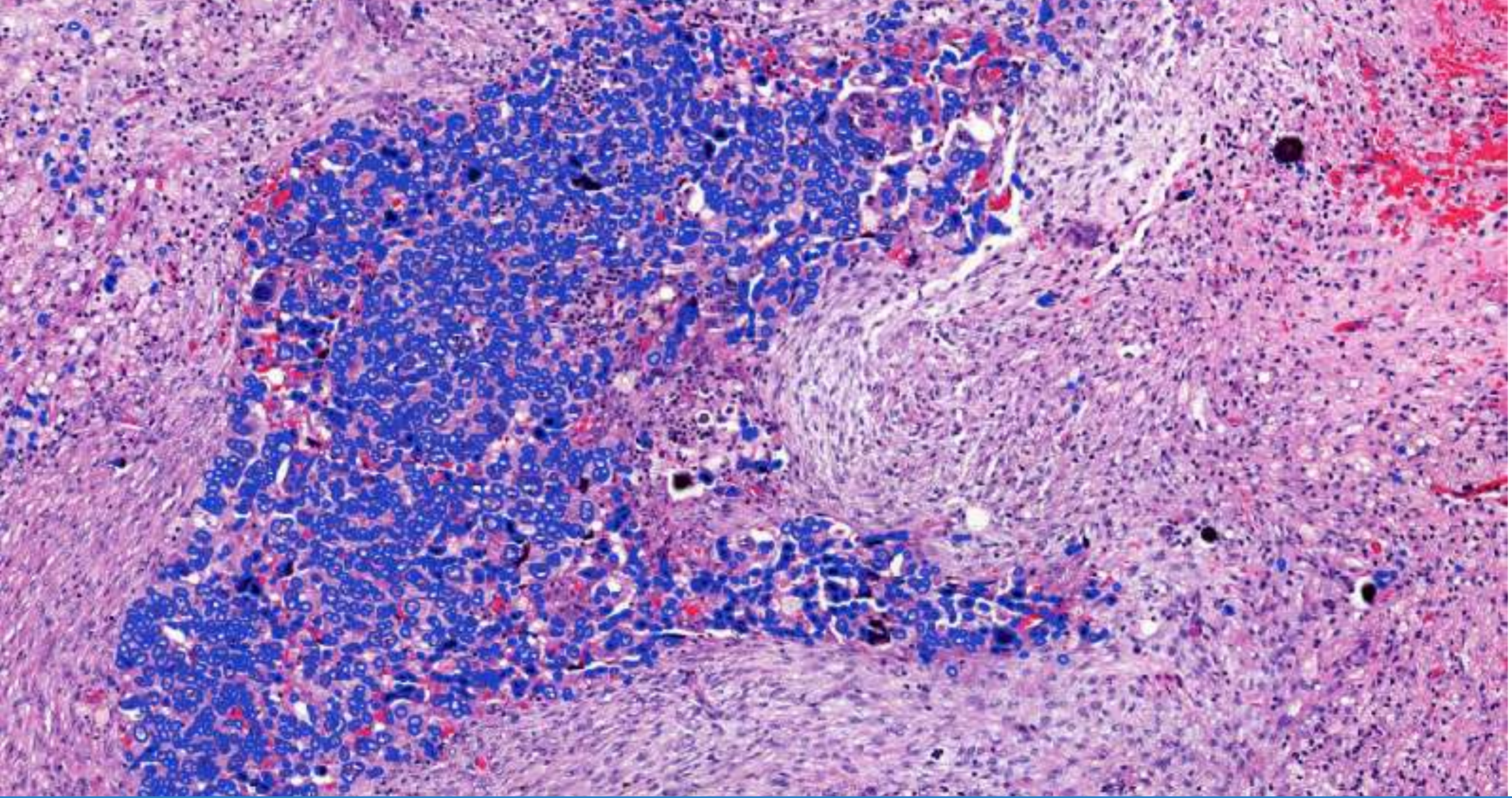

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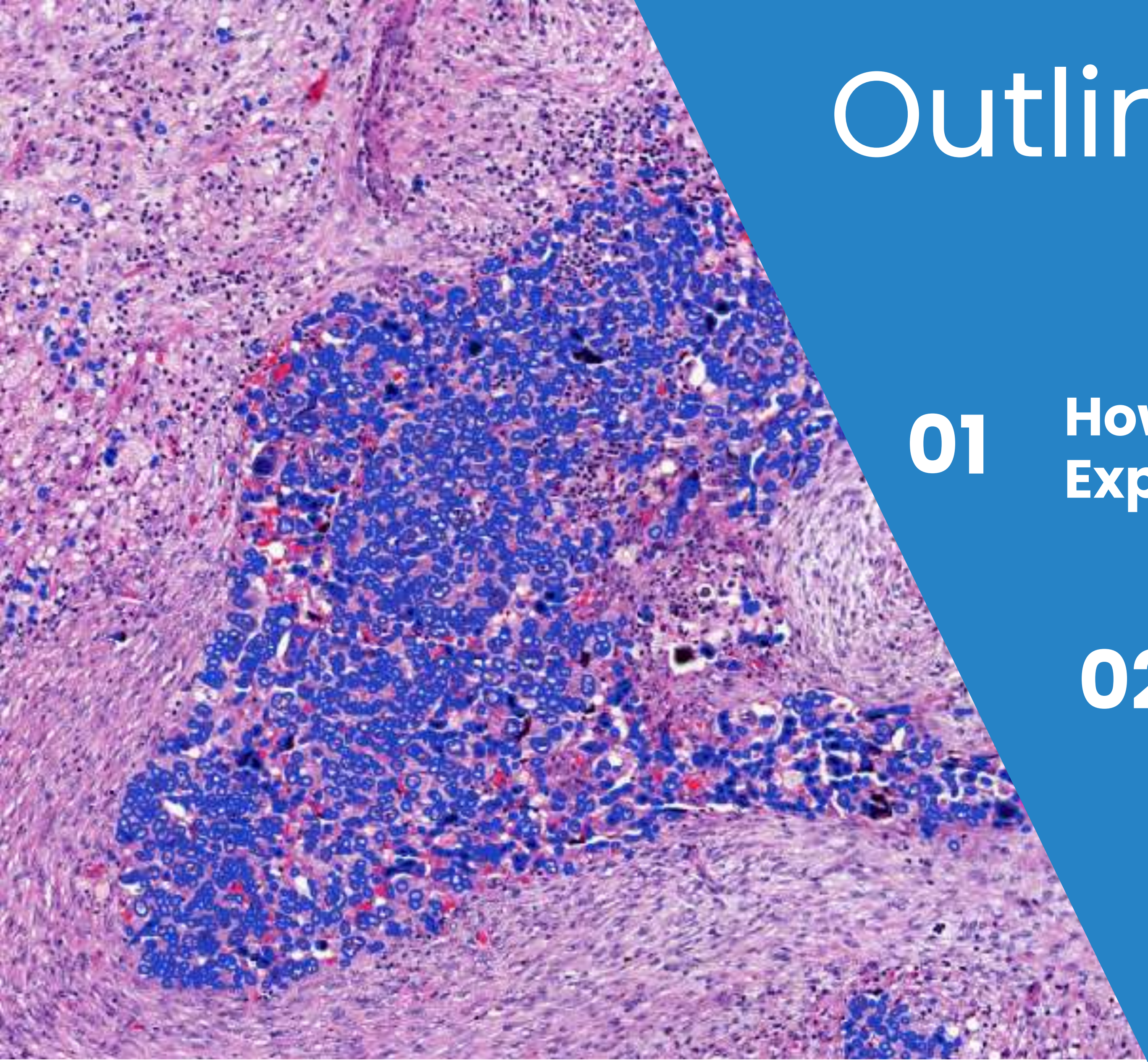
Artificial intelligence technologies in medicine: current innovations and upcoming scenarios

Prof. Elisa Ficarra, PhD

elisa.ficarra@unimore.it



Outline

01 **How to validate AI models? Explainable AI could help?**

02 **Proposal for Emilia-Romagna AI platforms for healthcare**

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1. How can AI models be trusted?

- In the EU, AI models must be certified under EU regulation

however, ….

EU AI Act
– Conformity Assessment for High-Risk AI System

Medical Devices Regulation
MDR

GDPR

- The procedures for AI models' assessment and certification are challenging, especially in complex use-cases (e.g., medical/clinical AI, or AI for rare disease or genetic pathology)

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Requirements for certification: checklist

1. Legal & Regulatory Classification (def. of AI system type)
2. Data Governance & GDPR
3. Risk Management & Quality Management System (including continuous monitoring plan)
4. Technical Documentation
5. **Validation & Benchmarking**
6. Conformity Assessment & Certification Path (internal control vs notified body)
7. Post-Market Monitoring & Transparency

Proposal: Explainable AI & multicenter clinical validation

Context:

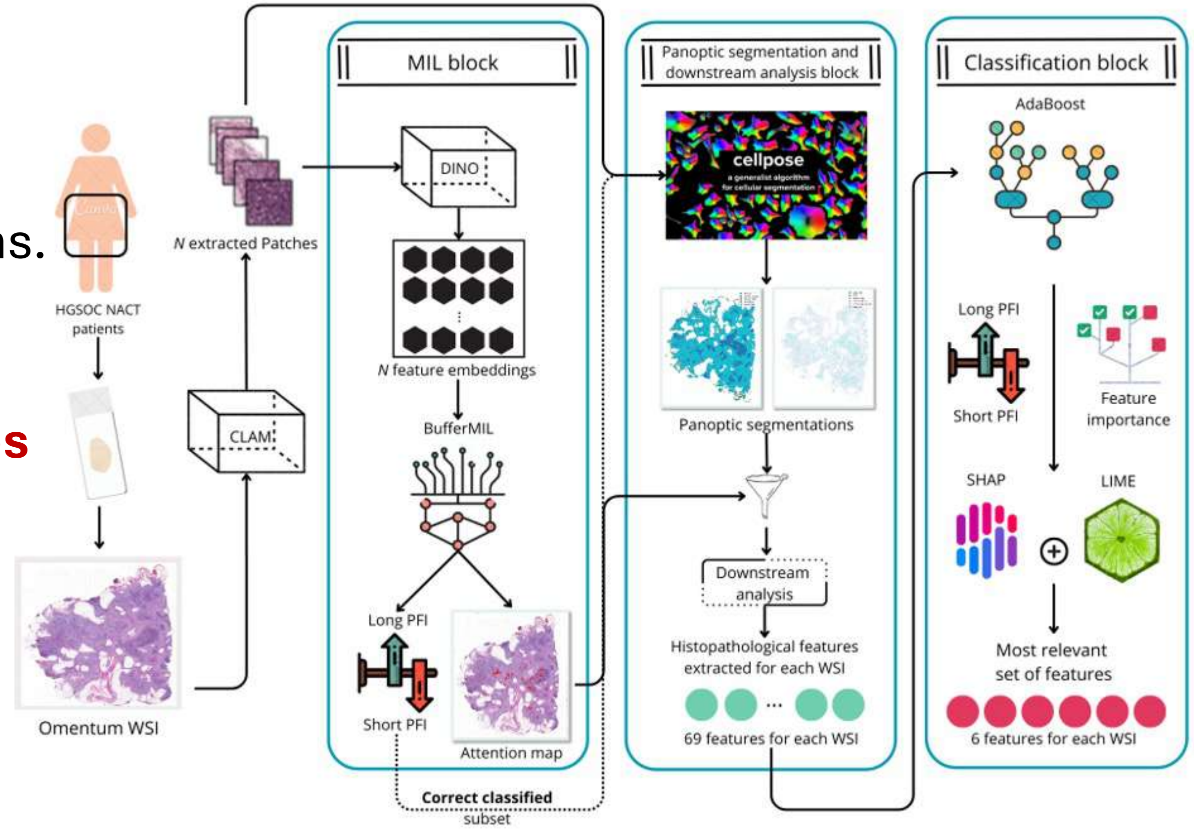
- Development of AI models for treatment response prediction and tumor resistance mechanisms characterisation.
- Assist pathologists with clinically relevant predictions.

Final goal:

- Definition of **Explainable histopathological features predictive of treatment response and clinical outcome**

Challenges:

- Lack of annotations for imaging data
- Genetic heterogeneity of the tumor (reflected in imaging variability)
- Data scarcity



3 framework blocks

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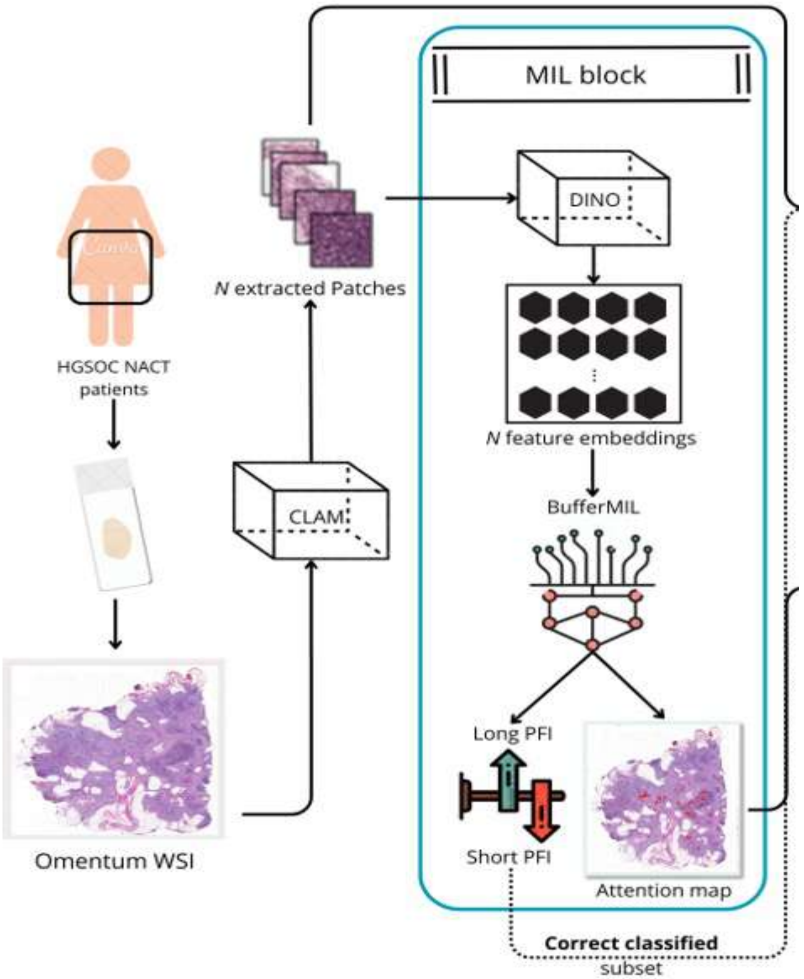
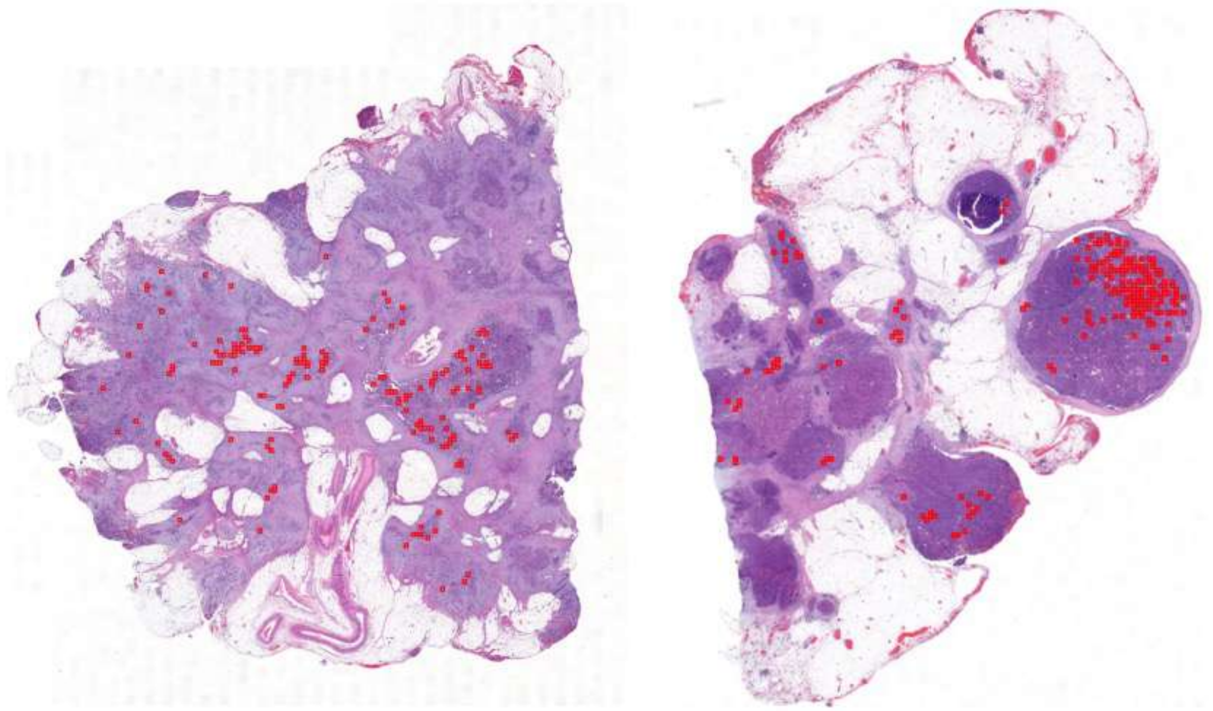
AI model structure (1)





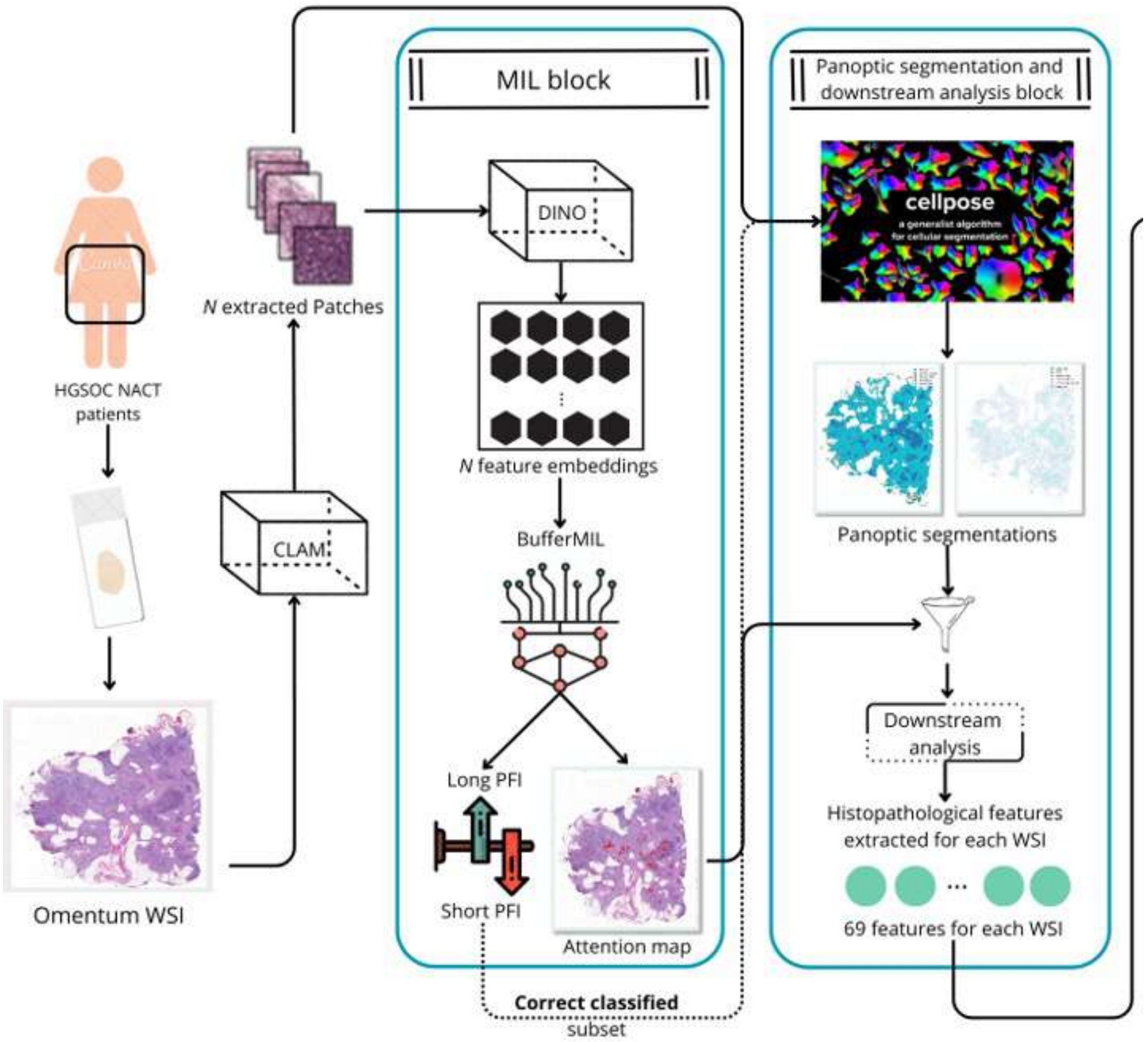
(a) Attention maps of a patient with *short PFI*

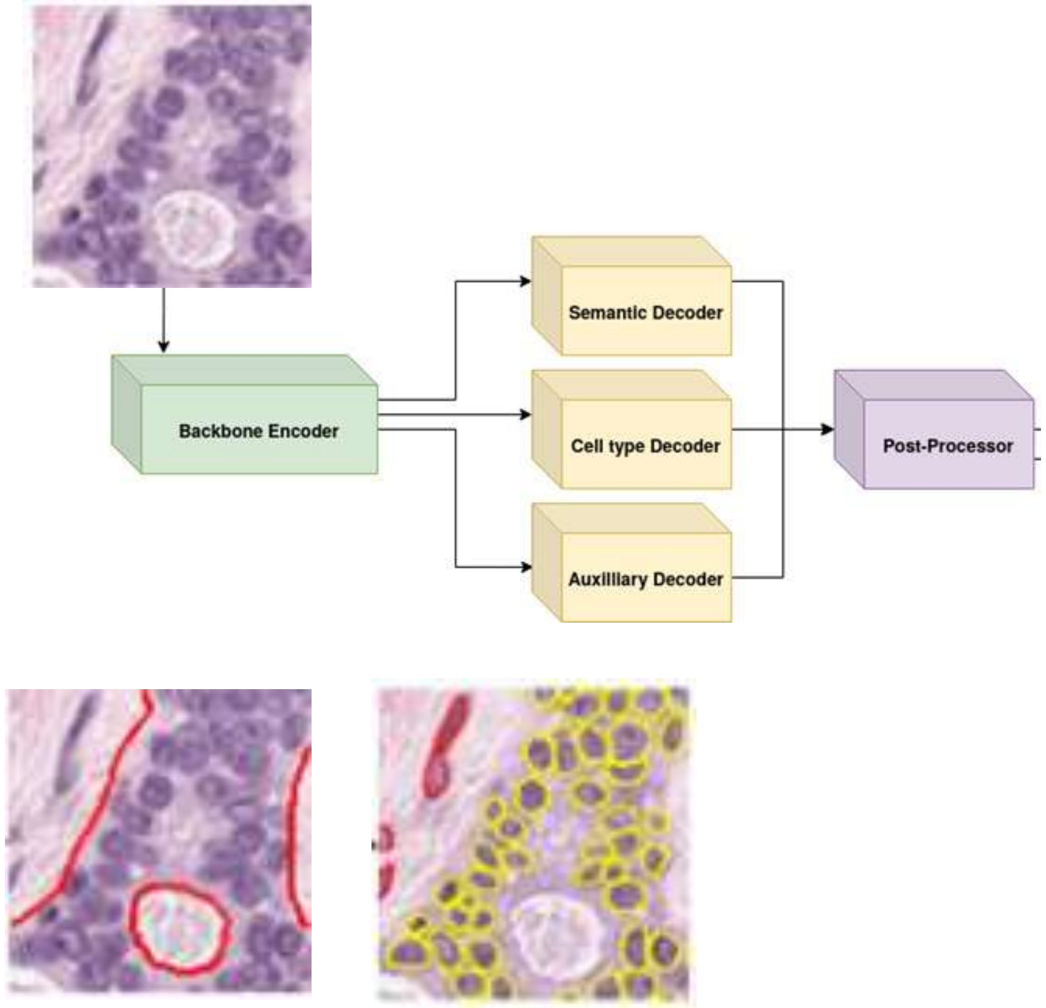
(b) Attention maps of a patient with *long PFI*

Figure 2: Example of attention maps obtained as output of the MIL block: the high attention patches are visualised in red in the figure

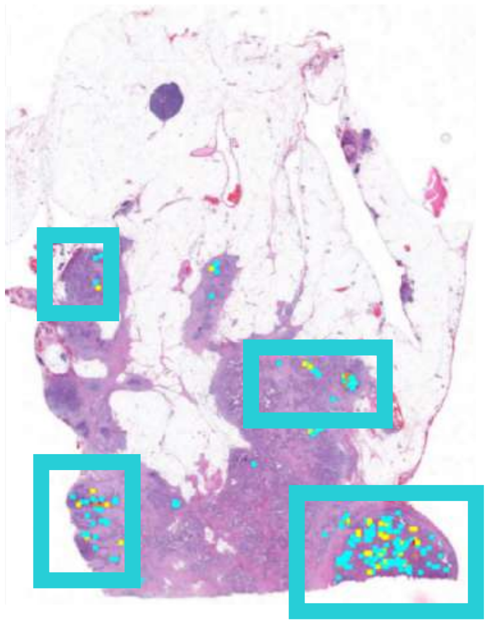
Extraction of relevant areas on the images without using annotations

AI model structure (2)

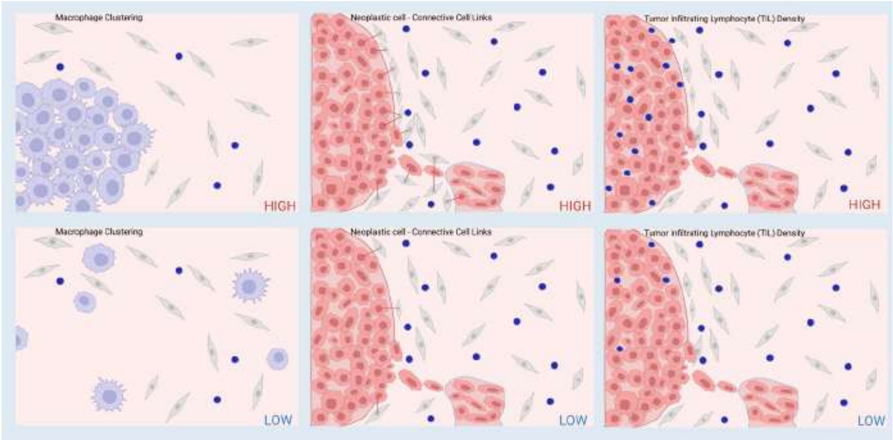




Standard histopathological features computation

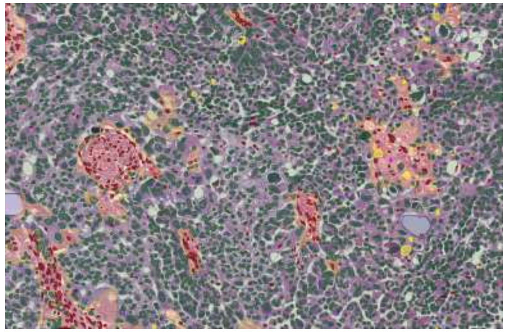


Computation of
Histological features
on attention areas *
*** Retained areas around 18%**



- Fraction of immune cells in neoplastic cell neighbourhoods
- Number of stromal cells
- Stromal clusters' areas, located distal to the tumour
- Macrophage diversity in neoplastic cell neighbourhoods
- Cell-cell variability of distances between tumour cells
- Max dispersion of tumour-adjacent immune clusters

Panoptic Segmentation of nuclei, cells, and tissue areas



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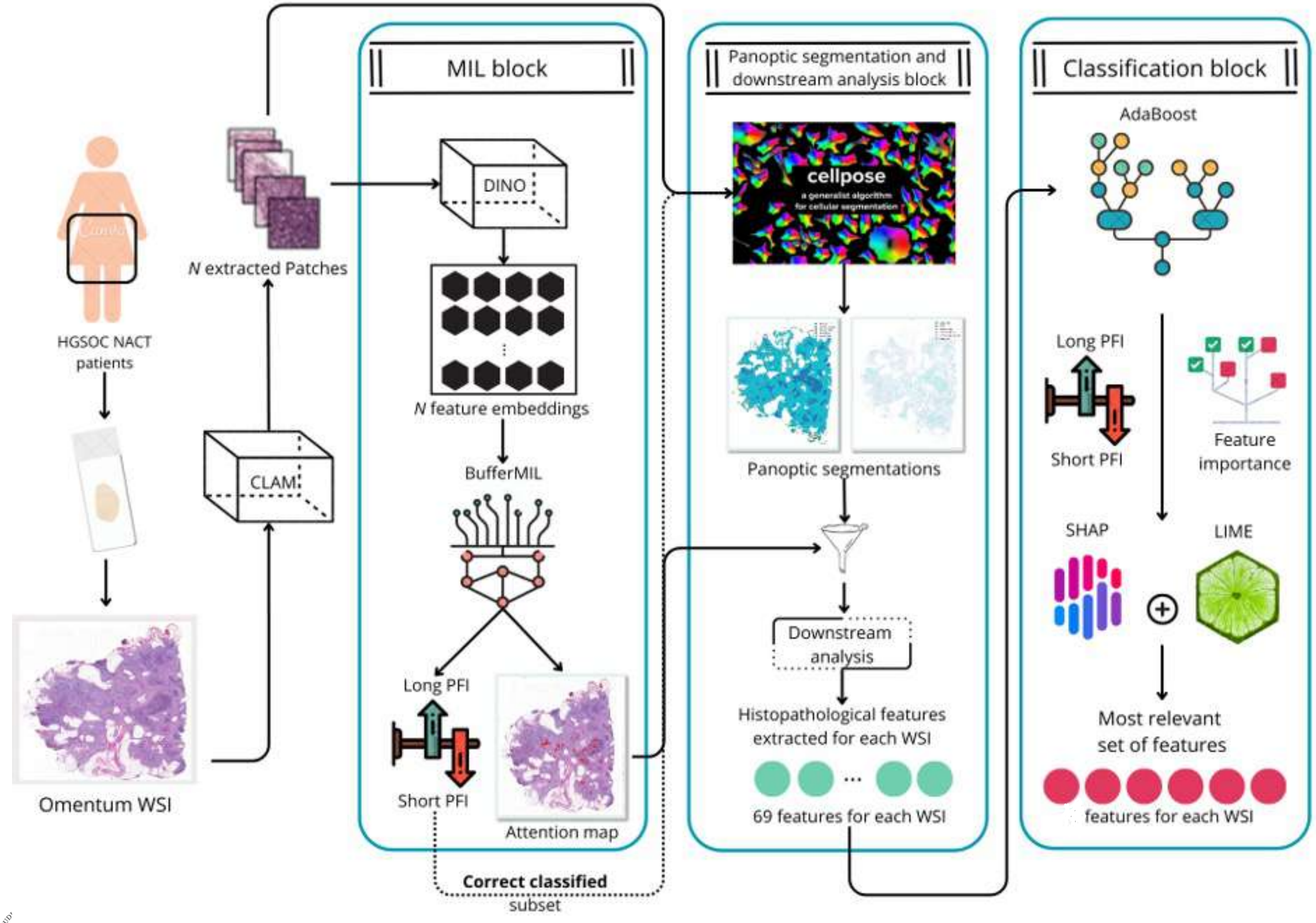
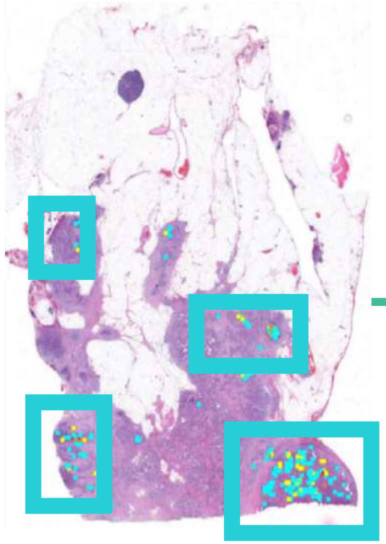
AI model structure (3)



- **Max value of tumor cell eccentricity** captures the highest degree of elongation among tumour cells, reflecting morphological irregularity.
- **Max value of tumor cell major axis length** represents the maximum length of tumour cells, potentially indicative of invasive or atypical morphologies.
- **Mean value of tumor cell fractal dimension** quantifies the average structural complexity of tumor cell shapes, with higher values denoting more irregular boundaries.
- **Number of stromal cells**: total count of stromal cells, representing the abundance of stromal components in the tissue.
- **Distal stromal area**: the stromal area located away from the tumor–stroma interface, describing the spatial extent of non-adjacent stroma.
- **Total stromal area**: the entire area occupied by stromal tissue in the slide, capturing overall stromal content.
- **Stromal cell proportion**: ratio of stromal cells to the total number of cells, indicating the relative dominance of the stromal component in the tumor microenvironment.

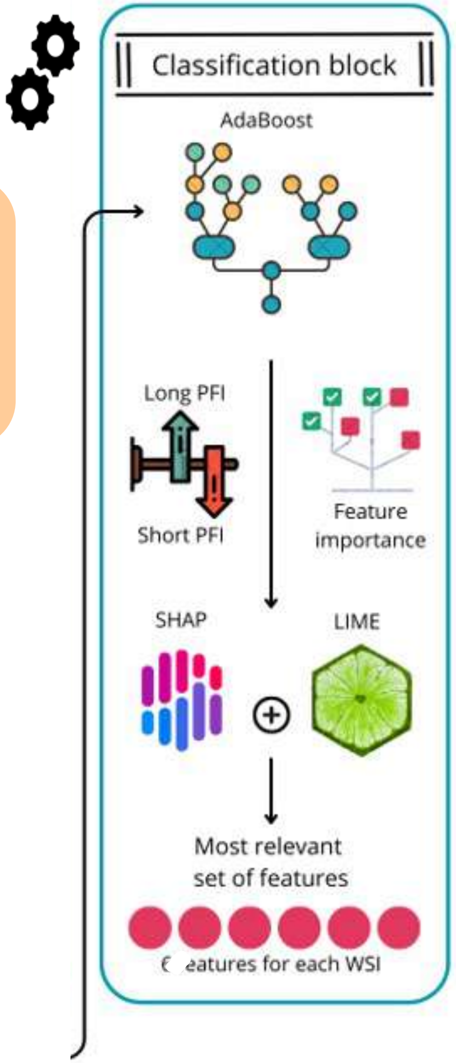
Results



Computation of features on attention areas *

* Retained areas around 18%

Model	AUC	Accuracy	F1-score *Long PFI*	F1-score *Short PFI*
PATHOS (with	**0,92 ± 0,048**	**0,93 ± 0,048**	**0,93 ± 0,088**	**0,91 ± 0,086**



Selection of a subset of features based on their prediction relevance -> improvement of prediction capability using selected features ONLY

	Predicted *Long*	Predicted *Short*
Actual *Long*	91.2%	8.8%
Actual *Short*	7.8%	92.2%
	Accuracy	**AUC**
	0.92	0.98

(d) XGBoost on high attention patches

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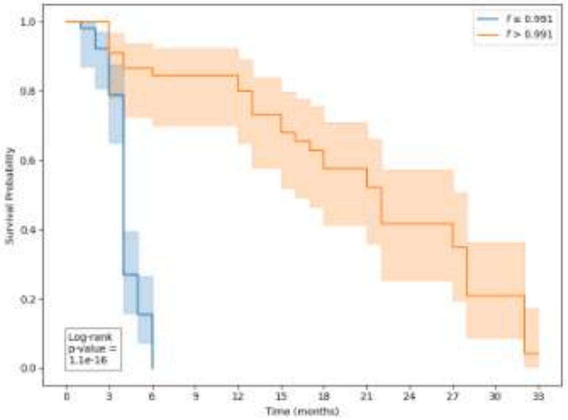
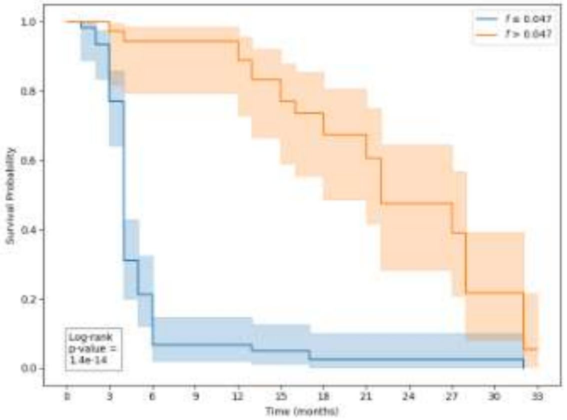
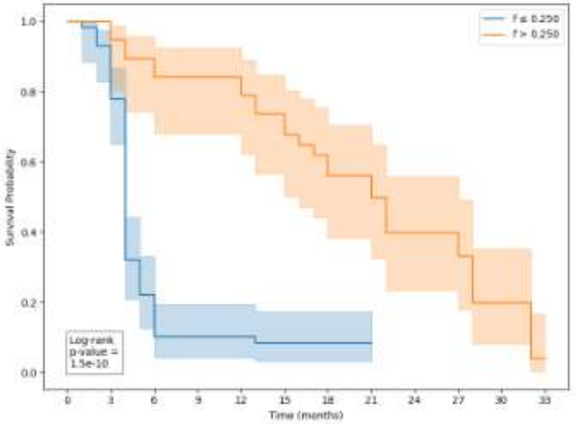
Stress the model by applying the same features to biologically related tasks



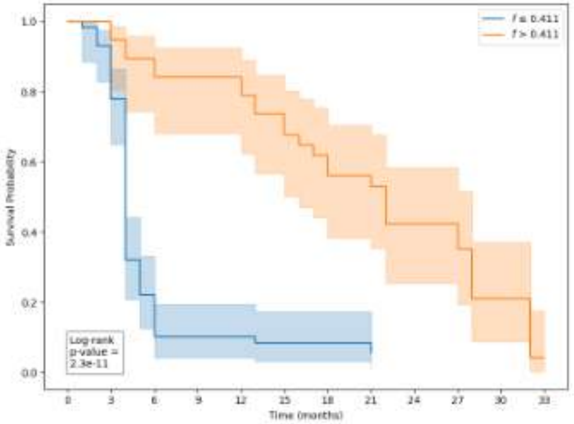
(a) f = Max eccentricity of tumour cells



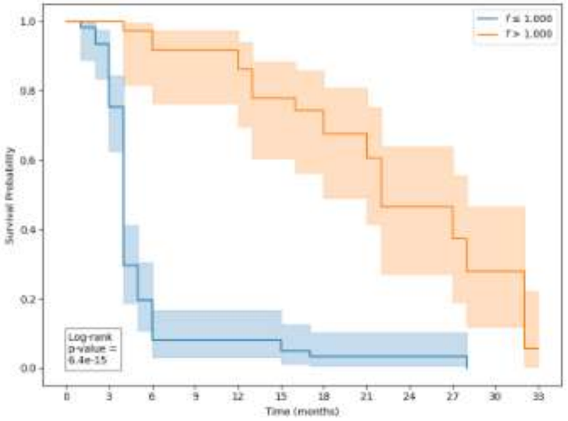
(b) f = Max major axis length of tumour cells



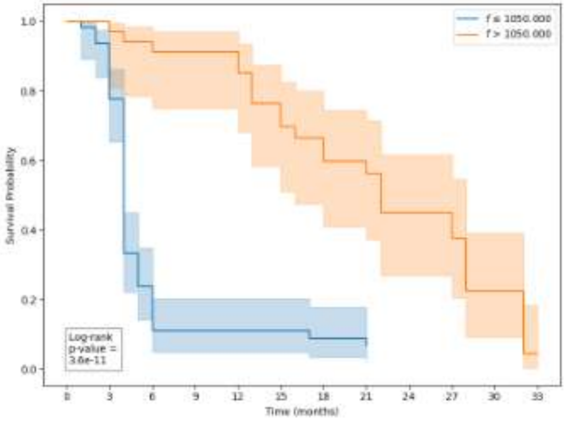
(e) f = Distal stromal area



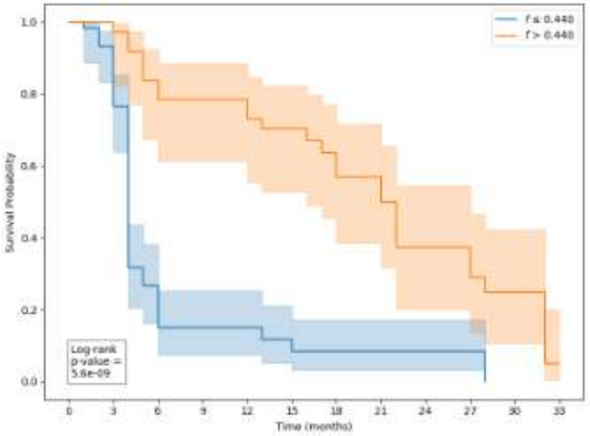
(f) f = Total stromal area



(c) f = Mean fractal dimension of tumour cells



(d) f = Number of stromal cells



(g) f = Stromal cell proportion

Multicenter clinical validation

- Selected explainable histopathological features are then being validated in multi-site labs, in different cohorts of patients from 2 different hospitals
- Results confirmed, so far, the treatment response predictive capability of the selected features
- At the same time, each step of the AI procedure is being validated in the same multicenter setting, assessing the robustness of the procedure

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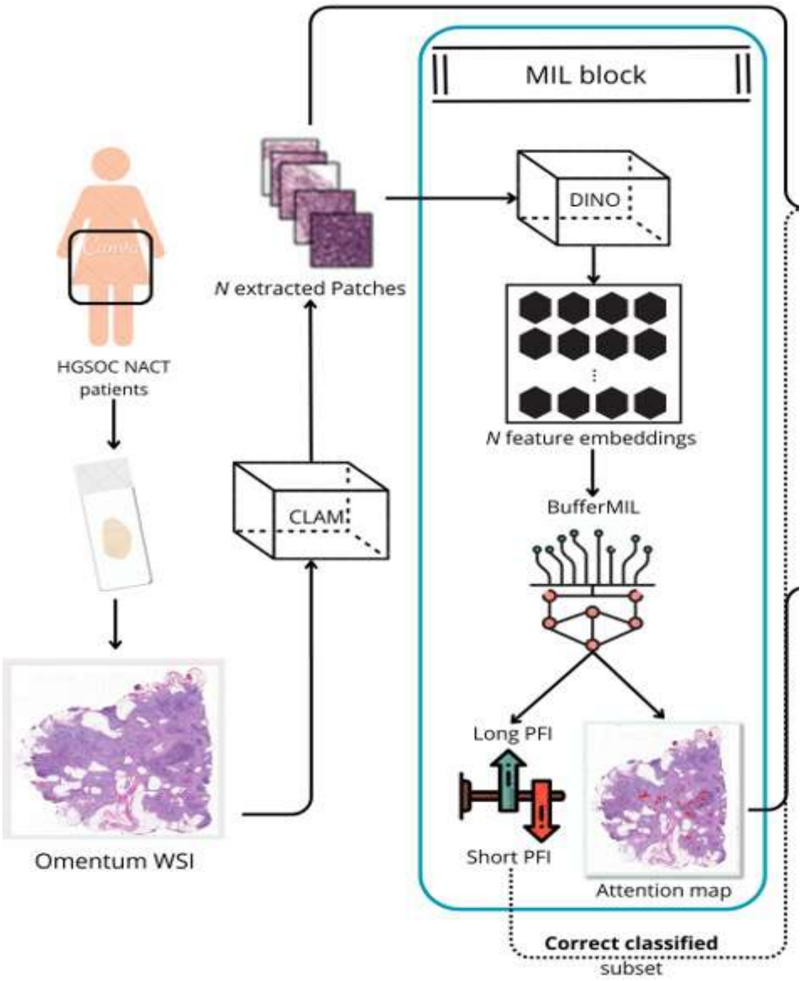
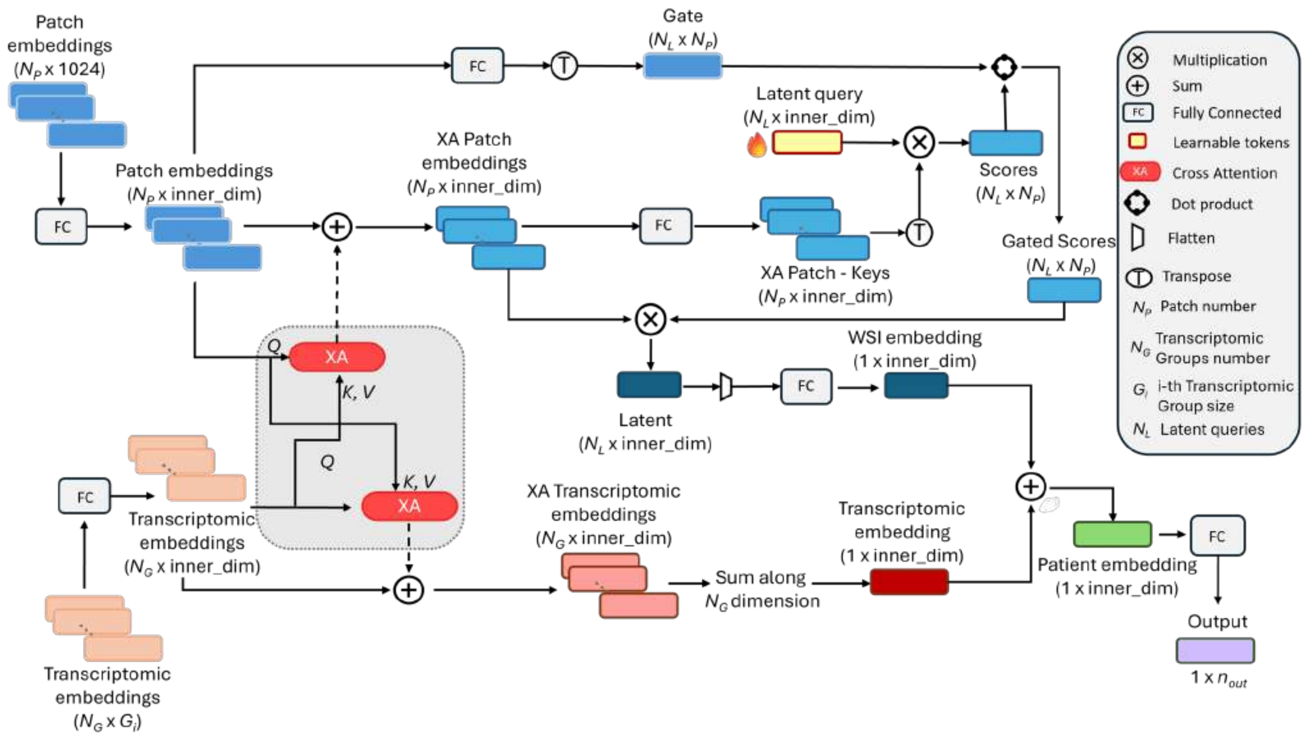
AI model's first block can be substituted with a multimodal learning block (see next slide)



AI multimodal model: integration of images and omics

Develop a **multimodal model** that:

1. Can improve chemotherapy response prediction in ovarian cancer despite data scarcity
2. Can be ***robust under missing-modality*** conditions (i.e., dataset incomplete)
3. Can explore the correlation between visual (histopathological) features and genetic profile
4. Can generalise to other tasks, such as overall survival (OS) prediction

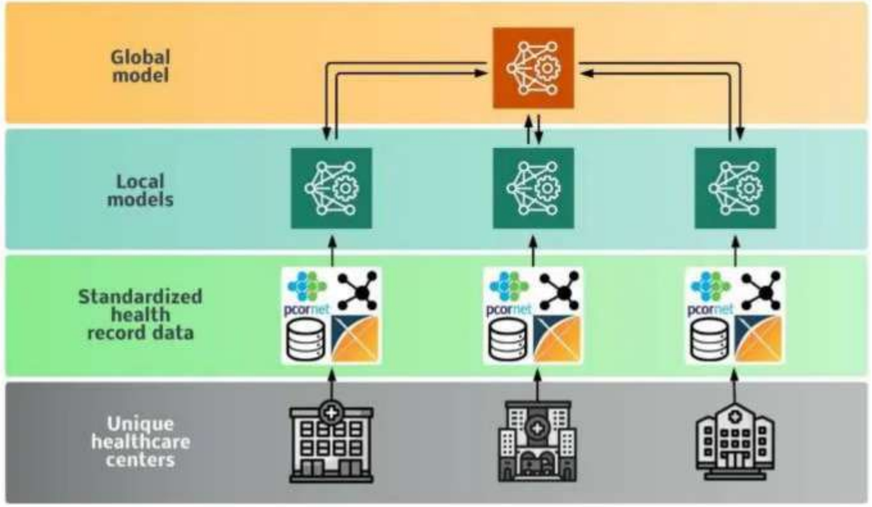


2) Federated Learning & multicenter clinical validation

Built Federated AI platforms for multimodal learning models for ER healthcare:

• Development of robust and reliable standards for AI models for secure clinical applications.
• AI-powered harmonisation agents to automate the standardisation of heterogeneous clinical data.
• Methodologies for federated unlearning and bias mitigation (including probing local models for imaging and text with counterfactual inputs to detect performance gaps across sensitive attributes).
• "Ethical and Legal by Design" framework to ensure compliance with regulations, such as the GDPR and AI Act.
• A multidimensional evaluation framework to assess model performance, fairness, and clinical plausibility
• Multicenter evaluation of models' robustness (centers that were not included in the Federated platform)
• Hybrid training where centralised databases are available

Federated Learning Model Architecture



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Multidisciplinary synergic organization

Build a **multidisciplinary synergic organisation** that integrates the skills and values of various Emilia-Romagna regional stakeholders:

- Healthcare Authorities, including regional centers of care and research, such as IRCCS (pro: scientific expertise; advanced digital systems; clinical validation studies; international networks)
- Universities (pro: algorithmic and AI expertise; vertical healthcare applications of these technologies)
- Huge HPC infrastructures, such as the DAMA technopole, **CINECA**, INFN (pro: cloud infrastructure, supercomputing; technical expertise; adherence to ISO/IEC certifications)
- Regulators: public (Healthcare Authorities and the Region) and private (nationally and internationally renowned law firms operating in the Medical Devices and Healthcare Data Processing sector)
- Industry (pro: industrialization and scale-up of solutions; certifications; integration into digital market ecosystems)

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Pilot use cases to drive the Federated AI platforms design

Two initial use cases:

1. ONCO-AI: Intelligent System to Support the Prescription of Antiblastic Drugs

2. AI-APPROPRIATENESS: Regional System for Monitoring Prescription Appropriateness in Specialist Services

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1. ONCO-AI: An Intelligent System for Supporting Antiblastic Drug Prescriptions

Objectives:

- Predictive analysis of the efficacy of antineoplastic drugs based on the patient's clinical and genetic profile.
- Decision support in selecting the most appropriate treatment based on guidelines, scientific evidence, and real-world data.
- Continuous monitoring and feedback on therapeutic adherence and clinical outcomes.
- Cost optimization through the identification of treatments with high therapeutic value.

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2. AI-APPROPRIATENESS: Regional System for Controlling Prescription Appropriateness in Specialist Services

AI federated learning models to:

- Analyze prescriptions in real time
- Compare them with clinical guidelines and dispensing criteria
- Integrate data related to the patient 's clinical history (and , in the future, additional data)
- Provide intelligent alerts to the physician in case of inconsistencies.

Objective:

- Reduce inappropriate prescriptions.
- Improve adherence to guidelines.
- Reduce waiting times for tests, visits, and procedures.

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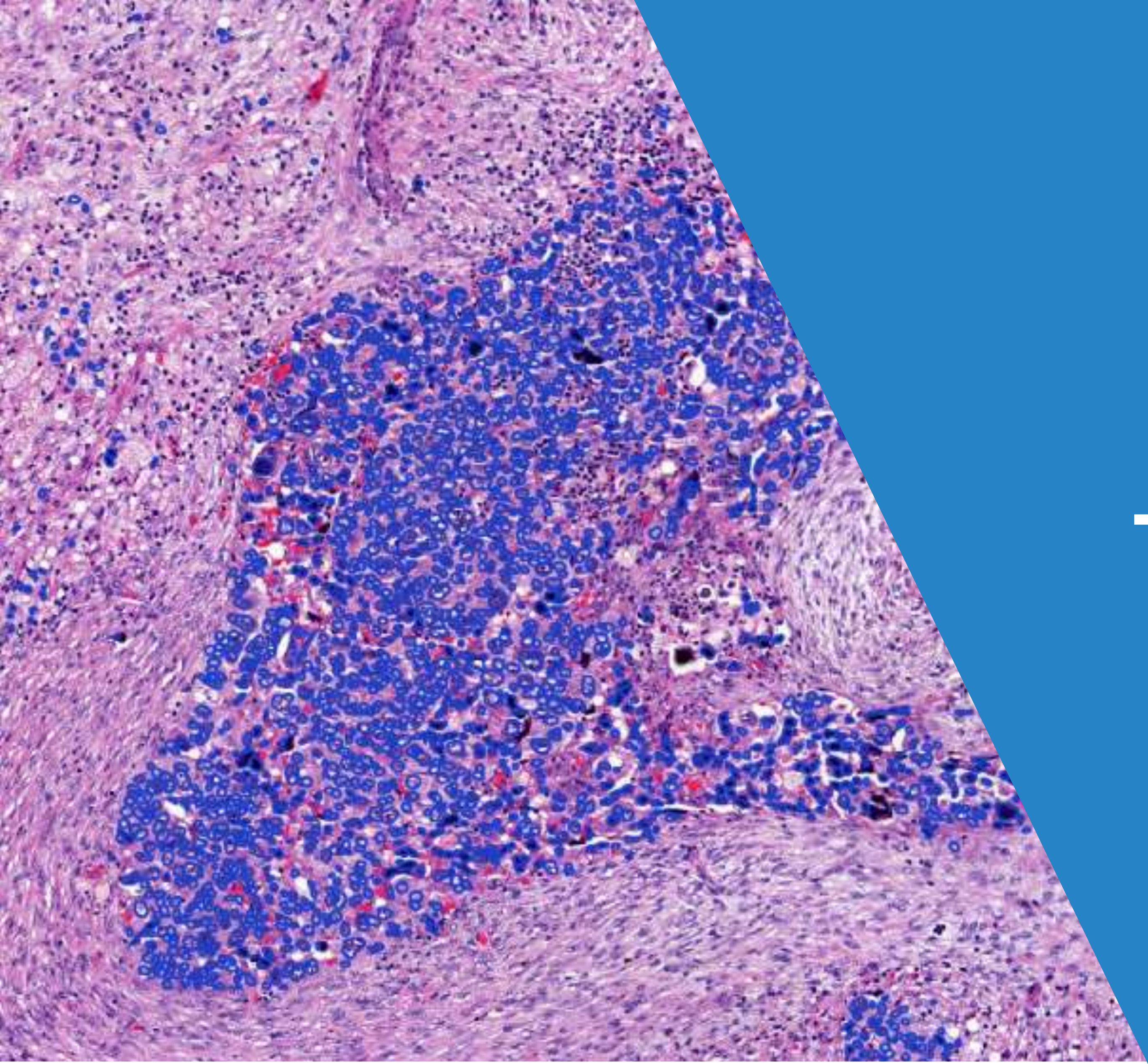
Unambiguous interpretation and definition of regulations for healthcare data sharing, secondary use of data, certification

- The design of the AI platform and technologies will benefit from collaboration with regulatory professionals. To this end, it aims to provide a strategic contribution to the structuring and support of multidisciplinary technical working groups for the operational implementation of European and national regulations, promoting alignment between the clinical world, research, industry, and regulatory authorities.

- Priorities:
- Secondary use of healthcare data
- Sharing of healthcare and clinical data
- Access and interoperability of the EHR
- Access to the European Health Data Space (EHDS)
- Certification of AI-based software
- Information feedback to patients/citizens



Thank you

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