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Evaluation of a Genome-Wide Methylome Enrichment Platform for Circulating Tumor DNA Quantification and Prognostic Performance in Renal Cell Carcinoma (RCC)

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BACKGROUND

- Circulating tumor DNA (ctDNA) can be utilized to identify the presence of cancer as well as minimal residual disease.
- Quantification of ctDNA using plasma-based tests can be a useful cancer management tool to assess prognosis; however, some methodologies also require tumor tissue for analysis or are limited to tumor types that tend to have higher amounts of associated ctDNA.
- For renal cell carcinoma (RCC), ctDNA quantification could help inform decision making around adjuvant immune checkpoint inhibitors (ICIs) as well as improved post-surgical surveillance.

AIM

- Demonstrate the feasibility of using a tumor-naive genome-wide methylome enrichment platform to quantify ctDNA in plasma and determine prognostic performance in RCC.

METHODS

COHORT

- Biobanked plasma samples were from individuals with newly diagnosed stage I-IV RCC (collected from 2015 to 2021; Princess Margaret Cancer Centre at University Health Network and the Ontario Tumour Bank[1]).
- All samples were obtained after cancer diagnosis but prior to surgery or other definitive treatment.

GENOME-WIDE METHYLATION ASSAY

- All samples were analyzed with a bisulfite-free, non-degradative genome-wide DNA methylation enrichment platform, using 5-10 ng of cfDNA extracted from plasma.
- The assay was based on the cell-free methylated DNA immunoprecipitation and high-throughput sequencing (cfMeDIP-seq) technique.[2]
- ctDNA was quantified from average normalized counts across informative regions.

ANALYSIS

- An event was defined as cancer recurrence, progression, or death due to renal cancer (whichever occurred earliest).
- A ctDNA quantity threshold for baseline prognostication was set such that 95% of samples without an event fell below the threshold (i.e. 95% specificity).
- Event-free survival was estimated using the Kaplan-Meier method, and the difference was assessed by the log-rank test using both the total population and individuals with stages I-III cancers.

1. Biological materials were provided by the Ontario Tumour Bank, which is supported by the Ontario Institute for Cancer Research through funding provided by the Government of Ontario.
2. Shen SY, Singhania R, Fehringer G, et al. Nature. 2018;563(7732):579-583.

RESULTS

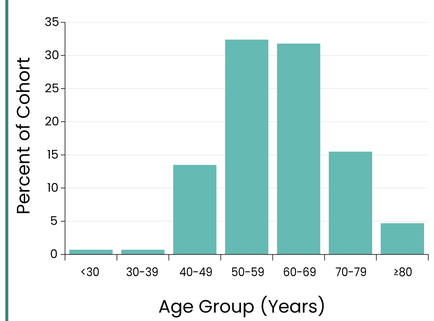
- The cohort included 148 samples from individuals with newly diagnosed, invasive RCC (Table 1, Figure 1).
  - The median follow-up time was 15.7 months, with 21 events.

Table 1. Clinico-Pathologic Information (N=148)

Characteristic		N (%)
Sex	Female	42 (28%)
	Male	106 (72%)
Stage	Stage I	64 (43%)
	Stage II	2 (1%)
	Stage III	23 (16%)
	Stage IV	15 (10%)
	Late Stage (III/IV)[1]	39 (26%)
	Unknown	5 (3%)
Histology	Clear Cell Carcinoma	112 (76%)
	Chromaphobe RCC	13 (9%)
	Papillary Carcinoma	12 (8%)
	Other	11 (7%)
Smoking History	Yes	81 (55%)
	No	64 (43%)
	Unknown	3 (2%)

1. For some samples, full TNM staging information was not available to determine the specific stage but was sufficient to determine that the stage was either III or IV.

Figure 1. Age at the Time of Sample Collection



- Individuals with ctDNA quantification above the cutoff displayed significantly worse event-free survival both in the overall cohort (Figure 2), and in the sub-population with stage I-III disease (Figure 3).

Figure 2. All Stage Kaplan–Meier Analysis Depicting Event-Free Survival

Individuals were stratified on the basis of ctDNA quantification being above or below the 95% specificity cutoff.

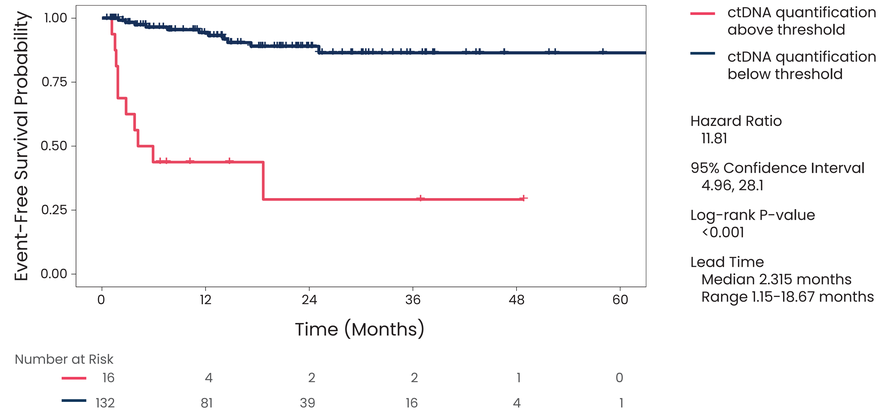
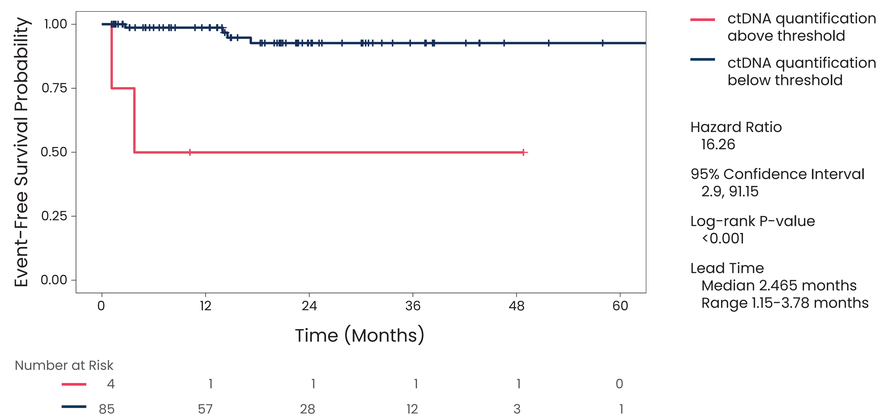


Figure 3. Stages I-III Kaplan–Meier Analysis Depicting Event-Free Survival

Individuals were stratified on the basis of ctDNA quantification being above or below the 95% specificity cutoff.



CONCLUSIONS

- This data demonstrates the feasibility of using a blood-based genome-wide methylome enrichment platform for ctDNA quantification and determining prognostic performance in RCC.
- The performance observed here represents a promising demonstration of prognostication in a cancer type that is typically difficult to detect due to low amounts of ctDNA.
- In addition, the assay utilized here is tumor-naive, meaning patient-specific tumor tissue is not required to generate a bespoke panel for ctDNA detection.
- This study utilized samples that were collected prior to treatment. Additional evaluation in post-treatment and longitudinal samples are necessary to evaluate the utility of this genome-wide methylome enrichment platform for MRD detection and recurrence monitoring in RCC.

CONTACT INFORMATION

Please contact Brian Rini (brian.rini@vumc.org) or Daniel De Carvalho (daniel.decarvalho@adelabio.com) with questions about this poster.

DISCLOSURES

The study was funded by Adela, Inc. Brian Rini has received research funding (to institution) from Pfizer, Hoffman-LaRoche, Incyte, AstraZeneca, Seattle Genetics, Arrowhead Pharmaceuticals, Immunomedics, BMS, Mirati Therapeutics, Merk, Surface Oncology, Aravive, Exelixis, Jannsen, Pionyr, and AVEO. Dr. Rini is a consultant for BMS, Pfizer, GNE/Roche, Aveo, Synthorx, Merck, Corvus, Surface Oncology, Aravive, Alkermes, Arrowhead, Shionogi, Eisai, Nikang Therapeutics, EUSA, Athenex, Allogene Therapeutics, and Debiopharm. Dr. Rini has stock in PTC therapeutics.

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