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Whole genome cell-free tumor DNA mutational signatures from blood for early detection of recurrence of low stage lung adenocarcinoma

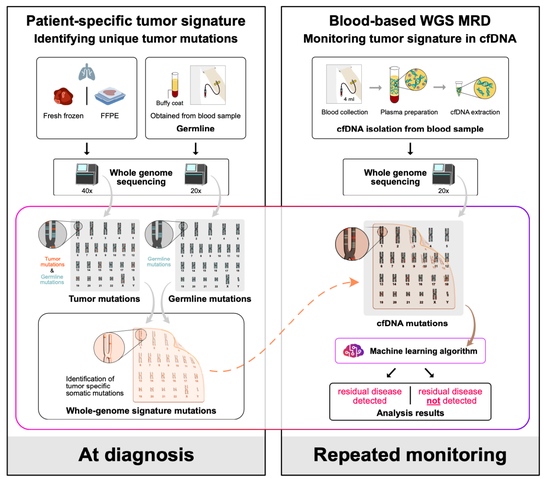
Ivy Tran[1], Alejandro Vargas[1], Reid Wilkins[1], Isabella Pizzillo[1], Kenneth Tokoro[2], Danielle Afterman[3], Tomer Lauterman[3], Maja Kuzman[4], Santiago Gonzalez[4], Dunja Glavas[4], James Smadbeck[4], Dillon Maloney[4], Jurica Levatic[4], Samuel Phillips[4], Sunil Deochand[4], Michael Yahalom[3], Ryan Ptashkin[4], Iman Tavassoly[4], Zohar Donenhirsh[3], Eric White[4], Ravi Kandasamy[4], Ury Alon[3], Paz Polak[4], Boris Oklander[3], Asaf Zviran[4], Matija Snuderl[1], Harvey I. Pass[2]

[1]Department of Pathology, NYU Langone Health, New York, NY, USA, [2]Department of Cardiothoracic Surgery, NYU Langone Health, New York, NY, USA, [3]C2i Genomics LTD, Haifa, Israel, [4]C2i Genomics Inc., New York, NY, USA

INTRODUCTION

Lung cancer remains the leading cause of cancer-related deaths. Surgery is the best option for early lung cancer, and the role of adjuvant therapy remains controversial. Liquid biopsy offers a noninvasive approach to monitor cancer burden. Targeted sequencing of circulating cell-free tumor DNA (ctDNA) in blood has shown success for diagnosis; however, low tumor burden and dynamic evolution of low stage disease is challenging for targeted panels. We hypothesized that a whole genome sequencing (WGS)-derived patient specific mutational signature from matched tumor-normal samples can provide a sensitive and specific approach for monitoring of lung adenocarcinoma patients.

C2INFORM ASSAY



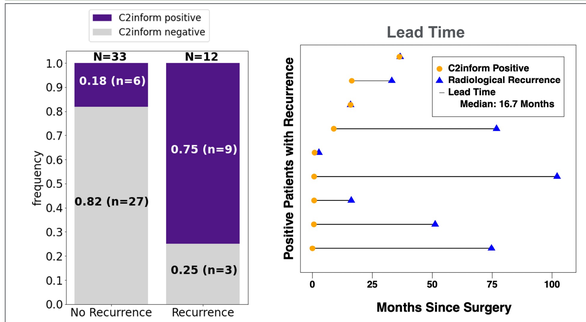
PATIENT CHARACTERISTICS

We successfully profiled 45 Stage 1 (44, 98%) or Stage 2 (1, 2%) lung adenocarcinomas with >5% tumor purity and <30% duplications rate. Of these, 33 patients showed no recurrence and 12 recurred. WGS of the ctDNA samples, derived from 1-2 mL plasma collected at the time of surgery and 3 to 18 surgical follow-ups, were tested using the C2inform assay.

	N (%)
Age (median, range)	68 (46-88)
Gender	
Female	31 (69)
Male	14 (31)
Smoking Status	
Current or former	31 (69)
Never	13 (29)
Unknown	1(2)

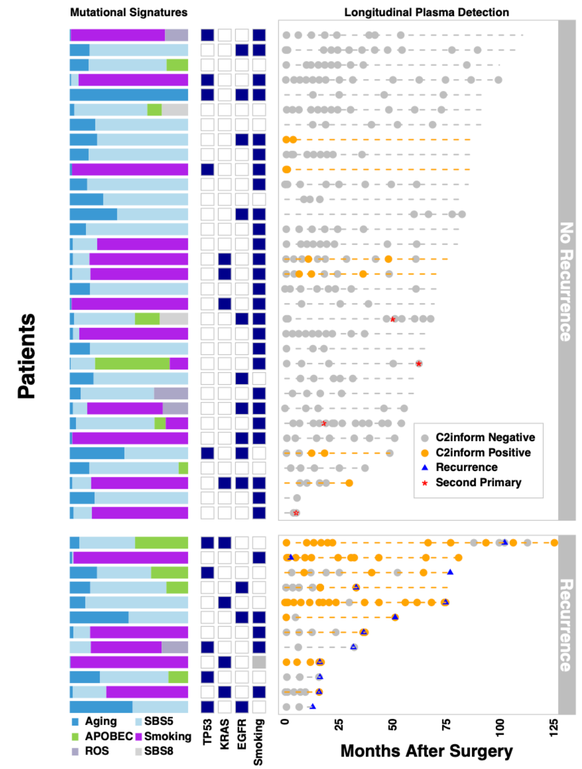
	N (%)
Stage	
IA	42 (93)
IB	2 (4)
II	1 (2)
EGFR positive	10 (22)
Disease recurrence	12 (27)
Alive at data cut-off	40 (89)

SENSITIVITY, SPECIFICITY, AND LEAD TIME

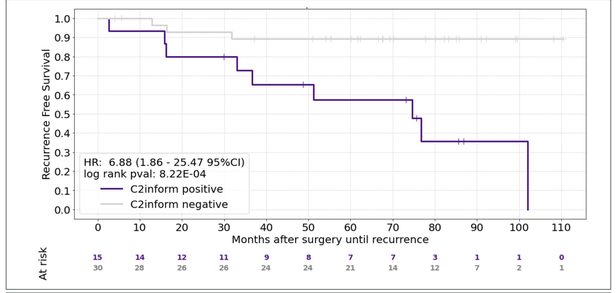


Tumor-specific signatures detected the presence of ctDNA in plasma with TF as low as 10^{-5}. Recurrence prediction had sensitivity=0.75, specificity=0.82, PPV=0.6 and NPV=0.9. WGS ctDNA predicted recurrence with a median lead time of 16.7 months before clinical/imaging recurrence.

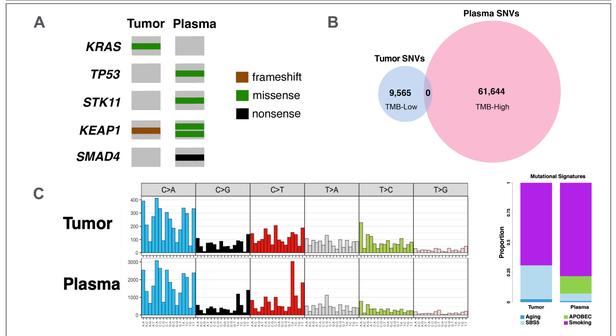
COHORT OVERVIEW



C2INFORM POSITIVE PREDICTS RECURRENCE



CASE STUDY OF SECOND PRIMARY



De novo calling of somatic mutations from cfDNA found (A) no overlap in driver alterations; (B) no overlap in SNVs and increase in mutation burden; (C) plasma specific APOBEC signature. Taken together this indicates the presence of a second primary.

CONCLUSIONS

Patient-specific WGS tumor signature enables specific and ultrasensitive tracking of minimal residual disease in plasma derived ctDNA from low stage lung adenocarcinoma patients. Molecularly positive status can be used to predict recurrence and identify patients with clinical low stage disease that may benefit from adjuvant therapy. WGS analysis of high tumor fraction plasma samples can also detect the presence of second primary tumors.

Corresponding Author: matija.snuderl@nyulangone.org

C2i Genomics

NYU Langone Health