Introduction/Background Endometrial Cancer (EC) are molecularly classified into polymerase-ε mutated (POLEmut), mismatch repair deficient (MMRd), p53 abnormal (p53abn) and no specific molecular profile (NSMP). With the incorporation of the molecular classification in risk-assessment of EC patients, clinical relevance of histopathological features became unclear. Deep Learning (DL) can identify morphology associated with molecular class from whole slide images (WSIs). We developed an interpretable DL model for image-based prediction of the molecular EC classification (im4MEC) to identify morpho-molecular correlates which may refine EC prognostic stratification.

Methodology Digital H&E-WSIs from 2028 molecularly classified EC of the transPORTEC repository were included. im4MEC used state-of-the-art DL models combining self-supervised learning and attention mechanism. Performance was calculated on the independent test set PORTEC-3 (N=393) using area under receiver-operating-characteristic curve (AUROC). Slide sub-regions with highest attention scores given by im4MEC were reviewed to identify morpho-molecular correlates which may refine EC prognostic stratification.

Results im4MEC achieved a macro-average AUROC of 0.876 on PORTEC-3, with highest of 0.928 among p53abn class. Top-attended sub-regions indicated significant association between dense lymphocyte infiltrates and POLEmut and MMRd EC; low tumor-stroma ratio and NSMP EC; high nuclear atypia and p53abn EC. Image-based molecular classification had a strong prognostic value in PORTEC-3 (p=1.1e-04; figure 1A). MMRd cases predicted as POLEmut had excellent prognosis; p53abn cases predicted as MMRd showed MMRd-like inflammatory morphology and slightly better prognosis; few NSMP cases predicted as p53abn showed p53abn-like strong nuclear atypia and worse prognosis (figure 1B,C, D).

Conclusion im4MEC shows promising performance for H&E-based molecular classification of high-risk EC patients, correlating with distinct clinical outcome. im4MEC robustly identifies known and novel morpho-molecular correlates which enable prognostic refinement. This work provides novel indicators for an improved risk stratification system integrating molecular and morphological data.