The Potential Clinical Impact of a Multi-Cancer Early Detection Test for Individuals With Missing Cancer Stage Information

National Comprehensive Cancer Network (NCCN)
2023 Annual Conference
March 31-April 2, 2023, Orlando, FL

Ali Tafazzoli,[1] Alissa Shaul,[2] Weicheng Ye,[2] Anuraag R Kansal,[1] A Mark Fendrick[3]
[1]GRAIL, LLC, a subsidiary of Illumina, Inc.,* Menlo Park, CA, United States; [2]Evidera, Bethesda, MD, United States; [3]Department of Internal Medicine; Center for Value-Based Insurance Design; University of Michigan, Ann Arbor, MI, United States

INTRODUCTION

- Recently, multi-cancer early detection (MCED) tests, which can simultaneously screen for multiple types of cancer, have been developed. These tests can shift detection of cancers to earlier stages relative to current standard of care (SoC) screening[1]
- When used alongside SoC, an economic analysis projects that these tests may improve survival outcomes and lower treatment costs[2]
- Cancer stage is prognostic and vital for estimating the clinical impact of strategies such as MCED tests
- However, missing cancer stage information is common in cancer registries and the proportion of these missing data often differs by cancer type and increases by age[3,4]

OBJECTIVE

- This study investigated different imputation approaches for missing cancer stage data and the resulting clinical impact of MCED tests

METHODS

- A Markov model was developed to compare annual MCED testing plus SoC screening vs. SoC alone in adults aged 50 to 79 years. All outcomes reported here are undiscounted
  - To handle an earlier diagnosis with MCED screening than with SoC screening alone, the model stage and time shifted the cancer diagnosis to an earlier time and age based on various model inputs, including cancer dwell times, frequency of MCED screening, and sensitivity of the MCED test
  - Further details of the model structure and methods, including the approach to stage and time shift as well as inputs, have been described previously[2]
- Incidence and survival data for 19 solid cancer groupings, representing > 80% of cancer incidence,[5,6] were informed by SEER data for both staged cancers and those with missing stage (Table 1)
- These data were analyzed by cancer type and age-group to inform the potential stage distribution of cancers with missing stage using two imputation approaches:

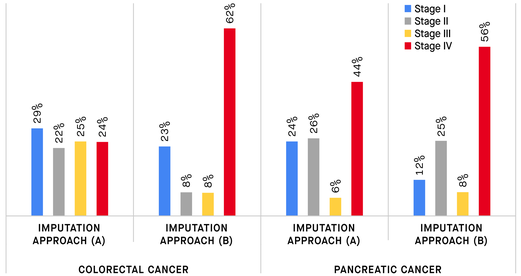
  (A) proportional to non-missing cancer incidence rates by stage, and

  (B) fitting stage distribution such that predicted survival matches observed survival data
- The proportional imputation method represents a hypothesis that cancer stage data is missing at random
- The fitted approach represents a hypothesis that missingness may be biased across stages (e.g., that later stages may be more likely to be missing vs earlier stages)[7]

KEY RESULTS: MODELED CLINICAL IMPACTS OF MCED TESTING WERE CONSISTENT IN THOSE WITHOUT CANCER STAGING INFORMATION

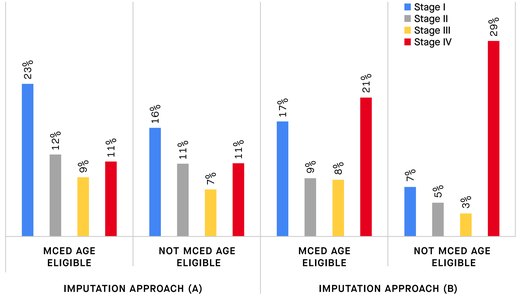
- The two approaches yielded notably different estimates of cancer stage among those with missing stage information (Table 1)
- These differences were not consistent among cancers. For example, approach (B) yielded a much larger estimate vs approach (A) of the proportion of cancers that were stage IV for colorectal cancer, while the two approaches yielded fairly similar estimates of stage distribution for pancreatic cancer (Figure 1)

Figure 1. Estimated Distribution of Cancer Stages by Imputation Approach



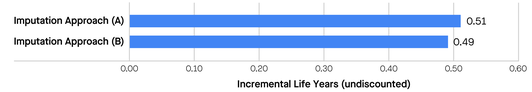
- The difference in stage distribution between the two imputation approaches was much larger among cancers diagnosed in individuals ≥ 80 years of age (i.e., not MCED age eligible) compared to cancers diagnosed in individuals between 50 and 79 years of age (i.e., MCED age eligible) (Figure 2)

Figure 2. Estimated Distribution of Cancer Stages by Age and Imputation Approach



- Despite the differences in the estimated stage distribution among cancers with missing stage data, the modeled benefits of MCED were very similar between the two imputation approaches (Figure 3)
- In both imputation approaches, the total life years for cancer patients with missing stage were increased by around 6 months in the group with MCED testing relative to SoC alone

Figure 3. Life Years Gained Through MCED Screening by Imputation Approach



- This may reflect that the screening program modeled included MCED from ages 50 to 79 and thus most cancers detected are those that would have been incident with SoC only between those ages
  - The estimated stage distribution in this age range differed much less between the two imputation approaches (see Figure 2)

Limitations

- Individuals with missing stage data may differ from those with stage data, leading to potential bias in the estimates of stage using either imputation approach
- These differences may increase (e.g., differences in health related to the onset of cancer) or reduce (e.g., long-term differences in frailty) the potential benefits of early cancer detection in this population

Table 1. Cancer Incidence by Cancer Grouping and Imputation Approach

Cancer Grouping	Incidence per 100,000 by Cancer Grouping and Stage[5,6]	Incidence by Stage Estimated for Cancers With Missing Stage							
		Applying Imputation Approach (A)				Applying Imputation Approach (B)			
	Missing Cancer Stage	Stage I	Stage II	Stage III	Stage IV	Stage I	Stage II	Stage III	Stage IV
Lung and bronchus	22.0	5.2	1.0	5.6	10.3	4.4	0.8	5.1	11.7
Colon and Rectum	32.8	9.9	7.1	8.2	7.6	11.4	2.9	2.8	15.7
Pancreas	7.2	0.8	1.8	0.6	4.0	2.1	1.7	0.4	2.9
Liver and Intrahepatic Bile Duct	6.2	2.3	1.1	1.5	1.3	0.5	0.2	1.7	3.7
Breast	10.2	5.2	3.3	1.1	0.7	2.4	1.5	3.1	3.2
Esophagus	2.5	0.5	0.5	0.5	0.9	0.3	0.3	0.3	1.7
Head and Neck	7.2	1.9	1.0	1.2	3.1	1.9	1.0	1.2	3.0
Stomach	5.6	1.8	0.7	0.6	2.4	3.0	0.5	0.4	1.8
Ovarian	4.4	0.7	0.4	1.7	1.6	0.2	0.1	0.6	3.4
Kidney and Renal Pelvis	3.3	1.9	0.2	0.5	0.6	1.2	0.2	0.3	1.6
Prostate	18.6	0.1	15.2	1.2	2.2	0.1	13.4	1.1	4.0
Lymphoma	6.7	2.0	1.1	1.2	2.5	4.5	0.7	0.5	1.0
Anus	1.3	0.3	0.5	0.4	0.1	0.4	0.4	0.3	0.2
Uterus	10.4	4.5	1.3	2.3	2.4	2.5	0.8	1.4	5.7
Bladder	3.4	1.7	0.9	0.3	0.5	1.3	0.6	0.3	1.2
Cervix	0.7	0.2	0.1	0.2	0.2	0.1	0.1	0.1	0.4
Urothelial	0.5	0.2	0.1	0.1	0.1	0.2	0.1	0.1	0.1
Other	99.7	56.6	17.7	12.4	13.0	29.0	8.9	11.7	50.1

Note: SEER 18 data from the years 2006-2015

CONCLUSIONS

- Despite the uncertainties inherent in the missing stage data, the modeled clinical impacts of MCED were consistent in those whose cancers have missing stage data
- MCED offers an opportunity to improve outcomes among individuals with missing stage data, a group who are disproportionately underserved and medically needy

References

1. Klein EA, et al. *Ann Oncol*. 2021;32(9):1167-1177.
2. Tafazzoli A, et al. *Pharmacoeconomics*. 2022;40(11):1107-1117.
3. Koroukian SM, et al. *Cancer Detect Prev*. 2007;31(3):199-206.
4. Herget K, et al. *Cancer Causes Control*. 2017;28(4):341-349.
5. SEER. 2019. https:// seer.cancer.gov/data-software/documentation/seerstat/nov2019/
6. SEER. 2021. https://seer.cancer.gov/seerstat/
7. Withrow DR, et al. *Int J Cancer*. 2023 Feb 8. doi: 10.1002/ijc.34463. Online ahead of print.

Disclosures

Study funded by GRAIL, LLC, a subsidiary of Illumina, Inc.* AT and ARK are employees of GRAIL, LLC, a subsidiary of Illumina, Inc.,* with equity in Illumina, Inc. AS and WY are employees of Evidera, which provides scientific consulting and other research services to pharmaceutical, device, government, and other non-government organizations. MAF is a consultant to GRAIL, LLC, a subsidiary of Illumina, Inc.* All financial relationships disclosed at abstract submission.

Acknowledgements

Study funded by GRAIL, LLC, a subsidiary of Illumina, Inc.*
Graphical and editorial assistance provided by Prescott Medical Communications Group (Chicago, IL).

*Currently held separate from Illumina, Inc. under the terms of the Interim Measures Order of the European Commission dated 29 October 2021