tribun HEALTH

Extract relevant predictive features from WSIs with Mixed Supervision

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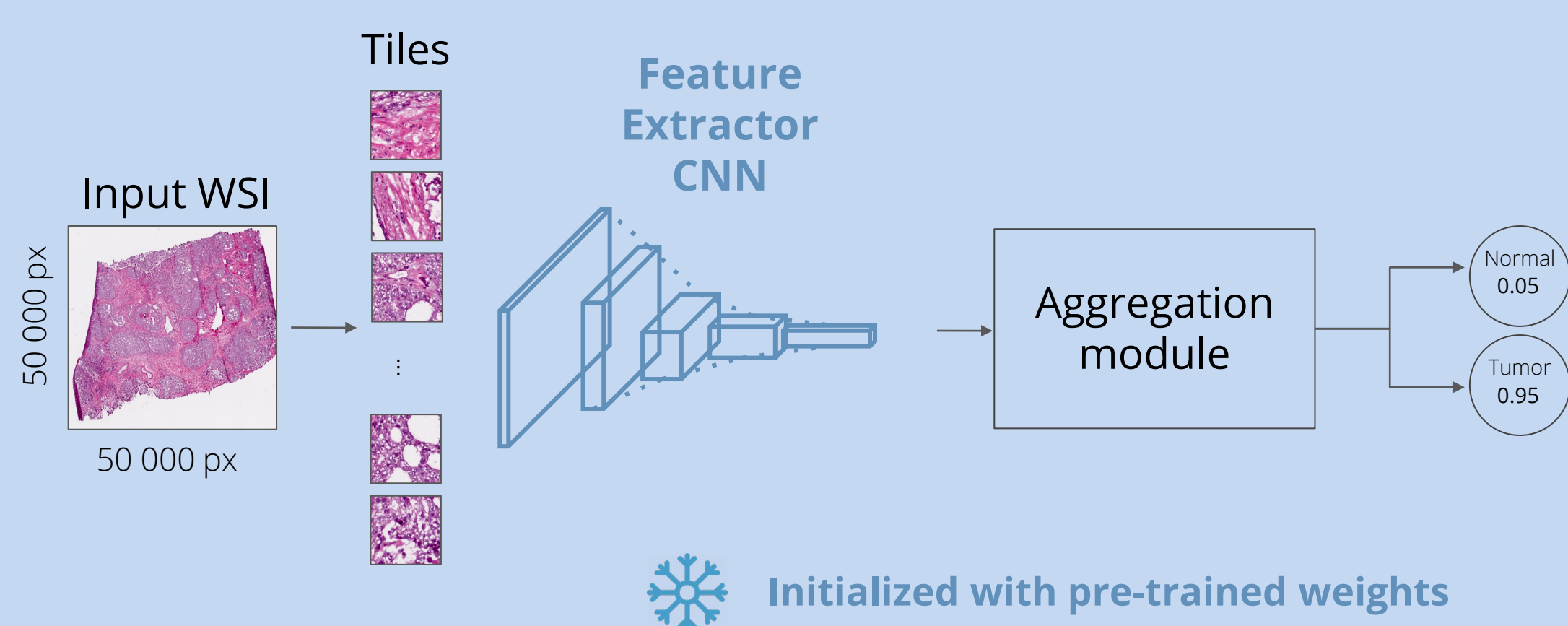
Context and Introduction

- In computational pathology, predictive models from Whole Slide Images (WSI) often rely on Multiple Instance Learning (MIL), where the WSIs are represented as a bag of tiles, encoded by a Convolutional Layers. Slide-level predictions are then achieved by building models on the aggregation of these tile encodings.
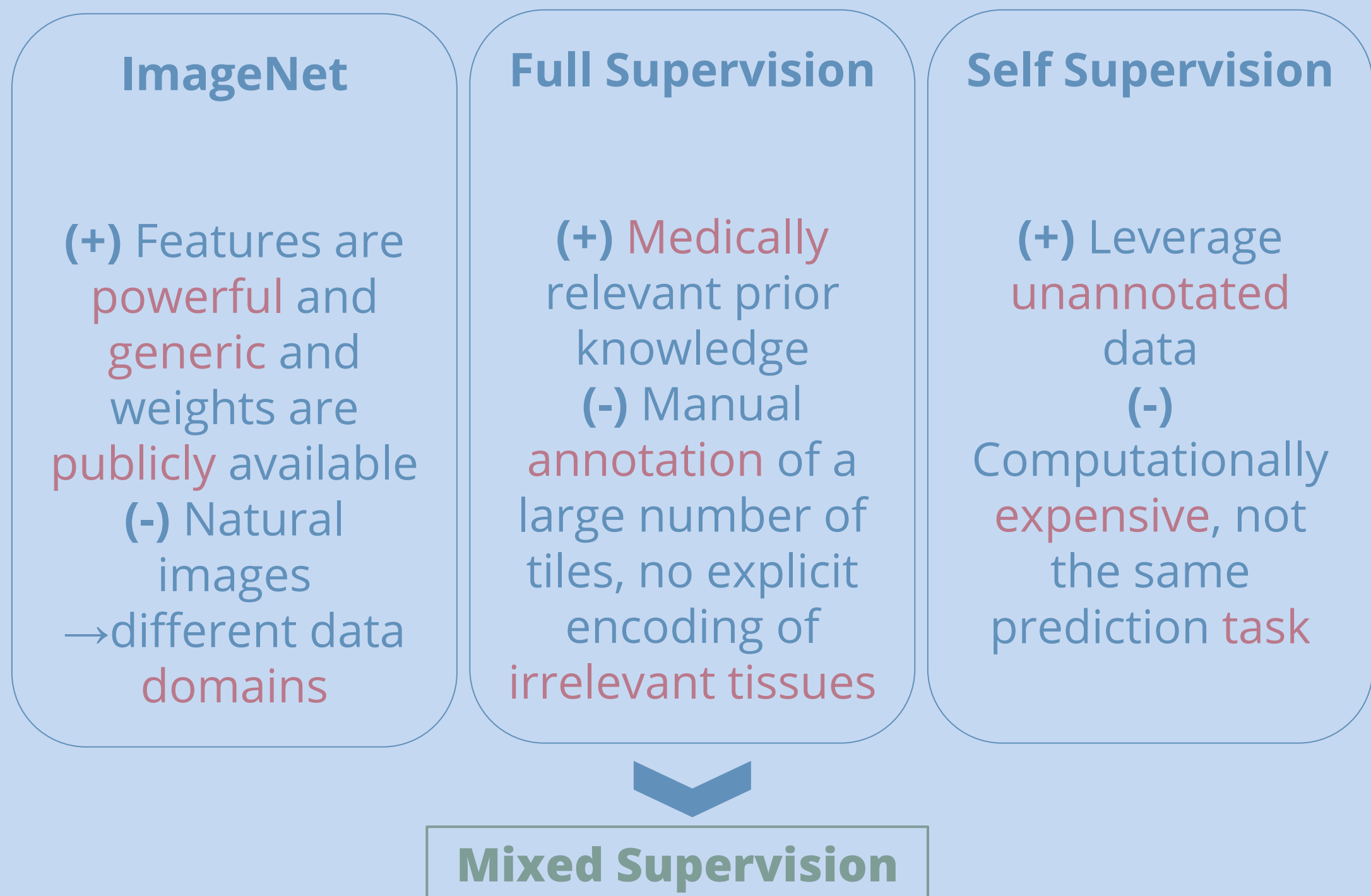 →**The tile encoding strategy plays a key role.**
- Encodings are usually obtained with **unrelated data sources** (Imagenet), **full supervision** or **self-supervision**.
- Additionally, annotated histopathological datasets are difficult to obtain and even when a small proportion of labelled annotation exists, it is not enough to support fully supervised techniques.
- Yet, even in small quantities, e**xpert annotations carry meaningful information** that one could **use to enforce biological context to deep learning models and make sure that networks learn appropriate patterns**.

## Multiple Instance Learning Architecture

Input WSI — 50 000 px × 50 000 px — Tiles — Feature Extractor CNN — Aggregation module — Normal 0.05 / Tumor 0.95

❄ Initialized with pre-trained weights

Pre-trained weights - current solutions and limits

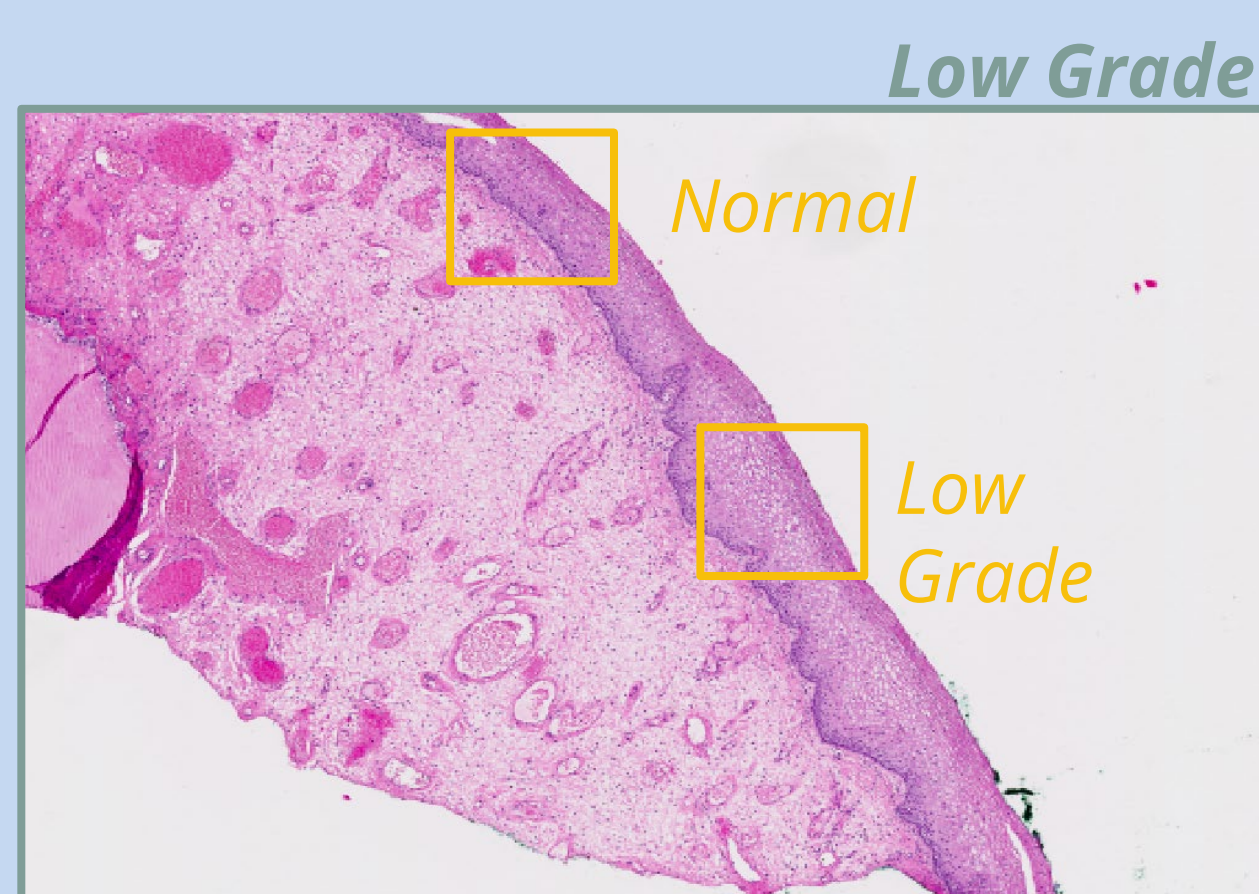| ImageNet	Full Supervision	Self Supervision
(+) Features are powerful and generic and weights are publicly available **(-)** Natural images →different data domains	**(+)** Medically relevant prior knowledge **(-)** Manual annotation of a large number of tiles, no explicit encoding of irrelevant tissues	**(+)** Leverage unannotated data **(-)** Computationally expensive, not the same prediction task

Mixed Supervision

Dataset

The Tissue Net Challenge [1] organized in 2020, the Société Française de Pathologie (SFP) and the Health Data Hub aimed at developing methods to automatically grade lesions of the uterine cervix in four classes according to their severity
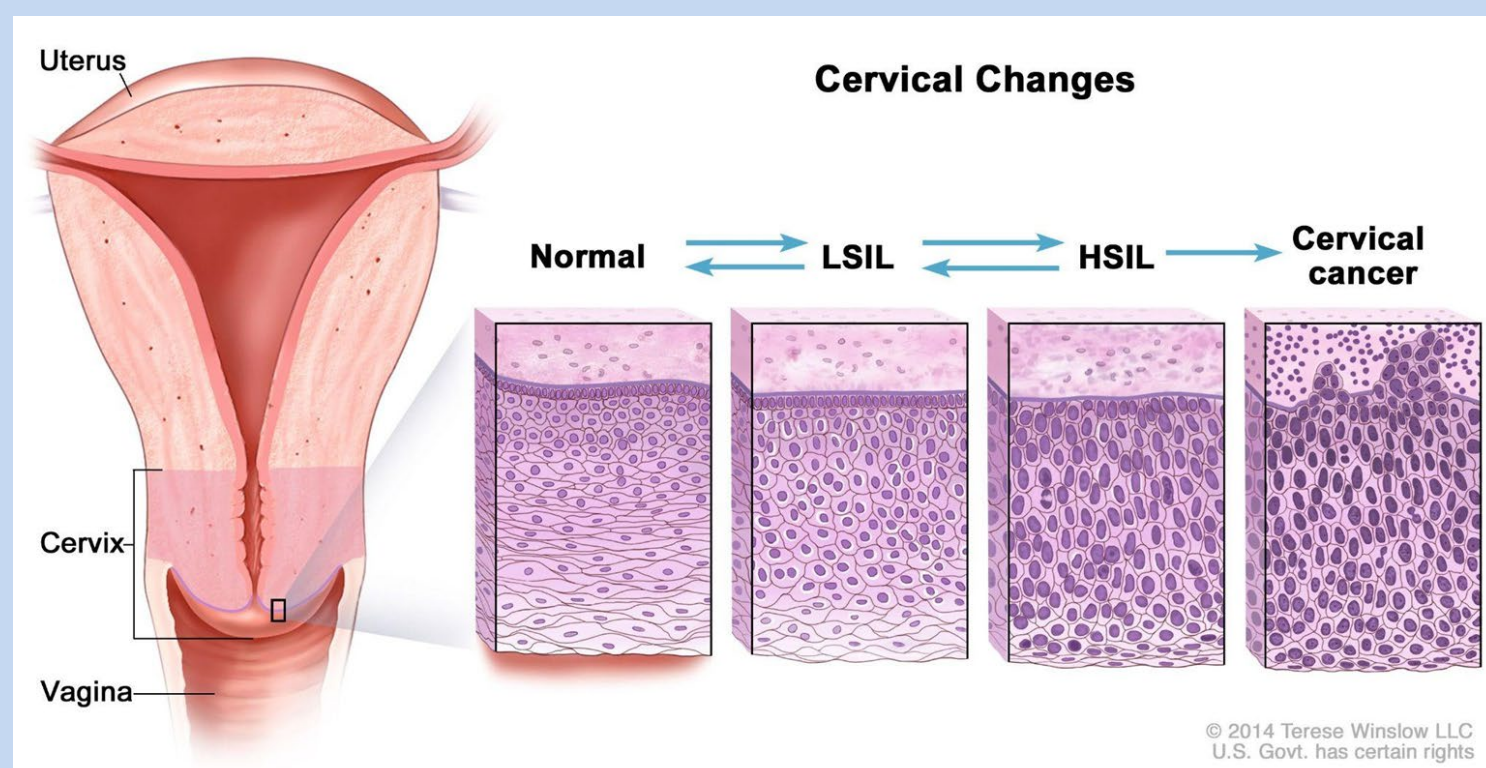
- **1015 WSI + labels** *from 20 centers
- **6000 Annotated Tiles + labels**
- **4 classes:**
  ○ Normal
  ○ Low Grade Lesion
  ○ High Grade Lesion
  ○ Carcinoma

Low Grade — Normal — Low Grade

Acknowledgments, References

[1] Delaune A, Valmary-Degano S, Loménie N, Zryouil K, Benyahia N, Trassard O, et al. Le premier data challenge organisé par la Société Française de Pathologie: une compétition internationale en 2020, un outil de recherche en intelligence artificielle pour l'avenir? In: Annales de Pathologie. Elsevier; 2022. p. 119-28.

CBIO – Centre for Computational Biology — PSL UNIVERSITÉ PARIS — ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS
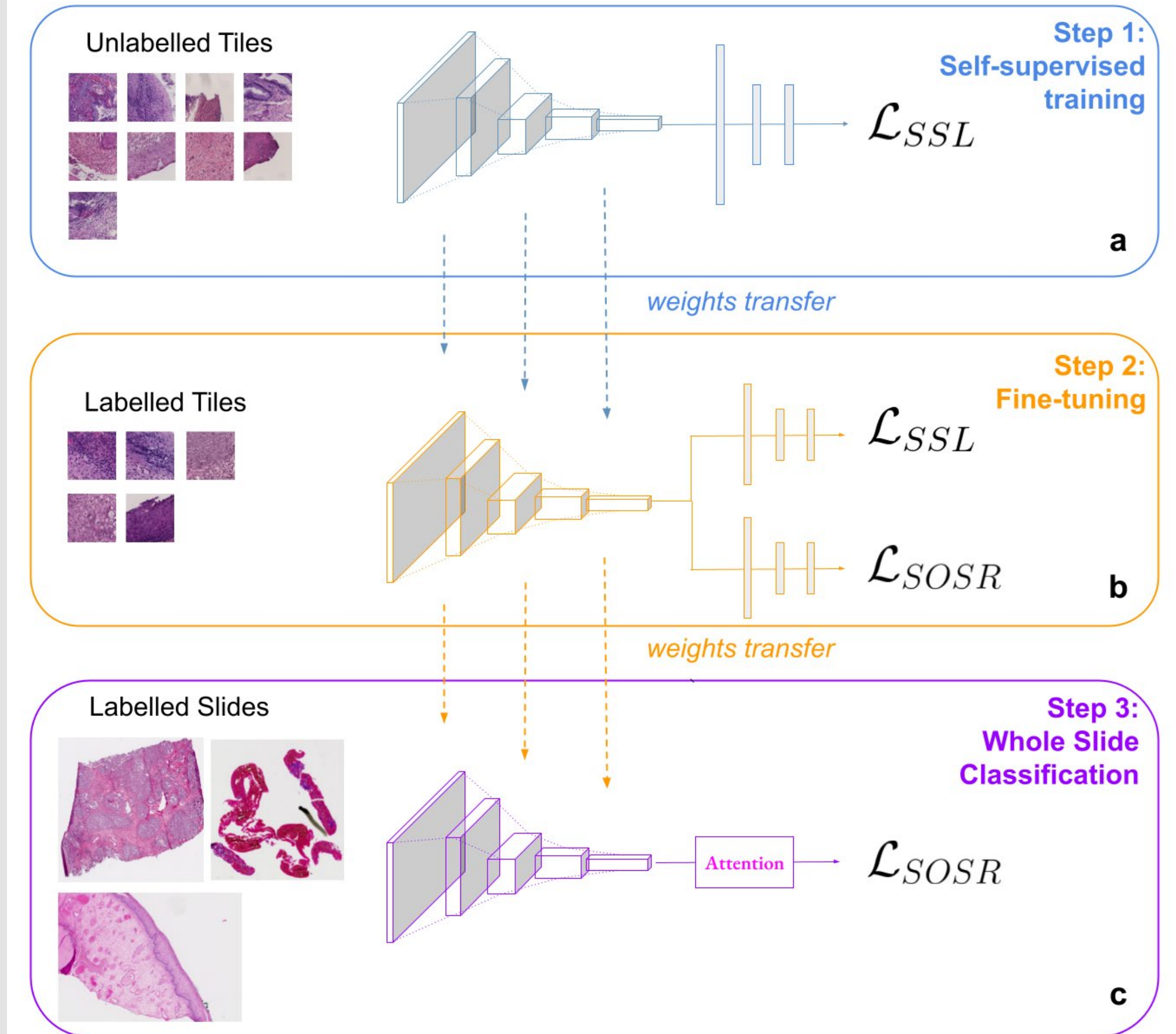
Method

Step 1: We train a self supervised model (SimCLR) from Unlabelled tiles (4M)

Step 2: We add a supervised branch to this model and perform a joint optimization between the self supervised loss and full supervised loss on labelled tiles.

Step 3: the fine tuned weights are transferred to train the WSI classification model for the grading of cervical biopsies from WSI.

Unlabelled Tiles — Step 1: Self-supervised training — $\mathcal{L}_{SSL}$ — a

weights transfer

Labelled Tiles — Step 2: Fine-tuning — $\mathcal{L}_{SSL}$ / $\mathcal{L}_{SOSR}$ — b

weights transfer

Labelled Slides — Step 3: Whole Slide Classification — Attention — $\mathcal{L}_{SOSR}$ — c

Results

Figure 1 - Feature Visualization (right)
Top Features for class "Normal" (0) and tiles expressing the most the feature. Features obtained with SSL and Mixed Supervision are clearly related to histopathological patterns. Nuclei, squamous cells, basal layers and other histological morphologies are identifiable
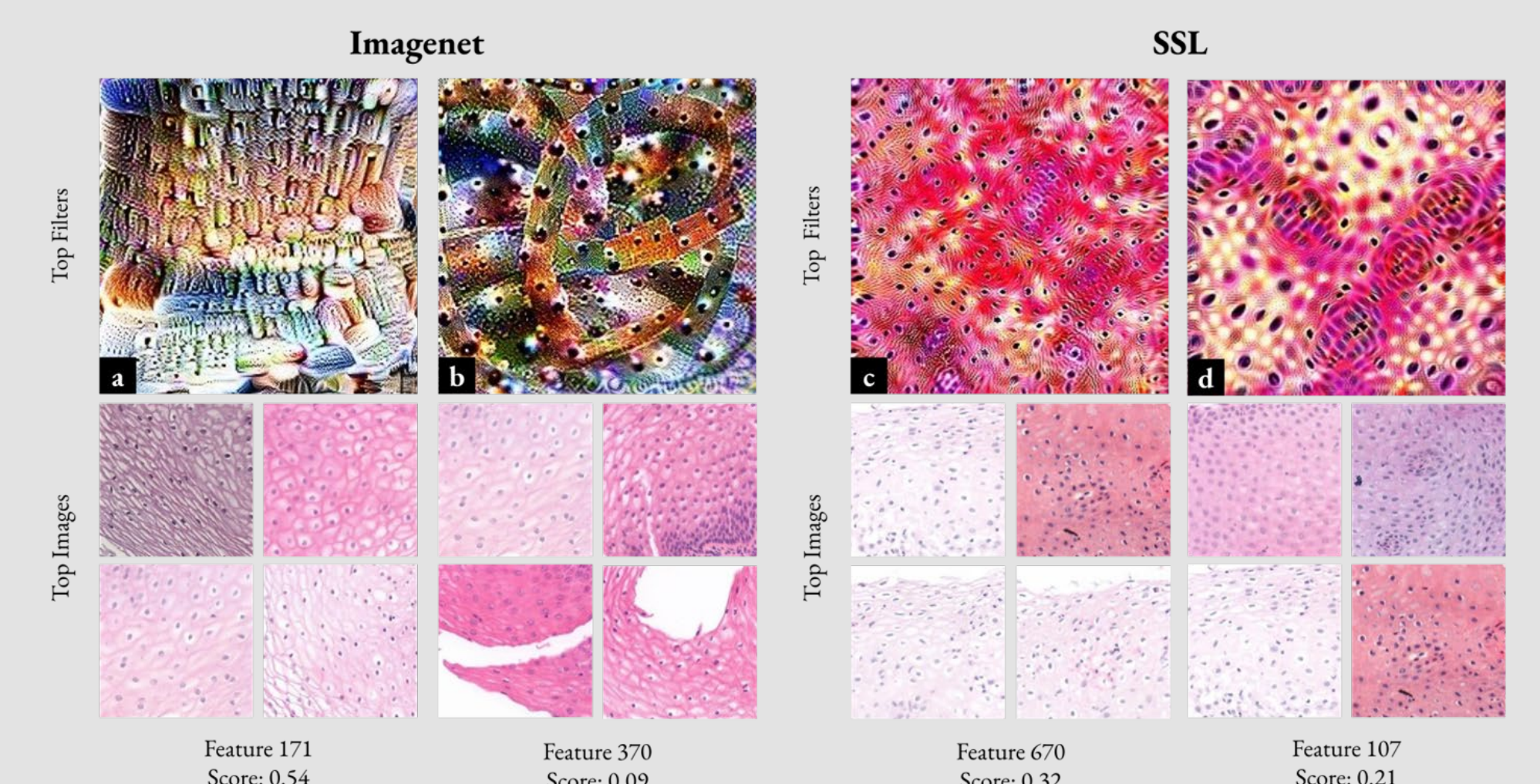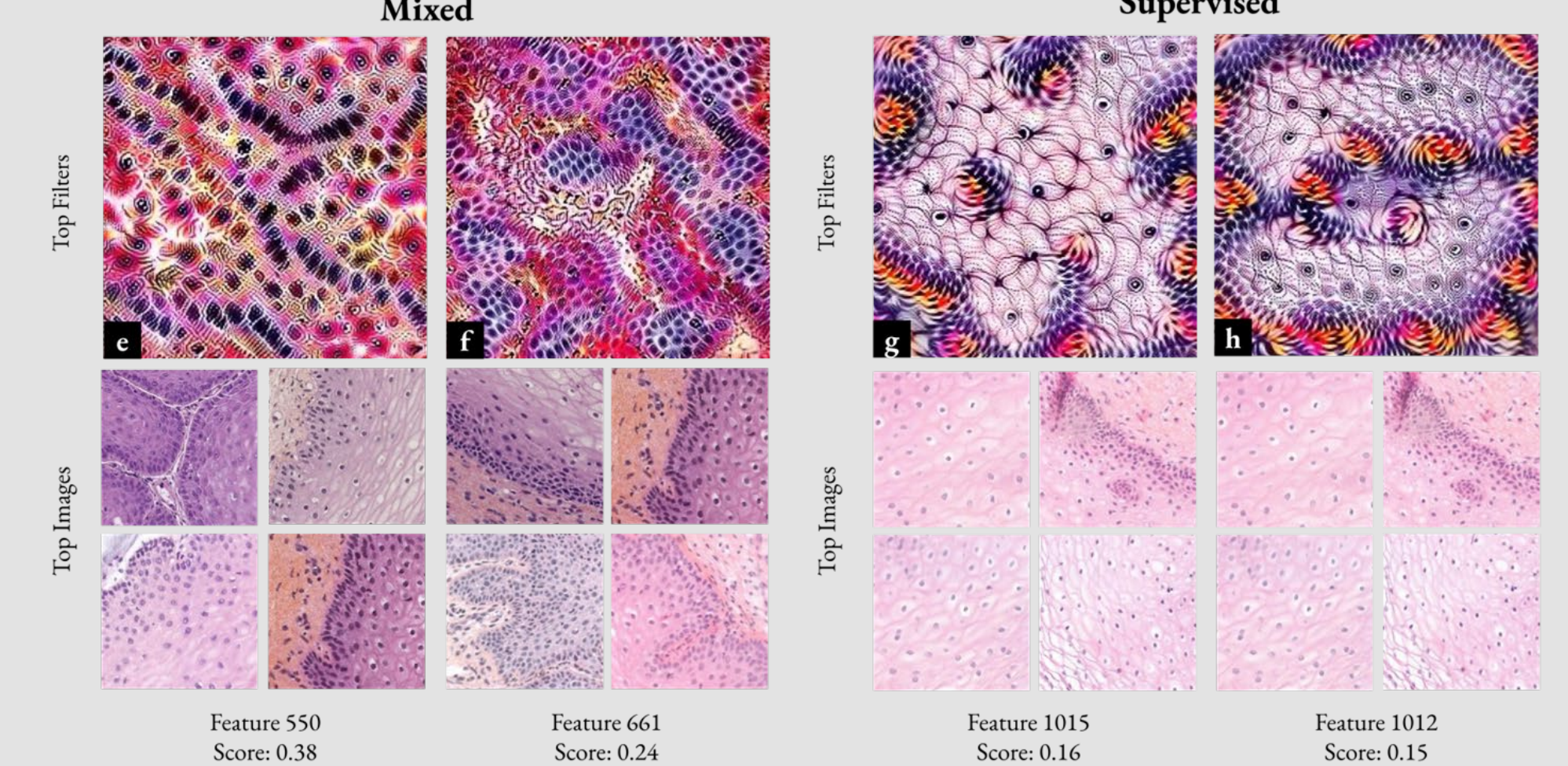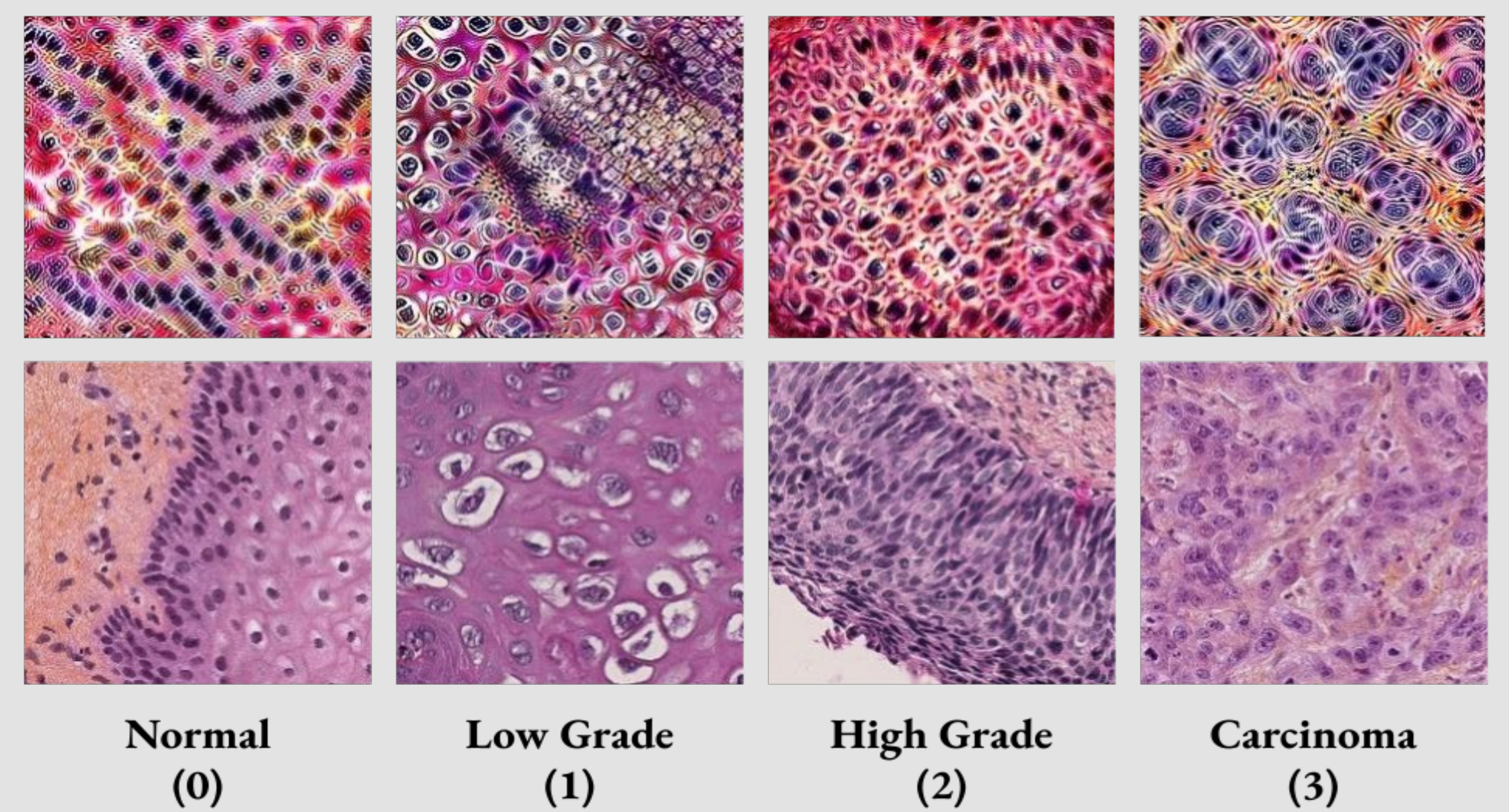
Figure 2 - Feature comparison per class (bottom)
The top row displays the top filter for the Mixed Supervised model for each class. The bottom row displays the tile expressing the feature the most. Extracted tiles correlate with class-specific biomarkers.

Imagenet — Top Filters — Top Images — Feature 171 Score: 0.54 / Feature 370 Score: 0.09

SSL — Top Filters — Top Images — Feature 670 Score: 0.32 / Feature 107 Score: 0.21

Mixed — Feature 550 Score: 0.38 / Feature 661 Score: 0.24

Supervised — Feature 1015 Score: 0.16 / Feature 1012 Score: 0.15

Most **predictive features** for each class

Tiles expressing the feature the most

Normal (0) — Low Grade (1) — High Grade (2) — Carcinoma (3)

Conclusion

- We proposed a method that allow to optimally **leverage small quantities of annotations in order to inject medically relevant knowledge in the features**
- The quantitative and qualitative analysis allowed us to better **understand** the impact of different range of **supervision** in feature extraction
- We were able for the first time to **visualize what a model is learning,** which can be useful for interpretability
- For future work, we believe that this visualization technique could be a great interest for **new biomarker discovery**, now that we have shown that it indeed identify already know features

Link to full article

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