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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

- Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality worldwide[1]
- 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[2]
- However, most HCCs are still found at later stages, highlighting a need for novel early detection strategies[3]
- Additionally, heterogeneity in HCC tumor biology and treatment response highlight a need for prognostic biomarkers[4]
- A blood-based multi-cancer early detection (MCED) test (Galleri,® GRAIL, Inc, 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 has been validated in a large-scale observational study (Circulating Cell-Free Genome Atlas, CCGA) and a multi-center interventional study (PATHFINDER)[5,6]
  - In the third and final CCGA substudy (NCT02889978), the MCED 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%[5]
  - Sensitivity of cancer signal detection was high in liver/bile duct cancer[5]
    - The overall sensitivity of cancer signal detection in liver/bile duct cancer in CCGA substudy 3 was 93.5% (95% CI: 82.5%-97.8%), and sensitivity by stage was 100.0% (61.0%-100.0%), 70.0% (39.7%-89.2%), 100.0% (70.1%-100.0%), and 100.0% (83.9%-100.0%) for stages I, II, III, and IV, respectively[5]

OBJECTIVE

- In this pilot study,[7] we explored the potential of the MCED test to detect HCC at an early stage in patients with cirrhosis

METHODS

- Biobanked K2EDTA 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 starting in 2016
- 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 treatment-naïve HCC (diagnosed histologically or radiographically)[2]
  - Controls were defined as those with cirrhosis but without confirmed HCC
- Cases and controls were matched on liver disease etiology and Child-Pugh score
- Samples were analyzed blinded to case-control status at GRAIL Clinical Laboratory (Menlo Park, CA)
- Subgroup analyses were stratified by Barcelona Clinic Liver Cancer (BCLC) stage,[9] liver disease etiology, and HCC treatment response (per modified RECIST), with sensitivities compared using the Chi-square test

KEY RESULTS: THE MCED TEST SHOWS PROMISE AS A NONINVASIVE BLOOD TEST FOR HCC SURVEILLANCE IN HIGH-RISK PATIENTS

Baseline Demographics and Clinical Characteristics

- We identified 44 patients (HCC cases, n=27; cirrhosis controls, n=17) who met inclusion criteria
- There were no substantial differences in 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 and ethnicity and liver disease etiology
  - Most patients had preserved liver function
- HCC cases included 41% BCLC stage 0/A (all within Milan Criteria) and 59% BCLC stage B

Table 1. Baseline Demographics and Clinical Characteristics

	HCC cases (n=27)	Cirrhosis 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 (%)			
Child Pugh A	18 (67)	11 (65)	29 (66)
Child Pugh B	9 (33)	6 (35)	15 (34)
BCLC stage, n (%)			
BCLC stage 0/A	11 (41)	–	–
BCLC stage 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]Single HCC nodule ≤5 cm or up to three nodules with the largest ≤3 cm, without macrovascular invasion or distant metastases.[8]

MCED Test Performance

- The MCED test detected a cancer signal in 78% (95% CI: 58%-91%) of HCC cases and none of the cirrhosis controls (**Table 2**)
  - The test detected a cancer signal in 55% (95% CI: 23%-83%) of cases with early-stage (BCLC stage 0/A) HCC and 94% (95% CI: 70%-100%) of those with BCLC stage B HCC
  - Test sensitivity was similar between HCC cases with viral (80% [95% CI: 52%-96%]) and non-viral (75% [95% CI: 43%-95%]) liver disease
- First CSO prediction (liver/bile duct) was correct for 100% (95% CI: 84%-100%) of cases with a cancer signal detected

MCED Test for Predicting Treatment Response

- All cases underwent transarterial chemoembolization (TACE) at the study sites as initial treatment
- The MCED test detected a cancer signal in 67% of cases with an objective radiographic response and 87% of those with progressive disease (*p*=0.24) (**Table 2**)
  - When stratified by BCLC stage, sensitivity appeared higher in patients with progressive disease versus objective response (BCLC 0/A, 67% vs 40%; BCLC B, 100% vs 86%; respectively)

Table 2. MCED Test Sensitivity

	Patients with cancer signal detected	Total patients	Sensitivity
HCC cases	21	27	78%
Stratified by BCLC stage			
BCLC stage 0/A	6	11	55%
BCLC stage B	15	16	94%
Stratified by liver disease etiology			
Viral etiology	12	15	80%
Non-viral etiology	9	12	75%
Stratified by HCC treatment response			
With objective response to TACE	8	12	67%
With progressive disease to TACE	13	15	87%

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

CONCLUSIONS

- Results of this pilot case-control study[7] suggest that the MCED test shows promise as a blood-based biomarker for HCC surveillance in high-risk patients
- The MCED test sensitivity and specificity of cancer signal detection were 78% and 100%, respectively, and CSO prediction accuracy was 100%; sensitivity for early-stage HCC was lower at 55%
- Notably, the MCED test is capable of detecting other cancer types besides HCC through a shared cancer signal[5]
- The results of this pilot study[7] are preliminary and larger longitudinal studies are warranted to confirm these results

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Disclosures

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