# Impact of Adherence on Real-World Performance of Multi-Cancer Early Detection (MCED) Tests: A Model-Based Analysis

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It is expected that the real-world performance of MCED will differ from that seen in trials. We developed a generalized model to support investigations into the key dynamics that will impact the performance of MCED testing in real world settings, such as adherence, sensitivity, specificity, and frequency.

## Methods

### OVERVIEW

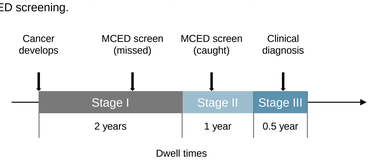
- We constructed a generalized, population cohort-based, cancer-agnostic, state-transition model in R[6-8], based on the work of Hubbell et al 2021[9], to estimate the benefits of an MCED screening program combined with usual care compared to usual care alone.
- Our generalized model utilizes MCED test sensitivity, diagnostic pathway, incidence rates, dwell times, survival, and MCED screening adherence and frequency. The model extends existing interception models by accounting for adherence to screening. Primary outcomes are stage shift at diagnosis and change in 5-year survival.

### STRUCTURE

- Using incidence from 2004 through 2019 by stage from SEER*Stat[10], the model projects backwards using dwell times[11] to determine when the cancer could have been detected by the MCED test. This creates a timeline for when the MCED test can first detect the cancer, when the cancer was detected by usual care, and when the cancer progresses to the next stage (**Figure 1**). We assume that 100% of positive MCED tests are evaluated to resolution.
- When the MCED test is given, the model checks to see if the screening occurred when the cancer was detectable (**Figure 2**).
  - If not, then the MCED test result is negative, and the cancer progresses. The MCED test is repeated at a user-specified interval.
  - If the cancer was detectable at the time of the MCED test and the cancer was not at the stage in which it was diagnosed by usual care, the model provides a test result using MCED sensitivity and patient adherence.
    - If the MCED test result was positive, the stage at diagnosis is provided.
    - If the MCED test result was negative or if the patient missed the MCED test due to low adherence, the cancer continues to progress and the MCED test is repeated.
- If the cancer was at the stage diagnosed by usual care, the testing cycle ends.
- The model outputs the 5-year survival rates by stage and the number of cancers identified at each stage.

Figure 1. Screening Example

A patient who would have been diagnosed with lung cancer in stage III without MCED screening is diagnosed in stage II with MCED screening.




### INPUTS

- We modeled a general US population cohort of 100,000 persons aged 50 to 79 years old.
- The lung cancer MCED test sensitivity ranges from 21.9% for stage I to 95.2% for stage IV[11] (**Table 2**).
- The MCED sensitivity range is narrower for pancreatic cancer, spanning from 60.0% to 95.9%.[11] The stage I sensitivity was lowered from 61.9% to 60.0% because the model does not allow for a better sensitivity in stage I than stage II (**Table 1**).
- Annual MCED screening was chosen to align with the recommended CT screening frequency for lung cancer.[5]
- Usual care is defined to be what was observed in SEER*Stat[10]; it is not modeled.
- Incidence inputs are categorized by stage. Overall, the incidence rate is much higher for lung cancer (87.7 per 100,000) than pancreatic cancer (13.0 per 100,000)[10] (**Table 3**).
- Four scenarios evaluating the impact of MCED test adherence (25%, 50%, 75%, and 100%) were modeled.

Table 1. Pancreatic Cancer Inputs

| Stage | Incidence[3] | 5-year survival[3] | Dwell time (years)[2] | MCED sensitivity[4] |
|---|---|---|---|---|
| I | 1.4 | 36.2% | 2 | 60.0%* |
| II | 5.3 | 14.0% | 1 | 60.0% |
| III | 1.9 | 3.7% | 1 | 85.7% |
| IV | 11.1 | 1.8% | 0.5 | 95.9% |

* Stage I sensitivity was lowered from 61.9% because the model does not allow for a better sensitivity in stage I than stage II.

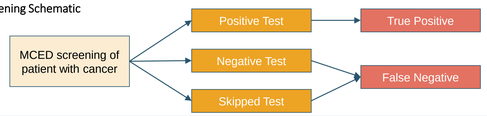
Table 2. Lung Cancer Inputs

| Stage | Incidence[3] | 5-year survival[3] | Dwell time (years)[2] | MCED sensitivity[4] |
|---|---|---|---|---|
| I | 25.6 | 65.8% | 2 | 21.9% |
| II | 5.5 | 41.2% | 1 | 79.5% |
| III | 29.2 | 19.2% | 0.5 | 90.7% |
| IV | 58.4 | 4.8% | 0.5 | 95.2% |

### ASSUMPTIONS

- This model omits prevalence. The patient population is limited to people with a cancer diagnosis; no newly diagnosed people are added over time.
- The model does not include MCED specificity and assumes that all positive tests are true positives. After a positive MCED test results, the timeline does not account for any confirmatory screening by usual care.
- If an MCED test is skipped due to adherence, it is treated as a false negative result (**Figure 3**).

Figure 3. MCED Screening Schematic




## Background

### OBJECTIVE

**Use an analytical model to determine the impact of adherence on the effectiveness of MCED screening programs, using lung and pancreatic cancer to illustrate our findings.**

### MCED TESTING

Even with current screening technologies, cancer remains a leading cause of death worldwide. Screening technology continues to evolve with more than 20 multi-cancer early detection (MCED) tests currently in development.[1] As recently evidenced in the NORDICC trial evaluating colonoscopies, an extremely effective screening tool, suboptimal adherence will impact the effectiveness of highly sensitive and specific assays MCED tests.[2]

### PANCREATIC CANCER

Pancreatic cancer is a leading cause of cancer-related death in the US among both men and women. Most cases are locoregionally advanced at presentation, and only 15 to 20 percent are potentially resectable.

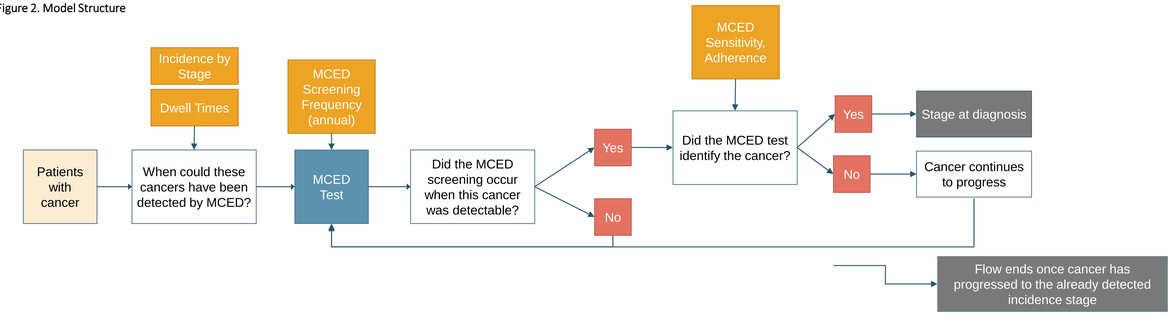
MCED testing is promising because there is no consensus as to the best imaging method for screening high-risk individuals, and there are few prospective data comparing outcomes from different screening strategies. Due to the burden, cost, and uncertain insurance environment for screening high-risk persons, adherence over time is generally poor. There is a strong unmet need for accurate, minimally burdensome tests that can be deployed in a screening environment among high-risk persons to identify pancreatic cancer at early, potentially curable stages of disease.

### LUNG CANCER

In 2018, more than 154,000 Americans died of lung cancer, a rate exceeding the three next most common cancers combined (colon, breast, and prostate cancers).[3] Death rates and incidence from lung cancer have been decreasing in both men and women since approximately 2000, due in part to decreasing smoking trends, increasing screening rates of high-risk patients, and advancing treatment options.[3]

Despite improvements, the percent of lung cancer patients with distant metastasis at diagnosis has remained near 55% since 2004.[4] The most compelling argument for MCED testing for lung cancer is that very few eligible persons, only 5.8%[5], are using the accepted standard of CT screening.

Figure 2. Model Structure




## Results

Figure 4. Pancreatic Cancer Stage Shift at 100% Adherence[14,15]

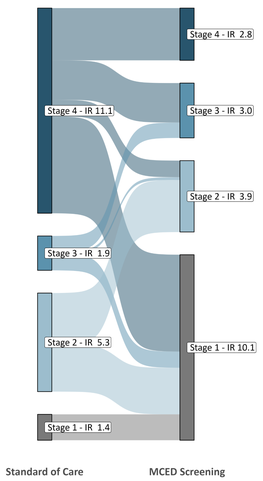



Figure 5. Lung Cancer Stage Shift at 100% Adherence[14,15]

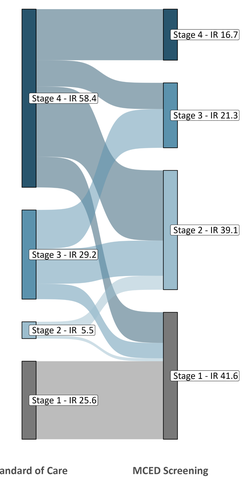



Table 3. Pancreatic Cancer Diagnoses Results for Stage III and IV

| MCED adherence | Diagnoses at stage III and IV (per 100,000) | | Reduction in diagnoses at stage III and IV | |
|---|---|---|---|---|
| | Usual care alone | MCED + usual care | Absolute | Percent |
| 100% | 13.0 | 5.8 | 7.2 | 55.3% |
| 75% | 13.0 | 7.6 | 5.4 | 41.5% |
| 50% | 13.0 | 9.4 | 3.6 | 27.6% |
| 25% | 13.0 | 11.2 | 1.8 | 13.8% |

Table 4. Lung Cancer Diagnoses Results for Stage III and IV

| MCED adherence | Diagnoses at stage III and IV (per 100,000) | | Reduction in diagnoses at stage III and IV | |
|---|---|---|---|---|
| | Usual care alone | MCED + usual care | Absolute | Percent |
| 100% | 87.7 | 38.0 | 49.6 | 56.6% |
| 75% | 87.7 | 50.4 | 37.2 | 42.5% |
| 50% | 87.7 | 62.8 | 24.8 | 28.3% |
| 25% | 87.7 | 75.3 | 12.4 | 14.2% |

### STAGE SHIFT

*Lung Cancer*

- The model estimated a 56.6% reduction in stage III and IV diagnosis with 100% MCED adherence in lung cancer (**Table 4**).
- As adherence rates dropped to 75%, 50%, and 25%, the shift in late-stage to early-stage lung cancer diagnosis falls to 41.5%, 27.6%, and 13.8%, respectively (**Table 4**).
- The observed incidence rate of stage I lung cancer diagnoses was estimated to increase from 25.6 to 41.6 per 100,000 with the addition of MCED testing at 100% adherence (**Figure 5**).

*Pancreatic Cancer*

- The proportion of stage shift in pancreatic cancer was estimated to be 55.3%, very similar to lung cancer. The shift in late-stage to early-stage was estimated to be 42.5%, 28.3%, and 14.2% as adherence drops to 75%, 50%, and 25%, respectively (**Table 3**).
- Adding MCED testing to usual pancreatic screenings increased the stage I incidence rate from 1.41 to 10.1 per 100,000 at 100% adherence (**Figure 4**).

### 5-YEAR SURVIVAL

- Adding the MCED test to usual care increased 5-year survival rates in both lung and pancreatic cancer at all adherence levels (**Table 7** and **Table 8**).
- Adherence level greatly impacted the magnitude of the benefit.
- The proportional increases in survival for each level of adherence were slightly higher in lung cancer than pancreatic.

Table 7. Pancreatic Cancer 5-Year Deaths per 100,000

| MCED adherence | Usual care alone | MCED + usual care | Absolute reduction | % reduction |
|---|---|---|---|---|
| 100% | 18.2 | 15.4 | 2.8 | 15.5% |
| 75% | 18.2 | 16.1 | 2.1 | 11.6% |
| 50% | 18.2 | 16.8 | 1.4 | 7.7% |
| 25% | 18.2 | 17.5 | 0.7 | 3.9% |

Table 8. Lung Cancer 5-Year Deaths per 100,000

| MCED adherence | Usual care alone | MCED + usual care | Absolute reduction | % reduction |
|---|---|---|---|---|
| 100% | 91.2 | 70.4 | 20.9 | 22.9% |
| 75% | 91.2 | 75.6 | 15.6 | 17.2% |
| 50% | 91.2 | 80.8 | 10.4 | 11.4% |
| 25% | 91.2 | 86.0 | 5.2 | 5.7% |

### IMPACT ON SCREEN DETECTED VERSUS CLINICAL DIAGNOSIS

- At every adherence level, a higher proportion of pancreatic cancers were diagnosed by MCED testing than usual care compared to lung cancers (**Table 5** and **Table 6**).

Table 5. Pancreatic Cancer Method of Diagnosis in MCED + Usual Care

| MCED adherence | Total dx by usual care | | Total dx by MCED | |
|---|---|---|---|---|
| | n per 100,000 | % of total | n per 100,000 | % of total |
| 100% | 6.2 | 32% | 13.5 | 68% |
| 75% | 9.6 | 49% | 10.1 | 51% |
| 50% | 13.0 | 66% | 6.8 | 34% |
| 25% | 16.4 | 83% | 3.4 | 17% |

Total incidence is 19.8 per 100,000

Table 6. Lung Cancer Method of Diagnosis in MCED + Usual Care

| MCED adherence | Total dx by usual care | | Total dx by MCED | |
|---|---|---|---|---|
| | n per 100,000 | % of total | n per 100,000 | % of total |
| 100% | 48.7 | 41% | 70.1 | 59% |
| 75% | 66.2 | 56% | 52.5 | 44% |
| 50% | 83.7 | 71% | 35.0 | 29% |
| 25% | 101.2 | 85% | 17.5 | 15% |

Total incidence is 118.8 per 100,000

## Discussion

### LIMITATIONS

- The model cohort was a general US population. SEER*Stat[10], the chosen data source, does not provide explicit data on subgroups or risk level, ie, smoking status in lung cancer or family history in pancreatic cancer. Modeling an entire population does not account for the large variation of risk between relevant subgroups of the population. With input data of sufficient detail, the model can accommodate for these variations.
- The model does not allow for the MCED test to have higher sensitivity at earlier stages than later stages. In this project the sensitivity to detect stage I pancreatic cancer (61.9%) was lowered to match the sensitivity of stage II (60.0%).[11]
- The model does not allow for variations in usual care, including patient adherence to screening or access to care.
- This work focused on two cancers both with aggressive rates of progression, and thus does not address the issue of overdiagnosis (patients diagnosed with cancer who would die of other causes).
- The resulting ratio of cancers detected by MCED vs usual care may be artificially low. From the SEER data, the model assumes that usual care detected the cancer on day 1 of that stage. In real-world practice this is unlikely, providing time in which an MCED test may occur and may diagnose the cancer ahead of usual care.

### FUTURE WORK

- Model enhancements could incorporate MCED specificity by applying a constant rate of false positives to the total number of tests conducted.
- Currently the model applies adherence randomly. However, adherence is associated with other factors including age and usage of outpatient services.[12] Varying MCED adherence through the testing cycle based on past adherence could be included in future model improvements.

## Conclusions

- **Emerging MCED tests are a paradigm shift in cancer screening, but the effectiveness is significantly impacted by adherence. In the case of lung cancer, we find that adherence to annual screening has a large impact on overall effectiveness. Accounting for patient adherence to screening improves estimates of value, reflecting the real-world use of these novel tests.**
- **This cancer agnostic model offers a relatively easy way to assess the potential stage shift and impact on life expectancy of adding an early detection screening to usual care. The model estimated that adding MCED testing to usual care reduced late-stage diagnoses and increased 5-year survival rates across all adherence rates. These primary outcomes can be used to support further research in other indications and subsequent cost-effectiveness analyses.**

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