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Summary

BRIDGING THE GAP IN COLORECTAL CANCER DETECTION BIOMARKER DISCOVERY: INTEGRATING SYSTEMATIC EVIDENCE AND MACHINE LEARNING TO IDENTIFY A 5-GENE PLASMA SIGNATURE FOR ENHANCING NON-INVASIVE ASSESSMENT

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A machine learning-driven analysis of plasma RNA sequencing identified and independently validated a 5-gene mRNA signature (TEF, METRNL, PIM3, PLEKHA4, ABCA2) for colorectal cancer detection, achieving an AUC of 0.85 in validation.

KEY POINTS

- Random Forest and Boosted Tree algorithms identified a 5-gene plasma mRNA signature consistently selected by at least three of four machine learning models, with Random Forest achieving AUC 0.83 in training and 0.85 in independent validation.
- A systematic review of 81 studies (2015-2025) revealed that 62% lack a complete discovery-training-validation pipeline and only 3% reported independent external validation, indicating limited reproducibility and risk of overfitting.
- The signature demonstrated diagnostic stability across truly independent plasma datasets (n=89 discovery, n=96 validation), suggesting consistent cross-platform performance.
- Current non-invasive screening with FIT is hindered by suboptimal specificity and high false-positive rates, resulting in unnecessary colonoscopies; multi-class RNA integration remains critically underexplored in colorectal cancer despite superior diagnostic potential in other cancers.

– Further prospective validation in plasma samples is needed to assess the signature's potential to improve colorectal cancer diagnosis strategies and reduce the burden of unnecessary colonoscopies.

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