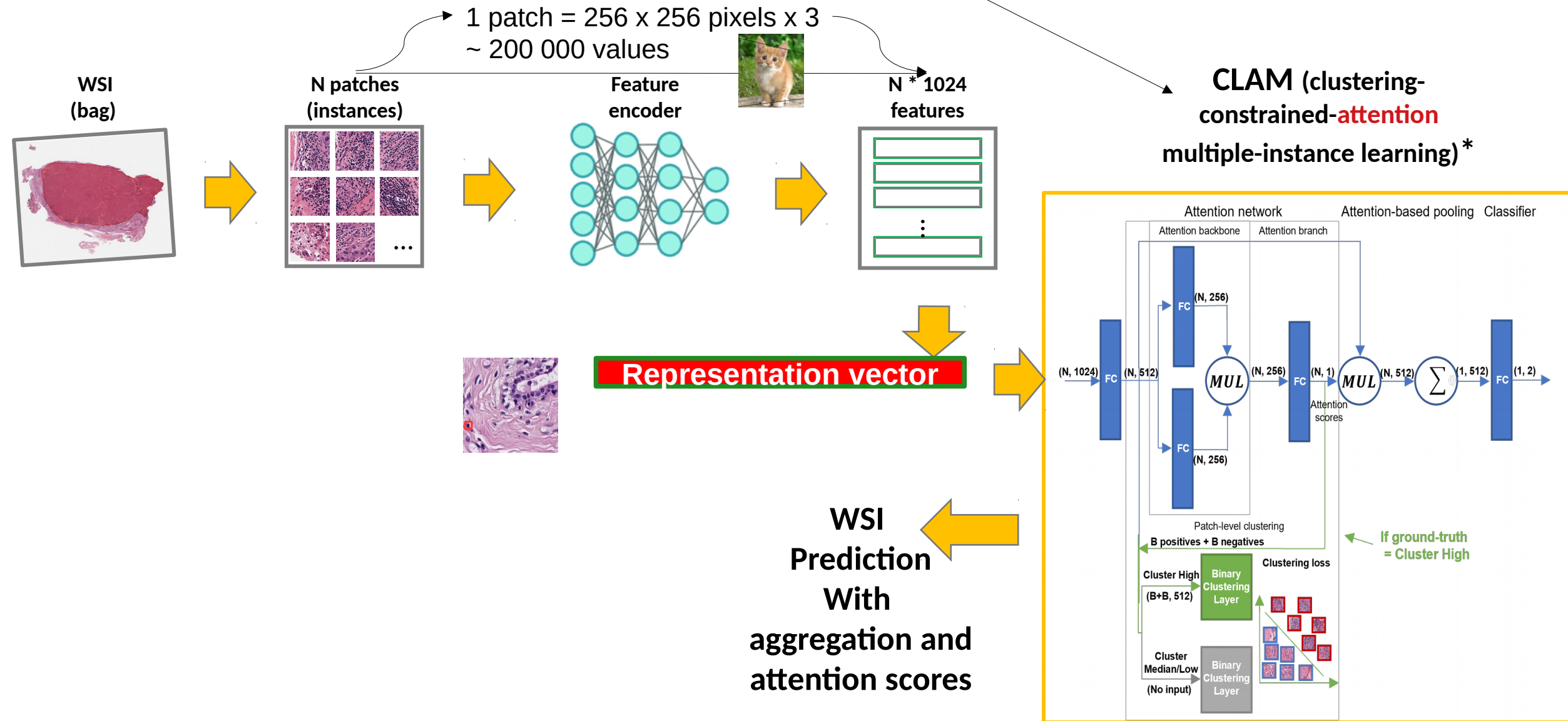
AI methodology for image-omics :

Weakly Supervised Learning with Attention (CLAM model)



AI methodology for image-omics :

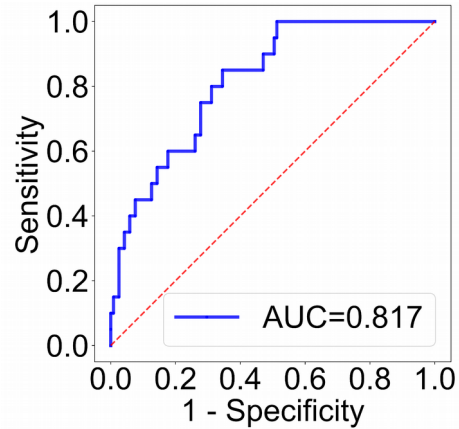
Weakly Supervised Learning with Attention (CLAM model)



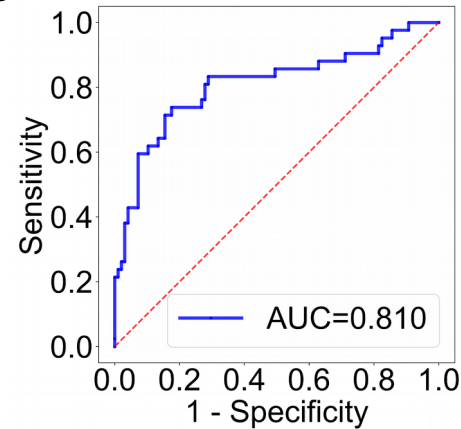
Validation data : Results (AUROC)

Best fold validation series (n=139 resections)

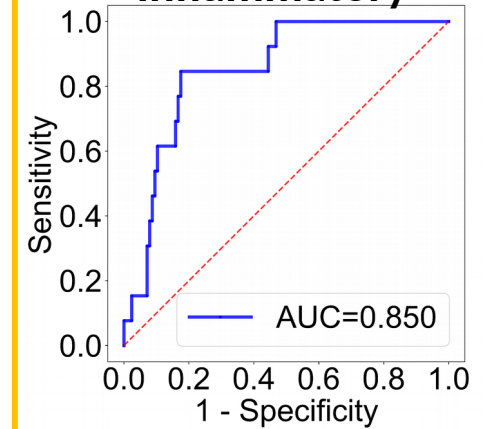
6-Gene Interferon Gamma



Gajewski 13-Gene Inflammatory

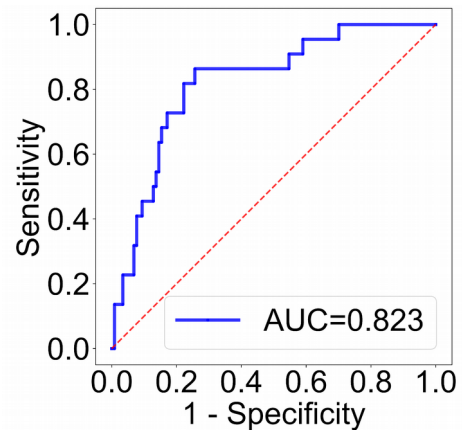


Inflammatory

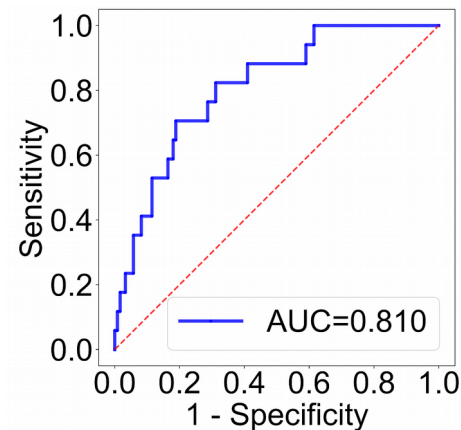


2nd
best

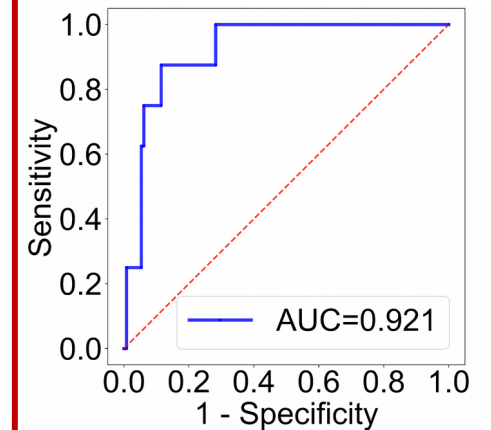
Interferon Gamma Biology



Ribas 10-Gene Interferon Gamma



T-cell Exhaustion

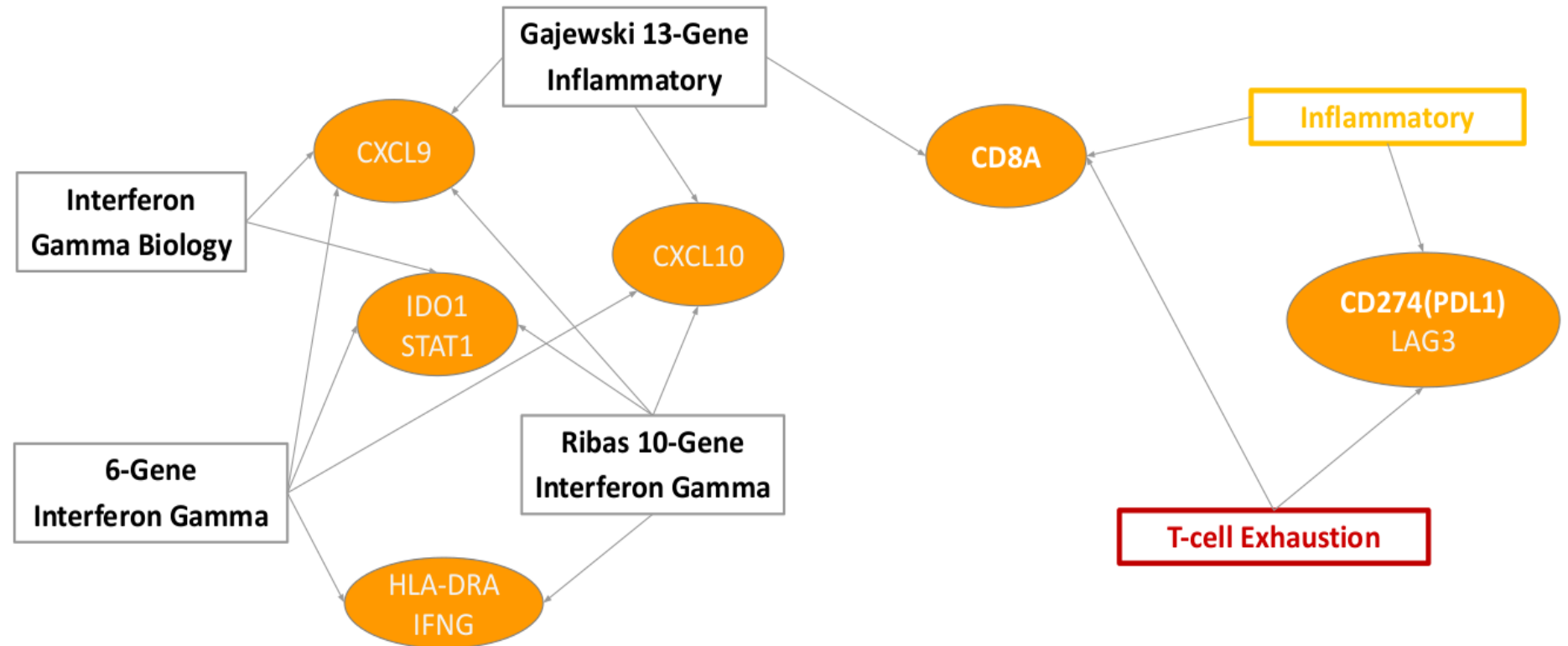


Best

Back to the gene signatures

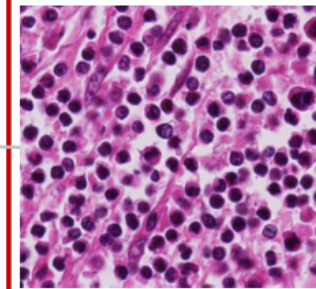
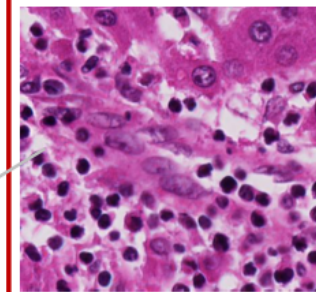
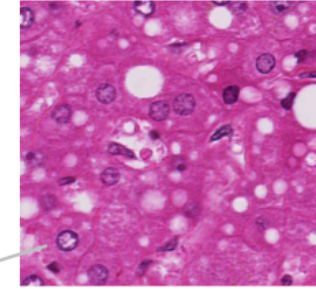
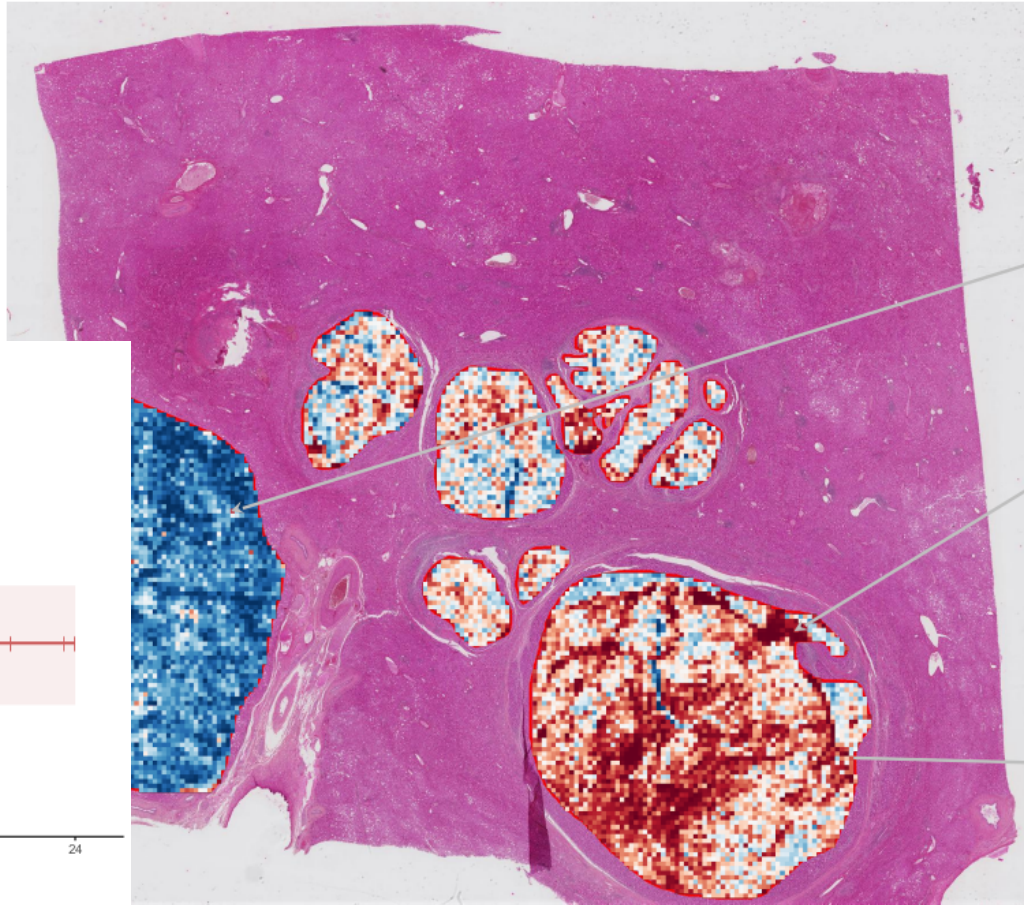
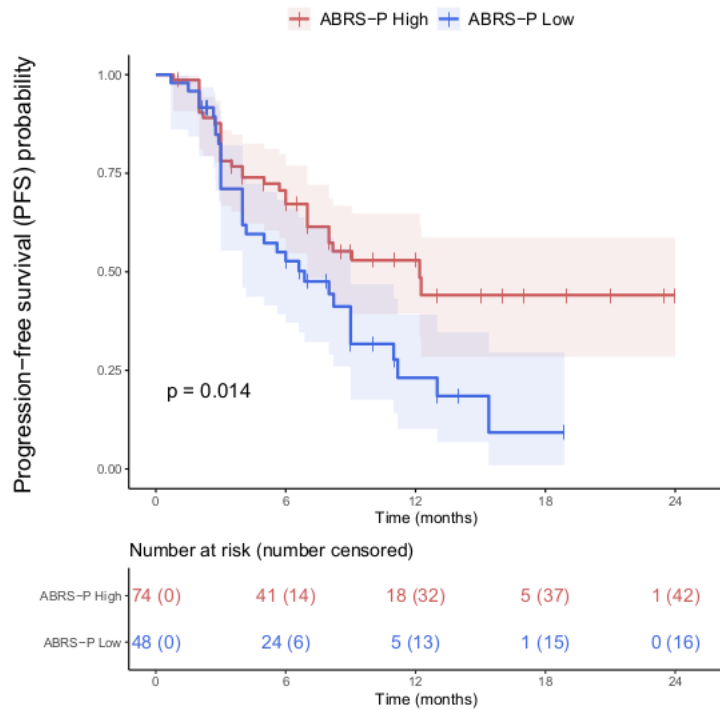
T-Cell Exhaustion : CD274/PD-L1, CD276, CD8A, LAG3, PDCD1LG2, TIGIT

Inflammatory : CD274/PD-L1, CD8A, LAG3, STAT1



Back to the gene signatures and the WSI

Towards new
AI-based
image-omics
biomarkers



In 3 signatures:

- 6G Interferon Gamma
- Interferon Gamma biology
- Ribas 10G Interferon Gamma

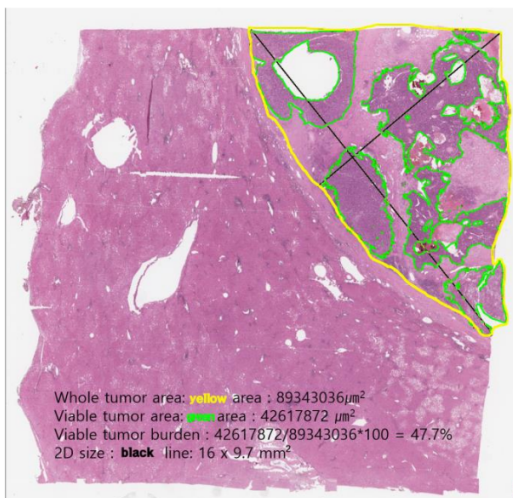
Enrichment in **lymphocytes, plasma cells, and neutrophils.**

Translational projects : can we skip manual annotation ?

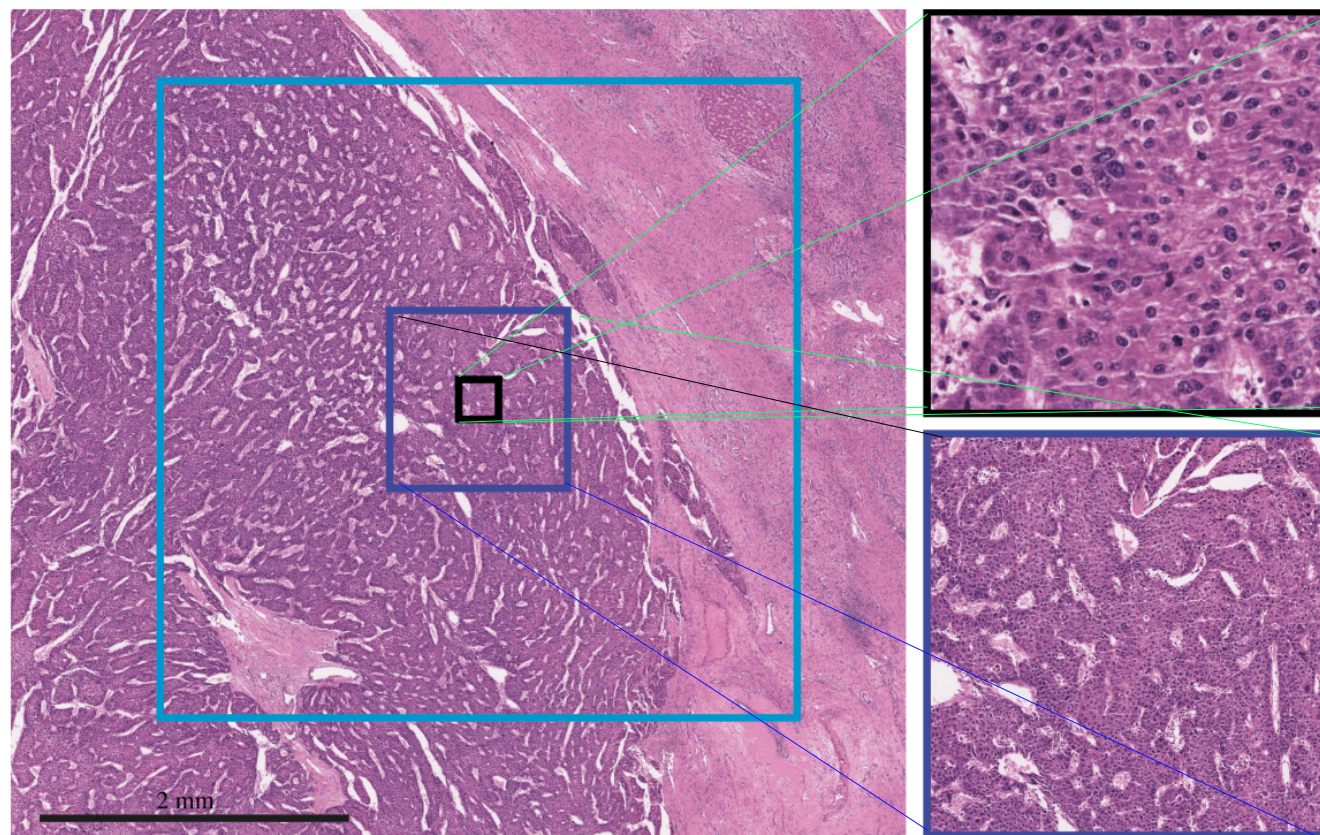
HCC neoplasm segmentation:

beyond the bag of patches, classification with context

| Zoom | Pixel length | Morphological changes |
|----------------------|--------------|--|
| 1-10 μm | 2-20 px | Aberrant and pleomorphic nuclei... |
| 10-100 μm | 20-200 px | Loss of relative cellular orientation... |
| 100 μm | 200 px | Aberrant tissue architecture... |
| 1000 μm | 2000 px | Pseudo-capsule... |



Liver Cancer Segmentation Challenge



Rüdiger Schmitz et al., “Multi-scale fully convolutional neural networks for histopathology image segmentation: From nuclear aberrations to the global tissue architecture,” *Medical Image Anal.*, vol. 70, pp. 101996, 2021.

<https://paip2019.grand-challenge.org/Dataset/>

Transformer-like architectures

Beyond CLAM (Attention mechanism),
ViT (for **V**ision **T**ransformer) and **self-attention** mechanism

BERT: Pre-training of Deep Bidirectional Transformers for Language Understanding

Jacob Devlin Ming-Wei Chang Kenton Lee Kristina Toutanova
Google AI Language
{jacobdevlin, mingweichang, kentonl, kristout}@google.com

Abstract

We introduce a new language representation model called **BERT**, which stands for **B**idirectional **E**ncoder **R**epresentations from **T**ransformers. Unlike recent language representation models (Peters et al., 2018a; Rad-

There are two existing strategies for applying pre-trained language representations to downstream tasks: *feature-based* and *fine-tuning*. The feature-based approach, such as ELMo (Peters et al., 2018a), uses task-specific architectures that include the pre-trained representations as addi-

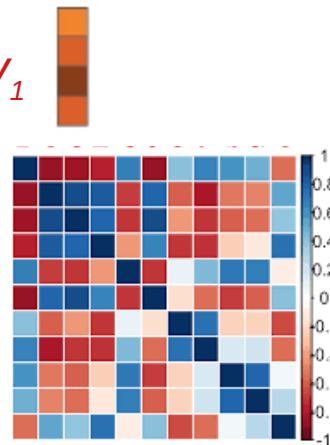
*“AI and medicine are working together to
 v_1 v_2 v_3 v_6
improve diagnosis and prognosis”.*
..... v_{11}

1. Embedding : CNN or else in a vector

Each word like “AI” becomes a vector v_1 and so on.

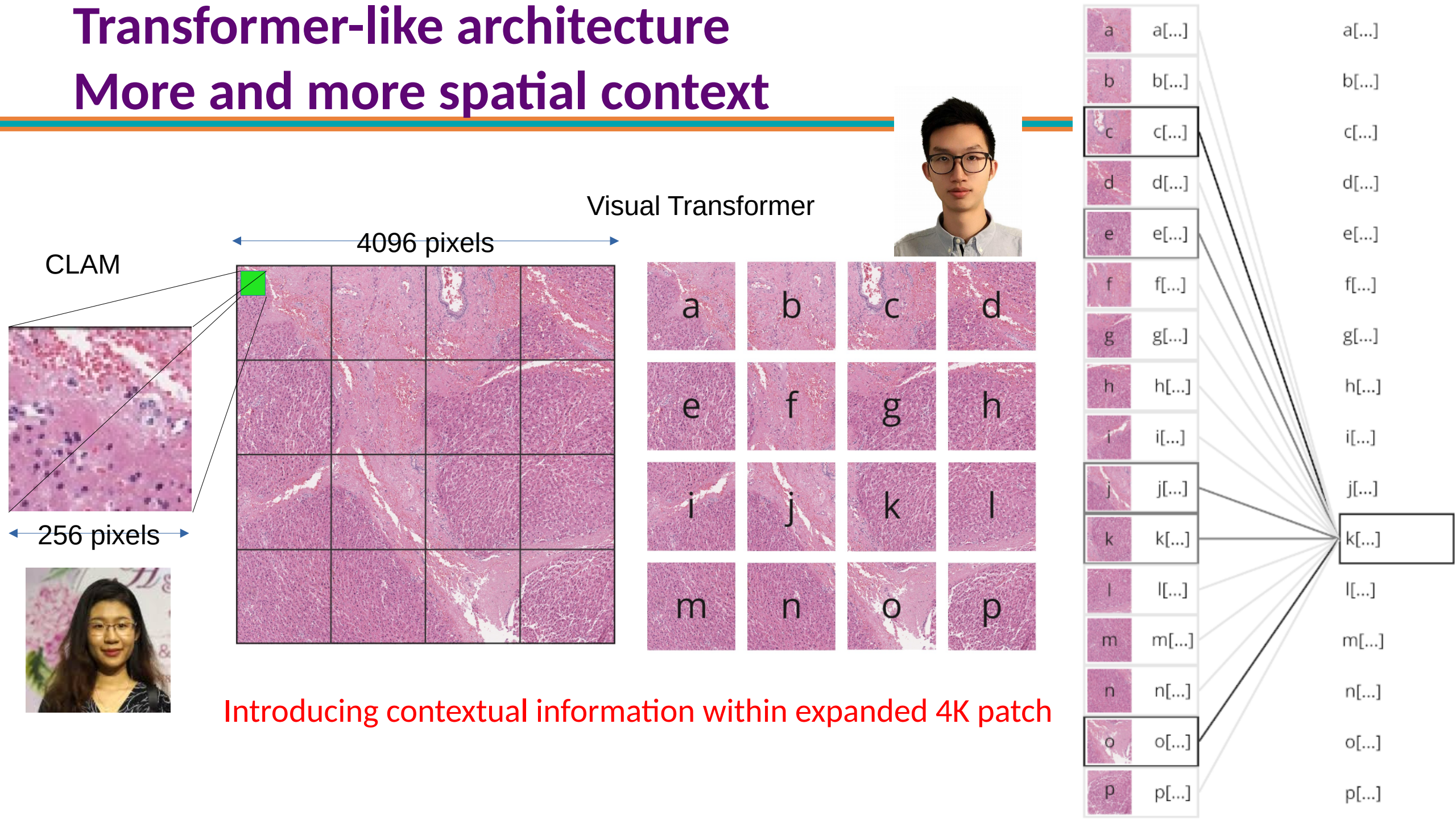
2. Then the Transformer learn dependencies and context in a matrix

v_1 and v_3 are related to v_6 and so on



Transformer-like architecture

More and more spatial context

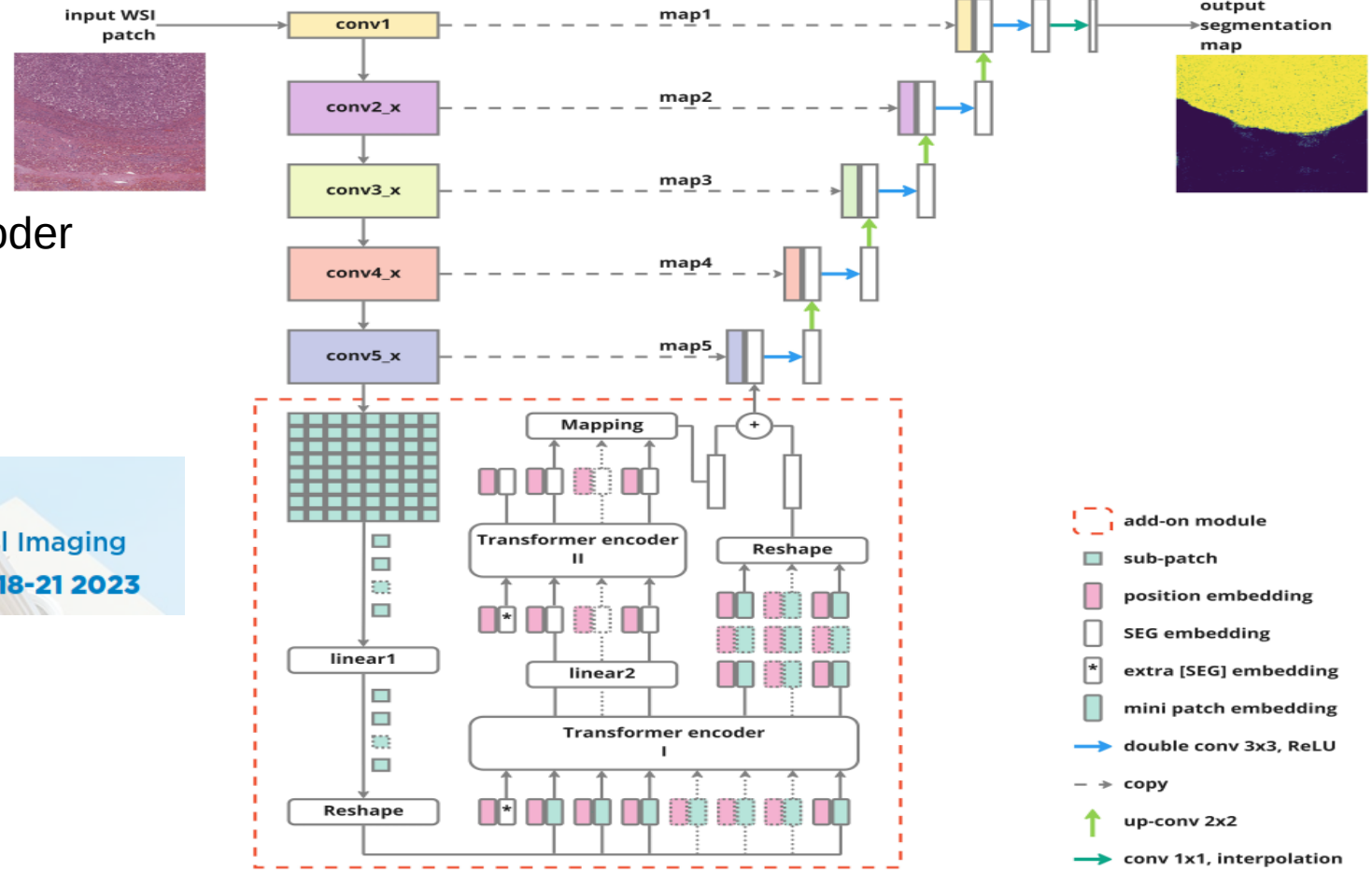


Transformer-like architecture

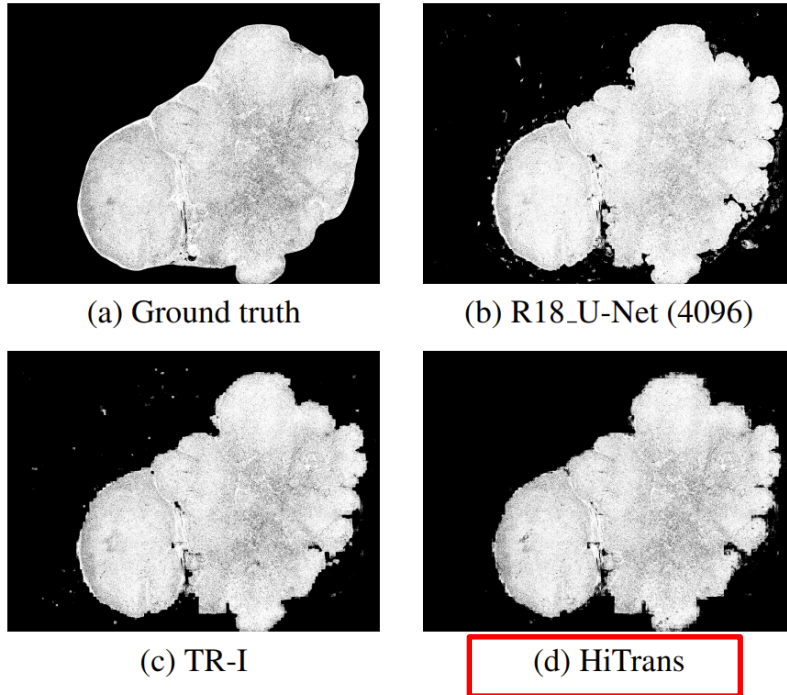
More and more spatial context

A new Architecture
HiTrans :

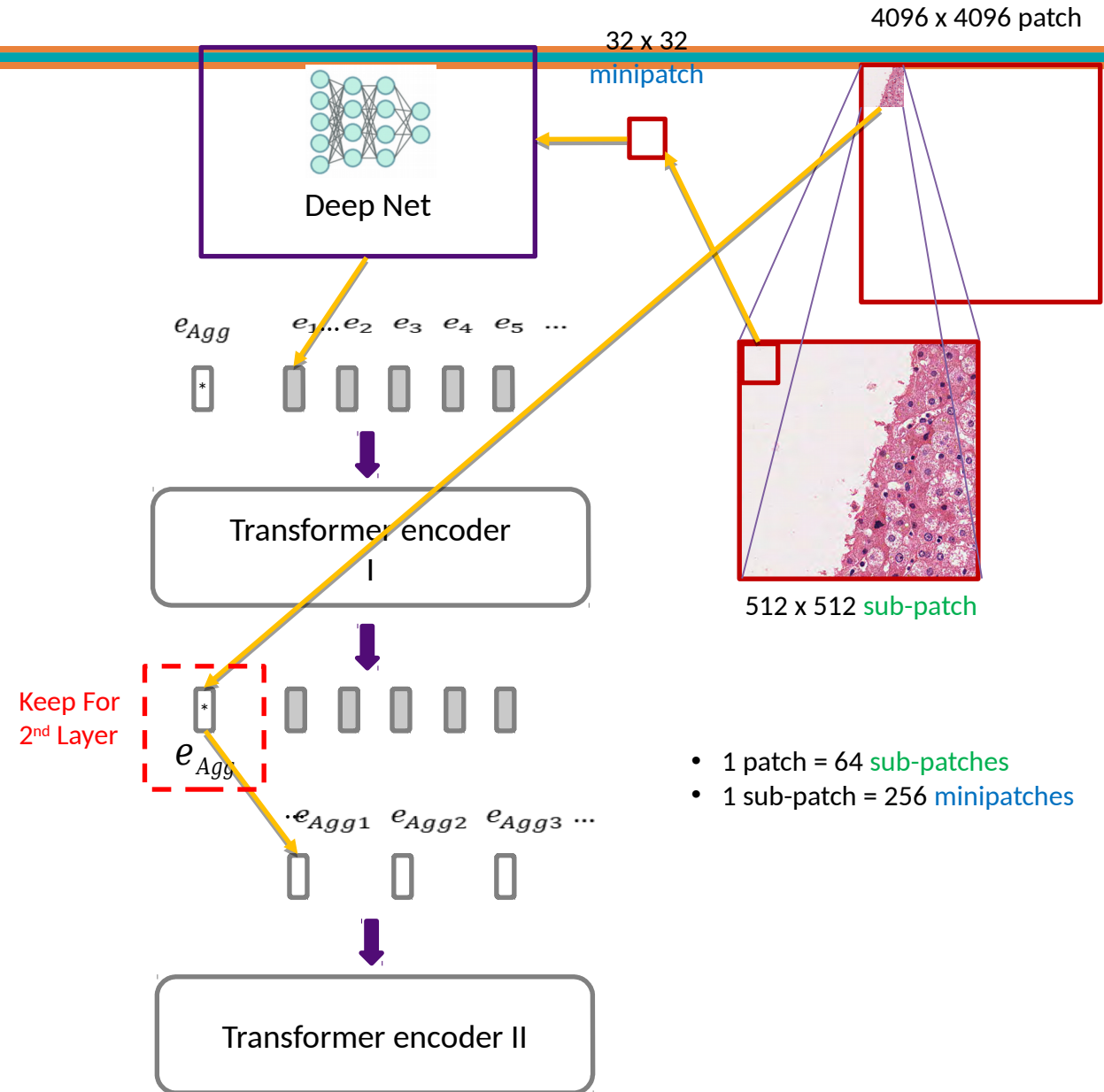
Hierarchy-based Transformer Encoder
for entire HCC neoplasm
segmentation



HiTrans: Hierarchical Transformer, a Context-aware framework



| Exp. | Method | Patch size | Avg. Jaccard |
|------|-----------|------------|---------------|
| 1 | R18_U-Net | 512 | 0.6609 |
| 2 | R18_U-Net | 4096 | 0.7202 |
| 3 | TR-I | 4096 | 0.7172 |
| 4 | HiTrans | 4096 | 0.7513 |



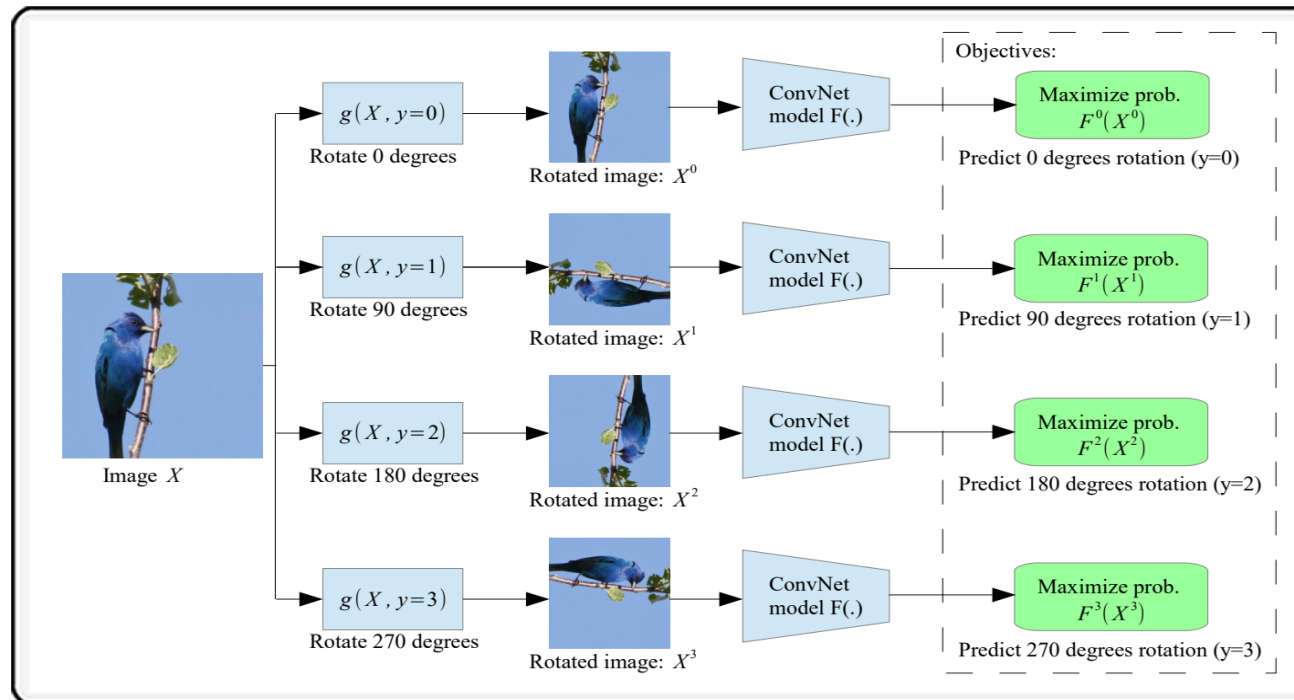
Translational projects : what is AI promise?

Automatic test for stratification on H&E WSI
CRC, HCC

What is AI promise ? New Foundation Models

Sparse annotations → **Self Supervised Learning (SSL)**
→ Learning better representations via pretext tasks

Representation vector



→ Fine-tuned for downstream tasks

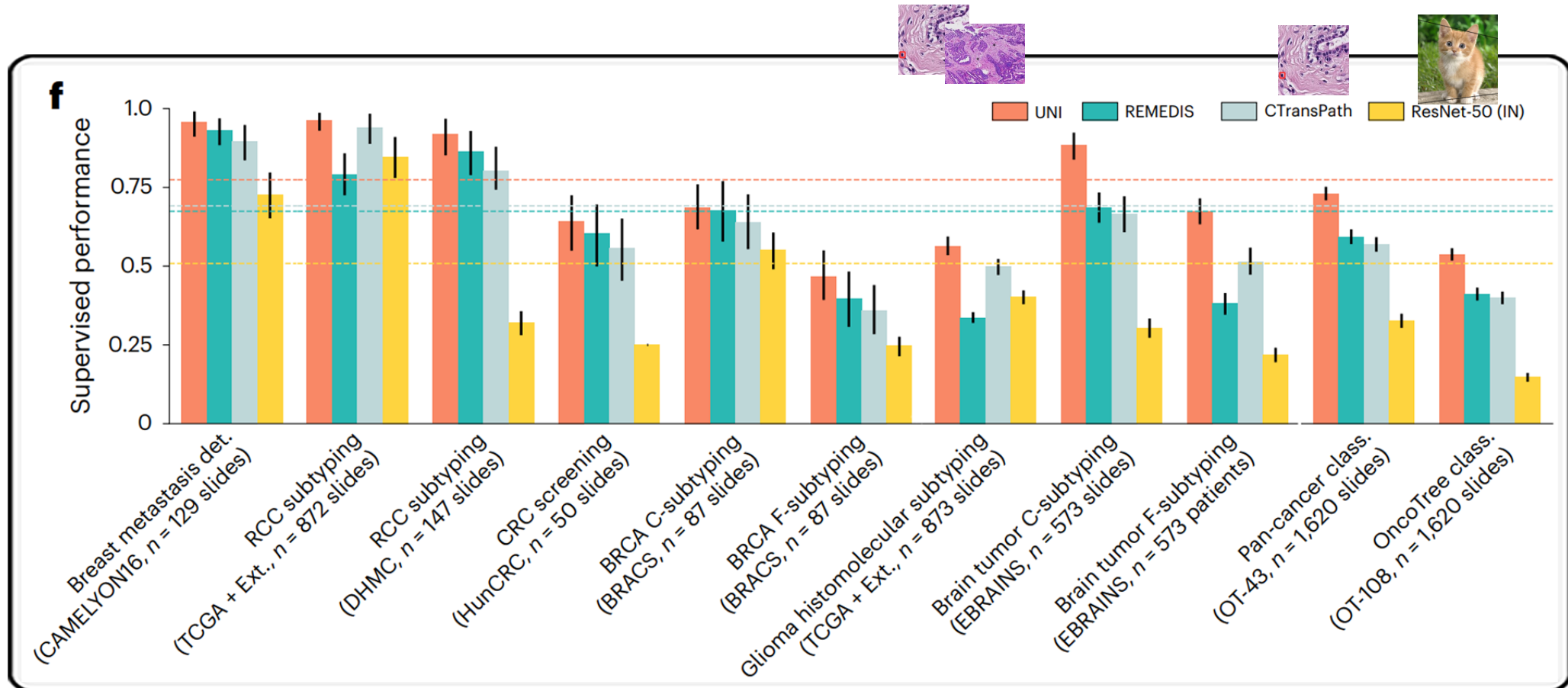
What is AI promise ? New Foundation Models

CTransPath

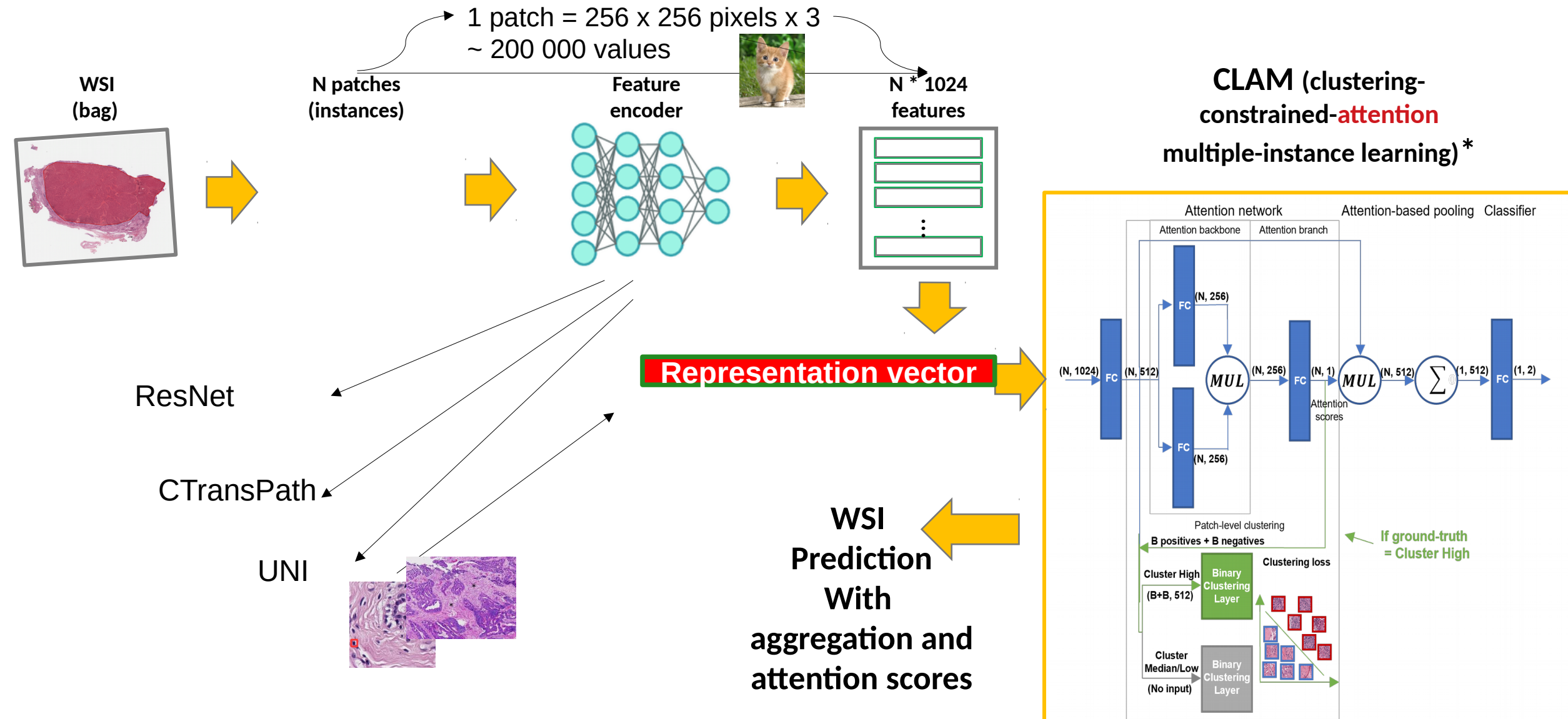
- Wang et al. 2022
- Trained on 32 000 WSIs
- CNN local and Transformer Global

UNI

- Chen et al. 2024
- Trained on more than 100 000 WSIs many organs and tissues
- SSL DINOv2 and Transformer



What is AI promise ? New Foundation Models

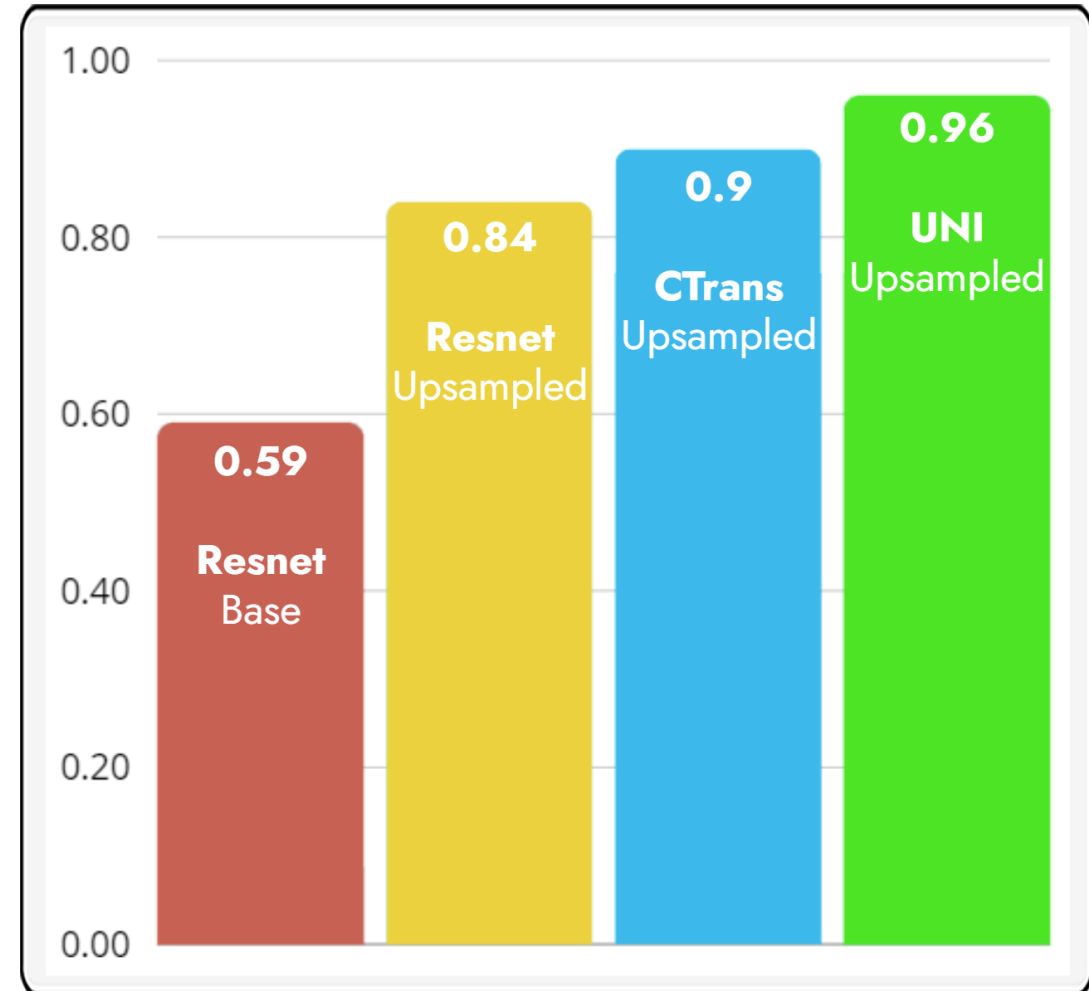


What is AI promise ? New Foundation Models

Back to ColoRectal Cancer

MSI/MSS prediction on H&E via UNI (+CLAM)

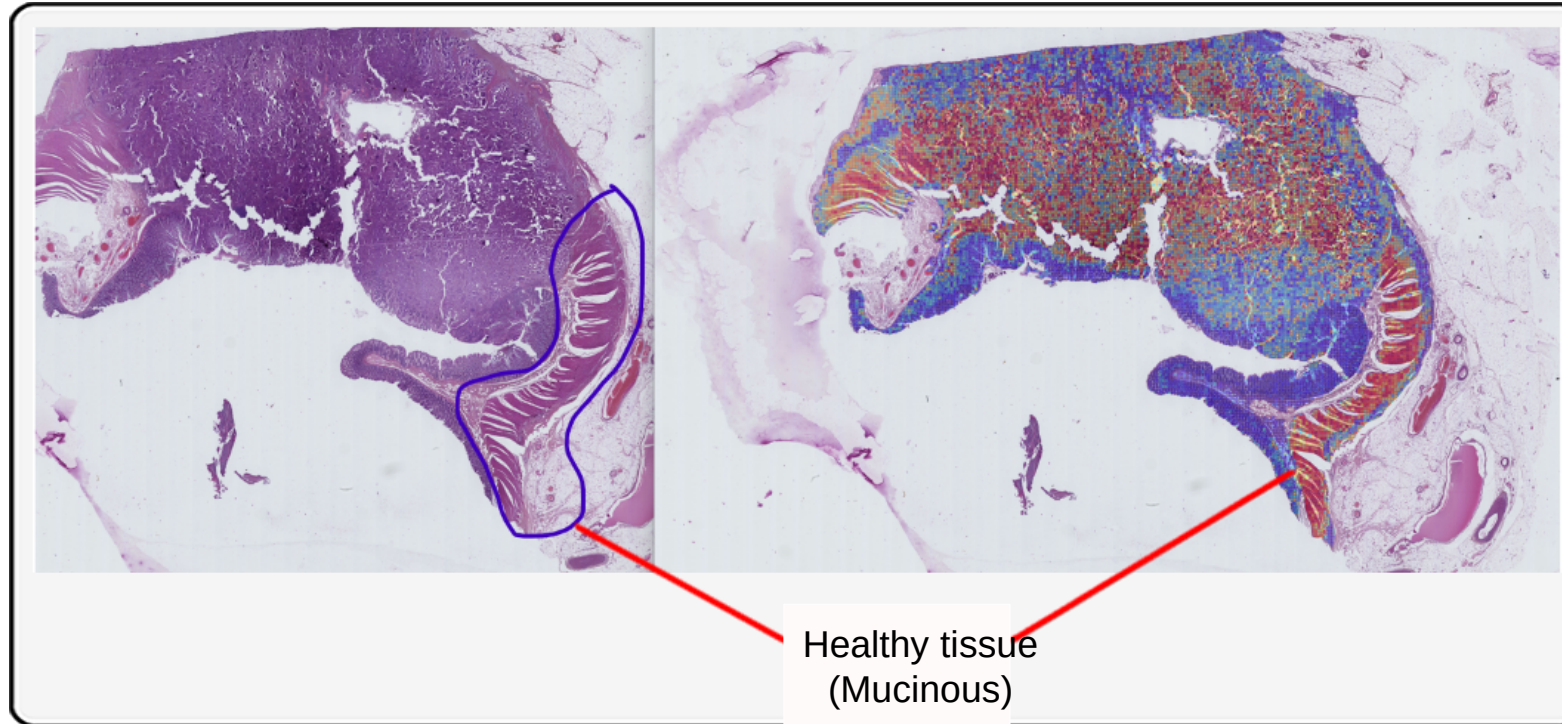
350 MSS and 240 MSI (after augmentation)



Internal report Sept. 2024
Yanis KOUADRI

What is AI promise ? New Foundation Models

MSI/MSS prediction on H&E via UNI + CLAM



Interpretability and feedback PUPH Jean-François EMILE

Internal report Sept.
2024
Yanis KOUADRI

Translational projects : what is AI promise?

So far :

- Companion test for lymphoid infiltration on IHC CRC WSI (Phase 2)
(based on IHC CRC WSI)
(To be published in Lancet Onco. Beginning 2025)



- Artificial intelligence-based pathology as a biomarker of sensitivity to atezolizumab-bevacizumab in patients with hepatocellular carcinoma: a multicentre retrospective study
(based on H&E HCC WSI)
(Lancet Onco. Nov. 2023)



- Deep learning-based phenotyping reclassifies combined hepatocellular-cholangiocarcinoma
(based on H&E HCC WSI)
(Nature Com. Dec. 2023)



- First experiments with new foundation model such as UNI for MSI/MSS in CRC and the mucinous tissue bias
(based on H&E CRC WSI)
(Internal Report, Sept. 2024)



<https://w3.mi.parisdescartes.fr/sip-lab/>

Digital Pathology Group /
Systèmes Intelligents de Perception (SIP) /
LIPADE lab



Zhuxian Guo, PhD student,
UPCité

Qinghe Zeng, PhD student,
UPCité

Amine Marzouki, IR,

Jean-François Emile, PUPH, Ambroise-Paré

Julien Calderaro, PUPH, Créteil

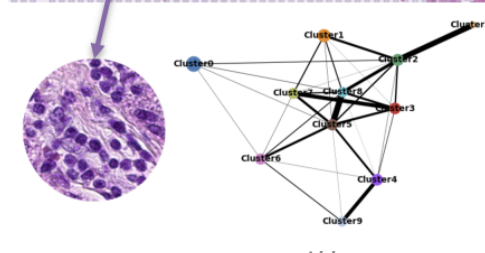
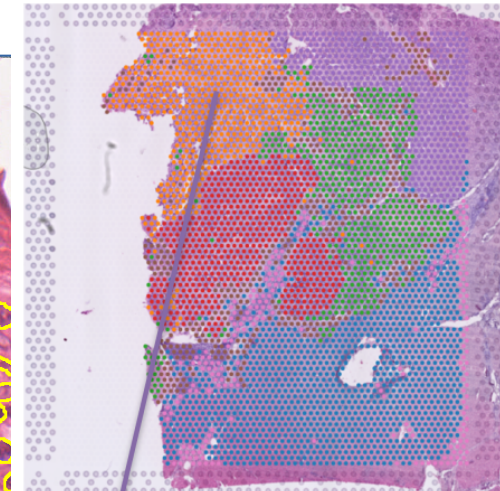
Philippe Bertheau, PUPH, Saint-Louis

François Ghiringhelli, PUPH, Dijon

Christophe Klein, IR, CRIC



Next...



NICOLAS.LOMENIE@U-PARIS.FR

MERCI



Prof. Camille Kurtz, UPCité

CLustering-constrained Attention Multiple instance learning (CLAM)

<https://github.com/mahmoodlab/CLAM>

$$\mathbf{W}_1 \in \mathbb{R}^{512 \times 1024}$$

$$\mathbf{h}_k = \mathbf{W}_1 \mathbf{z}_k^\top$$

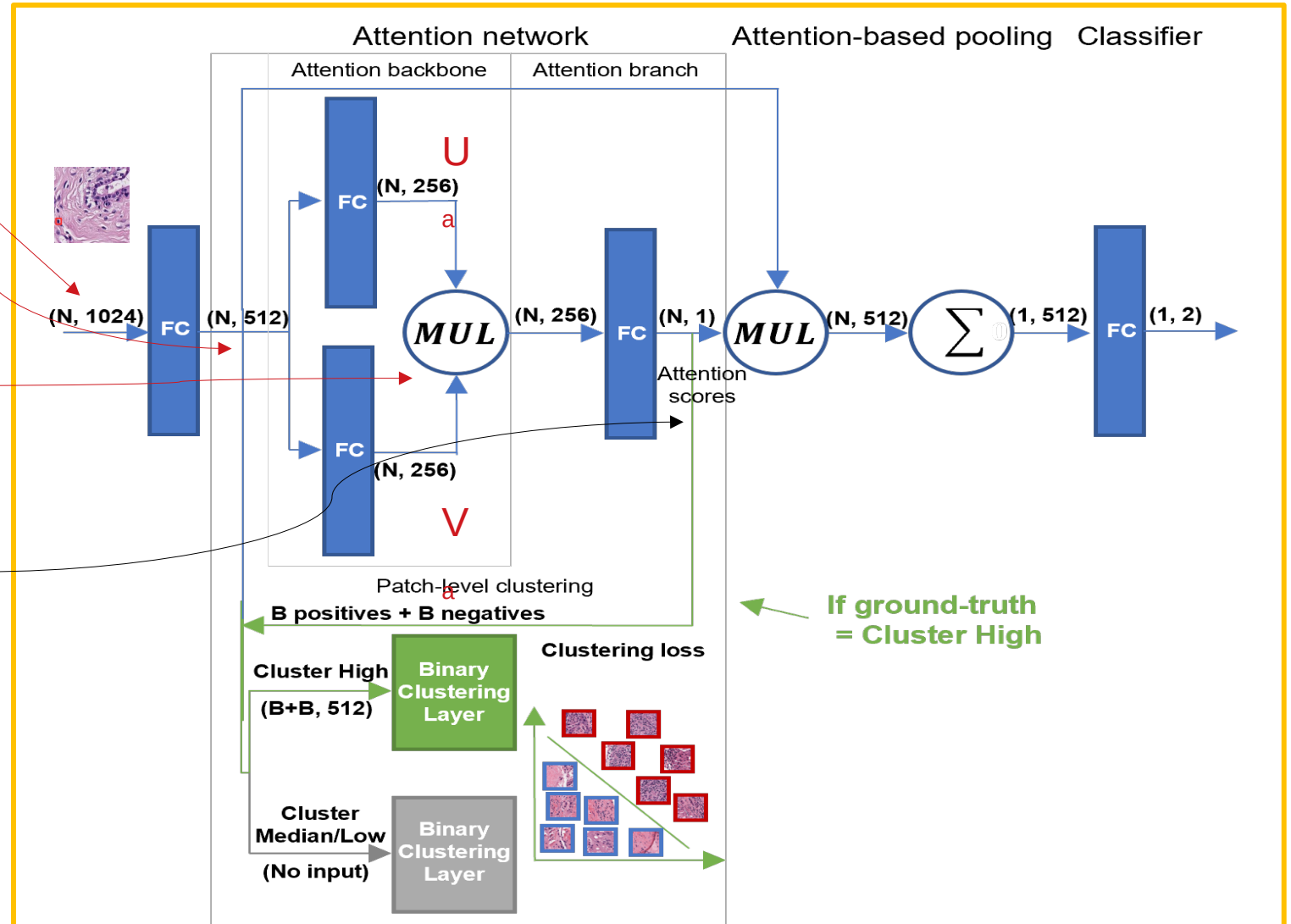
$$\mathbf{U}_a \in \mathbb{R}^{256 \times 512} \text{ and } \mathbf{V}_a \in \mathbb{R}^{256 \times 512}$$

$$a_{k,m} = \frac{\exp \{ \mathbf{W}_{a,m} (\tanh(\mathbf{V}_a \mathbf{h}_k^\top) \odot \text{sigm}(\mathbf{U}_a \mathbf{h}_k^\top)) \}}{\sum_{j=1}^N \exp \{ \mathbf{W}_{a,m} (\tanh(\mathbf{V}_a \mathbf{h}_j^\top) \odot \text{sigm}(\mathbf{U}_a \mathbf{h}_j^\top)) \}}$$

$$\mathbf{h}_{slide,m} \in \mathbb{R}^{1 \times 512} \quad \mathbf{h}_{slide,m} = \sum_{k=1}^N a_{k,m} \mathbf{h}_k$$

$$\mathbf{W}_{c,m} \in \mathbb{R}^{1 \times 512}$$

$$s_{slide,m} = \mathbf{W}_{c,m} \mathbf{h}_{slide,m}^\top$$

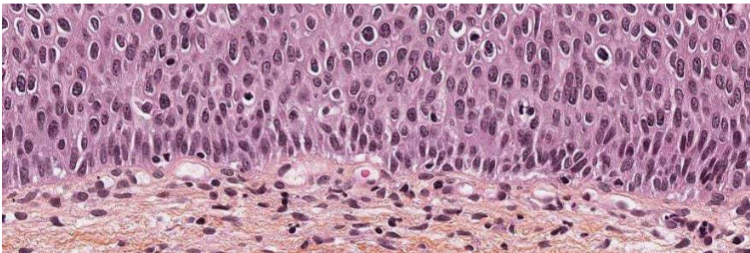


DRIVEN DATA COMPETITIONS ABOUT CAREERS DRIVEN

TissueNet: Detect Lesions in Cervical Biopsies

HOSTED BY FRENCH SOCIETY OF PATHOLOGY

RESULTS HOME PROBLEM DESCRIPTION DATA RESOURCES SUBMISSION FORMAT ABOUT



The French Society of Pathology and the Health Data Hub are very enthusiastic about the data challenge results! They show that AI will sooner or later be part of the tools that pathologists use on a daily basis.

DRIVEN DATA Competitions How it works Partner with us

HEALTH
VisioMel Challenge: Predicting Melanoma Relapse

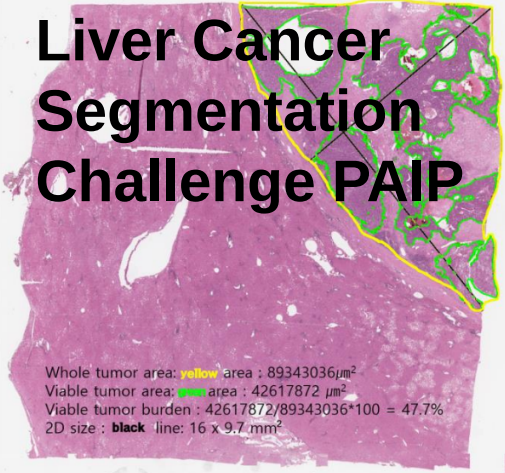
Use digitized microscopic slides to predict the likelihood of melanoma relapse within the next five years.

✓ \$25,000 awarded May 2023 550 joined

<https://www.health-data-hub.fr/data-challenge-visiome/>

https://youtu.be/wwCS_-rjcxU


Liver Cancer Segmentation Challenge PAIP



Whole tumor area: **yellow** area : 89343036 μm^2
 Viable tumor area: **green** area : 42617872 μm^2
 Viable tumor burden : 42617872/89343036*100 = 47.7%
 2D size : **black** line: 16 x 9.7 mm²

Grand Challenge Challenges Algorithms Help Sign In Register

Challenges / TIGER / Home



TIGER

Tumor Infiltrating lymphocytes in breast cancer

Info Forum Leaderboards Join

Welcome to TIGER

TIGER is the first challenge on fully automated assessment of tumor-infiltrating lymphocytes (TILs) in H&E breast cancer slides. It is organized by the Diagnostic Image Analysis Group (DIAG) of the Radboud University Medical Center (Radboudumc) in Nijmegen (The Netherlands), in close collaboration with the International Immuno-Oncology Biomarker working Group (www.tilsinbreastcancer.org).

The goal of this challenge is to evaluate new computer algorithms for the automated assessment of tumor-infiltrating lymphocytes (TILs) in Her2 positive and Triple Negative breast cancer (BC) histopathology slides. In recent years, several studies have shown the predictive and prognostic value of visually scored TILs in BC as well as in other cancer types, making TILs a powerful biomarker that can potentially be used in the clinic. With TIGER, we aim at developing computer algorithms that can automatically generate a "TIL score" with a high prognostic value.

Home Contact Videos Data Code Rules Evaluation Timeline Prizes Submission Requirements