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Performance of a Multi-Cancer Early Detection (MCED) Test for Detection of Hepatocellular Carcinoma (HCC) in Patients with Cirrhosis

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INTRODUCTION

- HCC is the third leading cause of cancer-related deaths in the world, with HCC-related deaths increasing in the United States[1,2]
- More than 80% of HCC cases develop in the setting of cirrhosis, informing the at-risk cohort for surveillance[3]
  - The American Association for the Study of Liver Diseases (AASLD) recommends HCC surveillance in individuals with cirrhosis through ultrasound imaging with alpha-fetoprotein (AFP) testing every 6 months[4]
- Most HCCs are found at later stages, highlighting a need for novel surveillance strategies[5]
- Additionally, increasing data show heterogeneity in tumor biology and treatment response, highlighting a need for treatment response biomarkers[6]
- A blood-based MCED test (Galleri®, GRAIL, LLC, Menlo Park, CA) that uses a targeted methylation assay and a machine learning algorithm to detect a shared cancer signal and predict cancer signal origin (CSO) using circulating cell-free DNA across cancer types is available as a complement to existing single-cancer screening tests[7-9]
  - When a cancer signal is detected, a "cancer signal detected" result is reported with one to two CSO prediction(s) to direct diagnostic workup

OBJECTIVE

- In this pilot study, we explored the potential of the MCED test to detect HCC in patients with cirrhosis and its association with treatment response

METHODS

- Starting from 2016, plasma samples were collected from patients recruited and consented by a team of research coordinators when being seen in Liver or Liver Cancer clinics at University of Texas Southwestern or Parkland Health
- In this case-control study, the biobanked plasma was processed from treatment-naïve patients aged >18 years, with Eastern Cooperative Oncology Group Performance Status 0-1, and with cirrhosis without uncontrolled ascites or hepatic encephalopathy
  - Cases were defined as patients with confirmed, treatment-naïve HCC (diagnosed radiographically or histologically)
    - HCC patients were identified using guideline-concordant imaging criteria (ie, Liver Imaging Reporting and Data System 5 lesion), which has been shown to have >95% positive predictive value for HCC
  - Controls were defined as patients without confirmed HCC (but with cirrhosis)
- Cases and controls were matched on liver disease etiology, Child Pugh score, and Barcelona Clinic Liver Cancer (BCLC) stage
- Test performance for HCC detection was assessed blinded to case-control status
- Potential for predicting treatment response was assessed as an exploratory analysis

SUPPORTING DATA

- In the third and final Circulating Cell-free Genome Atlas substudy (NCT02889978), the MCED test was validated; the test detected a shared cancer signal with a specificity of 99.5% and a sensitivity of 51.5% and predicted CSO with an accuracy of 88.7%[9]
  - Sensitivity of cancer signal detection was high in liver/bile duct cancer[9] (**Table S1**)

Table S1. Sensitivity of Cancer Signal Detection in Liver/Bile Duct Cancer by Stage in CCGA Substudy 3

Clinical stage	Total	Test positive	Sensitivity (95% CI)
All	46	43	93.5% (82.5%–97.8%)
I	6	6	100.0% (61.0%–100.0%)
II	10	7	70.0% (39.7%–89.2%)
III	9	9	100.0% (70.1%–100.0%)
IV	20	20	100.0% (83.9%–100.0%)
Missing	1	1	100.0% (5.1%–100.0%)

CCGA, Circulating Cell-free Genome Atlas; CI, confidence interval.

KEY RESULTS: THE MCED TEST'S PERFORMANCE SHOWS ITS POTENTIAL FOR HCC DETECTION AND ASSOCIATION WITH TREATMENT RESPONSE

Baseline Demographics and Clinical Characteristics

- Forty-four patients with cirrhosis (HCC cases, n=27; noncancer controls, n=17) were included in this pilot study
- There were no significant differences in baseline demographics and clinical characteristics between cases and controls (**Table 1**)
  - Median age was 63 years and 59% of patients were male
  - Patients were diverse regarding race/ethnicity and cirrhosis etiology
  - 66% and 34% of patients had Child Pugh A and B cirrhosis, respectively
- HCC cases were diverse in terms of BCLC stage and Milan Criteria

Table 1. Baseline Demographics and Clinical Characteristics

	Cases (n=27)	Controls (n=17)	Overall (N=44)
Median age, years	64	60	63
Male, n (%)	18 (67)	8 (47)	26 (59)
Race/ethnicity, n (%)			
Non-Hispanic White	10 (37)	6 (35)	16 (36)
Hispanic	9 (33)	7 (41)	16 (36)
Black	8 (30)	4 (24)	12 (27)
Cirrhosis etiology, n (%)			
Hepatitis C virus	14 (52)	8 (47)	22 (50)
Hepatitis B virus	1 (4)	1 (6)	2 (5)
MASLD	7 (26)	4 (24)	11 (25)
Alcohol-associated	5 (19)	4 (24)	9 (20)
Child Pugh score, n (%)			
A	18 (67)	11 (65)	29 (66)
B	9 (33)	6 (35)	15 (34)
BCLC stage, n (%)			
O/A	11 (41)	–	–
B	16 (59)	–	–
Within Milan criteria[a], n (%)	11 (41)	–	–

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease.
[a](1) A single HCC nodule ≤5 cm or up to three nodules with the largest ≤3 cm and (2) no macrovascular invasion[10]

MCED Test Performance by Case/Control Status

- MCED test sensitivity and specificity of cancer signal detection was 78% and 100%, respectively (**Table 2**)
- CSO prediction accuracy was 100%
  - All cases with a cancer signal detected had a CSO prediction of liver/bile duct

Table 2. Sensitivity and Specificity of Cancer Signal Detection

	Cases (n=27)	Controls (n=17)
Cancer signal detected	21	0
No cancer signal detected	6	17
	Sensitivity = 21/27 = 78%	**Specificity = 17/17 = 100%**

MCED Test for Predicting Treatment Response

- All cases underwent transarterial chemoembolization (TACE) as initial HCC treatment
- The MCED test detected a cancer signal in 67% of cases with an objective response to TACE and 87% of those with progressive disease (p=0.24) (**Table 3**)

Table 3. Sensitivity of Cancer Signal Detection by Treatment Response

	Cases with an objective response to TACE (n=12)	Cases with progressive disease after TACE (n=15)
Cancer signal detected	8	13
No cancer signal detected	4	2
	Sensitivity = 8/12 = 67%	**Sensitivity = 13/15 = 87%**

TACE, transarterial chemoembolization.

CONCLUSIONS

- Our pilot data suggest that the MCED test is a potential tool for HCC detection and treatment management
  - The test has potential value as a **noninvasive blood test for HCC detection** in patients at high risk for HCC (eg, patients with cirrhosis)
  - The test, with further research and optimization, has potential value as an **HCC treatment management tool** that uses signal detection as a treatment response biomarker
- The results of this pilot study are preliminary and a larger longitudinal study is needed to confirm results

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