

Interpreting the Model: Biologic Pathways Underlying a Clinically Validated Multimodal Digital Pathology AI Biomarker in Metastatic Prostate Cancer

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Abstract

Background: Prostate cancer (PCa) spans indolent localized to lethal metastatic castration-resistant disease, underscoring the need for biologically grounded risk tools. ArteraAI multimodal artificial intelligence (MMAI), an NCCN guideline-supported biomarker for localized PCa and backed by Simon Level 1B evidence, has been validated as a prognostic marker across the spectrum of PCa. As an AI model incorporating a self-supervised learning (SSL) component, aspects of MMAI remain, non-human-interpretable, as the specific features learned by the SSL are not fully characterized. We therefore aimed to determine which aspects of tumor biology are reflected in MMAI's features and which pathways it identifies as mediators of metastatic progression that may be leveraged for novel therapeutic strategies.

Methods: We analyzed men with metachronous oligometastatic castration sensitive prostate cancer (omCSPC) including those enrolled on STOMP, ORIOLE, and OLIGOPELVIS clinical trials. MMAI was computed from diagnostic H&E whole-slide images along with age, PSA, and T stage using the commercial Prostate Prognostic Model v1.2. AI attention heatmaps guided 10x Visium spatial transcriptomics in representative high MMAI patients to nominate candidate pathways for evaluation in our full clinical cohort. Cohort-level correlates of continuous MMAI were tested with bulk RNA-seq (n=104) and targeted DNA sequencing (mutations n=181; copy-number alterations n=132).

Results: A total of 187 patients underwent MMAI scoring. Regions of high vs low AI attention were morphologically indistinguishable by expert genitourinary pathology review. High-attention regions were biologically heterogeneous including regions of proliferative malignant epithelium with enrichment of MYC targets (p<0.001) and oxidative phosphorylation (p=0.001) and reduced androgen-response signaling (p<0.001) as well as stroma adjacent to malignant glands, enriched for EMT (p<0.001) and myogenesis (p<0.001). Within the full omCSPC cohort, increasing MMAI correlated with higher ssGSEA enrichment of MYC targets (p<0.001), mTORC1 signaling (p<0.001), EMT (p<0.001), myogenesis (p<0.001), and oxidative phosphorylation (p<0.001). MYC copy-number gain was more frequent in the highest versus lowest MMAI quartile (48% vs 25%, p = 0.03). In TCGA-PRAD, high-MMAI tumors again demonstrated MYC and mTORC1 enrichment and more frequent MYC gain (34% vs 14%, p = 0.01).

Conclusions: MMAI aligns with core drivers of aggressive prostate cancer providing the first evidence that this clinically-validated unsupervised AI is reading real tumor biology. Mapping these features improves interpretability and suggests translational opportunities for novel therapeutic strategies.

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immediate family ownership interests in Exact Sciences, and patent applications licensed to Veracyte through his institution. Tamara Lotan, Ana Kiess, Daniel Song, Stephane Supiot, Piet Ost, and Phuoc Tran report consulting or advisory roles, honoraria, institutional research funding, travel support, employment, and/or other relationships with one or more of the following companies: Advanced Accelerator Applications, AIRA Matrix, Astellas Pharma, AstraZeneca, Bayer, BioProtect, Candel Therapeutics, DeepBio, Dendreon, Exact Sciences, GenomeDx, Isoray, Janssen Oncology, Lantheus Medical Imaging, Merck, Myovant Sciences, Myriad Genetics, Novartis, Noxopharm, Pfizer, POINT Biopharma, Reflexion Medical, Regeneron, and Ventana Medical Systems. Tamara Lotan additionally reports institutional research funding from ArteraAI. Phuoc Tran reports a patent related to compounds and methods of use in ablative radiotherapy. Amol C. Shetty reports immediate family employment at AstraZeneca. All other authors declare no competing interests.