Methylated DNA Biomarkers and Incident Cancer in the American Cancer Society (ACS) Cancer Prevention Study-3 (CPS-3) Cohort

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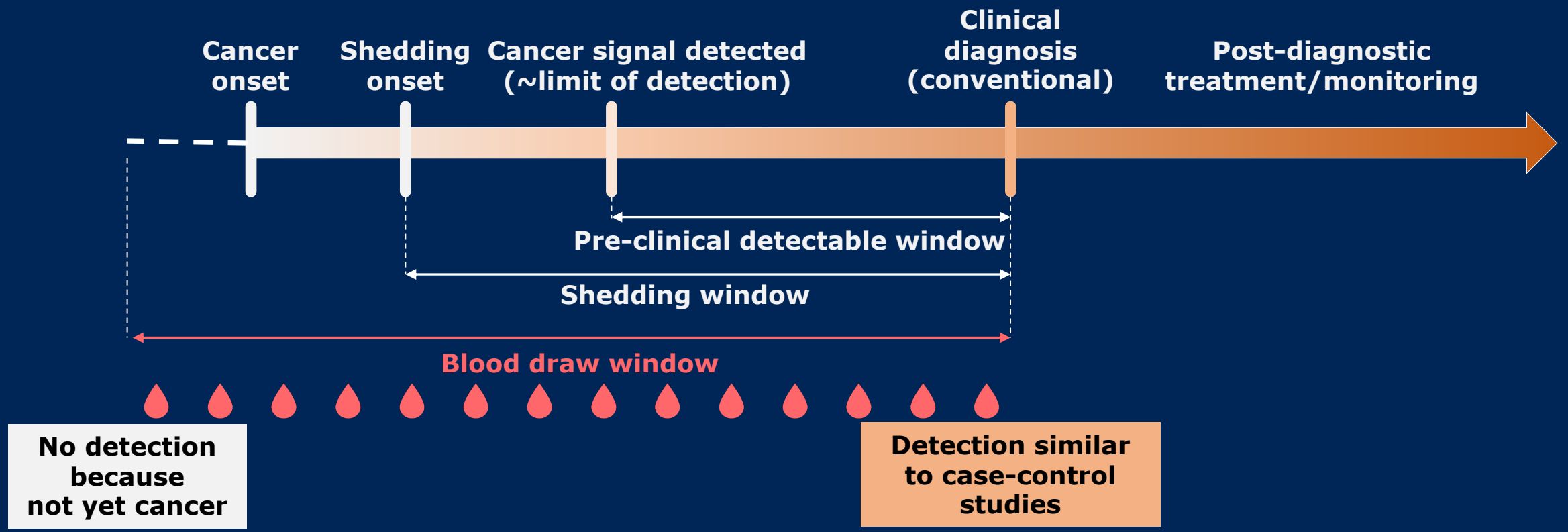
Abstract 3004

Cancer Signal Detection In Blood Is Determined By Cancer Biology[1-4]



1.Cheng et al. 2022. doi:10.21203/rs.3.rs-1203227/v1. 2. Chen et al. 2020. *Nat Commun*. 2020;11(1):3475. doi:10.1038/s41467-020-17316-z. 3. Harlid et al. *Cancers*. 2021;13(17):4406. doi:10.3390/cancers13174406. 4.Liu MC, et al. *Ann Oncol*. 2020;31(6):745-759. doi:10.1016/j.annonc.2020.02.011

The ACS CPS-3 Biobank Provides An Opportunity To Explore Preclinical Cancer Biology

ACS CPS-3[1] is a large prospective cohort study of 300K volunteers:

- Not initially diagnosed with cancer who gave blood samples and were followed for incident cancer
- With sufficient biobanked plasma volume available for retrospective characterization of MCED signal

Opportunity:

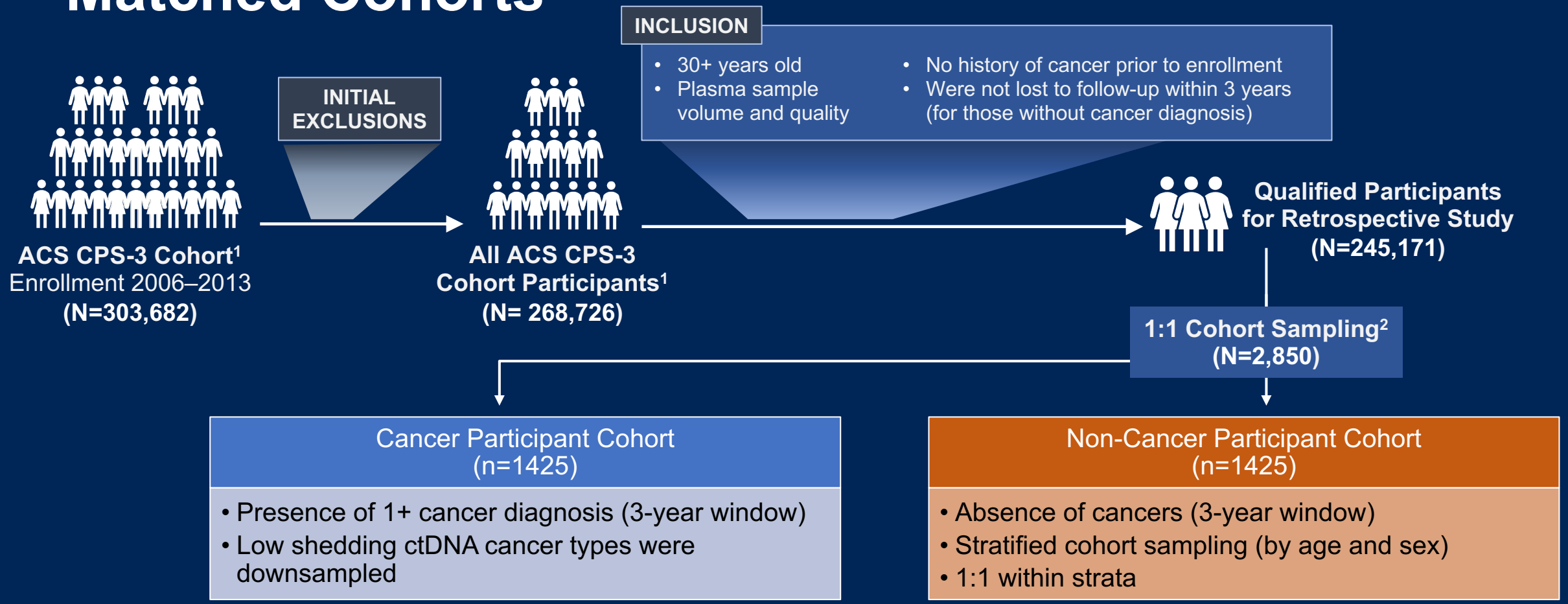
- Observe detectability of MCED signal in the "preclinical detection window" between blood draw and conventional diagnosis (up to 3 years)

Limitations:

- **Plasma processing differences (potential signal degradation):**
  - CPS-3 samples: EDTA tubes; 1 spin; frozen plasma aliquot 9-15 years
  - MCED standard: Streck tubes; 2 spins; fresh plasma
- **Low-risk population:** aged 30-65 years at lower-than-average risk of deadly cancers compared to SEER

ACS, American Cancer Society; CPS-3, Cancer Prevention Study-3; ctDNA, circulating tumor DNA; EDTA, Ethylenediaminetetraacetic acid; MCED, multi-cancer early detection; SEER, Surveillance, Epidemiology, and End Results.1. American Cancer Society. Accessed April 28,2023. https://www.cancer.org/research/cps3-cancer-prevention-study-3.html

ACS CPS-3/GRAIL Study Design Subsampled To Matched Cohorts



ACS, American Cancer Society; CPS-3, Cancer Prevention Study-3.

1. Patel AV, et al. *Cancer*. 2017;123(11):2014-2024. doi:10.1002/cncr.30561. 2. Gray RJ. 2009 Sep;15(3):411]. *Lifetime Data Anal*. 2009;15(1):24-40. doi:10.1007/s10985-008-9095-z

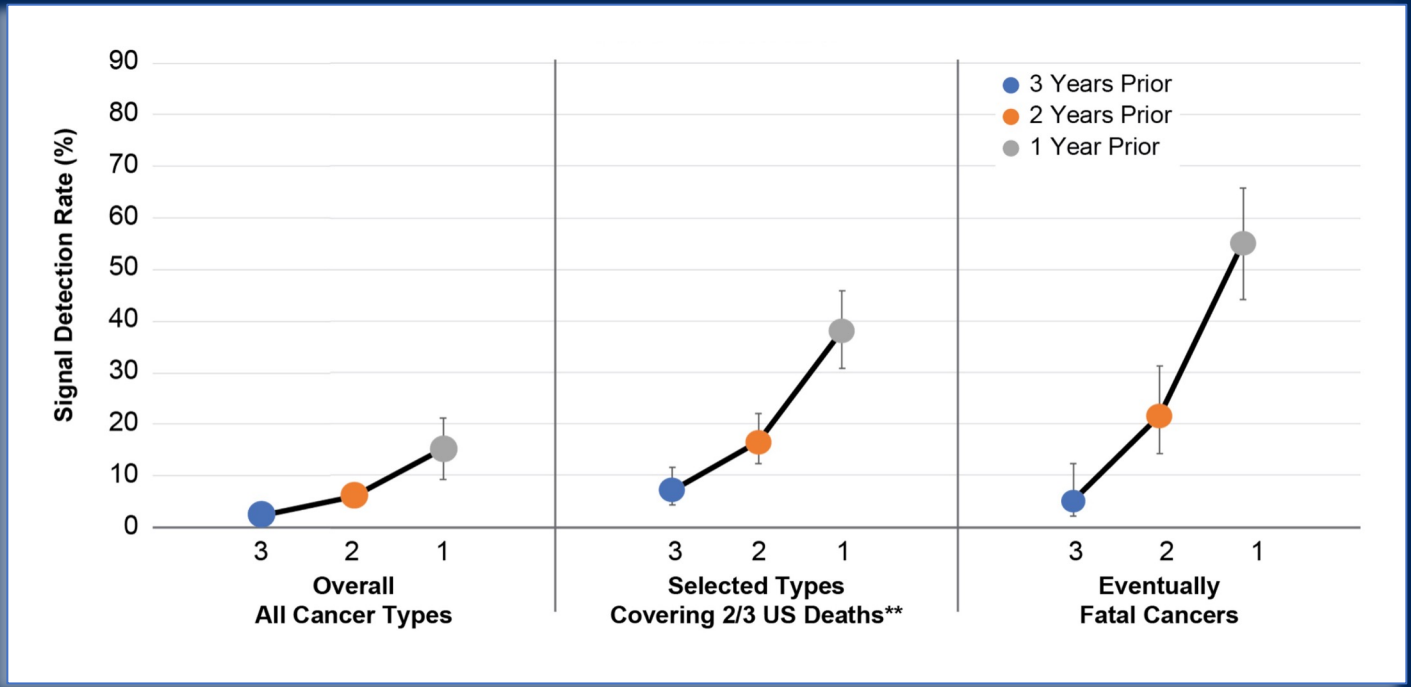
CPS-3 Cohort Demographics Differ From Standard Populations By Cancer Risk Factors

- Lower cancer incidence and mortality rates than SEER-expected[1]

Participant Characteristics*	Selected Cancer (n=1383)	Selected Non-Cancer (n=1371)	Selected Total (n=2754)
N (Cohort population)	2472	230,050	232,522
Age, mean, years (SD)	53.0 (9)	47.7 (10)	47.8 (10)
Sex, Female, n (%)	1824 (74)	175,114 (76)	176,938 (76)
White, non-Hispanic, n (%)	2143 (87)	192,870 (84)	195,013 (84)
Never Smoker, n (%)	1620 (66)	159,863 (70)	161,484 (69)
College Degree, n (%)	1265 (51)	115,184 (50)	116,450 (50)

*Counts and percentages with weighting applied to reflect the original study population.
SD, standard deviation; SEER, Surveillance, Epidemiology, and End Results.
1.Surveillance Epidemiology and End Results (SEER) Program. SEER*Stat Databases: November 2018 Submission. Incidence - SEER Research Data, 18 Registries, Nov 2019 Sub (2000-2017). Linked To County Attributes - Time Dependent (1990-2017) Income/Rurality, 1969-2017 Counties. National Cancer Institute; 2020. Accessed April 15, 2020. www.seer.cancer.gov

Both Cancer Characteristics And Time Between Blood Draw And Diagnosis Affect Detection Rate



- Lower overall detection rate than expected from SEER was observed as expected in a population with reduced rates of deadly cancers relative to other cancers*
- Aggressive cancers (selected types) had higher detection rates
- Eventually fatal cases in any cancer type had higher detection rates
- False positive rate was 0% (95% CI: 0.0%, 0.3%)

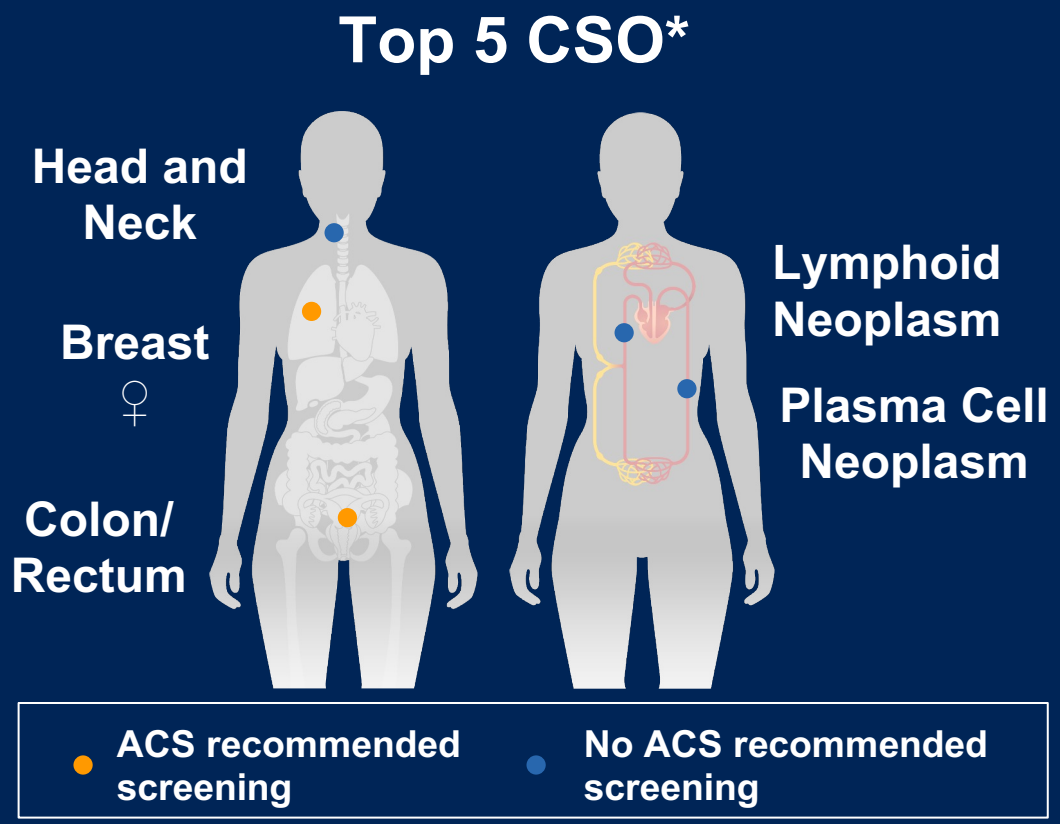
Sample storage may have affected absolute signal detection rate.

*Performance with weighting applied to represent the original study population. **Selected cancer types representing 2/3 of US deaths includes 12 cancer types (anus, bladder, colon/rectum, esophagus, head and neck, liver/bile-duct, lung, lymphoma, ovary, pancreas, plasma cell neoplasm, stomach).
CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results.

The Accuracy Of Prediction Of Cancer Signal Origin (CSO) Was High

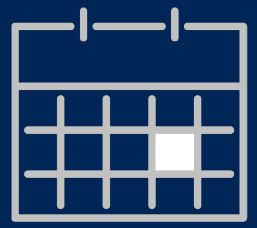
Top 1 CSO overall accuracy of prediction was:

- **95%** (95% CI: 90.4%, 100.0%) in Year 1
- **88%** (95% CI: 76.2%, 94.4%) in Year 2
- **81%** (95% CI: 57.0%, 93.4%) in Year 3



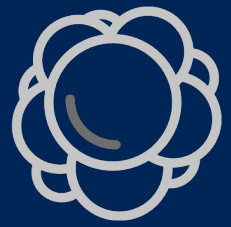
*Ranking with weighting applied to represent the original study population.
ACS, American Cancer Society; CI, confidence interval; CSO, cancer signal origin.

Detection Rates Are Consistent With ~1 Year Average Detectable Window



323 days

average time between blood draw and diagnosis among those detected



40%

of cancers detected found beyond 1 year

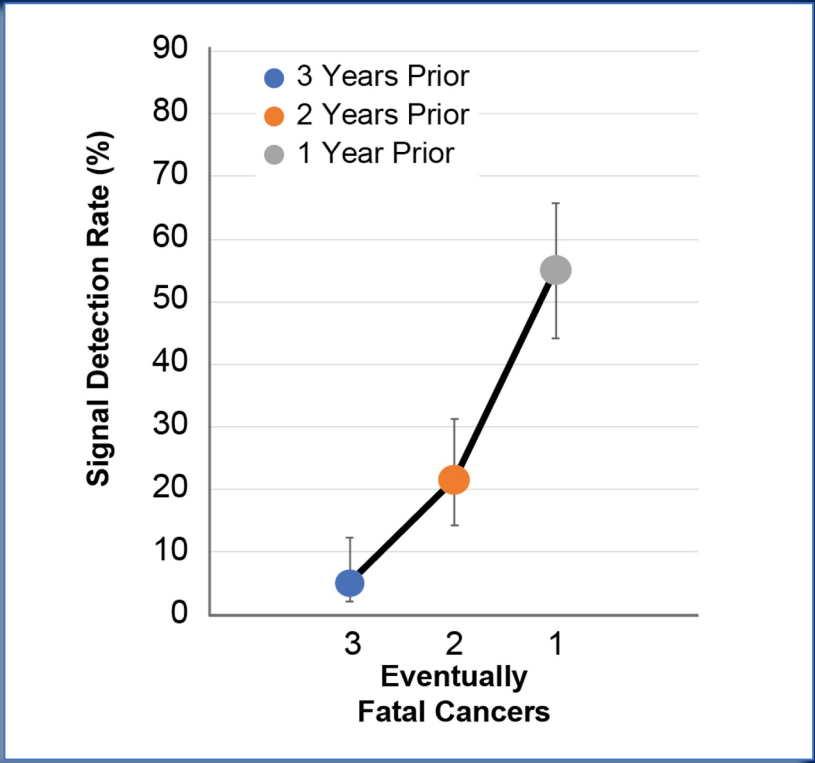
991 days

lead time for a colorectal cancer at regional stage

Cancers up to the end of the study period were still being detected

Stage or cancer status at blood draw not known.

The Shedding Rate Of Eventually Fatal Cancers Suggests Potential To Intervene Early And Predict Risk



Sample storage may have affected absolute signal detection rate. Performance with weighting applied to represent the original study population.

- The high efficiency of detecting eventually fatal cancers in this non-interventional study has implications for risk of death
  - This suggests overdiagnosis of indolent cancers is not likely
  - Individuals with negative test results are diagnosed with cancers already well controlled (<50% risk for those in the first year)
- Results suggest an average ~one-year detectable window
  - This window size may allow earlier intervention to occur

Conclusions: Explored Cancer Biology In A Relatively Low-Risk Adult Population

- The cohort was comprised of healthy, largely female and never smoker volunteers aged 30-65 at lower-than-average risks of overall cancer and particularly, deadly cancers
- Because the cohort banked analyzable plasma, it offered a unique opportunity to probe the preclinical detectable time window
  - However, non-standard plasma processing may impair cancer signal detection
- The results should be re-assessed in the intended use population aged 50-79 and ideally using MCED-standard sample processing

MCED, multi-cancer early detection.

Conclusions: Rapid Changes In Cancer Biology Occur Before Clinical Diagnosis

- Cancer signals were detected in preclinical blood draws
  - Potential for limits to signal due to plasma processing differences
  - With high efficiency for eventually fatal cancers
    - Underscoring the need for earlier intervention in those cases
  - Up to 3 years prior to conventional diagnosis
    - With average lead time ~one year
    - Potential for annual screening intervals
- Further assessment is needed to understand methylation cancer biology in
  - Fresh samples with current storage and processing practices
  - Pre-diagnostic samples and more specifically in serial samples from interventional studies

Thank You!

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For modeling of these time scales and prognosis, see poster 3060