Leveling the Playing Field When Comparing Multi-Cancer Early Detection (MCED) Tests: Weighting by Cancer Type and Stage

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INTRODUCTION

- MCED tests are evaluated using the same performance measures as other screening tests, but comparing performance among MCED tests is complicated if they target different cancer types
- MCED tests are intended to be used and evaluated as a single test with one specificity, not as a panel of individual cancer screening tests
- Healthy volunteerism in cancer screening studies is well understood to result in lower overall cancer risk, earlier stage at diagnosis, and skewed cancer types among study participants, which makes results non-representative of general populations in ways that affect test performance measures
- Studies that target high-risk populations are expected to yield a higher cumulative incidence of cancer, as well as a distinct distribution of cancer types
- All of these issues affect the comparability of MCED test performance across study populations, necessitating methods to standardise cancer types and stages to evaluate the performance of different MCED tests

OBJECTIVE

- We developed a method of weighting (i.e., standardising) to a national population with the goal of comparing the performance characteristics of different MCED tests to detect cancers at an earlier stage, while accommodating different study designs and intended use populations

METHODS

- As external standard weights, we used age-, sex-, cancer-type-, and stage-specific cancer incidence rates for adults aged 50-79 years in 2019 from the US Surveillance, Epidemiology, and End Results registries[3]
- The weights sum to 100% for all invasive cancer types and stages to enable comparison of overall sensitivities for detecting total cancer
- Sample weights for US women aged 50-79 years are shown in **Supplementary Table 1**
- We used the published cancer-type- and stage-specific sensitivity of a commercially available MCED test[1]

RESULTS: TO EVALUATE THE ABILITY OF AN MCED TEST TO DETECT CANCER AT EARLIER STAGES, PERFORMANCE CHARACTERISTICS SHOULD BE WEIGHTED TO ACCOUNT FOR THE DISTRIBUTION OF CANCER TYPES TYPICALLY DIAGNOSED AT LATER STAGES IN THE GENERAL POPULATION

Figure 1. Conceptual model of an MCED test ("cfdna") as a complement to cancer screening based on the usual standard of care ("soc"). To account for differences in the distribution of cancer types by stage, MCED test performance at each stage can be weighted by the distribution of cancer types at all stages (here, excluding unstaged cancers). Weighted test characteristics reflect the potential overall performance of the MCED test as an adjunct to the SOC in an actual screening population of patients with occult cancers at all types and stages.

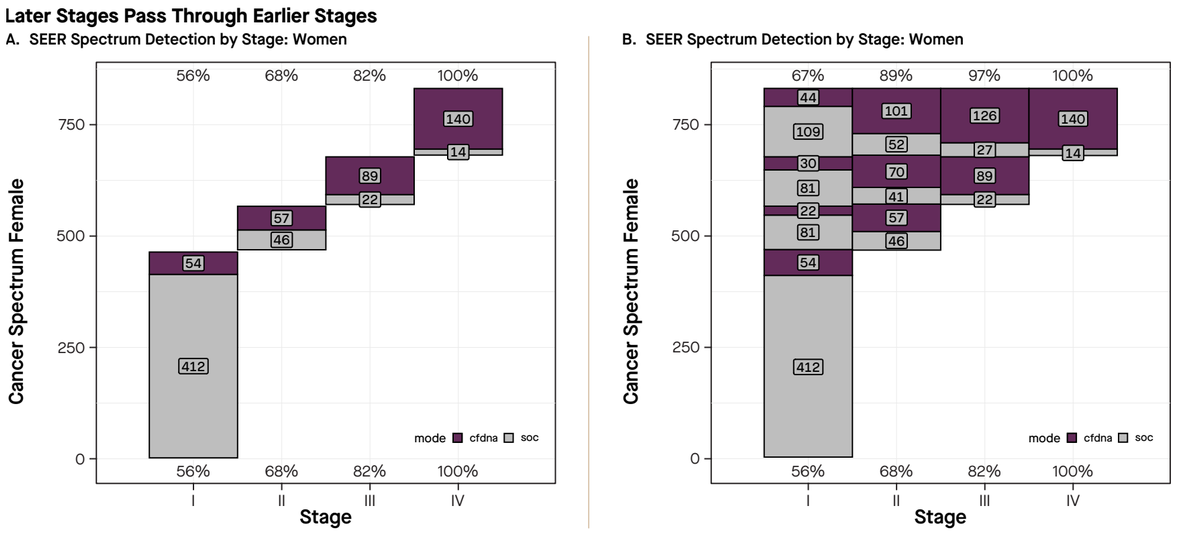

Table 1. MCED test sensitivity reported by Klein et al. (2021),[1] weighted to age-adjusted cancer-type- and stage-specific incidence rates among US women aged 50-79 years at diagnosis in 2019, SEER 17 geographic regions

Cancer Type	Overall	Stage 1	Stage 2	Stage 3	Stage 4	Women, Same Stage	Women, Later Stages
All Types	51.5%	16.8%	40.4%	77.0%	90.1%		
Anus	81.8%	25.0%	75.0%	100.0%	100.0%	0.5%	0.5%
Bladder	34.8%	17.6%	17.6%	75.0%	100.0%	0.3%	0.3%
Breast	30.5%	2.6%	47.5%	85.5%	90.9%	6.3%	5.2%
Cervix	80.0%	58.3%	100.0%	100.0%	100.0%	1.0%	1.2%
Colon/Rectum	82.0%	43.3%	85.0%	87.9%	95.3%	5.7%	7.8%
Esophagus	85.0%	12.5%	64.7%	94.1%	100.0%	0.3%	0.4%
Gallbladder	70.6%	0.0%	33.3%	75.0%	100.0%	0.4%	0.6%
Head/Neck	85.7%	63.2%	82.4%	84.2%	96.0%	1.5%	2.4%
Kidney	18.2%	4.9%	18.8%	18.8%	54.5%	0.4%	0.4%
Leukemia, Lymphoid	41.2%	-	-	-	-	0.6%	0.5%
Leukemia, Myeloid	20.0%	-	-	-	-	0.3%	0.3%
Liver/Intrahepatic Bile	93.5%	81.3%	81.3%	100.0%	100.0%	1.1%	1.5%
Lung	74.8%	21.9%	79.5%	90.7%	95.2%	8.8%	15.9%
Lymphoma	56.3%	27.3%	58.3%	66.3%	66.3%	1.9%	3.3%
Melanoma	46.2%	0.0%	0.0%	0.0%	100.0%	0.2%	0.2%
Ovary	83.1%	50.0%	80.0%	87.1%	94.7%	2.6%	4.3%
Pancreas	83.7%	61.0%	61.0%	85.7%	95.9%	2.5%	5.0%
Plasma Cell	72.3%	-	-	-	-	1.3%	1.1%
Prostate	11.2%	3.2%	4.9%	14.0%	83.3%	0.0%	0.0%
Sarcoma	60.0%	40.0%	58.3%	58.3%	85.7%	0.4%	0.5%
Stomach	66.7%	16.7%	50.0%	80.0%	100.0%	0.7%	1.1%
Thyroid	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Urothelial Tract	80.0%	0.0%	80.0%	80.0%	100.0%	0.2%	0.2%
Uterus	28.0%	16.7%	30.0%	73.9%	100.0%	0.3%	2.2%
Unknown Primary	94.4%	-	-	-	-	1.2%	1.1%
Other	50.8%	18.2%	69.2%	69.2%	69.2%	0.0%	0.9%
						38.5%	**56.7%**

*MCED test sensitivity was assumed to increase with later stage; therefore, where estimated sensitivity decreased with later stage for a given cancer type,[1] sensitivity was imputed by applying a weighted isotonic regression, with weights determined by the number attempted.[2] Stage was ignored and a single sensitivity value was applied for leukemias, plasma cell neoplasms, and cancers of unknown primary site, which are usually unstaged.

- We used the published aggregate test sensitivity of 51.5% (at 99.5% specificity) for a commercially available MCED test.[1] After weighting to the US population to account for age, sex, cancer type, and stage, the overall MCED test sensitivity was 38.5% for women and 44.0% for men, reflecting a higher proportion of stage 1 cancers and a different distribution of cancer types in the US population than in the study population
- To evaluate the impact of an MCED test on the desired outcome of stage shift from later to earlier stages, we developed methods for weighting cancer-type- and stage-specific test sensitivity to account for the distribution of cancer types typically diagnosed at later stages in the general population
  - Care should be taken to avoid double-counting cancers at multiple stages
- **Figure 1** conceptualises this approach by treating the distribution of cancer types across all stages combined as being relevant for each stage, but noting that localised and regional cancers are already detected by usual care in the observed fraction of cancers. This measures the total effective sensitivity of an MCED test as a complement to usual care
- **Table 1** shows cancer-type and stage-specific sensitivity of an MCED test for more than 20 cancer types as published,[1] after weighting to the distribution of type- and stage-specific age-adjusted incidence rates of cancer among 50- to 79-year-old US women in 2019 ("Women, Same Stage"), and after weighting to the distribution of type-specific incidence rates among women at later stages (e.g., weighting sensitivity at stage 2 to the distribution of cancer types at stages 3 and 4) ("Women, Later Stages")
- When the sensitivity of the commercially available MCED test was weighted to the incidence of cancer types at later stages in US women, overall sensitivity increased to 56.7%
  - The higher overall sensitivity weighted for stage shift reflects better early-stage sensitivity for cancer types with relatively greater incidence at later stages in US women

Supplementary Table 1. Weights for standardisation by cancer type and stage according to the American Joint Committee on Cancer, 8th edition, for women aged 50-79 years based on cancer incidence rates (per 100,000, age-standardised to the World 2000-2025 Standard Million population within the truncated age range) in US SEER 17 geographic regions, diagnosis year 2019. Weights sum to 100% (with rounding error) across all cancer types and stages by sex.[3] For brevity, only the 10 most common cancer types are shown.

		Stage 1		Stage 2		Stage 3		Stage 4	
	Total Rate	Rate	Weight	Rate	Weight	Rate	Weight	Rate	Weight
All Types	830.22	457.56	55.1%	104.41	12.6%	110.27	13.3%	157.98	19.0%
Breast	302.22	227.26	27.4%	39	4.7%	18.12	2.2%	17.84	2.1%
Colon/Rectum	65.74	18.17	2.2%	15.23	1.8%	16.95	2.0%	15.38	1.9%
Kidney	27.43	18.12	2.2%	1.57	0.2%	4.09	0.5%	3.65	0.4%
Lung	109.47	33.97	4.1%	8.75	1.1%	20.61	2.5%	46.14	5.6%
Lymphoma	32.11	8.56	1.0%	5.19	0.6%	6.1	0.7%	12.26	1.5%
Melanoma	35.84	28.2	3.4%	3.72	0.4%	2.44	0.3%	1.48	0.2%
Ovary	22.07	5.73	0.7%	1.98	0.2%	7.55	0.9%	6.8	0.8%
Pancreas	25.93	4.87	0.6%	3.55	0.4%	3.71	0.4%	13.79	1.7%
Thyroid	30.06	23.39	2.8%	5.07	0.6%	0.57	0.1%	1.02	0.1%
Uterus	79.11	57.49	6.9%	3.6	0.4%	9.75	1.2%	8.27	1.0%

CONCLUSIONS

- This method of weighting by age, sex, cancer type, and stage facilitates comparison of performance characteristics among different MCED tests targeting different cancer types or evaluated in distinct study populations
- Weighting to a general older-adult population more accurately reflects potential test performance in the intended use population and enables more rigorous evaluation of the benefits and harms of screening with MCED tests

References

1. Klein EA, et al. *Ann Oncol.* 2021;32(9):1167-1177
2. Hubbell E, et al. *Cancer Epidemiol Biomarkers Prev.* 2021;30(3):460-468
3. SEER Research Data, 17 Registries, Nov 2022 Sub (2000-2020), released April 2023

Disclosures

Ellen T. Chang, Christina A. Clarke, and Earl A. Hubbell are employees of GRAIL, LLC, with equity in Illumina, Inc., and own equity in the company. Dr. Hubbell also has multiple patents in the field of cancer detection pending to GRAIL, LLC. Alpa V. Patel reports institutional research funding from GRAIL, LLC. Graham A. Colditz reports a consulting/advisory role for GRAIL, LLC; royalties as an author for Up-to-Date; and other support from NIH outside of the submitted work. Allan Hackshaw reports stock and ownership interests in Illumina and Thermo Fisher Scientific; honoraria from Abbvie, Almirall, AstraZeneca, Boehringer Ingelheim, Clovis Oncology, Daiichi Sankyo, Ipsen, Kyowa Kirin International, Pfizer, SERVIER, Takeda, and UCB; consulting/advisory roles for Abbvie, Evidera, Roche, and GRAIL, LLC; assistance for travel to meetings from GRAIL, LLC; and institutional research funding from AstraZeneca, Autolus, Bristol-Myers Squibb/Sanofi, Boehringer Ingelheim, MSD, Pfizer, Roche, and GRAIL, LLC.

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