Modeled Comparison of Population Blood-based Cancer Screening Approaches: Multiple Single-Cancer Early Detection Tests vs. One Multi-Cancer Early Detection Test

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INTRODUCTION

- Emerging technologies show promise to help detect the 75% of all cancer that does not yet have a recommended screening test.[1]
- The rapid expansion in capabilities for early detection has presented the need to evaluate each early detection innovation as part of a broader system of screening.
- Blood-based tests in development that may become available include (1) sensitive single-cancer tests (SCED) with moderate false positive rates (FPRs) and (2) moderately sensitive multi-cancer tests (MCED) with very low FPRs.[1]
- Although we expect that both SCED and MCED tests are part of a suite of genomic tools expected to improve cancer screening, SCED and MCED tests may be optimized for different contexts.
- Given limited resources and opportunity costs in healthcare, many experts have debated whether a supplementary system of SCED tests or an MCED system is better suited to achieve the goals of cancer screening in average risk individuals for whom screening is age-appropriate.
- We compared two hypothetical cancer screening systems (many SCED tests vs. one MCED test) for population-level impact.

OBJECTIVES

- Evaluate both hypothetical cancer screening systems, SCED and MCED, in detecting a set of 11 cancer types by:
  - Estimating effectiveness (e.g. number of cancers detected)
  - Estimating efficiency (e.g. number needed to screen [NNS], positive predictive value [PPV], true positive rate [TPR], etc)
  - Estimating costs
  - Estimating cumulative risk of false positives for an individual
- Calculate the incidence, sensitivity, and specificity required to optimize the SCED and MCED systems for effectiveness and efficiency.

METHODS

- We envisioned two hypothetical screening systems, each targeting 11 cancer types responsible for the most US cancer-related deaths (excluding prostate) (**Table 3**).
- These cancer types included lung & bronchus, breast, colorectal, pancreas, liver & biliary, esophagus, myeloid malignancy, lymphoid malignancy (including lymphoma), ovarian, urinary bladder, and uterus.
- We applied these systems to a simulated population of 100,000 aged 50–79 using Surveillance, Epidemiology, and End Results (SEER) incidence data, with 100% adherence, over one year of screening. We assumed real-world U.S. Preventative Services Task Force (USPSTF) screening is already present.

Table 3. SCED and MCED Screening System Assumptions

	SCED System	MCED System
Number of Tests	11 Single Cancer	1 Multi-cancer
Sensitivity (per test)	87%*	59%†
FPR (per test)	11%*	0.4%†
Cost (per test)	$100	$1000

*FPR, false positive rate. *Comparable to mammography. †The MCED system used a single test modeled after Klein et al. 2021, with performance limited to 11 subtypes for fair comparison (aggregate sensitivity 59% and FPR 0.4%)*

KEY RESULTS: WHILE A CANCER SCREENING SYSTEM USING A 'ONE TEST FOR ONE CANCER' APPROACH WITH MULTIPLE, HYPOTHETICAL SCED TESTS DETECTS MORE CANCERS, IT IS INEFFICIENT AND EXPENSIVE COMPARED TO AN MCED SYSTEM, DUE TO THE HIGH RATE OF FALSE-POSITIVE TESTS REQUIRING DIAGNOSTIC WORKUPS

Table 1. Number of Cancers Detected and Diagnostic Workups in Cancer-Free People for SCED vs. MCED Screening Systems

	5 USPSTF Screens	11 SCED Screens*	1 MCED Screen*
Total # of Cancers Targeted	652	492	492
Total # of Tests Performed*	70,192	949,805	99,805
Cancers Detected (CD)	195	428	300
Diagnostic Workups (DW) in People Without Cancer	8,883	115,174	397
DW/CD	46	269	1

**SCED and MCED systems are each applied after USPSTF screening*

- The hypothetical SCED screening system compared to the MCED system (**Table 1**):
  - Detected 1.4 times more of the targeted cancers (428 vs 300)
  - Incurred 289 times more diagnostic workups in cancer-free people (115,174 vs 397)
- For reference, in an average-risk population of 100,000, real-world USPSTF screening would detect 195 of the 652 cancers (colorectal, breast, cervical, lung, and prostate) and incurs 8,883 diagnostic workups in cancer-free people (**Table 1**).

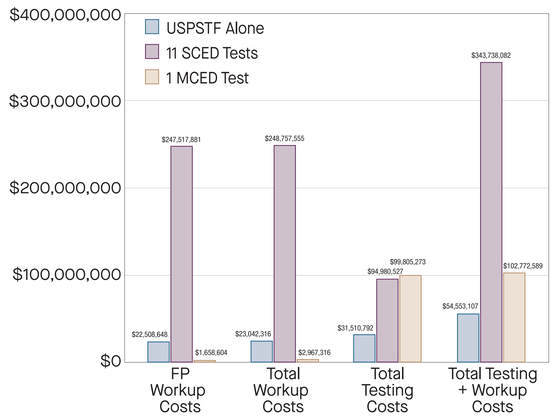
Table 2: Screening Efficiency Metrics of SCED vs. MCED Screening Systems

	5 USPSTF Screens	11 SCED Screens	1 MCED Screen
PPV	2.15%	0.37%	43.07%
NNS	360	2,219	332
TPR	30.00%	87.00%	49.00%
FPR	9.00%	80.00%	0.40%
NPV	99.90%	99.99%	99.81%

FPR, false positive rate; NNS, number needed to screen; NPV, negative predictive value; PPV, positive predictive value; TPR, true positive rate.

- A hypothetical SCED system was much less efficient than the MCED system (**Table 2**):
  - With ~100-fold lower PPV (0.4% vs 43%)
  - Incurred ~7x the number of screens needed to find one cancer (2,219 vs 332)
- For reference, real-world USPSTF screening has a PPV of 2.15% for the 5 cancers it targets and requires 360 screening tests to detect 1 cancer (**Table 2**).

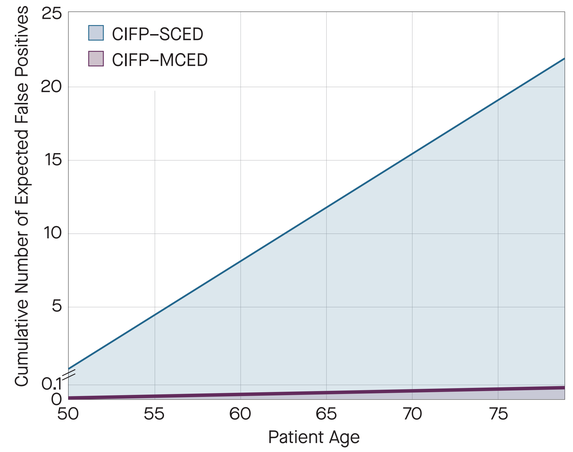
Figure 1: Screening costs per 100,000 of SCED vs. MCED Screening Systems



Workup costs are based on National Comprehensive Cancer Network Guidelines and Medicare converted to commercial costs using a 2.3 multiplier. False Positive (FP) workup costs are costs associated only with workups for false positives. All workup costs associated with MCED use a 1.5 multiplier given the expected complexity of positive MCED results. Testing costs are the direct costs of the screening tests (e.g. 1 SCED test has a $100 testing cost).

- Estimated total costs among 100,000 individuals were ~3.5 times higher ($345M and $103M, respectively) for SCED vs. MCED screening systems (**Figure 1**).
  - False positive workups accounted for most of SCED screening system costs, while costs of testing accounted for most of the MCED screening system costs.

Figure 2: Cumulative Incidence of False Positives (CIFP) per Individual in SCED vs. MCED Screening Systems



- Individuals receiving a hypothetical SCED annual screening system from ages 50–79 would be expected to receive over 21 false positives on average, compared to less than 0.12 cumulative false positives in an MCED screening system, on average (**Figure 2**).
- In order for an SCED system to be as efficient (i.e. same PPV) as an MCED system, each test would require >99.5% specificity and individuals in the screened population would need to have over 10 times average risk for each of the 11 cancers.

CONCLUSIONS

- These findings are a proof-of-principle of the sheer scale of the potential harms associated with a cancer-by-cancer screening system, compared to a multi-cancer screening system.
- An SCED screening system carries a significantly higher risk of harm (false positive result, unnecessary workups, high costs) compared to benefit (true cancer detected) for the average-risk patient — compared to an MCED screening system.
  - This is concordant with real-world evidence on cancer screening harms; the Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) trial demonstrated that for an individual in cancer-by-cancer screening, the cumulative risk of a false positive is greater than 50% by the 14th screen.[2]
- This modeling study demonstrates an MCED system may be more efficient in average-risk screening contexts.
- Screening effectiveness and efficiency would be even better for an MCED system (agnostic to test signal or cancer incidence) that could detect a greater number of individually rare cancer types.

References

1. American Cancer Society. *Cancer facts & figures 2022*. Atlanta (GA): American Cancer Society; 2019. Available from: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2022.html (Accessed October 1, 2022)
2. Croswell JM et al. *The Annals of Family Medicine*. 2009;7(3):212–222.

Disclosures

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