LB252

Novel performance quantification of MCED testing to aid clinical decisions:
Analysis of a sequential reflex blood-based methylated ctDNA test

Harbinger Health

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BACKGROUND

Circulating tumor DNA (ctDNA) offers promising non-invasive cancer detection via liquid biopsy. Multi-cancer early detection (MCED) tests can screen multiple cancers simultaneously from blood samples. However, current evaluations report aggregate performance metrics that mask biological heterogeneity in ctDNA shedding across cancer types, stages, and molecular profiles.

Aggregate performance metrics obscure cancer-specific test performance, creating a critical knowledge gap that impedes proper assessment of clinical validity and utility for individual cancer types—ultimately hindering appropriate implementation of MCED technologies in clinical practice.

OBJECTIVES

The Cancer ORigin Epigenetics-Harbinger Health (CORE-HH) study (NCT05435066) was a multi-cancer prospectively enrolled case-control study that evaluated a novel sequential reflex ctDNA-based test. Using this study, we aimed to define a framework for performance assessment of MCED tests that produces metrics that are clinically meaningful and actionable. We define a statistical analysis framework that provides estimation and inference for:

1. The specificity and the intrinsic accuracy (sensitivity) of the MCED test ***for each individual cancer type***
2. The negative predictive value (NPV) and the positive predictive value (PPV) ***for each tissue of origin (TOO) test classification***

This cancer-specific analytical approach provides a clinically meaningful and informative assessment of MCED performance, enabling proper implementation of strategies that account for performance variability across cancer types and test readouts.

METHODS & MATERIALS

Peripheral blood samples (NCT05435066) from treatment-naïve cancer patients (N=1057) and individuals with no reported cancer (N=957) were analyzed using a sequential reflex test by Harbinger Health. The primary test profiles ctDNA methylation for cancer signal detection; non-negative samples proceed to a Reflex Test analyzing a broader set of biomarkers for cancer signal confirmation and TOO localization. Test performance was established using 10-fold cross-validation with patient-level splits. Cancer incidence for age>50 was estimated at 1.32% based on SEER 22 data. Prospective PPV was calculated using cancer-specific intrinsic accuracy estimated from the case-control study in combination with SEER incidence values.

RESULTS

Characteristics	Cancer (N=1057)	Non-Cancer (N=957)
Sex		
Female	600 (56.8%)	634 (66.2%)
Male	457 (43.2%)	323 (33.8%)
Age (Years)		
Mean (SD)	62.5 (11.18)	52.5 (15.29)
(Min, Max)	20, 79	20, 79
Race		
White	825 (78.1%)	619 (64.7%)
Black or African American	91 (8.6%)	251 (26.2%)
Asian	12 (1.1%)	28 (2.9%)
American Indian or Alaska Native	9 (0.9%)	1 (0.1%)
Native Hawaiian or other Pacific Islander	2 (0.2%)	2 (0.2%)
Two or more Races	5 (0.5%)	6 (0.6%)
Other Race	21 (2.0%)	15 (1.6%)
Unknown/Missing/Not reported	92 (8.7%)	35 (3.7%)
Ethnicity		
Not Hispanic/Latino	863 (81.6%)	831 (86.8%)
Hispanic/Latino	89 (8.4%)	100 (10.4%)
Unknown/Missing/Not reported	105 (9.9%)	26 (2.7%)

Table 1. Cohort demographics summary.

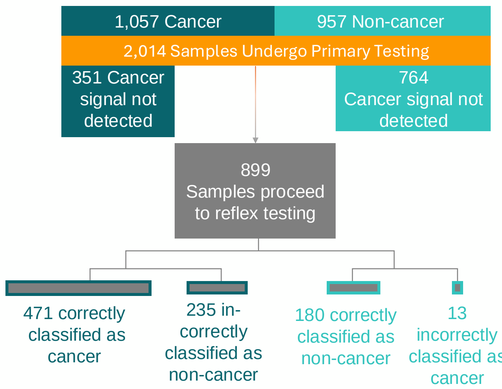

Figure 2. Performance of a sequencing liquid biopsy testing strategy for cancer detection. Data flow diagram illustrating progression of 2,014 samples (1,057 cancers and 957 non-cancers) through primary and reflex testing. The test achieved an overall sensitivity of 44.6% (471/1,057) and a specificity of 98.6% (944/957).

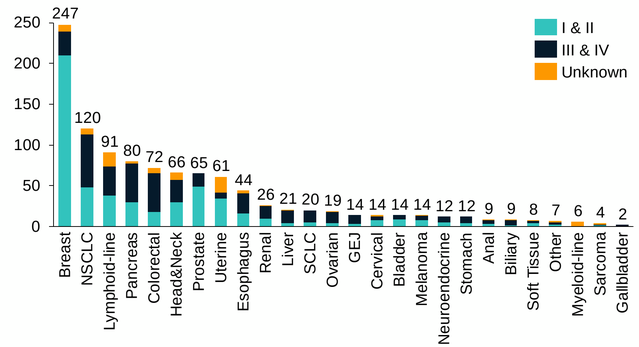

Figure 1. Distribution of cancer types and stages in the study. Vertical axis representing the total number of cases for each cancer type, stratified by stage

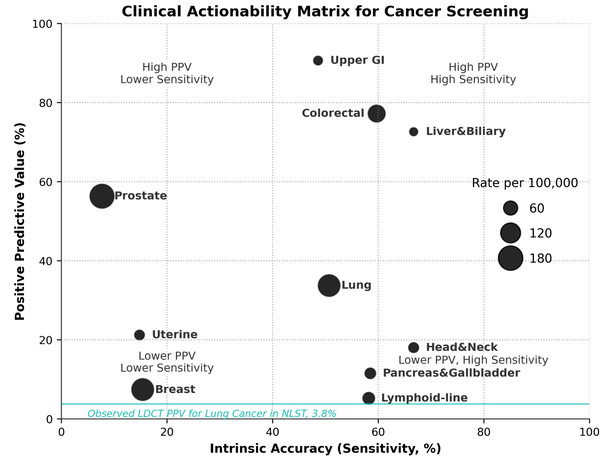

Figure 3. Performance and clinical actionability matrix. This matrix plots intrinsic accuracy (proportion of correct TOO readout category among cases of a specific cancer type) against TOO-specific PPV (proportion of correct cancer case-types among all those with a specific TOO readout) for the 10 cancer groups reported by our MCED. The upper right quadrant represents ideal screening performance with both high intrinsic accuracy and PPV. Bubble size represents cancer incidence per 100,000 according to SEER 22.

DISCUSSION

- The 98.6% specificity achieved (Figure 2) represents an important benchmark for population screening, substantially reducing false positives that could lead to unnecessary procedures, patient anxiety, and healthcare resource strain.
- This MCED test shows particular promise for cancers currently lacking organized screening programs. For pancreaticobiliary cancers, the identification of 32 of 49 cases (including 2 of 7 early-stage cases) in a modeled 100,000-person cohort represents a meaningful shift from typically late-stage diagnosis to earlier intervention opportunities. Similarly, for hepatobiliary cancers, the combination of 73% PPV and 60% early-stage sensitivity offers a favorable risk-benefit profile for a population that typically faces high mortality due to late detection.
- TOO-specific PPVs provide valuable guidance for clinical risk-benefit assessment (Figure 3). Cancers with very high PPVs—upper GI (91%), colorectal (77%), and hepatobiliary (73%)—demonstrate exceptionally favorable risk-benefit profiles, as the high likelihood of true disease minimizes unnecessary interventions. Notably, lung cancer's 34% PPV substantially exceeds the established 3.8% PPV from the NLST study, suggesting a potentially improved risk-benefit profile compared to current lung screening standards.
- The odds {PPV/(1-PPV)} for correct classification offer a practical framework for risk stratification and patient counseling. The 10:1 odds for upper GI cancer from an upper GI TOO readout suggests a highly favorable risk-benefit ratio for patients with this signal, while the 1:8 odds for pancreaticobiliary cancer indicates a more balanced risk-benefit profile where clinical judgment becomes particularly important in weighing the impact of unnecessary workup compared to identifying high mortality cancer.
- The proposed analysis framework enables modeling of downstream healthcare utilization, critical for health systems and payers evaluating the comprehensive economic impact of implementing the test to aid in decision making.

CONCLUSIONS

This analytical framework quantifies misclassification rates for each TOO readout, informing diagnostic pathways. It supports MCED test optimization, standardizes cross-platform comparisons, and clarifies follow-up risk-benefit tradeoffs—potentially expediting diagnosis, lowering costs, and improving equity. The reported sequential reflex test demonstrates high performance for early cancer detection and localization, warranting prospective validation in diverse populations. These insights support strategic deployment of MCED in high-risk populations and provide a path toward more personalized screening.

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DISCLOSURES

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