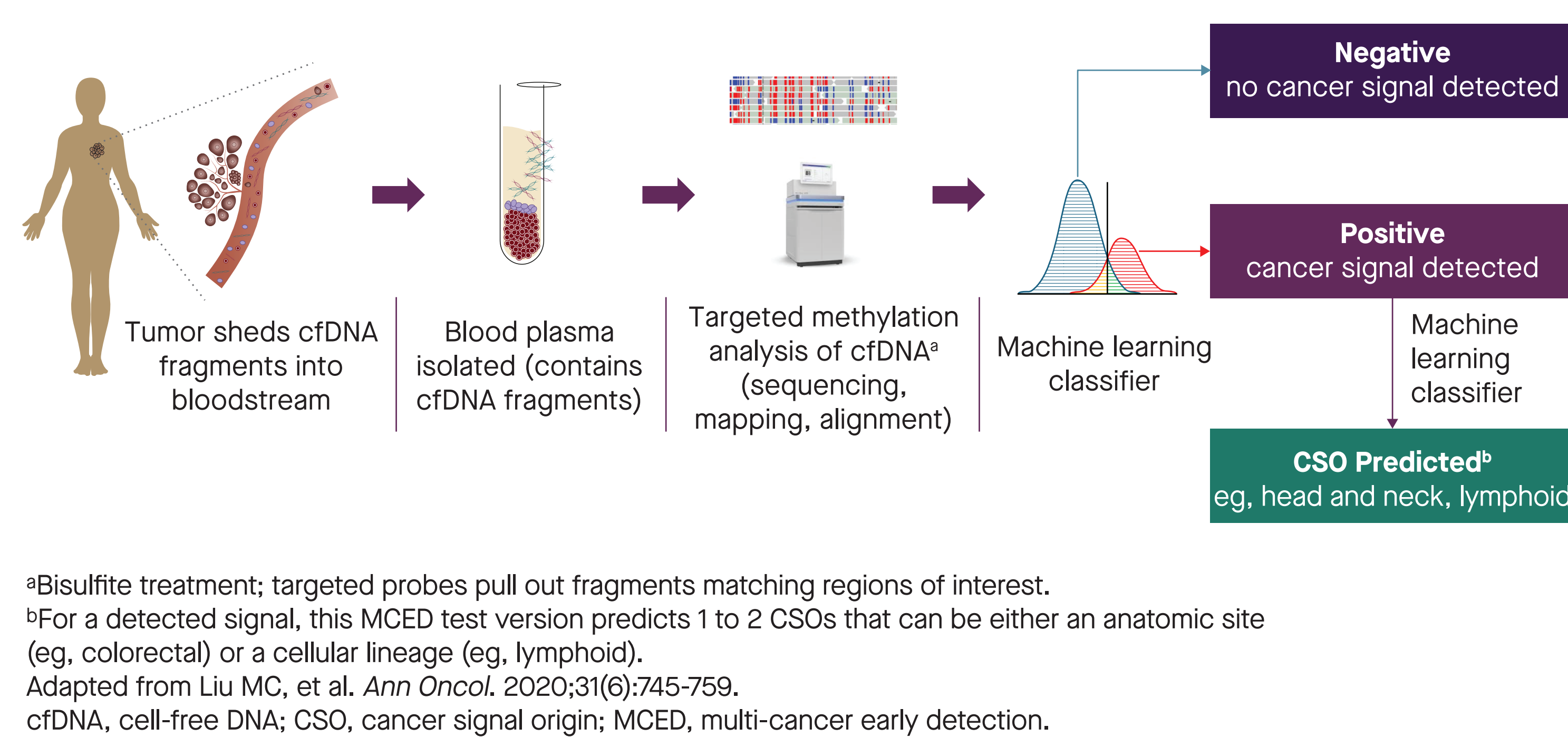


Candace Westgate,¹ Arushi Chadha,² Anuraag Kansal,³ Claire O'Connell,³ Andrew Epstein,² Eric Fung,³ Mylynda Massart⁴¹Community Health Network, Westfield, IN, USA; ²Medicus Economics, LLC, Milton, MA, USA; ³Grail, Inc., Sunnyvale, CA, USA; ⁴University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

INTRODUCTION

- Cancer is the second-leading cause of death in the US and Europe, even with improvements in screening and treatment.^{1,2} Detecting cancer at an earlier stage can increase the likelihood of favorable outcomes and lower mortality^{3,4}
- Despite the availability of screening tests for common cancer types (eg, mammograms, colonoscopy),⁵ screening remains unavailable for most cancers, resulting in a need for broader early detection approaches
- Blood-based multi-cancer early detection (MCED) tests detect cancer-associated signals by measuring one or more biomarkers in blood^{6,7}
 - Multiple MCED tests are under investigation,⁶ and some are commercially available in the US
 - Galleri® (GRAIL, Inc.) is an MCED test that uses DNA methylation patterns in cell-free DNA to detect a cancer signal and predict the cancer signal origin (CSO), which guides diagnostic workup after a positive (cancer signal detected) test result^{7,8} (**Figure 1**)
- In PATHFINDER 2 (NCT05155605), a large prospective multicenter study of this MCED test in a diverse US intended-use population, usage of imaging was similar among participants without and with a cancer diagnosis (81.3% vs 85.5%), whereas invasive procedures were nearly half as frequent among those without cancer (46.3% vs 88.6%)⁹
- Because the benefits and potential harms of MCED screening depend not only on test performance but also on downstream diagnostic evaluation, understanding real-world workup patterns is essential

Figure 1. A Clinically Validated Targeted Methylation MCED Test.



OBJECTIVE

- To characterize real-world receipt of diagnostic workups following a positive Galleri MCED test result by CSO and confirmed cancer status

KEY RESULTS: IN REAL-WORLD PRACTICE, MCED TEST FOLLOW-UP WAS ALIGNED WITH CSO PREDICTIONS, WITH FEWER INVASIVE PROCEDURES PERFORMED IN PATIENTS WITHOUT CANCER

- Among 285 patients with a positive MCED test result and ≥360 days of follow-up, 150 (52.6%) were in the Cancer Identified group and 135 (47.4%) were in the No Cancer Identified group based on claims within 360 days of the positive MCED test result (**Figure 2**)
 - 147/150 (98.0%) patients in the Cancer Identified group underwent ≥1 diagnostic procedure, including a mean (SD) of 1.25 (1.44) imaging procedures (0.39 [0.66] whole-body) and 1.25 (0.78) invasive procedures (**Figure 2, Figure 3**)
 - 121/135 (89.6%) patients in the No Cancer Identified group underwent ≥1 diagnostic procedure, including a mean of 1.17 (1.60) imaging procedures (0.21 [0.51] whole-body) and 0.70 (0.96) invasive procedures (**Figure 2, Figure 3**)
- Diagnostic workups were appropriate to the CSO and varied by CSO and cancer status (**Figure 3**)
 - Patients with hematologic CSOs had fewer imaging and invasive procedures than patients with solid tumor CSOs when no cancer was identified (mean 0.41 vs 1.41 imaging and 0.19 vs 0.86 invasive procedures per patient), consistent with the role of laboratory testing in diagnosing hematologic cancers (**Figure 3A**)
 - Observed workups aligned with the first diagnostic investigation recommended for each predicted CSO¹⁰: imaging use was highest where imaging is recommended first (mean 1.38 Cancer Identified vs 1.63 No Cancer Identified), invasive procedures were highest where direct visualization is recommended first (1.63 vs 1.23) (**Figure 3B**)
 - The specific level of workup differed by CSO within each cancer status group (**Figure 3C**)
 - Whole-body imaging (PET, PET-CT, or same-day chest and abdomen-pelvis CT) was performed in 48 patients (32.0%) in the Cancer Identified and 24 patients (17.8%) in the No Cancer Identified groups; the difference was driven by PET or PET-CT utilization (24.0% vs 7.4%)
 - Surgical procedures were uncommon, with 17 performed in the Cancer Identified group and 1 in the No Cancer Identified group

Figure 3. Mean Number of Imaging and Invasive Procedures Per Patient.

A. Solid vs Hematologic Cancer Types

Imaging Procedures				Invasive Procedures			
CSO Group	Cancer Identified	No Cancer Identified	Δ	CSO Group	Cancer Identified	No Cancer Identified	Δ
Solid*	1.25 N=109	1.41 N=103	-0.16	Solid*	1.33 N=109	0.86 N=103	0.47
All CSOs	1.25 N=150	1.17 N=135	0.08	All CSOs	1.25 N=150	0.70 N=135	0.55
Hematologic*	1.24 N=41	0.41 N=32	0.83	Hematologic*	1.02 N=41	0.19 N=32	0.83

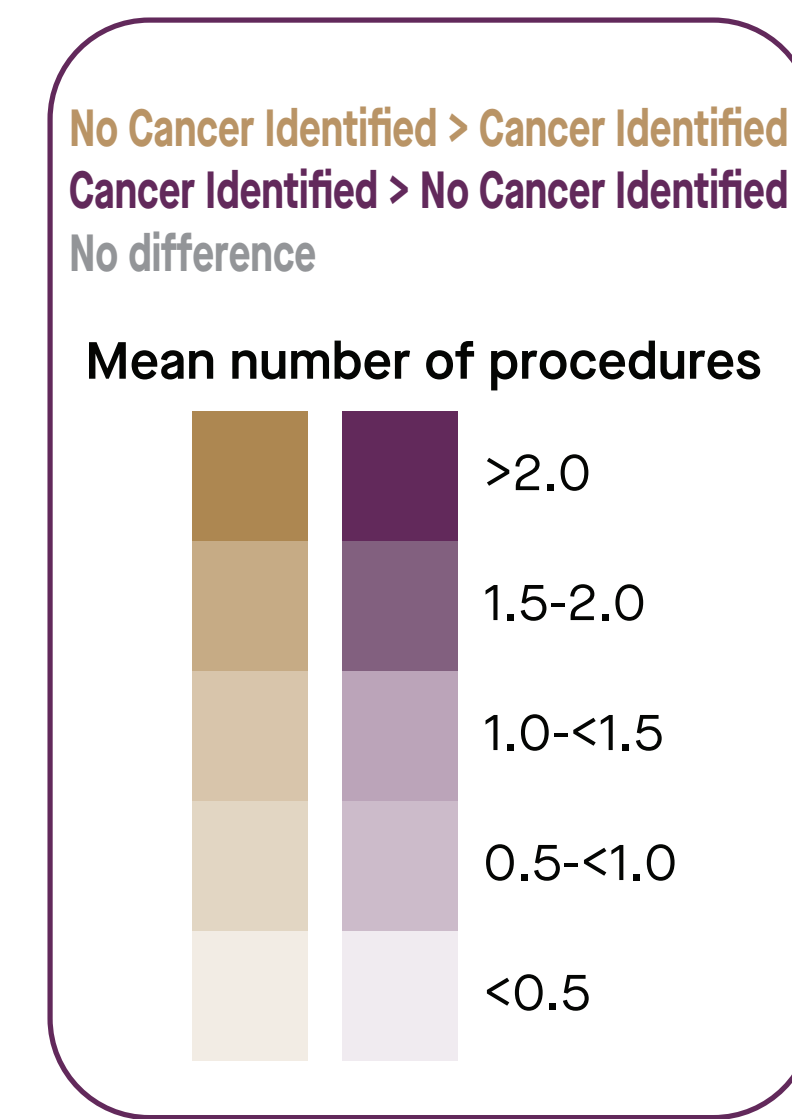
*Includes CSO predictions of Anus, Bladder/Urothelial Tract, Bone & Soft Tissue, Breast, Cervix, Colon/Rectum, Head & Neck, Kidney, Liver/Bile Duct, Lung, Melanocytic Lineage, Ovary, Pancreas/Gallbladder, Prostate, Stomach/Esophagus, Thyroid, and Uterus.
*Includes CSO predictions of Lymphoid Lineage, Myeloid Lineage, and Plasma Cell Lineage.

B. First Procedure Type

Imaging Procedures				Invasive Procedures			
CSO Group	Cancer Identified	No Cancer Identified	Δ	CSO Group	Cancer Identified	No Cancer Identified	Δ
Imaging First*	1.38 N=69	1.63 N=68	-0.25	Direct Visualization First*	1.63 N=40	1.23 N=35	0.40
Direct Visualization First*	1.02 N=40	0.97 N=35	0.05	Imaging First*	1.16 N=69	0.68 N=68	0.48
All CSOs	1.25 N=150	1.17 N=135	0.08	All CSOs	1.25 N=150	0.70 N=135	0.55
Hematologic (Lab First)*	1.24 N=41	0.41 N=32	0.83	Hematologic (Lab First)*	1.02 N=41	0.19 N=32	0.83

First procedure types are sourced from Atwood C, et al. 2026.¹⁰
*Includes CSO predictions of Bladder/Urothelial Tract, Bone & Soft Tissue, Breast, Kidney, Liver/Bile Duct, Lung, Melanocytic Lineage, Neuroendocrine, Ovary, Pancreas/Gallbladder, Prostate, and Uterus. Bladder, Prostate, and Uterus CSOs have a lab or imaging procedure recommended first and are included with the "Imaging First" group.
*Includes CSO predictions of Anus, Colon/Rectum, Head & Neck, and Stomach/Esophagus.
*Includes CSO predictions of Lymphoid Lineage, Myeloid Lineage, and Plasma Cell Lineage.

Data are presented in diverging heatmaps. Δ = difference in mean number of procedures per patient (Cancer Identified vs No Cancer Identified). CSO, cancer signal origin.

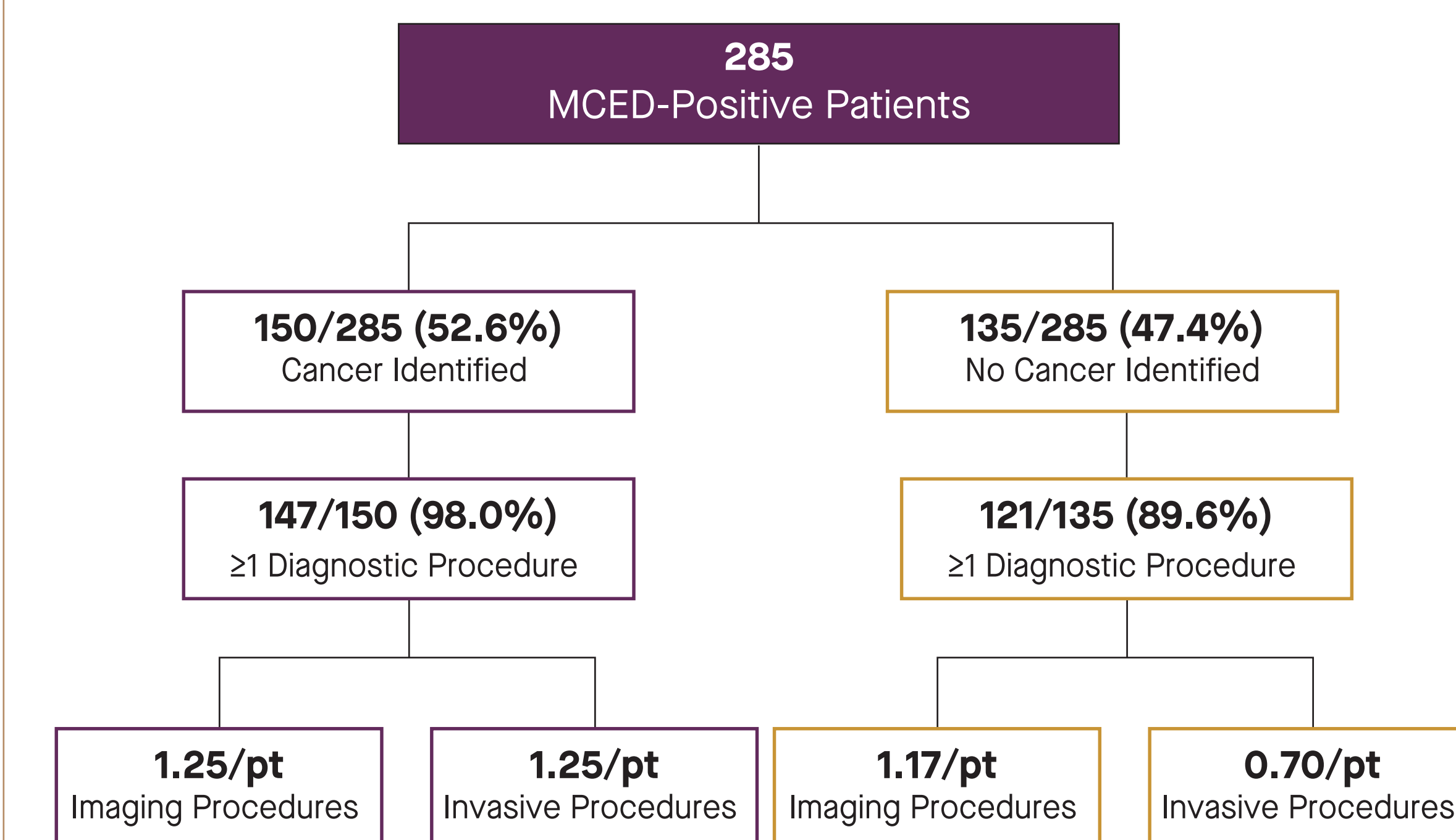


C. Biological CSO Grouping

Imaging Procedures				Invasive Procedures			
CSO Group	Cancer Identified	No Cancer Identified	Δ	CSO Group	Cancer Identified	No Cancer Identified	Δ
Pancreas & Hepatobiliary*	0.71 N=7	1.37 N=16	-0.66	Prostate	0.79 N=14	1.60 N=5	-0.81
Gynecologic*	1.40 N=5	2.00 N=6	-0.60	Gynecologic*	1.00 N=5	1.00 N=6	0
Colorectal & Anal*	0.40 N=20	1.00 N=21	-0.60	Colorectal & Anal*	1.30 N=20	1.24 N=21	0.06
Other Solid Tumors*	0.67 N=12	1.27 N=11	-0.60	Other Solid Tumors*	1.25 N=12	0.82 N=11	0.43
Prostate	1.36 N=14	1.80 N=5	-0.44	Upper GI*	1.17 N=6	0.67 N=3	0.50
Breast	1.70 N=23	2.09 N=11	-0.39	All CSOs	1.25 N=150	0.70 N=135	0.55
Upper GI*	1.00 N=6	1.00 N=3	0	Pancreas & Hepatobiliary*	1.14 N=7	0.56 N=16	0.58
All CSOs	1.25 N=150	1.17 N=135	0.08	Breast	1.22 N=23	0.55 N=11	0.67
Lung	2.12 N=8	1.63 N=19	0.49	Plasma Cell Neoplasm	1.00 N=11	0.29 N=7	0.71
Lymphoid Neoplasm	1.23 N=30	0.48 N=25	0.75	Lymphoid Neoplasm	1.03 N=30	0.16 N=25	0.87
Head & Neck	1.93 N=14	0.91 N=11	1.02	Head & Neck	2.29 N=14	1.36 N=11	0.93
Plasma Cell Neoplasm	1.27 N=11	0.14 N=7	1.13	Lung	1.62 N=8	0.42 N=19	1.20

*Includes CSO predictions of Pancreas and Liver.
*Includes CSO predictions of Ovary and Uterus.
*Includes CSO predictions of Colon/Rectum and Anus.
*Includes CSO predictions of Bladder/Urothelial Tract, Bone & Soft Tissue, Kidney, Melanocytic Lineage, and Neuroendocrine.
*Includes CSO prediction of Stomach/Esophagus.

Figure 2. Post-MCED Test Diagnostic Evaluation Was Similar Across Groups, With Fewer Invasive Procedures Among Patients Without Confirmed Cancer.



Among MCED-positive patients with ≥360 days of follow-up, the proportion undergoing ≥1 diagnostic procedure and the mean number of imaging and invasive procedures per patient are shown.
MCED, multi-cancer early detection; pt, patient.

CONCLUSIONS

- In real-world clinical practice, diagnostic intensity following communication of a positive MCED test result appropriately differed by cancer status, with patients with no identified cancer experiencing similar numbers of imaging but fewer invasive procedures
- Workups aligned with the first investigation recommended by an expert panel for each CSO,¹⁰ and the level of imaging and invasive procedures varied appropriately by CSO
- Findings support the practical implementation of the MCED test in real-world clinical settings
- Real-world diagnostic workup patterns were generally consistent between real-world use and clinical studies,⁹ indicating that the MCED test performs as expected outside the research setting

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Disclosures

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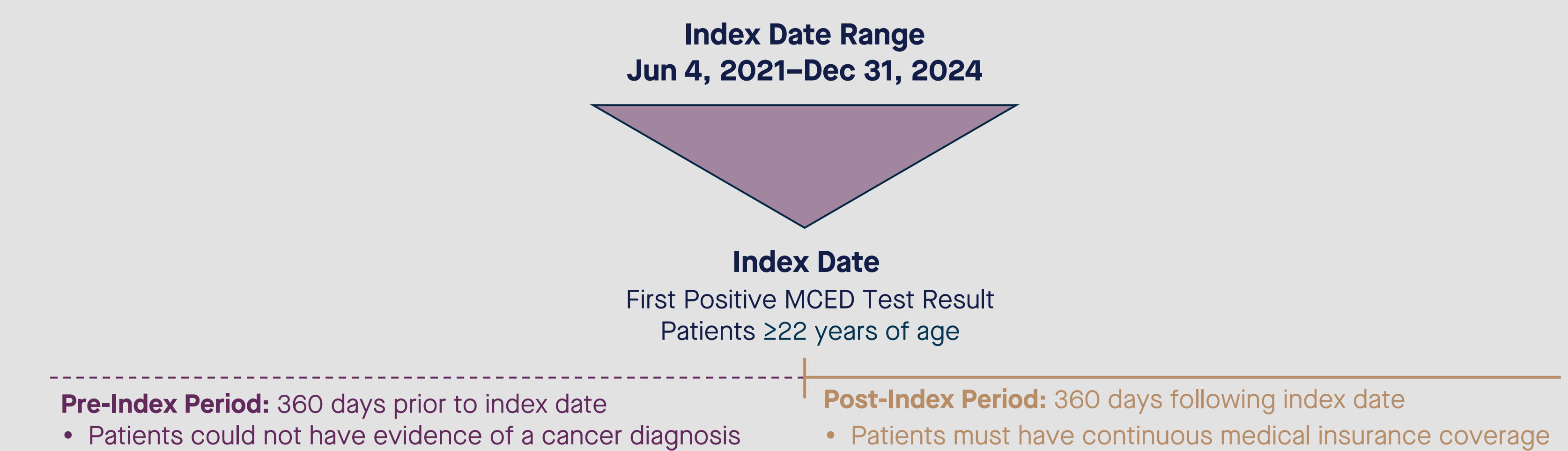
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Figure S1. Study Design of Claims Database Analysis of Diagnostic Workups Following a Positive MCED Test Result.



METHODS

- This retrospective analysis used closed commercial medical claims from the Komodo Research Database linked via tokenization to a cohort of Galleri MCED-tested patients
- The study design for this analysis is shown in **Figure S1**
 - The index date was a patient's first positive MCED test result between June 4, 2021 and December 31, 2024
 - Patients with a cancer diagnosis (defined below) in the year before index were excluded
 - Patients had to be ≥22 years on their index date and have ≥360 days of continuous medical insurance enrollment following index date
- Cancer status during follow-up was determined using a claims-based algorithm
 - Patients were classified as having a cancer diagnosis if within 360 days of index they had either:
 - ≥1 inpatient hospitalization claim with a cancer diagnosis code
 - ≥2 outpatient claims with a primary or secondary diagnosis code for malignancy, occurring ≥30 days apart on or after the index date and before the end of medical insurance coverage
 - Patients without a cancer diagnosis within 360 days of index were labeled "No Cancer Identified"

- A diagnostic test was identified in claims data based on the presence of specific Current Procedural Terminology (CPT) procedure codes following the index date
 - Procedure billing codes were categorized by clinician review as diagnostic, diagnostic after specific MCED CSO results, or not diagnostic
 - Claims for cancer screening tests, eg, screening colonoscopy, were included as potential diagnostic workups to be conservative in the estimate of workup burden
- Diagnostic procedures were further classified as invasive, imaging, or laboratory-based
 - Invasive procedures included endoscopy, biopsy, and surgery; imaging procedures included CT, MRI, X-ray, PET, ultrasound, and mammography
 - Surgical procedures included hysterectomy, laparoscopy, operative laryngoscopy, and open lymph node biopsy; endoscopic procedures such as esophagogastroduodenoscopy and colonoscopy were not considered surgical
- The diagnostic episode ended at
 - Cancer confirmation for patients with a cancer diagnosis, based on the date of biopsy or other tissue collection procedure
 - Where no tissue collection procedure was present in claims, cancer confirmation date was imputed (in order) from pathology claims, imaging claims, or initial ICD-10 coding for cancer
 - The first 60-day gap without diagnostic procedures for patients without cancer diagnosis