WV Immunotherapy Response Explorer (WIRE): Interpretable AI for Predicting Immunotherapy Response in Appalachian Cancer Populations

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Abstract:

Lung cancer remains a leading cause of cancer-related mortality in the United States, with an estimated 226,650 new cases and 124,730 deaths projected in 2025. These challenges are further exacerbated in underserved regions such as Appalachia, where disparities in access to precision oncology persist. Immune checkpoint inhibitors (ICIs) have significantly improved outcomes in several cancers, including non–small cell lung cancer (NSCLC); however, a substantial proportion of patients do not benefit and may experience unnecessary toxicity and cost. Current biomarkers, such as PD-L1 expression and tumor mutational burden (TMB), remain insufficient particularly for populations underrepresented in clinical studies.

To address this gap, we present the WV Immunotherapy Response Explorer (WIRE), an interpretable artificial intelligence framework designed to improve prediction of immunotherapy response in Appalachian cancer populations. WIRE integrates two complementary modeling approaches: IRnet-v2, a pathway-informed graph neural network for mechanistic prediction, and G2PDeep, a deep learning platform for multi-omics biomarker discovery. By combining tumor transcriptomic profiles with curated biological pathway knowledge, our framework enables both accurate prediction and biologically interpretable insights into treatment response.

We are constructing a regional pilot cohort through collaboration with the Edwards Comprehensive Cancer Center (ECCC) and Marshall Health Network (MHN), incorporating RNA-seq data and associated clinical variables, including immunotherapy history and established biomarkers. These data will be used to evaluate and refine predictive performance relative to standard clinical markers.

In addition, we are developing a secure, clinician-oriented web portal that translates model outputs into actionable insights, including patient-level response probabilities and key pathway drivers. This platform aims to bridge the gap between advanced AI modeling and real-world clinical decision-making.

Overall, WIRE provides a scalable and interpretable framework for precision immunotherapy, with a focus on improving outcomes and reducing disparities in underserved populations.