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Abstract 2601: Biomarker tail genes in blood plasma cell-free RNA enable accurate detection of prostate cancer

Annelien Morlion; Philippe Decruyenaere; Kathleen Schoofs; Jasper Anckaert; Nickolas J. Ramirez; Justine Nuytens; Eveline Vanden Eynde; Kimberly Verniers; Celine Everaert; Guy Brusselle; Steven Callens; Filomeen Haerynck; Dimitri Hemelsoet; Eric Hoste; Jo Lambert; Nicolaas Lumen; Fritz Offner; Koen Paemeleire; Vanessa Smith; Lies Van den Eynde; Jo Van Dorpe; Amber Vanhaecke; Hans Van Vlierberghe; An Mariman; Olivier Thas; Jo Vandesompele; Pieter Mestdagh

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Abstract

The purpose of this study was to assess whether transcripts exhibiting strongly deviating abundance in plasma mRNA profiles can reliably differentiate prostate cancer from non-cancer states. To do so, we focused on biomarker tail genes (BTG), defined as protein-coding genes whose cell-free transcript abundance in an individual sample deviates by at least three standard deviations from a healthy control reference distribution. We applied the BTG identification and classification workflow to blood plasma samples from individuals with newly diagnosed prostate cancer (n = 132; 62 early-stage, 70 late-stage) and hy donors (n = 48). Classification thresholds were established using a train-test cross validation oach (70%), and performance was evaluated in held-out validation samples (30%) and in a separate -malignant cohort including healthy donors (n=37) and patients with non-malignant conditions (n=88).

Across training and validation analyses, a consensus set of 247 prostate cancer BTG enabled discrimination between prostate cancer samples and healthy controls, with sensitivity and specificity reaching 100% in the validation cohort of male donors. Of note, the number of BTG per plasma sample was not associated with disease stage, and classification remained highly accurate in age-matched subsets, indicating limited influence of age on results. When applied to a cohort of individuals with diverse non-malignant conditions, the established BTG threshold yielded 94.4% specificity, and none of patients with benign prostatic hyperplasia were misclassified (n=5). To explore redundancy within the BTG set, we evaluated both cluster-derived subsets and algorithmically selected minimal panels. Multiple small subsets, including a ten-gene panel identified by a greedy selection strategy, achieved perfect classification within the validation cohort, demonstrating that strong discriminatory power is retained even when BTG sets are substantially reduced. In conclusion, blood plasma BTG constitute a highly accurate signature for prostate cancer detection, and the ability of small BTG subsets to reproduce full-set performance highlights opportunities for targeted assays. Further evaluation in broader populations and across cancer stages will refine the potential of BTG-based approaches for early detection and monitoring. (The last two authors contributed equally to this work)

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