ST177

Validation of a Reflex cfDNA Methylation-based Multi-Cancer Early Detection (MCED) Blood Test in Individuals with Obesity

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BACKGROUND

Obesity affects over 40% of U.S. adults and is a well-established risk factor for at least 13 types of cancer, including esophagus, gallbladder, stomach, liver and pancreas.[1,2] Individuals with obesity experience lower cancer screening rates, are more likely to present with advanced-stage disease and are at greater risk of poor clinical outcomes.[3-5] Multi-cancer early detection (MCED) testing provides a non-invasive opportunity to accelerate cancer detection in individuals with obesity, a group underserved by current screening paradigms.

OBJECTIVES

The Cancer ORigin Epigenetics-Harbinger Health (CORE-HH) study (NCT05435066) is a multi-cancer prospectively enrolled case-control study. Using a blinded validation dataset from this study, we evaluated the performance of a ctDNA methylation-based MCED test in individuals aged 45–79 with obesity (BMI ≥ 30 kg/m^2).

METHODS & MATERIALS

Peripheral blood samples (NCT05435066) from individuals aged 45–79 with obesity (BMI ≥ 30 kg/m^2) who were either treatment-naïve cancer patients (N = 142) or individuals with no reported cancer (N = 454) were analyzed using a sequential reflex test by Harbinger Health. As previously described,[6] the primary test profiles ctDNA methylation for cancer signal detection; initial non-negative samples proceed to a reflex test analyzing a broader set of biomarkers for cancer signal confirmation and tissue-of-origin (TOO) localization.

We report the estimates and confidence intervals (CIs) for the MCED test's specificity, and for each cancer type, conventional sensitivity (the probability of detecting a cancer signal when cancer is present, regardless of TOO) and the clinically meaningful metric of intrinsic accuracy (the probability of correct TOO readout category for a given cancer type).[7]

In a modeled cohort of 100,000 individuals derived using SEER 22 cancer incidence values for age >50 years with an overall incidence of 1.6%, the expected number of cases was obtained. For each case-type, the expected number that are detected by the test was calculated using estimates of the test's cancer-specific intrinsic accuracy.

RESULTS

Table 1. Cohort demographics summary.

Characteristics	Cancer (N = 142)	Non-Cancer (N = 454)
Sex		
Female	64 (45.1%)	244 (53.7%)
Male	78 (54.9%)	210 (46.3%)
Age (Years)		
Mean (SD)	67.1 (7.5)	62.3 (8.9)
Race		
White	125 (88.0%)	320 (70.5%)
Black or African American	6 (4.2%)	55 (12.1%)
Asian	0 (0.0%)	2 (0.4%)
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)
Native Hawaiian or other Pacific Islander	3 (2.1%)	0 (0.0%)
Other race	2 (1.4%)	6 (1.3%)
Unknown/Missing/Not reported	6 (4.2%)	71 (15.6%)
Ethnicity		
Not Hispanic/Latino	119 (83.8%)	355 (78.2%)
Hispanic/Latino	11 (7.7%)	27 (5.9%)
Unknown/Missing/Not reported	12 (8.5%)	72 (15.9%)
BMI (kg/m^2)		
Median [IQR]	33.8 [31.8, 36.8]	34.4 [32.1, 38.9]
(Min, Max)	(30.1, 48.5)	(30.0, 62.5)

Table 2. Performance of reflex testing strategy for cancer detection.

Characteristics	All stages	Stage I+II
Specificity (95% CI)	98.5 (97.0-99.3)	
Conventional Sensitivity	60.6 (52.4-68.3)	35.3 (24.7-47.2)
Intrinsic Accuracy (95% CI)		
All cancers	47.9 (39.8-56.1)	30.9 (21.0-42.9)
Lung	39.4 (28.8-51.2)	15.2 (6.4-31.9)
Head & Neck	66.7 (47.0-81.8)	66.7 (39.6-85.9)
Hepatobiliary	80.5 (23.2-98.3)	100.0 (22.4-100.0)
Pancreatobiliary	50.0 (27.9-72.1)	25.0 (5.6-65.3)
Upper GI	42.9 (23.7-64.5)	20.0 (4.6-56.4)

Figure 1. Distribution of cancer types and stages in the study. Vertical axis representing the total number of cases for each cancer type, stratified by stage.

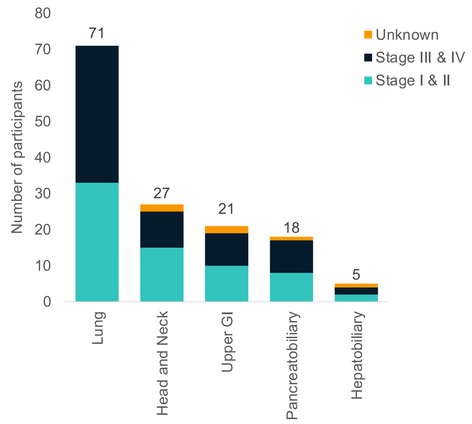
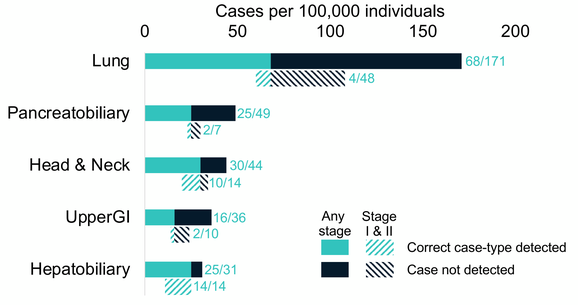


Figure 2. Case-type detection. Estimated number of cases detected by MCED test with correct TOO readout by case type using SEER22 incidence estimates in a modeled cohort of 100,000 individuals over 50 years of age. Proportion of correct cases for each readout are shown.



DISCUSSION & CONCLUSIONS

- The circulating tumor DNA (ctDNA)-based reflex screening test for early detection of multiple cancers based upon DNA methylation signature derived from developmental biology addresses an unmet need for population-level early detection by interrogating cancers without screening programs, particularly among individuals with obesity, where cancer risk is elevated and underserved by current clinical guidelines.
- The observed 98.5% specificity and 60.6% overall conventional sensitivity achieved represents an important benchmark for population screening in individuals with obesity.
- High performance was observed for solid cancers with either low screening adherence or lacking organized screening programs (e.g., pancreaticobiliary, hepatobiliary), highlighting a critical clinical gap the test could address. For hepatobiliary cancers, the identification of 25 of 31 cases (including 14 of 14 early-stage cases) in a modeled 100,000-person cohort represents a meaningful shift from typically late-stage diagnosis to earlier intervention opportunities.
- The non-invasive format of MCED testing is less affected by body habitus relative to other cancer screening methods and may help reduce barriers related to physical discomfort, stigma and procedural avoidance. Given the elevated risk of cancer in individuals with obesity, MCEDs present a valuable approach to enhance screening equity and enable earlier intervention.
- These results underscore the potential for this MCED test to address a critical gap in early detection and merit prospective evaluation in diverse populations and real-world settings.

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DISCLOSURES

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