Test performance of a DNA methylation–based liquid biopsy biomarker for detection and classification of pleural mesothelioma (PM)

Sabine Schmid[1,2], Sami Ul Haq[2], Luna Zhan[2], M. Catherine Brown[2], Devalben Patel[2], Frances Shepherd[2], Natasha Leighl[2], Adrian Sacher[2], Marc De Perrot[2], Bc John Cho[2], Fatemeh Zaeimi[2], Miguel García-Pardo[3], Benjamin Lok[2], Scott Bratman[2], Ming Tsao[2], Martin Früh4, Penelope Bradbury[2], Geoffrey Liu[2]

1. Inselspital, University Hospital Bern, Bern, Switzerland; 2. University Health Network, Toronto, Canada; 3. Ramon y Cajal University Hospital, Madrid, Spain; 4. Cantonal Hospital St.Gallen, St.Gallen, Switzerland

UHN Princess Margaret Cancer Centre

Abstract #8082

BACKGROUND

- **ctDNA profiling in PM is difficult** due to molecular heterogeneity and few recurrent mutations
- Diagnosis can be **challenging** and may require repeat biopsies
- Cell-free methylated DNA immunoprecipitation sequencing (**cfMeDIP-seq**) of cfDNA analyzes **non-invasively differentially methylated regions** (DMRs)
- cfMeDIP-seq evaluates epigenetic changes that could serve as **potential biomarkers** for **diagnosis**, **histological differentiation**, and **prognosis** in PM

HYPOTHESES

- cfMeDIP-seq can distinguish PM histologies
- cfMeDIP-seq can distinguish PM from non-cancer controls (NCC)
- cfMeDIP-seq can identify prognostic subgroups in PM

METHODS

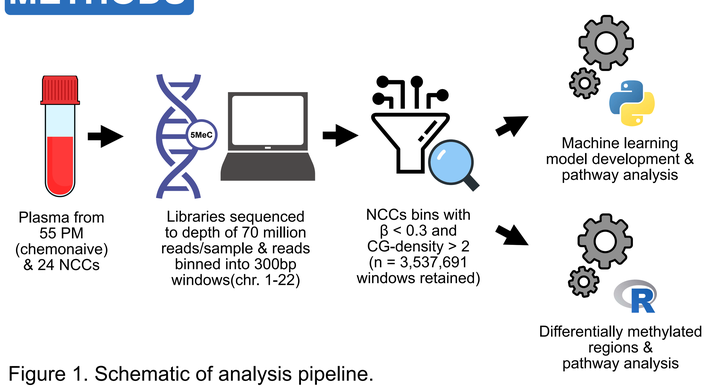

Figure 1. Schematic of analysis pipeline.

- Plasma samples from a prospective cohort of PM patients collected at Princess Margaret Cancer Centre were analyzed
- Only plasma samples collected at baseline, prior to initiating before any treatment, were analyzed

RESULTS

Characteristic	N (%)
Sex	
Female	8 (15)
Male	47 (85)
Age at diagnosis (years)	70.5 (64.7 to 74)
Histology	
Biphasic	6 (11)
Epithelioid	40 (73)
Sarcomatoid	9 (16)
Asbestos exposure	
No	10 (18)
Yes	40 (73)
Unknown	5 (9)

Table 1. Overview of PM cohort (N = 55) by sex, age at diagnosis, clinical stage, histology, and past asbestos exposure.

cfMeDIP-seq distinguishes epithelioid and sarcomatoid histologies

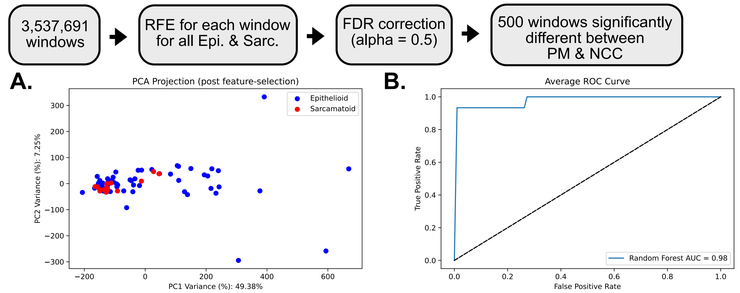

Figure 2. A random forest classifier was developed (stringent filter, mean beta-value 5) with 500 windows (A), distinguishing epithelioid and sarcomatoid with 83% accuracy, 74% precision, and an AUC of 0.98 across 5-fold cross-validation cohorts (B).

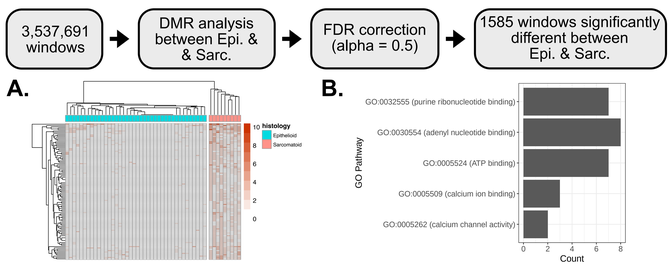

Figure 3. DMR analysis of epithelioid vs. sarcomatoid (A) revealed 1,585 significantly different windows (adjusted $p < 0.05$). Gene ontology analysis (B) indicated significant enrichment in RNA processing pathways.

cfMeDIP-seq distinguishes PM from NCC

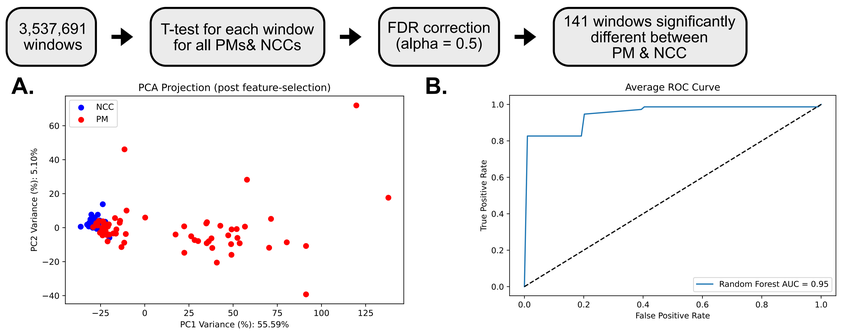

Figure 4. A random forest classifier was developed (stringent filter, mean beta-value 5) with 141 windows (A), distinguishing PM from NCC with 91% accuracy, 88% precision, and an area under the ROC curve (AUC) of 0.95 across 5-fold cross-validation cohorts (B)

cfMeDIP-seq identifies prognostic groups in PM

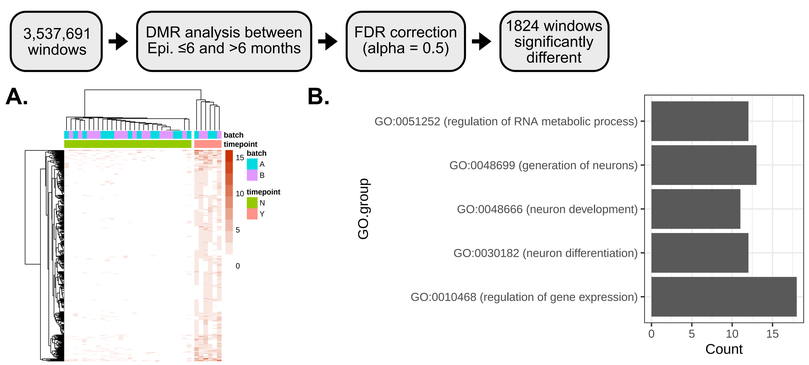

Figure 5. DMR analysis (A) of epithelioid PM Patients with overall survival (OS) ≤ 6 months and >6 months revealed 1824 windows significantly different (adjusted $p < 0.05$). Gene ontology analysis (B) indicated significant enrichment in neuronal signalling pathways.

CONCLUSION

If validated, cfMeDIP-seq of ctDNA offers a novel, non-invasive approach for accurate diagnosis and histological differentiation, while epigenetic biomarkers may reveal insights into PM biology and enable personalized care.