Abstract #821

Machine Learning Models Can Quantify CD8 Positivity in Melanoma Clinical Trial Samples

STUDY BACKGROUND

The presence of CD8+ T cells in the tumor microenvironment is associated with response to immunotherapy and can inform patient treatment decisions[1-3]. However, characterization of immune cells in the tumor microenvironment is subject to challenges of manual scoring and inter-pathologist scoring variability[4,5].

To support the quantification and scoring of CD8+ T cells, PathAI has developed machine learning (ML)-based models that can identify and quantify CD8+ lymphocytes within the stroma and parenchyma regions of melanoma and other tumor types.

Here, we focus on the ML model for melanoma showing recent results for ML-based identification and quantification of CD8+ lymphocytes and concordance with manual pathologic assessment in data derived from multiple clinical trials.

PATHAI CD8 MODELS

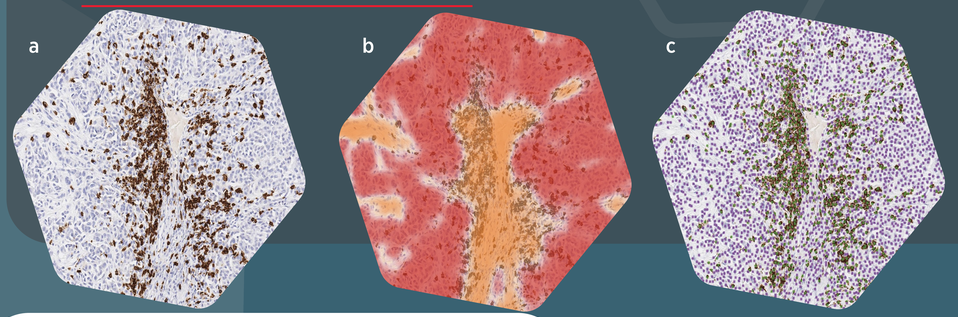
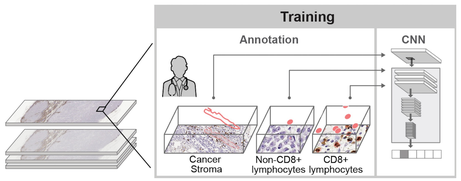


Figure 2. PathAI CD8 models. a) Melanoma tissue stained for CD8 (clone c8/144b, Dako). b) Tissue-level overlay showing model predictions for regions of necrosis (black), cancer stroma (orange), and cancer epithelium (red). c) Cell-level overlay showing model predictions for CD8+ lymphocytes (green) and non-CD8+ cell types (purple).

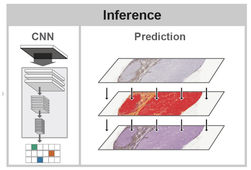
DEVELOPMENT

- Machine learning models were developed to quantify CD8+ lymphocytes in melanoma using 201 commercially procured pathology resections representing both primary and metastatic cases and stained for CD8 using clone C8/144b (Dako).
- Models were trained using the PathAI research platform on digitized whole slide images (WSI). Training utilized annotations provided by the PathAI network of expert pathologists identifying slide artifacts, parenchyma, cancer stroma, and necrosis, as well as CD8+ lymphocytes and other CD8- cell types (Figs. 1,2).
- Examples of melanin, such as that observed in tumor cells and pigment-laden macrophages (melanophages), were added to non-CD8+ cell types to train the ML models to separate true CD8 positivity from pigmented cells.

Figure 1. Machine Learning Model Training and Predictions



Convolutional neural network (CNN)-based ML models were trained using manual annotations provided by pathologists identifying features including cancer stroma, non-CD8+ lymphocytes and CD8+ lymphocytes.

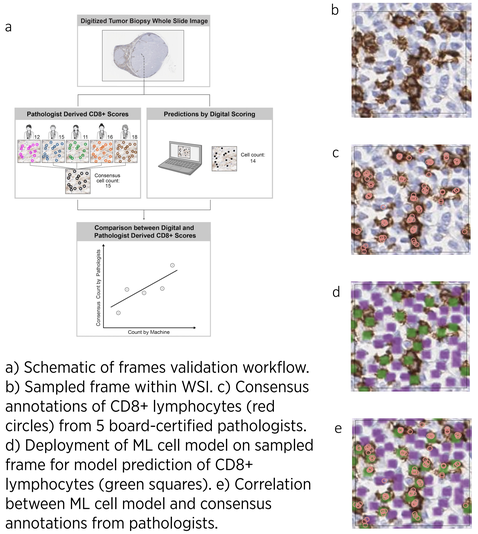


Inference on study samples generates tissue- and cell-level predictions. Examples of tissue-level predictions include stroma and parenchyma. Examples of cell-level predictions include CD8+ lymphocytes and non-CD8+ cell types.

VALIDATION

- After training, models were validated on clinical trial samples that were "held out," that is, not used for training. These samples included resection and clinical biopsy samples from dermal, lymph node and visceral sites, representing patients with metastatic melanoma disease. Frames of small tissue regions (75 x 75 microns) were selected from test set slides and exhaustively annotated by five pathologists (Fig. 3).
- Held out test frames (n = 112) from 90 WSI baseline samples were used. Model performance was evaluated based on the concordance of model predictions and pathologist annotations in these representative regions using Pearson correlation. Inter-pathologist agreement was also calculated.

Figure 3. Frames Analysis Workflow



a) Schematic of frames validation workflow. b) Sampled frame within WSI. c) Consensus annotations of CD8+ lymphocytes (red circles) from 5 board-certified pathologists. d) Deployment of ML cell model on sampled frame for model prediction of CD8+ lymphocytes (green squares). e) Correlation between ML cell model and consensus annotations from pathologists.

RESULTS

ML-based quantification of CD8 positivity in lymphocytes showed high concordance with manual pathologist consensus counts (**Fig. 4**). In frames validation of CD8+ counts on the test set of WSI, there was high correlation between the ML model and pathologist consensus counts (r=0.92 [95% CI 0.88-0.94]). This correlation was comparable to the agreement among the five expert pathologists (r=0.88 [95% CI 0.85-0.91]).

Figure 4. Performance of PathAI ML Model

Cell type	Pearson (95% CI): ML vs consensus n=112	Pearson (95% CI): Inter-pathologist n=112
CD8 positivity in lymphocytes	0.92 (0.88, 0.94)	0.88 (0.85, 0.91)
All other cell types	0.84 (0.78, 0.89)	0.92 (0.89, 0.94)

CONCLUSIONS

- ML model-predicted CD8+ cell counts are highly concordant with pathologist scores on WSI samples from melanoma-focused clinical trials at the frame level.
- PathAI is currently developing machine learning-based models to identify and quantify CD8+ lymphocytes within the stroma and parenchyma regions of tumors from other cancers including non-small cell lung cancer, renal cell carcinoma, breast cancer, gastric cancer, head and neck squamous cell carcinoma, and urothelial carcinoma.
- These data demonstrate the capability of AI-powered digital pathology to accurately and reproducibly quantify CD8+ lymphocytes in clinical trial samples. Future work will aim to use these models for comprehensive immunophenotyping and evaluation of the tumor microenvironment, with the goal of improving immunotherapies for better patient outcomes in the setting of translational research, prospective clinical trials and medical devices.

AUTHORS

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