GRAIL

Stage Shift by Screening with a Multi-Cancer Early-Detection Test: **Microsimulation Modeling** to Inform the Design of a Pragmatic Randomized Controlled Trial

Jing Zhang, Jerome V. Braun, Noah Simon, Earl Hubbell, Nan Zhang

2021 Joint Statistical Meetings
August 12, 2021

Overview

- Only 4 cancer types have USPSTF-recommended routine screening programs.
- **~ 2/3rd** cancer deaths in the US are **from cancers without screening modalities**.[1]

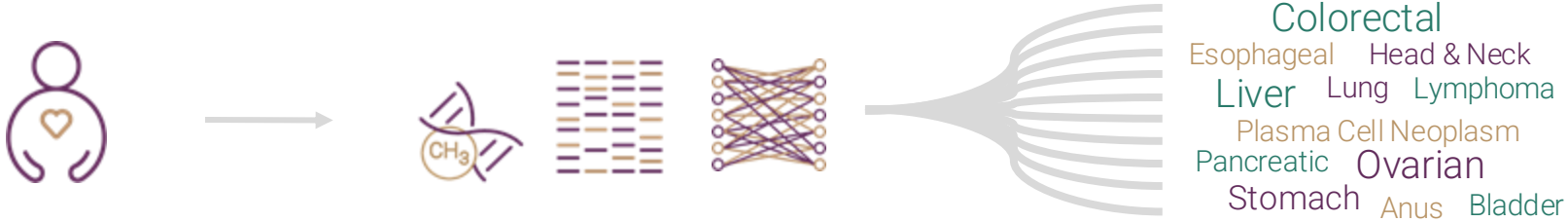
Screened Cancers		Limitations	
Breast Cancer	Lung Cancer	Discomfort & Inconvenience	Radiation Exposure
			
Colon Cancer	Cervical Cancer	False Positives	Missed Cancers
			

USPSTF, United States Preventive Services Task Force.

[1]American Cancer Society. Cancer facts & figures 2020. *CA Cancer J Clin*. Published online 2020.

Overview

GRAIL Has Developed a **Multi-Cancer Early Detection (MCED)** Test -- Galleri™[1]



Single blood draw

Detect cancer signal with **targeted methylation sequencing** and **machine-learning** classifiers

50+ AJCC cancer types

Test is **intended to complement guideline-recommended screening** (eg, mammography)

Designed to detect **many lethal cancers, including unscreened types**

High specificity (99.5%) minimizes false positives and unnecessary work-ups

AJCC, American Joint Committee on Cancer.

[1]Galleri was developed, and its performance characteristics determined, by the GRAIL. Inc. Clinical Laboratory in Menlo Park, CA USA. Galleri has not been cleared or approved by the U.S. Food and Drug Administration.

Overview

- **UK NHS's Long Term Plan:**
  - **To increase detection of stage I or II cancers to 75% by 2028**.
- UK NHS is conducting a large-scale **pragmatic randomised controlled trial (PRCT)** of this MCED test to evaluate stage shift:
  - **Primary Objective:** To show **significant reduction in late-stage cancers.**
    - Late-stage reduction is a surrogate endpoint for cancer-specific mortality reduction (advocated by experts in cancer screening).
    - Late-stage reduction will be achieved earlier in time, which offers an opportunity to start to save lives earlier.
  - To contribute to the **NHS's Long Term Plan**.

- This PRCT will take **a few years** to assess stage shift.

MCED, Multi-Cancer Early Detection; NHS, National Health Service; PRCT, Pragmatic Randomized Controlled Trial.

Overview

<u>Question:</u> Is there any modeling that can efficiently provide insight into the possible outcomes of the NHS PRCT?

- **Microsimulation** can be an efficient and flexible approach.
  - Individual trajectories instead of deterministic mean response.
  - Account for variation: stochastic & individual characteristics.
- **But few tackle multi-cancer tests**.

Therefore

- We **proposed a novel microsimulation** model targeting multi-cancer tests.
  - **Simulated the NHS's PRCT.**
  - **Modeled Stage shift.**
    - Additionally, with extended follow-up, modeled mortality reduction.

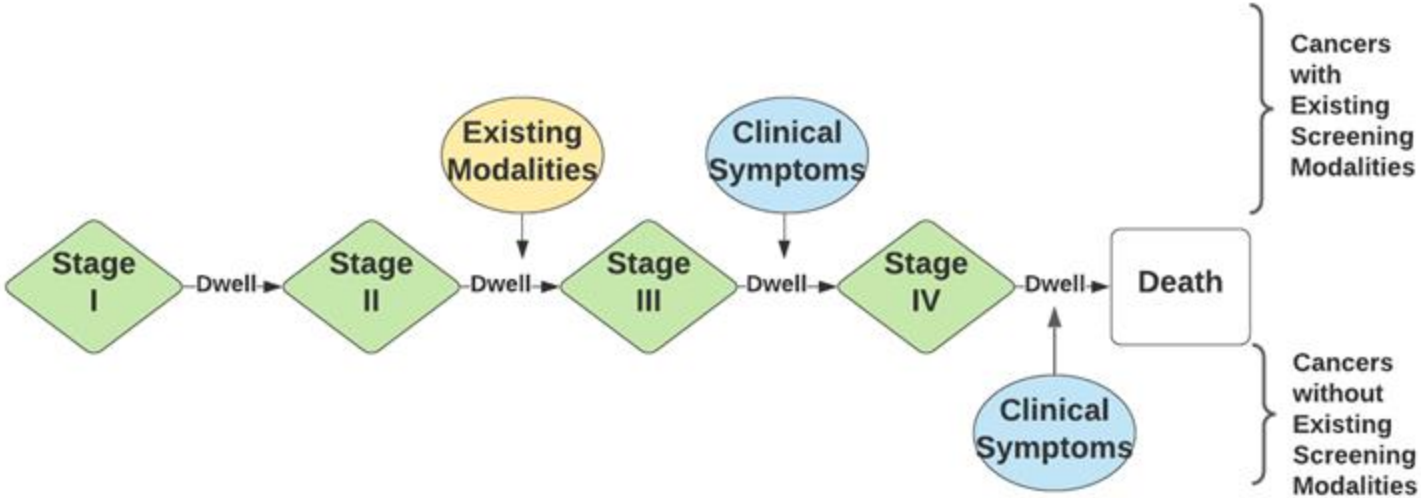
MCED, Multi-Cancer Early Detection; NHS, National Health Service; PRCT, Pragmatic Randomized Controlled Trial.

Methods: **Natural History of Cancer and Individual Cancer Trajectories**

Natural history of cancer

Methods: **Natural History of Cancer and Individual Cancer Trajectories**

Hypothetical illustration of detection by routine care

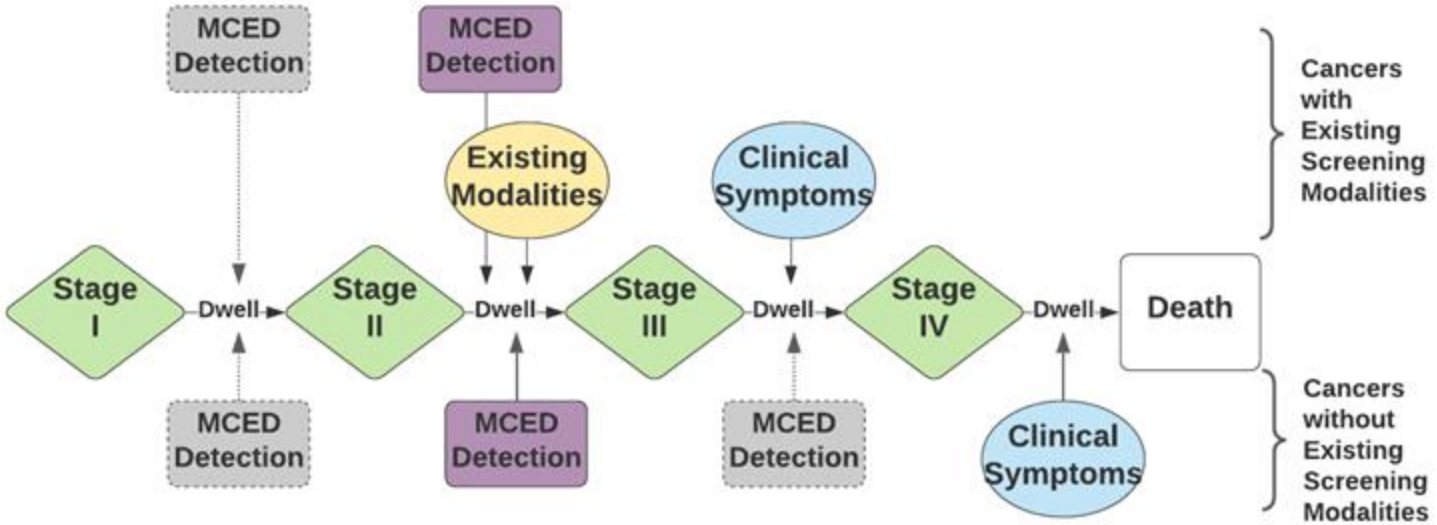


Note that for cancers without existing screening modalities, clinical symptoms can arise at any stage, but are most likely at later stages, particularly stage IV.[1]

[1]Narayan A, Fischer A, Zhang Z, Woods R, Morris E, Harvey S. Nationwide cross-sectional adherence to mammography screening guidelines: national behavioral risk factor surveillance system survey results. *Breast Cancer Res Treat*. 2017;164(3):719-725.

Methods: **Natural History of Cancer and Individual Cancer Trajectories**

Hypothetical illustration of earlier interception by the MCED



"MCED Detection" in purple is one arbitrary example and "MCED detection" in gray shows other possibilities. "MCED Detection" during the dwell time between stage II and III will result in a diagnosis of stage II cancer.
Note: The MCED's intended use population is asymptomatic.

MCED, Multi-Cancer Early Detection.

Methods: **Modeling Natural History of Cancer and Detection by Routine Care**

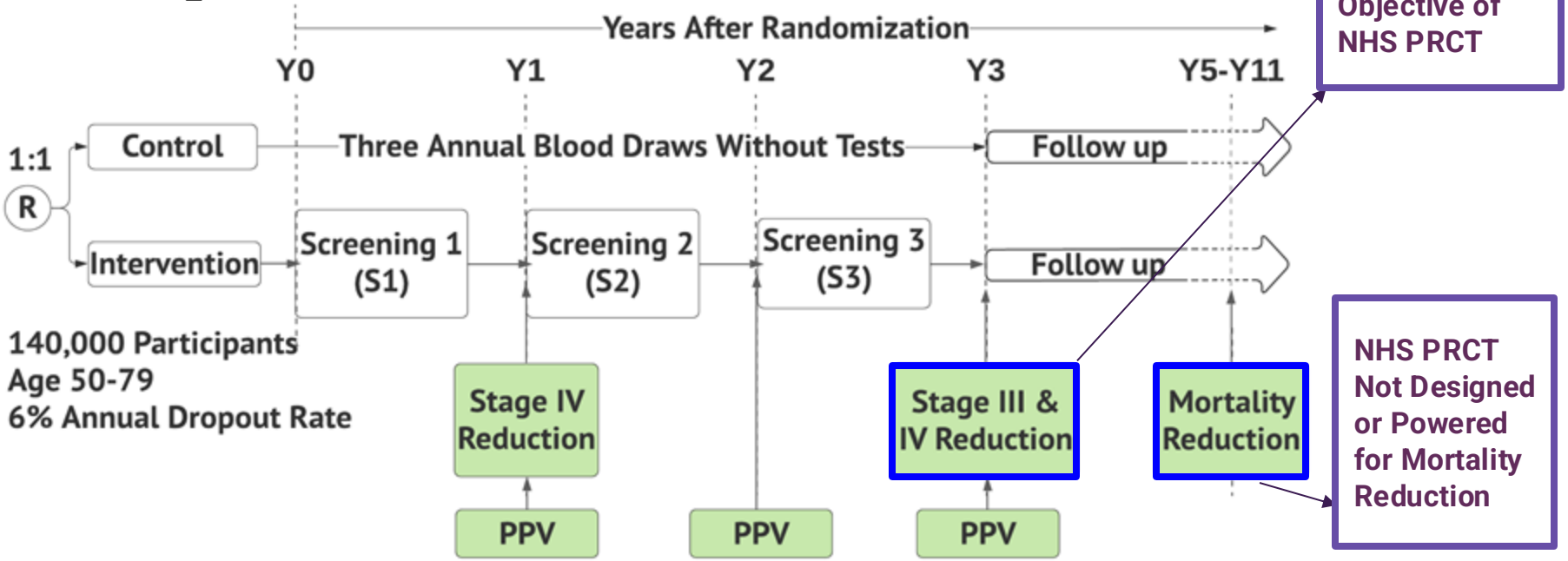
- Used the **CCGA3** test performance data.
- Used **US SEER** incidence, stage and survival input data.
- **T(Original diagnosis): Exponential** distribution with mean rate to match the SEER incidence.
- **Cancer type & Original stage: Multinomial** distribution according to empirical SEER data.
- **Preclinical trajectory** = T(Original diagnosis) - △T (current stage) - △T(previous stages).
- **△T**=Dwell time: **Exponential** distribution; Representing tumor growth rate.
  - Slow (3-7 years in stage I), fast (2-4 years), and aggressively fast (1-2 years).[1]
- **T(Original mortality): Linear** interpolation of empirical SEER survival data.

CCGA3, Circulating Cell-free Genome Atlas (CCGA; NCT02889978) Sub-study 3; SEER, Surveillance, Epidemiology, and End Results (National Cancer Institute).

[1]Hubbell E, Clarke CA, Aravanis AM, Berg CD. Modeled reductions in late-stage cancer with a multi-cancer early detection test. *Cancer Epidemiol Prev Biomark*. 2021;30(3):460-468.

Methods: **Modeling Screening with the MCED Test**

Screening Schema



Screening schema illustrating both the simulated pragmatic PRCT structure and the outcome measures at different study lengths.

MCED: Multi-Cancer Early Detection; PPV, Positive Predictive Value; PRCT, Pragmatic Randomized Controlled Trial.

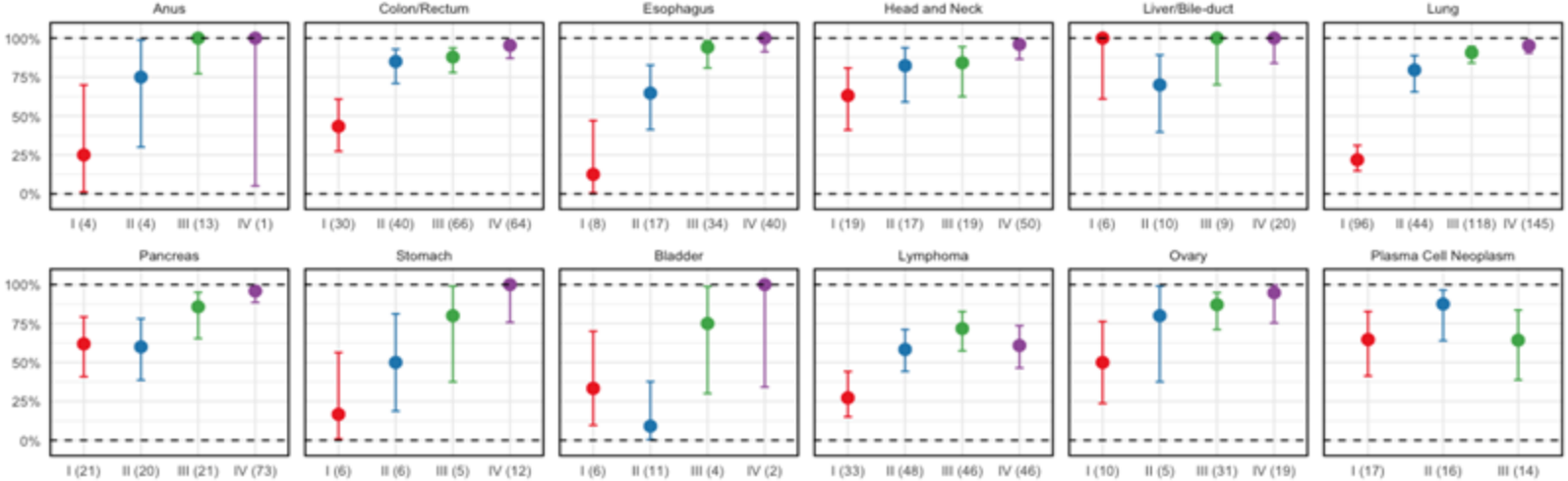
Methods: **Modeling Screening with the MCED test**

- Screening with the MCED test can detect cancers at earlier stages and extend survival.
  - **Detection by the MCED** of preclinical invasive cancer was **dependent on the MCED's sensitivity**.
  - **Detected at an earlier stage** ⇒ **An update of cancer-specific mortality event**.
    - Surviving to the original date of diagnosis;
    - Following the interpolated distribution for survival **based on the updated stage** at detection translated to the original diagnosis time.
  - Updated time to cancer diagnosis, stage and mortality.

MCED, Multi-Cancer Early Detection.

Methods: **Modeling Intervention by Screening with the MCED test**

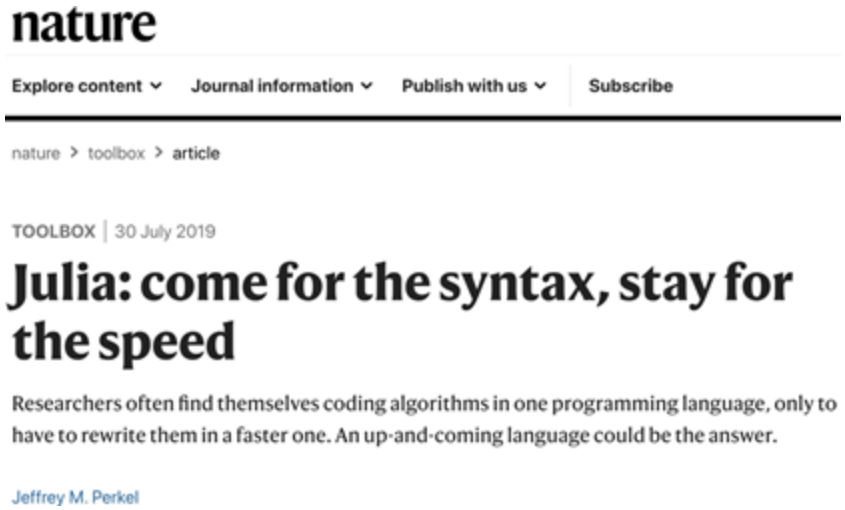
- **CCGA3** study provided performance data.
  - The **overall specificity was 99.5%**.
  - **Sensitivity by cancer class by stage** was estimated using isotonic MCMC.
    - Example: sensitivities of cancers that account for ⅔ deaths in the US.



CCGA3, Circulating Cell-free Genome Atlas (CCGA; NCT02889978) Sub-study 3; MCED, Multi-Cancer Early Detection; MCMC, Markov-chain Monte Carlo.

Methods: **Powerful Language Julia with Parallel Computing**

- Julia is an **open-source** language that combines the **interactivity and syntax of "scripting" languages**, such as R and Python, with **the speed of "compiled" language** such as C.
- **Rapid** prototyping and production.
- Overcomes the two-language problem.
- User-friendly distributed computing.
    - **Parallel running across 96 cores on Amazon EC2 M5 instance.**
- **Fast, easy, powerful!**



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Julia: come for the syntax, stay for the speed

Researchers often find themselves coding algorithms in one programming language, only to have to rewrite them in a faster one. An up-and-coming language could be the answer.

Jeffrey M. Perkel

Outcomes: **Intercept Cancers Earlier in Time**

Table 1. Cumulative proportions of more cancers detected in the interventional arm compared with the control arm after three rounds of screening*

Tumor growth‡	Prevalent screening	Y3 (Cum.§)	Y11† (Cum.)
Slow	123.83% (102.77% to 146.98%)	44.58% (35.96% to 53.56%)	7.71% (3.87% to 11.51%)
Fast	72.63% (55.63% to 88.62%)	26.06% (18.26% to 34.72%)	**3.74% (−0.17% to 8.12%)**
Aggressively fast	32.10% (19.32% to 46.87%)	11.87% (5.41% to 18.91%)	**1.45% (−2.41% to 5.52%)**

*CIs that include 0 are in bold.
†Y11 reflects a study length of 11 years after randomization.
‡Three different tumor growth rates were represented by three sets of dwell times in modeling.
§Cum.=Cumulatively.

- Prevalent screening (screening-naive): intercepted most cancers (that would **eventually surface clinically**) that were routine care **undetectable** but MCED **detectable** at the time of screening.
- Incident screenings (screening-experienced): intercepted additional such cancers and newly developed cancers also earlier in time.
- MCED intercepted cancers years earlier.

CI: Confidence Interval; MCED, Multi-Cancer Early Detection.

Outcomes: **Significant Reduction in Stage III and IV Cancers**

Table 2. Cumulatively absolute and relative reductions of stage III and IV cancers after three rounds of screening*

Tumor growth†	Stage III and IV cancers		Absolute reduction	Relative reduction	Power‡
	Control	Intervention			
Slow	735 (683 to 789)	558 (508 to 609)	177 (104 to 249)	23.93% (14.86% to 32.34%)	97.60%
Fast	737 (686 to 786)	533 (486 to 587)	203 (126 to 278)	27.49% (18.05% to 35.97%)	>99%
Aggressively fast	734 (680 to 785)	511 (462 to 555)	223 (151 to 296)	30.31% (21.85% to 38.11%)	>99%

*Results summarized at Y3.
†Three different tumor growth rates were represented by three sets of dwell times in modeling.
‡Power to detect a significant reduction with a two-sided test.

- Relative reduction of late stage cancer is >23%.
- Power to detect a significant reduction is >97%.

Outcomes: **Increased Detection of Early-Stage Cancers**

Table 3. Cumulative proportion of stage I and II cancers after three rounds of screening*

Tumor growth†	Control	Intervention
Slow	62.07% (59.89% to 64.26%)	**80.06%** (78.16% to 81.82%)
Fast	62.04% (60.26% to 64.01%)	**78.18%** (76.18% to 80.15%)
Aggressively fast	62.13% (59.99% to 64.19%)	**76.43%** (74.46% to 78.39%)

*Results summarized at Y3.
†Three different tumor growth rates were represented by three sets of dwell times in modeling.

- **NHS Long Term Plan achievable.**
- Proportion of detected stage I and II cancers increased from approximately 62% to **over 76%** for all tumor growth rates.
- Note: 62% is for US population based on SEER data; UK may have a lower percentage of early stage cancers[1].

[1]Coleman MP, Forman D, Bryant H, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. *The Lancet*. 2011;377(9760):127-138.
NHS, National Health Service; SEER, SEER, Surveillance, Epidemiology, and End Results (National Cancer Institute).

Outcomes: **FPs, PPVs**

S1 = Screening 1
S2 = Screening 2
S3 = Screening 3

MCED Positive Result

	True Positive			False Positive		
	S1	S2	S3	S1	S2	S3
Slow	1102 (1004 to 1204)	220 (106 to 322)	206 (102 to 311)	331 (298 to 365)	308 (244 to 370)	281 (207 to 362)
Fast	722 (654 to 797)	203 (118 to 280)	190 (102 to 277)	339 (304 to 376)	314 (253 to 374)	290 (203 to 370)
Aggressively Fast	405 (360 to 451)	172 (112 to 232)	162 (97 to 233)	**344** (307 to 381)	**318** (257 to 380)	**294** (214 to 376)

	PPV (S1)	PPV (S1 & S2)	PPV (S1, S2 & S3)
Slow	76.87% (74.62% to 79.24%)	67.40% (64.95% to 69.96%)	62.41% (60.06% to 64.67%)
Fast	68.06% (64.93% to 71.25%)	58.63% (55.76% to 61.49%)	54.18% (51.61% to 56.91%)
Aggressively Fast	**54.04%** (50.10% to 58.02%)	**46.52%** (43.39% to 49.73%)	**43.57%** (40.86% to 46.15%)

FP: False Positive; MCED: Multi-Cancer Early Detection; PPV: Positive Predictive Value.

- Low false positive numbers: false positive rate= 0.5%.
- Estimated PPV: higher than those of most accepted single cancer screening tests.

Additional Modeling Outcomes: **Cancer-specific Mortality Reduction**

Table 4. Cancer-specific mortality reduction

Study length	Tumor growth†	Deaths per 1000 person-years		Rate ratio	Power‡
		Control	Intervention		
Y5*	Slow	1.88 (1.74 to 2.02)	1.50 (1.37 to 1.64)	0.80 (0.72 to 0.89)	97.6%
	Fast	1.88 (1.74 to 2.03)	1.53 (1.40 to 1.66)	0.81 (0.72 to 0.90)	95.6%
	Aggressively fast	1.88 (1.74 to 2.02)	1.55 (1.43 to 1.68)	0.83 (0.74 to 0.92)	92.0%

*Results reflect a study period of 5 years after randomization.
†Three different tumor growth rates were represented by three sets of dwell times in modeling.
‡Power to detect a significant mortality reduction with a two-sided exact test.

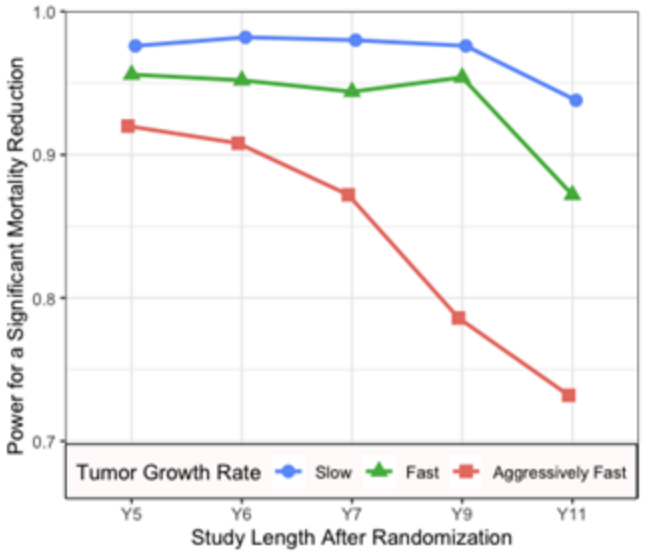
- Around 20% mortality reduction.
- Power >=92%.

Note:

- The NHS PRCT was not designed to show mortality reduction.
- Late-stage reduction is a surrogate endpoint and can be achieved earlier, providing an opportunity to save lives earlier.

NHS, National Health Service; PRCT, Pragmatic Randomized Controlled Trial.

Additional Modeling Outcomes: **Cancer-specific Mortality Reduction**



Power to detect a significant mortality reduction for different lengths of follow-up under different tumor growth rates.

- A drop in power is likely starting from Y7-Y9 due to the lack of routine, periodic screenings (i.e., only three rounds in the NHS PRCT and our modeling).
- A limited screening period with an extended observation period may underestimate the benefit of screening.[1]

Note:

- The NHS pragmatic RCT was not designed to show mortality reduction.
- Late-stage reduction is a surrogate endpoint and can be achieved earlier, providing an opportunity to save lives earlier.

[1]Duffy SW, Smith RA. A note on the design of cancer screening trials. *J Med Screen*. 2015;22(2):65-68.
NHS, National Health Service; PRCT, Pragmatic Randomized Controlled Trial.

Discussion: **Complexities Addressed & Remaining Limitations**

Complexities Addressed

- UK data not available ⟶ used **US SEER data**. However, late-stage cancer more frequent in the UK ⟶ our results could be **conservative**.
- Preclinical natural history of cancers detectable by cfDNA is largely unknown ⟶ conducted **Robust analysis** by varying the dwell time (i.e., tumor growth rate) scenarios.
- Uncertainties in sensitivity estimates ⟶ applied **MCMC**.

Remaining Limitations

- **Did not model the pathways to diagnosis**; assumed to be effective.
- **Did not model overdiagnosis** (cancers that would not surface clinically).
- Extrapolated performance from a **case-control** study to a **preclinical** domain.

cfDNA, cell-free DNA; MCMC, Markov chain Monte Carlo; SEER: Surveillance, Epidemiology, and End Results (National Cancer Institute).

Discussion: **Key Summary**

Proposed a **novel microsimulation** modeling to demonstrate potential benefit of adding the MCED test to routine care.

- **Early-stage** cancer detection increased from approximately 62% to **over 76%**.
- **Relative reduction of late-stage** cancer was **over 24% (Power>97%).**
- Estimated **PPV** was **higher** than most accepted single cancer screening tests.
- The likelihood of **severe harm** due to the MCED test was **low**, with an FP rate of 0.5%.

Additionally with a much longer follow-up period,

- Stage shift resulted in a **cancer-specific mortality reduction** of around **20%**.

Modeling results informed that:

A widespread adoption of the MCED test in the UK may help the NHS achieve its Long Term Plan of diagnosing 75% cancers at early stage by 2028, save lives, and improve cancer care.

MCED, Multi-Cancer Early Detection; NHS, National Health Service; PPV, Positive Predictive Value.

Acknowledgement

- We thank **Dr. Christina A. Clarke** for obtaining the SEER incidence and survival data.
- We thank **Dr. Stephannie Shih** for assistance in generating the tables and figures.
- We thank **Drs. Arash Jamshidi, Deepshikha Bhandari, Megan Hall, Amy Sinor-Anderson, I-Zu Huang, Phillip Kiefer, Nathan Hunkapiller, Harpal Kumar** and **Josh Ofman** for their constructive comments.