Prognostic significance of blood-based multi-cancer detection in circulating tumor DNA (ctDNA): 5-year outcomes analysis

Charles Swanton, MD, PhD[1]; Alan Bryce, MD[2]; Allen L Cohn, MD[3]; Matthew Margolis, MS[4]; Earl Hubbell, PhD[4]; April Sagan, PhD[4]; Oliver Venn, PhD[4]; Michael Seiden, MD, PhD[5]

[1]Cancer Evolution and Genome Instability Laboratory, The Francis Crick Institute, London, UK; [2]City of Hope Cancer Center, Phoenix, AZ; [3]Rocky Mountain Cancer Center; Denver, CO; [4]GRAIL, Inc., Menlo Park, CA; [5]N Power Medicine, Redwood City, CA.

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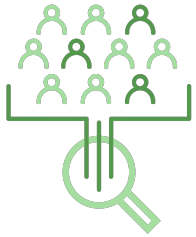
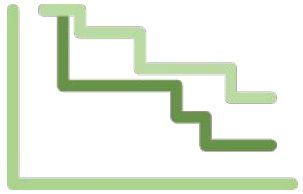
Key Takeaways of 5-Year Follow-up Analysis of a Multi-Cancer Early Detection (MCED) Test



MCED Testing of Participants **with Known Cancer Status**



Comparison of **Observed** to **Expected** Survival Removes Expected Variation in Survival

Survival differences between detected and undetected cases largely explained by clinical factors

- Undetected cancers follow a more indolent course, particularly at early stages
- Survival for cases with a cancer signal detected was similar to cases detected by conventional means, even at early stages

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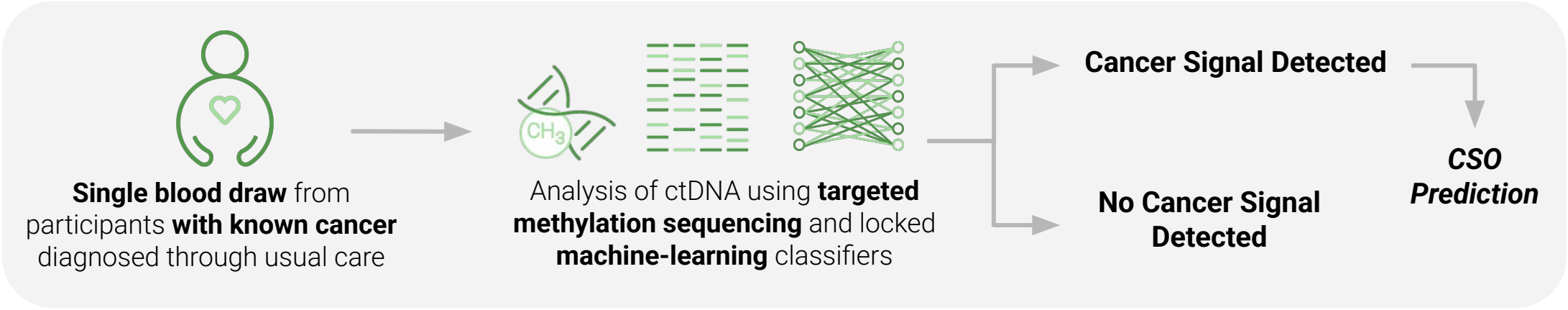
MCED Tests Detect a Cancer Signal and Predicts the Site of Origin

An MCED test that uses targeted methylation sequencing of circulating tumor DNA (ctDNA) in blood was developed in the case-control **Circulating Cell-free Genome Atlas (CCGA) Study**[1] (NCT02889978)

- The MCED test detects **a shared cancer signal associated with many cancer types**, most without guideline-recommended screening, with high specificity (≥99.5%)
- If a cancer signal is detected, the test will also return the predicted site of cancer signal origin (CSO)

MCED Testing Process in CCGA



MCED, multi-cancer early detection.

1. Klein EA, et al. *Ann Oncol*. 2021;32(9):1167-1177.

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Analysis of ctDNA May Have Prognostic Implications Beyond Early Cancer Detection

High levels of ctDNA in the blood have been associated with:[1-3]

- Later stage cancers
- Poorer prognosis
- Aggressive cancers
- Metastasis

Tumors that do not shed detectable levels of ctDNA have been associated with:[1,2,4]

- Early-stage cancers
- Better prognosis
- Indolent cancers
- Less recurrence

What is the prognostic value of cancer signal detection by a ctDNA-based MCED test?

ctDNA, circulating tumor DNA; MCED, multi-cancer early detection.

1. Abbosh C, et al. Nature. 2023;616(7957):553-562; 2. Black JRM, et al. Nat Med. 2025;31(1):70-76; 3. Xu R, et al. Nat Mater. 2017;16(11):1155-1161; 4. Øgaard N, et al. Br J Cancer. 2024;131(10):1707-1715.

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Reframing Our Understanding of Survival in Those With a Detected/Not Detected MCED Test Result

Previous CCGA analysis (Chen, et al)[1]

- *Early version of the MCED test validated in the second CCGA substudy*
- *3-year longitudinal follow-up*

Conclusion: *Cancers not detected by the MCED test had better prognosis than cancers detected and SEER-based expected survival*

New CCGA analysis

- Refined version of the MCED test clinically validated in the third CCGA substudy[2]
- 5-year longitudinal follow-up
- Used updated statistical model to account for confounding variation in cancer type and stage

CCGA, Circulating Cell-free Genome Atlas study; MCED, multi-cancer early detection; SEER, Surveillance, Epidemiology, and End Results.

1. Chen X, et al. Clin Cancer Res. 2021; 27(15):4221-4229; 2. Klein EA, et al. *Ann Oncol.* 2021;32(9):1167-1177.

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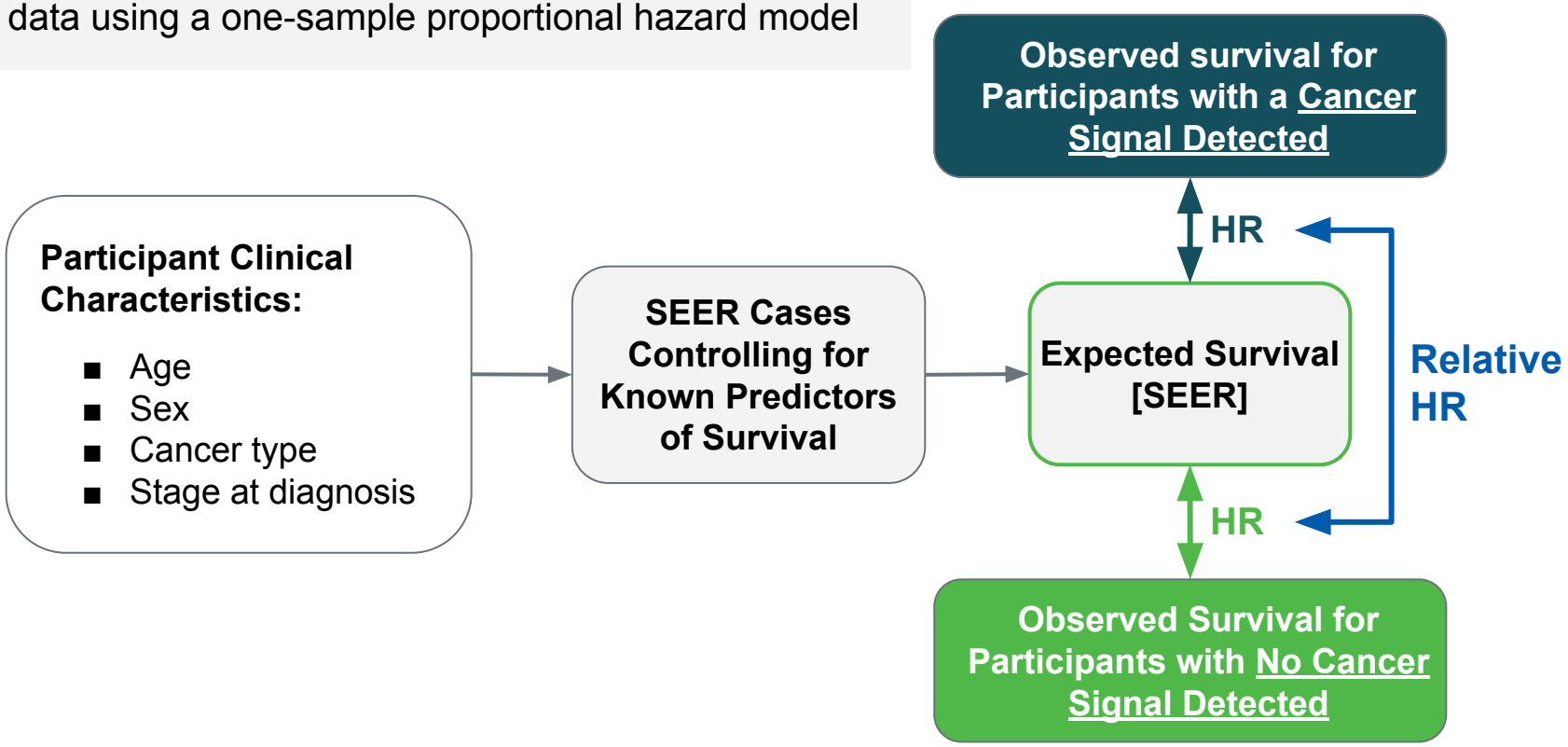
Standardization to SEER Reference Reduces Expected Variation From Known Survival Predictors

Observed survival at 5 years was compared with **expected survival** calculated from SEER reference data using a one-sample proportional hazard model



What Factors Might Contribute to Differences in Relative HR Between Signal Detection Groups?

- More indolent cancers
- Harder to treat cancers
- Recruitment of healthy volunteers

HR, hazard ratio; SEER, Surveillance, Epidemiology, and End Results.

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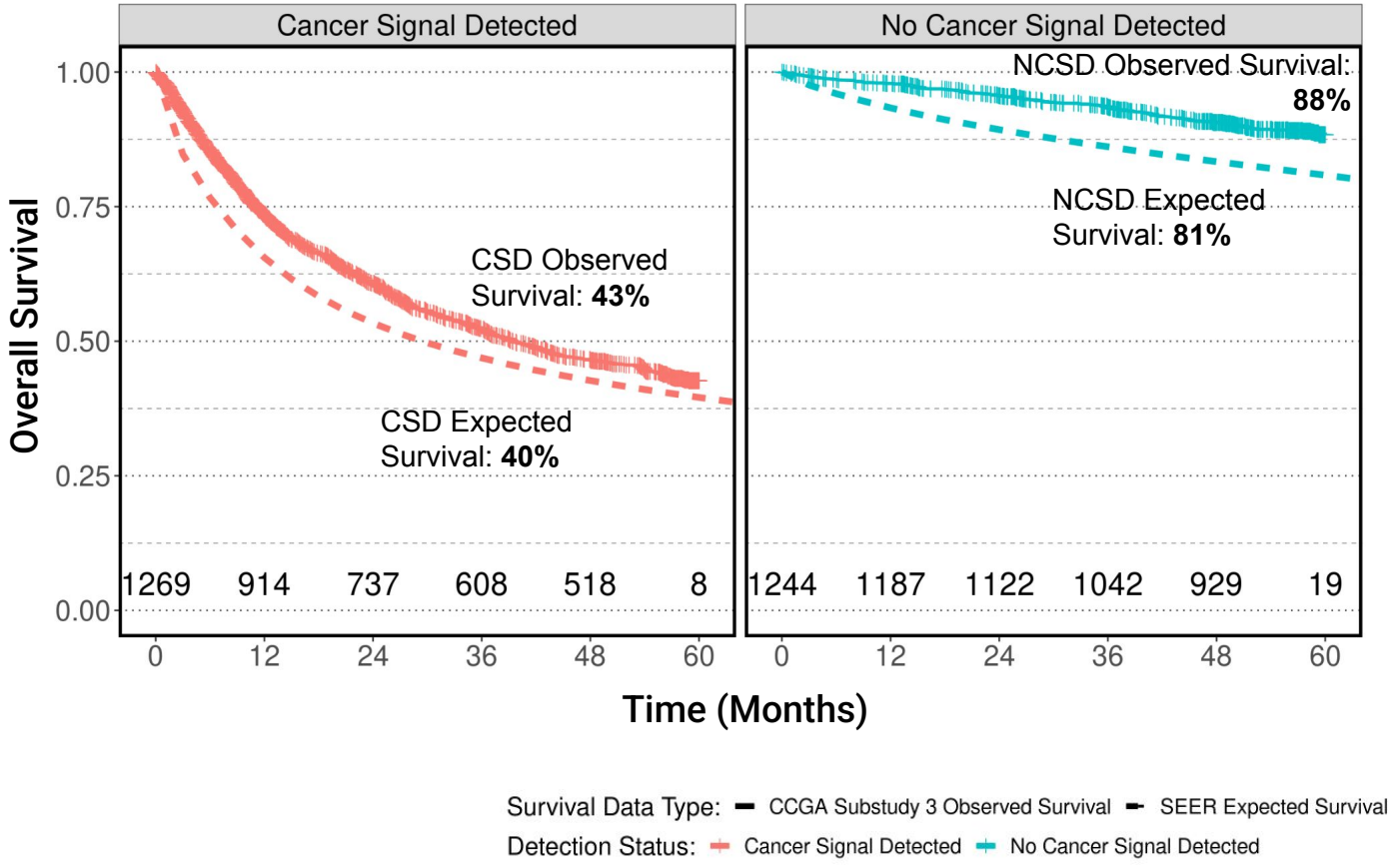
Survival Advantage for NCSD Versus CSD Cancers Remains After Controlling for Known Survival Predictors

Observed Survival[a] Vs Expected Survival by Signal Detection Status



Hazard Ratios for Cancer Signal Detection Groups and SEER Reference Population

	Hazard Ratio	95% CI	P-value
NCSD VS SEER	0.42	0.35 – 0.50	5.06e-26
CSD VS SEER	0.72	0.67 – 0.78	1.26e-16
NCSD vs CSD	0.60	0.50 – 0.72	6.19e-09

- The majority of variation resulted from known clinical factors
- Both groups show improved survival compared with expectations, suggesting healthy cohort relative to SEER

CI, confidence interval; CSD, cancer signal detected; NCSD, no cancer signal detected; SEER, Surveillance, Epidemiology, and End Results.
[a]Defined as the time from the date of blood sample collection to the date of death or last date the participant was confirmed alive.

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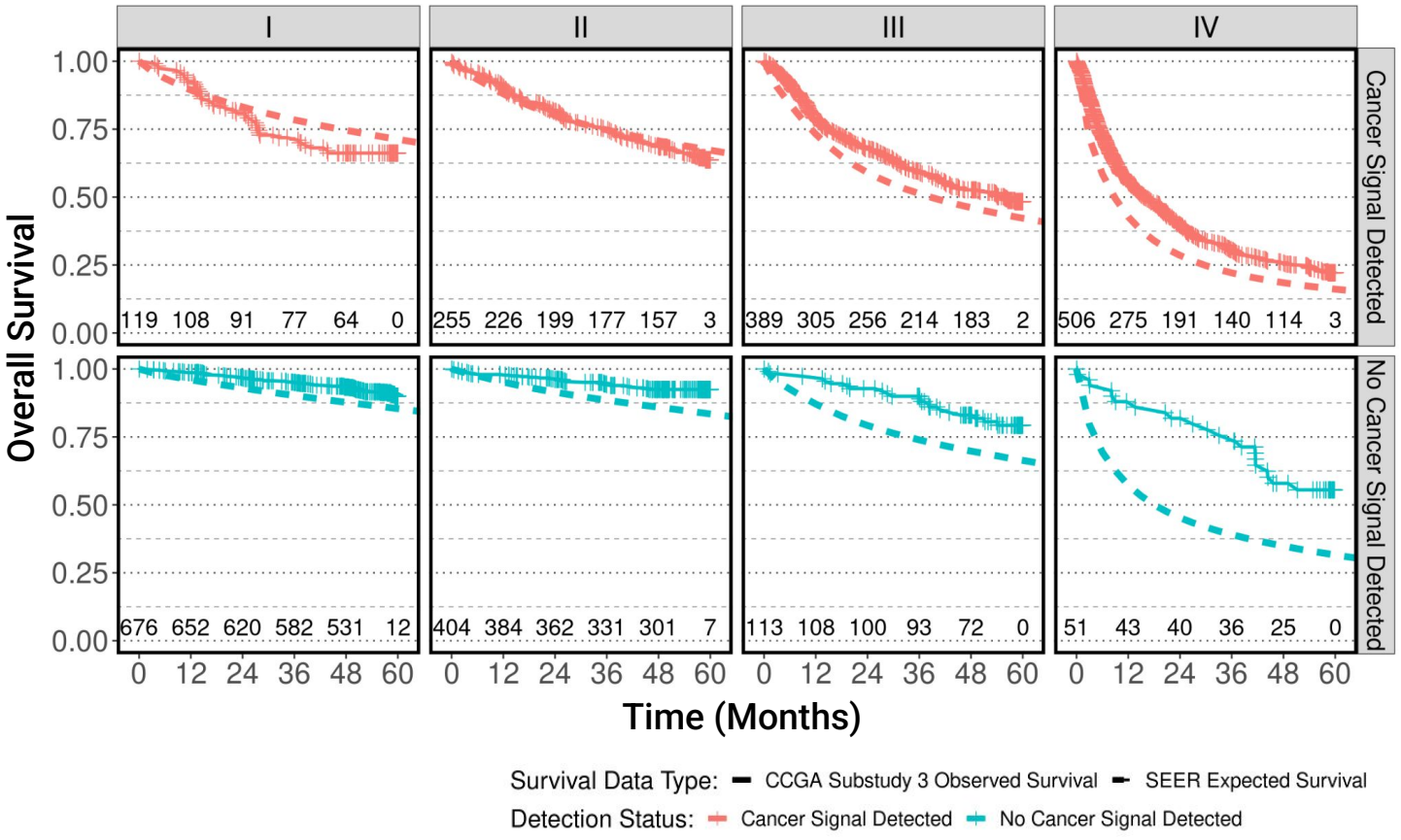
Observed Survival Curves Were Similar to or More Favorable Than Expectations—Even at Early Stages

Observed Survival[a] Vs Expected Survival by Stage and Signal Detection Status



Stage	CSD vs SEER	NCSD vs SEER
I	66% vs 71%	90% vs 85%
II	64% vs 67%	92% vs 83%
III	48% vs 42%	79% vs 66%
IV	22% vs 16%	56% vs 32%

- Across stages, observed survival curves for CSD cancers were generally similar to SEER-based expectations
- NCSD cancers had dramatically better survival than expected at later stages

CSD, cancer signal detected; NCSD, no cancer signal detected; SEER, Surveillance, Epidemiology, and End Results.
[a]Defined as the time from the date of blood sample collection to the date of death or last date the participant was confirmed alive.

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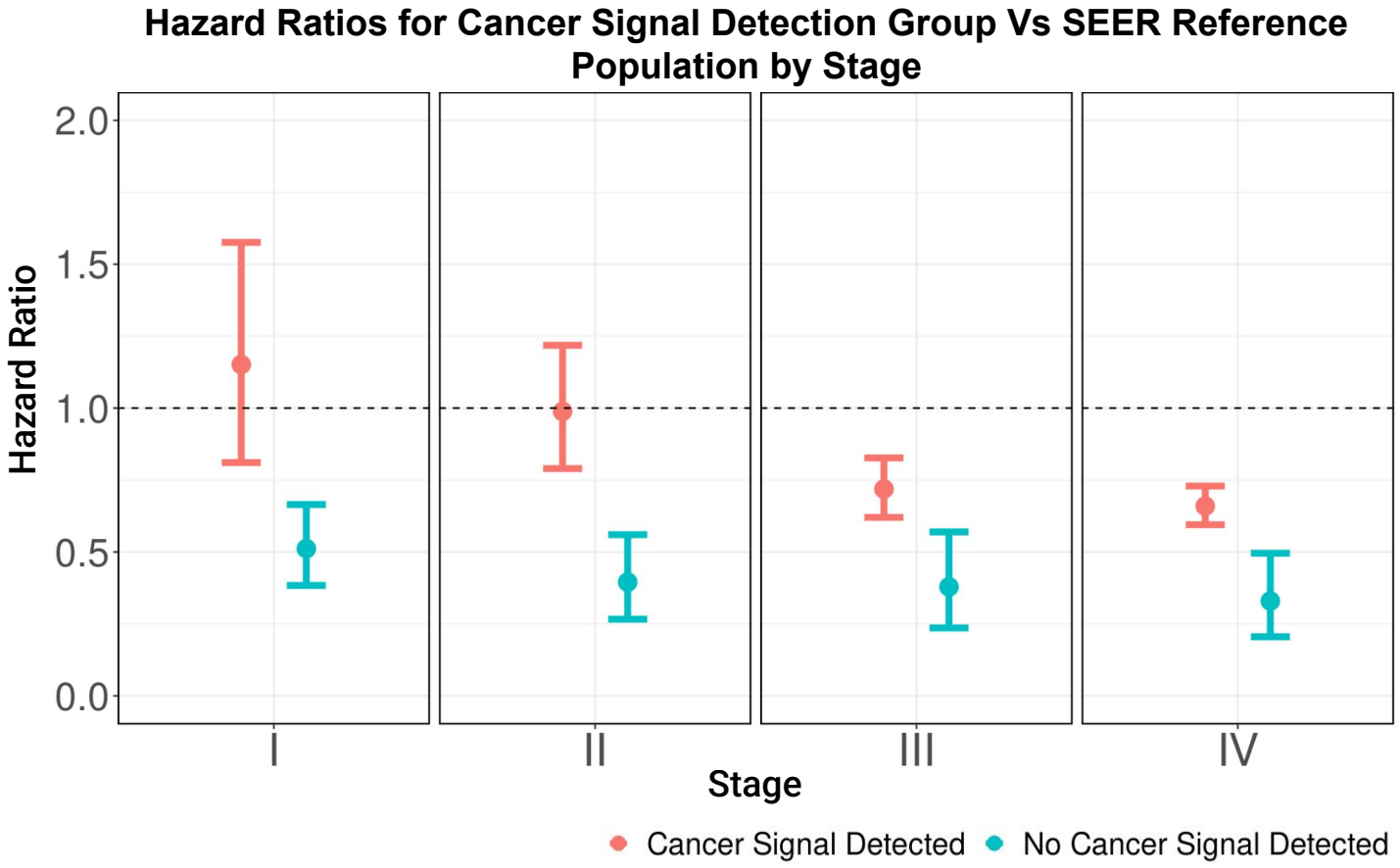
Early-Stage Cancers Detected by MCED had Survival Similar to Early-Stage Cancers in the SEER Population



- Hazard ratios were calculated comparing matched SEER reference populations to signal detection groups
- For NCSD, hazard ratios were <1 at all stages
- For CSD, hazard ratios were <1 at stages III and IV and ≥1 at stages I and II but not statistically significant

CSD, cancer signal detected; MCED, multi-cancer early detection; NCSD, no cancer signal detected; SEER, Surveillance, Epidemiology, and End Results.

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Extended Follow-Up of CCGA Participant Outcomes Improves Understanding of Survival and MCED Detection

Strengths

- Broad sampling of cancer types and stages across multiple care systems
- SEER reference data used as a synthetic control to account for variation in cancer type and stage correlated with detection
- 5-year follow-up post blood draw, a typical timespan for cancer survivor status

Limitations

- Non-interventional – Observational data diagnosed through usual care
- Complex cancer type and stage information with limited clinical covariates
- Healthy volunteer bias could impact observed survival
- Overall survival without cancer-specific causes of death

CCGA, Circulating Cell-free Genome Atlas study; MCED, multi-cancer early detection; SEER, Surveillance, Epidemiology, and End Results.

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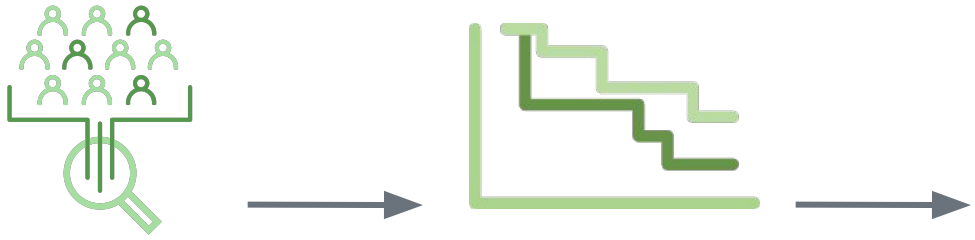
In Summary, 5-Year Follow-Up Analysis Suggests That Cancer Signal Detection May Inform Prognosis

CCGA Substudy 3 Outcomes Analysis



MCED Testing of Participants **with Known Cancer Status**

Comparison of **Observed** to **Expected** Survival Removes Expected Variation in Survival

Survival differences between detected and undetected cases largely explained by clinical factors

- There was evidence of a healthy volunteer bias when compared to age, sex, and tumor matched controls
- NCSD cancers follow a more indolent course than detected cancers
- Importantly, while CSD cancers had a meaningful risk of death, survival was similar to cases detected by conventional means, even at early stages

CCGA, Circulating Cell-free Genome Atlas study; CSD, cancer signal detected; MCED, multi-cancer early detection; NCSD, no cancer signal detected.

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We acknowledge the contributions to this effort by the patients, staff, and healthcare providers who provided clinical data as part of the Circulating Cancer Genome Atlas Study.

Questions?