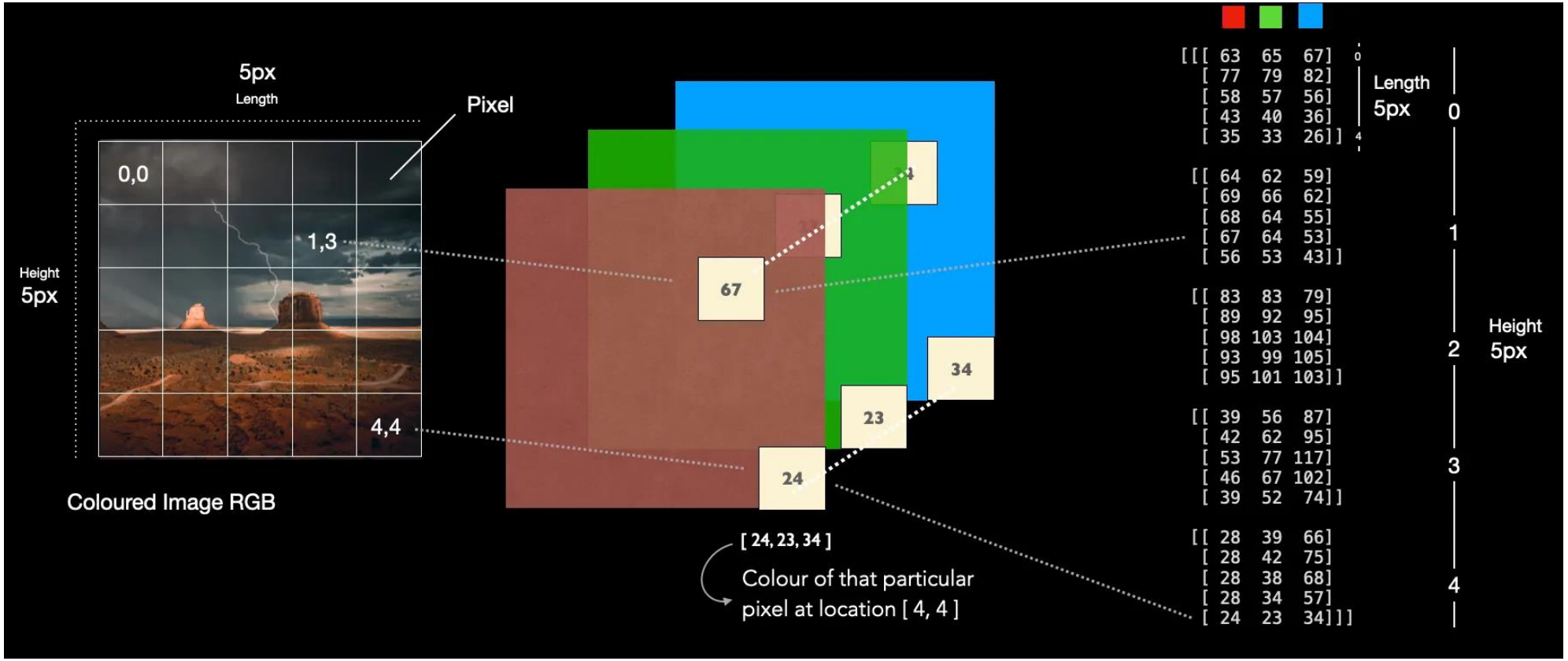

KOÇ
ÜNİVERSİTESİ

Artificial Intelligence in Digital Pathology

Reza Kazemzadeh

IMAGE

What is a DIGITAL IMAGE???



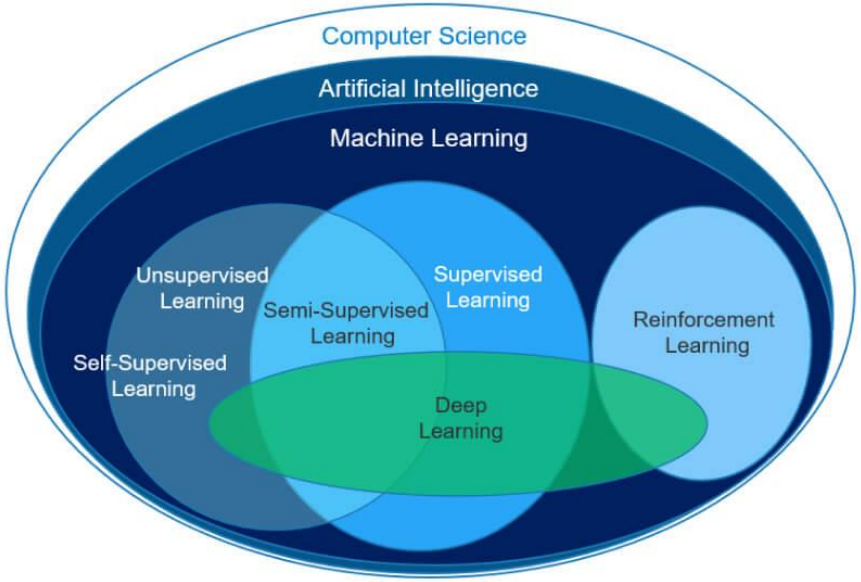
Artificial Intelligence: An Overview

What is Artifical Intelligence?

The capability of machines to perform tasks that typically require human intelligence

Capabilities:

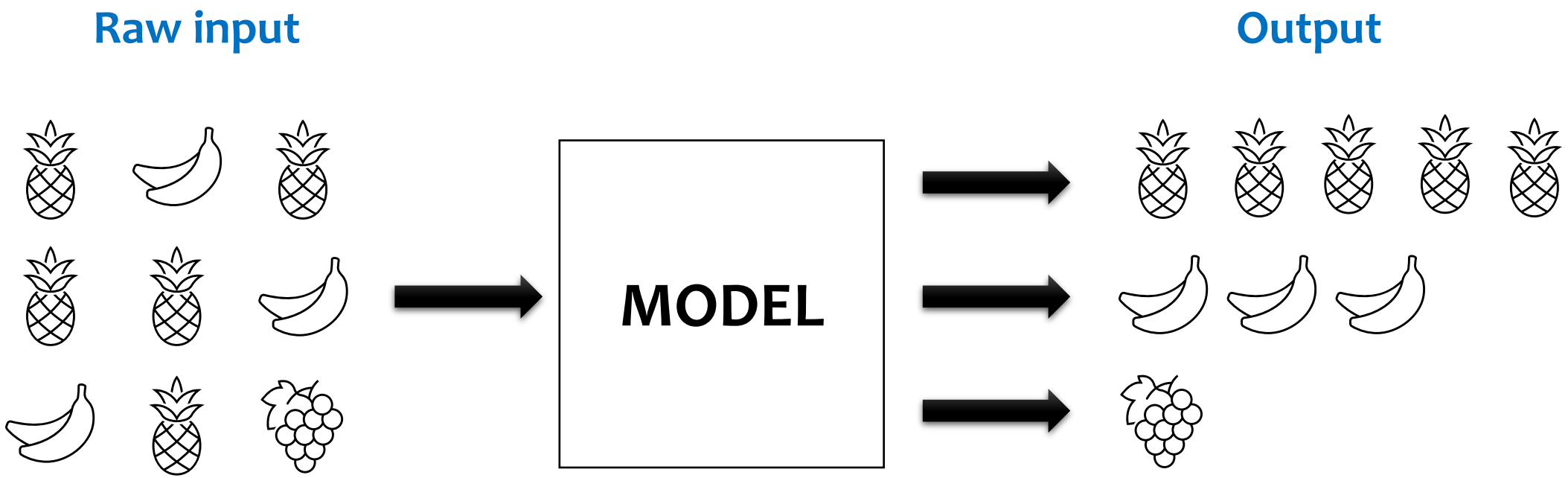
- Learning from data
  - (NOT MEMORIZING)
- Recognizing patterns
- Making decisions
- Solving problems



AI Tasks and Outputs

What Does AI Actually Do?

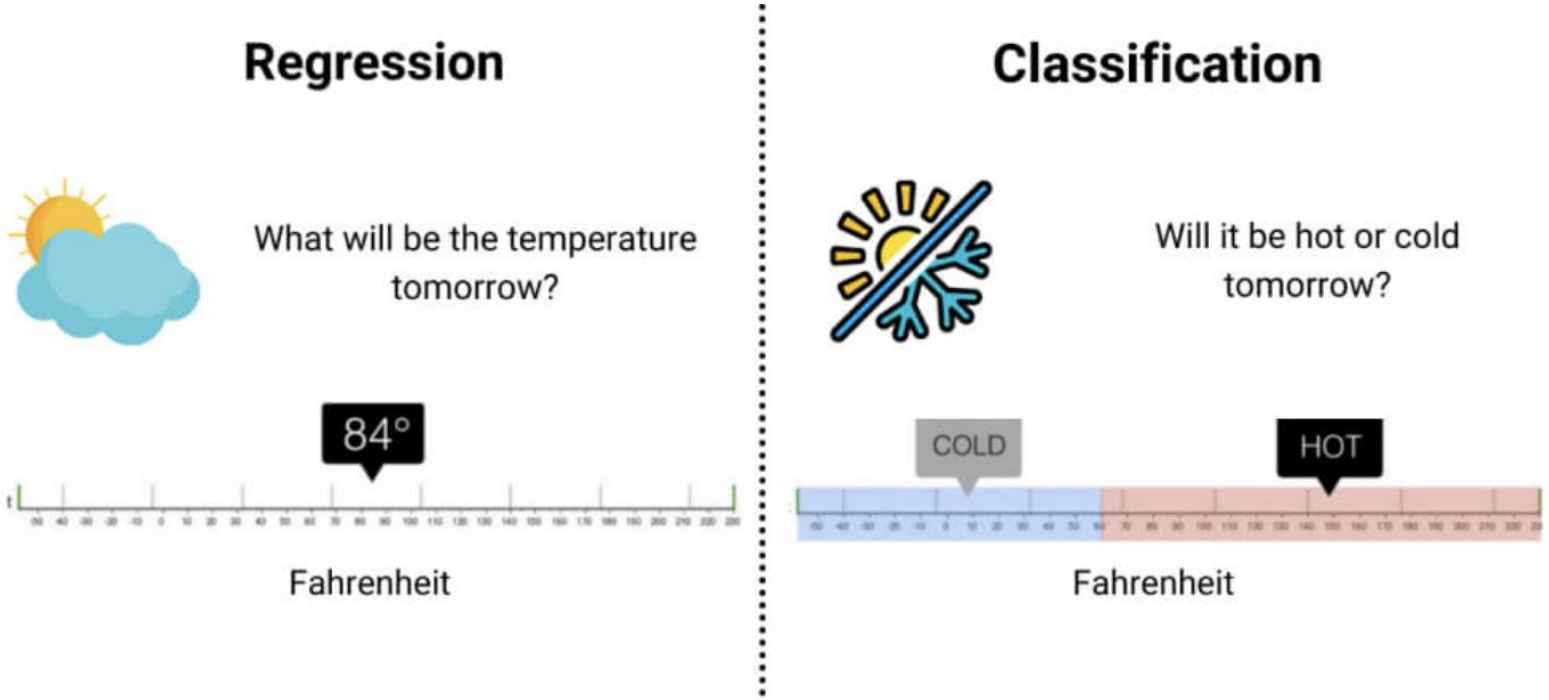
Classification



AI Tasks and Outputs

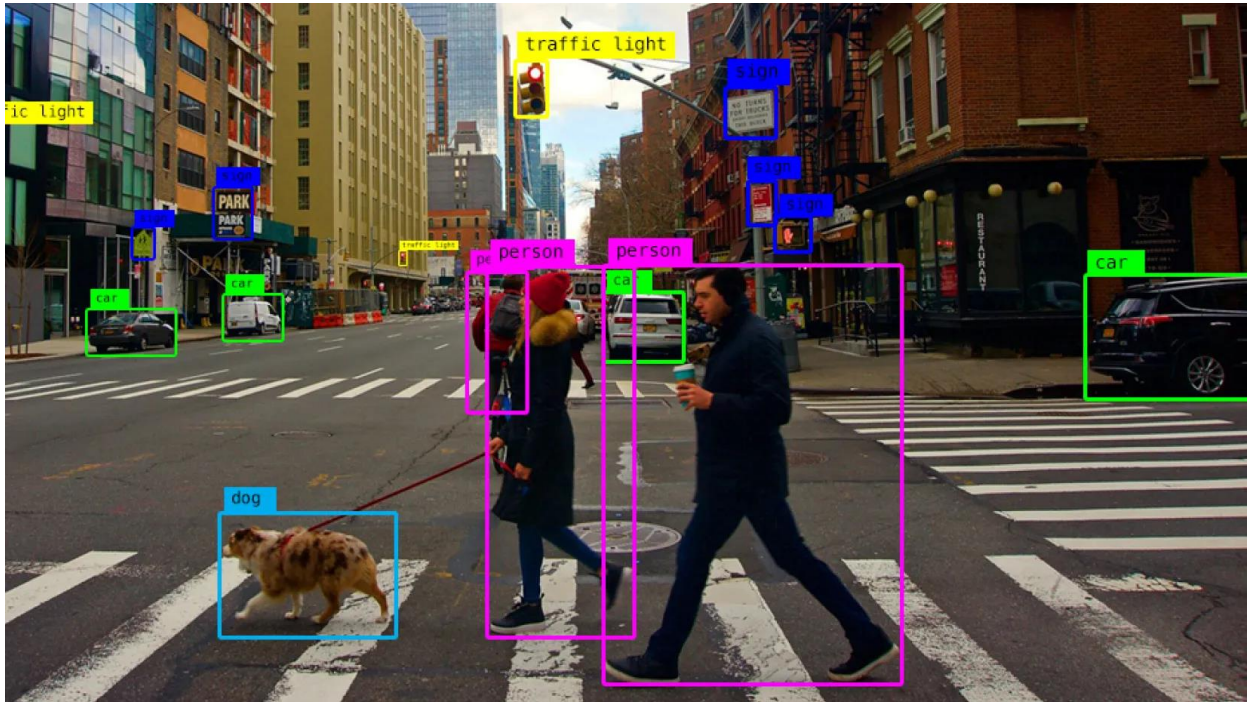
What Does AI Actually Do?

Regression



What Does AI Actually Do?

Detection/Localization



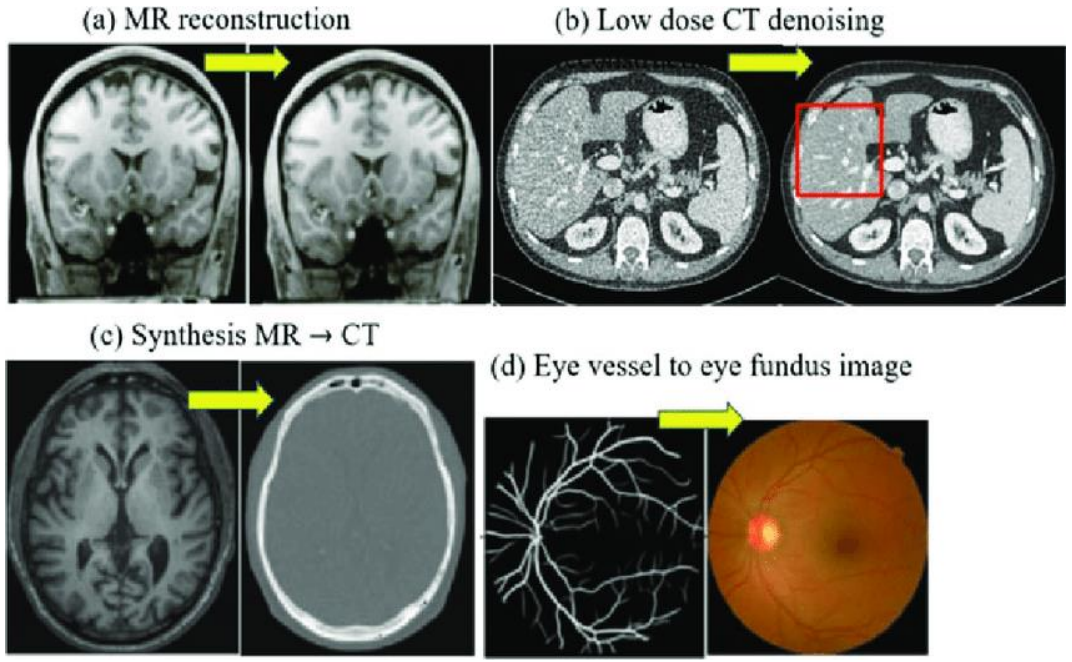
What Does AI Actually Do?

Segmentation

AI Tasks and Outputs

What Does AI Actually Do?

Generation



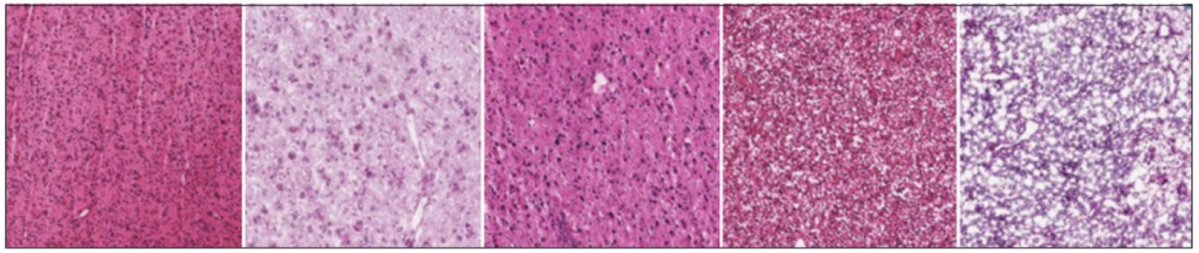
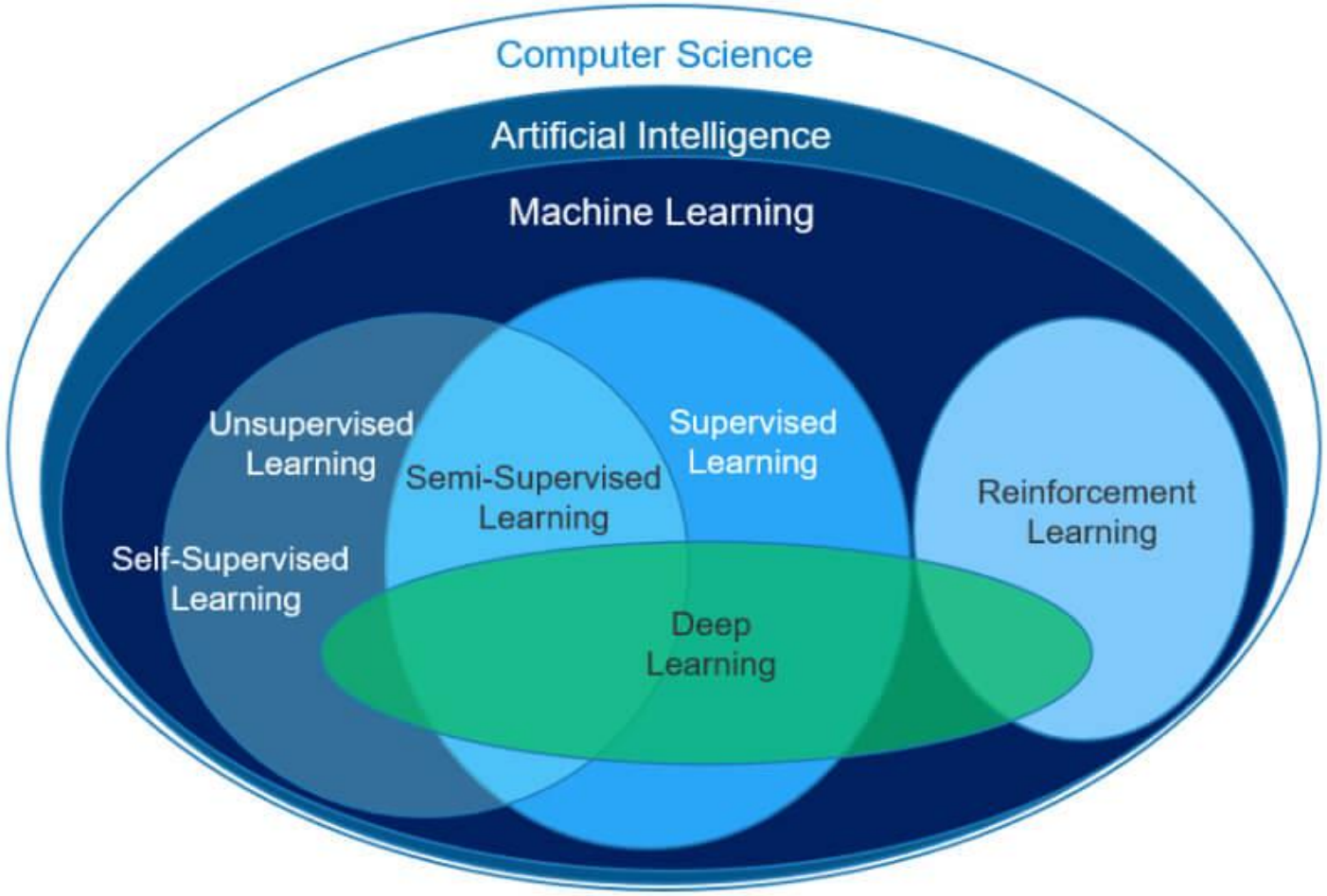


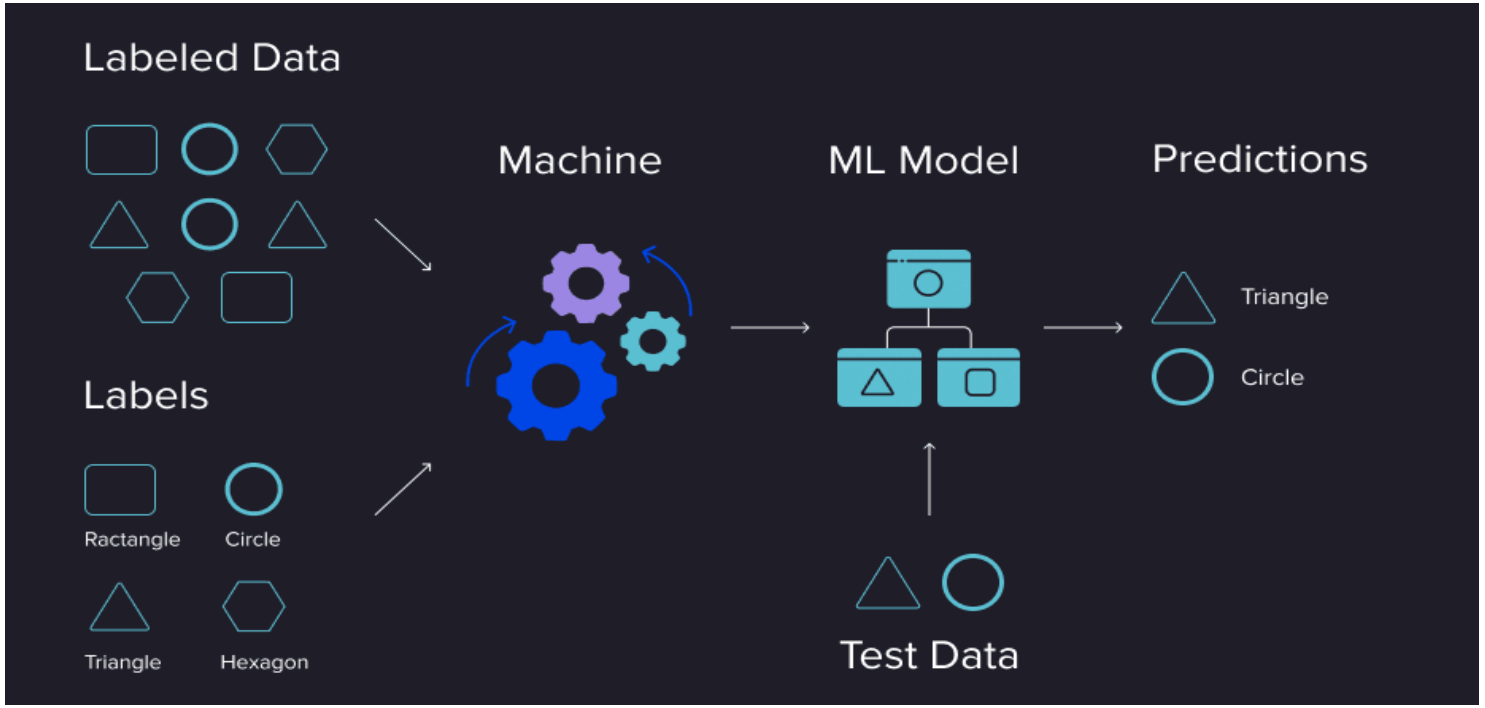
Figure 3: Original H&E stained glioblastoma pathology slides obtained from The Cancer Genome Atlas database[44] showing diverse color variations in the sample images

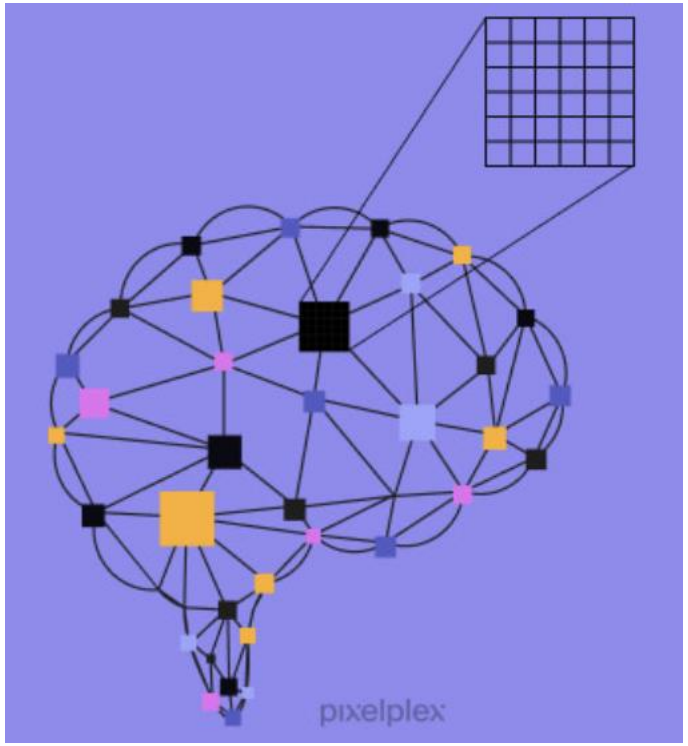
Machine Learning Subsets



Machine Learning Subsets

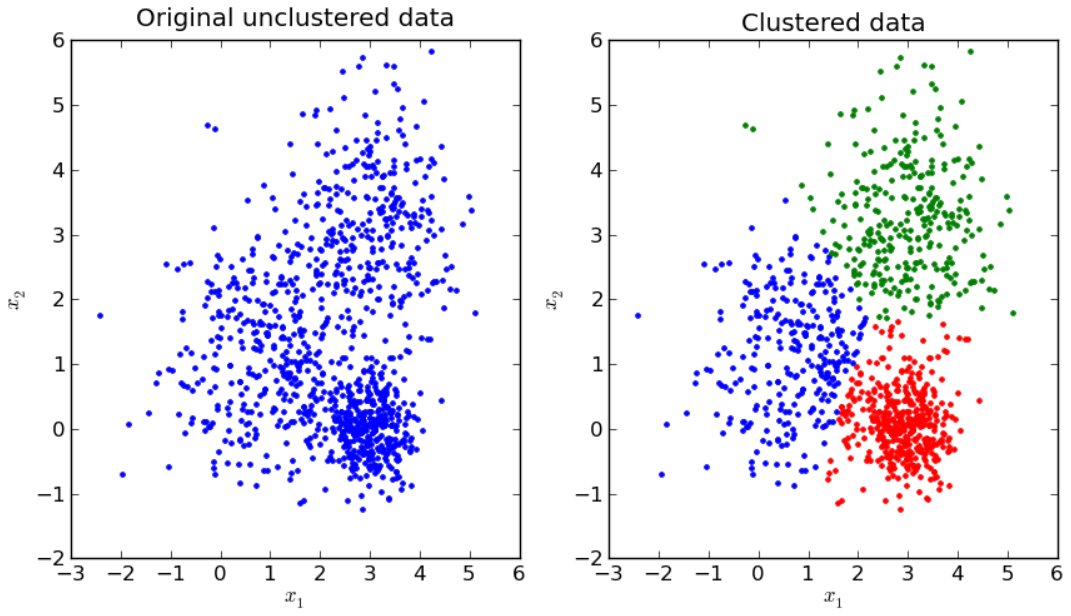
- **Supervised Learning**

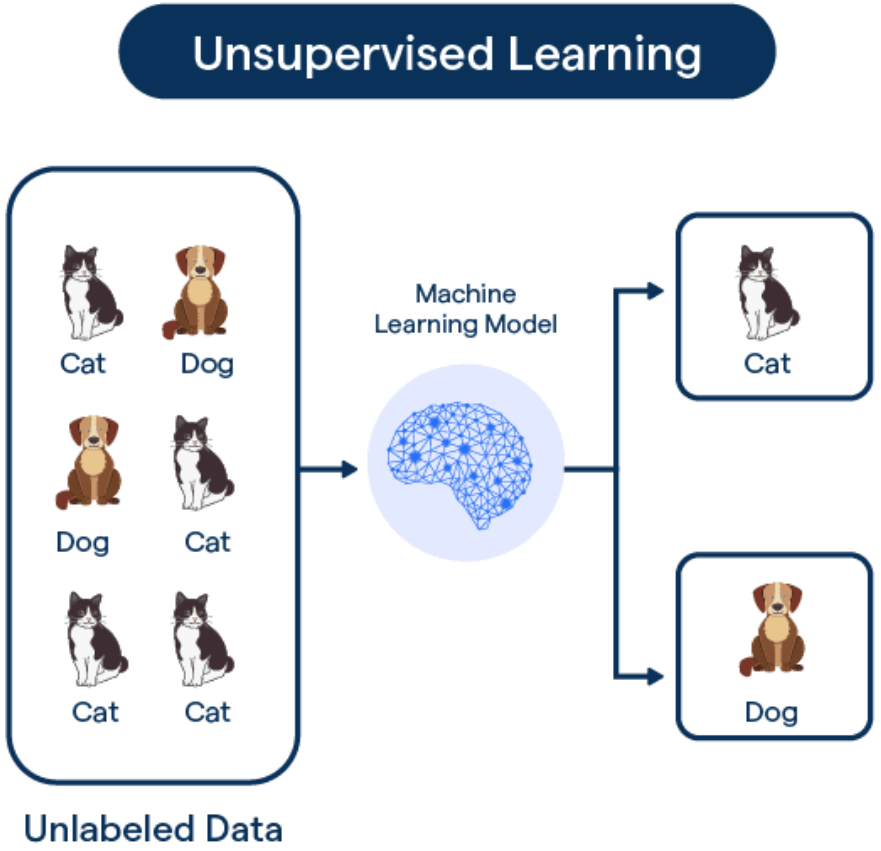




Machine Learning Subsets

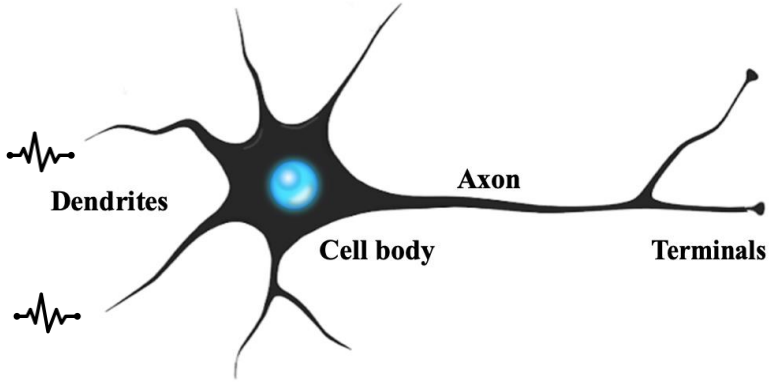
- **Unsupervised Learning**

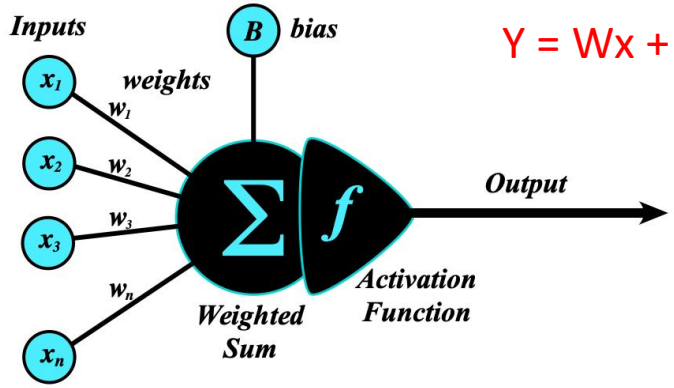




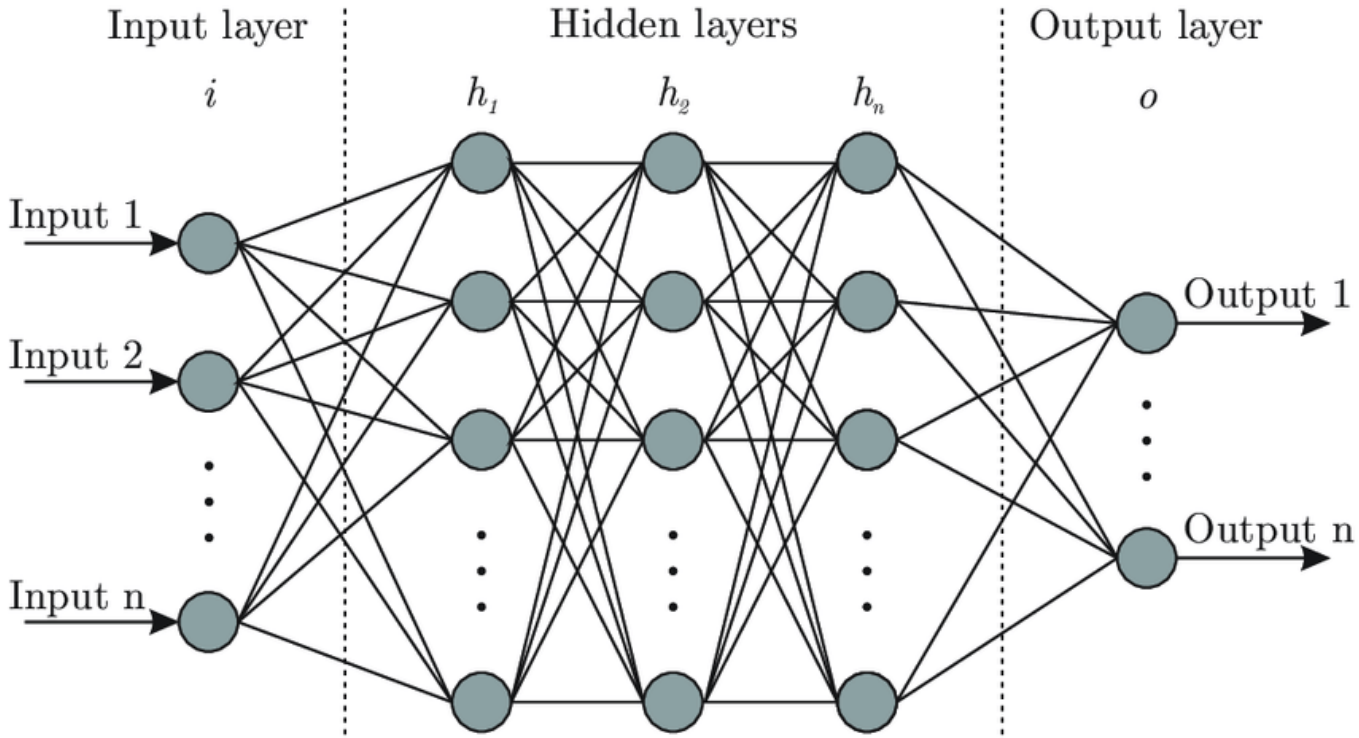
Neural Networks

Computational models inspired by the human brain's structure, consisting of interconnected nodes (neurons) organized in layers.



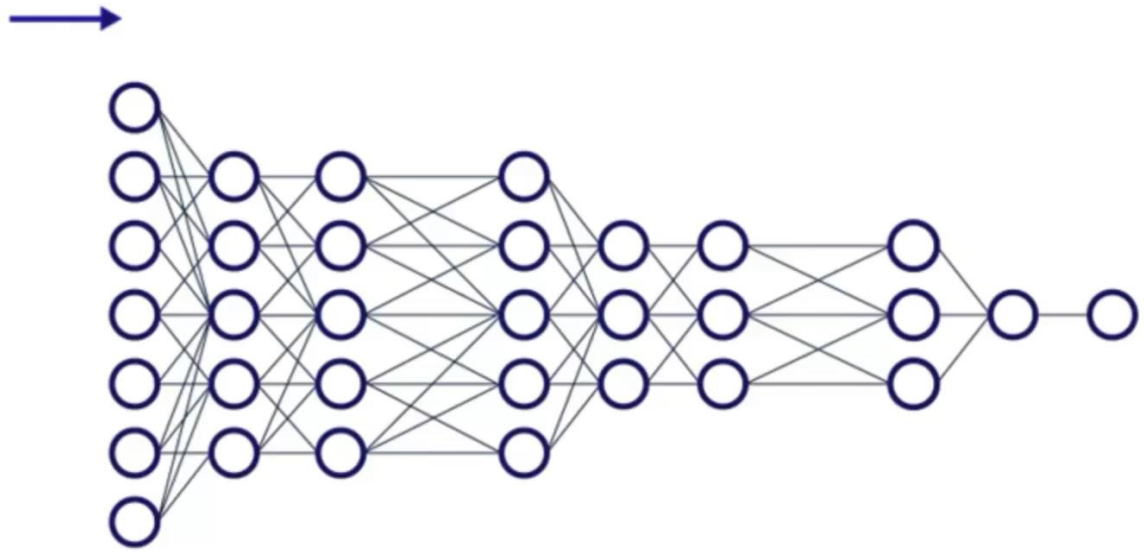


Y = Wx + B



Neural Networks

Model Training and Updating Weights

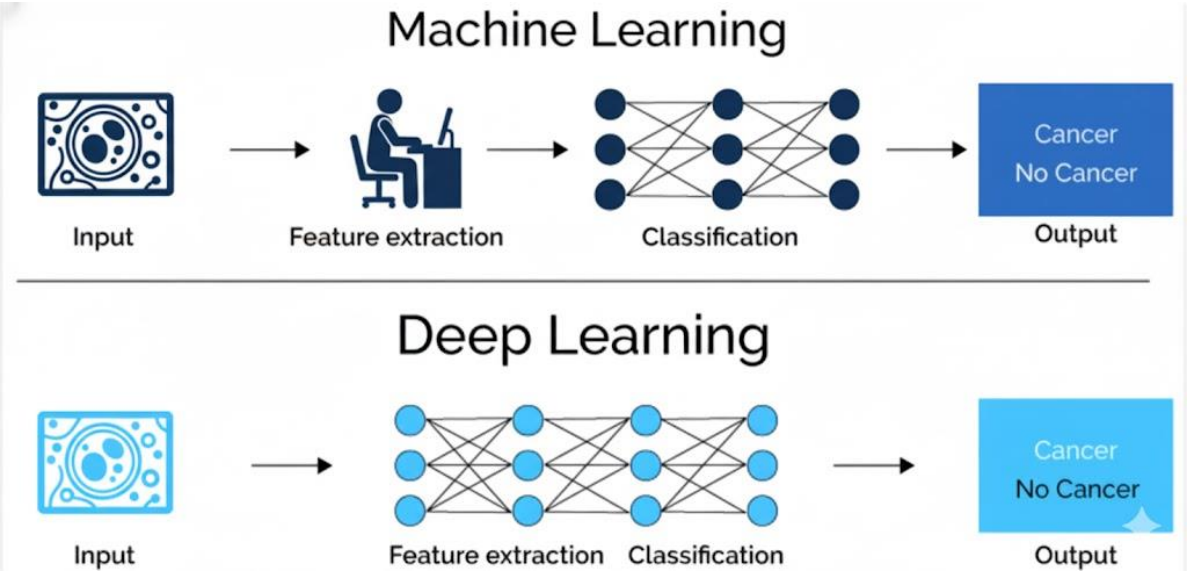


Deep Learning

Definition: Neural networks with MANY hidden layers, capable of learning hierarchical representations of data.

Why "Deep" Matters:

- *Layer 1* might detect edges and basic shapes in an image
- *Layer 2* might recognize textures and simple patterns
- *Layer 3* might identify tissue structures
- *Layer 4* might recognize complex cellular arrangements
- ***Final layers*** make the diagnosis (e.g., cancer vs. normal)

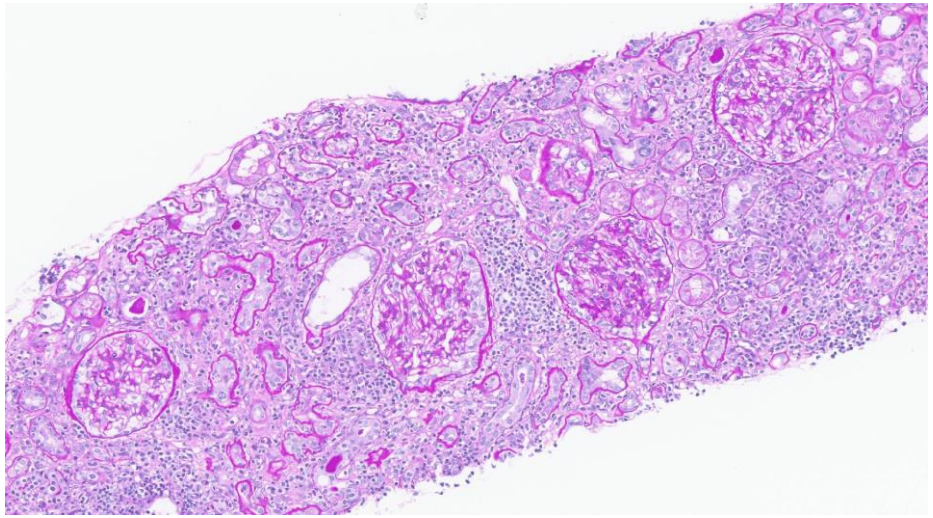


Deep Learning vs. Traditional ML

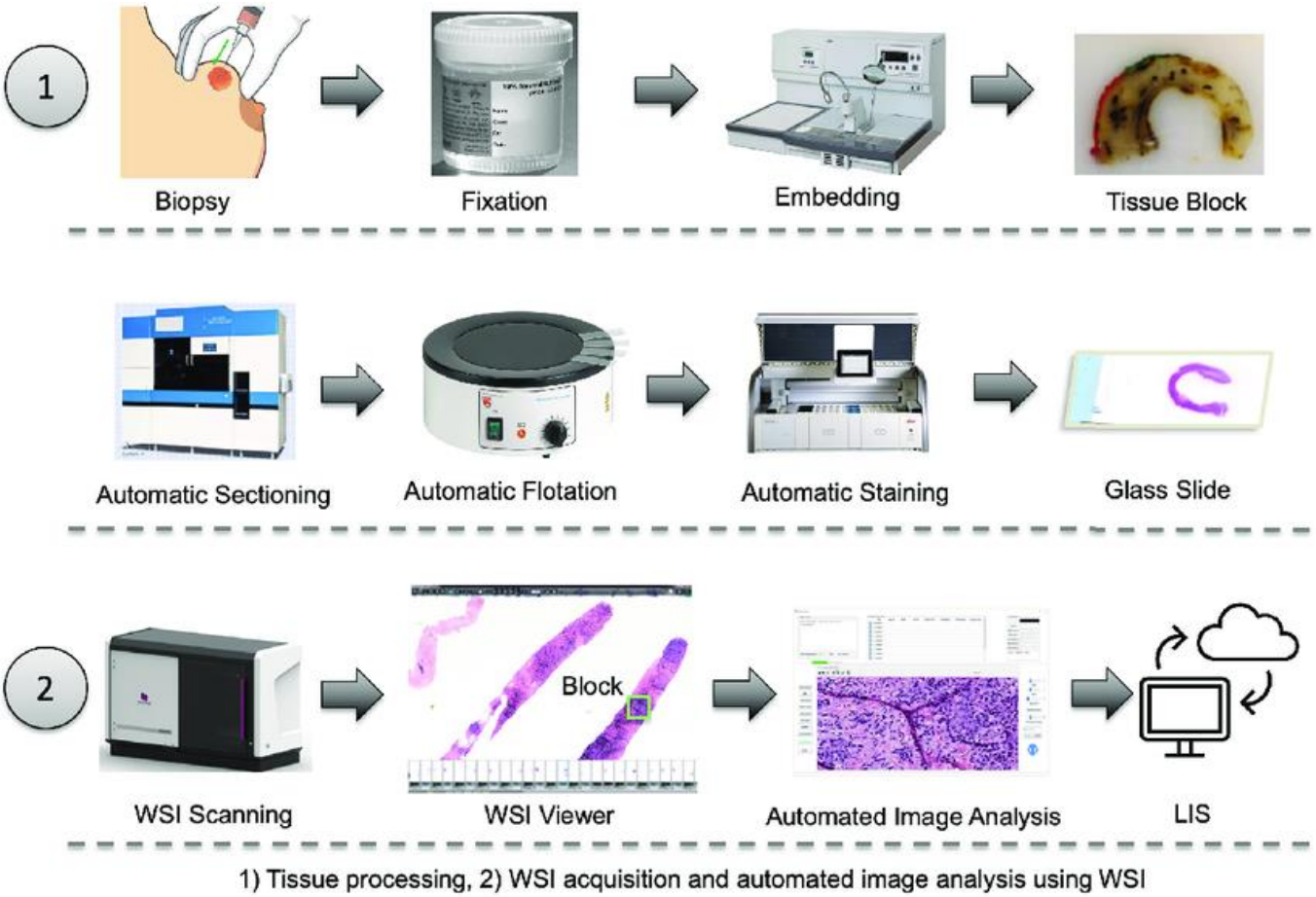
The key difference:

- Deep Learning excels at **unstructured data** (images), while traditional Machine Learning works better for **structured data** (tables/numbers)

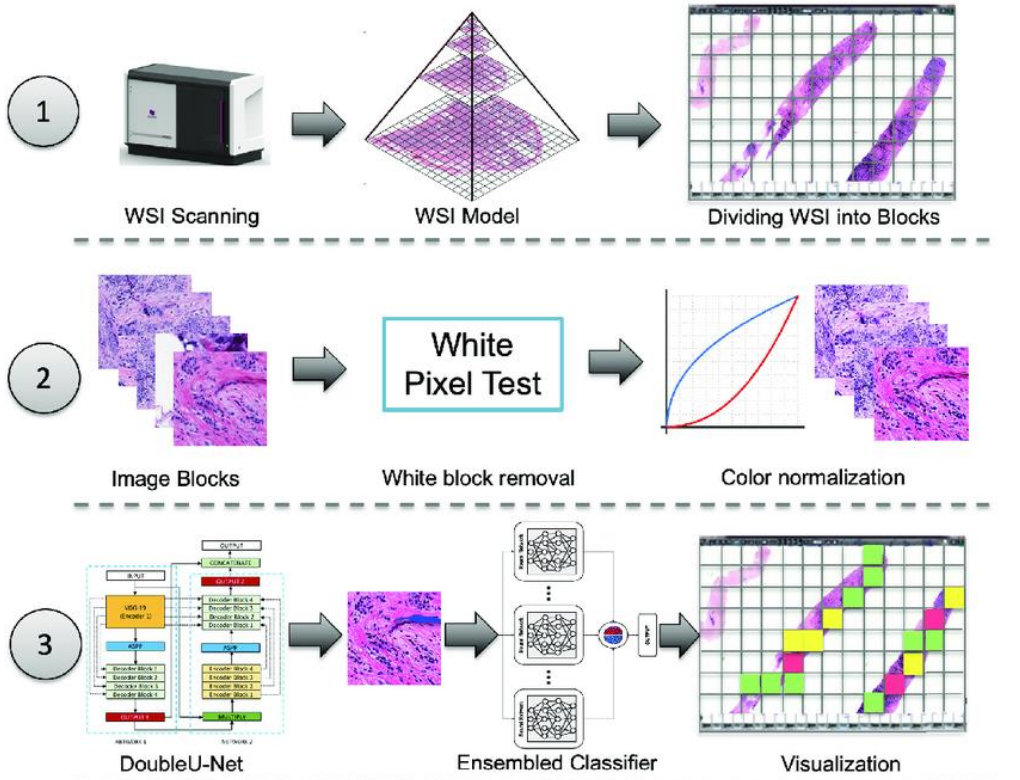
Characteristic	Patients with Spontaneous Thrombosis (N=153)	Patients with Secondary Thrombosis (N=146)	Control Subjects (N=150)
Age — yr	67.0±16.7	65.8±17.4	65.4±15.7
Male sex — no. (%)	71 (46.4)	65 (44.5)	68 (45.3)
Smoker — no. (%)	40 (26.1)	49 (33.6)	45 (30.0)
Hypertension — no. (%)	46 (30.1)	37 (25.3)	46 (30.7)
Hyperlipidemia — no. (%)	25 (16.3)	17 (11.6)	25 (16.7)
Obesity — no. (%)	11 (7.2)	12 (8.2)	16 (10.7)
Diabetes — no. (%)	16 (10.5)	12 (8.2)	18 (12.0)
Screened for thrombophilia — no. (%)	68 (44.4)	64 (43.8)	—
Thrombophilia — no.	25†	15‡	—



Digital Pathology



1) Tissue processing, 2) WSI acquisition and automated image analysis using WSI

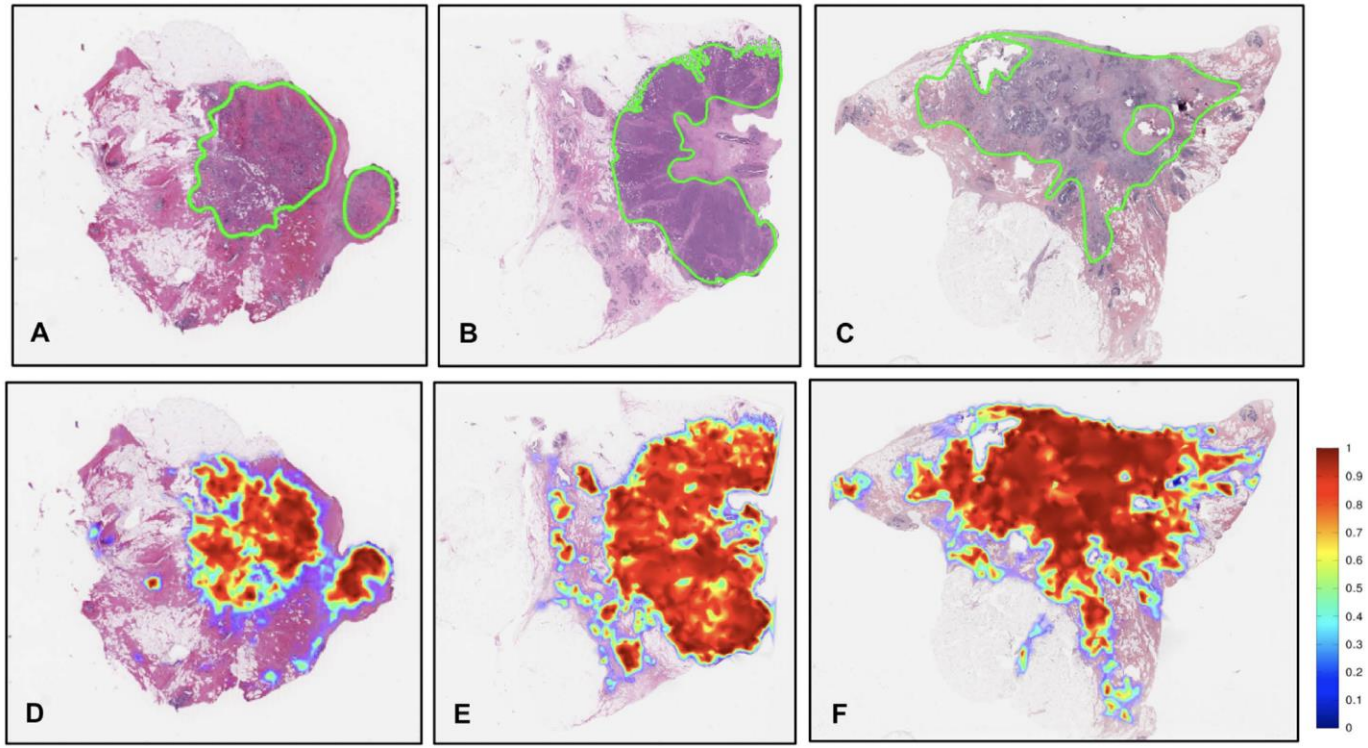


1) WSI acquisition, 2) pre-processing and 3) artifact segmentation, severity classification and visualization

Application of AI in Digital Pathology

Accurate and reproducible invasive breast cancer detection in whole-slide images: A Deep Learning approach for quantifying tumor extent

Trained on almost 400 cases
Tested on 200 Cases
Result: Dice Coefficient: 0.75



DICE COEFFICIENT

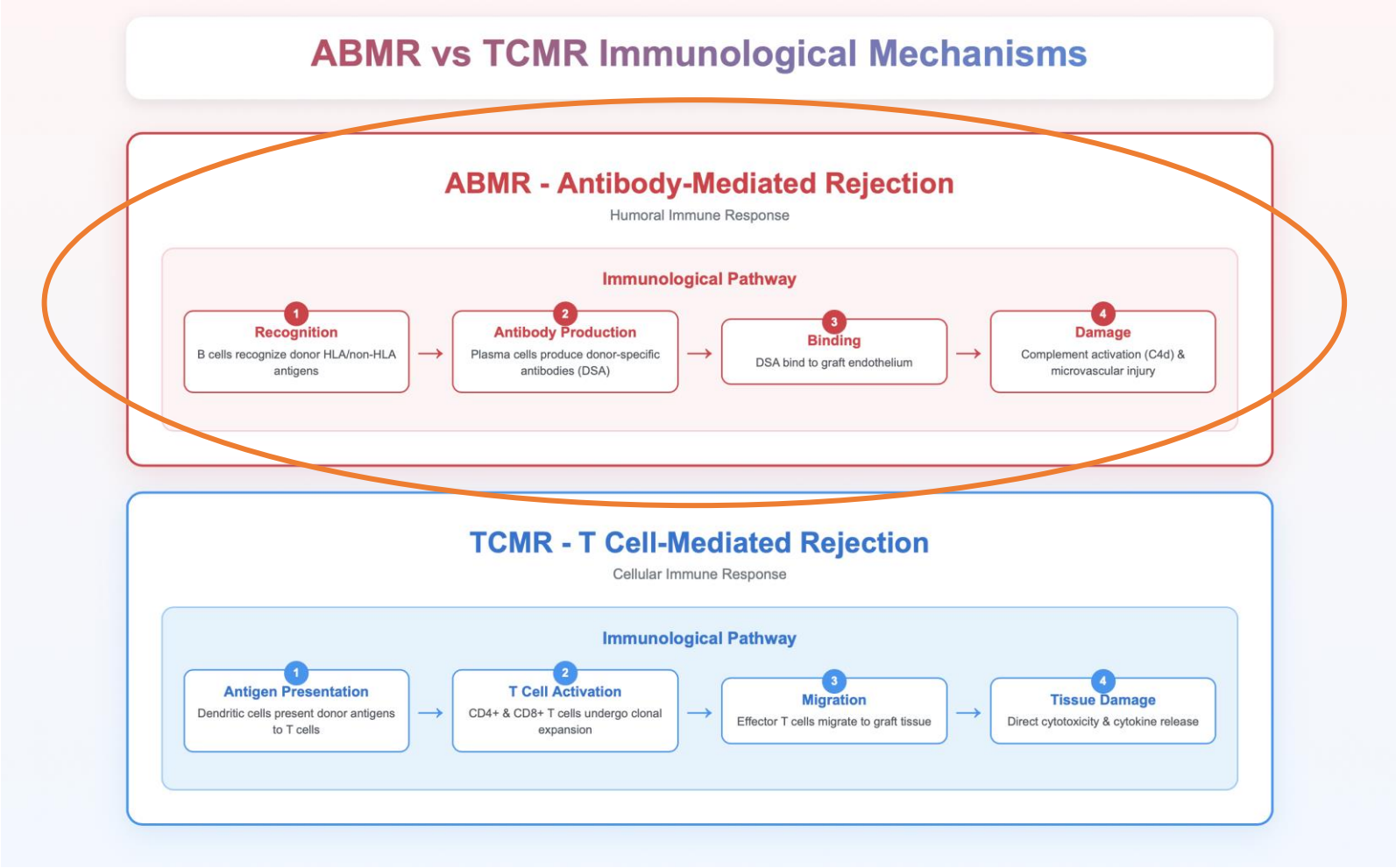
Is an overlap based metric that compares an automatic segmentation (A) with a reference segmentation (B). The closer the coefficient is to 1, the better the automatic segmentation is considered to be.

$$2 \times \frac{A \cap B}{A + B}$$

Digital Pathology | Renal Rejection | Banff | Our Work

Angel Cruz-Roa et al. Scientific Reports, 2017

Renal Rejection



Current Diagnosis of AMR

Banff Criteria for ABMR Diagnosis

Antibody-Mediated Rejection in Kidney Transplantation

1 Histologic Evidence

Acute tissue injury:

- **Microvascular inflammation**
  - Glomerulitis (g > 0)
  - Peritubular capillaritis (ptc > 0)
- **Acute tubular injury**
- **Arteritis** (v > 0)
- **Acute thrombotic microangiopathy**

2 Antibody Interaction

Evidence of current/recent antibody interaction with vascular endothelium:

- **Linear C4d staining** in peritubular capillaries (C4d2 or C4d3)
- **OR**
- **Moderate microvascular inflammation** (g + ptc ≥ 2) in absence of recurrent glomerulonephritis
- **OR**
- **Increased gene expression** of endothelial-associated transcripts

3 Serologic Evidence

Donor-specific antibodies (DSA):

- **HLA or non-HLA DSA** detected in serum
- DSA to:
  - HLA Class I (A, B, C)
  - HLA Class II (DR, DQ, DP)
  - Non-HLA antigens (MICA, etc.)

BANFF FOUNDATION FOR ALLOGRAFT PATHOLOGY

Digital Pathology › Renal Rejection › Banff › Our Work

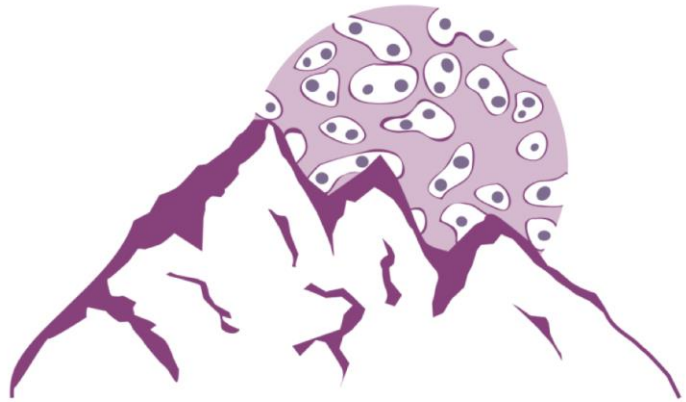
Challenges and Critical Limitations

Inter-observer variability:

- Studies documenting approximately 30% diagnostic difference rates between expert pathologists.

Bottlenecks regarding diagnostic workflow:

- 3-7 days for routine cases
- Nephropathologist demands



BANFF FOUNDATION
FOR ALLOGRAFT PATHOLOGY

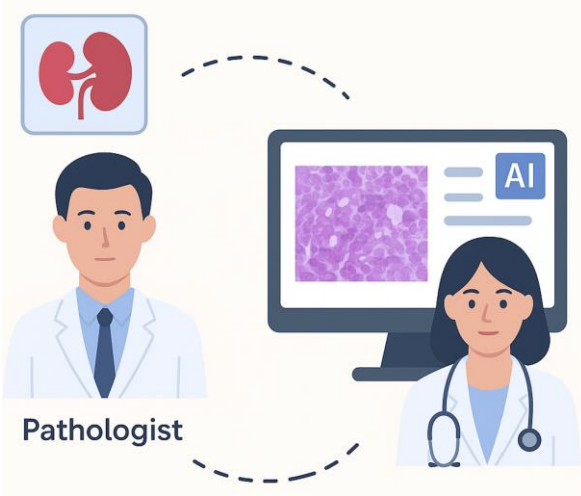
Digital Pathology > Renal Rejection > Banff > Our Work

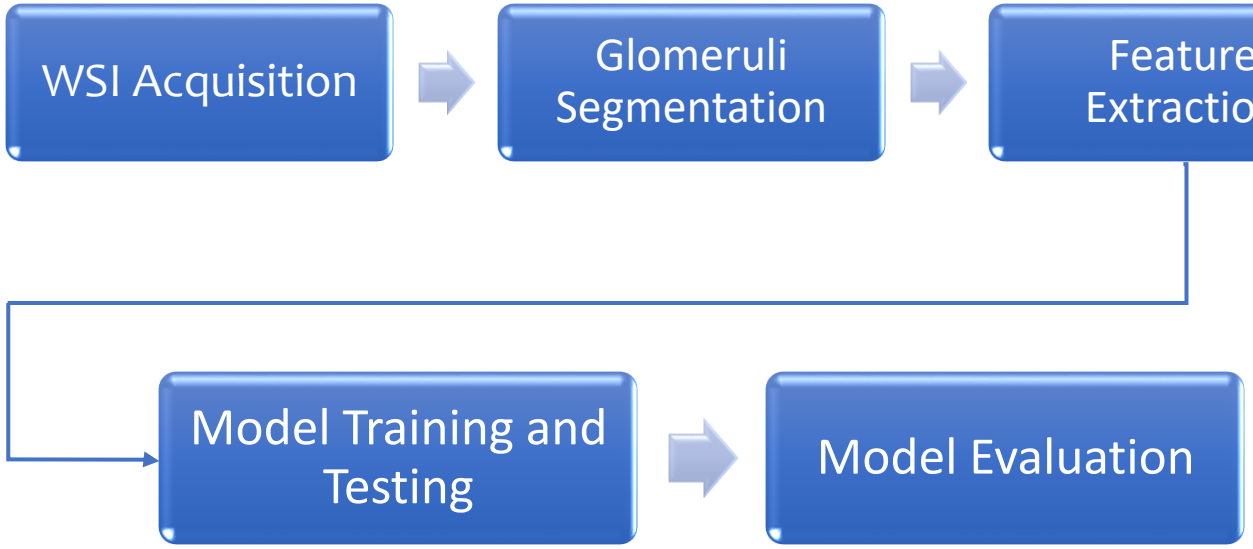
Byron Smith et al. Transplant International, 2019; Ilaria Girolami et al. Journal of Nephrology, 2022

Our Work

- Objective
- Workflow

AMR versus NoAMR



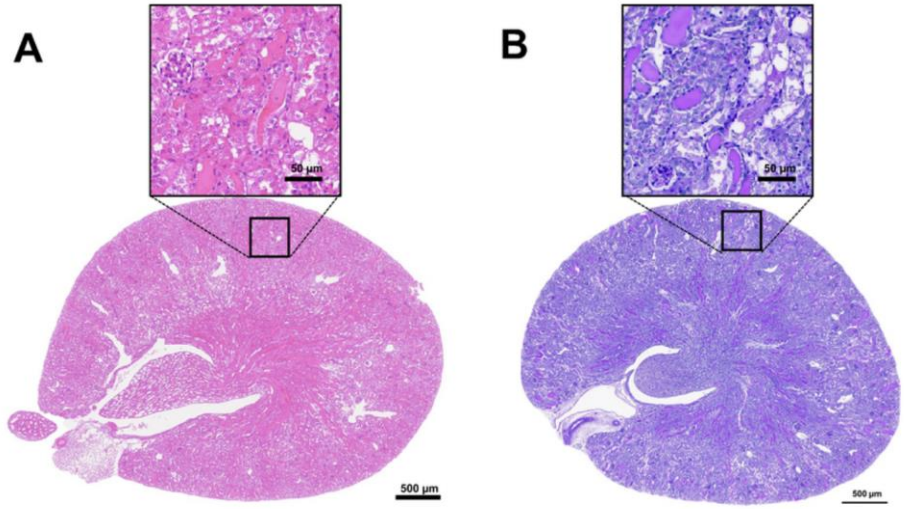


Digital Pathology > Renal Rejection > Banff > Our Work

Specific Challenges in Pathology Data Acquisition

- **Whole slide images (WSI)** represent one of the most challenging data types in medical imaging, with typical resolutions reaching 100,000 × 100,000 pixels and file sizes ranging from 0.5-4 GB per slide at 40× magnification.

- Staining variability represents another major challenge (Color normalization and standardization preprocess is needed)



WSI Acquisition | Glomeruli Segmentation | Feature Extraction | Model Training

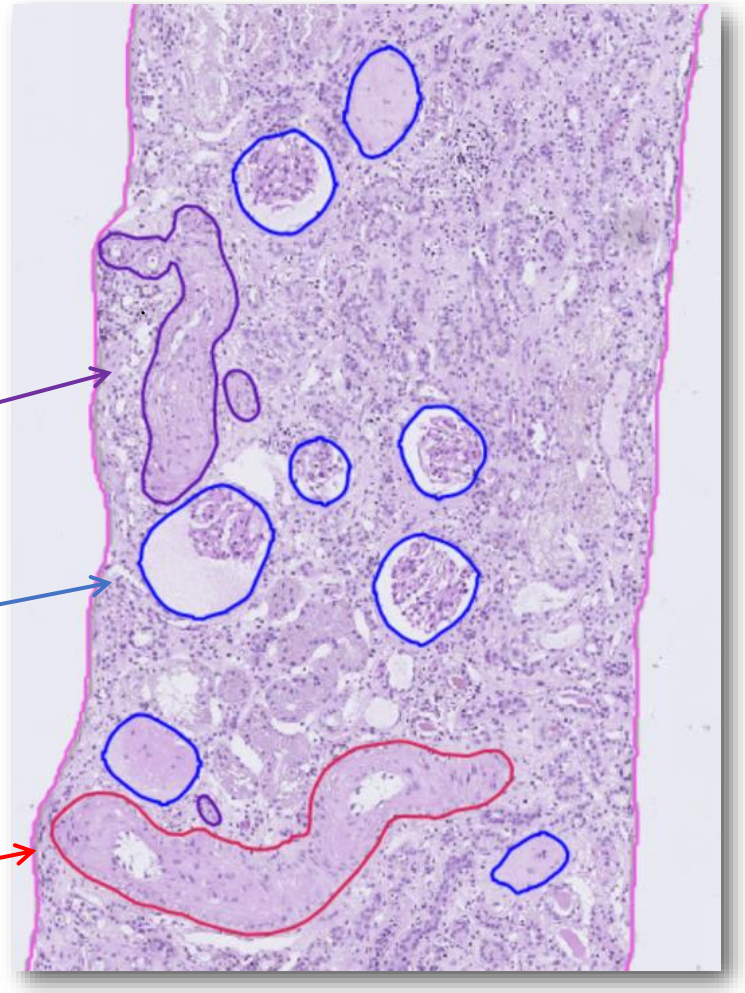
How we overcame this challenge?

- Joined a Consortium Consisting of :
  - **Germany, United States, Italy, Spain, France, Hungary**
- About 1800 WSIs belonging to 344 cases in total has been shared with us (165 AMR, 179 NoAMR).
- Each containing several Hematoxylin and Eosin (H&E), Periodic Acid-Schiff (PAS), Trichrome (Tri) stained WSIs.
- 200 of cases have information of Pathology report (including Banff scores)
- 56 cases has fully annotated compartments by Senior Pathologist (Prof. Jan Ulrich Becker)
- 12 cases from Koç University (6 AMR, 6 NoAMR)

WSI Acquisition → Glomeruli Segmentation → Feature Extraction → Model Training

Auto-Segmentation Model

- Consortium shared their Auto-Segmentation model which is able to Segment Glomeruli, Arteriole and Artery in the Kidney Pathology images.



WSI Acquisition | Glomeruli Segmentation | Feature Extraction | Model Training

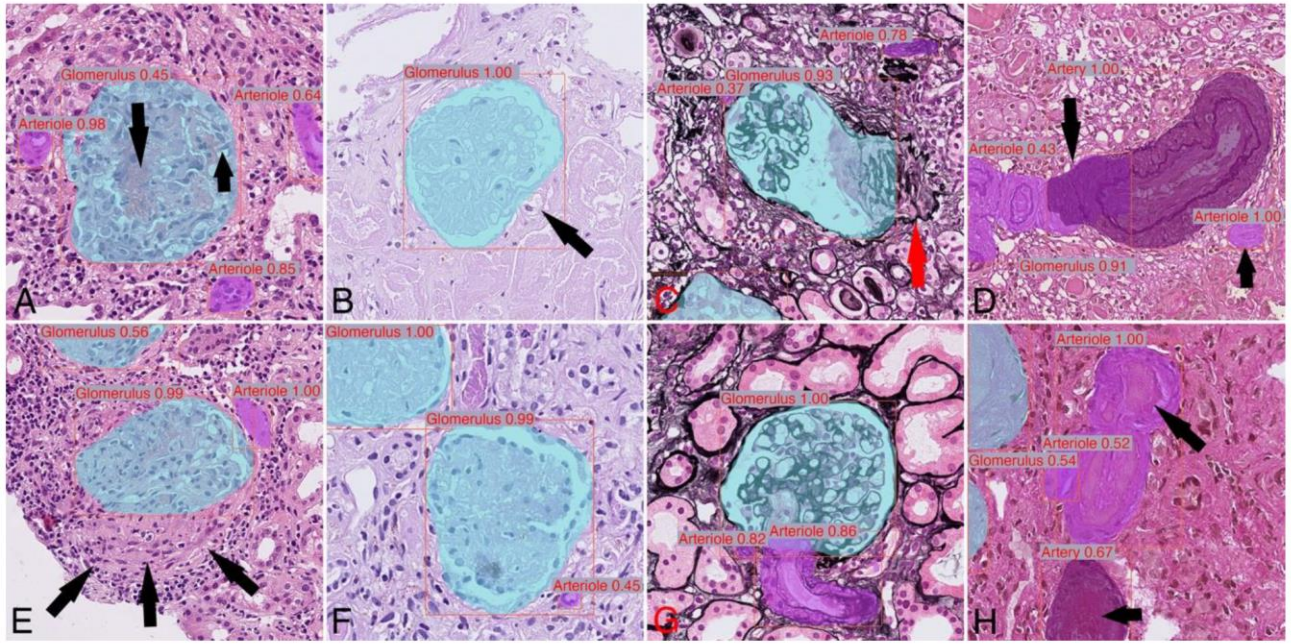
Glomeruli Segmentation

Segmentation of diagnostic tissue compartments on whole slide images with renal thrombotic microangiopathies (TMAs)

Trained on 538 WSIs
(7694 Glomeruli, 10838 Arteriolie, 1658 Artery)
Tested on 128 WSIs
(2200 Glomeruli, 3099 Arteriolie, 532 Artery)

32732 tiles extracted for the task

Results: (F1-scores):
Glomeruli: 0.86
Arteriolie: 0.36
Artery: 0.66



WSI Acquisition | Glomeruli Segmentation | Feature Extraction | Model Training

Huy Q. Vo et al. , 2022

Auto-Segmentation Model

WSI Count Info:

	AMR	NoAMR	Total
PAS	543	517	**1060**
H_E	380	373	**753**
Total	**923**	**890**	**1813**

Glomeruli Count Info:

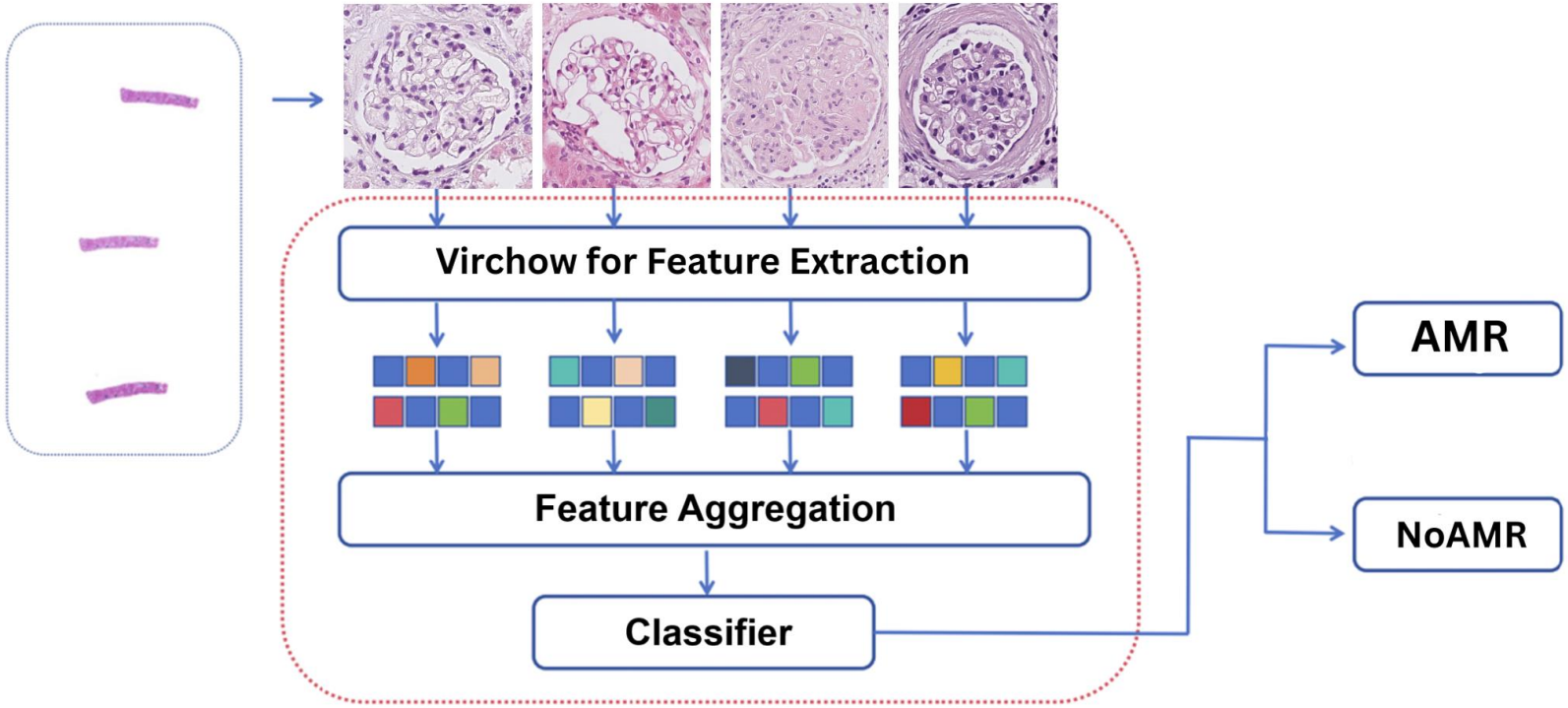
	AMR	NoAMR	Total
PAS	**8560**	**7375**	**15935**
Average	15.76	14.26	15.03
Std	12.38	9.88	11.25
H_E	**6011**	**5094**	**11105**
Average	15.81	13.65	14.74
Std	11.44	10.03	10.81
Total	**14571**	**12469**	**27040**
Average	15.78	14.01	14.91
Std	11.99	9.94	11.07

WSI Acquisition → Glomeruli Segmentation → Feature Extraction → Model Training

Feature Extraction

- **Virchow:** A Foundation Model for Computational Pathology

- **Architecture & Training:**
  - Model: Vision Transformer Huge (ViT-H/14) with 632 million parameters Training. Data: 1.5 million H&E stained whole-slide images from ~100,000 patients

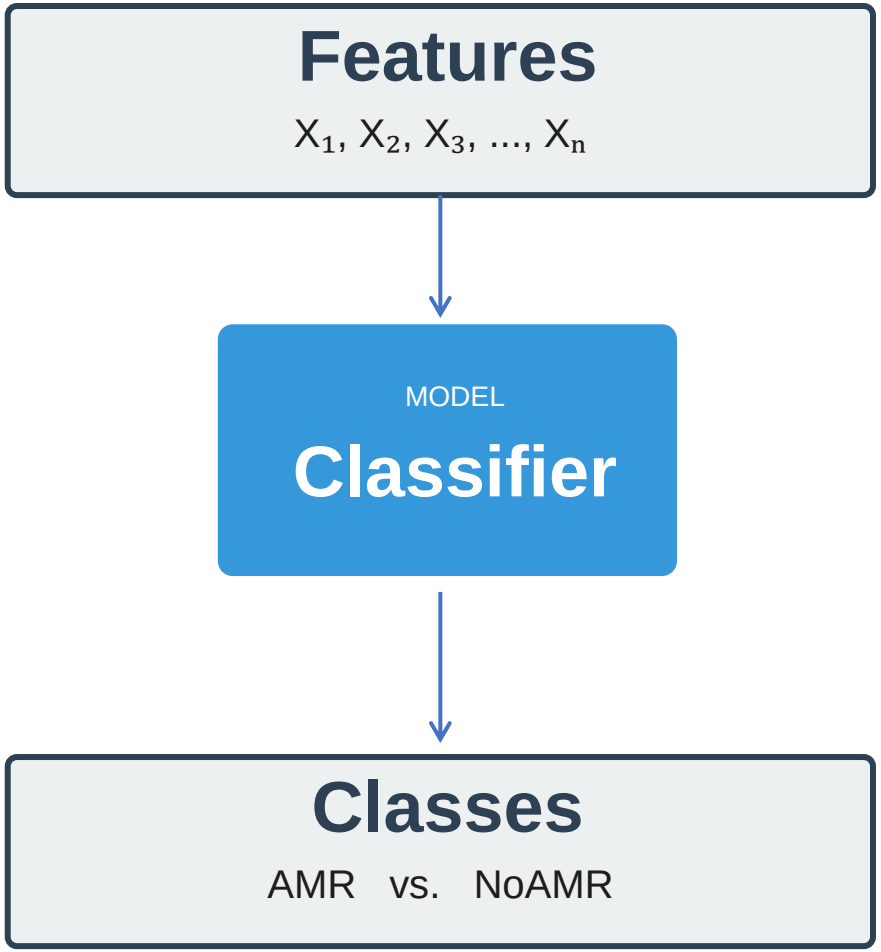


WSI Acquisition | Glomeruli Segmentation | Feature Extraction | Model Training

Huy Q. Vo et al. ,Nature Medicine, 2024

Model Training

- For training a **Classification Model** in total 144 combination of hyperparameters were tried, including:
- Patching method (Resized, aggregated patches)
- Case Aggregation method (Majority Voting, Any Positive)
- Classifier method (Average Pooling, Weighted Pooling, Max Pooling, Attention-based MIL, Attention Aggregation)
- Dropout (0.25, 0.5)
- Learning Rate (0.001, 0.005, 0.0001)
- Random state (10, 20, 42)



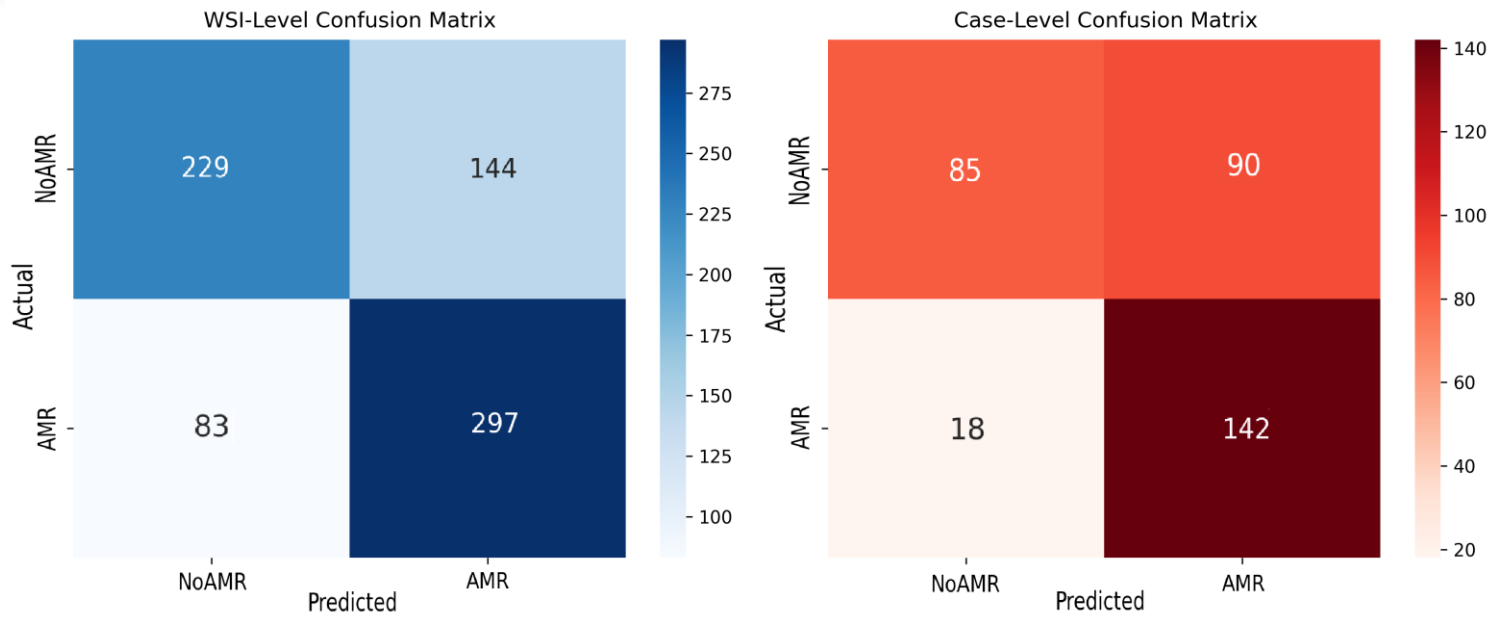
WSI Acquisition → Glomeruli Segmentation → Feature Extraction → Model Training

Results

- Best result was achieved so far with this configurations:

  - Patching method: Aggregated Patches
  - Case Aggregation method: Majority Voting
  - Classifier method: Weighted Pooling
  - Dropout: 0.25
  - Learning Rate: 0.001
  - Random state: 20

- WSI F1-Score: 0.7237 ± 0.0516
- Case F1-Score: 0.7195 ± 0.0474
- WSI Accuracy: 0.6980 ± 0.0680
- Case Accuracy: 0.6806 ± 0.0574



To Sum Up

Our ultimate objective is to leverage cutting-edge Deep Learning techniques, harnessing our robust dataset to achieve highly accurate and reliable outcomes in AMR diagnosis

Special Thanks to

Prof. Dr. Caner Süsal

Prof. Çiğdem Gündüz Demir

Prof. Dr. Dilek Ertoy Baydar

Prof. Dr. Jan Ulrich Becker

Teşekkürler!

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