Multimodal Machine Learning Analysis of over 220,000 Tumor Profiles to Accurately Diagnose Molecular and Morphological Subtypes of Cancer

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Abstract

Background: The diagnosis of a malignancy is typically informed by clinical presentation and tumor tissue features including cell morphology, immunohistochemistry, and molecular markers. Additionally, multi-omic approaches[1] and deep learning models using digital pathology[2] have augmented expert pathologists and led to improved diagnoses but are often not employed together on the same patient. The opportunity exists for a truly multimodal, multi-omic machine learning classifier that comprehensively assesses all aspects of a tumor from the molecular underpinnings to the morphological and histological phenotypic presentation to provide the most accurate diagnosis while at the same time providing predictive biomarker data from the same specimen.

Methods: Whole transcriptome data from 220,246 tumor profiles, large panel and whole exome data from over 170,000 tumor profiles, and digital pathology features from over 50,000 tumors were used to construct a multi lineage classifier. The classifier was trained on 256 OncoTree[3] classifications corresponding to established WHO diagnoses where a tumor of each class has been observed at least 30 times in our dataset. The dataset was split 50% for training and the other 50% for testing, UMAP was employed for dimensionality reduction, and ensemble models were used for making the final calls. Truth was established by traditional pathologist-directed diagnostic work up.

Results: Tumor lineage classifiers predicted the correct classifications where the primary site was known with accuracies ranging between 97% and 100% when using the 32 highest level OncoTree categories corresponding to human tissues. Accuracy on the most granular OncoTree categories varied with many between 90 and 95%. When applied to CUP cases (n = 3589), an unequivocal OncoTree classification could be obtained over 90% of the time.

Multimodal Methodology

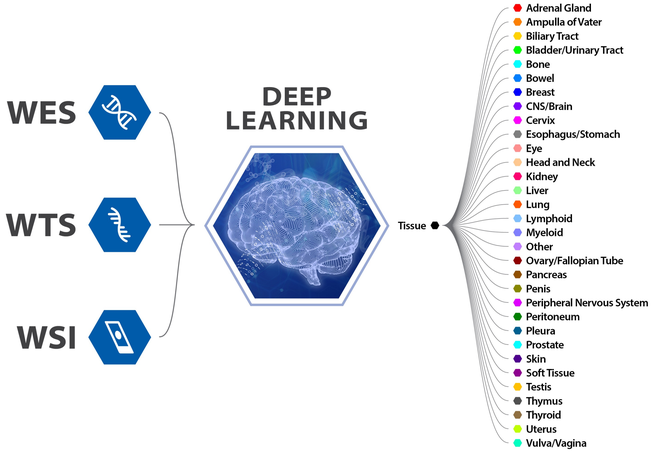

Figure 1 – Whole Exome, Whole Transcriptome, and Whole Slide Imaging Data are combined in a Deep Learning framework to predict OncoTree classifications.

WSI Features

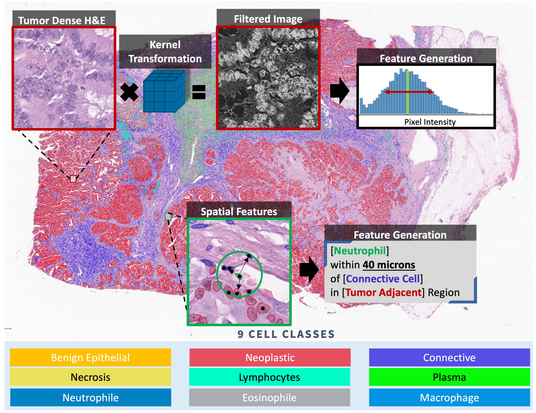

Figure 2 - Example of the NRF pipeline on a whole slide image. First a deep learning model segments and assigns every nucleus on a slide to one of 9 pathologist-identifiable cell types. Afterwards three major feature types are extracted: Cell-based characterizations, neoplastic region characterizations, and spatial relationships.

Distribution of Calls Per Classification

True Tumor Type

Predicted Tumor Type	ADRENAL GLAND	AMPULLA OF VATER	BILIARY TRACT	BLADDER	BONE	BOWEL	BRAIN	BREAST	CERVIX	EYE	HEAD NECK	KIDNEY	LIVER	LUNG	LYMPH	MYELOID	OVARY	PANCREAS	PENIS	PERITONEUM	PLEURA	PNS	PROSTATE	SKIN	SOFT TISSUE	STOMACH	TESTIS	THYMUS	THYROID	UTERUS	VULVA
ADRENAL GLAND	28	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	5	1	1	0	0	0	0
AMPULLA OF VATER	0	57	16	0	0	12	0	0	0	0	0	0	0	1	0	0	0	10	0	0	0	0	0	0	0	5	0	0	0	0	0
BILIARY TRACT	0	2	79	0	0	2	0	0	0	0	0	0	3	2	0	0	1	8	0	0	0	0	0	0	0	2	0	0	0	0	0
BLADDER	0	0	0	94	0	1	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
BONE	0	0	0	0	73	0	2	2	0	0	2	1	0	0	0	0	0	0	0	0	0	0	0	0	13	0	0	0	0	0	0
BOWEL	0	0	0	0	0	96	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
BRAIN	0	0	0	0	0	0	99	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
BREAST	0	0	0	0	0	0	0	98	0	0	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CERVIX	0	0	2	0	4	0	0	0	82	0	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	2	7
EYE	0	0	0	0	1	0	0	0	0	82	0	0	0	0	0	0	0	0	0	0	0	0	0	17	0	0	0	0	0	0	1
HEAD NECK	0	0	0	1	0	1	0	1	0	0	81	0	0	6	0	0	0	0	1	0	0	0	0	4	0	3	0	0	0	0	0
KIDNEY	0	0	0	1	0	0	0	0	0	0	0	96	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
LIVER	0	0	6	0	0	1	0	0	0	0	0	0	89	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
LUNG	0	0	1	0	0	0	1	0	0	0	1	0	0	94	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0
LYMPH	0	0	1	0	0	0	1	2	0	0	1	0	0	1	83	5	0	0	0	0	0	0	0	1	0	1	1	0	0	0	0
MYELOID	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	77	0	0	0	0	0	0	0	4	12	4	0	0	0	0	0
OVARY	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	86	0	0	0	0	0	0	0	0	0	0	0	0	6	0
PANCREAS	0	1	5	0	0	2	0	0	0	0	0	0	0	2	0	0	0	87	0	0	0	0	0	0	0	1	0	0	0	0	0
PENIS	0	0	0	2	0	12	0	0	0	0	10	0	0	2	0	0	0	0	50	0	0	0	0	21	2	0	0	0	0	0	0
PERITONEUM	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	38	0	40	20	0	0	0	0	0	0	3	0
PLEURA	0	0	0	0	0	0	0	1	0	0	0	1	0	12	0	0	1	1	0	15	68	0	0	0	0	1	1	0	0	0	0
PNS	0	0	0	0	2	0	0	0	0	0	0	2	0	2	0	0	0	0	0	0	0	80	0	4	11	0	0	0	0	0	0
PROSTATE	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	99	0	0	0	0	0	0	0	0
SKIN	0	0	0	0	1	0	0	0	1	3	0	0	1	0	0	0	0	0	0	0	0	0	0	90	1	0	0	0	0	0	2
SOFT TISSUE	0	0	0	0	1	0	2	0	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	1	85	1	0	0	0	5	0
STOMACH	0	0	2	0	0	3	0	0	0	0	1	0	0	1	0	0	0	1	0	0	0	0	0	0	0	90	0	0	0	0	0
TESTIS	0	0	0	0	0	0	2	0	0	0	0	4	0	2	0	0	2	0	0	0	0	0	0	0	4	0	76	9	0	0	0
THYMUS	0	0	0	0	0	0	0	0	0	0	0	0	0	28	0	0	0	0	0	0	0	0	0	2	0	0	13	88	0	2	0
THYROID	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	97	0	0
UTERUS	0	0	0	0	0	0	0	0	2	0	0	0	0	1	0	0	6	0	0	0	0	0	0	0	2	0	0	0	0	88	0
VULVA	0	0	0	2	0	8	0	1	10	0	4	0	0	1	0	0	1	0	0	0	0	0	0	6	0	1	0	0	0	1	65

Table 1 – Proportion of cases identified by the algorithm for each tumor type.

Multimodal Model Performance

Sensitivity	Specificity	PPV	NPV	Accuracy	Call Rate	CUP Call Rate
91.8%	99.7%	91.8%	99.7%	99.5%	99.3%	96.6%

Table 2 – Performance metrics on an independent test set of 68,712 cases.

Robust to Metastasis and Tumor Percentage

	TOP1_Accuracy	TOP2_Accuracy	TOP3_Accuracy	Call Rate
All Cases	91.8%	96.0%	97.4%	99.3%
Primary Only	93.9%	97.2%	98.2%	99.5%
Metastatic Only	88.7%	94.2%	96.2%	99.0%
<50% Tumor	91.9%	96.0%	97.5%	99.4%
<50% Tumor and Metastatic Only	88.0%	93.7%	96.0%	99.0%

Table 3 – Performance metrics on subsets of the independent test set from a primary site (n=40,787), metastatic site (n=26,703), samples with low tumor percentages (n=41,471) and samples from metastatic sites with low tumor percentages (n=15,817)

Conclusions

Combining multi-omic and digital pathology information into a comprehensive multimodal artificial intelligence platform can provide comprehensive information to pathologists to aid in diagnosis. This tool can be used to meet an unmet clinical need to define the lineage of CUP cases, which when coupled with biomarker data, will provide an opportunity to examine whether this information can be used to improve the outcomes of patient with CUP.

References

1. Abraham et al., Translational Oncology 2021
2. da Silva et al., J Pathology 2021
3. Kundra, et al., OncoTree: A Cancer Classification System for Precision Oncology. JCO Clinical Cancer Informatics 2021:5, 221-230