Development of a virtual Cyclin E1 biomarker using Deep Learning from H&E slides for predicting Cyclin E1 overexpression in gynecological malignancy

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SUMMARY

The purpose of this study was to develop and validate a virtual immunohistochemistry (vIHC) algorithm capable of predicting Cyclin E1 (CCNE1) protein expression levels from hematoxylin and eosin (H&E)-stained whole-slide images in gynecological malignancy encompassing primarily high-grade serous ovarian carcinoma (HGSOC) and uterine serous carcinoma (USC). CCNE1 is a key cell-cycle regulator whose gene amplification (copy number ≥6) strongly correlates with protein overexpression (H-score >50) and enhanced sensitivity to WEE1 inhibitors and their combination with PKMYT1 inhibitors – see MYTHIC clinical trial zedoresertib+lunresertib[1].
Conventional IHC requires precious tissue and additional, time-consuming wetlab processing. The ViewsML virtual biomarker platform derived from routinely available H&E slides provides a scalable alternative to wetlab IHC with a strong potential of accelerating patient selection for targeted therapies.

METHODS

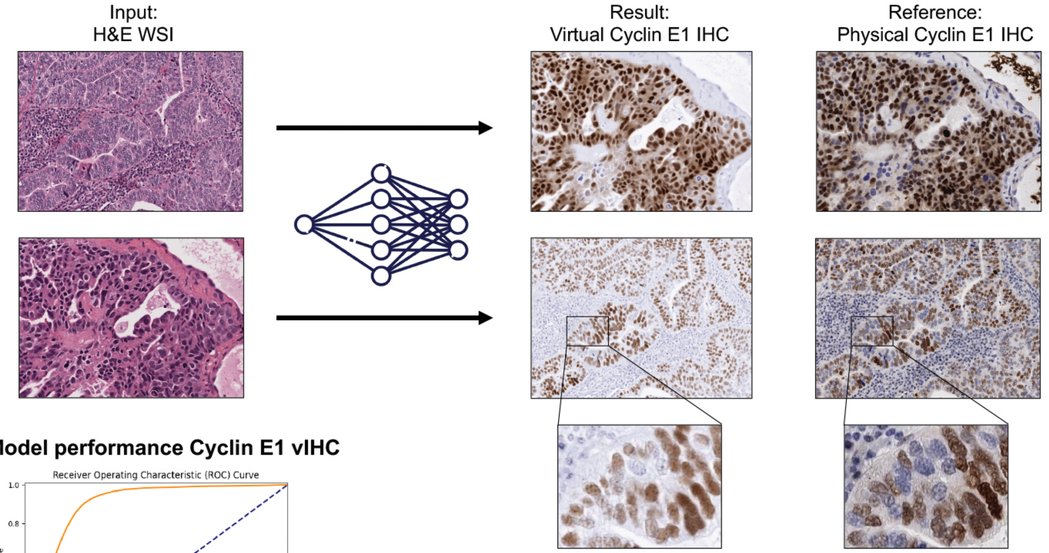
HGSOC and USC formalin-fixed paraffin-embedded (FFPE) tissue sections were provided by Debiopharm. Sections were H&E stained as per standard protocol and whole slide image scans (WSI) taken on a Ventana DP600. In a second step, slides were de-coverslipped and de-stained before Cyclin E1 IHC was performed and new WSI scans were obtained. Overall, Sixty-nine paired WSI (50 HGSOC and 19 USC) were analyzed.

ViewsML precisely aligned the paired H&E/IHC WSIs and then trained neural network models to learn morphological and nuclear features predictive of Cyclin E1 expression intensity (0–3+). Model performance was evaluated using per-cell sensitivity, specificity, and concordance with physical IHC intensity and H-score classifications, including ROC AUC metrics. Concordance between predicted and true Cyclin E1 expression was evaluated through nuclear localization distinguishing weak, moderate, and strong staining patterns, allowing quantitative assessment of Cyclin E1-positive tumor fractions across HGSOC and USC.

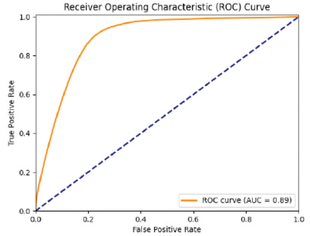
RESULTS

A Workflow

B Application of virtual Cyclin E1 model



C Model performance Cyclin E1 vIHC



CONCLUSIONS

This study demonstrates the feasibility of an AI-driven virtual Cyclin E1 IHC assay that successfully predicts Cyclin E1 staining intensities on single cell level only by processing whole slide images from H&E stained slides (AUC=0.89). This virtual IHC approach **conserves valuable patient tumor tissue** and **reduces the turnaround time** for assessment of Cyclin E1 levels down to minutes instead of days or weeks. Moreover, H&E staining of tumor biopsies is a standard procedure for pathology assessment at the stage of cancer diagnosis and is hence available for the vast majority of cancer patients. Given that the hospital is equipped with a WSI scanner, even hospitals in less developed countries are able to get a vIHC assessment at much **lower costs** compared to e.g. Next Generation Sequencing (NGS).
The Cyclin E1 vIHC tool presented here has the potential of accelerating future biomarker screening regarding patient selection and access, facilitating improved enrichment for Cyclin E1-associated therapeutic trials.
Additionally, this virtualized IHC approach also allows multiplexing by integration of multiple virtual biomarkers to test biomarker hypotheses or further refine patient selection.

REFERENCES

[1]T. Yap et al., First data disclosure of Phase I trial of the first in class combination of WEE1 inhibitor zedoresertib with PKMYT1 inhibitor lunresertib in patients with advanced solid tumors harboring CCNE1, FBXW7 or PPP2R1A genomics alterations, Clinical Trial Plenary Session CT022, AACR 2026

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