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Real-world data and clinical experience from over 100,000 multi-cancer early detection tests

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Blood-based multi-cancer early detection (MCED) has the potential to simultaneously screen for multiple deadly cancers with high positive predictive value. To assess real-world performance, we evaluated the Galleri® MCED test (GRAIL, Inc.) across 111,080 individuals (median age 58 years, 55.5% males). This MCED test analyzes methylation patterns of cell-free DNA to detect presence of a cancer signal and predict the anatomical cancer signal origin (CSO) to facilitate diagnostic evaluation. Cancer signal detection rate was 0.91% (1011/111,080), consistent with clinical studies and independent modeled values. Providers reported clinical outcome for 459 of 1011 individuals with cancer signal detected MCED tests. Of these, 258 had an invasive cancer diagnosis, spanning 32 cancer types. The MCED test correctly predicted the CSO in 87% of cases with a reported cancer type, consistent with previous clinical studies. CSO enabled efficient workup in most patients, with a median 39.5 days from result receipt to cancer diagnosis.

Cancer is the second leading cause of death in the United States (US), with an estimated death toll of 1680 Americans per day in 2024[1]. It is a broad and diverse disease comprising thousands of distinct types. Currently, only four cancers have United States Preventive Services Task Force (USPSTF) grade A/B screening recommendations–breast, colorectal, cervical, and lung (in high-risk individuals)[2–5]. Prostate cancer screening is determined on an individual basis (USPSTF grade C)[6]. Although these screening programs have been effective in reducing cancer mortality, ~83% of cancer-related deaths in the US result from cancers detected outside of recommended screening strategies[7]. Inherent barriers to screening include access, eligibility, and adherence to guidelines[8–11]. For example, the American Lung Association estimates 16% of eligible individuals participate in lung cancer screening[12]. Globally, the majority of cancers are diagnosed after patients present with symptoms[13,14]. By the time of diagnosis, such cancers are often later-stage, more likely to be metastatic, less amenable to treatment, and associated with shorter overall survival and lower cure rate than asymptomatic, early-stage cancers[13,14].

Another challenge with current cancer screening tests is that they are optimized for high-sensitivity detection of single cancers at the expense of test specificity (≥10% false positive rate)[15–18]. The utilization of multiple independent single-cancer screening tests leads to additive false positive rates, accumulating a high combined false positive rate, which in turn results in risks to patients and inefficient use of healthcare resources[16–20]. Additive false positive rates complicate implementation of new single-cancer screening tests for currently unscreened cancer types. The increasing combined false positive rate would overwhelm disease prevalence.

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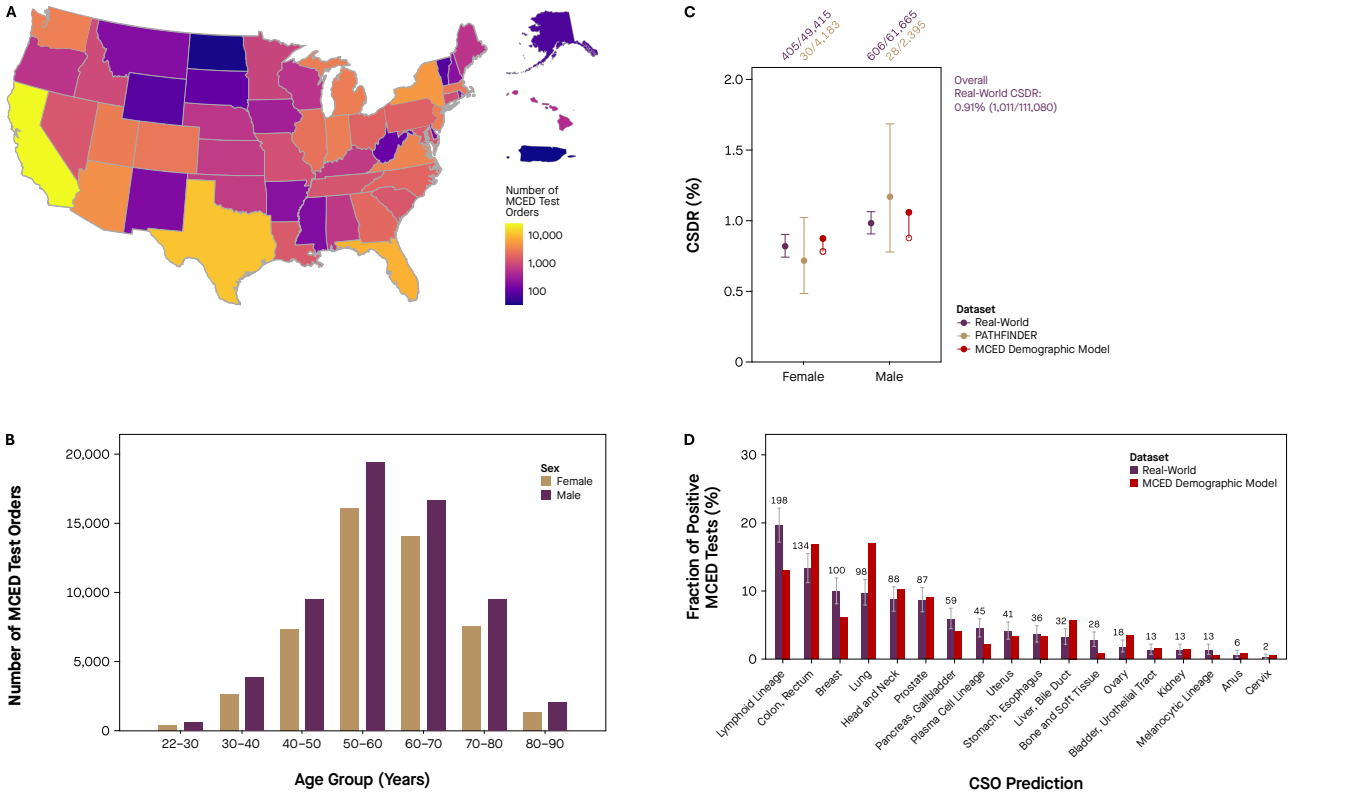

Fig. 1 | Characteristics and MCED test results in the real-world population (*N* = 111,080). Distribution of MCED test orders by **A** geography (geographic information available for *n* = 109,666 MCED test orders) and **B** age and sex. **C** CSDR by sex from the real-world dataset (purple), PATHFINDER[24] (gold), and the MCED demographic model (red). The fraction of positive (cancer signal detected) MCED test results out of all administered tests are noted above the graph. For the MCED demographic model (red), the open circle indicates the modeled CSDR with a correction for never-smokers[34]. Error bars denote the 95% binomial confidence interval. **D** Distribution of predicted CSO for the 1011 positive MCED test results from the real-world dataset (purple) and MCED demographic model (red). The number of positive MCED tests per CSO category is indicated within the graph. Error bars denote the 95% binomial confidence interval. Source data are provided as a Source Data file. CSDR cancer signal detected rate, CSO cancer signal origin, MCED multi-cancer early detection.

Recent advances in machine learning applied to high-throughput DNA sequencing of samples collected in large clinical studies have enabled the development of blood-based multi-cancer early detection (MCED) tests[21–25]. When the potential detection of multiple cancers is considered collectively, the benefit of utilizing such an MCED test at a population-scale could outweigh potential risks (eg, false positives, overdiagnosis, or increased anxiety). MCED tests are intended to be used along with guideline-recommended single-cancer screening tests[26] in order to provide coverage for invasive cancers that are currently not screened. Importantly, MCED tests prioritize a single, high specificity for detection across multiple cancer types[21]. Consequently, MCED tests minimally add to the false positive burden when used along with existing USPSTF-recommended screening. Additionally, the accessible nature of a test that uses a peripheral blood sample could help maximize early cancer detection across the population, including within under-served communities, before the onset of clinical symptoms.

One MCED test (Galleri®, GRAIL, Inc., Menlo Park, CA, USA)[27] available for clinical use in the US as a laboratory-developed test is based on targeted methylation sequencing of cell-free DNA (cfDNA) circulating in peripheral blood. It uses machine learning algorithms to detect cancer-specific DNA methylation patterns and predict the origin of the cancer signal (ie, cancer signal origin [CSO]). The technology was developed and validated in a large-scale observational study (Circulating Cell-Free Genome Atlas, CCGA)[21–23] and a multi-center interventional study (PATHFINDER)[24], and it demonstrated similar performance across racial and ethnic groups[28]. This MCED test is intended for use in individuals with an elevated risk of cancer, such as those age 50 years and above, where it demonstrated a positive predictive value (PPV) of 43.1%[24]. The MCED test PPV is several fold higher than the PPV reported for available single-cancer screening tests for asymptomatic, high-risk populations in the US, such as mammography (PPV 4.4-28.6%)[17], FIT (PPV 7.0%)[29], and low-dose CT (PPV 3.5-11%)[18,30,31].

We examine the real-world experience of this MCED test, considering age and sex, to assess how the test performs in clinical practice. Importantly, we can compare these real-world observations to previously reported clinical study results to assess the robustness and generalizability of the test. Here, we report the real-world data and clinical experience from over 100,000 MCED tests.

Results

Population demographics and MCED test results

We report real-world data on 111,080 MCED tests that were ordered, processed, and had results returned between April 19, 2021 and October 14, 2023, from 8160 healthcare providers across all US states (Fig. 1A). Among those tested, 44% (*n* = 49,415) were female with a median age of 58 years (interquartile range [IQR]: 51–67 years), and 56% (*n* = 61,665) were male, also with a median age of 58 years (IQR: 50–67 years) (Fig. 1B).

Results were returned for more than 98% of MCED tests that were ordered and processed. Reasons for the test cancellations (<2% of tests) included pre-analytical and analytical factors, such as insufficient blood volume for testing, severe hemolysis, or not meeting required quality control metrics (eg, sample library concentration or depth of sequencing). Median turnaround time (time between accessioning of the sample in the laboratory and return of results) was 6.1 business days.

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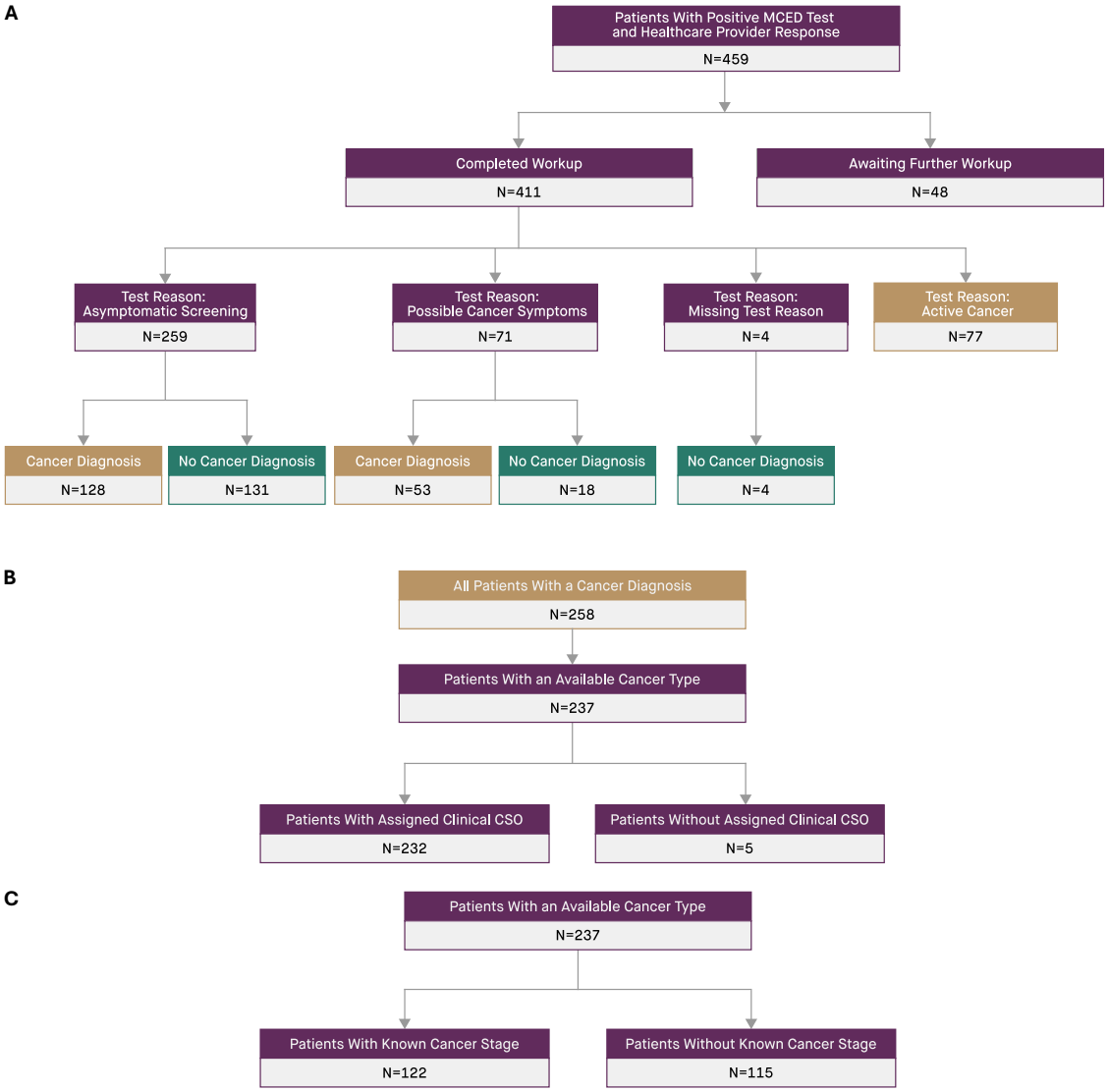

Fig. 2 | Clinical outcomes reported after a positive MCED test result. A Flow diagram of individuals with clinical follow-up. Clinical follow-up was reported by healthcare providers for 459 individuals with a positive MCED test result. 48 individuals who were reported to have ongoing workup were excluded from analysis. Individuals who were reported to have completed workup ($n = 411$) were divided into those reported to have ordered the MCED test without cancer-associated symptoms ($n = 259$, asymptomatic screening), with cancer-associated symptoms ($n = 71$, possible cancer symptoms), or with active cancer at the time of MCED testing ($n = 77$). The number of patients with or without a cancer diagnosis following the positive MCED test is also shown. **B** Breakdown of all diagnosed cancers by reported or missing stage. **C** Breakdown of all diagnosed cancers by reported or missing cancer type. Source data are provided as a Source Data file. CSO cancer signal origin, MCED multi-cancer early detection.

The cancer signal detected rate (CSDR) is the proportion of positive (cancer signal detected) MCED tests out of all MCED tests administered. In this real-world population, the observed overall CSDR was 0.91% (95% confidence interval [CI]: 0.86–0.97%; 1011/111,080). The CSDR was 0.82% (95% CI: 0.74–0.90%; 405/49,415) in female individuals and slightly higher in male individuals (0.98%; 95% CI: 0.91–1.1%; 606/61,665) ($p = 0.005$, Fisher test) (Fig. 1C).

This MCED test predicts the CSO by recognizing cfDNA methylation patterns specific to organs, tissues, or cell lineages, and is intended to help guide the diagnostic workup following a positive MCED test result. As expected, relatively common cancers like lymphoid lineage, colon/rectum, breast, lung, and prostate were more frequently predicted, whereas uncommon cancers in the cervix, anus, kidney, bladder, and ovary were not frequently predicted (Fig. 1D). The MCED demographic model also predicted the CSO distributions, which generally showed good agreement with the observed CSO distribution results (Spearman $r = 0.85$). Female and male individuals had broadly similar CSO distributions with some differences due to sex-associated cancers (Supplementary Fig. 1A, B).

Clinical outcomes: empirical positive predictive value and time to diagnosis

As part of a Quality Assurance Program, outcome data from the ordering healthcare providers were requested for the 1011 patients with a positive MCED test result; data were obtained for 459 patients (45% follow-up rate) (Supplementary Fig. 2A). Patients with follow-up data were slightly older (median age 70 years) and included more male patients (64%) than patients without follow-up data (median age 68 years and 57% male; Supplementary Fig. 2B).

Among patients with follow-up data, 11% (48/459) were awaiting further diagnostic workup at the time of data collection (Fig. 2A). Of the remaining 411 patients who had completed diagnostic evaluation, 63% (258/411) had been diagnosed with invasive cancer. At the time of the MCED testing, 259 patients were not reported to have cancer-

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Table 1 | ePPV among patients with positive MCED tests by test order reason and demographics

	ePPV	95% CI	n/N
Asymptomatic			
Overall	49.4%	43.2–55.7	128/259
Sex			
Female	51.5%	41.2–61.8	50/97
Male	48.1%	40.2–56.1	78/162
Age Group, Years			
<50	47.4%	24.4–71.1	9/19
50-65	51.4%	39.2–63.6	36/70
65+	48.8%	41.1–56.6	83/170
Symptomatic			
Overall	74.6%	62.9–84.2	53/71
Sex			
Female	70.8%	48.9–87.4	17/24
Male	76.6%	62.0–87.7	36/47
Age Group, Years			
<50	75.0%	19.4–99.4	3/4
50–65	69.2%	38.6–90.9	9/13
65+	75.9%	62.4–86.5	41/54

CI confidence interval, *ePPV* empirical positive predicted value, *MCED* multi-cancer early detection.

associated symptoms ("asymptomatic"), and 128 of these patients were ultimately diagnosed with cancer, resulting in an empirical PPV (ePPV) of 49.4% (128/259; 95% CI: 43.2–55.7%). The median time to diagnosis for asymptomatic patients with an available diagnosis date ($n = 115$) was 43 days (IQR: 20–94). Though the intended use of the MCED test is among asymptomatic patients, some healthcare providers elect to apply the test to individuals with cancer-associated symptoms or with active cancer. Seventy-one patients were reported to have cancer-associated symptoms ("symptomatic" individuals, but no diagnosed active cancer) at the time of the test. Of these symptomatic patients, 53 were ultimately diagnosed with cancer, resulting in an ePPV of 74.6% (53/71; 95% CI: 62.9–84.2%). For those with an available diagnosis date ($n = 47$), the median time to diagnosis was 30 days (IQR: 14–50). ePPV did not vary much by sex and age for either of these populations (Table 1). Considering asymptomatic and symptomatic patients together, a total of 181 patients were diagnosed with a new invasive cancer or cancer recurrence, with a median time to diagnosis of 39.5 days (IQR: 17–74). Separate from these new cancer diagnoses, a subset of positive MCED test results came from providers who ordered the MCED test for patients with a known active cancer (77/411; Fig. 2A).

Clinical outcomes: anatomical location and stage of diagnosed cancers

In 258 patients with cancer detected by a positive MCED test result, 268 cancers were diagnosed (10 patients were diagnosed with multiple primaries). There was sufficient clinical detail for 247 cancers in 237 patients to identify the cancer type as defined by the American Joint

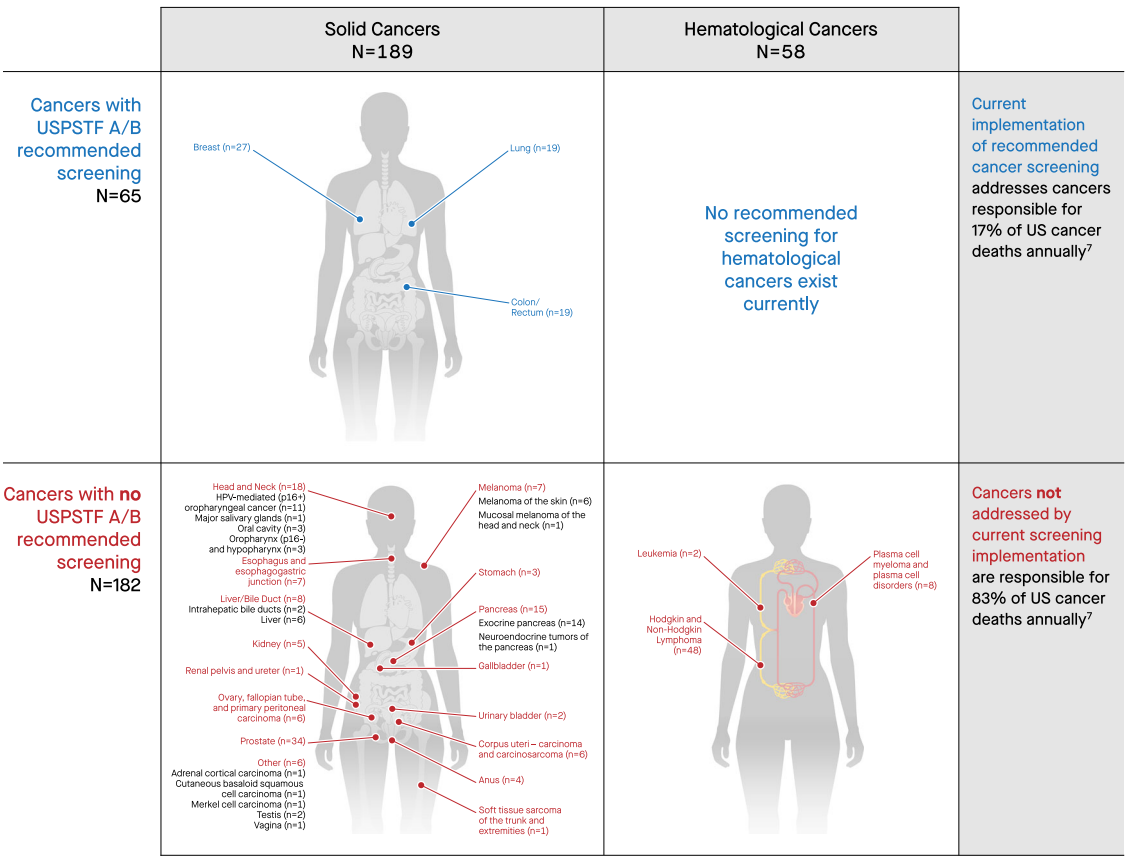

Fig. 3 | Cancers detected by the MCED test. Among patients with a positive MCED test result and a cancer diagnosis with a reported cancer type ($n = 247$ cancers), 32 distinct AJCC cancer types were represented. Cancers are indicated by organ location and AJCC notation. When multiple AJCC types correspond to the same organ location, each type is listed in black under the location header. Cancers with existing USPSTF grade A/B screening recommendation are denoted in blue, and cancers without existing USPSTF grade A/B recommended screening are denoted in red. The fraction of cancer deaths not addressed by current implementation of recommended screening are as previously calculated in Ofman et al.[7]. Source data are provided as a Source Data file. AJCC American Joint Committee on Cancer, MCED multi-cancer early detection, USPSTF United States Preventive Services Task Force.

Table 2 | Examples of clinical workup in patients with early-stage cancer and rapid diagnosis following a positive MCED test result

Patient	Age Range (years)/sex	CSO Prediction	Days to Diagnosis[a]	Diagnostic Evaluation		Final Diagnosis
				Test	Result	
1	65–69/male	Pancreas/ Gallbladder	34	CA19-9	Elevated	Stage I Pancreatic adenocarcinoma
				MRCP	1.3 × 1.2 cm pancreatic lesion	
				Endoscopic ultrasound-guided biopsy	Cyst fluid negative; histology showed adenocarcinoma	
2	60–64/male	Stomach/ Esophagus	20	CT chest/abdomen/pelvis	Small esophageal mucosal mass	Stage I Esophageal adenocarcinoma
				Upper endoscopy and biopsy	Adenocarcinoma	
3	60–64/female	Liver/Bile Duct	26	CT chest/abdomen/pelvis	Multiple liver lesions	Stage II Hepatocellular carcinoma
				CT-guided biopsy	Hepatocellular carcinoma	
4	60–64/male	Liver/Bile Duct	32	CT abdomen	1.5 cm liver lesion	Stage I Hepatocellular carcinoma
				CT-guided biopsy	Hepatocellular carcinoma	

CA 19-19 carbohydrate antigen 19-19, *CT* computed tomography, *MRCP* Magnetic Resonance Cholangiopancreatography.
[a]Time from return of a positive MCED test result report to clinical diagnosis.

Committee on Cancer (AJCC) (Fig. 2B). As expected in a real-world population, a wide range of distinct cancer types ($N = 32$) were detected (Fig. 3). The majority of cancers diagnosed (74% [182/247]) have no USPSTF grade A/B–recommended screening (ie, cancer types other than breast, colon/rectum, cervix, or lung).

Cancer stage information was reported in 124 cancers from 122 patients (Fig. 2C). Of these cancers, 18% (22/124), 10% (13/124), 24% (30/124), and 48% (59/124) were detected at stage I, II, III, and IV, respectively. Stage I/II cancers detected included anus, colon and rectum, corpus uteri - carcinoma and carcinosarcoma, esophagus and esophagogastric junction, exocrine pancreas, Hodgkin and non-Hodgkin lymphomas, HPV-mediated (p16+) oropharyngeal cancer, kidney, liver, lung, oral cavity, plasma cell myeloma and plasma cell disorders, and prostate.

Detailed information on diagnostic workups was not typically available but was assessed when provided. Amongst asymptomatic cancer detections with detailed information, rapid workups were reported for a moderately differentiated (G2) stage I adenocarcinoma in the neck of the pancreas (34 days), a stage I cancer of the esophagus/esophagogastric junction (20 days), a stage II hepatocellular carcinoma (26 days), and a stage I high-grade hepatoma (32 days). Workup details for these cases are presented in Table 2.

Clinical outcomes: cancer signal origin predictions

Among 237 patients with a cancer diagnosis and reported cancer type, the predicted CSO matched the cancer diagnosis in 87% (207/237) (Fig. 4A). Accuracy of the predicted CSO was similar for the subset of patients aged 65 years or older (85% [135/158]). Incorrect CSO predictions were sparsely distributed across the range of predicted CSOs (Supplementary Fig. 3). The fraction of MCED test–predicted CSOs that matched the diagnosis (ie, prediction accuracy), ranged between 82% and 97% across CSOs that were predicted for at least 10 separate patients (Fig. 4B), which was also in good agreement with previous clinical study results[23,32]. CSOs that were infrequently predicted ($N < 10$ predictions) were analyzed as a single group, which also demonstrated high prediction accuracy (87%).

MCED demographic modeling

We compared the observed results from the full real-world dataset comprising 111,080 administered MCED tests to an MCED demographic model based on population demographics, SEER cancer incidence[33], and previously published MCED test performance characteristics (see "Methods"). The demographic model agreed well with the observed CSDR by sex (Fig. 1C). These results were also consistent with the CSDR observed in the prospective, interventional PATHFINDER study, which enrolled participants aged 50 years or above (Fig. 1C)[24]. As expected, given that cancer incidence increases with age, the real-world observed CSDR increased significantly with age ($p = 3.3 \times 10^{-138}$, logistic regression). The age trend was consistent with the MCED demographic model and similar to what was observed in the PATHFINDER study[24] (Supplementary Fig. 4). The observed CSDR was 1.9% in the subset of individuals 65 years or older, compared with 0.46% in individuals younger than 65 years ($p = 4.2 \times 10^{-109}$, Fisher test) (Supplementary Fig. 5).

Additionally, the model-predicted CSO distributions generally showed good agreement with the observed CSO distribution results (Spearman $r = 0.85$; Supplementary Fig. 1A, B). When evaluating modeled CSO distribution by age, we found the most common modeled CSO predictions for both sexes were consistent with what was observed in the overall real-world population (Supplementary Fig. 1).

One important but unknown factor in the model was the rate of smoking in the real-world population relative to SEER. In a hypothetical SEER population of never-smokers[34], the modeled CSDR was lower, perhaps explaining some of the difference between the observed versus modeled results (Fig. 1C). Smoking can affect the incidence of many cancer types[34], and is especially relevant in lung cancer, however, smoking status in this real-world population is largely unavailable. The modeled rate of lung cancer CSO in the SEER population was higher than the real-world observed rate. However, the modeled rate in the hypothetical SEER population of never-smokers[34] was lower than the observed rate, suggesting an intermediate amount of smoking in the real-world population reported here (Supplementary Fig. 1C, D).

Discussion

The blood-based MCED test assessed in this analysis detects cancer-specific DNA methylation patterns[35] across the spectrum of cancer types and stages, using cfDNA sequencing and machine learning algorithms. The MCED test has been previously validated in large-scale, case-control, observational, and prospective interventional studies and is commercially available for clinical use[22–24]. The data herein represent the clinical experience with the MCED test in a real-world setting within a large cohort of >100,000 test takers and a diverse set of healthcare providers across the US, including private practices, healthcare systems, and telemedicine, providing proof of principle for broad adoption and implementation.

The MCED test successfully detected cancer signals from various high-mortality or high-incidence cancers, including cases in early stages (I and II). In later rounds of screening, we expect a higher proportion of early-stage diagnoses[36], as the current data reflect findings from individuals undergoing their first MCED screening (prevalence round), where later-stage cancer diagnoses are likely to be more

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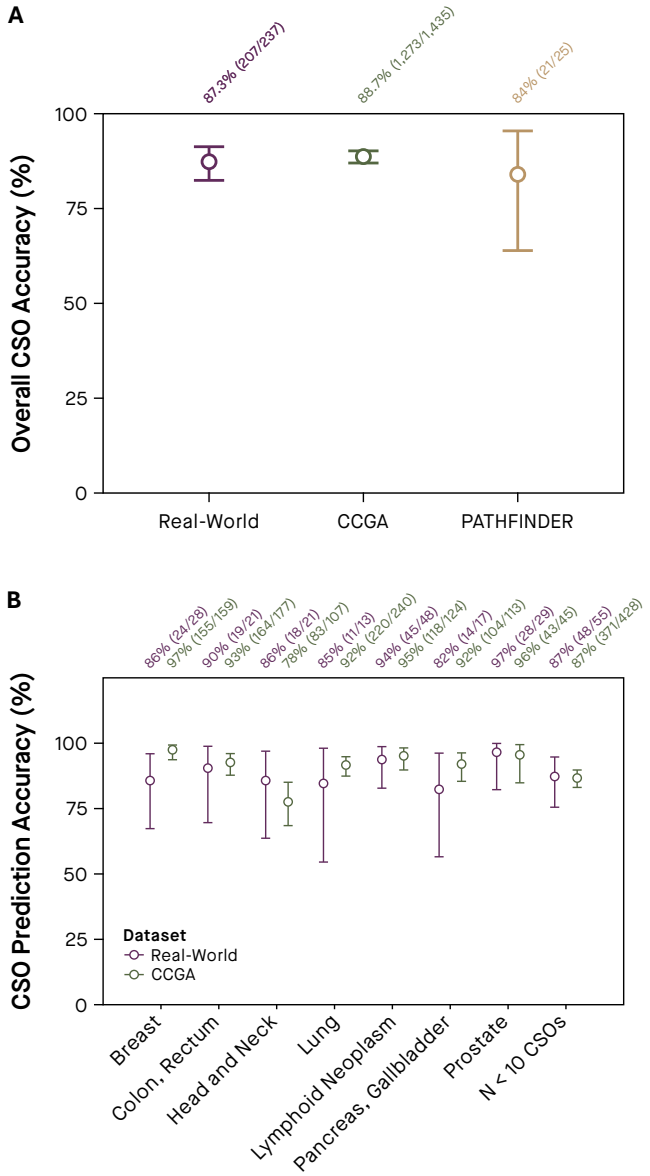

Fig. 4 | MCED test CSO prediction accuracy observed in real-world data is consistent with previous independent clinical studies. A Overall CSO accuracy observed in real-world patients with a cancer diagnosis and reported cancer type ($n = 237$) (purple), CCGA validation study (green)[23], and PATHFINDER clinical study (gold)[24]. **B** CSO prediction accuracy by CSO in the real-world dataset (purple) and CCGA (green) datasets (PATHFINDER CSO data was not included due to low sample size per CSO). CSO prediction accuracy is the fraction of MCED test–predicted CSOs that match the diagnosed cancer. Aggregate CSO prediction accuracy for all CSOs with less than 10 observations in the real-world population is displayed as "$N < 10$ CSOs". Patient population for (**B**) is the number of patients with an assigned clinical CSO ($n = 232$). The CSO accuracy percent and number of correct CSO predictions out of all CSO predictions given for patients with a reported cancer type per **A** dataset or **B** CSO category are noted above each graph. Error bars denote the 95% binomial confidence interval. Source data are provided as a Source Data file. CCGA3 Circulating Cell-free Genome Atlas substudy 3, CSO cancer signal origin.

common, as was observed here, because no previous screening has been done. Preliminary analysis of patients with year-over-year MCED testing found a higher percentage of stage I diagnoses compared with patients taking their first test[36].

Seventy-four percent of the diagnosed cancers in this real-world setting lacked current recommended screenings, similar to the 74% observed in the PATHFINDER study[24]. Without the MCED test, these cancers might not have been detected until the onset of symptoms, potentially leading to diagnoses at more advanced stages. In the US, ~83% of annual cancer deaths are not covered by existing screening programs[7], underscoring the potential for MCED testing to address a critical unmet need to augment existing early detection efforts.

The remaining 26% of detected cancers were screened-for cancers (breast, colon/rectum, cervix, or lung). This proportion aligns with the findings from the PATHFINDER study, where 32% of cancer detections were for cancers with recommended screening[24]. Notably, the PATHFINDER participant population was highly adherent to recommended screening (92% were adherent for colorectal cancer and 80% for breast cancer screening). If MCED testing is widely adopted, the test's low false positive rate of 0.5%, compared with the ~10% baseline false positive rate each for fecal occult blood test[15], mammography[17], and low-dose CT[18], would only marginally increase the overall false positive burden of screening while significantly increasing the number of cancers detected in the population. Additionally, the MCED test can potentially detect rapidly growing interval cancers, such as triple-negative breast cancers, which may develop between standard screening intervals[37]. As a simple blood test, MCED augmentation of recommended screening may also improve access and compliance.

Many of the cancers detected by the MCED test were types that are typically aggressive and fast-growing, and rapid diagnosis following detection is key to improving survival[38–43]. We observed that the MCED test is highly accurate in predicting the CSO (87%) in the real world, and that the performance is consistent with what was observed in the PATHFINDER (85% [70–94%])[24] and CCGA (89% [87–90%])[23] studies. The time to diagnosis in the real-world population (median 39.5 days [IQR: 17–74]) is shorter than what was observed in the PATHFINDER study (79 days)[24]. A retrospective claims database of newly diagnosed cancer patients reported a mean time to diagnosis of 156.2 days (SD 164) in standard of care practice (ie, without MCED testing)[44]. These observations demonstrate the potential value of CSO predictions in facilitating rapid diagnostic resolution.

Along with the high CSO accuracy, ePPVs were also consistent with previous studies. Nearly half (49.4%, 128/259) of asymptomatic individuals with a completed workup were reported to have an invasive cancer diagnosis following a positive MCED test result, similar to the PPV of 43.1% reported previously in the PATHFINDER study[24]. ePPV was similar for both sexes and across age. Though this MCED test is intended for use in asymptomatic patients, some providers used it to assist in the evaluation of patients presenting with cancer-associated symptoms; in this population, the observed ePPV was 74.6%, similar to the 75.5% PPV reported in the SYMPLIFY study of this MCED test in symptomatic patients[32]. Although the negative predictive value (NPV) of the MCED test could not be determined for the real-world dataset given that clinical outcomes were not collected for negative MCED test results, prior clinical studies demonstrated an NPV of 99.4% (95% CI: 99.4-99.5%)[23] and 98.5% (98.2-98.8%)[24].

Across all 111,080 MCED tests administered, the observed CSDR was comparable to an empirical modeled CSDR obtained from previously published test data[23,24,45] and cancer incidence extrapolated from SEER using only age and sex as variables. This indicates that the performance of the MCED test can be accurately forecasted in target populations from demographic information alone. More detailed modeling of specific populations may require additional factors, such as smoking rates or other specific risk factors, to be included in the model.

A key strength of this study is the analysis of MCED test performance and implementation in a very large real-world population of over 100,000 individuals. Yet, there are certain challenges and limitations inherent in reporting real-world data outside of a clinical study. Follow-up is voluntarily reported by healthcare providers for patients with a positive MCED test, and data collection is limited by information collected on the test requisition form and provider report.

Consequently, details beyond age and sex (eg, self-reported race/ethnicity, smoking, prior history of cancer) are not known for the majority of the population. Additionally, calculation of metrics that require clinical determination of negative (no cancer signal detected) MCED test results, including sensitivity, specificity, and NPV, are not possible. Large interventional studies are required for comprehensive assessment of clinical utility, and the ongoing PATHFINDER 2 (NCT05155605), NHS-Galleri (ISRCTN 91431511), and REACH (NCT05673018) studies are designed to measure these performance metrics that cannot be accurately derived from the real-world data analysis presented here.

For patients with a positive MCED test, we obtained a 45% response rate from healthcare providers, enabling the calculation of test performance amongst true positives and false positives. Obtaining provider responses to surveys is a known challenge, with large variations in response rates depending on the survey format and incentives for completion. A systematic review of interventions to improve healthcare provider survey response rates reported a wide range, with rates as low as 17%[46]. There is the potential for ascertainment bias, which could have implications on empirical performance measures of the MCED test. For example, some healthcare providers may be more likely to provide follow-up data for true positive results, while others may be more likely to report false positive results. Though we cannot exclude the possibility of reporting bias, three lines of evidence suggest that the population with follow-up is comparable with the complete positive MCED test population. First, very little demographic difference is observed between patients with and without follow-up. Second, the observed real-world CSDR, CSO accuracy, and ePPV are similar to what we have reported in prior clinical studies, suggesting that the population is comparable. Third, a model based on independent study data predicts our real-world performance accurately.

Another potential limitation is an early adopter bias of individuals who opted for MCED testing. This population may be enriched for individuals who make healthier lifestyle choices than the general population. This enrichment would align with the suggested lower amount of smoking in the real-world population than SEER, given the lower rate of lung cancer CSOs in real-world versus SEER data.

Monitoring and assessing the real-world performance of MCED tests are crucial for evaluating their practical application in clinical settings. Our results align with a recently published independent analysis of real-world use of the MCED test at Mayo Clinic, in which 73% of positive MCED tests resulted in a new cancer diagnosis in asymptomatic individuals[47]. Though the tested population was relatively small (N = 2244), this type of implementation analysis provides evidence for the feasibility of MCED testing in routine clinical workflows. Moreover, the concordance between our real-world data on >100,000 administered MCED tests and prior clinical studies underscores the test's robustness and ability to generalize from clinical trials to everyday practice. This report illustrates the MCED test's capacity to identify cancer across a large intended-use population, detecting 32 distinct types of cancer. The MCED test facilitated clinically significant cancer diagnoses, supported by accurate CSO predictions, which were correct 87% of the time and enabled prompt and efficient diagnostic evaluations. Over half of the positive MCED test results led to a confirmed cancer diagnosis following a diagnostic workup. These diagnostic rates reveal a PPV that is 7–10 times greater than the PPV reported for approved single-cancer screening tests for asymptomatic, high-risk populations in the US, such as mammography, FIT, and low-dose CT[17,18,29–31].

Collectively, this real-world experience underscores the potential of MCED testing to broaden the spectrum of detectable cancers while maintaining a low false positive rate when integrated with existing recommended screening protocols in clinical practice. Continuing robust and extensive monitoring of MCED test performance in real-world use will support further improvements in the performance of the MCED test. Future versions of the test may be refined by incorporating real-world data into training the machine learning algorithms that underlie the test. Additionally, the continued collection of real-world use data will allow for future studies of MCED test performance and implementation in clinical practice.

Methods

MCED test workflow

The MCED test was trained on data from 6689 individuals including more than 50 cancer types and has been validated on more than 10,000 individuals from the CCGA, STRIVE, and PATHFINDER clinical studies[22–24]. The MCED test demonstrated a single, high 99.5% specificity in a diverse population of participants without diagnosed cancer and a range of sensitivities depending on cancer type and stage[23], due to the amount of circulating tumor DNA shed into peripheral blood[21]. The test has been available for clinical use since April 2021. The test requires a prescription by a licensed provider in the US (and Puerto Rico) based on cancer risk assessment (family and personal clinical history, hereditary predisposition, smoking history, history of prior cancer, occupational exposure, etc.) followed by a single blood draw. The peripheral whole blood sample is shipped to a Clinical Laboratory Improvement Amendments–certified and College of American Pathologists–accredited laboratory at GRAIL for processing. cfDNA from the blood sample are isolated and processed using next-generation targeted methylation sequencing and machine learning algorithms to detect a cancer signal and predict the tissue/organ from which it originated (CSO). The patient's biological sex is the only additional input to the cancer prediction algorithm to ensure that incompatible CSOs are not reported. A positive (cancer signal detected) or negative (no cancer signal detected) MCED test result is returned to the healthcare provider along with a CSO prediction for positive MCED test results. CSO is intended to direct subsequent diagnostic evaluation procedures.

Test result data

This report includes analysis of de-identified data from MCED tests ($N = 111{,}080$) returned to ordering providers from April 19, 2021, to October 14, 2023, in patients aged ≥22 years from testing locations in the US (and Puerto Rico) and excludes tests from patients enrolled in GRAIL-sponsored clinical studies, any subsequent MCED tests in a patient following the initial MCED test, and tests from locations limiting external data sharing.

Clinical outcomes data

In addition to de-identified test result data, this report also includes analysis of de-identified data regarding clinical outcomes for cancer signal detected (positive) MCED test results ($N = 411$) returned for the period of time (and with the exclusions) noted above. These data were collected as part of GRAIL's Quality Assurance Program designed to monitor the implementation and safety of the MCED test in clinical practice. In compliance with the requirements of the US Health Insurance Portability and Accountability Act (HIPAA) of 1996 and its implementing regulations, GRAIL, Inc. collects clinical outcomes from ordering providers following a Galleri cancer signal detected (positive) test result. More specifically, the goal of the Quality Assurance Program is to understand the diagnostic evaluation conducted by the healthcare provider in order to ascertain the clinical cancer status of patients with positive MCED test results, namely when a cancer is diagnosed (true positive) or not (false positive). In cases where a positive MCED test result is obtained, pursuant to the Quality Assurance Program, ordering healthcare providers are contacted for clinical cancer status information and reason for ordering the test. For true positives, when possible, details on time to diagnosis (time from test return to cancer diagnosis), diagnostic workup, cancer type, and cancer stage are obtained. False positives are determined when the healthcare provider reports that no further workup is planned in the absence of a cancer diagnosis.

Collection of clinical outcomes is attempted for positive MCED test results. For negative MCED test results, outcomes are recorded when reported to GRAIL, but collection is not systematically attempted. Responding is purely voluntary. GRAIL continues to monitor the safety and implementation of Galleri testing in clinical practice through the Quality Assurance Program.

After a GRAIL Laboratory Director completes quality review of these clinical outcomes data for the Quality Assurance Program, the data are fully deidentified (in accordance with HIPAA's expert determination method as set forth in 42 CFR §164.514(b)), and subsequently may be used for secondary purposes including research. The patient-level data collected for the Quality Assurance Program is not shared outside of GRAIL.

Use of such deidentified data (including data reviewed and analyzed for this manuscript) for secondary activities related to evaluating, developing, and improving the test is made under an existing IRB-approved protocol (WIRB-Copernicus Group [WCG] IRB Protocol #20222358) that includes a waiver of informed consent. In this report, we provide results of these activities with de-identified data in order to provide an assessment of MCED implementation in clinical practice and performance in a real-world population.

Data analysis

The CSDR was defined as the number of MCED tests with a positive result divided by all tests. Increasing CSDR with age was determined from significance of the non-zero age coefficient in a logistic regression model of a positive MCED test result against year of age and sex. The empirical positive predicted value (ePPV) is the cancer diagnosis rate in the population of patients who had a positive MCED test and a healthcare provider report of symptomatic or asymptomatic screening with a completed workup. Patients with a known active cancer at the time of ordering the test were not included. ePPV was computed as the number of patients in the population with an invasive cancer diagnosis divided by the total number of patients in the population.

The clinical CSO was determined systematically from the diagnosed cancer information (when available) by following a pre-specified set of definitions for each CSO and was used as the true label to compare with the MCED-predicted CSO[23]. CSO prediction accuracy was calculated on the 237 patients with a positive MCED test result and a cancer diagnosis with a reported cancer type. The CSO was considered correct if the CSO predicted on the test report matched the clinical CSO; patients with multiple primaries only required one of the diagnoses to match, in line with how cases were analyzed in previous case-control[23] and interventional prospective[24] studies. For test reports containing two CSO predictions, only the first CSO prediction was used. Patients with diagnosed cancers that did not have a clinical CSO label (n = 5, including 2 testis, 1 Merkel cell, 1 vagina, and 1 cutaneous basaloid squamous cell carcinoma) were included and treated as incorrect CSO predictions. The CSO confusion matrix tallies the combination of each predicted CSO (y axis) against each clinical CSO (x-axis) across 232 patients with an assigned clinical CSO (Supplementary Fig. 3). For patients with multiple diagnosed cancers, the clinical CSO of the correctly matching predicted CSO is shown; if neither clinical CSO is correct then the first diagnosed cancer is shown. The 5 patients diagnosed with cancers without a clinical CSO are excluded from the CSO confusion matrix. The diagnostic accuracy of each CSO is computed across the top of the CSO matrix and the prediction accuracy of each CSO along the right-hand side.

All calculations were done in R (version 4.3.2).

CSDR modeling

The expected CSDR for this real-world population was estimated using a weighted average model previously reported[48] based on cancer incidence from SEER and published MCED test performance. Briefly, CSDR is defined as the following:

$$CSDR = \left(\sum_{k,l} N_{k,l} \cdot \left(\sum_{i,j} P_{i,j,k,l} + F_l\right)\right) / \sum_{k,l} N_{k,l} \quad (1)$$

- N is the number of tests broken down by single year of age (l) and sex (k)
- F is the false positive rate per age and is predicted from the best-fit model to the training[22] and validation[23,24] data. In the population reported here, the predicted average rate of false positives is 0.42% for females and 0.43% for males, similar to the 0.5% rate across both sexes reported previously[23,24]. The empirical specificity may be impacted by a complex set of factors such as age or other biologic characteristics, as has been reported with other cancer detection tests[49,50]. P is the true positive rate defined as (Eq. 2):

$$P_{i,j,l} = I_{i,j,l} \cdot \zeta_j \cdot S_{i,j} \cdot T_{i,j} \quad (2)$$

and broken down by single year of age (l), stage (i), and cancer type (j). It is determined by three factors:

- I is cancer incidence from the SEER database according to the ICD−O−3 codes listed in Klein et al.[23] averaged over 2006–2015.

$$I_{i,j,l} = \sum_k N_{k,l} I_{i,j,k,l} / \sum_k N_{k,l} \quad (3)$$

- Incidence adjusted to the test age distributions $N_{k,l}$ and broken down by sex (k), stage (i) and cancer type (j), is included in Source Data File 1.
- ζ_j is an optional correction factor to account for the reduced incidence per cancer type in a hypothetical population of never-smokers[34] (see SEER_NS model in Source Data File 1).
- S is the sensitivity per cancer type and stage obtained from the CCGA3 validation substudy of MCED test performance[23]. In order to account for some of the variability in estimating sensitivity across stages in some cancer types with low numbers, isotonic regression was applied to the published sensitivity data to ensure increasing sensitivity with stage for each cancer type. Cancers labeled as 'neuroendocrine cells of lung or other organs' were treated as 'lung' since small cell lung cancer is the most common anatomical location for cancers with neuroendocrine histology.
- T is the detectability timescale for each cancer type and stage and can vary depending on screening history, but for a prevalence round screen (ie, with no prior test), the expression simplifies to a single scale factor (see Source Data File 1). The detectability timescale was originally derived from localized, regional, and distant staging and then mapped to stages I, II/III, and IV, respectively[45].

CSO modeling

The distribution of detected CSOs is expected to vary with age and sex based on how the underlying incidence of cancer types change in the population (Supplementary Fig. 6). The relative distribution of detected CSOs from true positives was determined from the expected distribution of true positive (P) CSOs as:

$$CSO'_{k,j} = \sum_{i,l} N_{k,l} \left(\sum_{j'} \left(P_{i,j',k,l} \cdot M_{k,j',j}\right)\right) / \sum_{i,l} N_{k,l}$$
$$CSO_{k,j} = CSO'_{k,j} / \sum_j CSO'_{k,j} \quad (4)$$

Where

- M is the confusion matrix reported in Klein et al.[23] describing the contribution of correct ($j = j'$) and incorrect ($j \neq j'$) CSO predictions across all CSOs. In order to account for unobserved CSO combinations due to the limited size of the validation cohort reported by Klein et al., we included an additional pseudo count in each column of the confusion matrix that is distributed uniformly across any unobserved CSO combinations in that column (see Source Data File 2). The subset of sex-specific CSOs was then set to zero for the opposite sex (ie, cervix, uterus, and ovary in males and prostate in females). Note that 'neuroendocrine cells of lung or other organs' was remapped to 'lung' as described in the "CSDR Modeling" section above.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

All data and content supporting the presented results are provided in the manuscript, supplementary material, source data files, or via GitHub link. Additional de-identified individual patient data are not available. SEER incidence and CSO confusion matrix are shared as Source Data Files 1–2. Source data are provided with this paper (see Source Data Figures file). Aggregate test results and demographic data are available at https://github.com/grailbio-publications/Matrana_Real_World_2025 (see also Code Availability). The genomic sequencing data used in this study have not been deposited in a public repository because it is personal and protected patient data under HIPAA. Source data are provided with this paper.

Code availability

Code used for generating figures is publicly available at https://github.com/grailbio-publications/Matrana_Real_World_2025.

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Author contributions

O.V., J.F.B., G.S., E.H., K.N.K., J.M.V., and R.S. contributed to conceptualization of analyses and methodology. J.F.B. and G.S. performed the statistical analysis, created figures, and provided resources for data access and creation of the data repository. J.F.B., G.S., and O.V. supported medical writing of the manuscript. M.Mat., V.S., D.K., M.P., J.L., M.Mc.M., L.B.M., O.V., J.F.B., G.S., E.H., K.N.K., J.M.V., R.S., and C.W. contributed to interpretation of results, provided clinical expertise, and critically reviewed and edited the manuscript for intellectual content.

Competing interests

Authors declare the following competing interests: O.V., J.F.B., G.S., and E.H. are current employees and K.N.K., J.M.V., and R.S. are former employees of GRAIL, Inc. with equity in GRAIL, Inc. and Illumina, Inc. C.W., V.S., J.L., and L.B.M. are speaker bureau members for GRAIL, Inc. V.S. is a consultant/advisor for GRAIL, Inc. J.L. has equity Illumina, Inc. and Quest Diagnostics.

Additional information

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