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Validation of a Reflex cfDNA Methylation-based Multi-Cancer Early Detection (MCED) Blood Test for Tumors Lacking Routine Screening in Asymptomatic Adults

Harbinger Health

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BACKGROUND

Screening programs are known to reduce mortality in colorectal, breast, and cervical cancers; however, most solid tumors, including gastric, pancreatic, biliary, ovarian, and head and neck, lack population-based screening despite a potential stage-dependent survival benefit. Even where screening programs exist, uptake can be low, such as for low-dose CT for lung, limiting impact on population health. These gaps drive late-stage diagnoses and high cancer mortality.

Circulating cell-free DNA (cfDNA) methylation profiling detects tumor-derived epigenomic signals across multiple cancer types from a single blood draw. Multi-cancer early detection (MCED) tests based on this approach can expand screening to cancers without established protocols and complement current methods.[1] Integration of MCED testing into routine clinical care offers the potential to detect high-mortality cancers earlier, reduce missed diagnoses, and expand the reach of early detection to cancers that currently lack screening options.[2]

OBJECTIVES

The Cancer Origin Epigenetics–Harbinger Health (CORE-HH) study (NCT05435066) prospectively enrolled adults aged 45–80 using a case-control design to evaluate a cfDNA methylation-based multi-cancer early detection (MCED) test.

Our objective was to evaluate the performance of a reflex cfDNA methylation–based multi-cancer early detection (MCED) workflow for high-mortality cancers lacking established screening options (hepatobiliary, pancreatobiliary, upper gastrointestinal, head and neck), and for lung cancer where LDCT is recommended but underutilized.

METHODS & MATERIALS

Peripheral blood samples were used to train predictive models on over 5,000 specimens, with blinded validation conducted in a mutually exclusive cohort of adults aged 45–80 (464 treatment-naïve cancer patients and 1049 non-cancer controls). A two-step testing workflow was applied: a primary test optimized for sensitivity to identify cancer signal, followed by reflex testing with a broader biomarker panel for high-specificity tissue-of-origin (TOO) classification. Performance metrics included specificity, crude sensitivity (probability of cancer signal detection irrespective of TOO), and intrinsic accuracy (probability of correct TOO classification by cancer type).[2]

RESULTS

Table 1. Cohort demographics summary.

Characteristics	Cancer (N=464)	Non-Cancer (N=1049)
Sex		
Female	194 (41.8%)	571 (54.4%)
Male	270 (58.2%)	478 (45.6%)
Age (Years)		
median [IQR]	67.5 [IQR 62,73]	64.0 [58,70]
Race		
White	375 (80.8%)	748 (71.3%)
Black or African American	33 (7.1%)	104 (9.9%)
Asian	6 (1.3%)	12 (1.1%)
American Indian or Alaska Native	6 (0.6%)	5 (0.5%)
Native Hawaiian or other Pacific Islander	4 (0.9%)	2 (0.2%)
Other Race	12 (2.6%)	11 (1.0%)
Unknown/Missing/Not reported	31 (6.7%)	167 (15.9%)
Ethnicity		
Not Hispanic/Latino	385 (83.0%)	837 (79.8%)
Hispanic/Latino	39 (8.4%)	50 (4.8%)
Unknown/Missing/Not reported	40 (8.6%)	162 (15.4%)

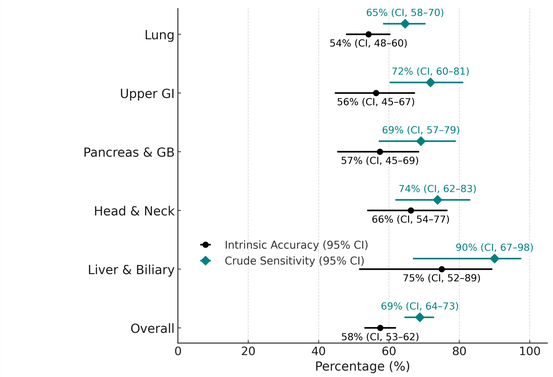
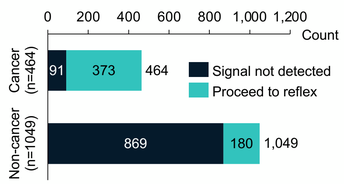
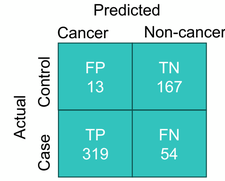


Figure 2. Crude sensitivity and intrinsic accuracy across cancer types with 95% confidence intervals (CI). Diamonds represent sensitivity, and circles represent intrinsic accuracy. Lines represent 95%CI. ***Additional findings:** Overall TOO accuracy (the mean, across cancer types, of the proportion of cancer-positive samples correctly classified by their true cancer type) was 83.6%. Discordant Head & Neck and Upper GI (Esophagus, esophagogastric junction, stomach) cases (6/7) were squamous cell carcinomas; among never-smokers outside USPSTF LDCT eligibility, intrinsic accuracy for early-stage lung cancer was 16.7%.* Abbreviations: GI, gastrointestinal; GB, gallbladder.

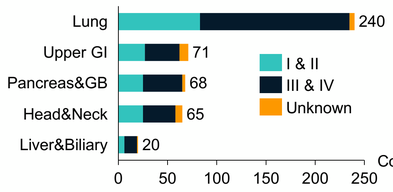
A. Primary testing outcomes (N=1513)



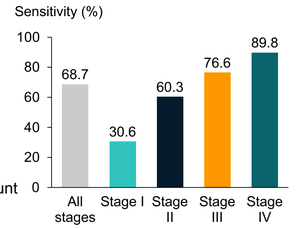
B. Reflex testing performance (N=553)



C. Distribution of cancer cases by stage



D. Crude sensitivity at 98.7% overall achieved specificity



E. Crude sensitivity per cancer group and stage

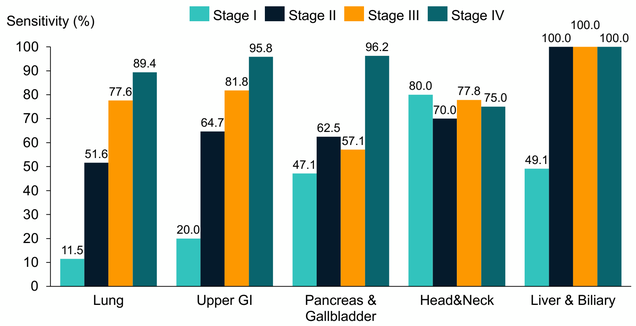


Figure 1. Two-step sequential testing. The primary test advanced 553/1513 (36.6%) to reflex, 373/464 (80.4%) cancers and 180/1,049 (17.2%) non-cancers (panels A-B). The test achieved 98.7% specificity, and early-stage sensitivity was 30.6% for Stage I and 60.3% for Stage II (panels C-D). Across cancer groups (panel E), Stage I sensitivity ranged from 11.5% (lung) to 80.0% Head&Neck); Stage II ranged from 51.6% (lung) to 100% (liver/biliary). Lung was the largest cancer cohort (n=240). Abbreviations: TP, true positive; FP, false positive; FN, false negative; TN, true negative. GI, gastrointestinal; GB, gallbladder

DISCUSSION

- The Harbinger cfDNA methylation–based MCED assay demonstrated high specificity (98.7%) across a diverse validation cohort, supporting its feasibility for population-level application where minimizing false positives is essential. Sensitivity was clinically meaningful overall (68.7%) and for early-stage disease (Stage I 30.6%; Stage II 60.3%). Performance was particularly strong in cancers lacking established screening programs, including hepatobiliary and upper gastrointestinal malignancies, highlighting the potential of MCED to address unmet needs in lethal cancers where early detection strategies are absent or underutilized.
- Intrinsic accuracy ranged from 54% to 75% across tumor types, with the strongest performance in hepatobiliary cancers. Lower accuracy in lung, upper GI, and pancreatobiliary tumors, particularly in early-stage disease, underscores areas for continued refinement. Discordance was concentrated in squamous cell carcinomas spanning head and neck and upper GI sites, reflecting biological overlap that remains a technical challenge for tissue-of-origin classification in methylation-based assays.
- From a clinical perspective, these findings establish a foundation for integrating reflex MCED into preventive care frameworks. High specificity and meaningful early-stage detection across several high-mortality cancers demonstrate the potential to complement guideline-based screening and expand early detection to previously unscreened populations. Further prospective evaluation, with attention to implementation in asymptomatic adults and alignment with existing screening infrastructures, will be critical to realizing the broader public health and equity benefits of this approach.

CONCLUSIONS

This blinded validation of a reflex cfDNA methylation–based MCED assay achieved 98.7% specificity and meaningful sensitivity for cancers without screening and for lung cancer, where LDCT is underused. The sequential workflow enabled detection across tumor types and stages, including early disease. These results support the feasibility of incorporating reflex MCED testing into preventive care for asymptomatic adults. By extending early detection beyond cancers with established programs, this approach provides a scalable strategy to intercept lethal tumors at treatable stages, reduce gaps in current screening, and inform population-level efforts to improve outcomes and promote health equity.

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DISCLOSURES

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