1282 CONCORDANCE ANALYSIS OF AI-POWERED CD8 QUANTIFICATION AND AUTOMATED CD8 TOPOLOGY WITH MANUAL HISTOPATHOLOGICAL ASSESSMENT ACROSS SEVEN SOLID TUMOR TYPES

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Background The degree of CD8+ lymphocyte infiltration into the tumor microenvironment, as well as the distribution of lymphocytes within the tumor and surrounding stroma (inflamed, excluded, or desert immunophenotypes), are key determinants for the potential efficacy of immunotherapy. Thus, accurate characterization of the tumor immune microenvironment is essential. However, manual histopathological assessment of CD8 topology is subject to many challenges, including subjectivity and reproducibility. We developed machine learning (ML)-based models for the identification and quantification of CD8+ lymphocytes and CD8-based CD8 topology classifiers across seven cancer types: urothelial carcinoma (UC), head and neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), gastric cancer (GC), colorectal cancer (CRC), pancreatic cancer (PC), and hepatocellular carcinoma (HCC).

Methods ML algorithms were developed to quantify CD8+ lymphocytes in UC, HNSCC, NSCLC, GC, CRC, PC, and HCC specimens from clinical trials and commercial sources (N=1603) using CD8+ cell detection models trained on digitized whole slide images of CD8 immunohistochemistry (Agilent-Dako clone C8/144b, Agilent). Annotations were provided by the PathAI network of expert pathologists to train algorithms for classifying tissue regions (including parenchyma and stroma) and cell types. To evaluate the performance of the CD8+ cell model, AI-predicted counts were compared to a consensus count from five independent pathologists for representative fields of view (frames) using Pearson correlation. Inter-pathologist agreement was also calculated. Using a distinct cohort of samples from each cancer type (N=1655), a simple, two-parameter CD8 topology classifier was trained using pathologist-provided CD8 topology scores and CD8 model-derived features. Classifier-predicted immunophenotype scores were compared to pathologist-generated scores using unweighted Cohen's kappa.

Results ML-based quantitation of CD8+ lymphocytes yielded counts with high concordance to manual pathologist consensus counts. Frames-based validation of CD8+ counts on held-out test sets from each cancer type confirmed this high correlation (table 1). For scoring CD8 topology, the performance of the CD8 topology classifier was comparable to that of individual pathologists (table 2), indicating non-inferiority of our models with pathologist-generated scores. Overall, our models met pre-determined success criteria for all seven cancer types.

Conclusions ML model-predicted CD8+ cell counts are highly concordant with pathologist-generated counts across seven solid tumor types, and tumor CD8 topologies were predicted with a simple and highly interpretable two-parameter classifier. These data demonstrate the power of AI-powered digital pathology for accurate and reproducible quantitation of CD8+ lymphocytes and automated immunophenotyping in clinical samples, further confirming the potential for AI-based biomarker measurements in immuno-oncology.

Acknowledgements We thank Mevlana Gemici and Aryan Pedawi for their contributions to this study.

Trial Registration Samples from the following clinical trials were used in this study: CA209-275 (NCT02387996), CheckMate 274(NCT02632409), CV202-103 (NCT03184870), Checkmate 9LA (NCT03215706), CA224-020 (NCT01968109), CheckMate 227 (NCT02477826), CheckMate 141 (NCT02105636), CheckMate040 (NCT01658878), CV202-103 (NCT03184870).

Ethics Approval Clinical trial protocols were approved by local institutional review boards or independent ethics committees and were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, defined by the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. All enrolled patients provided written informed consent based on Declaration of Helsinki principles prior to enrollment. This study was performed in accordance with the Bristol Myers Squibb Bioethics policy (https://www.bms.com/about-us/responsibility/position-on-key-issues/bioethics-policy-statement.html) and adhered to the World Medical Association Declaration of Helsinki for Human Research.

Abstract 1282 Table 1 Frames-based quantitative validation of CD8+ cell model performance. For each cancer type, quantitation of CD8+ lymphocytes was measured between pathologists and between our model and the consensus score. Pearson correlation and 95% confidence intervals are shown for each cancer type.

Cancer Subtype	Inter-pathologist (Mean Pathologist vs. Consensus) [Pearson, 95% CI]	PathAI Model vs. Consensus [Pearson, 95% CI]
UC	0.93 [0.90 - 0.95]	0.95 [0.92 - 0.97]
HNSCC	0.95 [0.92 - 0.97]	0.95 [0.92 - 0.97]
NSCLC	0.95 [0.92 - 0.97]	0.96 [0.93 - 0.97]
GC	0.89 [0.82 - 0.93]	0.91 [0.86 - 0.95]
CRC	0.95 [0.92 - 0.96]	0.95 [0.92 - 0.97]
PC	0.91 [0.87 - 0.94]	0.92 [0.88 - 0.95]
HCC	0.94 [0.90 - 0.96]	0.96 [0.94 - 0.98]

Abstract 1282 Table 2 Quantitative feasibility assessment of CD8 topology scoring. For each cancer type, concordance of CD8 topology was assessed between our model and individual pathologists, as well as between pathologists. Cohen's Kappa and 95% confidence intervals are shown for each cancer type.

Cancer Subtype	Inter-pathologist (Pairwise) [Kappa, 95% CI]	PathAI Model vs. Individual Pathologist (Pairwise) [Kappa, 95% CI]
UC	0.47 [0.39 - 0.56]	0.48 [0.41 - 0.56]
HNSCC	0.37 [0.32 - 0.42]	0.41 [0.35 - 0.46]
NSCLC	0.39 [0.33 - 0.47]	0.47 [0.41 - 0.53]
GC	0.45 [0.37 - 0.53]	0.41 [0.31 - 0.51]
CRC	0.35 [0.28 - 0.42]	0.38 [0.29 - 0.46]
PC	0.30 [0.18 - 0.43]	0.25 [0.14 - 0.36]
HCC	0.33 [0.25 - 0.41]	0.39 [0.31 - 0.46]

http://dx.doi.org/10.1136/jitc-2022-SITC2022.1282