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ACCURATE BREAST CANCER INTRINSIC SUBTYPING USING DNA-ONLY BIOMARKERS WITH APPLICATIONS TO MULTI-COHORTS

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Breast cancer intrinsic subtyping is critical for precision therapy and prognostic assessment. We applied the DNA-level multi-omics classifier UGES (Unified Genetic and Epigenetic Subtyping) [1] to two independent cohorts, TCGA (n = 931) and METABRIC (n = 1134), using a hierarchical learning strategy to progressively distinguish Basal-like, HER2-enriched, Luminal A, and Luminal B subtypes. UGES demonstrated excellent overall classification performance, achieving an AUC of 0.963 on the combined test set. In the challenging task of discriminating Luminal A from Luminal B tumors, UGES reached an AUC of 0.948, substantially outperforming a single-step strategy (0.828), highlighting the benefit of the stepwise approach. Compared with PAM50, UGES reclassified 11.57% of samples, with the most notable change being 11.25% of PAM50 Luminal A samples reassigned to UGES Luminal B. Additionally, UGES improved the sensitivity for HER2-enriched subtype recognition by 28.92%. Survival analyses revealed that

UGES-defined subtypes provided stronger prognostic discrimination, with significant survival differences observed across most subtype pairs, particularly for HER2 compared with other subtypes. These findings demonstrate that UGES offers a robust and clinically relevant framework for breast cancer subtyping across independent cohorts, providing a reliable tool for real-world data analysis and clinical decision-making in precision oncology.

References

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