LUXEMBOURG INSTITUTE OF HEALTH

Machine Learning Seminar

AI-driven digital pathology: A step towards precision medicine

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12.06.2024

Outline

Background

AI in Digital Pathology
- Whole Slide Imaging

Methods
- Supervised learning
- Multiple instance learning
- Self-supervised learning
- Multi-task learning

Results
- Tumor subtype prediction
- Tumor segmentation
- Molecular profile prediction

Challenges & Outlook

Q & A

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Multiomics Data Science
@ Department of Cancer Research

Bioinformatics

- Genomics
- Epigenomics
- Transcriptomics
- Proteomics
- Clinical data

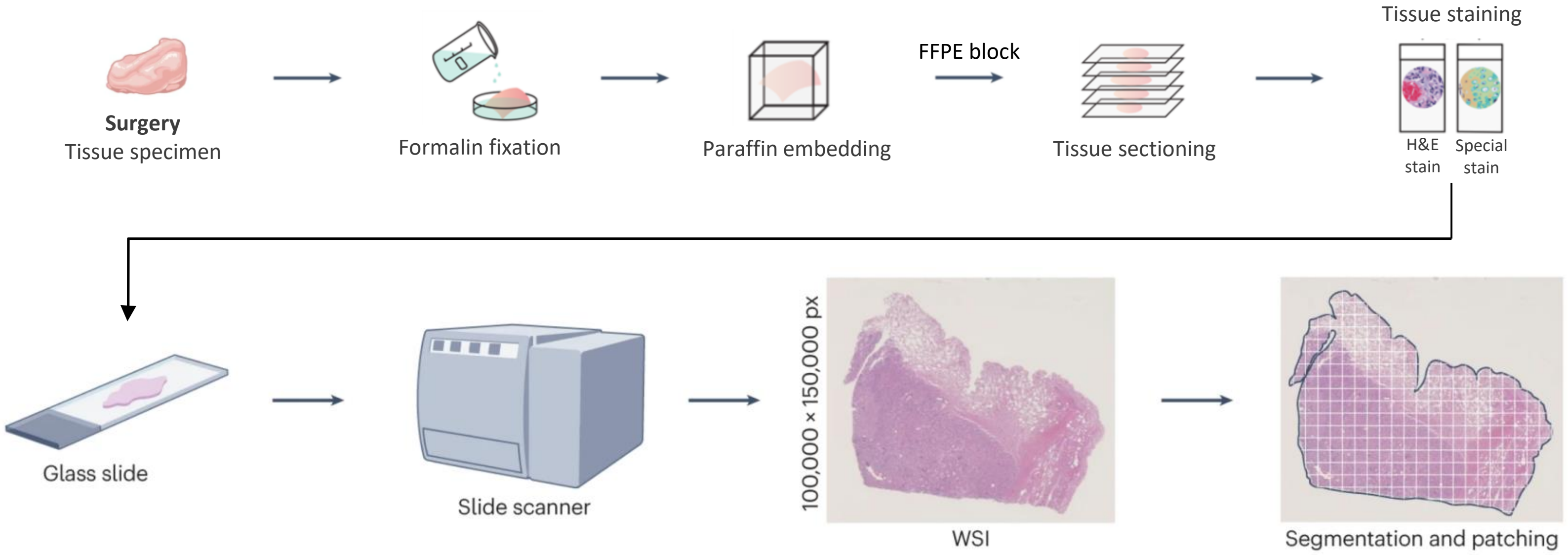
AI

- Biomedical signal processing
- Medical image analysis

Digital (computational) pathology

- Field within pathology that involves the digitization of traditional glass slides, tissue samples, and other pathology specimens
- Whole-slide imaging (WSI) creates and analyses high-resolution, digital representations of histological slides and specimens

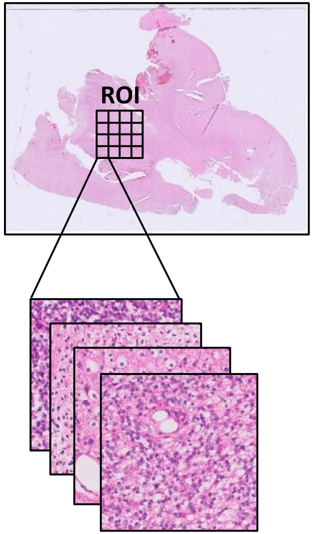
From tissue to Whole Slide Image (WSI)



Adapted from Song *et al.* Artificial intelligence for digital and computational pathology. *Nat Rev Bioeng* (2023)

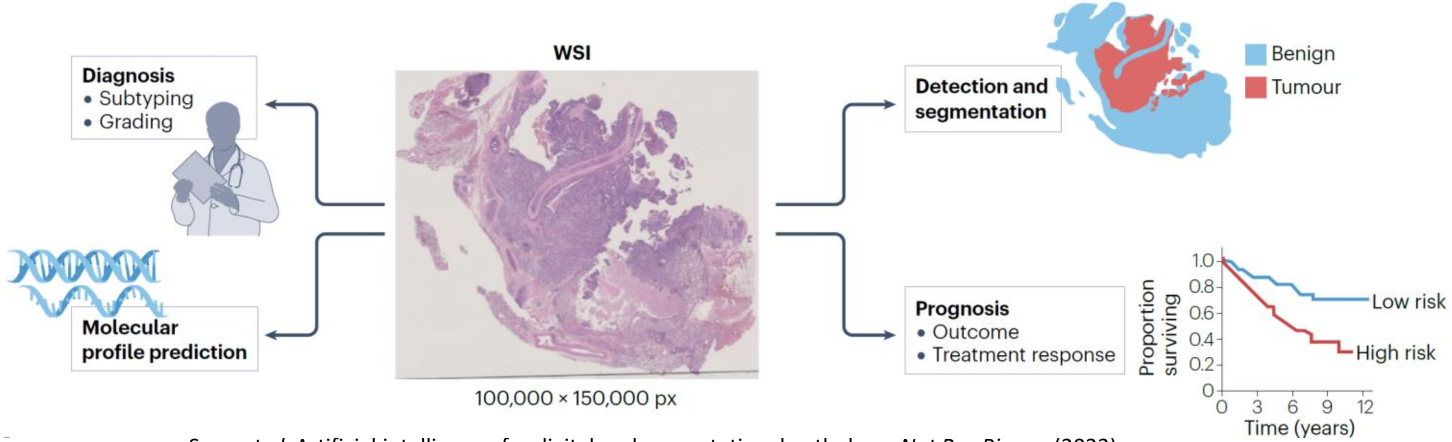
Whole Slide Imaging

- Resolution up to 150 000 × 150 000 pixels
- Several gigabytes of storage space
- Processed in patches
- Typically 20× or 40× magnification
  - Lower magnification -> more context at lower resolution
  - High magnification -> small context at high resolution



AI in digital pathology

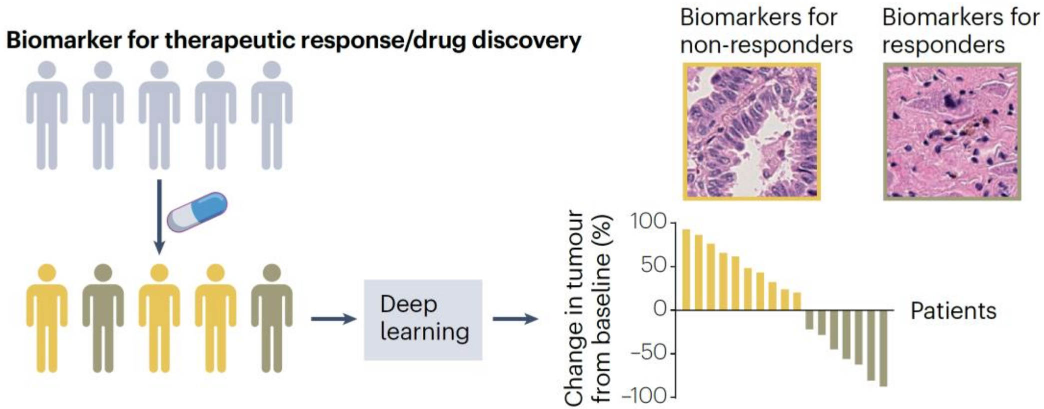
- **Automatic clinical diagnosis**
- **Automating routine tasks that pathologists perform in daily practice**
- Discovering new morphological biomarkers for clinical outcomes of interest
- Drug development



Song *et al.* Artificial intelligence for digital and computational pathology. *Nat Rev Bioeng* (2023)

AI in digital pathology

- Automatic clinical diagnosis
- Automating routine tasks that pathologists perform in daily practice
- **Discovering new morphological biomarkers for clinical outcomes of interest**
- **Therapy and drug development**



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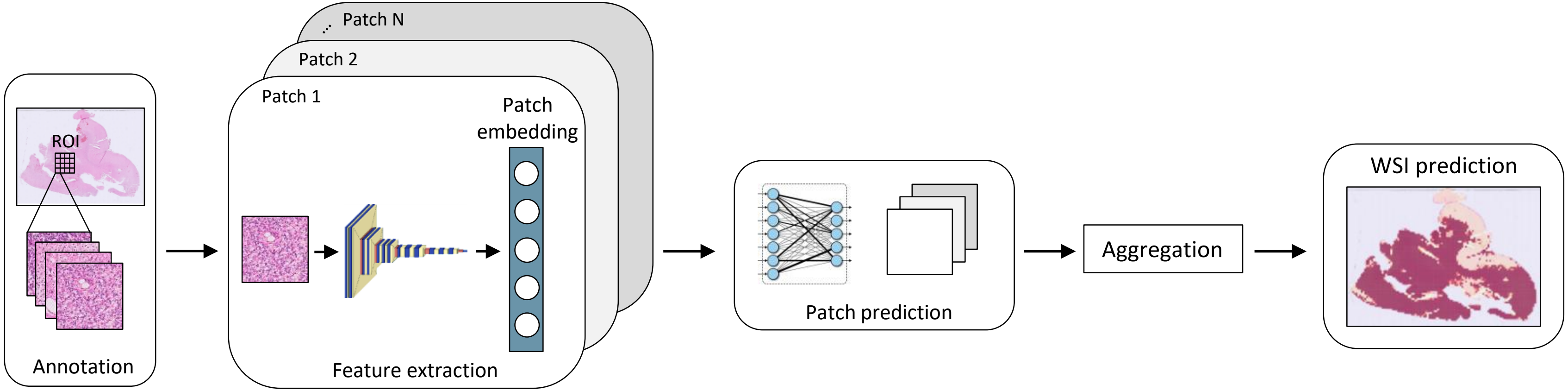
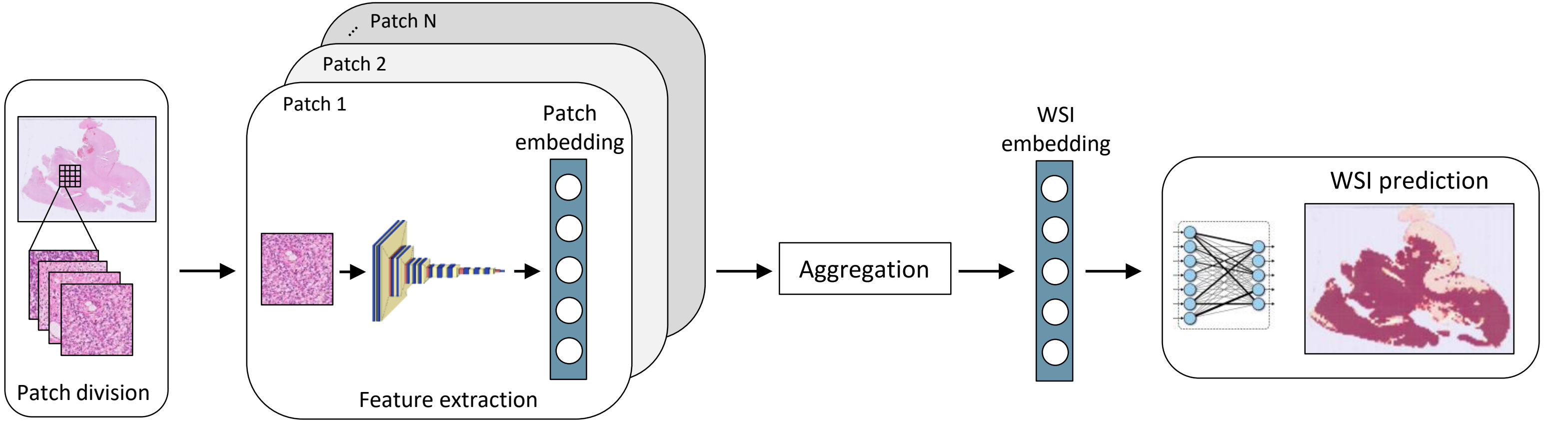
Supervised learning

- Requires patch level annotations



Multiple instance learning

- Only WSI level annotations, no patch level annotations



Transfer learning

Out-of-domain transfer learning

- Generalizability of out-of-domain image representations for a domain of histopathological images

In-domain transfer learning

- In-domain adaptation using self-supervised and multi-task learning approaches for pretraining the models

Out-of-domain transfer learning

Problem

- Lack of annotated datasets of histopathological images

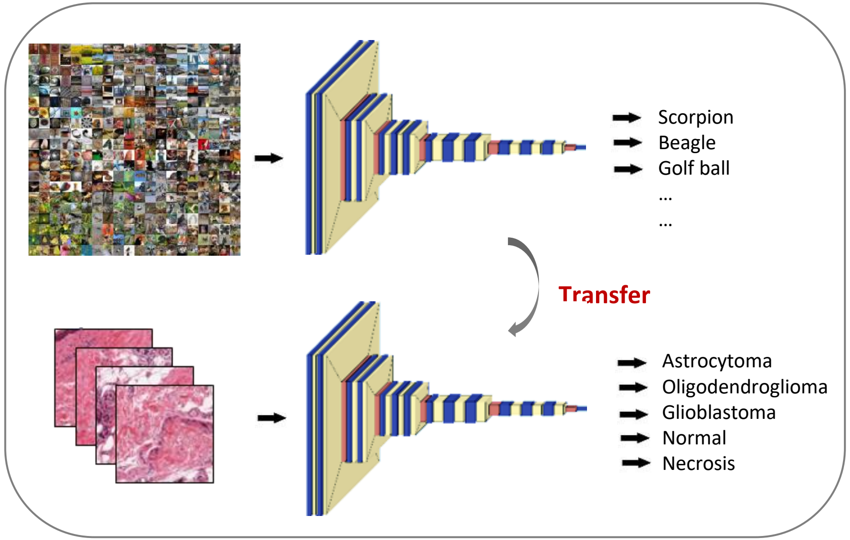
Out-of-domain transfer learning

Problem

- Lack of annotated datasets of histopathological images

Solution

- Transfer knowledge from another domain where large-scale data is available
- ImageNet dataset
  - Natural images classified into 1000 classes
- Pretrain the model on ImageNet and fine-tune on the target histopathological dataset
  - Low-level image features shared across domains



In-domain transfer learning

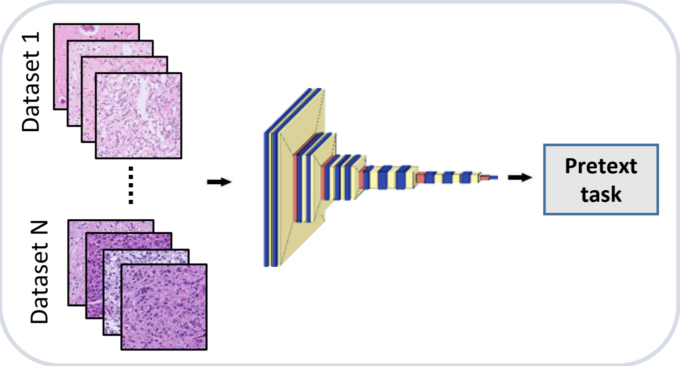
Problem

- Lack of annotated datasets of histopathological images

Solution

- Use domain-specific pretraining
- Large number of public (un)annotated small-size and medium-size datasets of histopathological images
  - Multiple origins
  - Different types of staining
  - Different resolution

In-domain transfer learning



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Self-supervised learning

- Find a classification pretext task that does not require pathologist annotations

In-domain transfer learning

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Self-supervised learning

- Find a classification pretext task that does not require pathologist annotations

Multi-task learning

- Multiple classification tasks using multiple small-size annotated datasets

In-domain transfer learning

Self-supervised contrastive learning

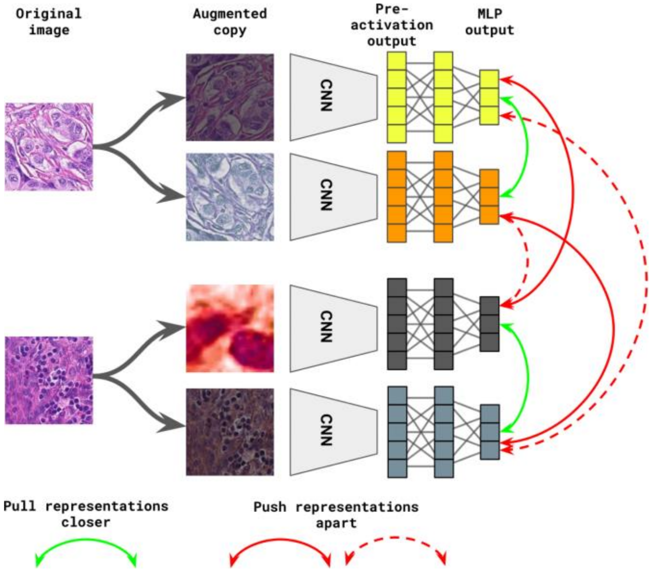
- **SimCLR, MoCo v3**
- Pretraining on 57 unannotated datasets of histopathological images
- 22 organs
  - Breast, lymph, colon, bone, prostate, liver, pancreas, bladder, cervix, esophagus, head, neck, kidney, lung, thyroid, uterus, bone marrow, skin, brain, stomach, ovary
- Different types of staining
- Different resolution

Pretext task

- Create two stochastically augmented versions of the same patch
- Maximize the similarity between these two inputs
- Emphasize dissimilarity to all other patches

Backbone network

- ResNet18, CNN+Swin-T



Ciga et al., Self supervised contrastive learning for digital histopathology, Machine Learning with Applications, 2022

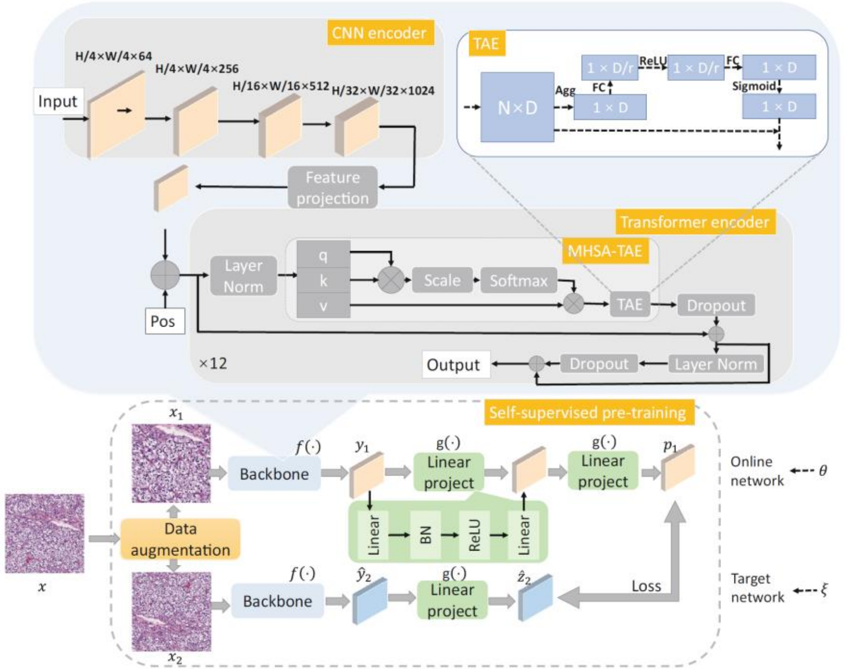
In-domain transfer learning

Non-contrastive learning

- Pretrained on 2 unannotated datasets of histopathological images
  - TCGA: 30 072 WSIs, 25 organs
  - PAIP: 2457 WSIs, 6 organs
  - 32 cancer subtypes
  - Up to 15 million of unlabeled patches in total

Bootstrap Your Own Latent (BYOL)

- Train two networks on augmented views of an image
- Online network predicts target representation
- Target network is the exponential moving average of the parameters of the online network

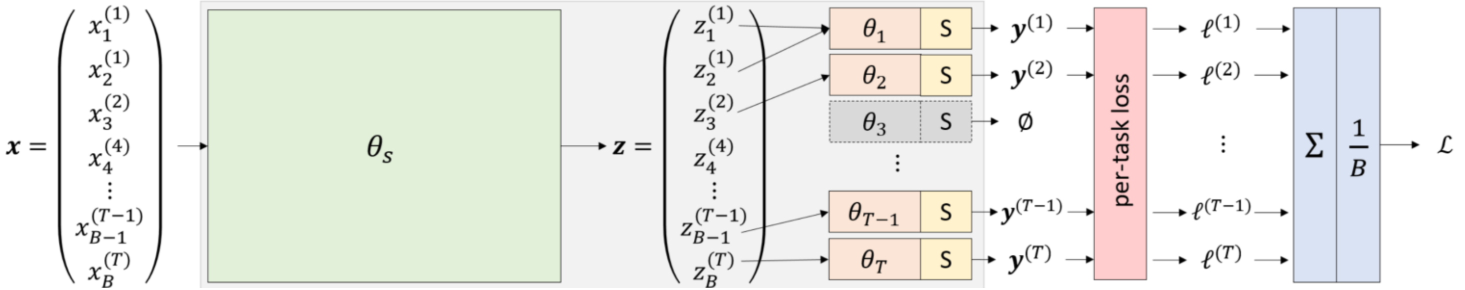


Wang *et al.*, TransPath: Transformer-Based Self-supervised Learning for Histopathological Image Classification, LNCS, Springer, 2021
Wang et al, Transformer-based unsupervised contrastive learning for histopathological image classification, Medical Image Analysis, 2022

In-domain transfer learning

Multi-task learning

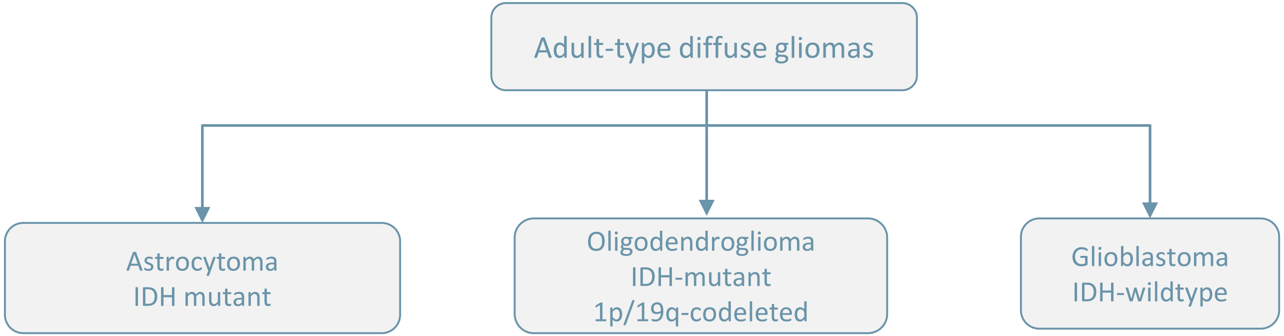
- Pretraining on 22 annotated datasets of histopathological images
- 883k patches in total
- Multiple organs
  - Breast, lymph, colon, thyroid, lung, kidney, bone
- **Backbone network**
  - ResNet50
  - DenseNet121



Mormont et al., Multi-task pre-training of deep neural networks for digital pathology, IEEE journal of biomedical and health informatics, 2020

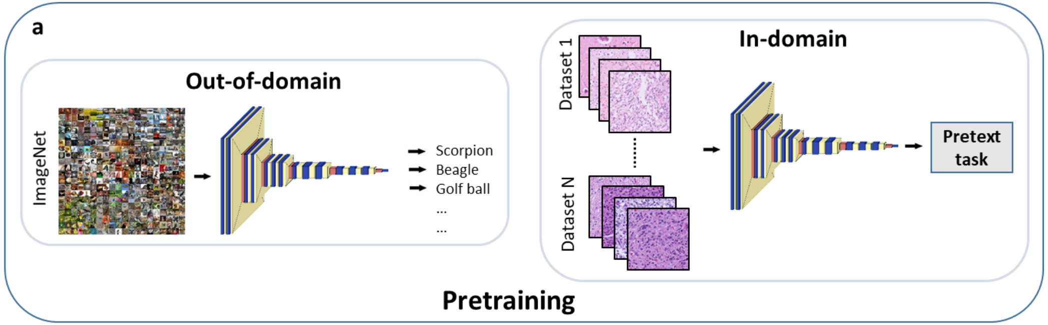
Use case 1: Tumor subtype prediction

- Adult-type diffuse gliomas – most common malignant tumors of the central nervous system
- Historically classified based on morphological characteristics
- Refinement of tumor classification based on molecular profiles



* WHO classification of CNS tumors (5th edition, 2021)

Use case 1: Tumor subtype prediction



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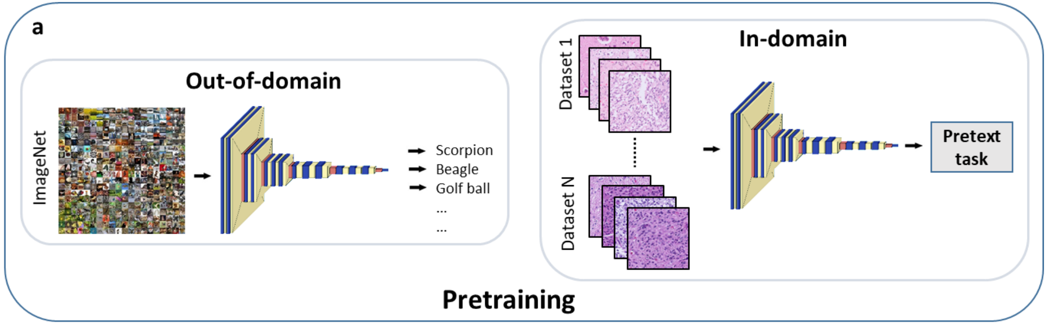

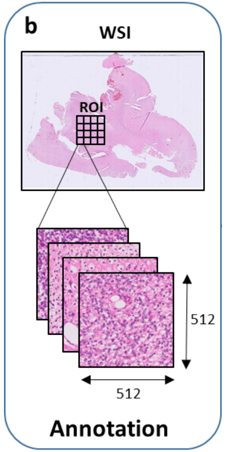

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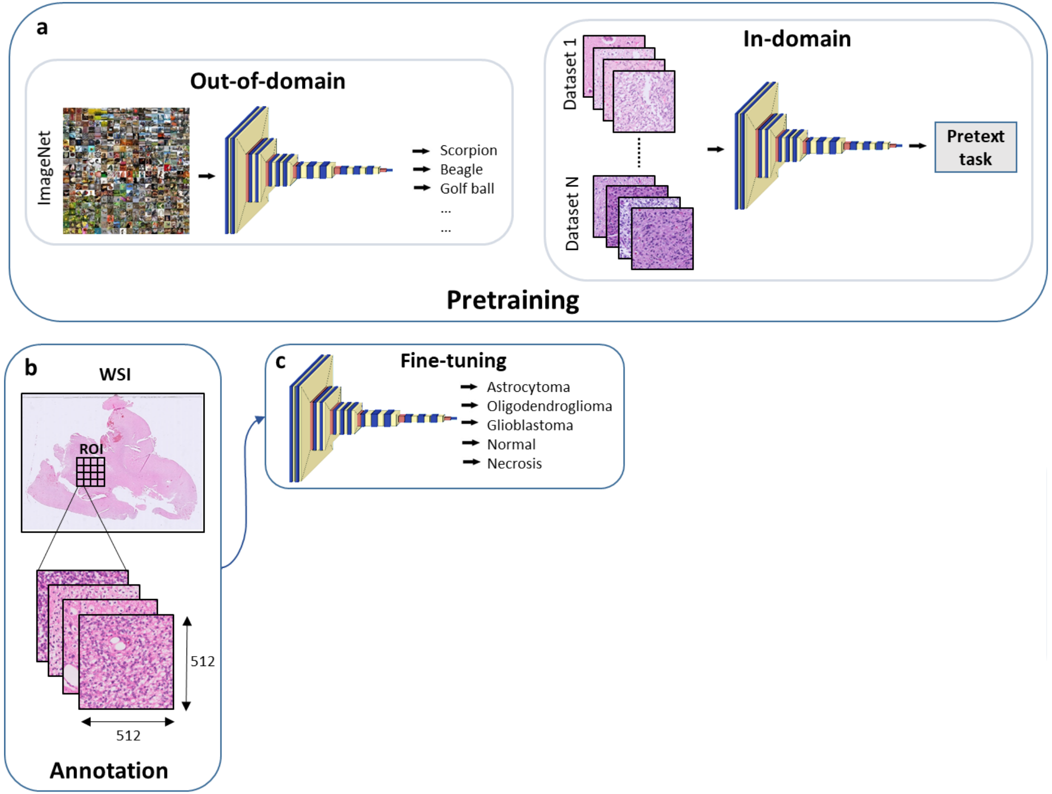

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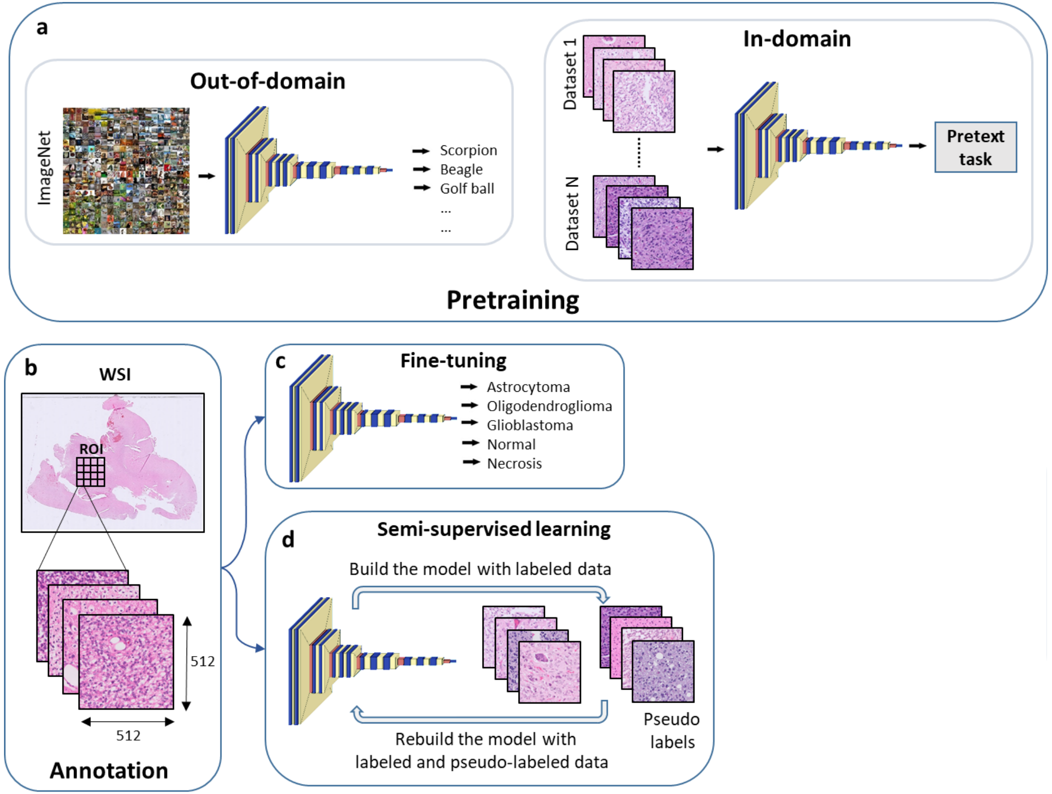
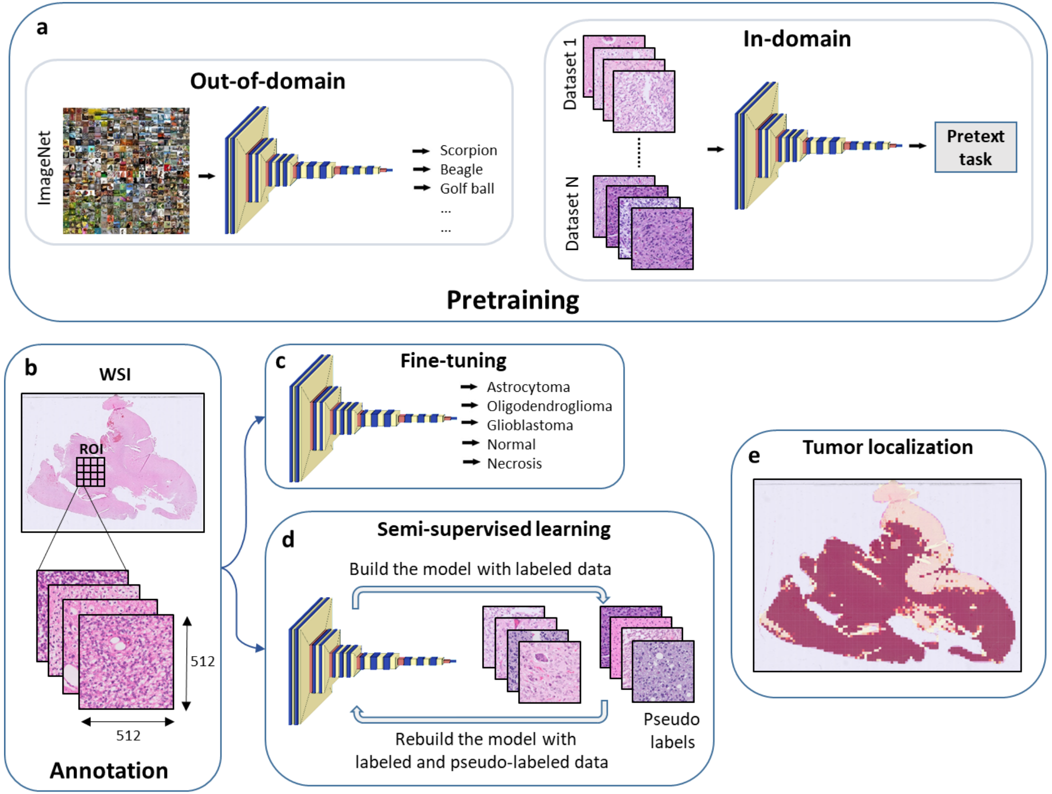


Use case 1: Tumor subtype prediction



Use case 1: Tumor subtype prediction

Data Preprocessing

- Regions of interest annotated by pathologist
- 512x512 patches sampled from the ROIs
- Image augmentation (training data)
  - Flipping and rotation (90º, 180º, 270º)

Class	Training data	Test data
IDH-mutant, non-codeleted (astrocytoma)	30040	465
IDH-mutant, 1p/19q codeleted (oligodendroglioma)	27072	431
IDH-wildtype (glioblastoma)	13064	241
Normal brain tissue	56291	2947
Necrosis	3112	90
Total	129579	4174

Out-of-domain transfer learning

- **Training from scratch**
- **Fine-tuning**
  - **Classification head**
    - Fully connected layers with 256 and 128 neurons
    - ReLU activation
    - Dropout equal to 0.5
    - Output fully connected layer with softmax activation
    - AdamW optimizer
    - Weighted categorical cross-entropy loss
    - Trained for max 10 epochs
    - Learning rate reduced after 5 epochs

Type of pretraining	Model	Balanced accuracy	Precision	Recall	F1 score	
No pretraining	VGG16	85.07	83.29	85.07	82.53	CNN
	VGG19	85.00	83.75	85.00	84.34	
	ResNet18	88.22	79.12	88.22	82.38	
	ResNet50	78.18	79.49	78.18	78.14	
	InceptionV3	79.26	79.78	79.26	79.42	
	MobileNetV2	84.54	85.20	84.54	84.59	
	DenseNet121	85.10	85.03	85.10	84.53	
	ViT-B/16	68.25	54.62	68.25	60.09	Transformer
	Swin-T	57.21	60.51	57.21	58.19	
	ResNet50-ViT-B/16	81.02	78.34	81.02	77.22	
Pretraining with ImageNet	VGG16	94.81	**97.04**	94.81	**95.72**	CNN
	VGG19	93.94	94.19	93.94	93.75	
	ResNet18	85.89	89.84	85.89	87.23	
	ResNet50	92.42	94.65	92.42	93.50	
	InceptionV3	85.70	91.02	85.70	87.25	
	MobileNetV2	84.70	84.46	84.70	83.45	
	DenseNet121	88.97	92.46	88.97	90.26	
	ViT-B/16	92.38	93.90	92.38	92.98	Transformer
	Swin-T	86.22	93.82	86.22	89.16	
	ResNet50-ViT-B/16	**94.87**	96.63	**94.87**	95.48	

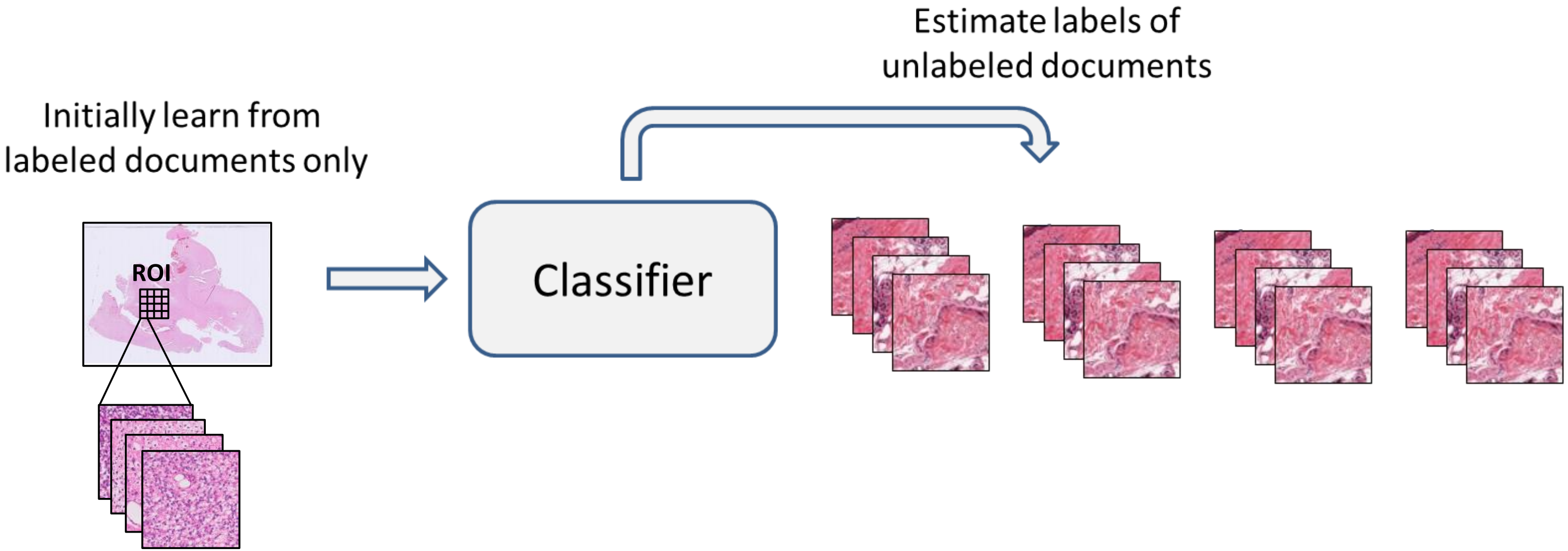
Out-of-domain transfer learning

Type of pretraining	Model	Balanced accuracy	Precision	Recall	F1 score
Pretraining with ImageNet	VGG16	94.81	**97.04**	94.81	**95.72**
	VGG19	93.94	94.19	93.94	93.75
	ResNet18	85.89	89.84	85.89	87.23
	ResNet50	92.42	94.65	92.42	93.50
	InceptionV3	85.70	91.02	85.70	87.25
	MobileNetV2	84.70	84.46	84.70	83.45
	DenseNet121	88.97	92.46	88.97	90.26
	ViT-B/16	92.38	93.90	92.38	92.98
	Swin-T	86.22	93.82	86.22	89.16
	ResNet50-ViT-B/16	**94.87**	96.63	**94.87**	95.48

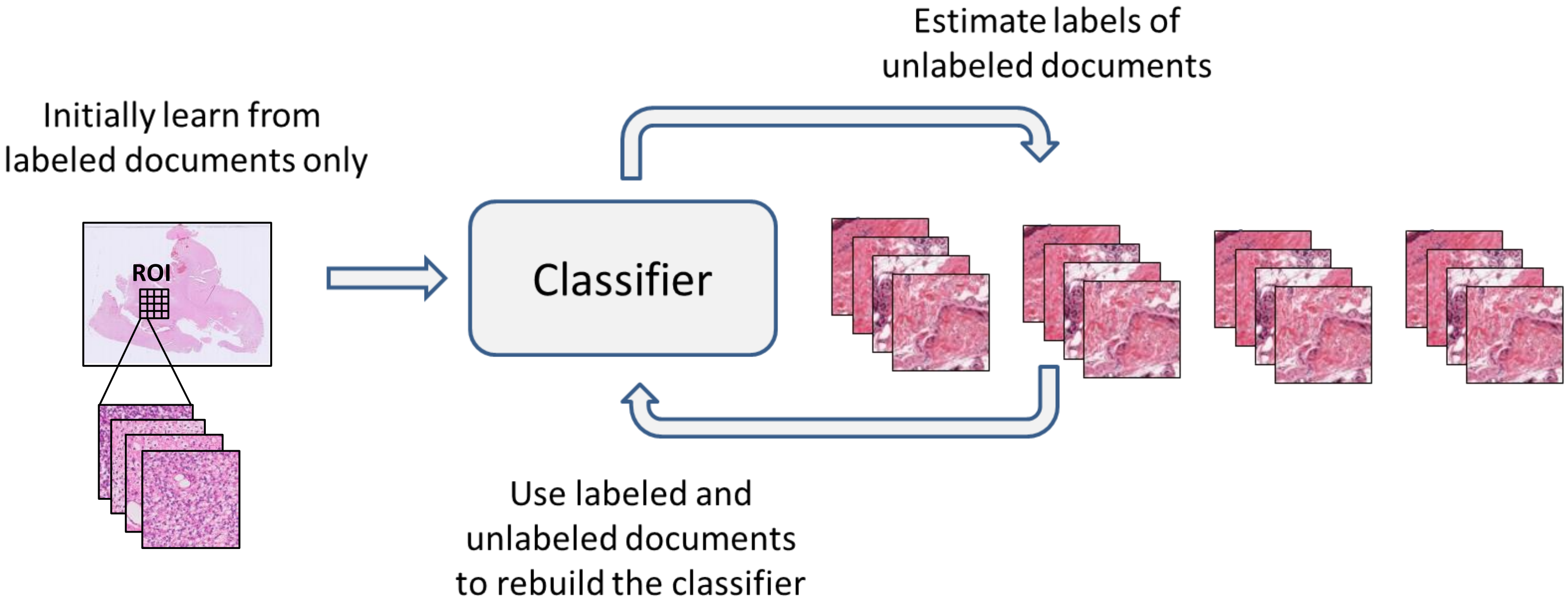
In-domain transfer learning

Type of pretraining	Model	Balanced accuracy	Precision	Recall	F1 score
Self-supervised learning	SimCLR (ResNet18)	91.57	91.25	91.57	90.60
	BYOL (ResNet50 + ViT-B/16)	**96.39**	**95.57**	**96.39**	**95.81**
	MoCo v3 (CNN + Swin-T)	93.45	94.65	93.45	93.45
Multi-task learning	ResNet50	93.15	92.86	93.15	92.54
	DenseNet121	94.31	89.66	94.31	91.43

Semi-supervised learning



Semi-supervised learning



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	MoCo v3 (CNN + Swin-T)	93.45	94.65	93.45	93.45
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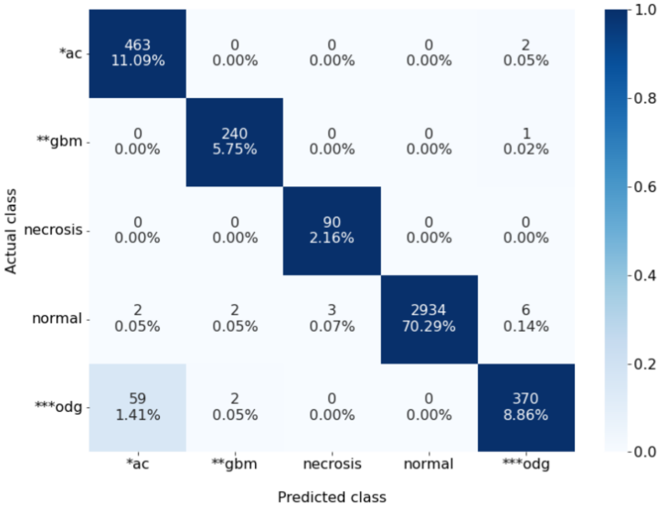
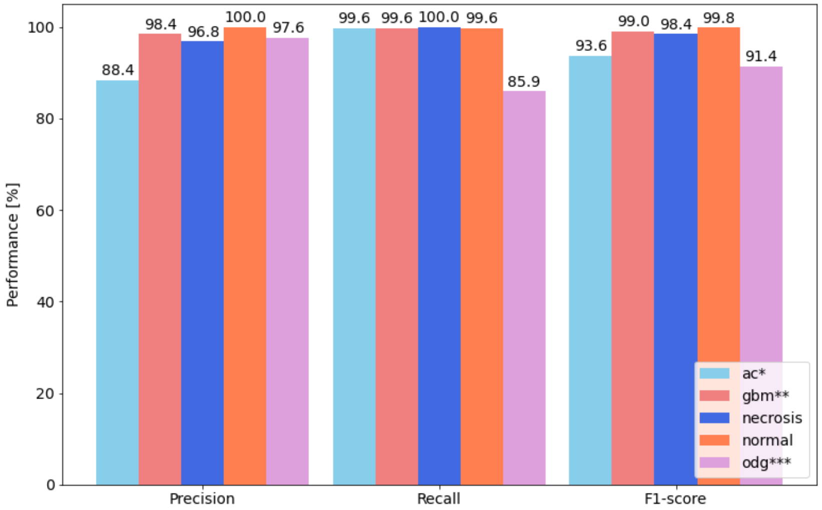
Type of pretraining	Model	Balanced accuracy	Precision	Recall	F1 score
Self-supervised learning	SimCLR (ResNet18)	96.55	95.27	96.55	95.62
	BYOL (ResNet50 + ViT-B/16)	**96.91**	96.11	**96.91**	96.42
	MoCo v3 (CNN + Swin-T)	96.56	97.03	96.56	96.58
Multi-task learning	ResNet50	96.48	**97.94**	96.48	**97.07**
	DenseNet121	96.63	93.01	96.63	94.57

Semi-supervised learning

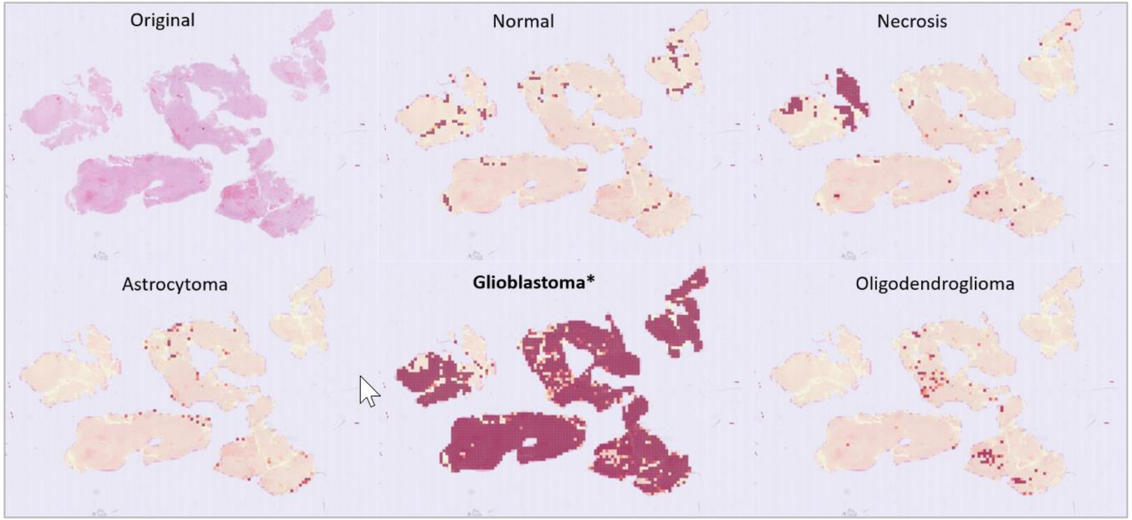




Tumor segmentation

Segmentation of diffuse gliomas in WSIs

- Overlay the predicted confidence scores for each patch on the WSI as a heatmap
- Draw the pathologist's attention to the most informative areas in the WSI corresponding to the tumor tissue

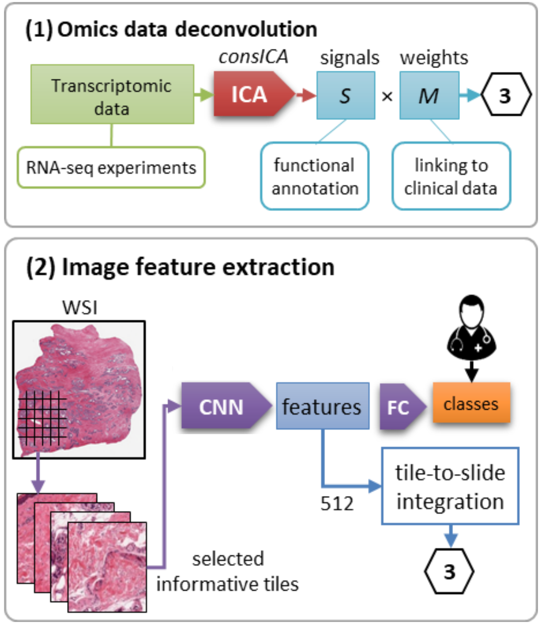


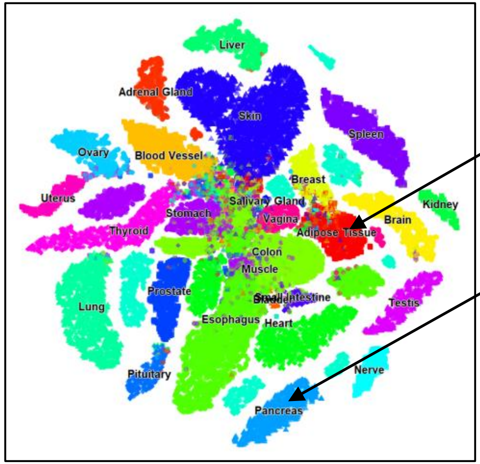
Use case 2: Molecular profile prediction

GTEx

670+ patients

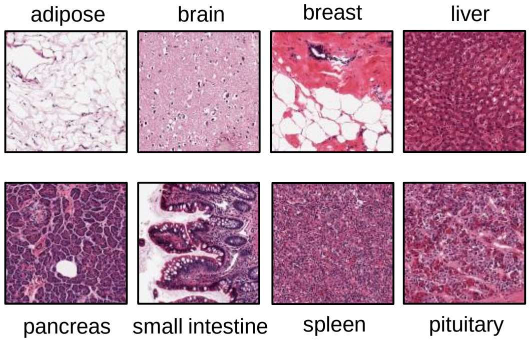
27 organs





Patch level clustering

Examples of patches classified with top accuracy



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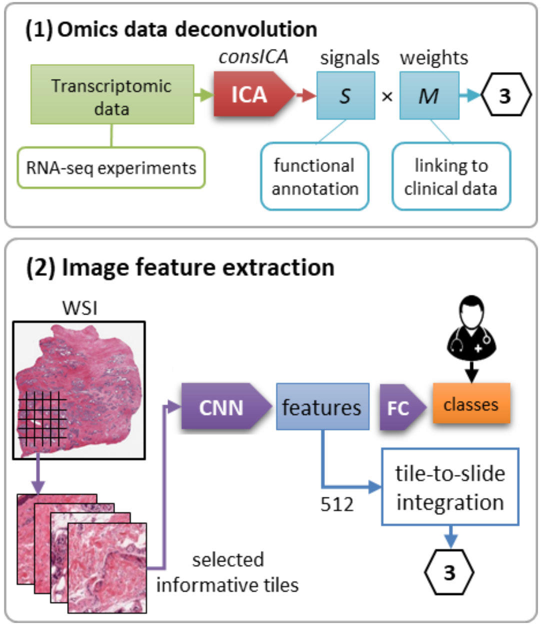

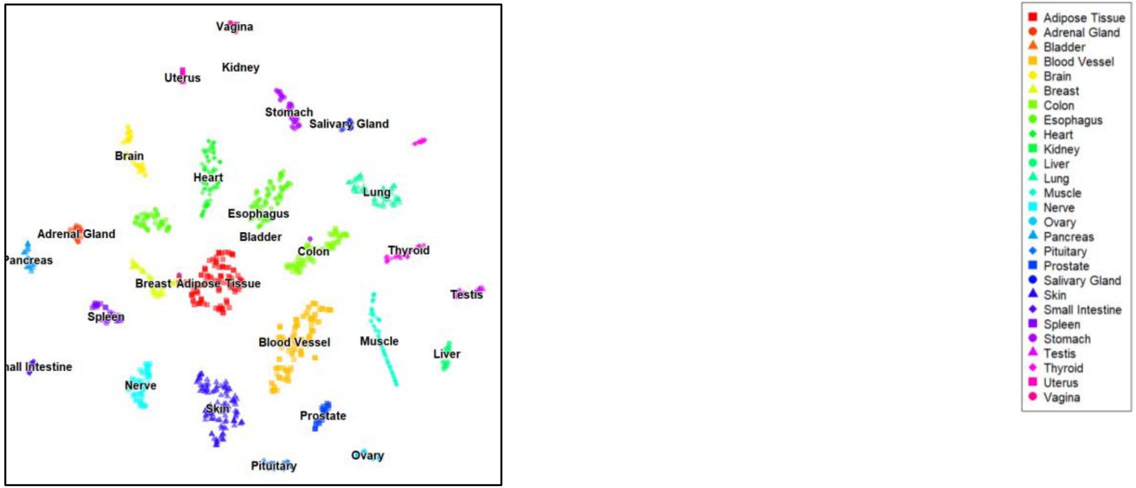

WSI level clustering

Use case 2: Molecular profile prediction

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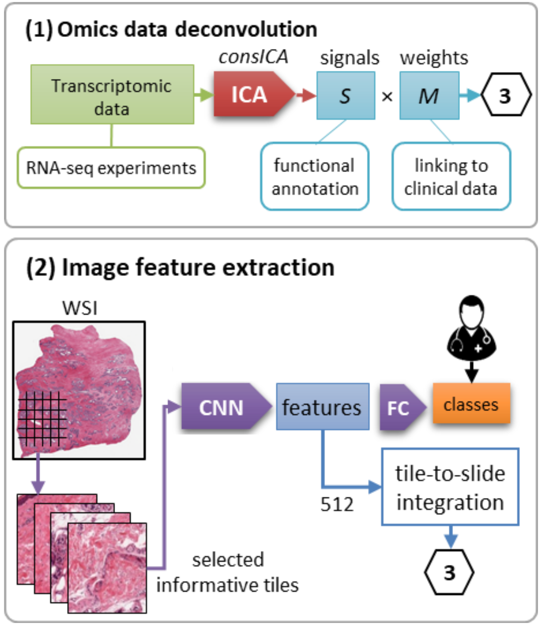

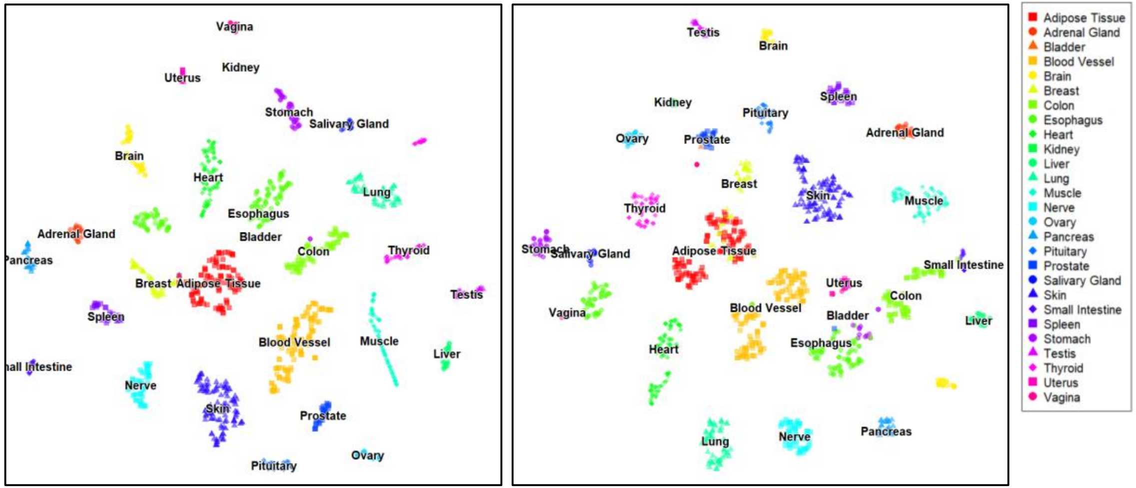

WSI level clustering **ICA-weights: RNA-seq**

Use case 2: Molecular profile prediction

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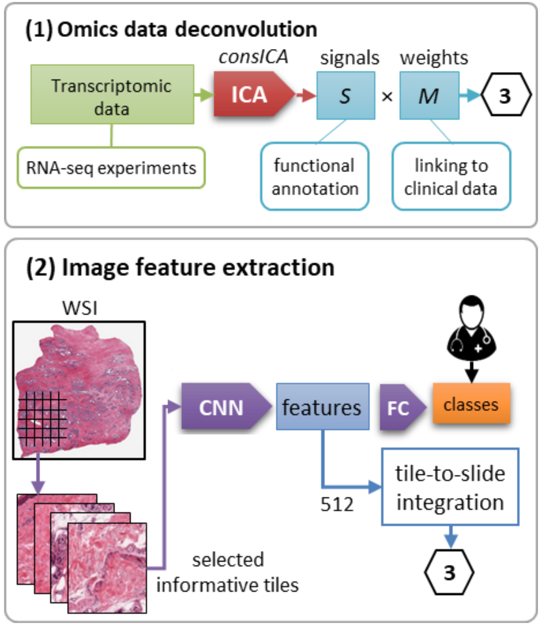
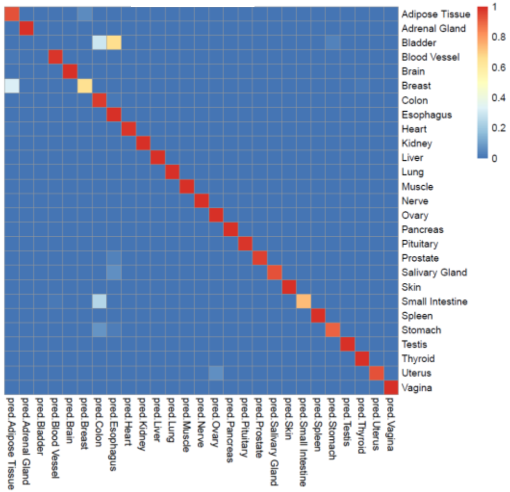
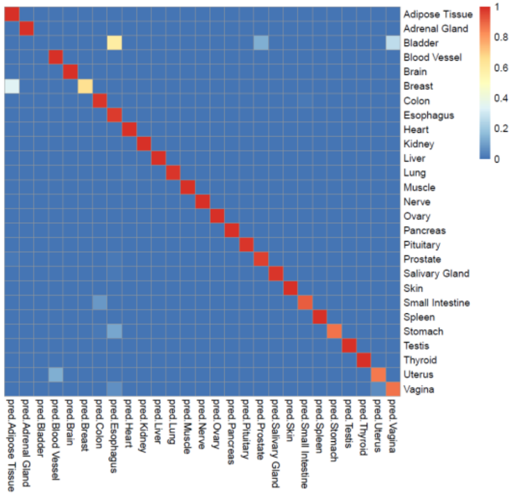




WSI level (CONCH*)

$\text{Acc}_{\text{balanced}} = 0.925$



ICA-weights: RNA-seq

$\text{Acc}_{\text{balanced}} = 0.927$

*Lu, M. Y., et al (2024). A visual-language foundation model for computational pathology. Nature Medicine.

Use case 2: Molecular profile prediction

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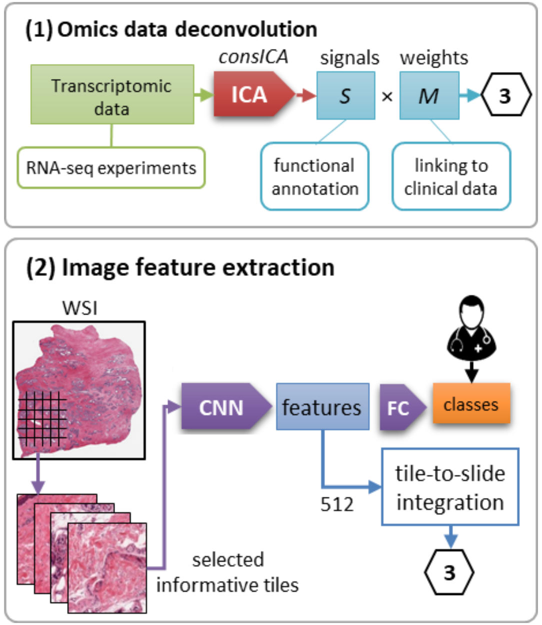

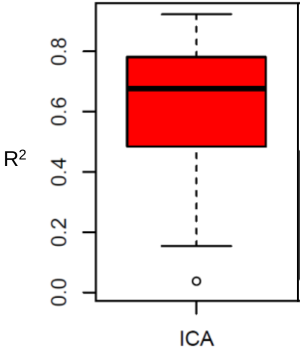

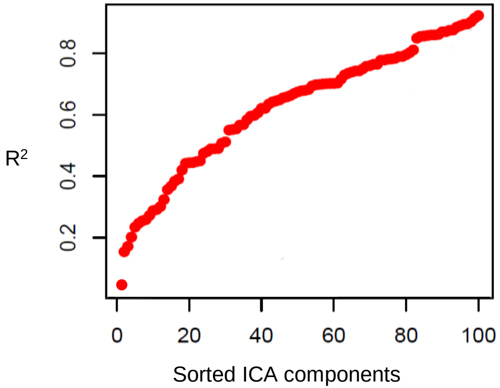

Outlook

Multimodal fusion

- Integration of image embeddings with omics and clinical data
- Prediction of molecular profiles from WSIs

Vision – language models

- Interpretation of morphological features on WSIs
- Automatic generation of pathology reports

Challenges

- **Only few works in digital pathology have made a clinical impact !**
  - FDA approved one clinical-grade AI solution for prostate cancer detection (Paige Prostate)
  - Several solutions received CE marks in the European Union
    - Mindpeak Breast Ki-67 HS – automated recognition and analysis of Ki-67 immunohistochemistry in breast cancer
    - DoMore Diagnostics Histotype Px Colorectal – colorectal cancer detection
    - NIO Glioma Reveal – identification of areas of cancer infiltration in patients with diffuse gliomas

Challenges

- Widespread adoption in clinical and pre-clinical settings remains a challenge
- Limitations
  - Dataset sizes are relatively small compared with the diversity within any given data
  - Biases due to different slide and staining procedures and equipment need to be mitigated
- Regulatory bodies do not having extensive experience with AI software

Acknowledgements

LUXEMBOURG
INSTITUTE
OF HEALTH

Department of Medical Informatics

Bioinformatics & AI Unit

Dr Petr Nazarov

Sang-Yoon Kim

LNS
LUXEMBOURG

National Center for Pathology

FRANKFURT
CANCER
INSTITUTE

Dr Michel Mittelbronn

Dr Katrin Frauenknecht

Dr Ann-Christin Hau

Dr Felix Kleine Borgmann

Thank you for your attention!

Questions?

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