Multi-Cancer Early Detection Test Sensitivity for Cancers With and Without Current Population-Level Screening Options

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INTRODUCTION

- Amongst the causes of the reduction of cancer mortality in recent decades are decreased smoking, improvements in treatment, and earlier cancer detection through screening.[1]
- Population screening is currently recommended by the United States Preventive Services Task Force (USPSTF) for four main cancers (breast, cervical, colorectal, and, upon discussion with a physician, prostate).[2,3]
- More than two-thirds of cancer-related deaths are due to cancers without screening tests.[4,5]
  - Solid tumors without screening tests include pancreatic, esophageal, and gastric cancers.
  - There are no recommended screening options for cancer types of hematologic origin, despite the fact that leukemia, lymphoma, and myeloma are expected to collectively account for 9% of all US cancer deaths in 2020.[1]
- A new type of test, called a multi-cancer early detection (MCED) test, can detect cancer signals across >50 types of cancer, including both heme and solid tumors, with a single blood draw.[6,7]
- MCED testing has the potential to address the gap not met by current cancer screening and may reduce cancer mortality.
- Previous publication of the Circulating Cell-free Genome Atlas (CCGA; NCT02889978) third substudy showed overall sensitivity of 51.5%, specificity of 99.5%, and true positive cancer signal origin prediction accuracy of 89% for the MCED test.[7]

OBJECTIVE

- To examine MCED test performance in hematologic cancers and in solid cancers with and without screening, using data from the CCGA third substudy.[7]

RESULTS: MCED TEST MAY COMPLEMENT EXISTING SCREENING AND CAN DETECT DEADLY CANCERS WITHOUT SCREENING OPTIONS

- A total of 2794 cancer participants were included in this post-hoc analysis
  - Solid screened: 1,175
  - Solid unscreened: 1,336
  - Hematologic: 283

Overall Sensitivity

Overall sensitivity for all ages and all stages by group are given below.

- Solid screened: overall 34% (95% CI: 31%, 37%)
  - Sensitivity was >80% for cervical and colorectal cancers and <40% for prostate and breast cancers.
- Solid unscreened: overall 66% (95% CI: 63%, 68%)
  - Sensitivity was >80% in 9 cancer classes (urothelial tract, anus, ovary, pancreas, multiple primaries, esophagus, head and neck, liver/bile duct, unknown primary).
  - Sensitivity was 0% in thyroid and 18% in kidney cancers.
- Hematologic: overall 55% (95% CI: 49%, 61%)
  - Sensitivity ranged from 20% (myeloid neoplasm) to 72% (plasma cell neoplasm).

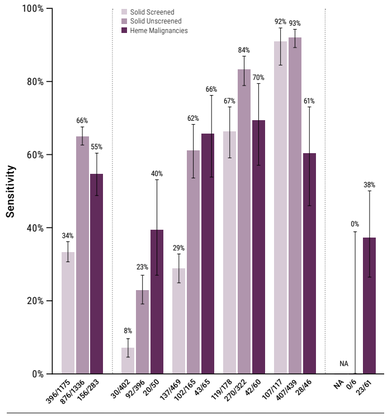
Overall sensitivity for those ≥50 years of age for all stages was similar to sensitivity for all ages.

- Solid screened: 30% (95% CI: 27%, 33%)
- Solid unscreened: 66% (95% CI: 64%, 69%)
- Hematologic: 54% (95% CI: 48%, 60%)

Overall sensitivity for all ages for clinical stages I-III is similar or slightly lower than that for all ages and all stages.

- Solid screened: 27% (95% CI: 25%, 30%)
- Solid unscreened: 52% (95% CI: 49%, 56%)
- Hematologic: 60% (95% CI: 53%, 67%)

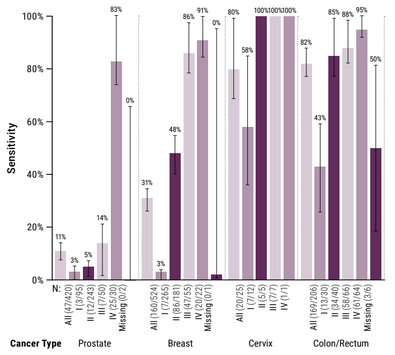
Figure 1. Sensitivity by Cancer Group and Clinical Stage



Cancer clinical stage for each group is plotted against sensitivity. Stages I-IV are plotted individually to the right. Error bars represent 95% confidence intervals. Missing indicates unavailable stage information. NE, not expected to be staged.

- Sensitivity generally increased by stage within the solid screened and solid unscreened groups and was similar across stages II-IV for the hematologic group (**Figure 1**).

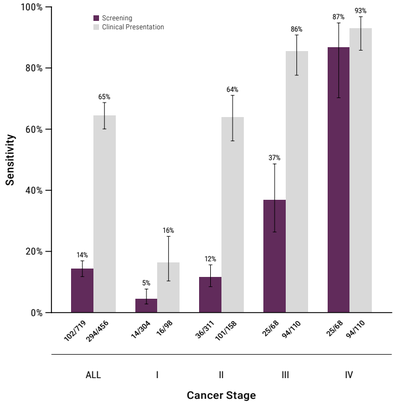
Figure 2. Sensitivity for Solid Screen Cancers by Stage



Sensitivity for solid screened cancers by cancer class and stage. Error bars represent 95% confidence intervals. Missing indicates unavailable stage information. NE, not expected to be staged.

- In cervical and colorectal cancers, cancer signals were readily detected across all stages (**Figure 2**).
- Within the solid screened cancers, prostate cancer had a sensitivity of 11% (8%, 15%) across all stages, but stage IV prostate cancer had a sensitivity of 83% (66%, 93%).
- Breast cancer also showed an overall sensitivity of 31% (27%, 35%) across all stages, but 86% (74%, 92%) and 91% (72%, 98%) in stages III and IV, respectively.

Figure 3: Solid Screened Cancers Diagnosed Through Screening or Clinical Presentation



MCED test sensitivity by stage for solid screened cancer cases that were diagnosed through screening (light green) or clinical presentation (grey). Error bars represent 95% Wilson confidence intervals.

- Across stages I-III, and particularly in stage II, this MCED test had higher sensitivity for cancer signal detection from cancers diagnosed through clinical presentation than through screening (**Figure 3**).

CONCLUSIONS

- Cancer signals were detected from cancers that lack recommended screening tests and contribute to significant cancer-related mortality, including solid cancers (eg, pancreatic, and liver and bile-duct), and cancers of hematologic origin (eg, lymphoma).[5]
- This post-hoc analysis of CCGA indicates that MCED testing has the potential to complement existing screening paradigms by detecting cancer signals for many cancers across solid and hematologic malignancies that currently have no screening recommendations.

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METHODS

CCGA Study

- The CCGA study (NCT02889978) is an observational, multi-center (142 sites across North America), case-control study that was divided into three substudies, as previously described.[6,7]
- The third and final CCGA substudy validated a MCED screening test for population use[7] and is the basis for the post-hoc analysis reported here (cancers only).
- Participants with cancer in the CCGA study were those who were either enrolled with a confirmed cancer diagnosis or high suspicion of cancer that was subsequently confirmed through a biopsy and/or surgical resection within the enrollment window.
  - Cancer diagnosis could have been prompted by routine screening or by clinical presentation.
- Blood sample collection and processing was performed as previously described[7] to extract targeted methylation data per genomic region from cell-free deoxyribonucleic acid (cfDNA) in each sample.

Post-Hoc Analysis

- Clinical data for each participant used in this post-hoc group analysis was collected from the electronic case report forms and abstracted from medical records, pathology report data, and radiology report data if available.

Class

- Cancer classes were defined as previously published.[7]

Heme Malignancy	Solid Screened	Solid Unscreened	
• Myeloid Neoplasm (Acute myeloid leukemia or chronic myeloid leukemia) • Lymphoid Leukemia • Plasma Cell Neoplasm • Lymphoma	• Breast • Cervix • Colon/Rectum • Prostate	• Anus • Bladder • Esophagus • Gallbladder • Head and Neck • Kidney • Liver/Bile-duct • Lung • Melanoma	• Ovary • Pancreas • Sarcoma • Stomach • Thyroid • Urothelial Tract • Uterus

Staging

- Clinical stage was assigned by the treating physician or a certified cancer registry professional according to the 7th or 8th edition of the AJCC Staging Manual.
- Cancers without staging classification in the manual were analyzed without staging information.

Cancer Groups

1. Solid screened: Solid cancers with USPSTF population-wide screening recommendations (breast, cervical, colorectal, and prostate cancers; note that prostate cancer is a Grade C recommendation, screening decision to be made by individual only after discussion with a physician).
2. Solid unscreened: Solid cancers without population screening (all carcinomas, sarcomas, and melanomas [excluding breast, cervical, colorectal, and prostate cancers]).
3. Heme malignancy: Hematologic cancers (myeloid neoplasms, lymphoid leukemias, lymphomas, and plasma cell neoplasms).

Sensitivity Calculations

The four sensitivity calculations presented here are:

1. Each group by cancer class.
2. Each group by clinical cancer stage.
3. Individual solid screened cancers by stage.
4. Screening versus clinical presentation cancer diagnosis in the solid screened group by stage.