

# AI for digital pathology

Matthieu Foll

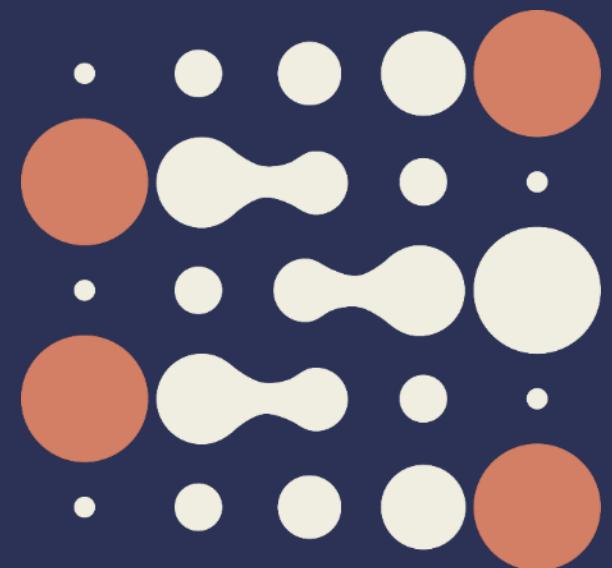
[follm@iarc.who.int](mailto:follm@iarc.who.int)

November 27<sup>th</sup> 2024

International Agency  
for Research on Cancer



World Health  
Organization



# Agenda

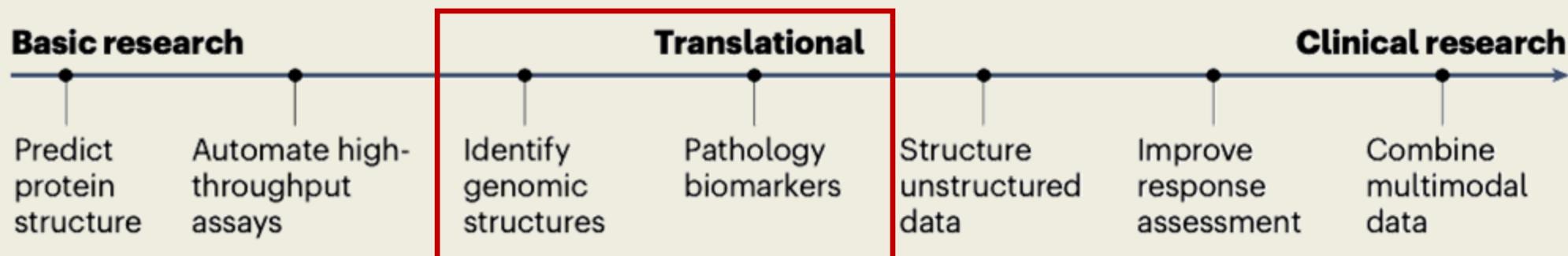
- Histopathology, genomics and deep-learning
- Machine learning paradigms
- Deep learning concepts and architectures
- Applications in histopathology
- Challenges and future directions

# Agenda

- Histopathology, genomics and deep-learning
- Machine learning paradigms
- Deep learning concepts and architectures
- Applications in histopathology
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# AI in Cancer Research

- AI evolved from theory to practical tool
- Enhances research productivity and discoveries
- Essential for modern cancer researchers



nature reviews cancer

<https://doi.org/10.1038/s41568-024-00694-7>

Review article

Volume 24 | June 2024 | 427–441

## A guide to artificial intelligence for cancer researchers

Raquel Perez-Lopez<sup>①</sup>, Narmin Ghaffari Laleh<sup>②</sup>, Faisal Mahmood<sup>③,4,5,6,7,8</sup> & Jakob Nikolas Kather<sup>②,9,10</sup>

# Histopathology

- **Study of tissue (“histo”) changes caused by disease (“pathology”).**
- **Central role in medicine and specifically for cancer:**
  - Gold standard for diagnostics (reference is WHO classification of tumors)
  - Disease grading: determines aggressiveness
  - Guides treatment decision (eg surgery, chemotherapy, radiation etc.)
- **Key methods:**
  - Tissue biopsy or surgical samples
  - Microscopic examination (20x-40x)
  - Staining techniques
  - Immunohistochemistry (IHC)
- **Challenges:**
  - Time-consuming manual analysis.
  - Inter-observer variability.
  - Limited reproducibility and scalability.

From Leica biosystems



From TCGA

## FINAL DIAGNOSIS:

1. Left temporal parietal tumor: Anaplastic astrocytoma, grade III of IV (WHO scale), see microscopic description, SEE NOTE ✓

## Comment:

The proliferation index of 7.2% is within the expected range for an anaplastic astrocytoma, grade III.



This diagnostic report has been personally interpreted by the signatory of record.

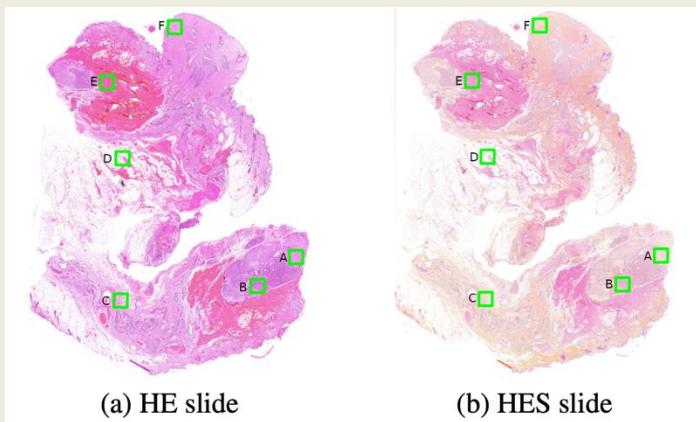
## Microscopic Description:

The tumor consists of a moderately pleomorphic and highly infiltrative proliferation of astrocytes.

There are rare mitoses. There is no endothelial proliferation or necrosis. Immunohistochemistry for the proliferation antigen ki67 was performed as follows: Ten 250 x 250 micron fields were counted and the percentage of labeled nuclei determined. Over 1,000 cells were counted. The proliferation index ranged from 4.4% to 12.5% with an overall average of 7.2%.

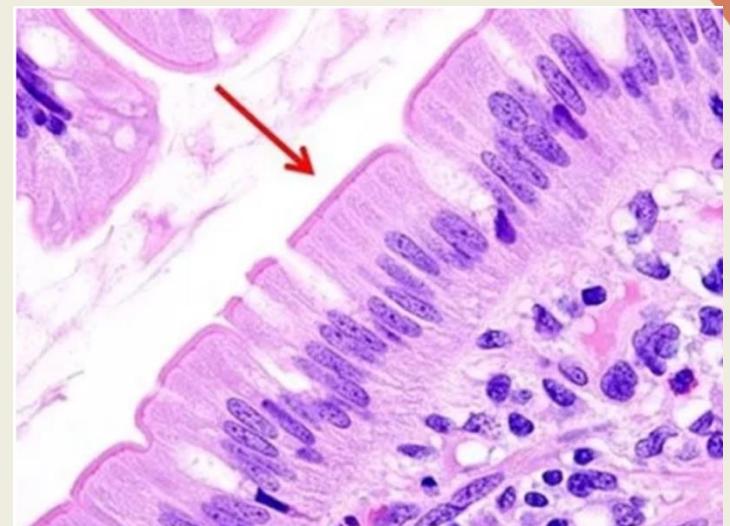
# Hematoxylin & eosin stain (H&E, HE)

- **2 stains:**
  - **Hematoxylin:** stains cell nuclei **purplish-blue**
  - **Eosin:** stains extracellular matrix and cytoplasm **pink**
  - Other structures taking on different shades, hues, and combinations of these colors
- **Saffron:**
  - Sometimes added to color collagen in orange (HES, very common in France)



Balezo et al. 2022

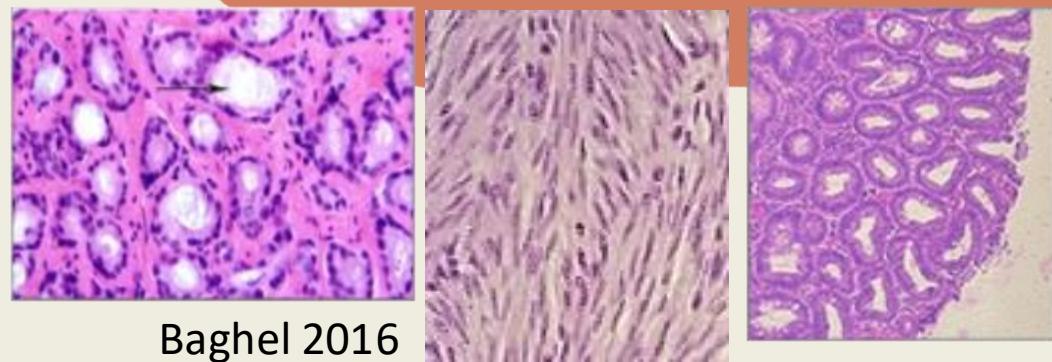
From Leica biosystems



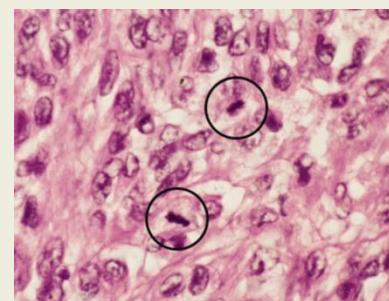
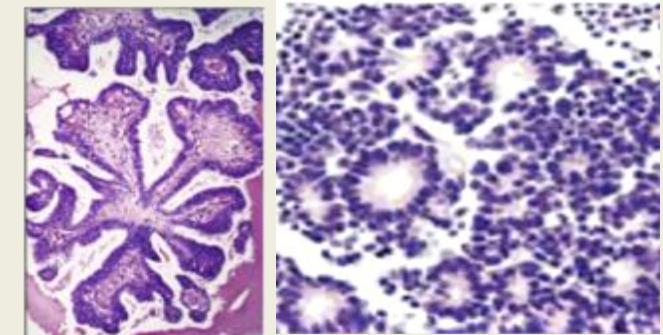
<https://portal.gdc.cancer.gov/image-viewer/MultipleImageViewerPage?caseId=e8d3d888-e5fc-4469-ad0b-2c1df6e04790>

# Key features

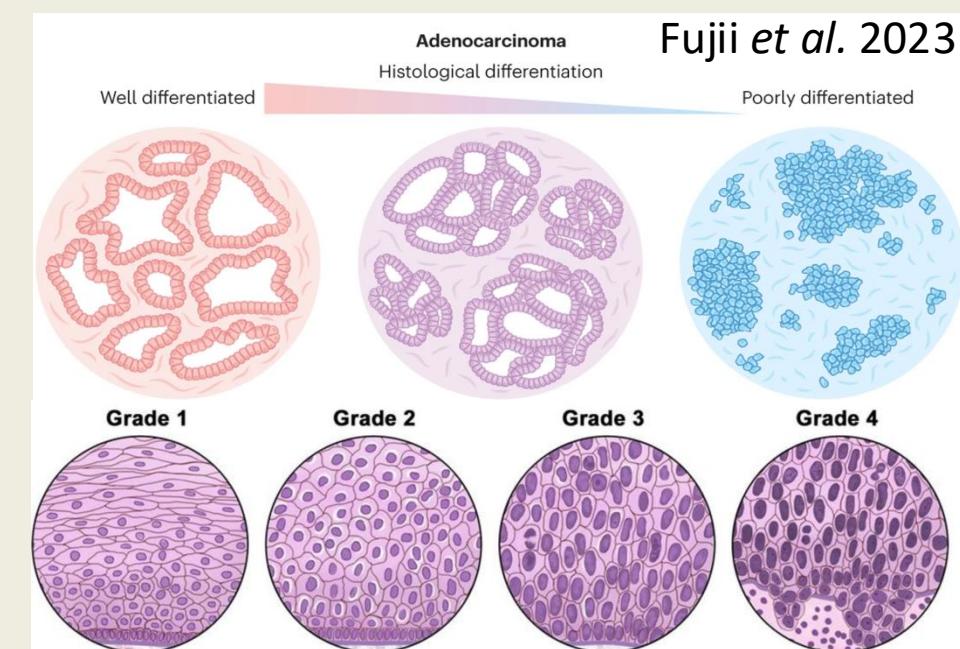
- **Tissue Architecture:** arrangement of cells and structures
  - E.g. Glandular, fascicular, tubular, papillary, rosette...
- **Cell morphology:** shape, size, nucleus, cytoplasm
  - Uniform vs pleomorph (variation in shape and size)
  - Enlarged nuclei, nuclear-cytoplasmic ration
  - Mitotic activity (indicating cell division)
- **Necrosis (cell death)**
  - Indicative of rapidly growing tumors
- **Immune response**
  - Presence of immune cells around tumor
- **Expression of specific protein**
  - Immunohistochemistry (IHC)
  - E.g. p53, HER2, Ki-67



Baghel 2016



Mitosis



Fujii et al. 2023

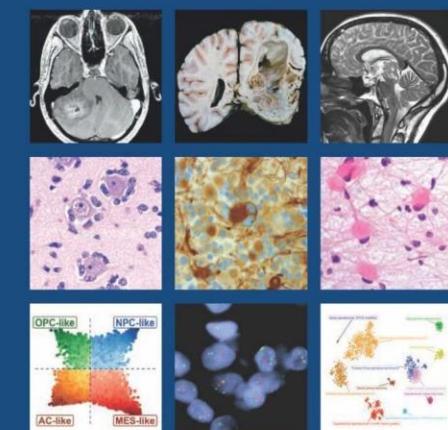
# Case study: Central Nervous System tumors

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
<i>Diffuse astrocytoma, IDH-wildtype</i>	9400/3
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
<i>Anaplastic astrocytoma, IDH-wildtype</i>	9401/3
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
<i>Epithelioid glioblastoma</i>	9440/3
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M-mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendrogloma, IDH-mutant and 1p/19q-codeleted	9451/3
<i>Anaplastic oligodendrogloma, NOS</i>	9451/3
<i>Oligoastrocytoma, NOS</i>	9382/3
<i>Anaplastic oligoastrocytoma, NOS</i>	9382/3
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanyctic ependymoma	9391/3
Ependymoma, <i>RELA</i> fusion-positive	9396/3*
Anaplastic ependymoma	9392/3
Other gliomas	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3
Neuronal and mixed neuronal-gliai tumours	
Dysembryoplastic neuroepithelial tumour	9413/0
Ganglioglioma	9492/0
Anaplastic ganglioglioma	9505/1
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
<i>Diffuse leptomeningeal glioneuronal tumour</i>	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	9395/3
Embryonal tumours	
Medulloblastomas, genetically defined	9475/3*
Medulloblastoma, WNT-activated	
Medulloblastoma, SHH-activated and <i>TP53</i> -wildtype	
Medulloblastoma, SHH-activated and <i>TP53</i> -mutant	
Medulloblastoma, non-WNT/non-SHH	9477/3*
<i>Medulloblastoma, group 3</i>	
<i>Medulloblastoma, group 4</i>	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
<i>Embryonal tumour with multilayered rosettes, NOS</i>	
Tumours of the cranial and paraspinal nerves	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0
Melanotic schwannoma	9560/1
Neurofibroma	9540/0
Atypical neurofibroma	9540/0
Plexiform neurofibroma	9550/0
Perineurioma	9571/0
Hybrid nerve sheath tumours	
Malignant peripheral nerve sheath tumour	9540/3
Epithelioid MPNST	9540/3
MPNST with perineural differentiation	9540/3
Lymphomas	
Meningioma	9530/0
Meningothelial meningioma	9531/0
Fibrous meningioma	9532/0
Transitional meningioma	9537/0
Psammomatous meningioma	9533/0
Angiomatous meningioma	9534/0
Microcystic meningioma	9530/0
Secretory meningioma	9530/0
Lymphoplasmacyte-rich meningioma	9530/0
Metaplastic meningioma	9530/0
Chordoid meningioma	9538/1
Clear cell meningioma	9538/1
Atypical meningioma	9539/1
Papillary meningioma	9538/3
Rhabdoid meningioma	9538/3
Anaplastic (malignant) meningioma	9530/3
Mesenchymal, non-meningotheelial tumours	
Solitary fibrous tumour / haemangiopericytoma**	
Grade 1	8815/0
Grade 2	8815/1
Grade 3	8815/3
Haemangioblastoma	9161/1
Haemangioma	9120/0
<i>Epithelioid haemangiopericytoma</i>	9133/3
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Ewing sarcoma / PNET	9364/3
Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma	8850/3
Desmoid-type fibromatosis	8821/1
Myofibroblastoma	8825/0
Inflammatory myofibroblastic tumour	8825/1
Benign fibrous histiocytoma	8830/0
Fibrosarcoma	8810/3
Undifferentiated pleomorphic sarcoma / malignant fibrous histiocytoma	8802/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0
Osteochondroma	
Osteosarcoma	9210/0
Osteosarcoma	9180/3
Melanocytic tumours	
Meningeal melanocytosis	8728/0
Meningeal melanocytoma	8728/1
Meningeal melanoma	8720/3
Meningeal melanomatosis	8728/3
Lymphomas	
Diffuse large B-cell lymphoma of the CNS	9680/3
Immunodeficiency-associated CNS lymphomas	
AIDS-related diffuse large B-cell lymphoma	
EBV-positive diffuse large B-cell lymphoma, NOS	
Lymphomatoid granulomatosis	9766/1
Intravascular large B-cell lymphoma	9712/3
Low-grade B-cell lymphomas of the CNS	
T-cell and NK/T-cell lymphomas of the CNS	
Anaplastic large cell lymphoma, ALK-positive	9714/3
Anaplastic large cell lymphoma, ALK-negative	9702/3
MALT lymphoma of the dura	9699/3
Histiocytic tumours	
Langerhans cell histiocytosis	9751/3
Erdheim-Chester disease	9750/1
Rosai-Dorfman disease	
Juvenile xanthogranuloma	
Histiocytic sarcoma	9755/3
Germ cell tumours	
Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumour	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature teratoma	9080/0
Immature teratoma	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumour	9085/3
Tumours of the sellar region	
Craniopharyngioma	9350/1
Adamantinomatous craniopharyngioma	9351/1
Papillary craniopharyngioma	9352/1
Granular cell tumour of the sellar region	9582/0
Pituitary adenoma	9432/1
Spindle cell oncocytooma	8290/0
Metastatic tumours	
The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) (742A). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intrapithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.	
*These new codes were approved by the IARC/WHO Committee for ICD-O. Italics: Provisional tumour entities. **Grading according to the 2013 WHO Classification of Tumours of Soft Tissue and Bone.	

WHO Classification of Tumours • 5th Edition

## Central Nervous System Tumours

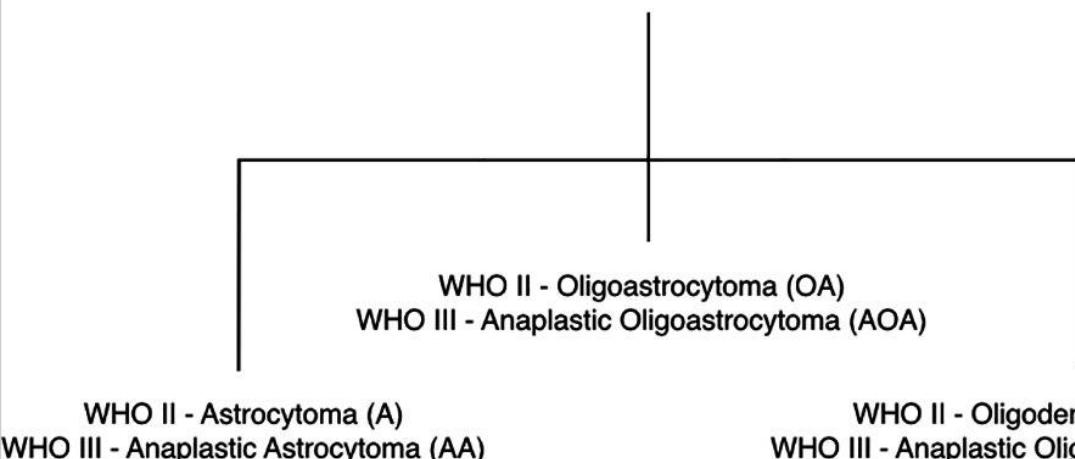
Edited by the WHO Classification of Tumours Editorial Board



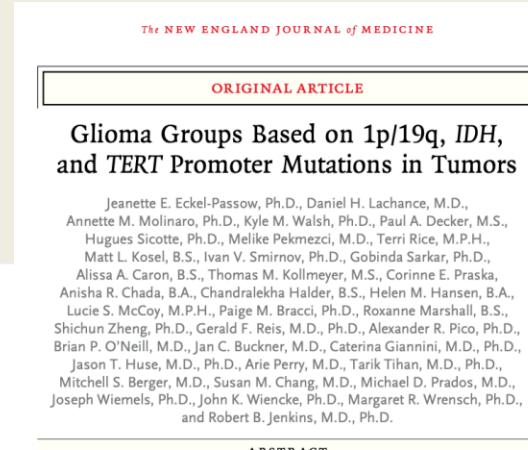
International Agency for Research on Cancer  
World Health Organization

# Genomics transformed glioma classification

## 2007 WHO Criteria



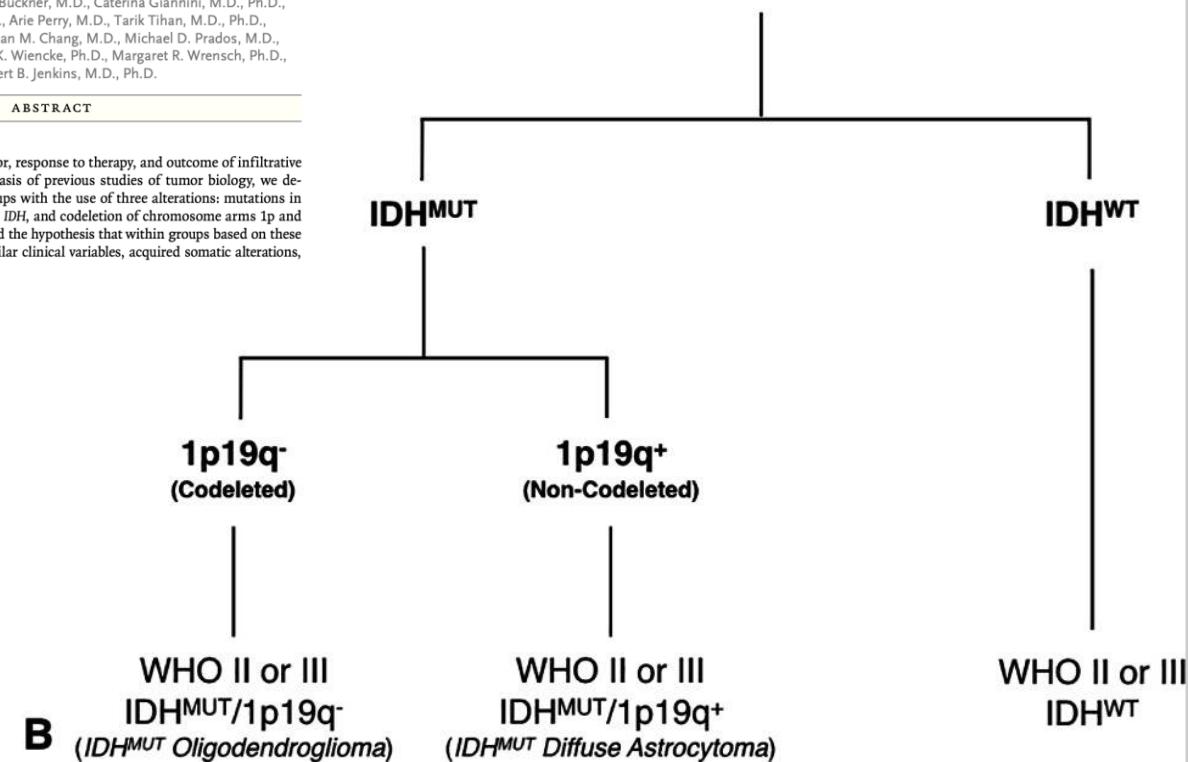
A



BACKGROUND

The prediction of clinical behavior, response to therapy, and outcome of infiltrative glioma is challenging. On the basis of previous studies of tumor biology, we defined five glioma molecular groups with the use of three alterations: mutations in the *TERT* promoter, mutations in *IDH*, and codeletion of chromosome arms 1p and 19q (1p/19q codeletion). We tested the hypothesis that within groups based on these features, tumors would have similar clinical variables, acquired somatic alterations, and germline variants.

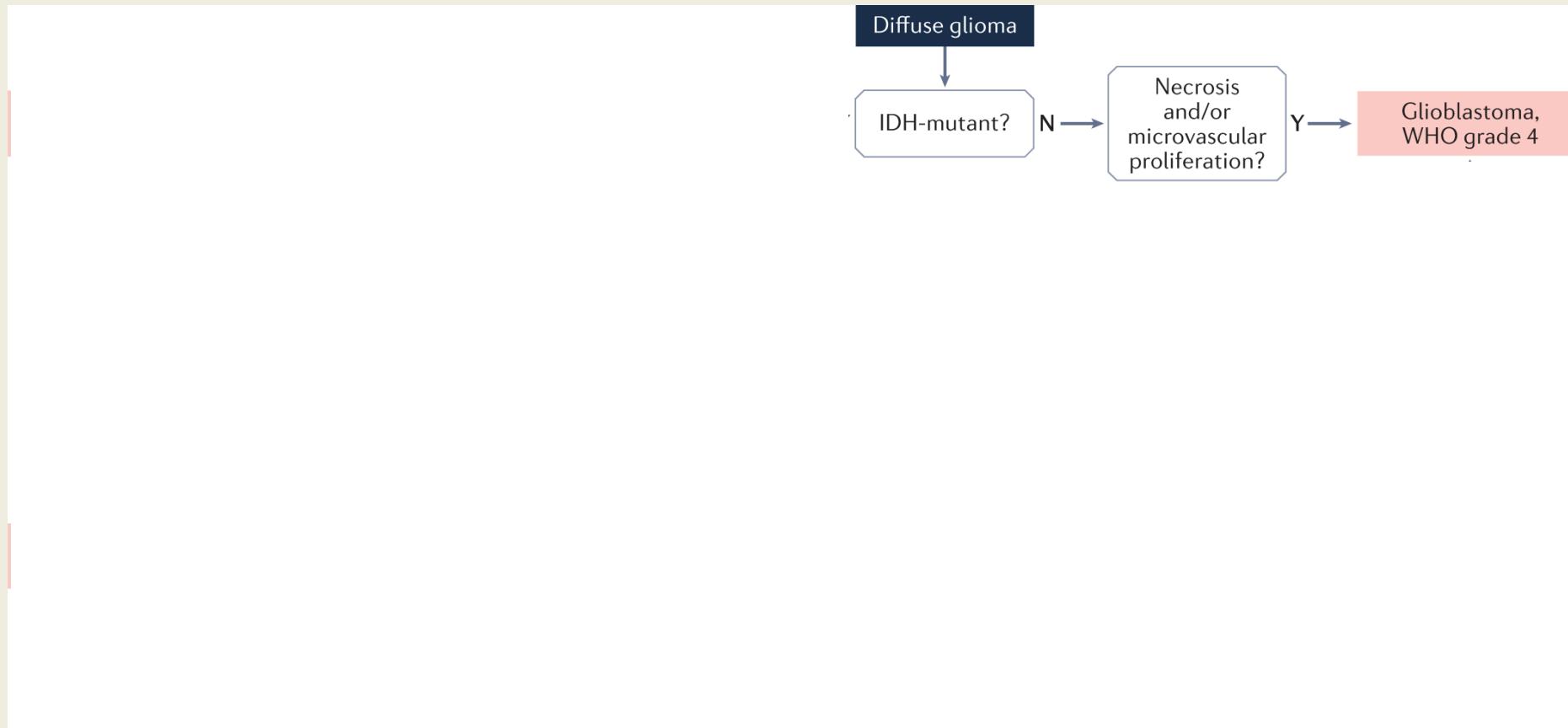
## 2016 WHO Criteria



B

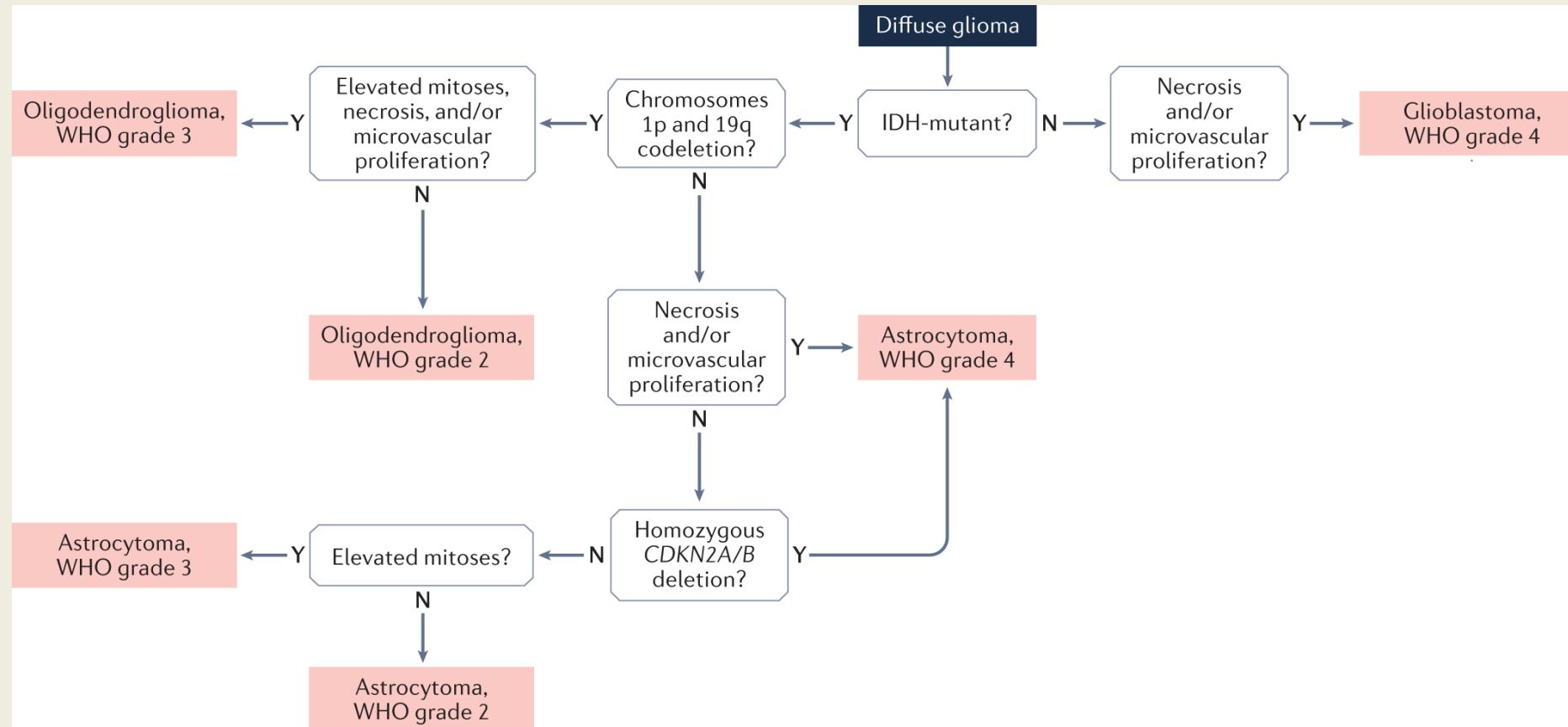
# Genomics transformed glioma classification

2021 WHO critetia



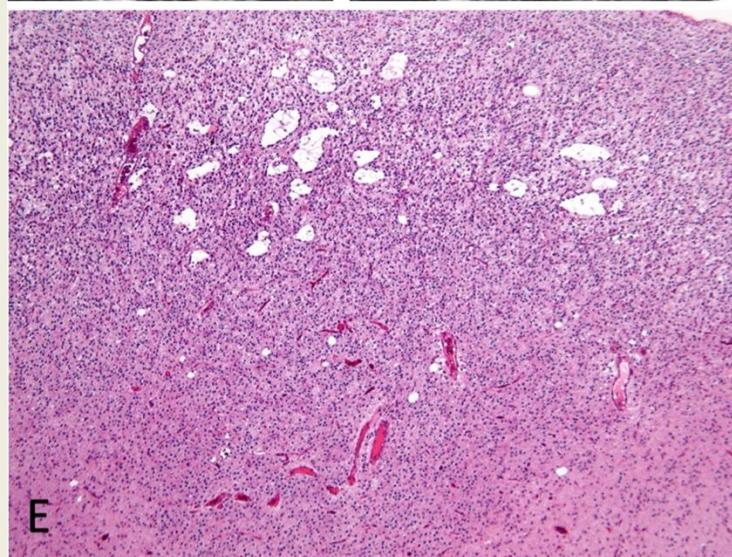
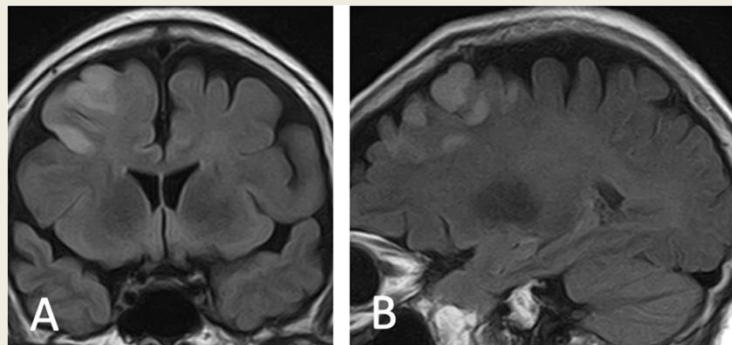
# Genomics transformed glioma classification

## 2021 WHO critetia

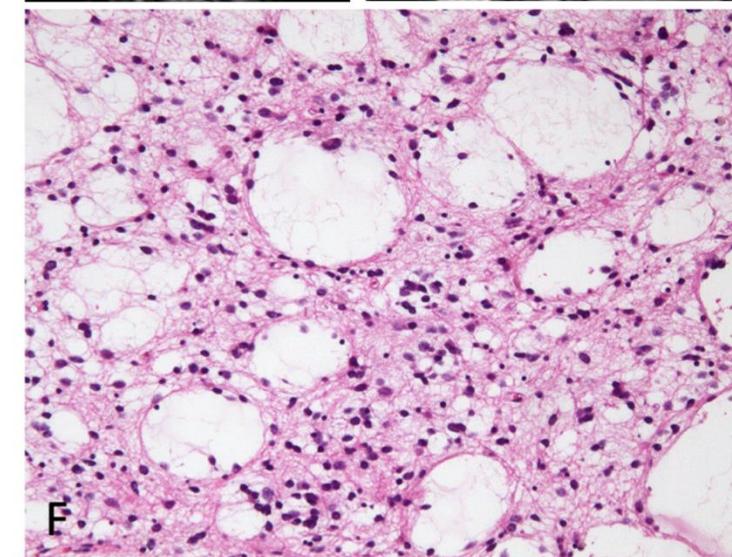
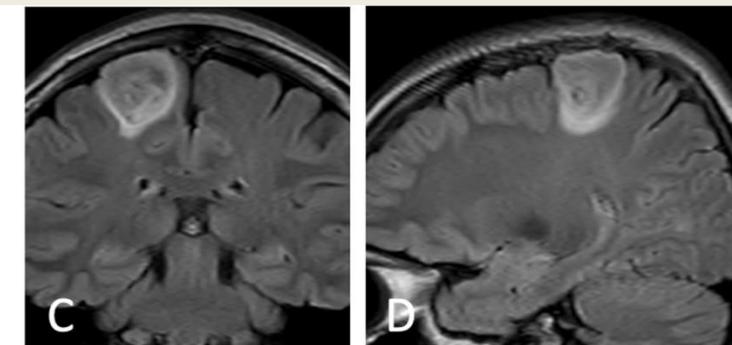


# Example

Oligodendrogloma, IDH-mutant,  
1p/19q codeleted, WHO grade 2

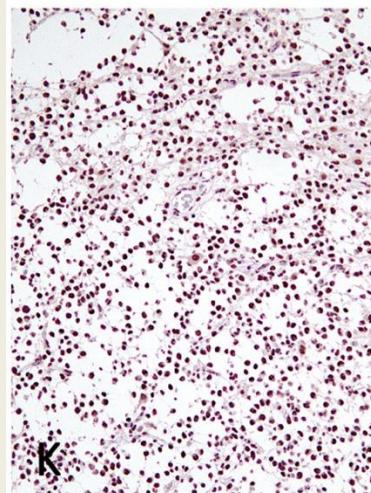
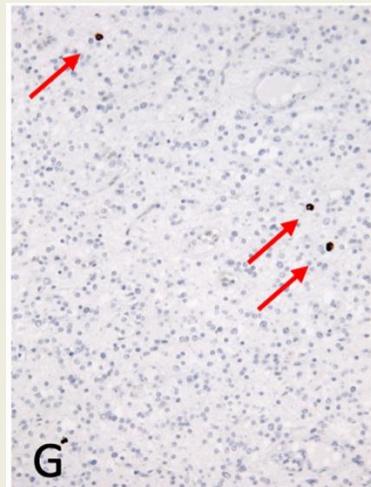


Astrocytoma, WHO grade 4

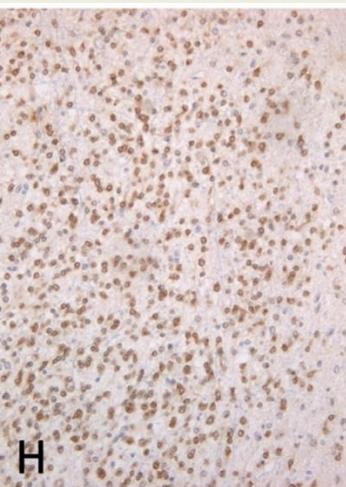


"Elongated and oval tumor cells with fine cytoplasmic processes embedded in the microcystic background"

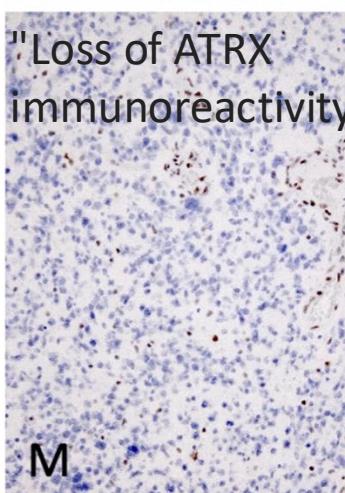
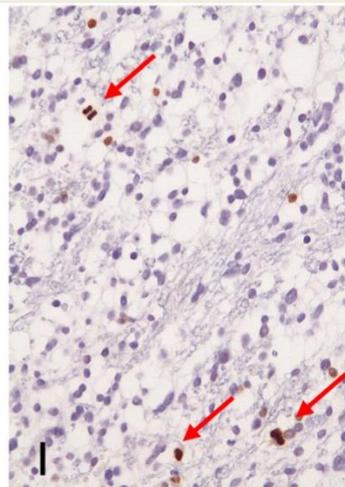
"Three mitoses  
(arrows) positive for  
the pHH3 antibody"



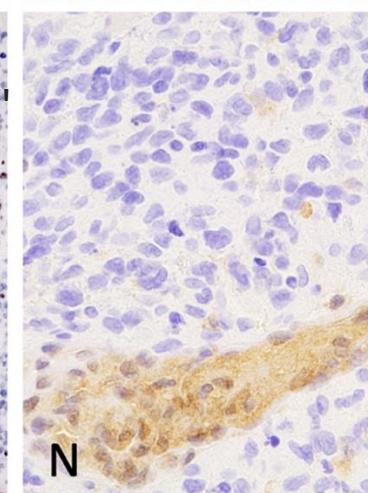
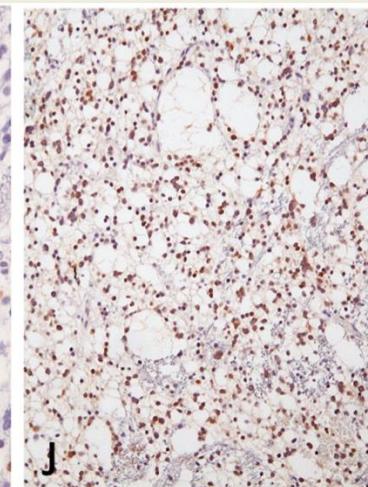
"Tumor cells  
diffusely positive  
for the IDH1R132H  
antibody"



"Three mitoses  
(arrows) positive for  
the pHH3 antibody"



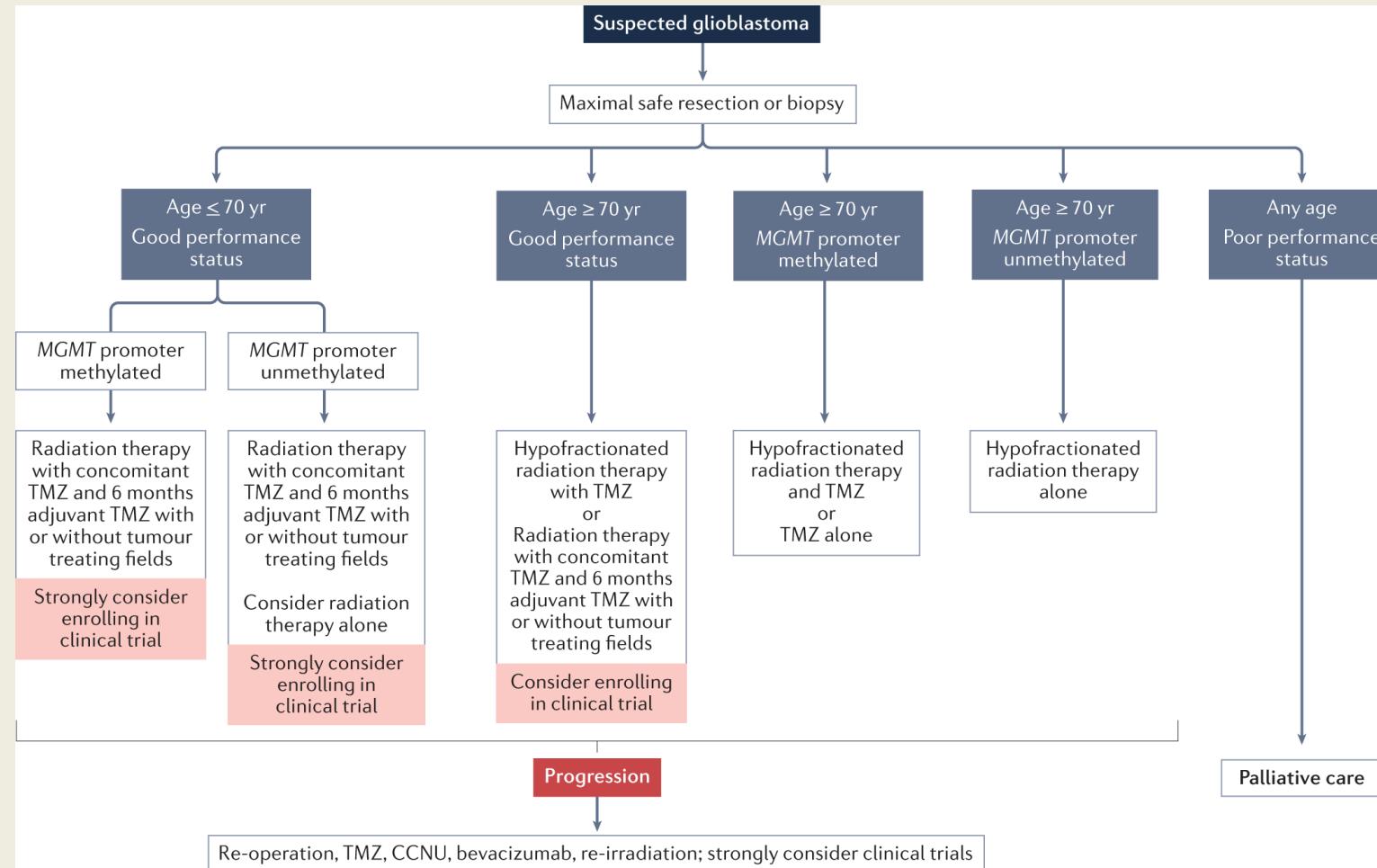
"Tumor cells  
diffusely positive  
for the IDH1R132H  
antibody"



"Retained ATRX  
immunoreactivity"

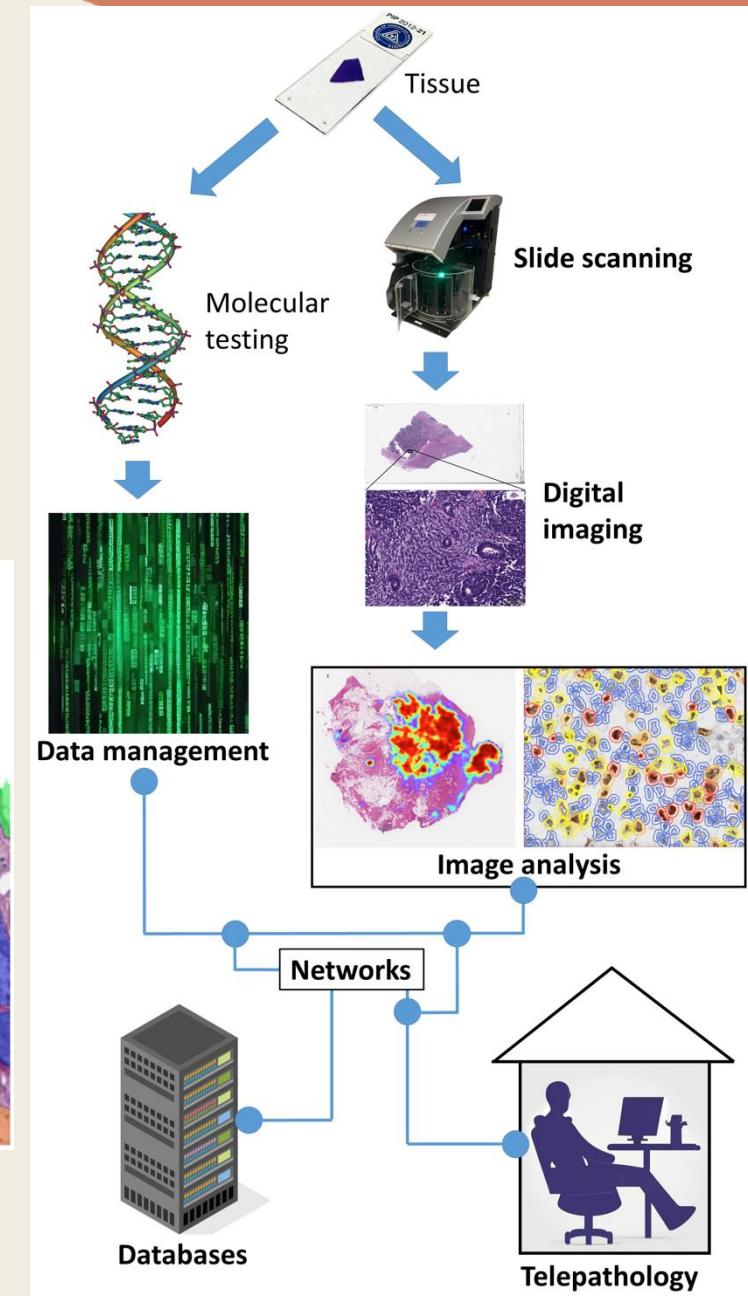
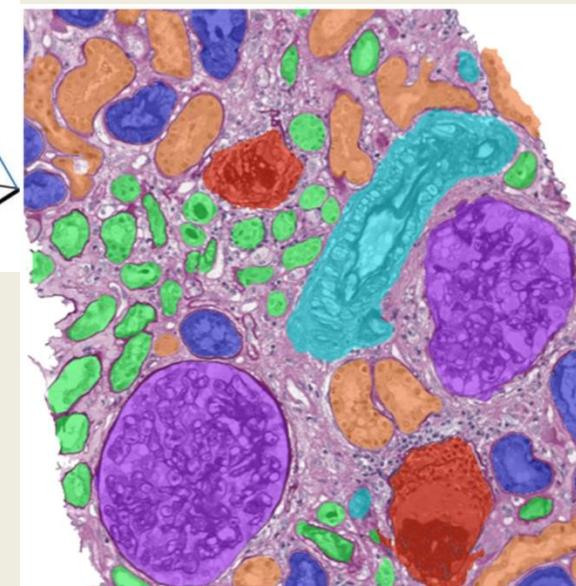
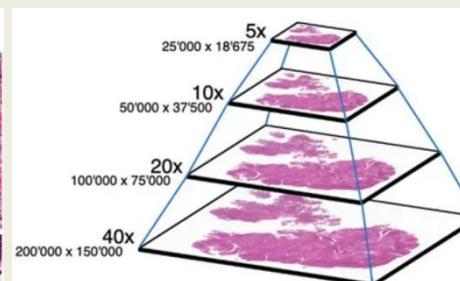
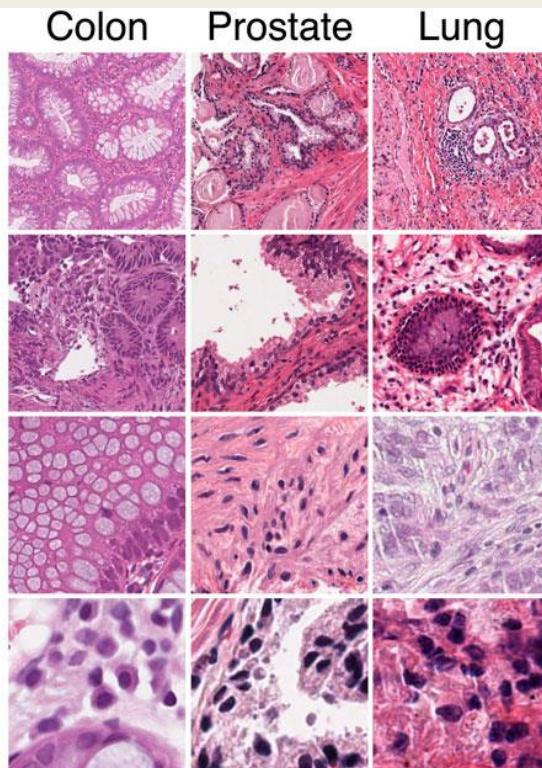
"Loss of MTAP  
immunoreactivity in  
tumor cells, indicating  
the *CDKN2A* homozygous  
deletion"

# Glioblastoma treatment

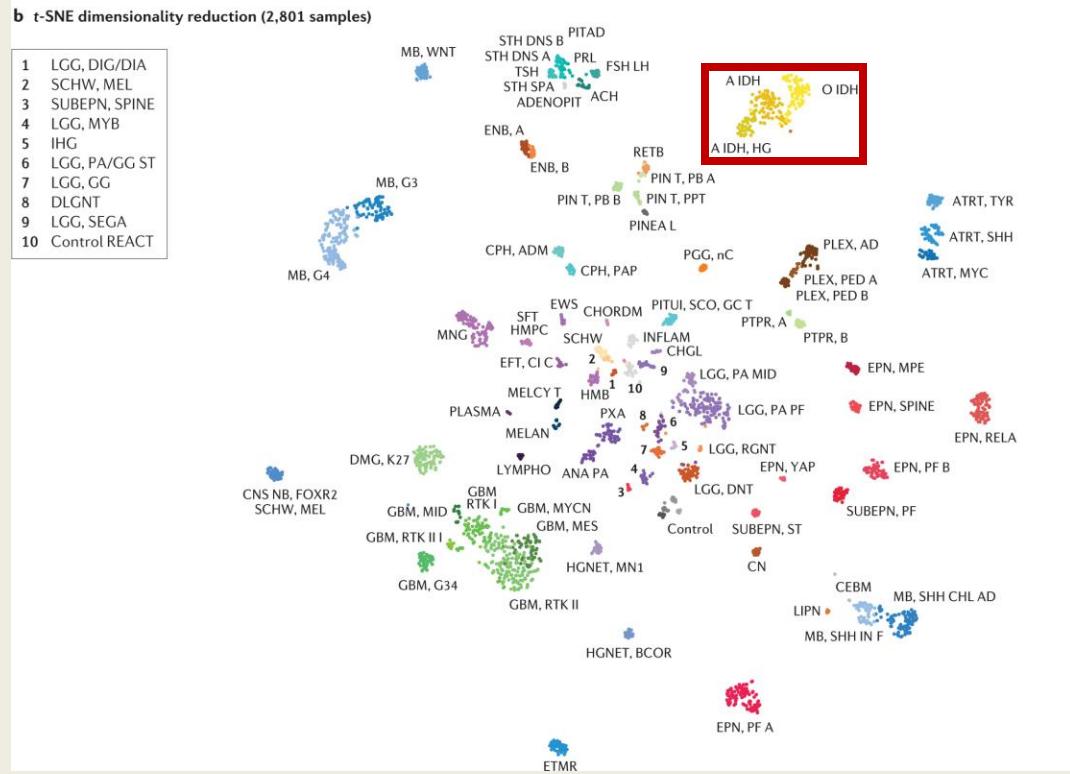
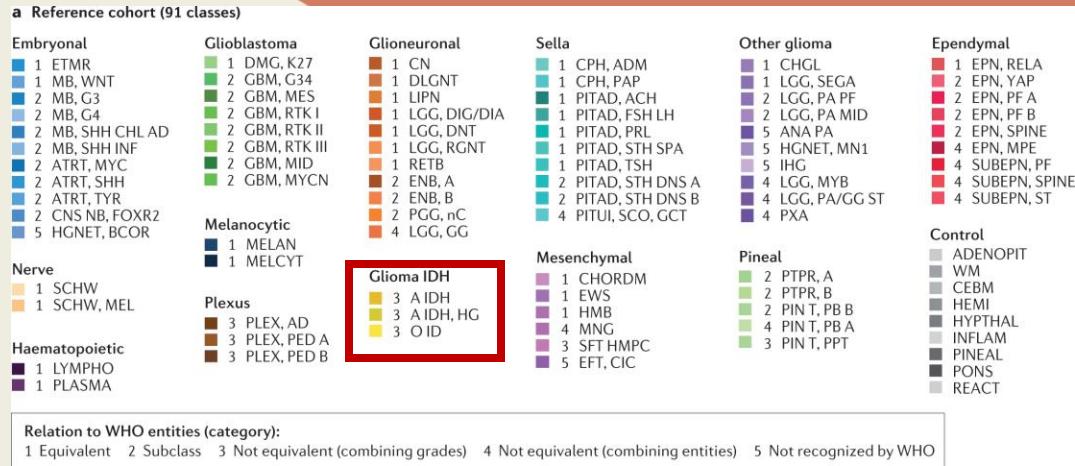
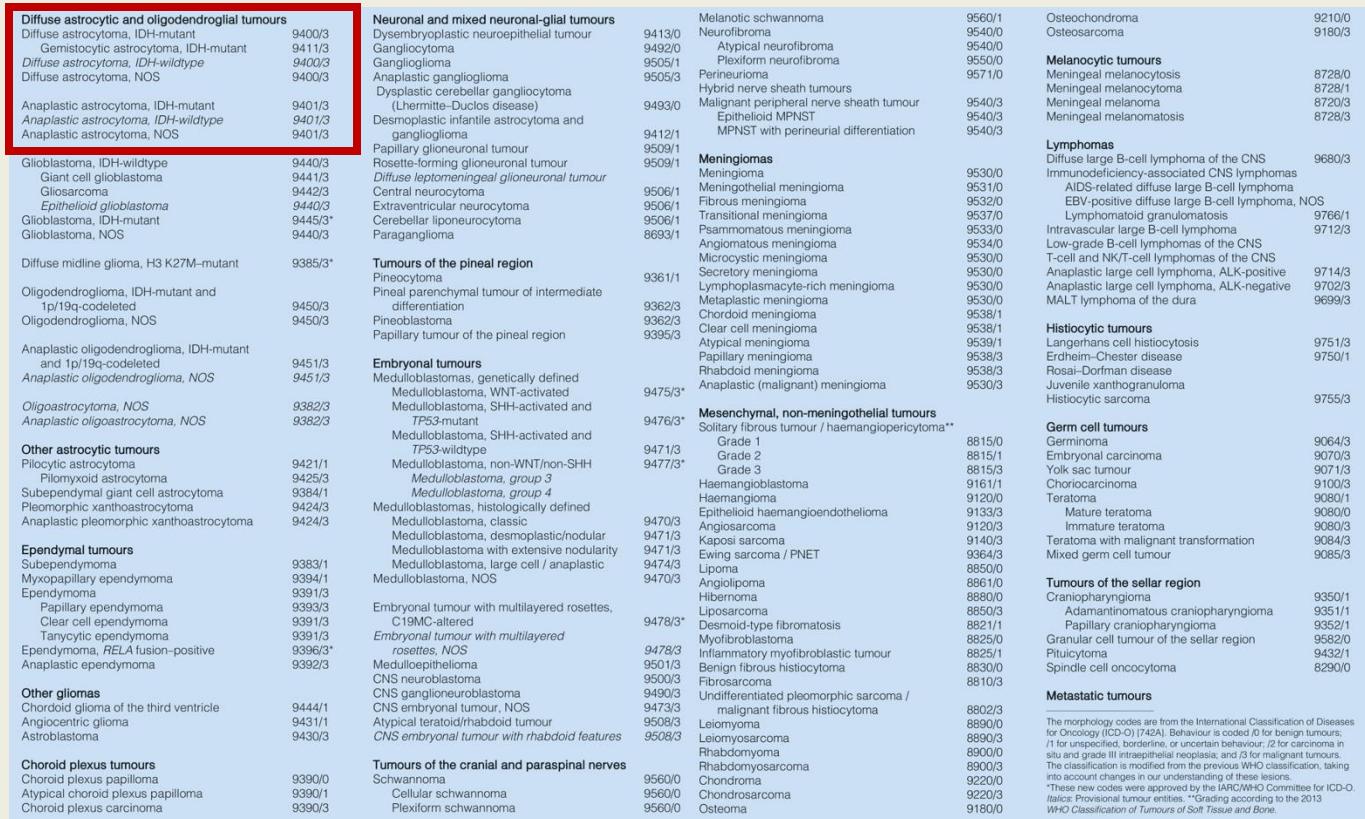


# From digital pathology to AI

- Whole slide scanner: automated robotic microscope capable of digitizing glass slides
- Generates giga-pixels Whole Slide Images (WSI)



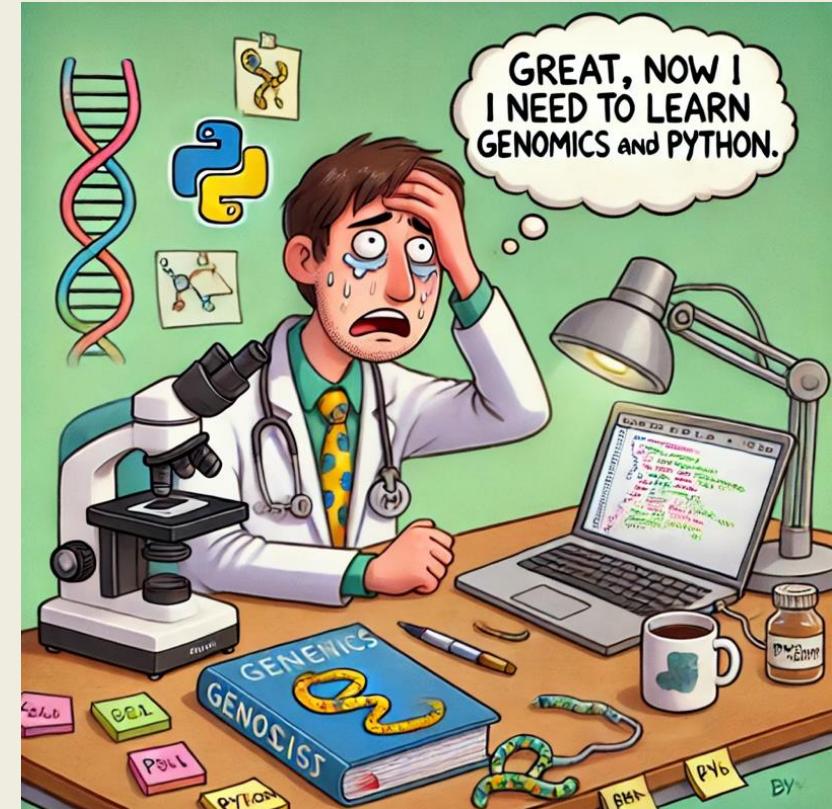
# Pathology vs genomics?



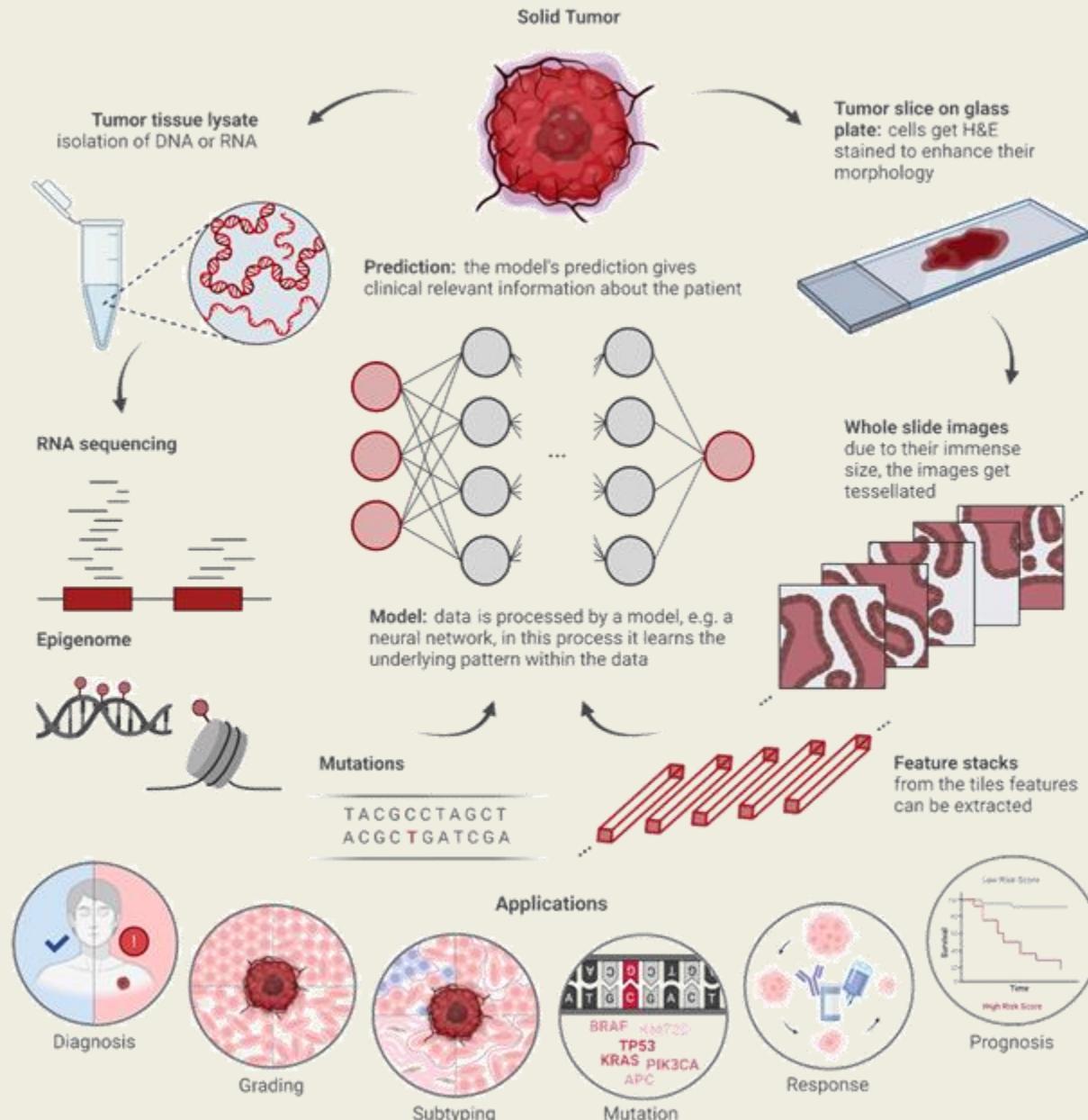
Horbinski *et al.* 2022

# The never-ending debate: Pathology vs. Omics vs. AI

- **Why do we still need pathology when we have omics?**
  - reproducible, high-throughput, reveals unseen mechanisms (mutations, pathways)
- **Why use omics when pathology shows it all?**
  - omics are complicated and costly, not standardized
- **Do we need pathologists or omics at all?**
  - Deep-learning can be trained as pathologists but in a reproducible and automated manner
  - Deep-learning can predict molecular features from images
  - But who will train the models?
- **Why not integrating pathology and omics using deep-learning?**



# Workflow of AI in histopathology and genomics

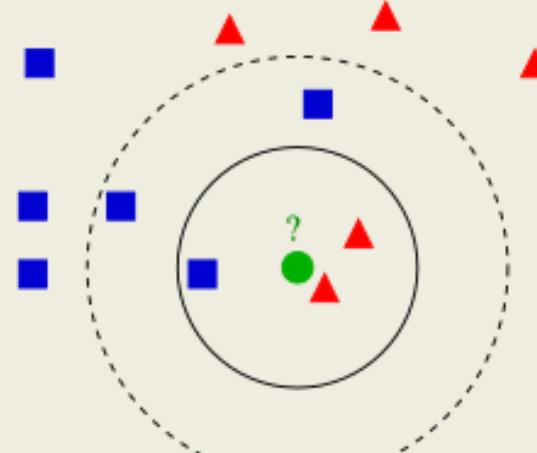
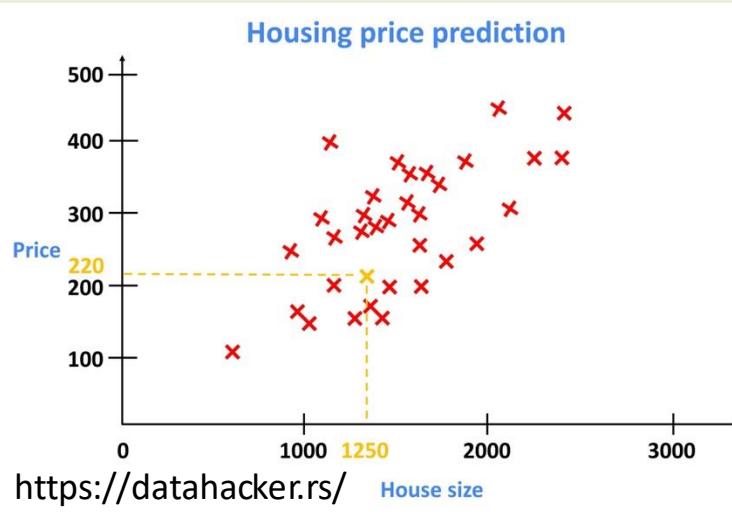


# Agenda

- Histopathology, genomics and deep-learning
- Machine learning paradigms
- Deep learning concepts and architectures
- Applications in histopathology
- Challenges and future directions

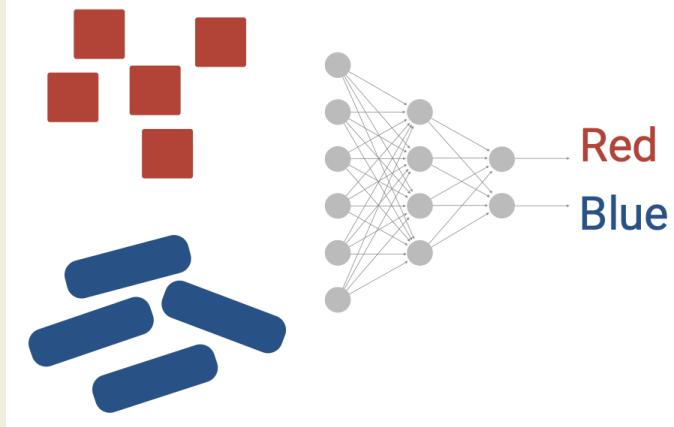
# Supervised Learning (SL)

- Models learn from labeled data (input-output pairs).
- Examples:
  - Tumor classification (e.g., malignant vs. benign).
  - Tumor segmentation (e.g., tumoral region vs non-tumoral region).
  - Mutation classification (benign vs pathogenic)
- Requires large, annotated datasets.
- Linear regression, k-nearest neighbors, Random Forest etc.

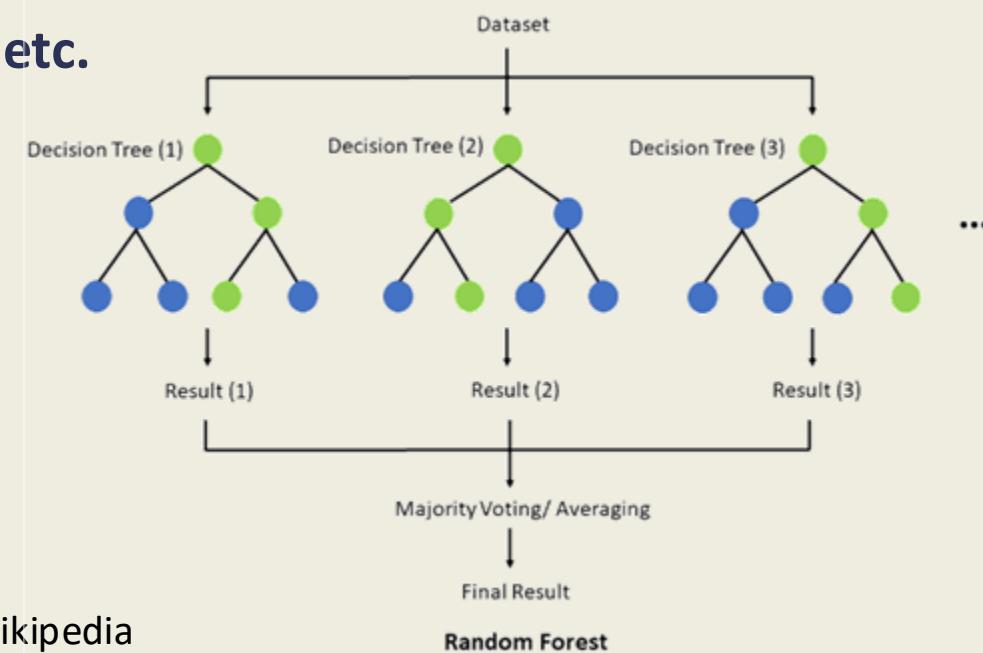


Wikipedia

**(A) Supervised**  
Data and Label (color) are given to the model during training. Model learns to predict the label.

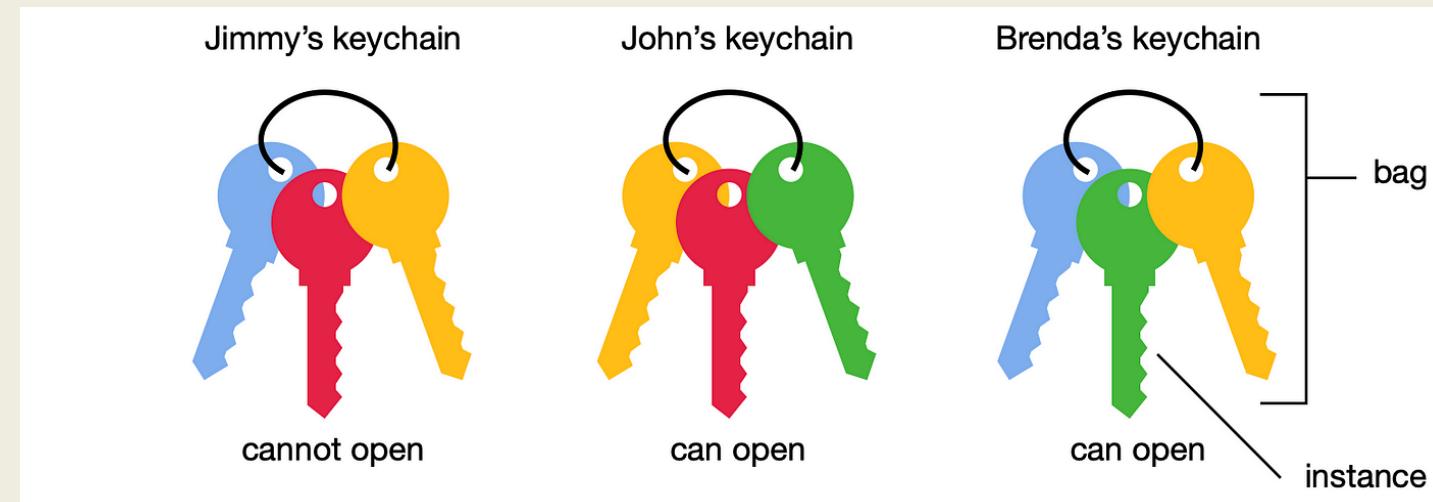
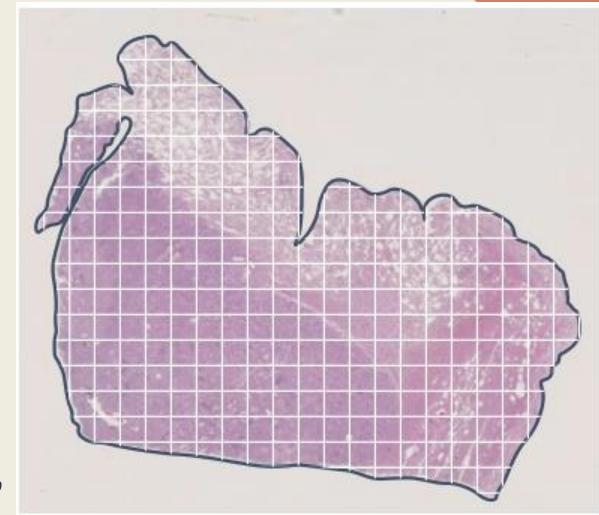


Ghosh et al. 2024



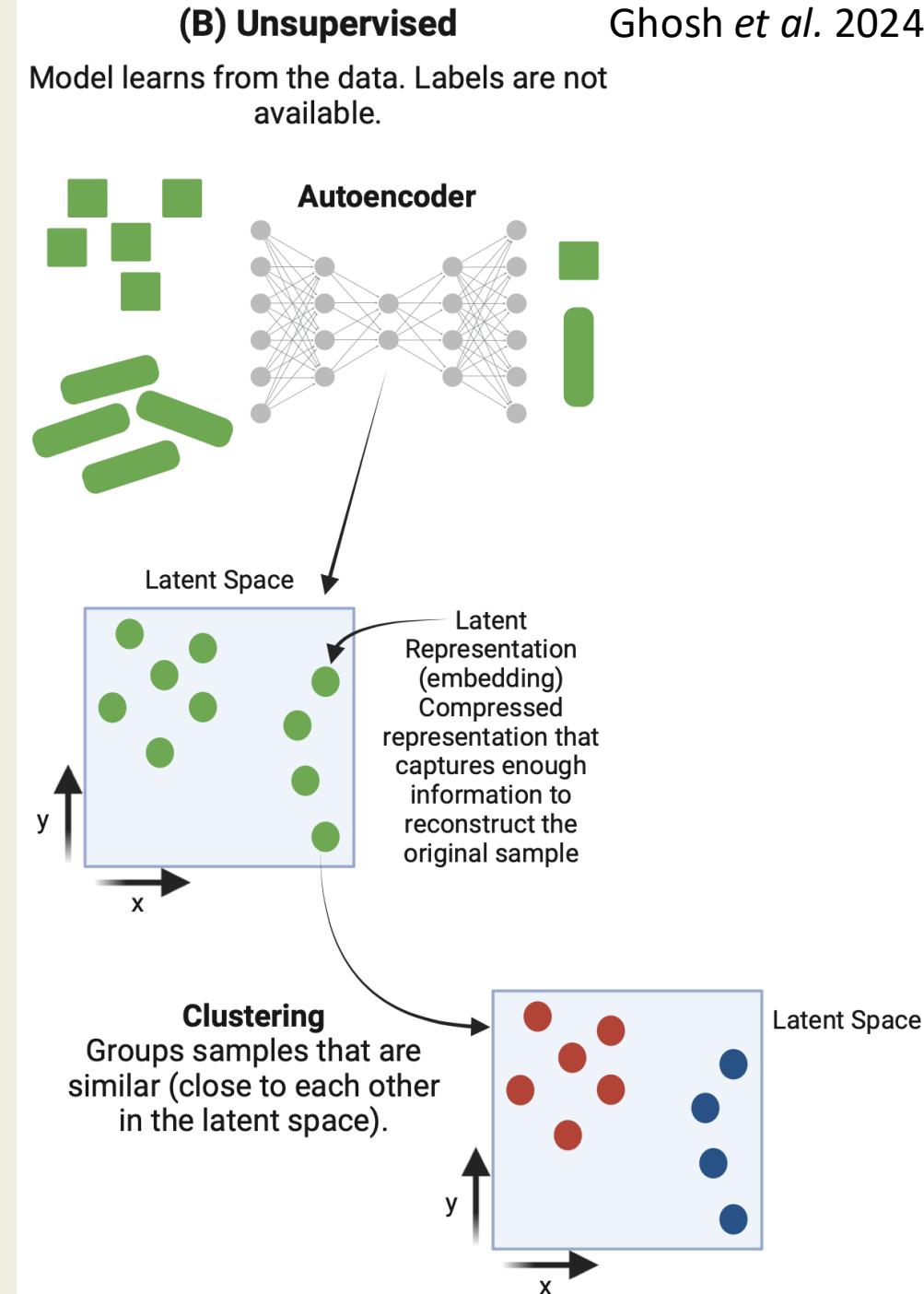
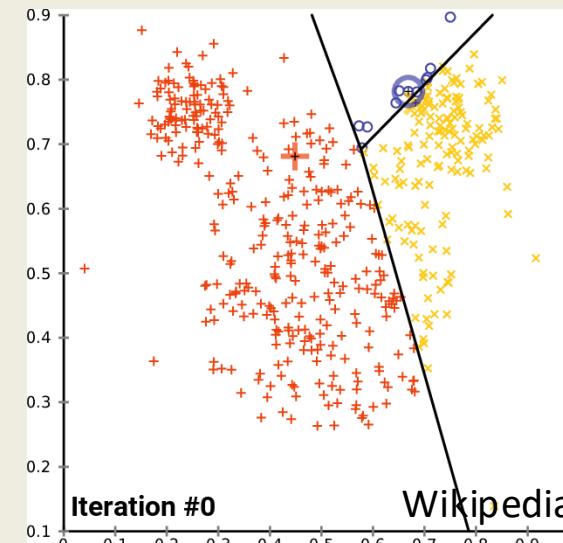
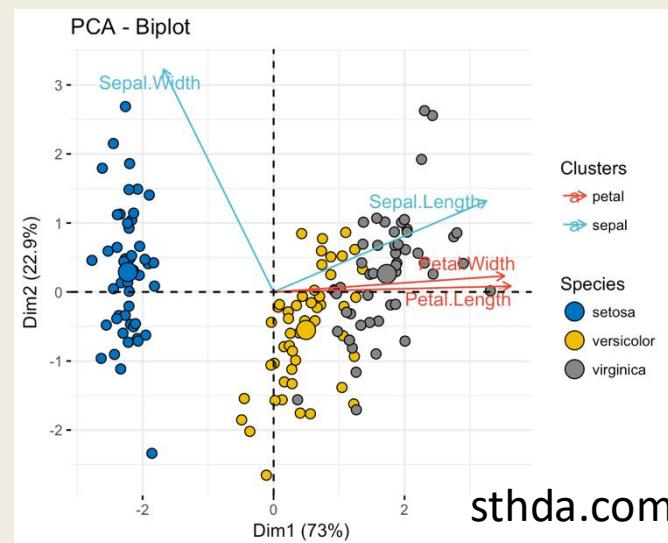
# Multi-Instance Learning (MIL)

- WSIs are too large to process directly, so they are divided into smaller patches
- The WSI is treated as a bag of instances (patches)
- The training label (e.g., tumor type) is assigned to the whole WSI (bag), not individual patches (instances)
- The model identifies which patches are most relevant for the label



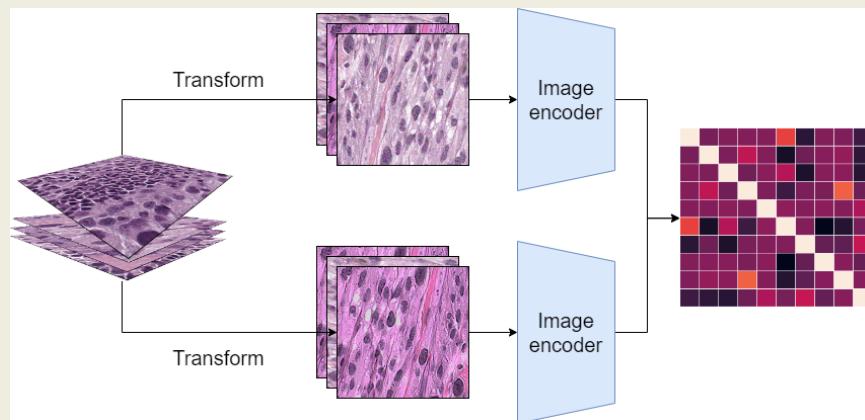
# Unsupervised Learning (UL)

- Models find patterns in unlabeled data
- Examples:
  - Clustering cell types.
  - Identifying tissue patterns.
  - Cancer subtype discovery
- Harder to validate outcomes
- Principal Component Analysis, k-means clustering



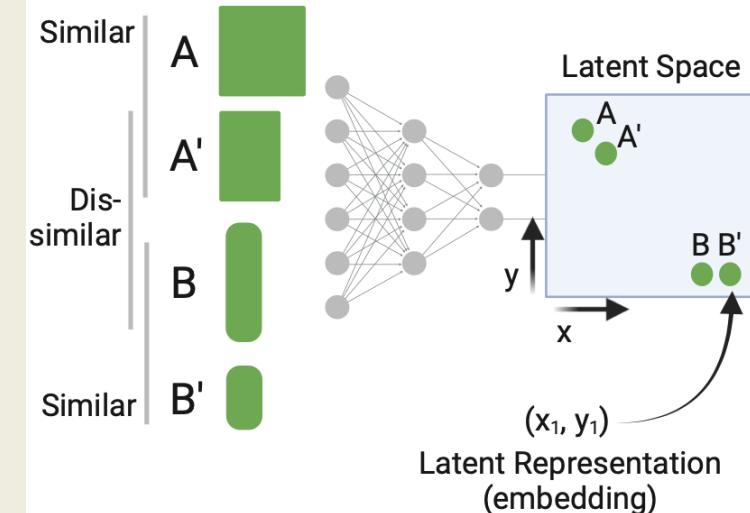
# Self-supervised Learning (SSL)

- Combines SL and UL with labels generated from the data itself.
- SSL formulates the objective to learn a latent spaces grouping together 'similar' data points.
- Example:
  - Image patch-level representations.
  - Pretraining on unlabeled WSIs for downstream tasks (e.g., segmentation).
- Barlow-Twins (Zbontar et al. 2021)
  - Maximize correlation between transformed versions of the same image
  - Minimize correlation between transformed versions of different images



## (C) Self-supervised

Model learns from labels generated from the data. Labels are not available.

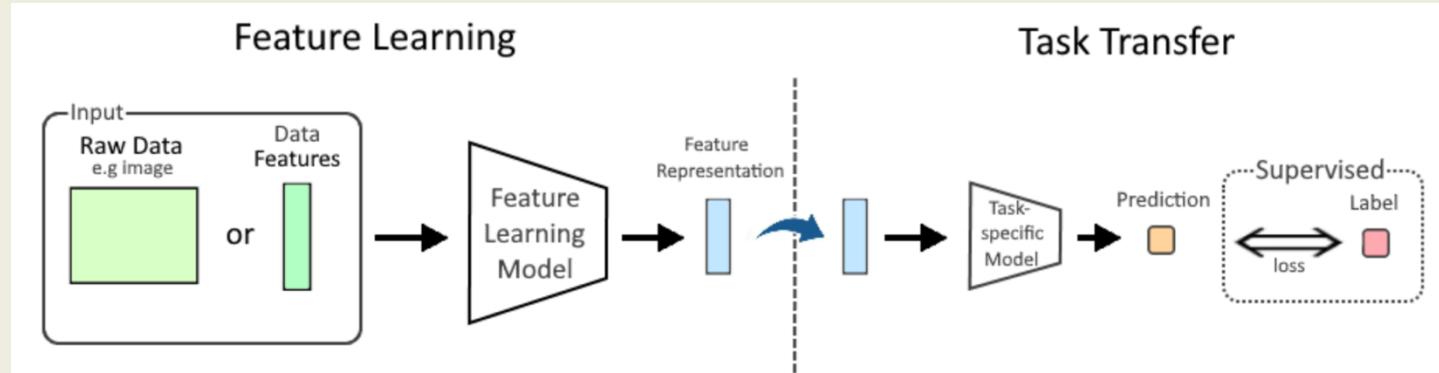


Self-supervised learning using **contrastive learning**. The model learns a latent space where similar samples are close to each other and dissimilar samples are well separated. Here A' and B' are generated by transforming A and B, respectively - a process referred to as data augmentation. The labels used for training the model, 'similar' and 'dissimilar', are therefore generated from the data.

Ghosh et al. 2024

# Transfer-learning

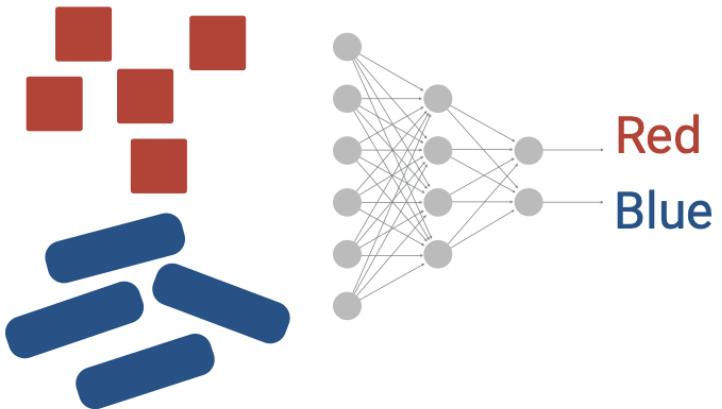
- Fine-tuning to further optimises general latent spaces for a specific task.
- Reduces the need for large annotated datasets.
- Combines SSL with SL or UL
- Example:
  - Large pretrained image models on natural images used for tumor segmentation



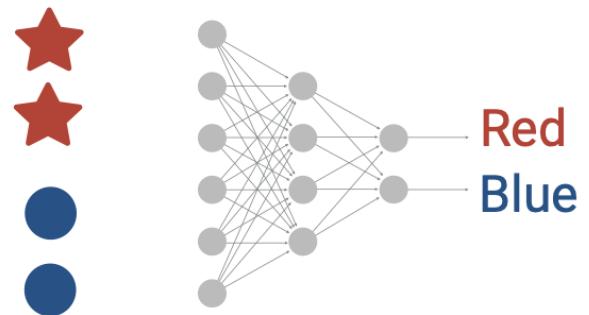
Wikipedia

## (D) Transfer Learning

1. Model is (pre-)trained on a related task with adequate data



2. Model is fine-tuned (trained further) on actual task with limited data



Ghosh et al. 2024

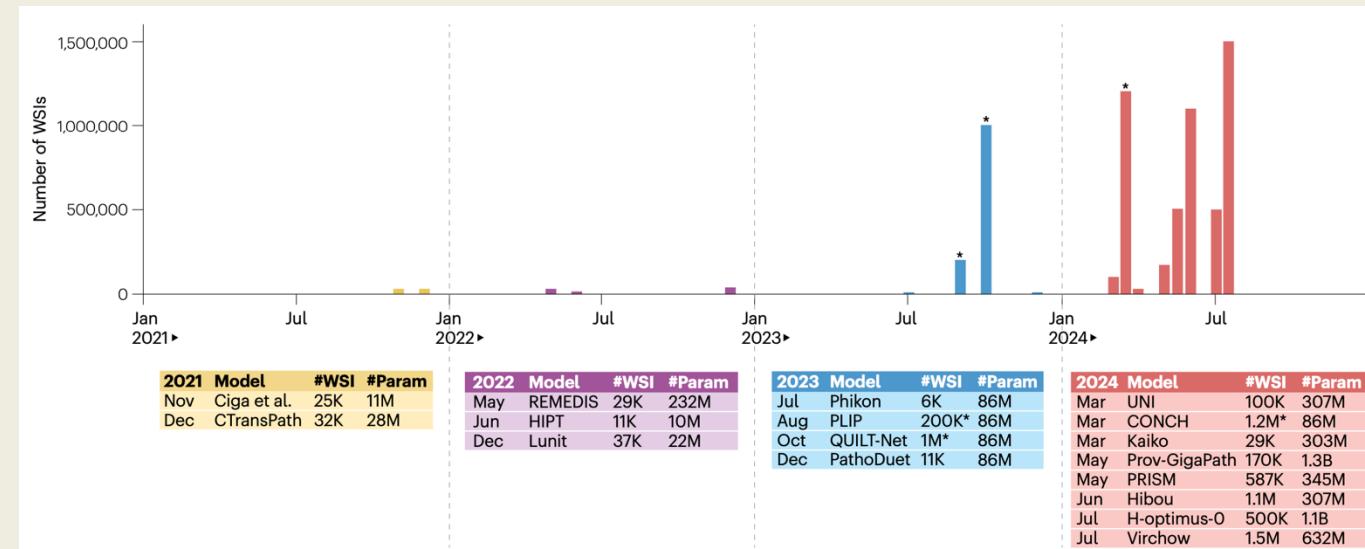
# The age of foundation models

Jana Lipkova &amp; Jakob Nikolas Kather

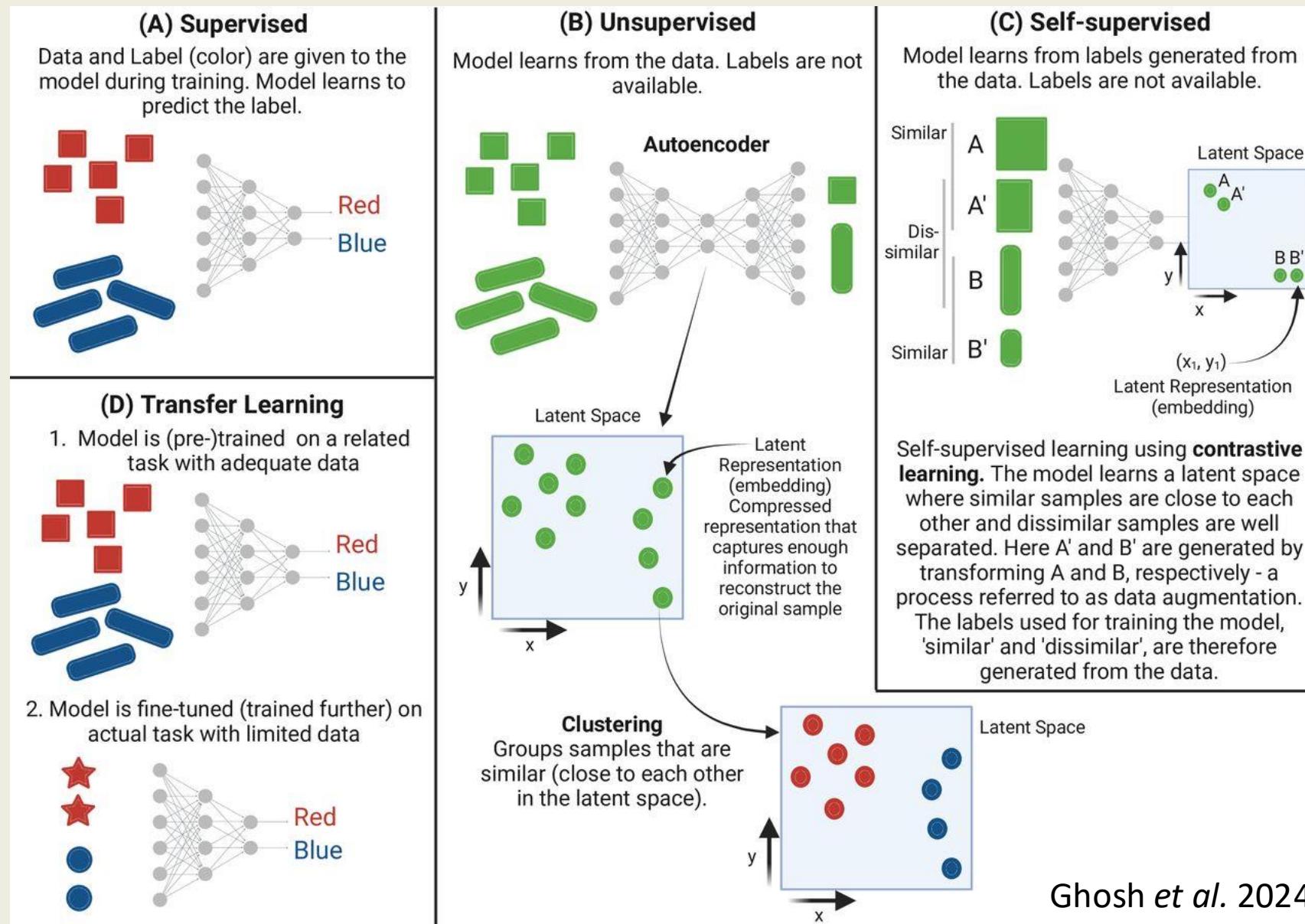
Check for updates

# Foundation models

- Defined as an "*AI model that is trained on broad data at scale, is designed for generality of output, and can be adapted to a wide range of distinctive tasks* » EU AI act.
- chatGPT is a language foundation model
- Such models also exist for images, music, coding, radiology, genomics, histopathology...



# Summary

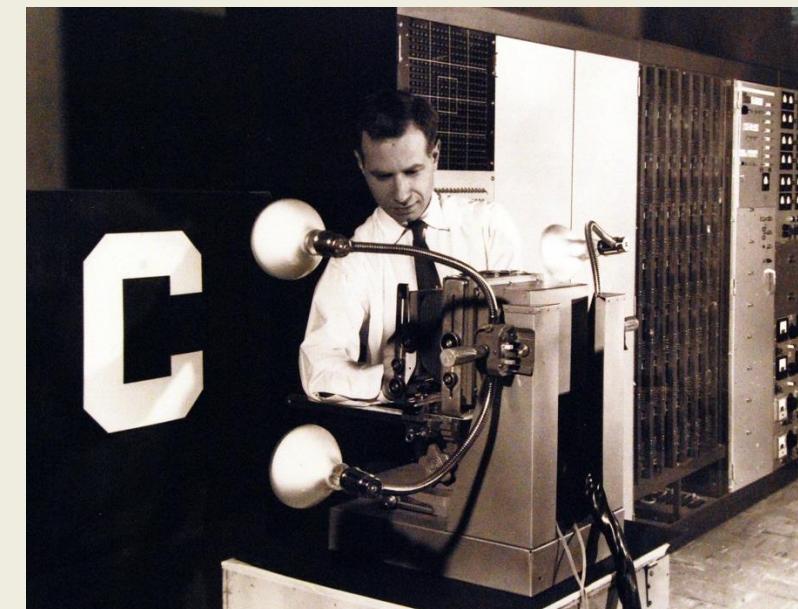
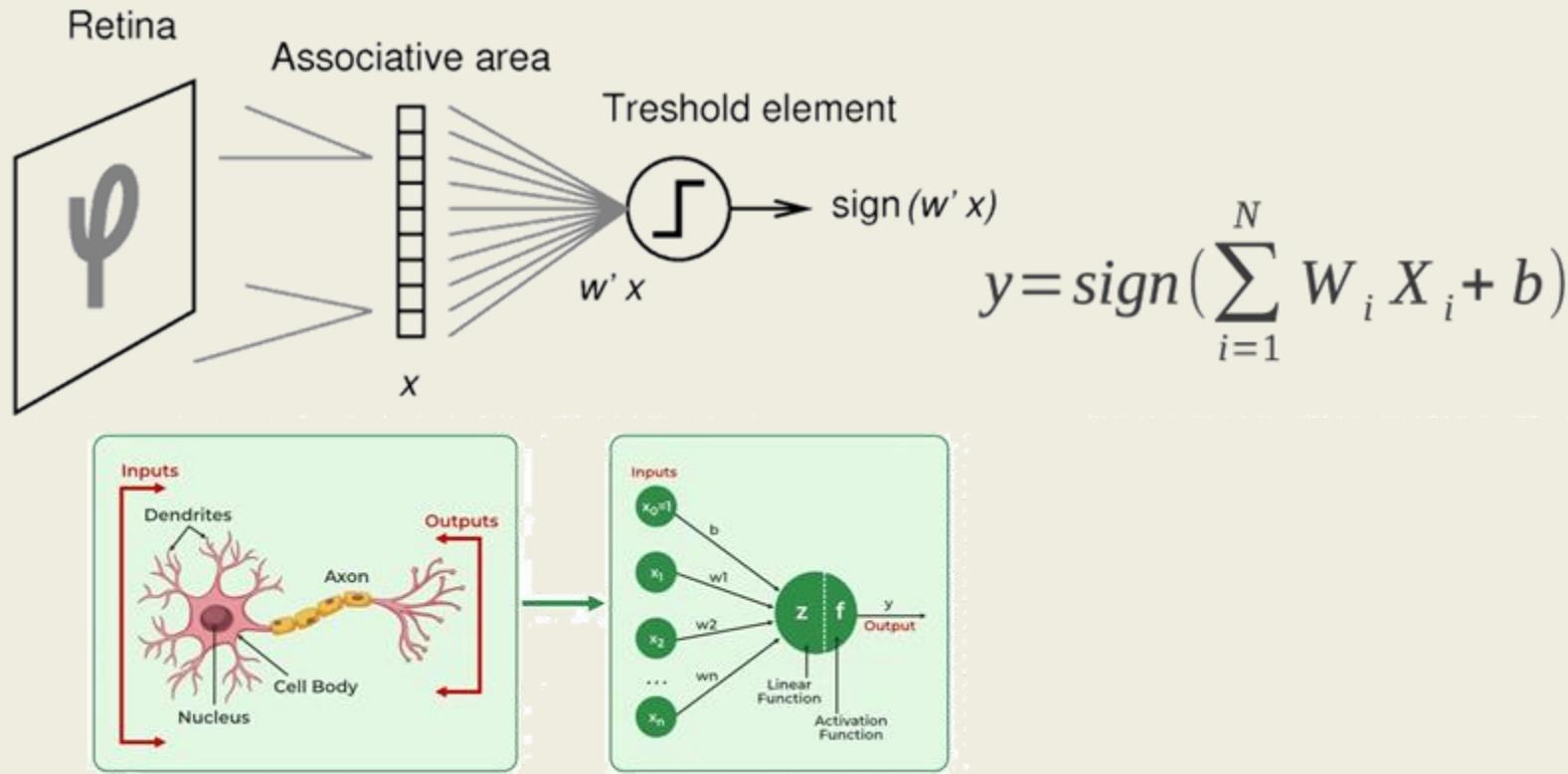


# Agenda

- Histopathology, genomics and deep-learning
- Machine learning paradigms
- Deep learning concepts and architectures
- Applications in histopathology
- Challenges and future directions

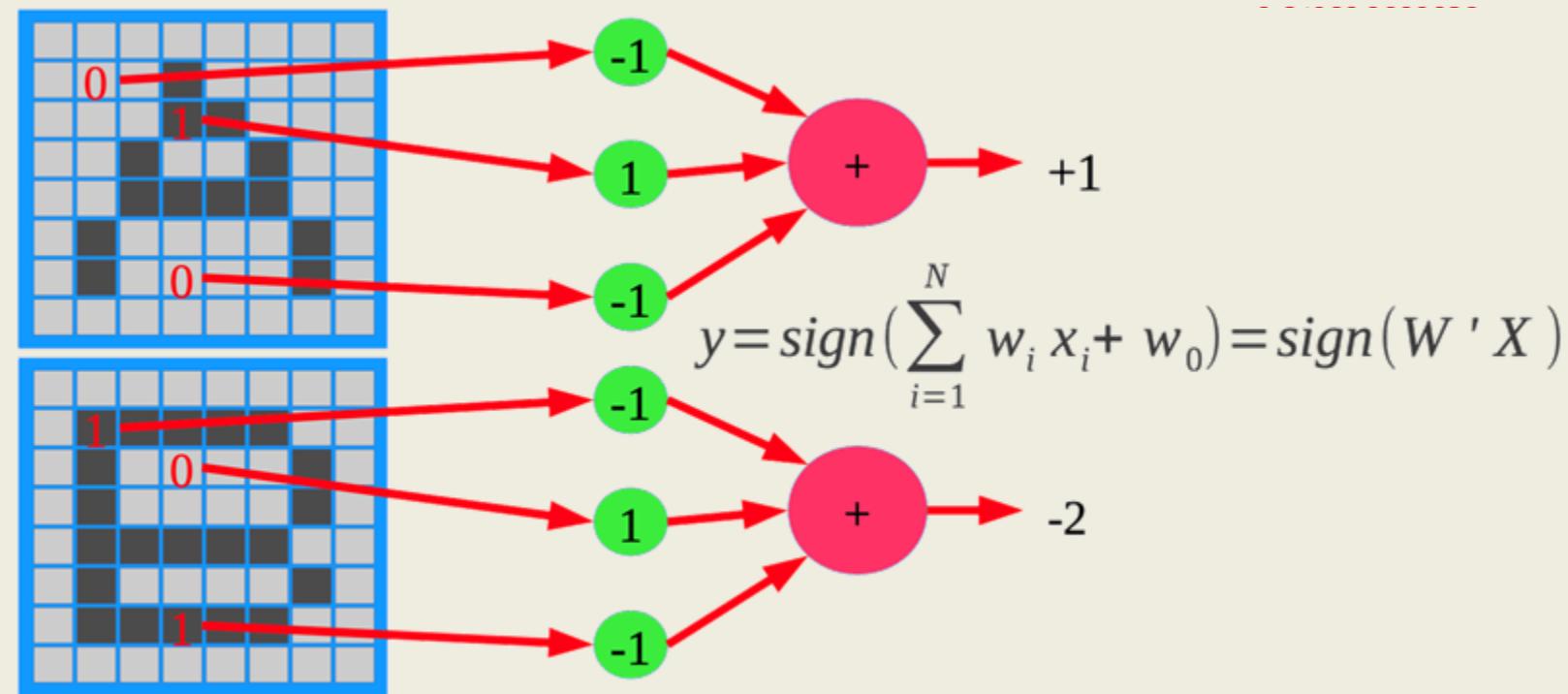
# The perceptron, the first neural network (1957)

- Simulated neuron with adaptive "synaptic weights"
- Computes a weighted sum of inputs
- Output is +1 if the weighted sum is above a threshold, -1 otherwise



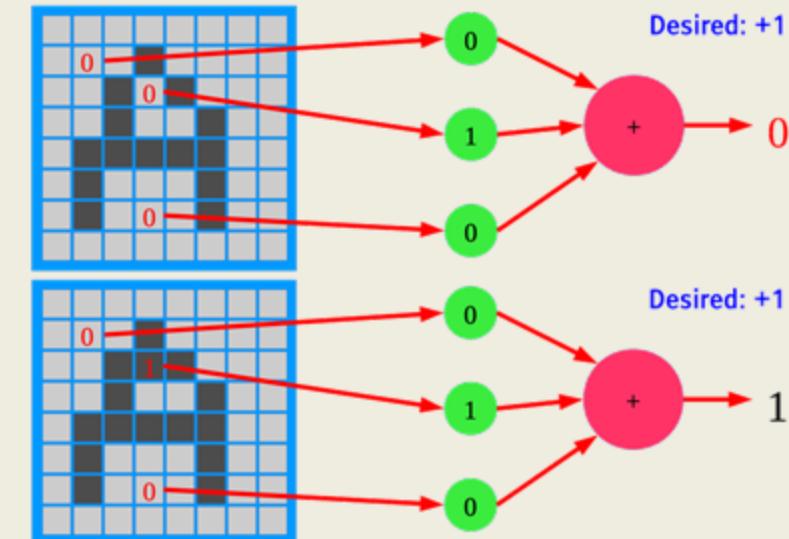
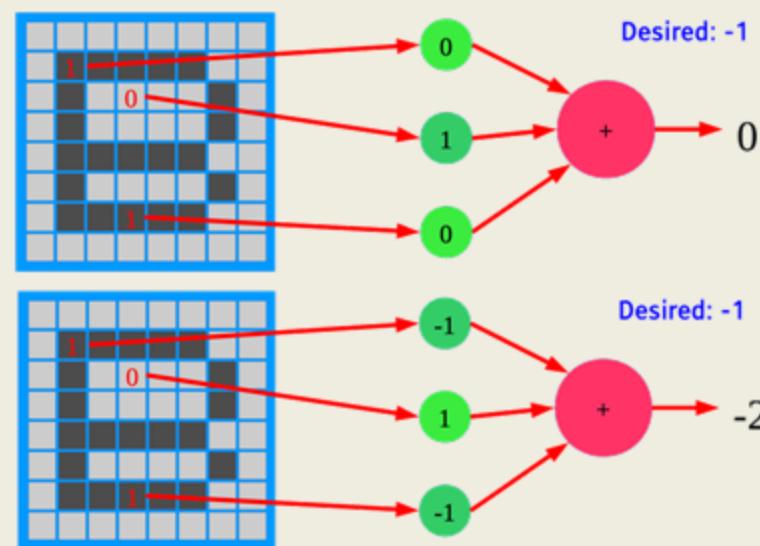
# The perceptron, the first learning machine (1957)

- Example: classifying letters A from B
- Goal: find the weight values that produce +1 for A and -1 for B
- Training set (supervised):  $(X,Y)=(A,+1),(B,-1),(A,+1),(B,-1),(A,+1),(B,-1),\dots$
- Learning: adjusting the weights so as to obtain the desired result = "backpropagation"



# The perceptron, the first learning machine (1957)

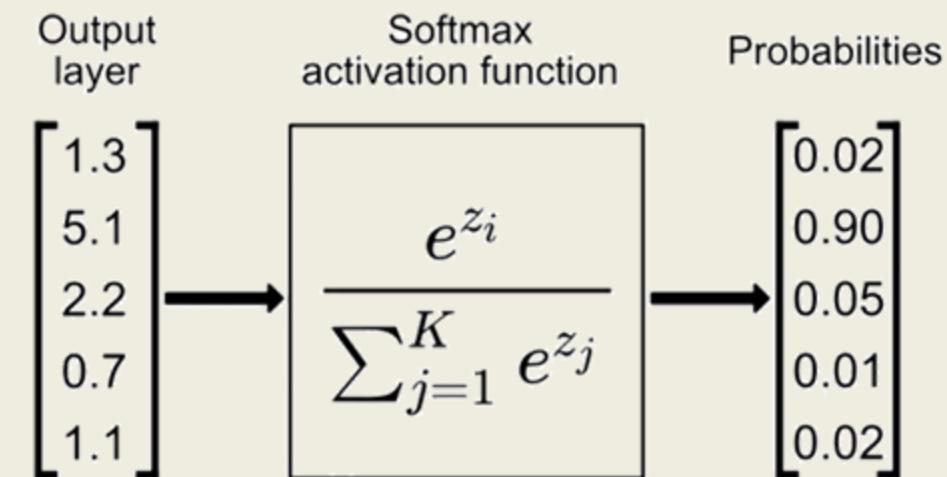
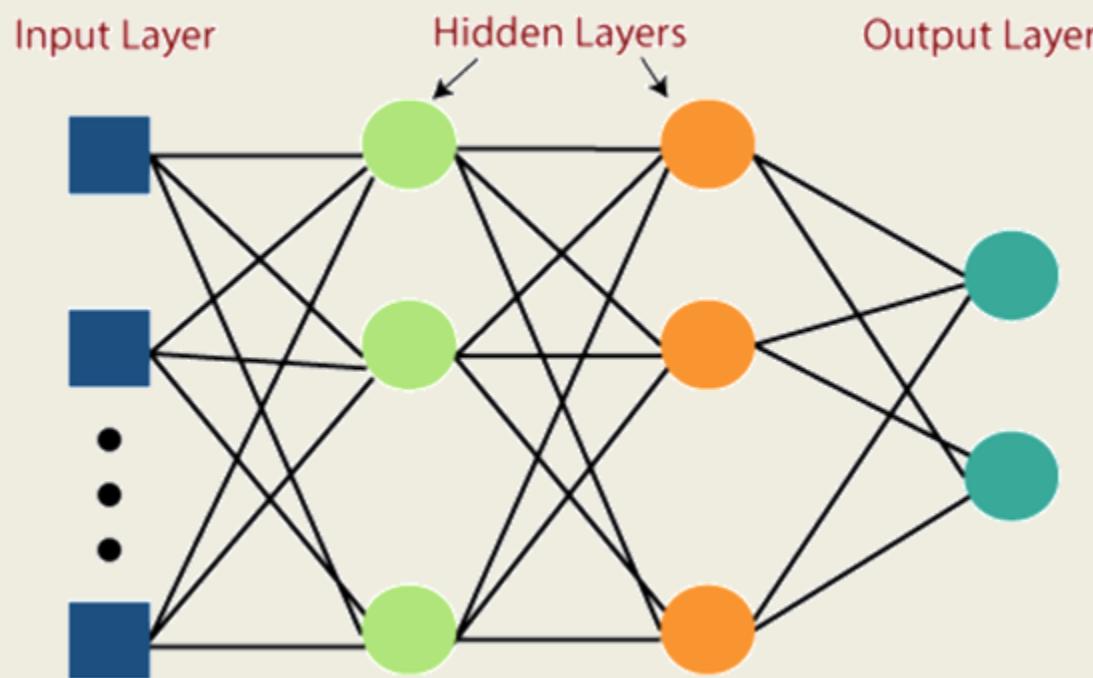
- Take one sample  $(X_k, Y_k)$ , if the output is larger than the desired output ( $\text{diff} = \text{"loss"}$ )
  - Decrease the weights whose input is 1
  - Increase the weights whose input is 0
- If the output is smaller than the desired output, do the converse, if equal, do nothing.
- Iterating over all training samples is called an "epoch", needs several to achieve convergence



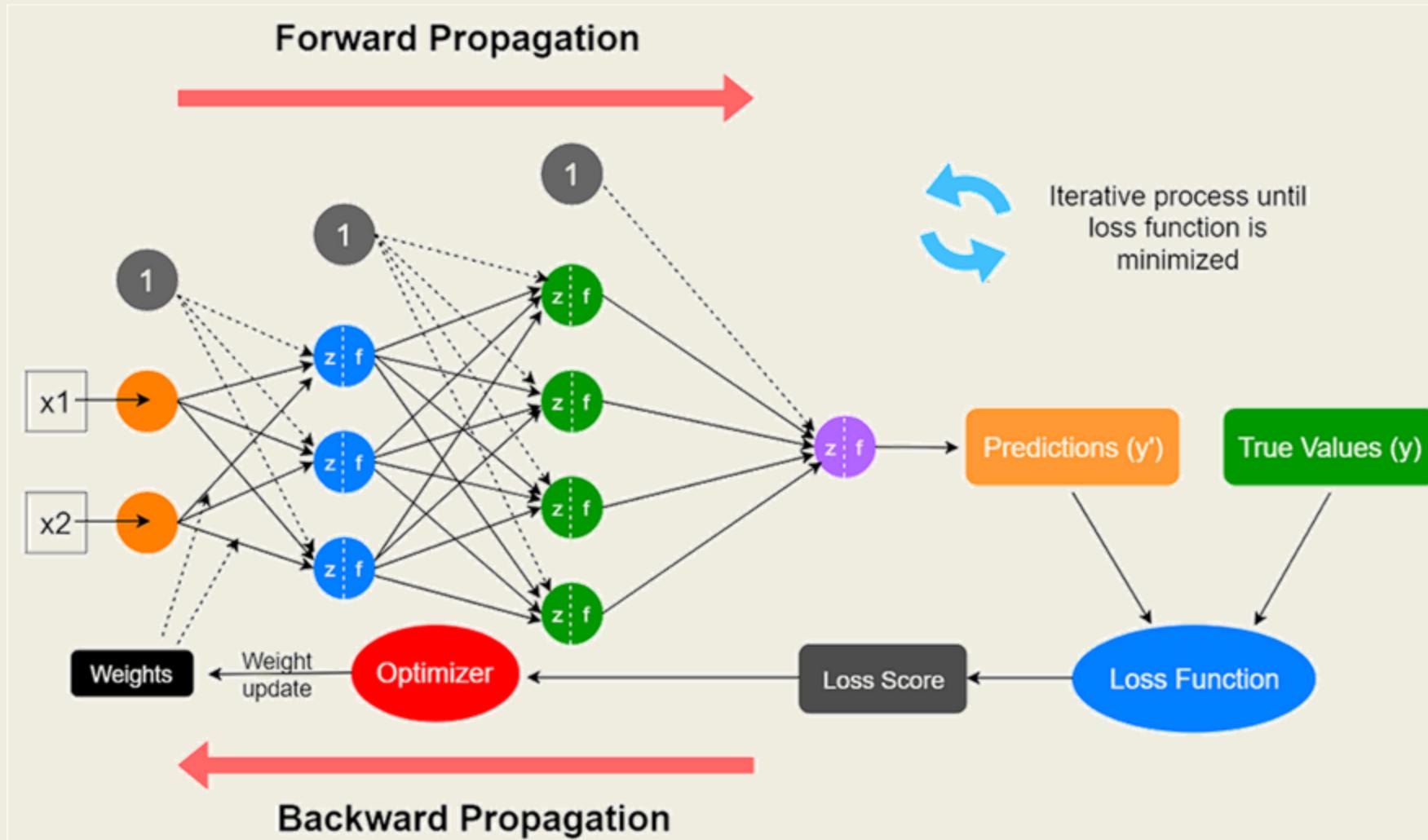
Easy to find simple R/Python code implementing this online

# Multilayer perceptron (MLP, 1980s)

- Deep networks learn and represent increasingly abstract and complex features in the data.
- Each hidden layer extracts higher-level representations of the input, allowing the network to capture non-linear relationships more effectively
- More complex "activation functions" allow multi-classification

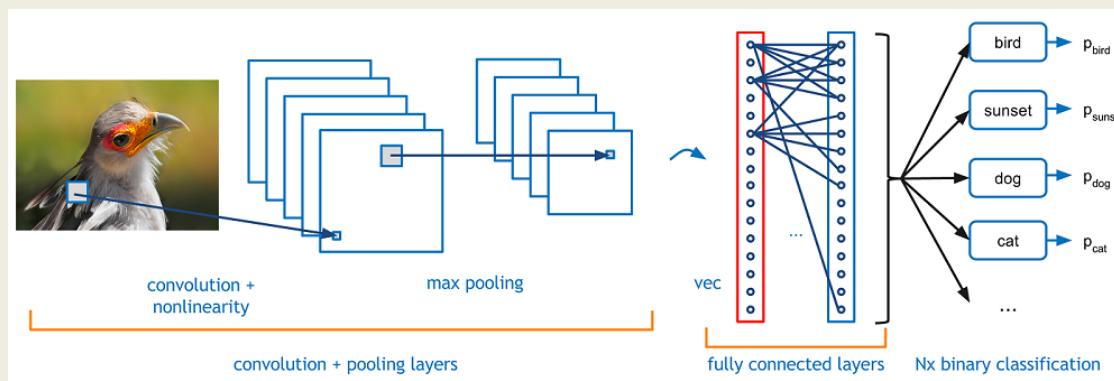


# Deep Neural networks



# Convolutional Neural Networks (1990s)

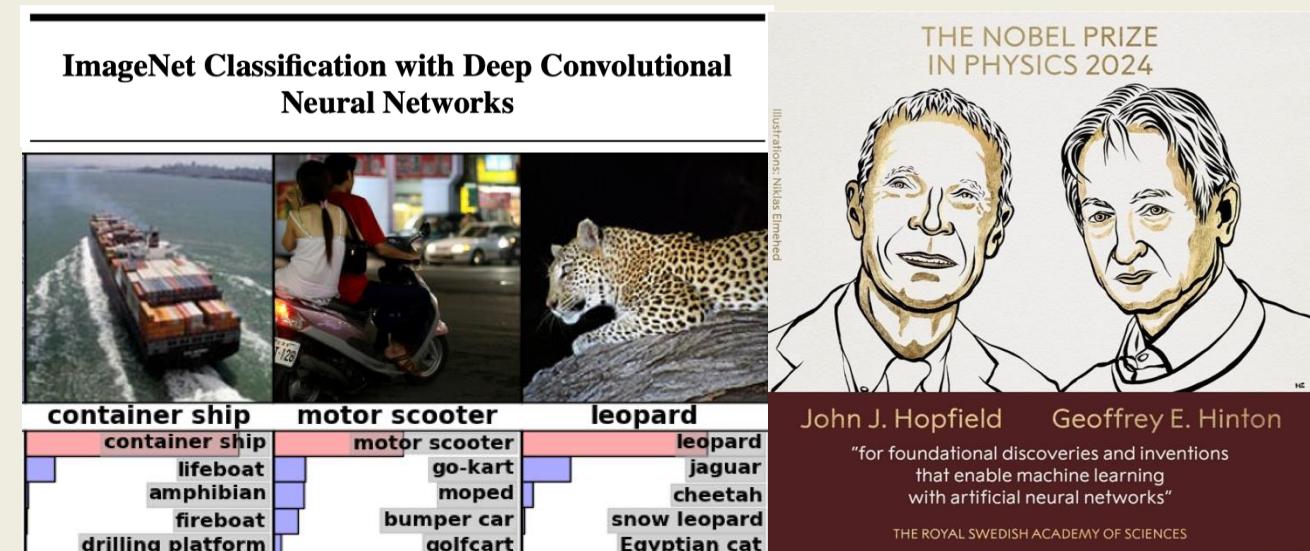
- Focus on small regions, like patches, to find patterns (convolution)
- Use pooling to reduce complexity
- Learn spatially invariant features
- Early layers detect simple patterns (e.g., edges, colors), deeper layers identify complex structures (e.g., shapes, objects).

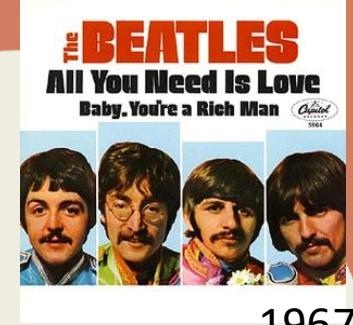


ImageNet Classification with Deep Convolutional  
Neural Networks



container ship	motor scooter	leopard
container ship	motor scooter	leopard
lifeboat	go-kart	jaguar
amphibian	moped	cheetah
fireboat	bumper car	snow leopard
drilling platform	golfcart	Egyptian cat



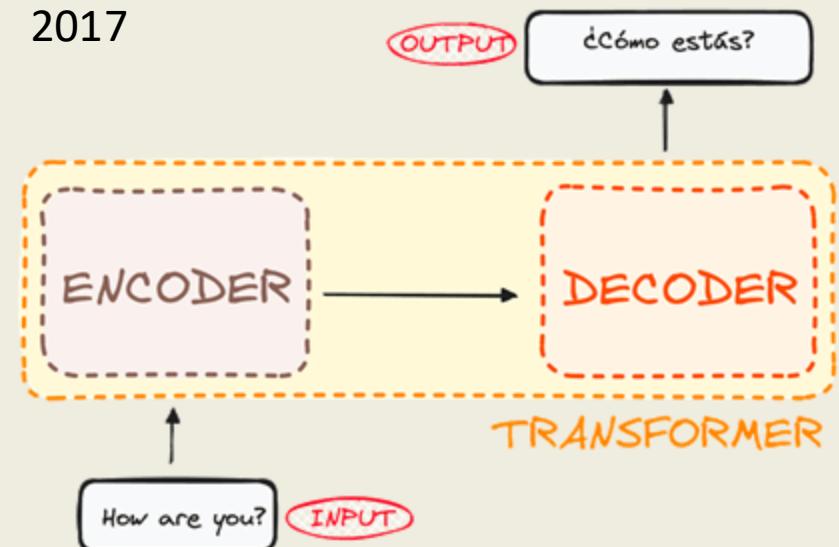


# Transformer architecture (2020s)

- The “T” in ChatGPT
- Attention mechanism (developed by Google)
  - Focus on important parts: highlights key parts of input (e.g., words, regions).
  - Assigns weights: gives higher weights to relevant information.
  - Dynamic context: adjusts focus based on input relationships.

## Attention Is All You Need

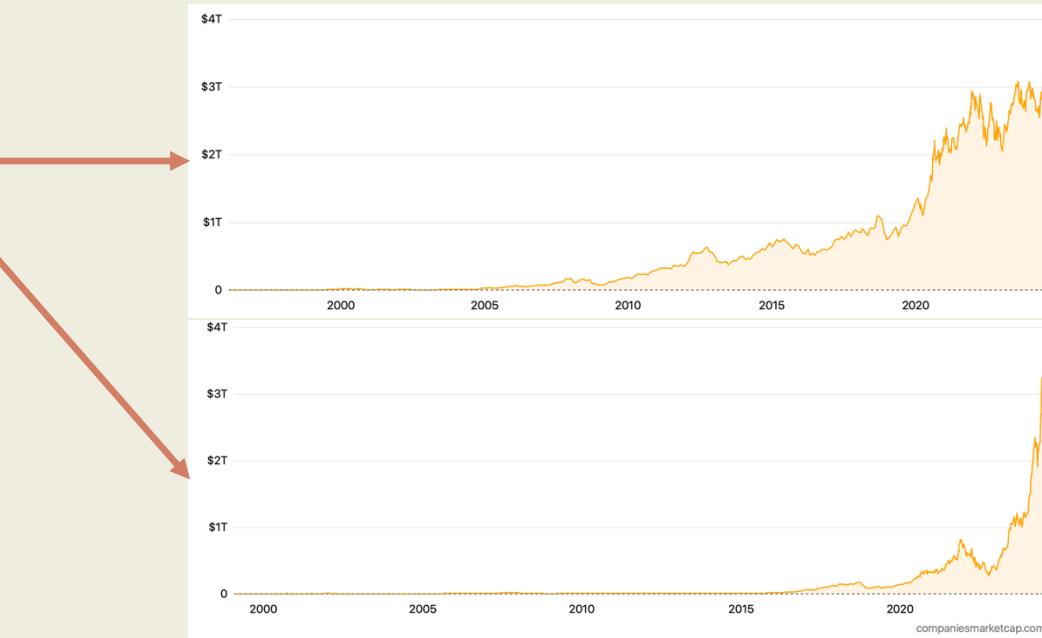
2017



# Infrastructure

- Py Torch & Tensorflow: deep-learning Python frameworks
- Hugging Face: platform to collaborate on models, datasets, and applications
- Google Colab: cloud computing notebook in web browser
- GPUs

Rank	Name	Market Cap
1	Apple AAPL	\$3.553 T
2	NVIDIA NVDA	\$3.353 T
3	Microsoft MSFT	\$3.182 T
4	Amazon AMZN	\$2.185 T
5	Alphabet (Google) GOOG	\$2.076 T



# Agenda

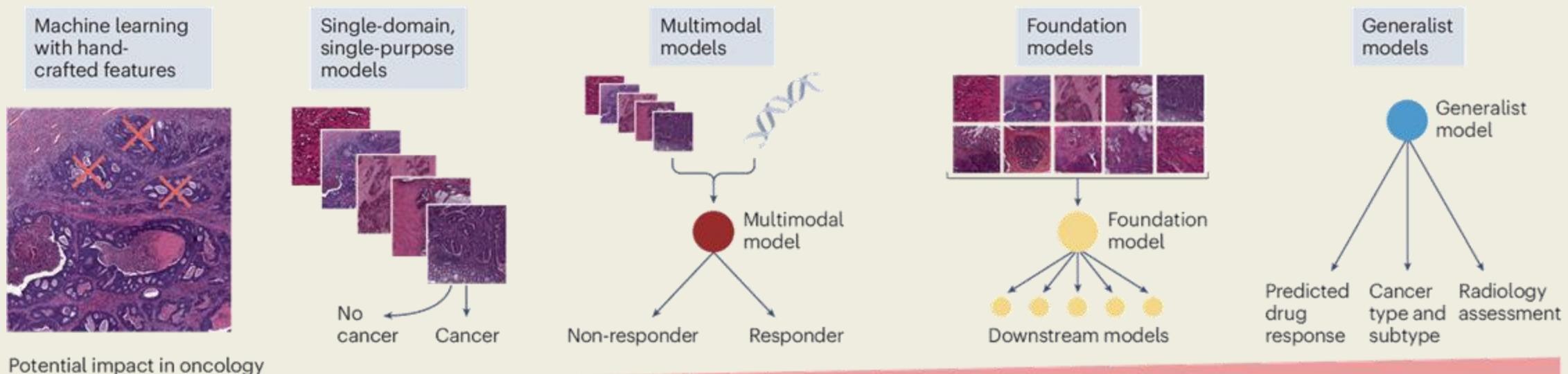
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- Machine learning paradigms
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# From digital pathology to AI

a



b

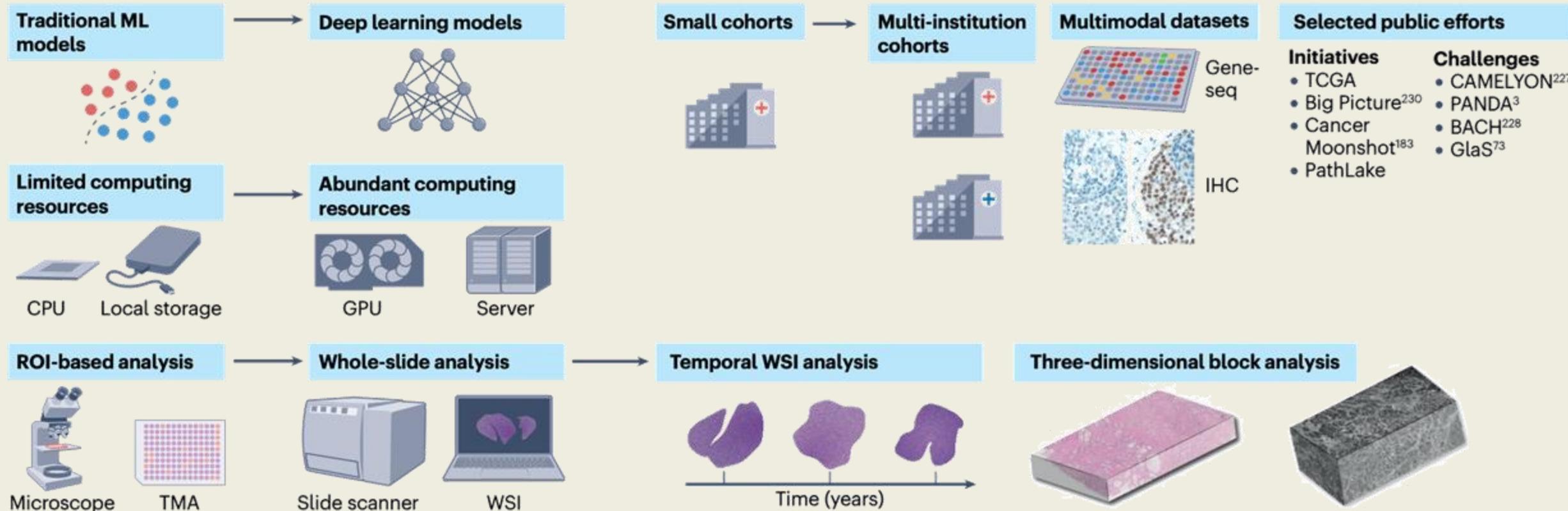


# Why now?

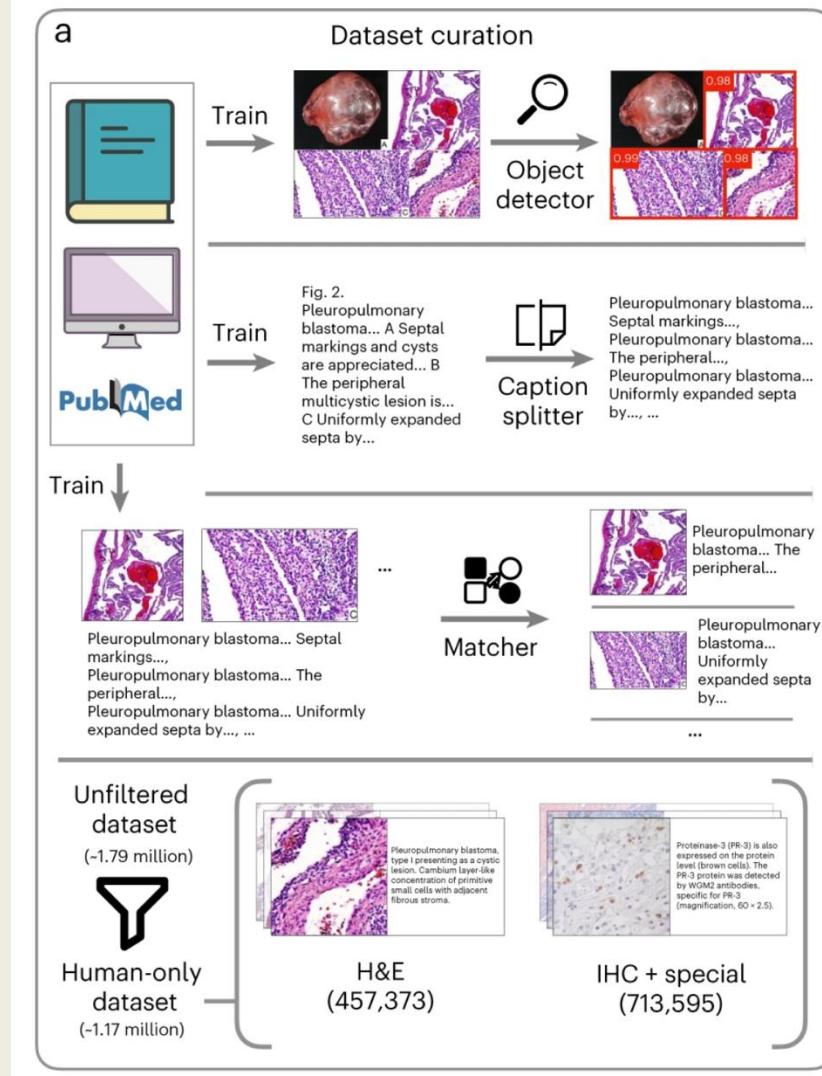
Review article

## Artificial intelligence for digital and computational pathology

Andrew H. Song<sup>1,2,3,4,8</sup>, Guillaume Jaume<sup>1,2,3,4,8</sup>, Drew F. K. Williamson<sup>1,2,3,4</sup>, Ming Y. Lu<sup>1,2,3,4,5</sup>, Anurag Vaidya<sup>1,2,3,4,6</sup>, Tiffany R. Miller<sup>1</sup> & Faisal Mahmood<sup>1,2,3,4,7</sup>



# Why now? Foundation models (eg CONCH)



Article <https://doi.org/10.1038/s41591-024-02856-4>

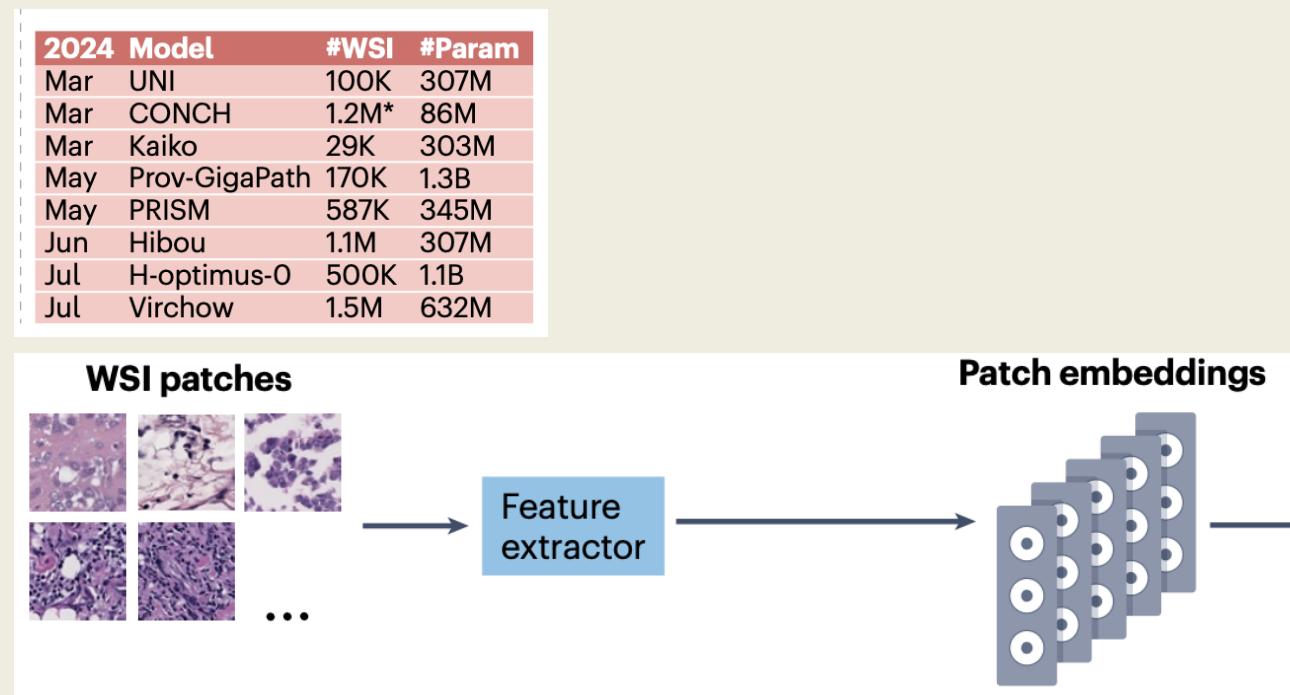
## A visual-language foundation model for computational pathology

**nature medicine**

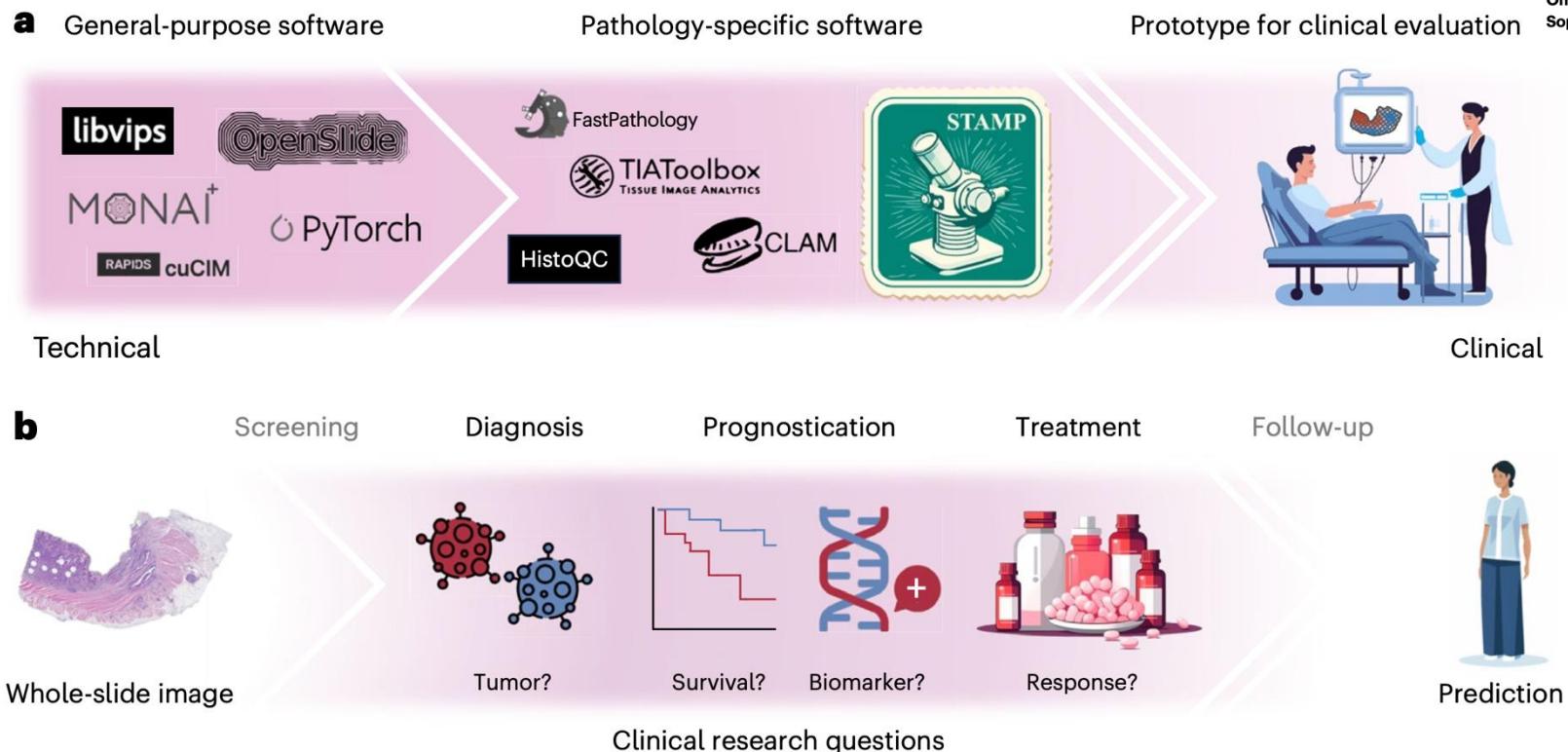
Received: 2 August 2023  
Accepted: 5 February 2024  
Published online: 19 March 2024

Ming Y. Lu <sup>1,2,3,4,5,11</sup>, Bowen Chen <sup>1,2,11</sup>, Drew F. K. Williamson <sup>1,2,3,11</sup>, Richard J. Chen <sup>1,2,3,4,6</sup>, Ivy Liang <sup>1,7</sup>, Tong Ding <sup>1,7</sup>, Guillaume Jaume <sup>1,2,3,4</sup>, Igor Odintsov <sup>1</sup>, Long Phi Le <sup>2</sup>, Georg Gerber <sup>1</sup>, Anil V. Parwani <sup>8</sup>, Andrew Zhang <sup>1,2,3,4,9</sup> & Faisal Mahmood <sup>1,2,3,4,10</sup>

2024 Model	#WSI	#Param
Mar UNI	100K	307M
Mar CONCH	1.2M*	86M
Mar Kaiko	29K	303M
May Prov-GigaPath	170K	1.3B
May PRISM	587K	345M
Jun Hibou	1.1M	307M
Jul H-optimus-O	500K	1.1B
Jul Virchow	1.5M	632M



# Why now? User-friendly



## Protocol

## From whole-slide image to biomarker prediction: end-to-end weakly supervised deep learning in computational pathology

Omar S. M. El Nahhas<sup>©1,2</sup>, Marko van Treeck<sup>1</sup>, Georg Wölfein<sup>©3</sup>, Michaela Unger<sup>1</sup>, Marta Ligero<sup>1</sup>, Tim Lenz<sup>1</sup>, Sophia J. Wagner<sup>4,5</sup>, Katherine J. Hewitt<sup>1</sup>, Firas Khader<sup>2,6</sup>, Sebastian Foersch<sup>7</sup>, Daniel Truhn<sup>2,6</sup> & Jakob Nikolas Kather<sup>©1,2,8,9</sup>

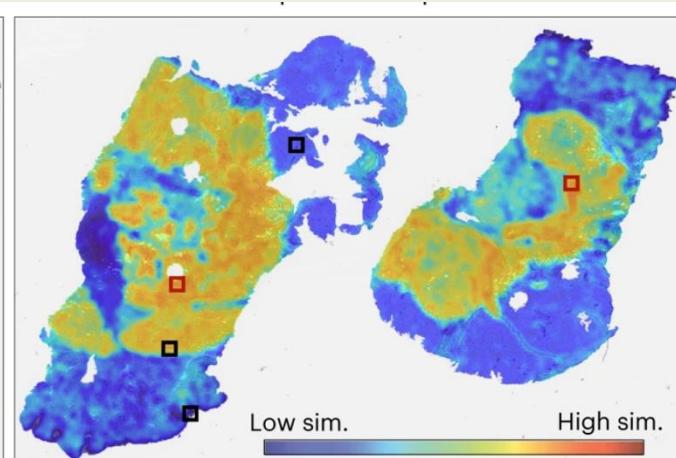
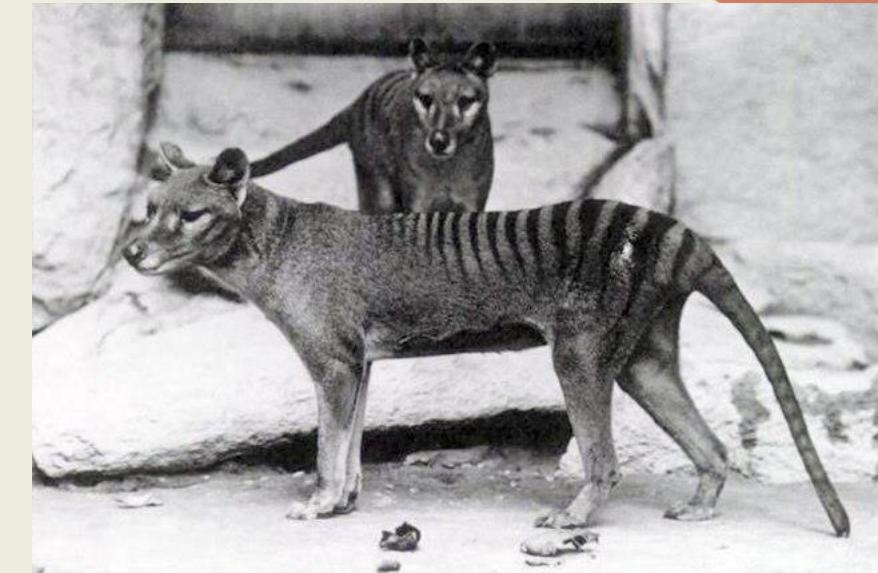
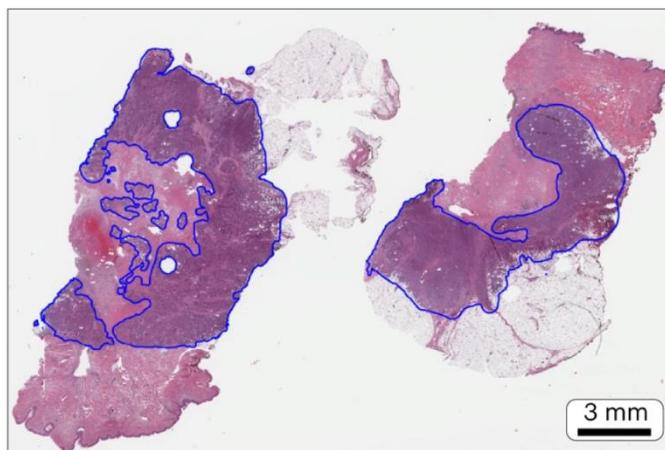
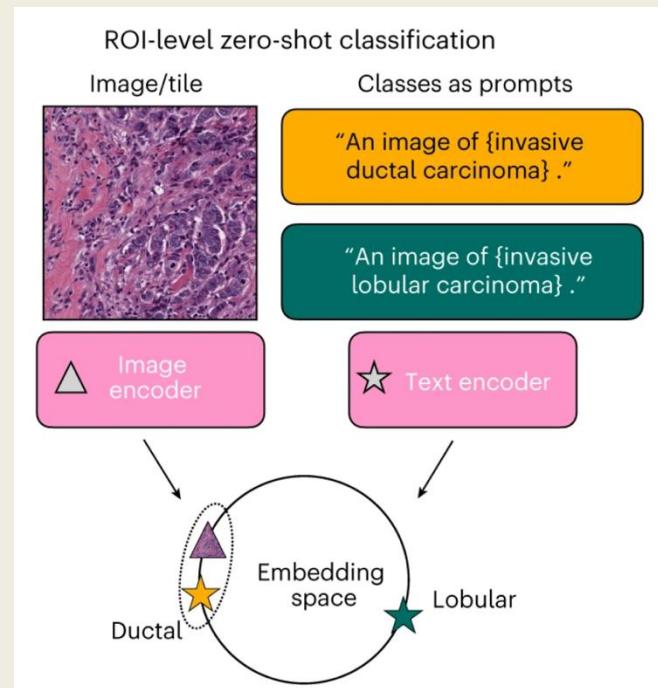
## Overview of all CLI commands of the STAMP software

stamp init: Create a new configuration file in the current directory  
 stamp setup: Download the required resources  
 stamp config: Show the configuration settings  
 stamp preprocess: Preprocess WSIs and extract features  
 stamp crossval: Train n\_splits models by using cross-validation

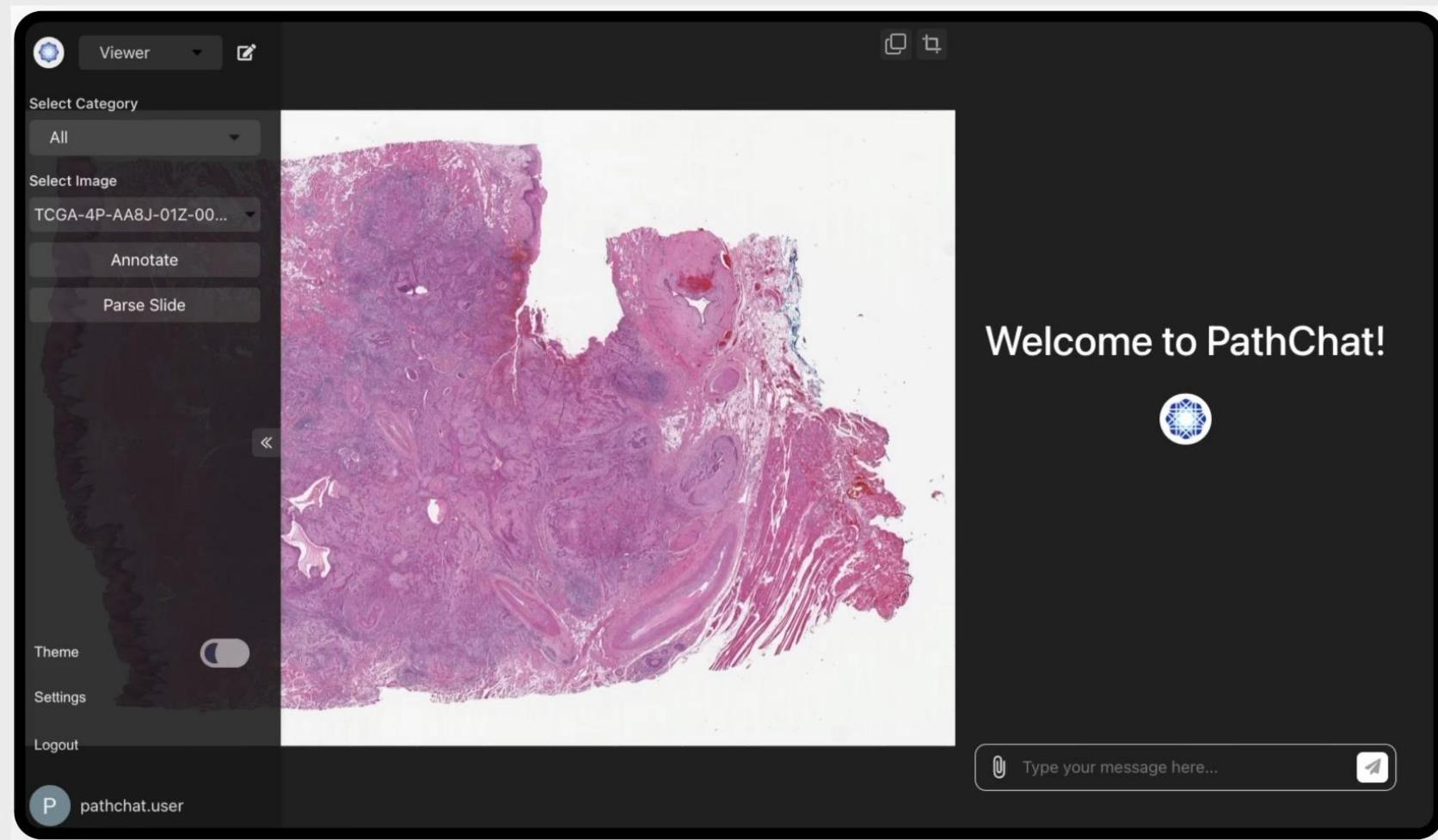
stamp train: Train a single model on the entire training cohort  
 stamp deploy: Deploy a trained model on an external testing cohort  
 stamp statistics: Compute the AUROC, AUPRC and corresponding 95% CI metrics  
 stamp heatmaps: Generate heatmaps and corresponding top tiles

# Foundation models

- One-(few) shot learning: after seeing only one occurrence of this Tasmanian tiger, I would easily recognize others
- Zero-shot learning with CONCH:

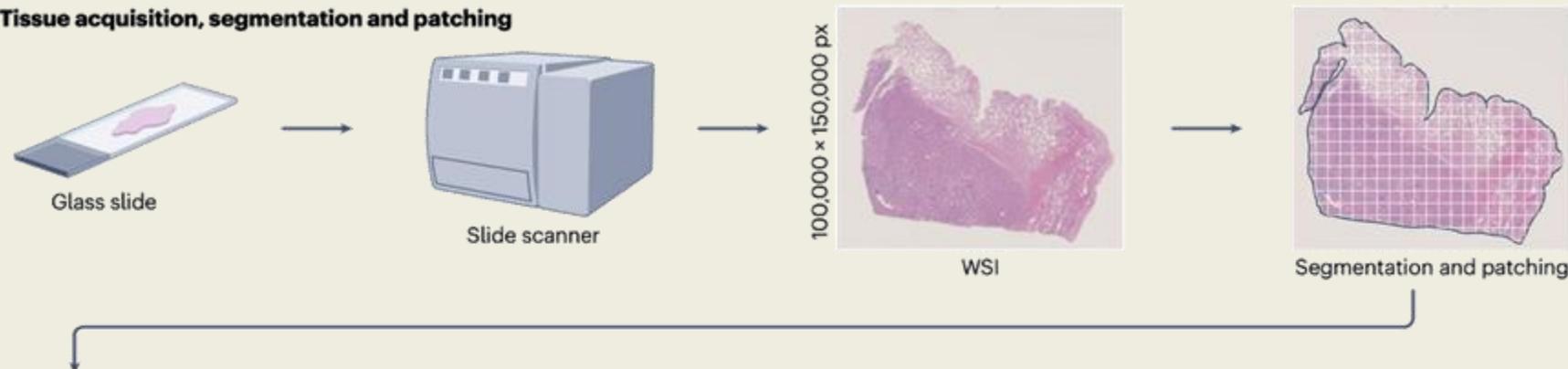


# PathChat: pathology chatbot derived from CONCH

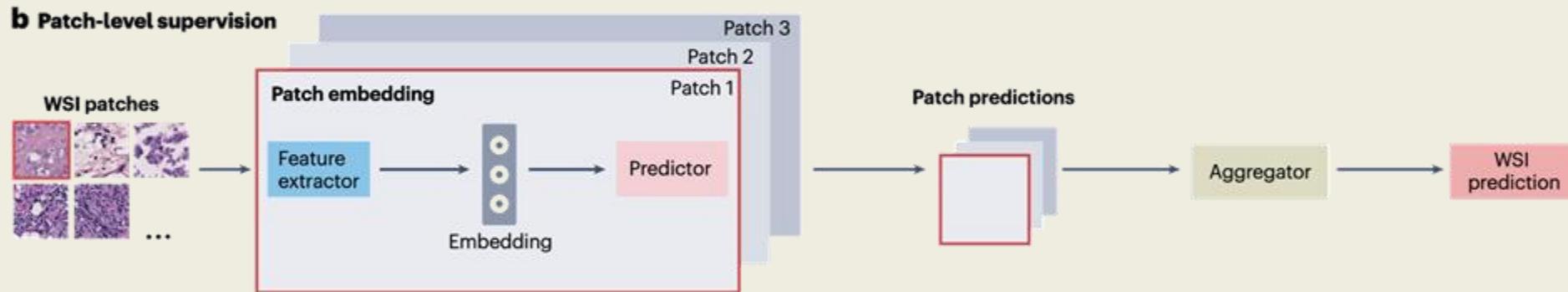


# Real-world WSI deep-learning workflow

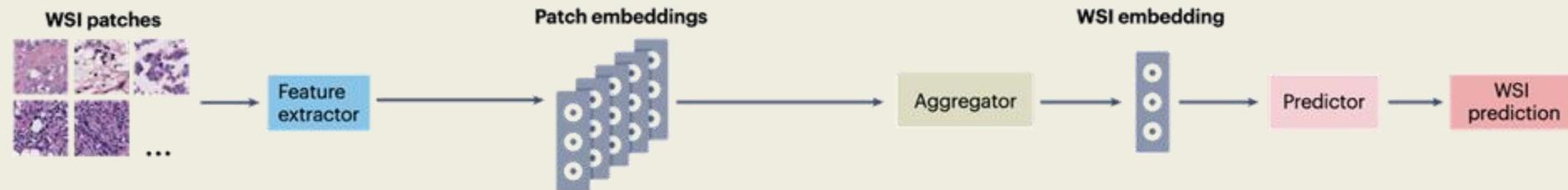
## a Tissue acquisition, segmentation and patching



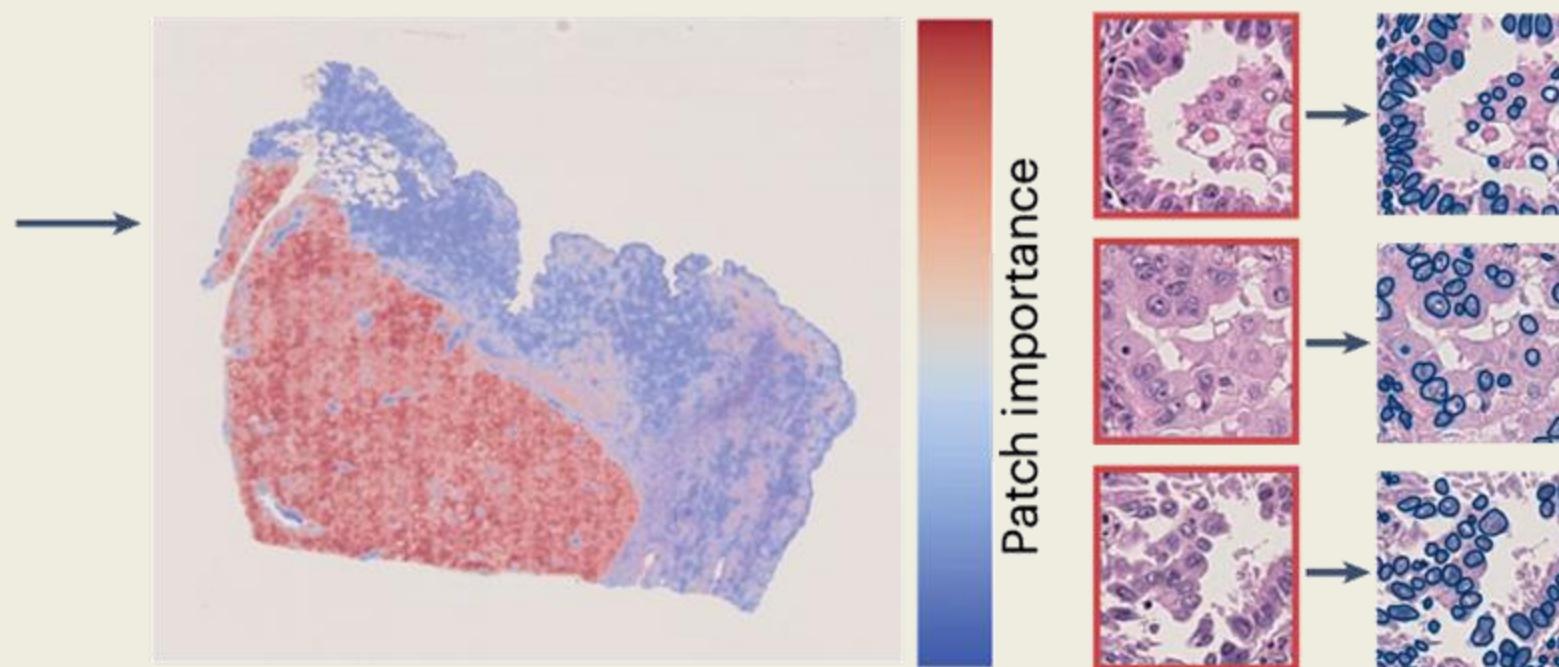
## b Patch-level supervision



## c MIL

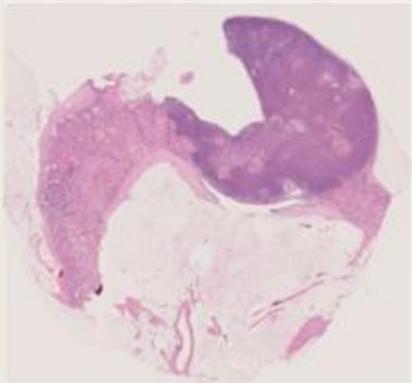


# Interpretability

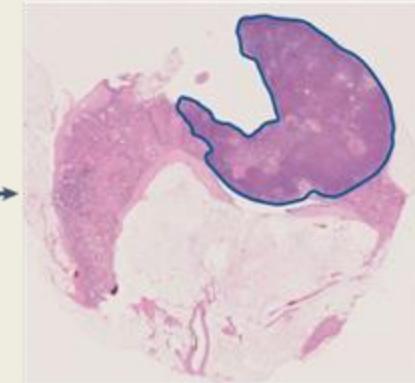


# AI for automation

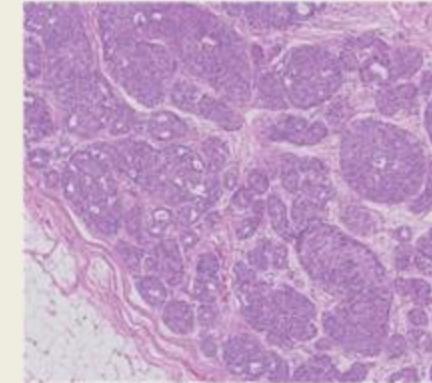
Tumour detection



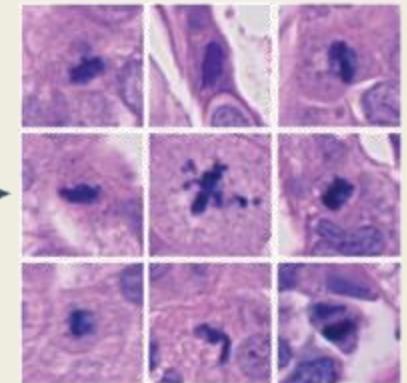
Semantic segmentation



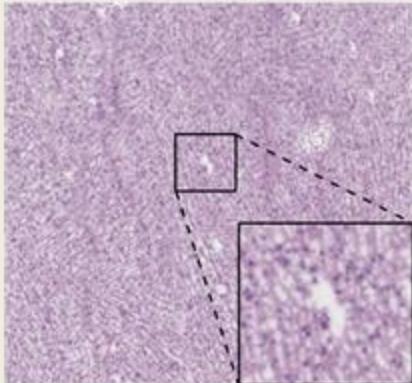
Mitotic count



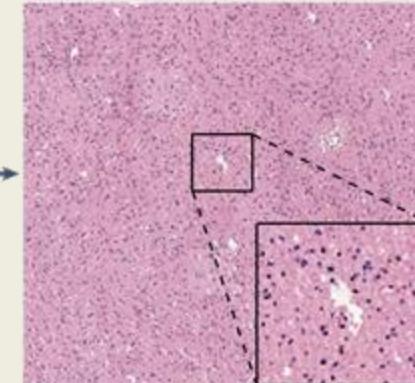
Instance segmentation



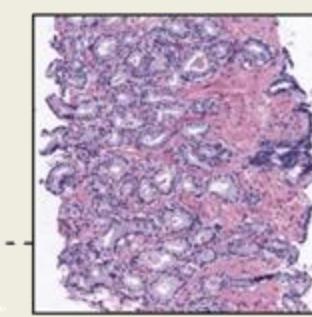
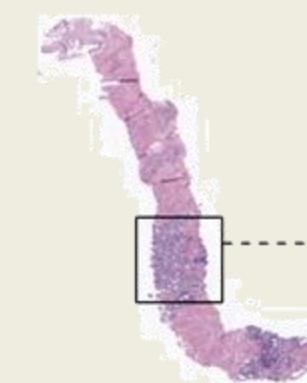
Stain enhancement



Generative modelling



Grading

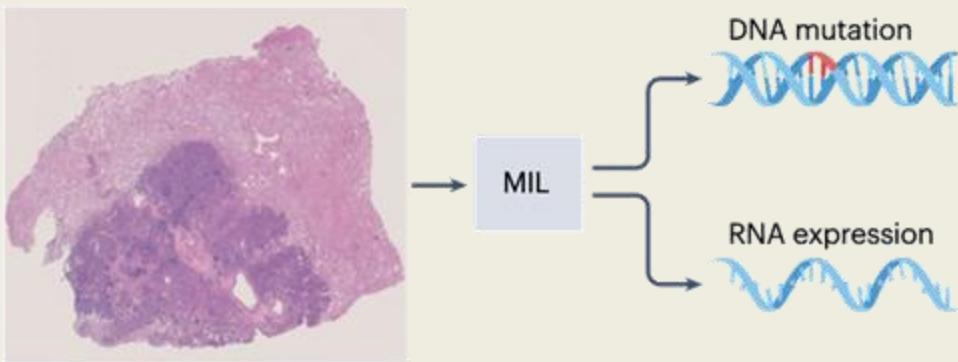


MIL

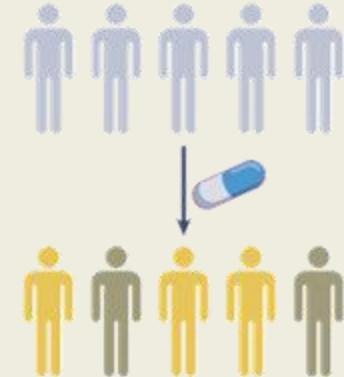
Pattern 3  
Pattern 4  
...

# AI for discovery

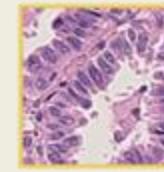
Prediction of molecular assays



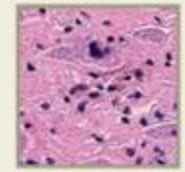
Biomarker for therapeutic response/drug discovery



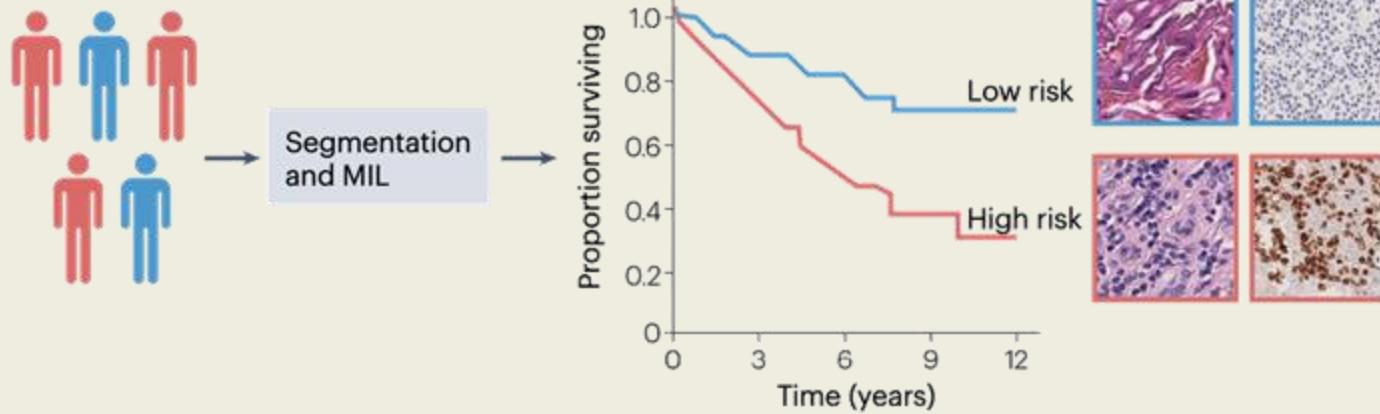
Biomarkers for non-responders



Biomarkers for responders



Biomarker for different risk groups



Applications for discovery

- Prediction**
- Mutation
  - RNA expression
  - Molecular subtype

- Biomarkers**
- Therapeutic response
  - Drug discovery

# Agenda

- Histopathology, genomics and deep-learning
- Machine learning paradigms
- Deep learning concepts and architectures
- Applications in histopathology
- Challenges and future directions

# Challenges

- Open-source models
- Data access
- Explainability
- Collaboration between AI researchers, cancer researchers, and pathologists/clinicians
- From tiles embeddings to WSI embeddings?
- Multi-modal integration (early fusion vs late fusion)

Andrew H. Song<sup>1,2,\*</sup>, Richard J. Chen<sup>1,2,\*</sup>, Tong Ding<sup>1,2</sup>, Drew F.K. Williamson<sup>1,2,†</sup>,  
Guillaume Jaume<sup>1,2</sup>, Faisal Mahmood<sup>1,2</sup>

<sup>1</sup>Mass General Brigham and <sup>2</sup>Harvard University

<https://doi.org/10.1038/s41586-024-07441-w>

Received: 30 November 2023

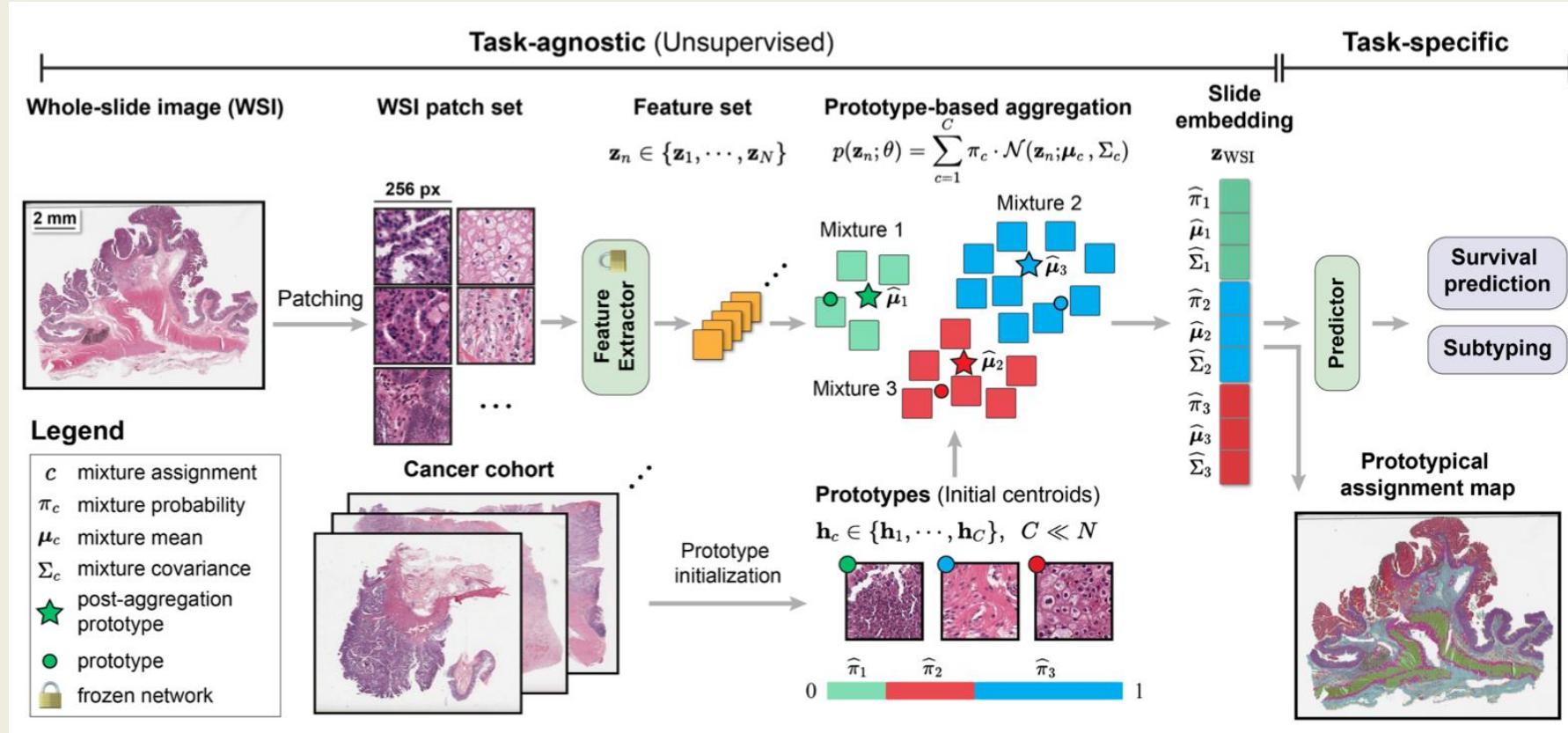
Accepted: 19 April 2024

Published online: 22 May 2024

Hanwen Xu<sup>1,2</sup>, Naoto Usuyama<sup>1,7</sup>, Jaspreet Bagga<sup>1</sup>, Sheng Zhang<sup>1</sup>, Rajesh Rao<sup>1</sup>,  
Tristan Naumann<sup>1</sup>, Cliff Wong<sup>1</sup>, Zelalem Gero<sup>1</sup>, Javier González<sup>2</sup>, Yu Gu<sup>1</sup>, Yanbo Xu<sup>1</sup>, Mu Wei<sup>1</sup>,  
Wenhui Wang<sup>1</sup>, Shuming Ma<sup>1</sup>, Furu Wei<sup>1</sup>, Jianwei Yang<sup>1</sup>, Chunyuan Li<sup>1</sup>, Jianfeng Gao<sup>1</sup>,  
Jaylen Rosemon<sup>3</sup>, Tucker Bower<sup>3</sup>, Soohie Lee<sup>4</sup>, Roshanthi Weerasinghe<sup>4</sup>, Bill J. Wright<sup>4</sup>,  
Ari Robicsek<sup>4</sup>, Brian Piening<sup>3,5</sup>, Carlo Bifulco<sup>3,5,6</sup>, Sheng Wang<sup>2,6,7</sup> & Hoifung Poon<sup>1,2</sup>

# WSI embedding

## PANTHER



"C=16 clusters, the extracted slide feature representation from PANTHER is 32784-dim"

<https://www.linkedin.com/pulse/scaling-pathology-foundation-models-from-roi-gigapixel-chen-suhve/>

# Multi-modal learning\*: RNAseq + WSI (early fusion)

TANGLE

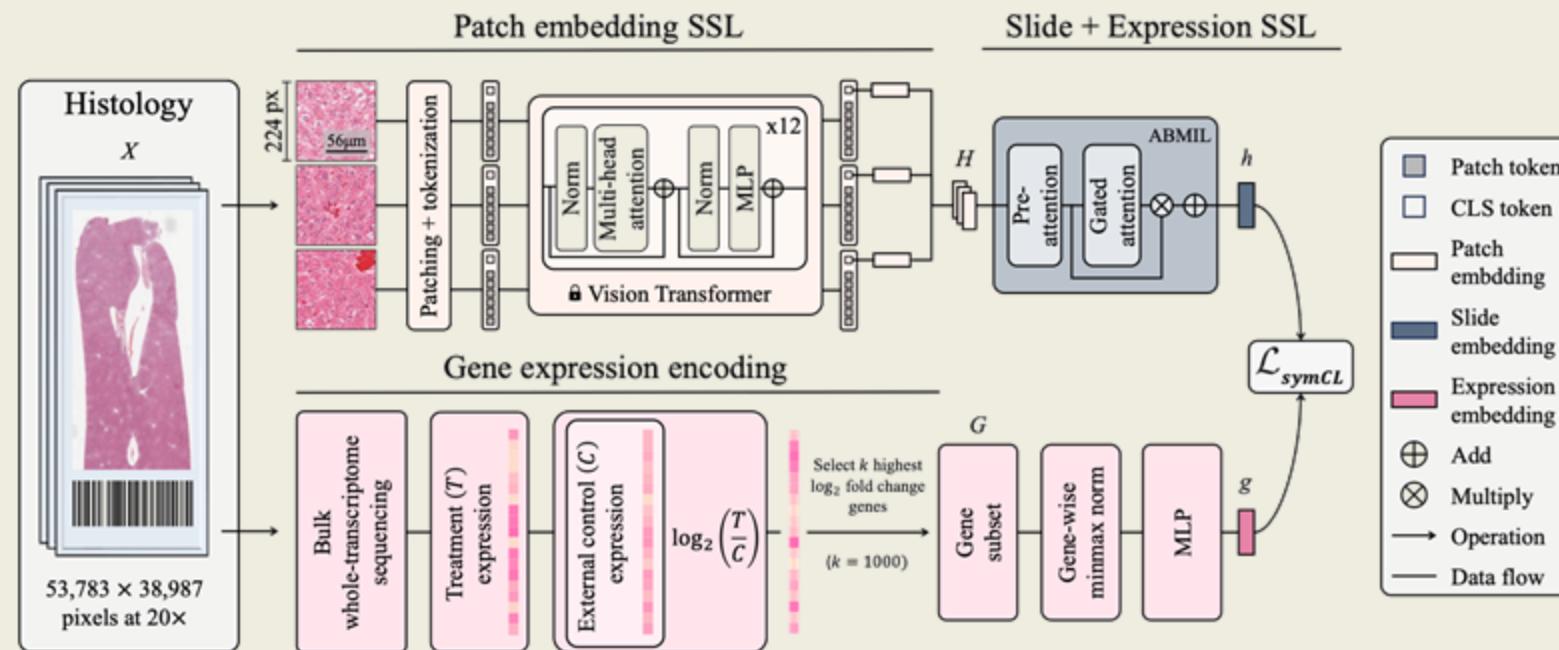
## Transcriptomics-guided Slide Representation Learning in Computational Pathology

\*+WSI embedding!

Guillaume Jaume<sup>1,2 \*</sup>, Lukas Oldenburg<sup>1,3 \*</sup>, Anurag Vaidya<sup>1,2</sup>, Richard J. Chen<sup>1,2</sup>,  
Drew F.K. Williamson<sup>1,2†</sup>, Thomas Peeters<sup>1</sup>, Andrew H. Song<sup>1,2</sup>, Faisal Mahmood<sup>1,2</sup>

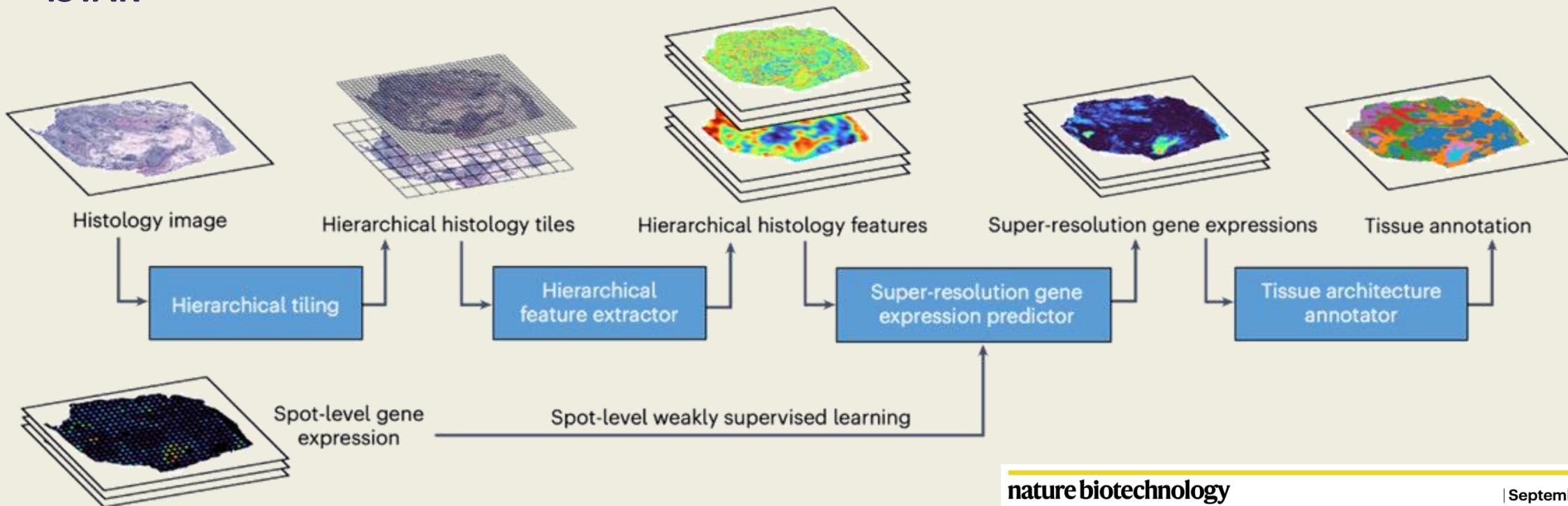
<sup>1</sup>Mass General Brigham, <sup>2</sup>Harvard University and <sup>3</sup>RWTH Aachen University

gjaume@bwh.harvard.edu, lukas.oldenburg@rwth-aachen.de, faisalmahmood@bwh.harvard.edu



# Multi-modal learning: spatial RNAseq + WSI

iSTAR



nature biotechnology

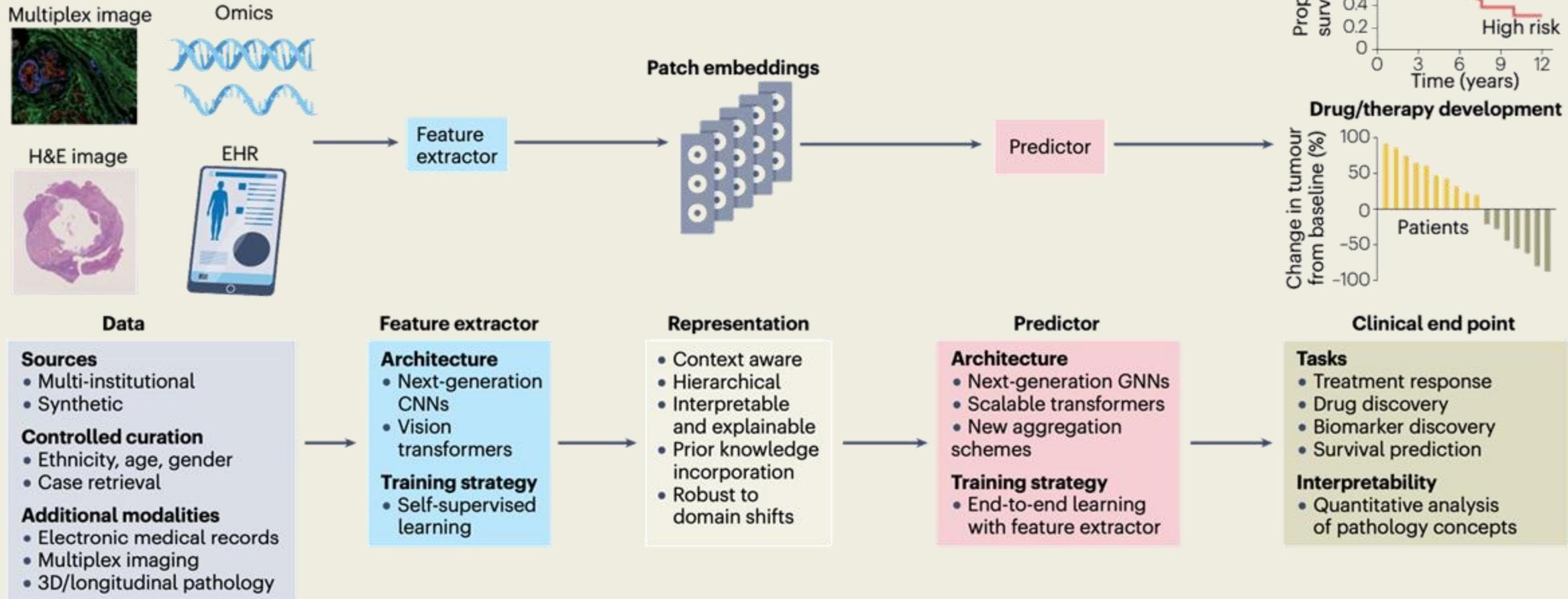
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Brief Communication

<https://doi.org/10.1038/s41587-023-02019-9>

**Inferring super-resolution tissue architecture by integrating spatial transcriptomics with histology**

# Future directions



# Machine Learning sucks\*!

\*compared to humans and animals

- **Supervised learning (SL) requires large numbers of labeled samples.**
- **Self-Supervised Learning (SSL) works great but...**
  - Generative prediction only works for text and other discrete modalities
- **We are nowhere near human-level AI today**
  - Any 16 year-old can learn to drive in 20 hours of training
  - Any 10 year-old can learn to clear the dinner table in one shot
  - Any house cat can plan complex actions
- **AI is still very impressive for a few specific tasks:**
  - Retains and recalls patterns from vast amounts of data that humans can't process efficiently
  - Works well for time-consuming tasks involving repetitive and structured data
  - Language: generates coherent, context-aware text instantly
  - Pathology: scans WSIs quickly for patterns
- **Moravec's paradox: things that are easy for humans are difficult for AI and vice versa.**

# Summary

## Concepts in pathology and artificial intelligence

### Pathology concepts

**Whole-slide image.** An image obtained by digitizing a glass slide at high resolution using a scanner.

**Digital pathology.** A set of tools and systems for the acquisition, management and diagnosis of pathology glass slides in a digital setting.

**Haematoxylin and eosin staining.** The reference stain for histological analysis of tissues for visualization of cell nuclei (in purple) with extracellular information and cytoplasm (in pink).

**Immunohistochemistry.** A collection of staining techniques used to identify specific antigens in cells (or markers).

**Tumour microenvironment.** The environment surrounding a tumour (composed of normal cells, extracellular matrix, signalling molecules and other components) that interacts with the tumour by influencing its growth and spread.

**Multiplex imaging.** An imaging technique for simultaneous testing of several markers in a tissue.

**Computational pathology.** Computational methods based on the microscopic analysis of cells and tissues for the study of disease.

### Artificial intelligence concepts

**Deep learning.** A machine learning technique in which a differentiable functional relationship is learned between some input and output (for example, for the classification or segmentation of images). The input–output relationship is parametrized by an artificial neural network composed of a series of linear projections and non-linear activations.

**Supervised learning.** A learning paradigm in which a labelled training dataset of input (for example, whole-slide images) and target (such as cancer subtype) pairs is used to train a neural network, such

that, once trained, the system can predict the target of external unseen data.

**Embeddings (representations).** A compressed and informative low-dimensional representation of a high-dimensional raw input.

**Segmentation.** The pixel-level delineation of the constituents of an image. In semantic segmentation, each pixel is associated with a category, whereas instance segmentation also identifies individual objects within each category.

**Convolutional neural network.** A class of neural networks designed to efficiently learn from images (leveraging parameter sharing) through the parametrization of trainable convolutional filters repetitively applied throughout the whole input.

**Graph neural network.** A class of neural networks designed to learn on graph-structured data. A graph neural network iteratively updates and aggregates information from the neighbour of each node to contextualize its representation.

**Transformer.** A deep learning architecture that uses self-attention to capture contextual relationships between elements of an input sequence. Vision transformers extend this principle to images.

**Self-supervised learning.** A learning paradigm in which the training signal is obtained from the input by leveraging its underlying structure. Self-supervised learning can be trained on orders of magnitude more data than supervised learning, as no labels are required.

**Early and late fusion.** In applications with multiple data modalities or magnification levels, early-fusion methods use a multimodal encoder to merge the data locally, whereas late-fusion methods create modality-level embeddings with unimodal encoders that are then fused for prediction.

# Recommended reads and resources

<https://github.com/open-pathology/awesome-pathology>

<https://www.cancerimagingarchive.net> / <https://portal.gdc.cancer.gov>

<https://faisal.ai>

