Supplemental Appendix 2

Table 1 (Page 1): Training configuration and hyperparameter details for the CNN pipeline, transformer pipeline with TransMIL and CLAM.

Page 2: Interpretability analysis, details of settings and methods used.

TRAINING CONFIGURATION AND HYPERPARAMETERS

PARAMETER	CNN Pipeline	Transformer + TransMIL	Transformer + CLAM-MB
INPUT	512×512 px tiles	512×512 px tiles → embeddings	512×512 px tiles → embeddings
FREEZE RATIO	0.5	Frozen encoder	Frozen encoder
OPTIMIZER	Adam, LR = 2×10^{-4}, WD = 1×10^{-5}	AdamW LR = 1×10^{-4}, WD = 1×10^{-2}	AdamW, LR = 1×10^{-4}, WD = 1×10^{-2}
BAG SIZE	N/A	512 embeddings	512 embeddings
INSTANCE SUPERVISION	N/A	None	Yes (K = 32)
DROPOUT	N/A	0.25	0.25
EPOCHS (MAX)	20	20	20
EARLY STOPPING	Patience = 3 (min 5 epochs)	Patience = 5	Patience = 5
TILE THRESHOLD PER SLIDE	≥ 300 tiles	≥ 300 tiles	≥ 300 tiles
TILE SUBSAMPLING	≤ 4,000 tiles	N/A	N/A
AGGREGATION	Mean pooling	Transformer self-attention	Attention pooling + gated classifier
LOSS FUNCTION	Cross Entropy	Cross Entropy	Cross Entropy
CROSS-VALIDATION	5-fold, slide-level stratified	5-fold, slide-level stratified	5-fold, slide-level stratified
HARDWARE	4× NVIDIA RTX A6000 (48 GB)	4× NVIDIA RTX A6000 (48 GB)	4× NVIDIA RTX A6000 (48 GB)

All analyses were implemented in Python 3.11 (SciPy 1.13, Statsmodels 0.15).

Interpretability Analysis – Settings and Methods

Tile Selection

- Selected 10 highest-predicted WSIs per molecular subtype (based on model probabilities).
- For each WSI, extracted the 8 highest-scoring tiles from attention heatmaps for the correctly predicted subtype.
- Total: 80 tiles per subtype.
- All tiles analyzed at native resolution.

Segmentation & Classification

- Performed nucleus-instance segmentation using **HoVer-Net** (Graham et al., 2019) via **TIAToolbox** (Pocock et al., 2022).
- Applied **PanNuke** (Gamper et al., 2019) label schema:
    1. Background
    2. Neoplastic epithelial
    3. Inflammatory
    4. Connective tissue
    5. Dead cells
    6. Non-neoplastic epithelial

Feature Extraction

- Restricted quantitative analysis to **neoplastic epithelial nuclei**.
- Computed shape features directly from instance contours:
    - Area (μm^2)
    - Perimeter (μm)
    - Eccentricity (from fitted ellipse)
    - Circularity = $4\pi \times \text{Area}/(\text{Perimeter}^2)$
- Derived summary metrics for each tile:
    - Mean nuclear area (μm^2)
    - Size dispersion, coefficient of variation of area (cv_area) = SD(area) / mean(area)
    - Pleomorphism Index (PI) = P90(area) / P10(area)
    - Coefficient of variation of eccentricity (cv_ecc)
    - Coefficient of variation of circularity (cv_circ)

Aggregation

- Summarized tile-level indices per slide and per molecular subtype.

Statistical Analysis

- Omnibus testing with **Kruskal–Wallis** for differences among four independent subtypes.
- Reported **epsilon-squared effect size**.
- If omnibus test was significant at $\alpha = 0.05$, performed **Dunn's post-hoc tests** with Holm correction for multiple comparisons.

Visualization

- Cell-type composition shown as **split violin plots** with jittered dot overlays for per-tile proportions.
- Nuclear morphometric distributions displayed as **violin plots**.