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Estimated Post-Test Probabilities of Cancers for Individuals Receiving Multi-Cancer Early Detection (MCED) Tests

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INTRODUCTION

- With the rise of MCED technologies, both patients and providers need to understand how to interpret each individual's test result as it relates to cancer risk, which can vary across the population depending on clinical factors
  - Clinical factors, such as age, sex, and smoking status, determine most of the absolute risk of cancer for individuals[1]
- With accumulation of knowledge of preclinical cancer biology, we can now estimate post–MCED test probabilities of cancer risk—for persons with either positive (cancer signal detected) and negative (no cancer signal detected) test results

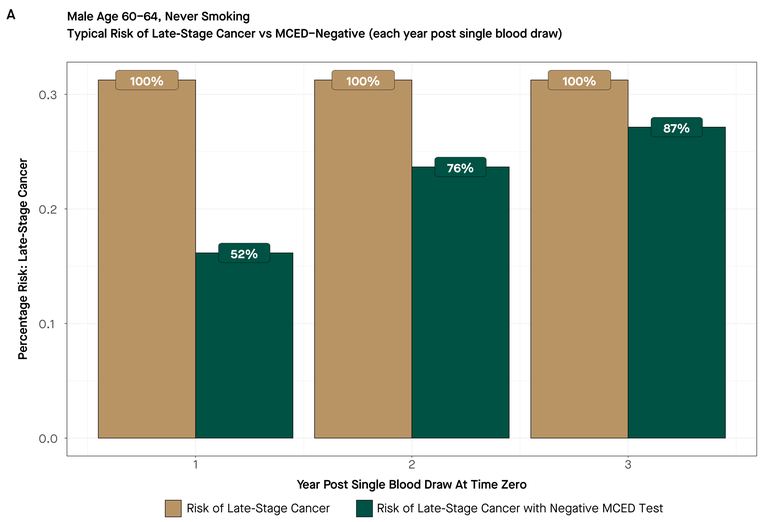
OBJECTIVE

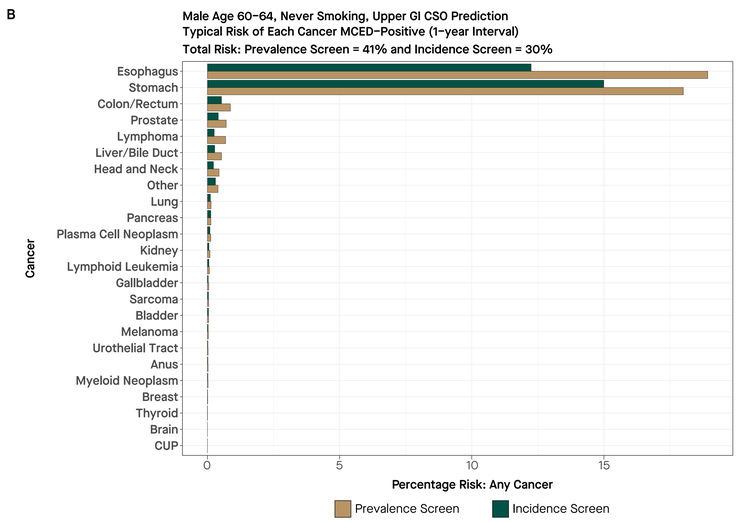
- Provide methods for estimating cancer risk for individuals given their:
  - Age, sex, and smoking status
  - MCED test result, either positive or negative, and a cancer signal origin (CSO) prediction (following a positive test result) suggesting a particular diagnostic path

NEGATIVE MCED TEST RESULTS CONFER A REDUCED LATE-STAGE CANCER RISK, BUT PROGNOSTIC POWER FADES YEARLY, SUGGESTING AN ANNUAL TESTING INTERVAL. POSITIVE MCED TEST RESULTS WARRANT CSO-DIRECTED DIAGNOSTIC WORKUPS.

- Across all the modeled clinical factors, individuals who received a **negative** MCED test result had:
  - 42%-56% (min-max) the rate of expected late-stage (III+IV) cancer diagnosis in the first year following their MCED test
  - 72%-82% the rate of expected late-stage cancer diagnosis in the second year if they did not return for an annual MCED test
- Across all the modeled clinical factors, individuals who received a **positive** MCED test result with CSO prediction had:
  - The greatest likelihood of cancer at the location indicated by the CSO prediction if the individual was confirmed to have cancer (97% of all individual-CSO combinations modeled)
  - A sufficient positive predictive value (see Methods)[2-5] at each CSO to justify workup (97% of all individual-CSO combinations modeled), with few exceptions (eg, a breast CSO prediction in male individuals)
- Despite factors such as a recent negative colonoscopy, which can reduce by 6-fold the odds of a clinical diagnosis, individuals with a positive methylation-based cancer signal and a CSO prediction of colon/rectum may have an absolute cancer risk exceeding 10% for colorectal cancer[6]

Figure 1. Example of Post–MCED Test Cancer Risk Assessment.
Male never-smokers qualify for only 1 US Preventive Services Task Force grade A/B screening—colorectal screening—which is responsible for a minority of their cancer risk. Despite this, the calculated absolute risk of a late-stage cancer per year is high in any given year (ie, comparable to >0.3% risk of cardiovascular mortality per year in 60-year-old never-smoker[7]). For this example population:





(**Panel A**) A negative MCED test result provides prognostic information suggesting a 50% reduced risk in the first year post–MCED test; however, this protective effect fades to 24% in the second year post-test, and halves again to 13% in the third year post-test.

CSO, cancer signal origin; CUP, cancer of unknown primary; GI, gastrointestinal; MCED, multicancer early detection.

(**Panel B**) A positive MCED test result with a CSO prediction of upper gastrointestinal tract occurs in a background of a pre-test absolute risk of any clinical cancer diagnosis in the next year of 1.1%. The post-test absolute risk (ie, positive predictive value) of being diagnosed with a current cancer is 41% if the test was performed during the prevalence round of screening (ie, this was the first time being screened) and 30% if the test was part of a later (ie, incidence) round of an annual screening program. This particular risk is split between stomach and esophagus cancer types, which share a common diagnostic procedure—endoscopy—with a small but noticeable risk distributed across other cancer types (note that ovary, uterus, and cervix are not possible risks for a male individual).

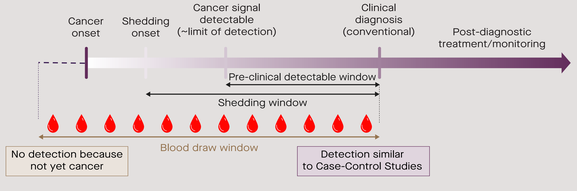
CONCLUSIONS

- This model provides important clinical context for interpreting MCED test results across common clinical covariates of age, sex, and smoking status; this includes the potential for a significant increase in late-stage, deadly interval cancers when testing at intervals longer than 1 year, which is in line with observations from the descriptive analysis of the American Cancer Society Cancer Prevention Study 3[8]
- For the majority of individuals with a positive MCED test result, using the CSO prediction to guide diagnostic workups is justified by comparison to usual clinical decision thresholds
  - Residual risk of cancer is often high if the CSO prediction is false; retesting can reduce the false positive rate while preserving true positive cancer cases[9]
- Utilization of conventional screening or imaging tests can significantly alter the pre-test probability of having certain cancers, for which we provide the example of colonoscopy and its effects over the 10 years post–negative screen (see Table in Supporting Data)
  - A methylation-based cancer signal plus CSO prediction is strongly predictive of current cancer risk, so much so that even undergoing recent conventional screening does not reduce the odds of having a cancer of that predicted type below clinically actionable risks
- This model is grounded in data; however, individuals are never precisely represented by averages, and these estimates are a starting point for clinical judgment and informed discussions
  - Computations here are simple enough to be implemented in Excel

METHODS

- Given individuals for our model were drawn from 2006-2015 data of cancer incidence and stage by sex (male/female) and age (5-year bands; ie, 50-54, 55-59, 60-64, 65-69, 70-74, and 75-79 years old) from the Surveillance, Epidemiology and End Results (SEER) 17 database
  - Adjustments for smoking status (never, former, current, or not known) on cancer incidence were drawn from Islami (2018)[10]
- Given modeled preclinical detectable windows (**Figure S1**) and fraction of detectable cancers:
  - Used data from the Circulating Cell-Free Genome Atlas substudy 3[11] (including CSO prediction accuracy of >85%) and the American Cancer Society Cancer Prevention Study 3[8]
  - Assumed an MCED test with a constant positive predictive value by age within the range modeled; ie, an increasing false positive rate proportionate to cancer incidence
- Post–MCED test probabilities were computed for:
  - Individuals with a negative test result who want estimates of future cancer risk and how that risk changes with time
  - Individuals with a positive test result and a given CSO prediction who need to know current cancer risks
- Technical details:
  - The detection window was exponentially distributed
  - Some cancers were not able to be modeled owing to no recorded stage or no reliable estimates of sensitivity
    - Eg, brain cancer, cancers of unknown primary, leukemia, plasma cell neoplasm, and cancers with a CSO category of "Other"
    - Exclusion from the model does not mean the cancer type will not occur in reality
  - 7% was taken as a clinically significant cutoff for positive predictive value, as it is comparable to 1) the likelihood of detecting cancer in individuals with Li-Fraumeni syndrome via recommended whole-body magnetic resonance imaging, and 2) the positive predictive value of Guy's Rapid Diagnostic Clinic in England focused on diagnostic workup of patients with symptoms concerning for cancer[2-5]

Figure S1. Knowing the Detection Window Allows Inference of Both the Cancer Signal Detection Rate and the Future Reduction in Cancer Risk With a Negative Test Result.



SUPPORTING DATA

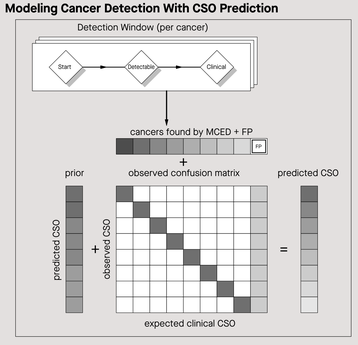
- The model uses certain facts and assumptions about the CSO classifier performance
  - Classifier is "optimal" given CSO prediction accuracy of 85%[11]
  - Classifier generates miscalls with the same probability distribution as the expected true distribution of calls (**Figure S2**)
    - Classifier knows rare cancers are rare
    - Classifier knows hard-to-detect cancers have a lower positivity rate
    - Optimized for "average population" (half male/half female, matching SEER)
    - Cross-talk between cancer types and false positives have same inherent classifier biases
- A recent study[6] computing the reduction in hazard post–negative colonoscopy for a cohort of Utah residents showed that compared with the state population, a negative colonoscopy was associated with lower standardized incident ratios for colorectal cancer that increased with time from the index colonoscopy (**Table**)

Table. In a Cohort of Utah Residents, a Negative Colonoscopy Was Associated With Lower Standardized Incidence Ratios for Colorectal Cancer That Increased With Time From the Index Colonoscopy.[6] Even considering this reduction in relative prior risk, an individual receiving a positive test result with CSO prediction of colon/rectum has a significant absolute risk of having colon/rectum cancer. Range here is across all age bands, sexes, and smoking exposure, as all qualify for colorectal cancer screening.

Year(s) Following Negative Index Colonoscopy	Standardized Incidence Ratio (95% CI)	Absolute Risk (%) of Colorectal Cancer [Mean (Min–Max)] if Positive Result With CSO Prediction of Colon/Rectum
1	0.15 (0.08–0.23)	9 (6–13)
2–5	0.26 (0.19–0.32)	15 (10–21)
5–6	0.33 (0.22–0.43)	19 (13–25)
7–10	0.60 (0.44–0.76)	29 (21–38)

CI, confidence interval; CSO, cancer signal origin.

Figure S2. Cancer Signal Origin Predictions Applied to Positive Cancer Signals, Which Consist of True Positives Found by the MCED Test and False Positives.



CSO, cancer signal origin; FP, false positive; MCED, multi-cancer early detection.

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Disclosures

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