# #1661
Translating cancer tissue methylation to cell-free DNA methylation for minimally invasive cancer detection.

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Introduction

- Cell-free circulating tumour DNA (ctDNA) is a minimally invasive biomarker
- There are large databases of cancer tissue research available
- Can we leverage tissue derived biomarkers to detect cancer in cfDNA?
- RenovaroCube ("The Cube") is an AI platform for cancer diagnostics

- TCGA is a large database containing cancer methylation data for multiple cancer types[1]
- cfMEDIP captures methylated cfDNA and allows for quantifying methylation levels in cfDNA

TCGA Tissue methylation → **The Cube** — **Marker Mining** → **MEDIP Methylation**
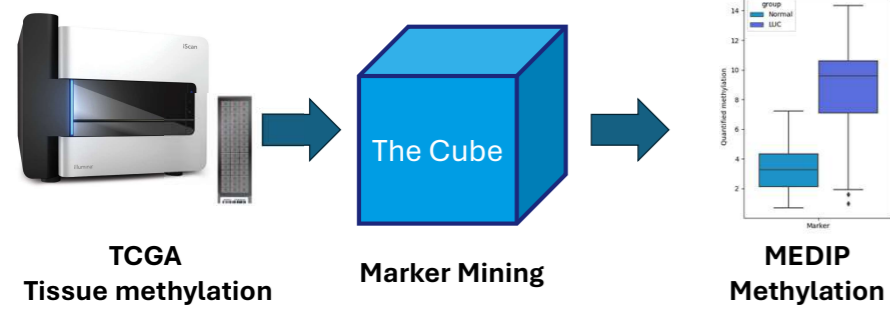
Methods
- Marker mining
  - TCGA methylation array data
  - RenovaroCube biomarker mining
- Publicly available cfMEDIP data[2,3]
  - Convert Illumina biomarkers to cfMEDIP biomarkers
  - Perform differentially methylated region analysis (DMR)
- Training set:
  - Healthy donors (n=24)
  - Cancer patients (n=73)
    - 23 Colorectal cancer
    - 25 Lung cancer
    - 25 Breast cancer
- Test set:
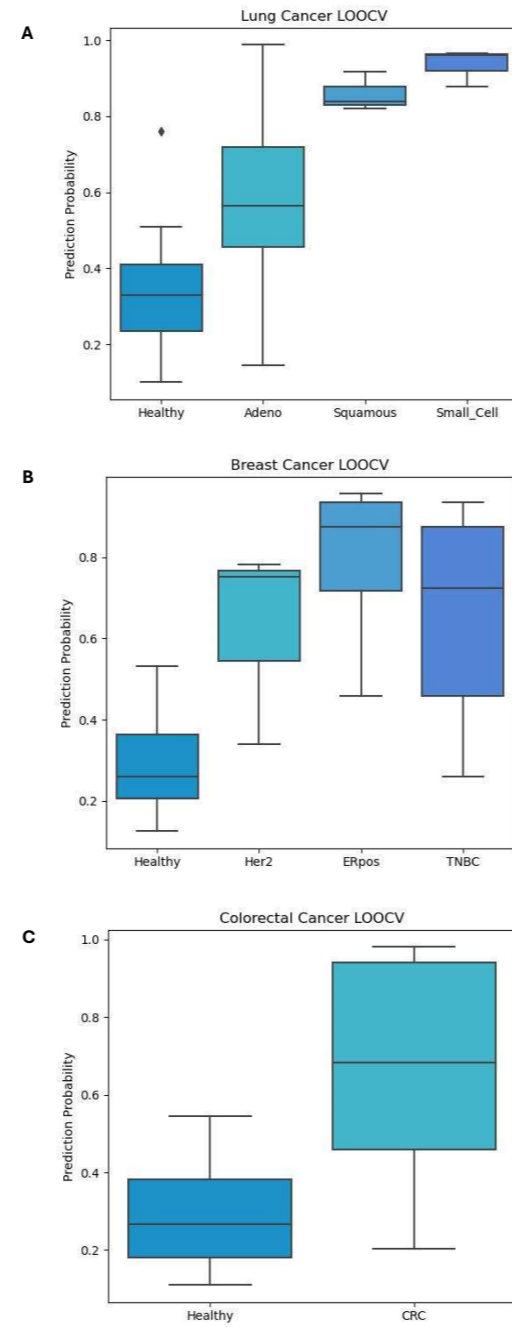 - Healthy donors (n=62)
  - Lung cancer patients (n=55)

Figure 2. *LOOCV Model prediction results for training sets. A: Lung cancer. B: Breast Cancer. C: Colorectal cancer*
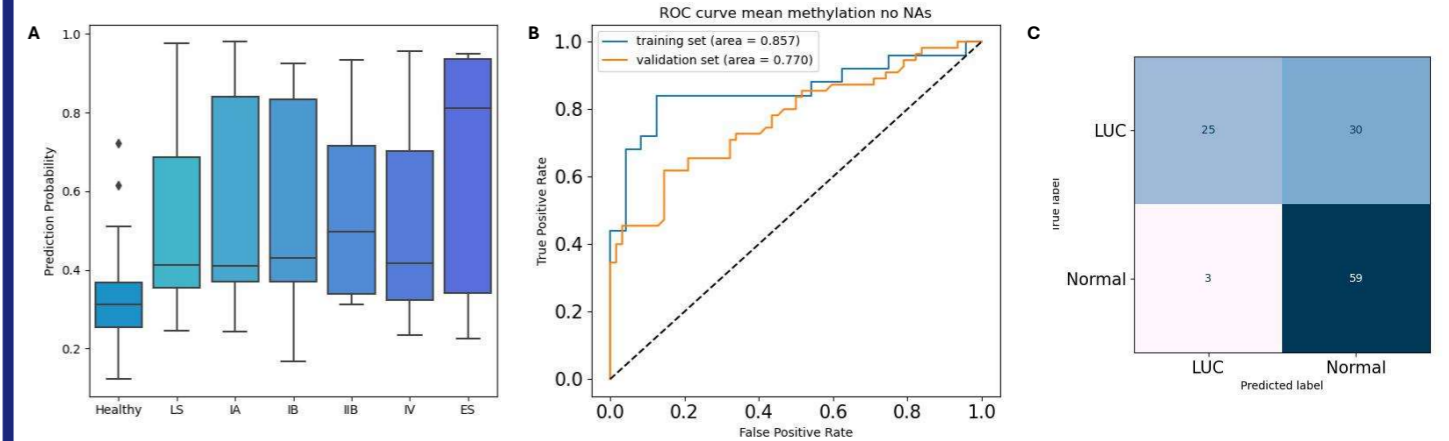

Figure 3. *Lung cancer model performance on independent test set. A: Box plot prediction probability per stage. B: ROC curve train/test sets. C: Confusion matrix test set.*

Results:
- DMRs selected: lung cancer 72, breast cancer 74 , colorectal cancer 121
- Many tissue derived DMRs show differential methylation in cfDNA
- Models set for high specificity maintain high specificity in independent test cohort

Table 1. *Model performance metrics set for high specificity*

	LUC – LOOCV	LUC-Test	CRC – LOOCV	BRCA - LOOCV
Accuracy	0.78	0.74	0.83	0.86
Sensitivity	0.59	0.49	0.65	0.72
Specificity	0.96	0.97	1.00	1.00

Conclusion:
- Tissue derived differentially methylated regions are detectable in cfDNA
- A highly specific model can be made using tissue derived methylation biomarkers
- More research is required to fully leverage years of tissue-based research into the field of liquid biopsies

References:
1. TCGA Research Network: https://www.cancer.gov/tcga.
2. Ul Haq S, Schmid S, Aparnathi MK, et al. Cell-free DNA methylation-defined prognostic subgroups in small-cell lung cancer identified by leukocyte methylation subtraction. iScience. 2022;25(12):105487. Published 2022 Nov 4. doi:10.1016/j.isci.2022.105487
3. Shen SY, Singhania R, Fehringer G, et al. Sensitive tumour detection and classification using plasma cell-free DNA methylomes. Nature. 2018;563(7732):579-583. doi:10.1038/s41586-018-0703-0

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