# Molecular Cancer Signal Localization in Multi-Cancer Early Detection (MCED) Testing Minimizes Radiation and Imaging Burden Compared to Whole-Body Imaging Approaches

Early Detection of Cancer Conference (EDCC)
October 21–23, 2025
Portland, OR

Mylynda Massart, MD, PhD[1]; Sana Raoof, MD, PhD[2]; Earl Hubbell, PhD[3]; Eric Klein, MD[3]*

[1]University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; [2]The Warren Alpert Medical School of Brown University, Providence, RI, USA; [3]GRAIL, Inc., Menlo Park, CA, USA *Presenting author

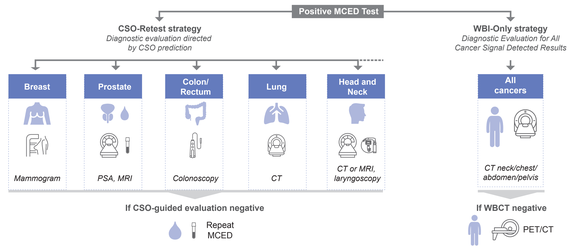
## INTRODUCTION

- Efficient strategies for diagnostic evaluation of MCED tests are needed to distinguish true positives (TPs) from false positives (FPs) with minimal burden and risk

## OBJECTIVE

- To compare 2 post-positive MCED test diagnostic resolution strategies: a Cancer Signal Origin (CSO)-guided approach with repeat MCED testing to resolve FPs (CSO-Retest Strategy) vs a Whole-Body Imaging (WBI)-Only Strategy employing WB computed tomography (CT) for test-positive individuals followed by positron emission tomography (PET)/CT scans to resolve FPs (**Figure 1**)

**Figure 1. CSO-Retest and WBI-Only diagnostic strategies**



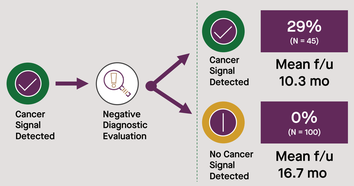

CSO, cancer signal origin; CT, computed tomography; MCED, multi-cancer early detection; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; WBCT, whole-body CT; WBI, whole-body imaging.

## METHODS

### CSO-Retest strategy assumptions

- All individuals with a cancer signal detected (CSD) result underwent a CSO-guided diagnostic evaluation
- Those with a negative CSO-guided diagnostic evaluation underwent an MCED retest, and those with no cancer signal detected (NCSD) upon retest had no further imaging or diagnostic investigation
- Those with a CSD on retesting could have a WBCT, MRI, or PET/CT based on clinical discretion
- MCED retesting was assumed to resolve approximately two-thirds of false-positive CSDs with a negative CSO-directed evaluation[1] (**Figure 3**)

**Figure 3. Resolution of false positives by MCED retesting after a negative CSO-directed evaluation[1]**




CSO, cancer signal origin; f/u, follow-up, MCED, multi-cancer early detection.

### WBI-Only strategy assumptions

- All CSDs underwent a WBCT
- Those with a negative WBCT underwent a WB PET/CT scan
- 75% of true positives with WBCT needed PET/CT as described by Tyson et al[2]

### Modeled scenarios

- The model recapitulated the calculations of Tyson et al,[2] assuming baseline MCED test performance of 44.4% positive predictive value (PPV), 99.5% specificity, and 88.7% CSO accuracy
- Calculations were performed for two separate clinically relevant scenarios where MCED testing was performed in 1,000 individuals:
  - Scenario 1 assumed ~1% MCED test positivity, reflecting epidemiologic estimates of 0.8%–1.2% for real-world populations[3]
  - Scenario 2 assumed a 1% rate of cancer in the population with ~45% sensitivity with a lower MCED specificity of 98.5% used for the WBI-Only strategy, yielding an approximately 2% positivity rate

### Estimated radiation exposure

- Radiation dose exposure for the recommended diagnostic evaluation for each CSO prediction for the CSO-Retest strategy compared to the WBI-Only strategy were estimated from published literature[4–10]

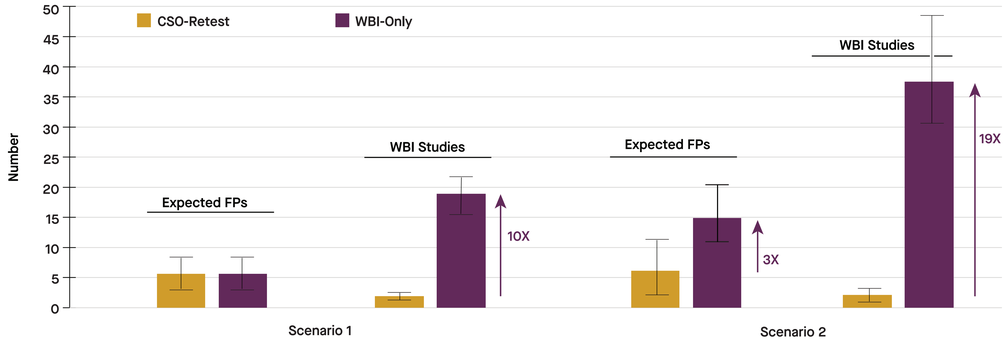
## KEY RESULTS: A CSO-GUIDED DIAGNOSTIC STRATEGY INCORPORATING TARGETED WORKUPS AND MCED RETESTING TO RESOLVE FPs MARKEDLY REDUCES RADIATION EXPOSURE COMPARED TO A WBI-ONLY APPROACH

**Table 1. Diagnostic journeys for Scenarios 1 and 2.**

| | SCENARIO 1 1% MCED TEST POSITIVITY | | SCENARIO 2 1% CANCER RATE AT 98.5% TEST SPECIFICITY FOR WBI-ONLY STRATEGY | |
|---|---|---|---|---|
| **Diagnostic Evaluation** | **CSO-Retest N (95% CI)** | **WBI-Only N (95% CI)** | **CSO-Retest N (95% CI)** | **WBI-Only N (95% CI)** |
| **Targeted diagnostic evaluation** | 10 (8.1–11.9) | – | 10.5 (6.9–15.9) | – |
| **Expected false positives[a]** | 5.6 (3.4–7.8) | 5.6 (3.4–7.8) | 6.1 (2.5–11.5) | 14.9 (11.3–20.3) |
| **MCED retests used** | 6.2 (4.2–8.3) | – | 6.7 (3.1–12.1) | – |
| **False positives resolved by MCED retest** | 4.2 (2.6–6) | – | 4.6 (1.9–8.9) | – |
| **Individuals remaining needing resolution** | 1.9 (1.4–2.6) | 10 (8.1–11.9) | 2 (1.1–3.5) | 19.3 (15.7–24.7) |
| **WBCT** | Up to physician discretion to choose WB MRI/CT/PET | 10 (8.1–11.9) | Up to physician discretion to choose WB MRI/CT/PET | 19.3 (15.7–24.7) |
| **WB PET/CT** | | 8.9 (7.2–10.7) | | 18.2 (14.6–23.6) |
| **Total WBI used** | 1.9 (1.4–2.6) | 18.9 (15.3–22.6) | 2 (1.1–3.5) | 37.5 (30.2–48.3) |

[a]For the CSO-Retest strategy, this includes false-positive tests and incorrect CSO prediction. CSO, cancer signal origin; MCED, multi-cancer early detection; MRI, magnetic resonance imaging; PET, positron emission tomography; WBCT, whole-body CT; WBI whole-body imaging.

**Figure 2. Comparison of expected false positives and WBI studies between the CSO-Retest and WBI-Only strategies.**




**References:** 1. Westgate C et al. *Ann Oncol.* 2024;35:S766-S767. 2. Tyson C et al. *JNCI Cancer Spectr.* 2025;9(2):pkaf011. 3. Matrana M et al. *Cancer Res.* 2025;85(8_Supplement_1):7202. 4. Smith-Bindman R et al. *JAMA Intern Med.* 2025;185(6):710-719. 5. Nawfel RD et al. *Radiology.* 2004;232(1):126-132. 6. Breast Cancer Mammogram | How Does a Mammogram Work? Accessed July 15, 2025. https://www.cancer.org/cancer/types/breast-cancer/screening-tests-and-early-detection/mammograms/mammogram-basics.html 7. Tsivian M et al. *J Endourol.* 2013;27(9):1102-1106. 8. Peisinakis K et al. *Eur J Radiol.* 2019;110:39-44. 9. Kaushik A et al. Indian *J Med Res.* 2015;142(6):721-731. 10. Lee DH et al. *Cancer Imaging.* 2023;23(1):126.

### ESTIMATED RADIATION EXPOSURE

- Estimated radiation exposure doses for initial diagnostic evaluations for the MCED with a CSO feature range from 0 to 26.1 mSv, while all initial diagnostic evaluations for the WBI-Only strategy carry an obligatory exposure of 28 mSv that comes with a CT of the neck/chest/abdomen/pelvis. (**Table 4**)
- Just over half (11/21) of the 21 CSO predictions in the CSO-Retest strategy have no radiation exposure on initial diagnostic evaluation using an MCED with a CSO feature. (**Table 4**)

**Table 4. Recommended diagnostic evaluations for MCED tests with and without molecular CSO predictions with estimated associated radiation doses.**

| CSO Predicted Cancer Type | Initial Diagnostic Evaluation | | | |
|---|---|---|---|---|
| | MCED with CSO Prediction | | MCED without CSO Prediction | |
| | Diagnostic Test | Estimated Radiation Dose (mSv) | Diagnostic Test[a] | Estimated Radiation Dose (mSv)[16] |
| **Anus** | Anoscopy or sigmoidoscopy | 0 | CT neck/ chest/ abdomen/ pelvis | 28 |
| **Bladder, Urothelial tract** | CT urogram & cystoscopy | 14.8[16] | | 28 |
| **Bone and Soft tissue** | MRI or CT chest/abdomen & pelvis | MRI 0 CT 24[15] | | 28 |
| **Breast** | Diagnostic mammogram (MRI if recent mammogram negative) | MRI 0 mammography 0.28[17] | | 28 |
| **Cervix** | Colposcopy & cytology with HPV testing | 0 | | 28 |
| **Colon/Rectum** | Colonoscopy | 0 | CT neck/ chest/ abdomen/ pelvis | 28 |
| **Head and Neck** | CT or MRI head & neck Laryngoscopy | MRI 0 CT 4[15] | | 28 |
| **Kidney** | Triple-phase renal CT | 26.1[18] | | 28 |
| **Liver/Bile-duct** | Triple-phase abdominal CT & AFP | 20.6[19] | | 28 |
| **Lung** | Chest CT | 8[20] | | 28 |
| **Lymphoid lineage** | CBC/diff & Bone marrow biopsy, PET-CT | 25[20] | | 28 |
| **Melanoma** | Full-body skin exam | 0 | | 28 |
| **Myeloid lineage** | CBC/diff & Bone marrow biopsy | 0 | | 28 |
| **Neuroendocrine tumor of lung or other organs** | CT chest/abdomen/pelvis | 24[15] | CT neck/ chest/ abdomen/ pelvis | 28 |
| **Ovary** | Transvaginal ultrasound and CA-125 | 0 | | 28 |
| **Pancreas/Gallbladder** | Pancreas protocol CT, Magnetic resonance cholangiopancreatography (MRCP) | CT 14 mSv[21] MRCP 0 | | 28 |
| **Plasma cell lineage** | CBC/diff & Bone marrow biopsy | 0 | | 28 |
| **Prostate** | PSA and Prostate MRI | 0 | | 28 |
| **Stomach/Esophagus** | Esophagoduodenoscopy | 0 | | 28 |
| **Thyroid** | Thyroid ultrasound | 0 | | 28 |
| **Uterus** | Transvaginal ultrasound | 0 | | 28 |

[a]Individual estimates of CT neck = 4mSv, CT chest = 8mSv, and CT abdomen/pelvis = 16mSv from reference 15. AFP, alpha-fetoprotein; CBC, complete blood count; CSO, cancer signal origin; CT, computed tomography; MCED, multi-cancer early detection test; MRI, magnetic resonance imaging; mSv, milliSieverts.

## CONCLUSIONS

- Using a previously reported modeling approach,[2] the CSO-Retest approach for diagnostic evaluation and resolution of FP test results is likely to have a substantially lower WBI burden and radiation exposure than a WBI-Only strategy
- These findings have important implications for MCED implementation with respect to diagnostic evaluation of those with a CSD, efficient resolution of false positives, minimizing radiation doses, cost, and accessibility of testing

**Disclosures:** MM is a member of the Speakers Bureau for GRAIL, Inc. SR serves as a scientific advisor to GRAIL, Inc., Exact Sciences, C the Signs, and Verily, and holds stock in Illumina. EH is an employee of GRAIL, Inc.; has multiple MCED patents held by GRAIL, Inc. pending and issued; and has ownership of GRAIL, Inc. and Illumina stock. EK is an employee of GRAIL, Inc., and has ownership of GRAIL, Inc. stock.

**Acknowledgements:** Graphics support was provided by Kristi Whitfield (PosterDocs); and project management assistance was provided by Prescott Medical Communications Group, a Citrus Health Group company. All support and study funding were provided by GRAIL, Inc.