Generation of an atlas characterizing the tumor immune microenvironment via AI-based histologic mapping of multiple cancer types at scale

Abstract #

STUDY BACKGROUND

- The composition of the tumor immune microenvironment (TME) is complex and challenging to quantify manually.
- Machine learning (ML) algorithms can be used to characterize the spatial distribution of cells and tissue regions of the TME from digitized H&E-stained whole slide images (WSI) of multiple cancer types.
- Based on ML-based TME characterization, we extracted TME-associated human interpretable features (HIFs) to generate an atlas characterizing the TME in several cancer types, including bladder cancer, breast cancer, and non-small cell lung cancer (NSCLC). We term this atlas Tumor Immune Microenvironment Atlas Project (TIMAP).

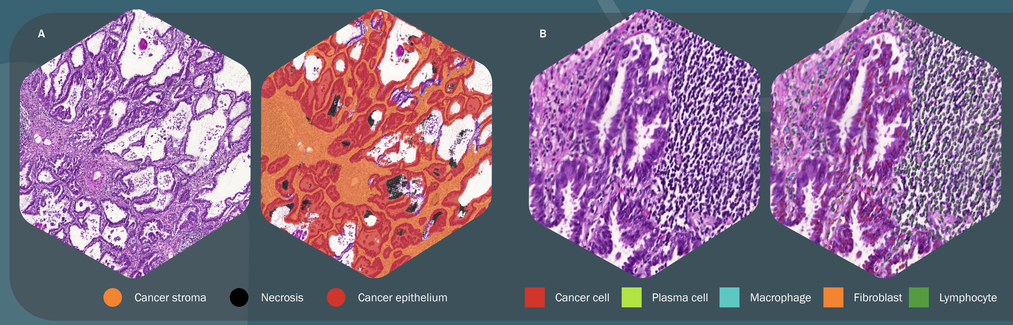

Figure 1. Example representations of TIMAP A) tissue models and B) cell models in NSCLC. For each model rendering, a labeled heatmap appears to the right of the corresponding H&E image.

METHODS

Model development and deployment. One ML model for each cancer type was developed using ground truth annotations from pathologists to identify and quantify cells (cancer cells, lymphocytes, macrophages, fibroblasts, and plasma cells) and regions of tissue (cancer epithelium, cancer-associated stroma, and necrosis) within the TME. Models were deployed on H&E-stained WSI of more than 12,000 biopsies and resections collected prior to trial intervention, including NSCLC (N=5,408), breast cancer (N=3,951), and bladder cancer (N=2,916), from 7 NSCLC, 4 breast cancer and 2 bladder cancer clinical trials sponsored by Genentech/Roche, as well a commercial NSCLC dataset.

Feature extraction. Spatially-resolved HIFs measuring area and count proportions and densities were extracted using model predictions.

Visualization of cancer types in HIF space. T-SNE was performed for dimensionality reduction and visualization of patients via HIFs, and hierarchical clustering was performed to generate clusters of HIFs.

Supervised prediction of cancer type using HIFs. Multinomial LASSO logistic regression was performed to reduce the multicollinearity of HIFs and predict cancer type based on HIFs.

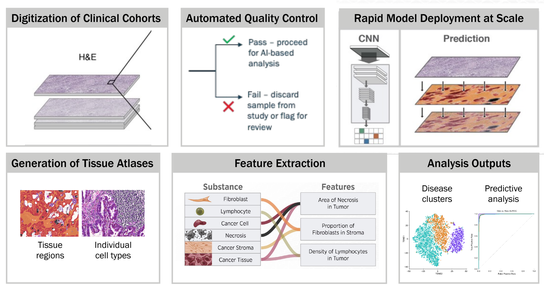

Figure 2. **Study workflow.** Briefly, H&E slides from 13 clinical trials were digitized prior to an automated quality control process to ensure optimal tissue quality. Cell types and tissue regions were predicted based on previously trained CNN-based models. Based on these predictions, HIFs were extracted. Quantitative analysis of HIFs allowed for downstream analyses based on TME features in each cancer type.

RESULTS

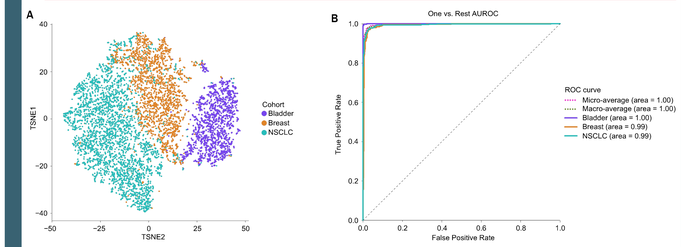

Figure 3. **Prediction of cancer type by all TIMAP HIFs.** A) T-SNE plots of the atlas features showed distinct clusters for each of the three indications. B) Multinomial LASSO logistic regression to analyze HIFs underlying differences between cancer types reported an average weighted F1 score of 0.986 and AUROC of 0.999 for 5-fold cross validation.

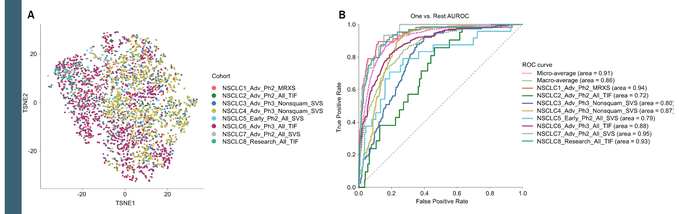

Figure 4. **Performance of TIMAP HIFs within a single cancer type.** A) T-SNE plots of the atlas features showed variable separation of NSCLC clinical trial cohorts. B) Multinomial LASSO logistic regression to analyze HIFs underlying differences between NSCLC cohorts reported an average weighted F1 score of 0.542 and AUROC of 0.858 for 5-fold cross validation.

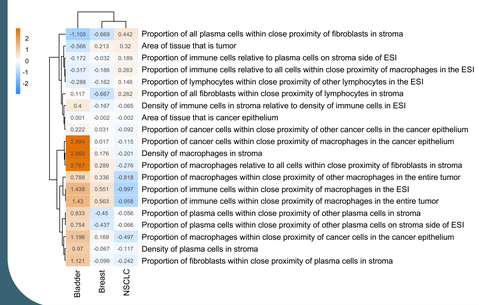

Figure 5. TIMAP HIF enrichment across cancer types. Unsupervised hierarchical clustering of TIMAP HIFs reveals distinct clusters based on HIF enrichment. Median z-scores are shown for each HIF.

RESULTS

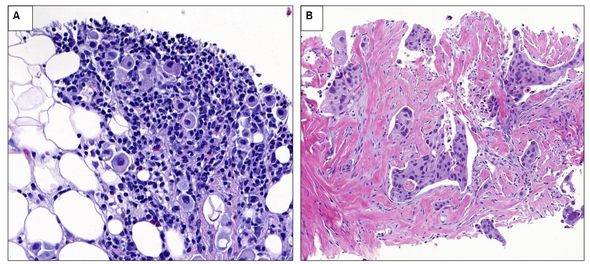

Figure 6. **Representative examples of enriched HIFs in H&E images.** A) High density of macrophages in stroma in bladder cancer. B) High density of fibroblasts relative to lymphocytes in stroma in breast cancer.

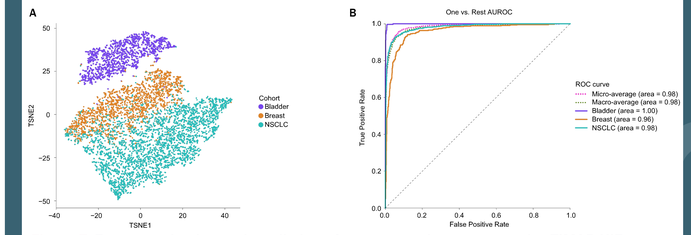

Figure 7. **Feature reduction and prediction of cancer type by representative TIMAP HIFs.** Representative HIFs were identified based on the analysis in Figure 3. A) T-SNE plots of the atlas features showed distinct clusters for each of the three indications. B) Multinomial LASSO logistic regression to analyze HIFs underlying differences between cancer types reported an average weighted F1 score of 0.969 and AUROC of 0.995 for 5-fold cross validation.

CONCLUSIONS

The application of AI-based, spatially-resolved, quantitative histopathology at scale shows that AI-identified HIFs can stratify cancer types. Furthermore, identified HIFs can reveal meaningful differences in the TME composition between cancer types. This ML-based characterization of the TME can be coupled with other modalities, such as RNA-seq, to further investigate the biology of distinct cancer types and the driving factors underlying treatment response. Work is ongoing to utilize these ML-derived TME atlas features to identify meaningful clinical differences between patients.

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ACKNOWLEDGMENTS

We thank the patients, families, and participating investigators in the clinical trials used in this study.

All trials were sponsored and funded by Genentech/Roche, and data analysis was performed by PathAI.

We thank Bioscience Communications for assistance with figure design and J. Brosnan-Cashman (PathAI) for poster preparation. This poster template was developed by SciStories LLC. https://scistories.com/

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Pathology Visions, October 16-18, 2022, Las Vegas, NV, USA