CancerSpot: A Multi-Cancer Early Detection Test Using Targeted Methylation Sequencing

Urvashi Bahadur[1], Divya Vishwanath[1], Prakash Hiremath[1], Nihesh Rathod[1], Swaraj Basu[1], Sampuran Chakraborty[1], Aastha Tripathi[1], Preetha RT[1], Aditi Chatterjee[1], Arunima Ghosh[1], Sameer Phalke[1], Subuhi Yete[1], Ankita Khan[1], Sweta Sanguri[1], Mohammed Rahman[1], Charles Cantor[2], Sewanti Limaye[3], Vamsi Veeramachaneni[1], Ramesh Hariharan[1];
[1]Strand Life Sciences, Bengaluru, India; [2]Strand Life Sciences Scientific Advisory Board, New York, NY;
[3]Sir H N Reliance Foundation Hospital and Research Centre, Mumbai, India

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Contact:
Ramesh Hariharan
Chief Executive Officer
ramesh@strandls.com

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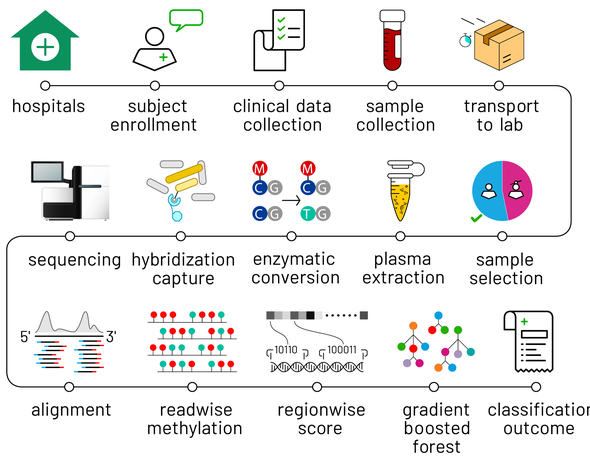
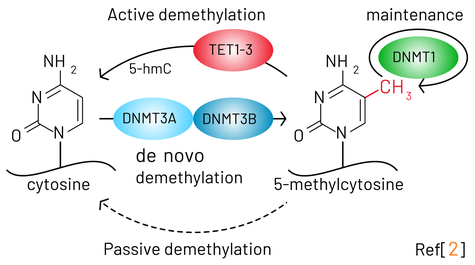
Introduction

Liquid biopsy-based cancer detection is a non-invasive method to identify cell-free DNA (cfDNA) fragment based signatures in the bloodstream, characterized by distinct methylation patterns. Tumor-derived cell-free DNA (ctDNA) fragments form a tiny fraction of all cell-free DNA (cfDNA) fragments present in the bloodstream. ctDNA fragments originating from some specific genomic regions can have altered methylation patterns. Here we present a non-invasive early cancer screening test based on methylation signatures from cfDNA (blood), identified using a custom panel.

Sample Journey



DNA Methylation



Ref[2]

Robust Against Confounders and Variability

Technical Variability
- Methylation signal consistency varies across sequencers and flow cells.
- ML Models refined to be robust to noise.

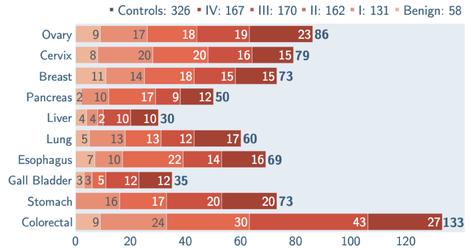
Low Tumor Specific Signal
- The scarcity of tumor derived cfDNA in blood makes detection challenging.
- Scoring schemes attuned to invisible cancer signal.

Conversion Efficiency
- Incomplete enzymatic conversion impacts downstream analysis.
- Algorithms for filtering false positive signals.

Methylation Variability
- Differences in methylation patterns exist across gender and age.
- Ensure diversity in age and gender.

Lifestyle Influence
- Tobacco and alcohol consumption alter methylation signatures.
- Include smoker and chewer in control cohorts.

Sample Distribution



Methods

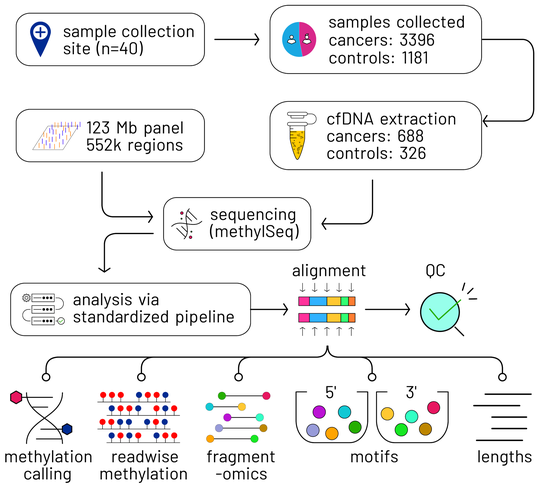
A custom genomics workflow prioritizes high-quality enzymatically converted reads to calculate methylation scores across genomic regions at the read level. Machine learning (ML) models were developed using methylation signatures from 7,000+ genomic markers. A gradient-boosted trees approach combined with repeated cross-validation incorporated data perturbations to account for variability in lab protocols and sequencing platforms.

Highlights

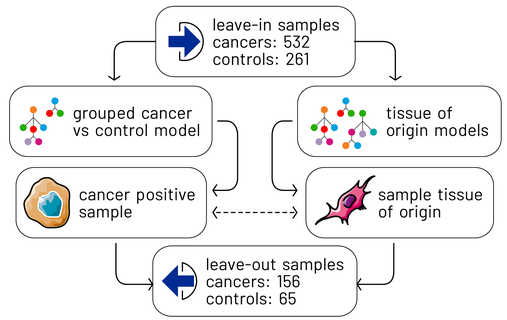
CancerSpot is a novel, non-invasive, blood-based screening assay for early cancer detection.

- Achieved **79% sensitivity** and **97% specificity** for detecting Stage I-III tumors across **10 cancer types**.
- Demonstrated **77% accuracy** in predicting the **tumor tissue of origin (TOO)** within the **top two predictions** for cancer-positive samples.
- Built on a **targeted MethylSeq assay**, integrated with a **scalable multi-omics pipeline**.
- Utilizes a **proprietary machine learning model**, trained on **over 1,000 samples**, to deliver robust early cancer predictions.

Sequencing and Analysis



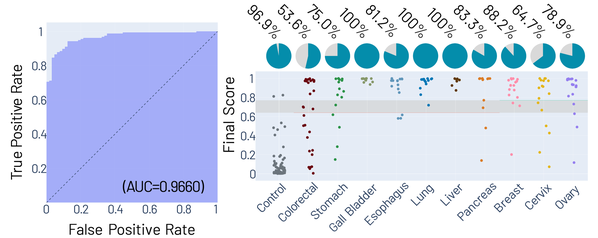
ML Classification



Results

CancerSpot achieved **79% sensitivity** and **97% specificity** for detecting Stage I-III tumors across 10 cancer types. It also demonstrated a **77% accuracy** in identifying the tumor tissue of origin (TOO) within the top two predictions. The robust workflow enhances detection of tumor-derived cfDNA signals, even in samples with low conversion efficiency, while mitigating background noise from normal cfDNA.

Model Performance



Cancer Detection

Control	Benign	I	II	III	IV	Total
96.92%	53.33%	79.31%	78.38%	78.38%	86.84%	78.20%

Tissue Detection (Top 2 Predictions)

Type	Control	Benign	I	II	III	IV	Total
Control	63/65	0/0	0/0	0/0	0/0	0/0	63/65
Colorectal	0/0	1/2	2/5	4/6	4/9	4/6	15/28
Esophagus	0/0	1/2	1/2	4/5	3/3	4/4	13/16
Gall Bladder	0/0	1/1	1/1	2/2	3/3	3/3	10/10
Liver	0/0	1/1	1/1	1/1	2/2	2/2	7/7
Lung	0/0	1/1	3/3	3/3	3/3	4/4	14/14
Pancreas	0/0	0/1	2/2	3/4	2/2	3/3	10/12
Stomach	0/0	0/0	4/4	2/4	4/4	2/4	12/16
Breast	0/0	2/3	3/3	4/4	2/3	4/4	15/17
Cervix	0/0	0/2	3/4	3/4	2/4	3/3	11/17
Ovary	0/0	1/1	3/4	3/4	4/4	4/5	15/19

References

1. Basu, S., Hiremath M, P., Rathod, N., Chatterjee, A., Vishwanath, D., Ghosh, A., Sanguri, S., Chakraborty, S., Tripathi, A., Preetha, R.T. and Nair, A., 2024. CancerSpot: A multi-cancer early detection test developed and validated on a retrospective cohort. medRxiv, pp.2024-12.
2. Ambrosi, C., Manzo, M. and Baubec, T., 2017. Dynamics and context-dependent roles of DNA methylation. Journal of molecular biology, 429(10), pp.1459-1475.