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Multicancer Detection (MCD) Testing in Gastrointestinal Cancers: An Evolving Tool for Early Diagnosis

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Abstract

Purpose of Review The current review aims to summarize the benefits and limitations of the novel multicancer detection tests (MCD) for diagnosing gastrointestinal (GI) malignancies.

Recent Findings Traditional cancer screening methods can reduce deaths in malignancies involving the GI tract. For GI cancers, screening options vary by type and often involve invasive techniques with limited sensitivity. MCDs offer a promising, non-invasive (simple blood draw) alternative by analyzing biomarkers such as cell-free DNA and RNA using advanced techniques and machine learning to detect cancers across multiple organ sites. Large studies like the PATHFINDER trial and THUNDER study have demonstrated the feasibility and accuracy of MCD assays in identifying cancer signals, with high sensitivity and specificity in some GI organs that lack routine screening tests (e.g., liver, pancreas, and stomach). Despite these advancements, MCD testing faces challenges, including high costs, lack of FDA approval, false positives, and limited data on clinical utility in reducing cancer-specific mortality. MCD should not be a substitute for age-appropriate cancer screenings but may complement existing methods, particularly for cancers with no current screening tools, such as cholangiocarcinoma and pancreatic cancer. Clinicians need to discuss the limitations of MCDs, including the potential for overdiagnosis, patient anxiety, and financial burden due to insurance coverage gaps.

Summary MCD is a promising, non-invasive test that can augment traditional cancer screening. As the role of MCD in cancer detection evolves, further research is essential to establish how it will be integrated into clinical practice, ensuring informed, shared decision-making with patients.

Keywords Multicancer detection (MCD) test · Cancer screening · Gastrointestinal cancer

Introduction

Cancer screening has proven to be safe and effective at reducing mortality in cancers with available screening techniques. However, approximately 70% of cancer-related deaths in the United States are attributed to cancers that lack recommended screening tests [1]. Current screening methods for gastrointestinal (GI) malignancies vary by cancer type [2]. The most recommended screening options for colorectal cancer include Cologuard (Exact Sciences, Madison, Wisconsin), a DNA-based stool test, and a colonoscopy. Other screening options include fecal occult blood testing (FOBT), fecal immunochemical testing (FIT), and sigmoidoscopy [3]. Colonoscopy is the gold standard for diagnosing and treating pre-cancerous lesions at the time of testing. Still, it is limited by the adequacy of the preparation and the patient's willingness to undergo an invasive procedure.

In other GI malignancies, screening is limited and often includes invasive procedures [4]. For hepatocellular carcinoma (HCC), the American Association for the Study of Liver Diseases (AASLD) recommends ultrasound (US) every six months, with or without alpha-fetoprotein (AFP) testing, for patients with cirrhosis or chronic hepatitis B [5]. However, the US's sensitivity is variable, and ongoing research into alternative imaging modalities and biomarkers

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to improve early detection is underway [5]. For patients at a genetically heightened risk, such as those with BRCA2 and Lynch Syndrome, or a significant family history without genetics, screening for pancreatic cancer includes MRI and endoscopic ultrasound (EUS) as recommended by the American Gastroenterological Association (AGA). Despite these methods, there are significant gaps in early detection due to the lack of specific biomarkers and the challenges in identifying precursor lesions [6–8]. Developing a screening mechanism to diagnose these cancers in early-stage disease would significantly improve public health by reducing mortality and increasing life years gained [1].

Novel biomarkers have been recently developed as potential cancer screening tools, including cell-free DNA (cfDNA), cell-free RNA (cfRNA), and metabolites in blood, urine, or breath using advanced laboratory techniques like quantitative polymerase chain reaction (qPCR), next-generation sequencing (NGS), and gas chromatography-mass spectrometry (GC-MS). These assays identify specific patterns that, when processed with artificial intelligence (AI) machine-learning algorithms, enable the simultaneous detection of potential cancers across multiple anatomic sites [9]. These technological advances offer exciting opportunities for screening that have not previously been available in these cancer types. They are noninvasive or minimally invasive and have recently been offered commercially as Multicancer Detection Testing (MCD).

Multicancer Detection (MCD) Testing

MCD screening assays are predominately multi-analyte, blood-serum assays that evaluate the epigenetic signature using targeted methylation-based cfDNA assays for cancers of various types. Some companies have called them multicancer early detection (MCED) tests. However, the early detection rates of MCDs depend on several factors, including the test used and the testing frequency. Figure 1 provides an overview of biomarker detection and analysis techniques used in current MCD tests, illustrating the multifaceted approaches that underpin multi-cancer detection. The analytical validation from an early MCD study demonstrates high specificity (99.3%) and accuracy in predicting cancer signal origin through machine learning analysis of over a million methylation sites, supporting the test's robustness for clinical use [10]. The PATHFINDER trial validated the feasibility of such tests in real-world outpatient settings, showing the ability to detect over 50 cancer types with low false positive rates. The investigators developed effective diagnostic pathways informed by predicted cancer signal origins for positive tests [11]. The Circulating Cell-free Genome Atlas (CCGA) study provided extensive clinical validation, confirming that the MCD assay could detect cancer signals across multiple types and predict the tissue of origin with 88.7% accuracy in true positives, demonstrating its utility as a complement to traditional single-cancer screening [12]. Collectively, these studies underscore the potential of MCD assays to revolutionize early cancer detection through epigenetic signatures and machine learning.

Table 1 summarizes several of the currently available research studies that have examined the role of MCD in the early detection of gastrointestinal cancers [11–31]. For example, in the THUNDER study, cfDNA methylation-based technology was used for the early detection of and localization of six types of cancers: colorectal, esophagus, liver, lung, ovary and pancreas. The cfDNA samples from 1693 participants were retrospectively collected to train and validate two MCD blood test models for different clinical scenarios. The models were then validated on a prospective independent cohort of 1010 age-matched participants. This study showed that the MCD had a sensitivity of 69.1% (64.8–73.3%) and specificity of 98.9% (97.6–99.7%) with high tissue origin accuracy of 83.2% (78.7–87.1%) in the independent validation set [26].

In another study, the CancerSEEK (Exact Sciences, Madison, Wisconsin) test was applied to 1005 patients with nonmetastatic clinically detected cancers of the ovary, liver, stomach, pancreas, esophagus, colorectal, lung, or breast. The median sensitivity of CancerSEEK for the eight cancer types was 70%. Notably, for several cancers that do not currently have available screening methodologies, such as cancers of the liver, stomach, pancreas, and esophagus, the test sensitivity ranged from 69 to 98%. The specificity of CancerSEEK was greater than 99%.[16]

The ECLIPSE study was a large-scale study of colonoscopy screening alternatives, and one of the colorectal cancer tests evaluated was the Shield™ test by Guardant Health [32]. This study evaluated the performance characteristics of the cfDNA blood-based test in patients ages 45 and older. The sensitivity for stage I, II, or III colorectal cancer was 87.5% (95% CI, 75.3 to 94.1), and sensitivity for advanced precancerous lesions was 13.2% (95% CI, 11.3 to 15.3). Specificity for any advanced neoplasia of 89.6% (95% CI, 88.8 to 90.3) [32].

Hence, these MCD tests offer a potential noninvasive approach to early cancer diagnosis, thereby identifying cancers at a stage when curative treatments can be offered. Multi-center clinical trials incorporating large and diverse populations will be needed to establish the clinical utility of these tests as a cancer screening tool. The ongoing UK NHS-Galleri trial is a landmark randomized controlled study evaluating the Galleri MCD test developed by (GRAIL, Menlo Park, California) [13]. It has enrolled over 140,000 participants aged 50–77 in England to determine

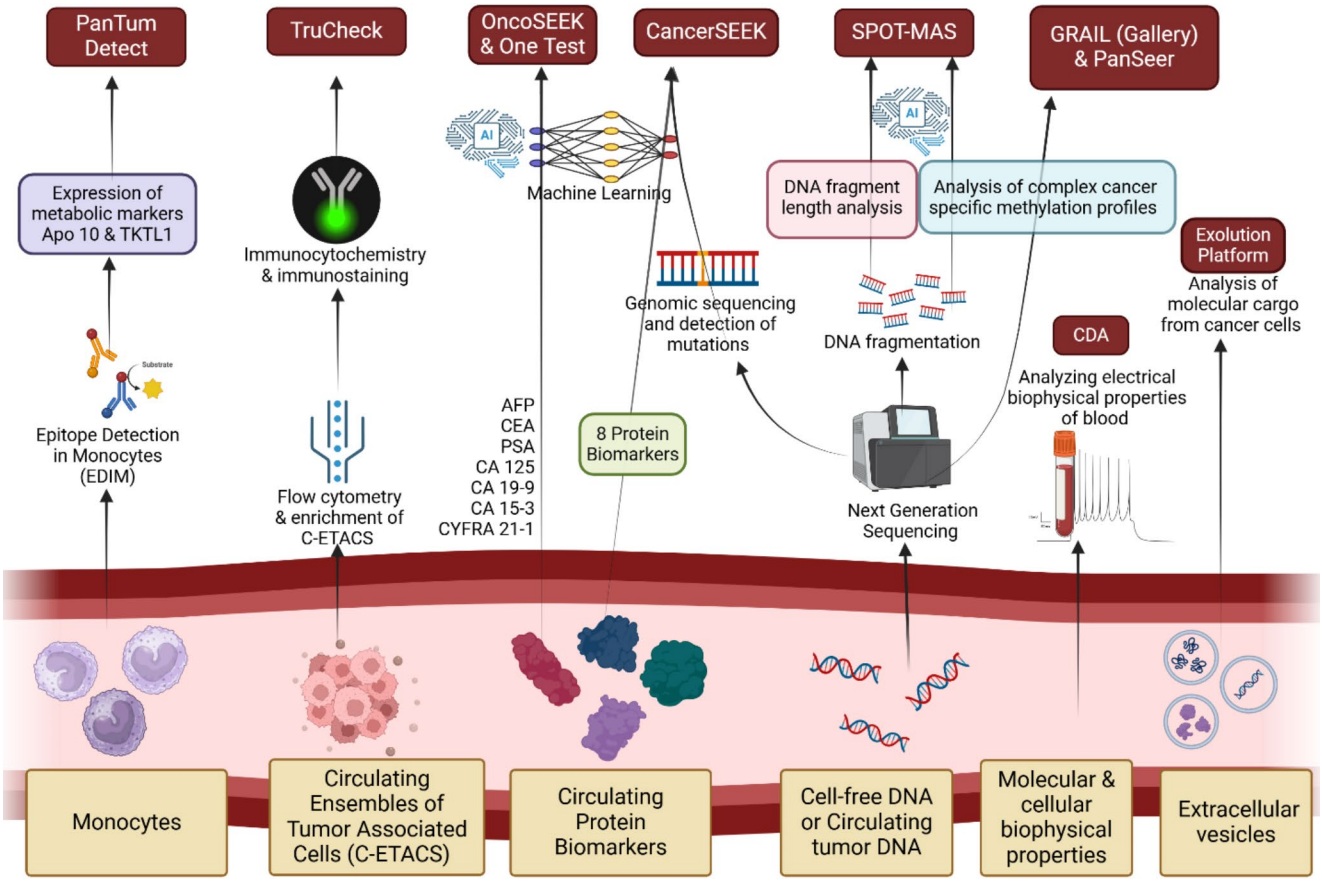

Fig. 1 Overview of biomarker detection techniques used in current multi-cancer detections tests. This figure outlines the key approaches employed in MCD platforms, including protein biomarker panels, genetic and epigenetic profiling of cell-free DNA using next-generation sequencing and fragment length analysis. Emerging technologies such as extracellular vesicle (EV) analysis and circulating tumor ensemble (C-ETAC) detection are highlighted, along with innovative methods such as Cancer Differentiation Analysis (CDA) that leverage biophysical signals. These techniques collectively represent the expanding landscape of non-invasive cancer detection methodologies. CDA; Cancer Differentiation Analysis, Apo10; of DNaseX, TKTL1; Transketolase-like1, AFP; Alpha Feto Protein, CEA; Carcinoembryonic antigen, PSA; Prostate Specific Antigen, CA; Cancer Antigen, CYFRA; Cytokeratin 19 fragment. Created in BioRender. Kandiah, P. (2024) https://BioRender.com/t511534

whether the test can reduce the incidence of late-stage cancer diagnoses in an asymptomatic population. Participants are randomized into two groups: an intervention arm, where blood samples are tested using the Galleri test, and a control arm, where samples are stored for future analysis. The primary goal is to demonstrate a statistically significant reduction in stage III and IV cancer diagnoses in the intervention group within 3–4 years of randomization. Results should be published in 2026.

In the United States, as a part of the Cancer Moonshot, the National Cancer Institute (NCI) Cancer Screening Research Network is set to initiate the Vanguard study in 2024, which is a multi-institutional, prospective randomized trial that will enroll 24,000 people into control or two different intervention arms. All participants will receive standard cancer screening, but the two intervention arms will also receive MCD assays [33]. Finally, The Advanced Research Projects Agency for Health (ARPA-H) has launched the Platform Optimizing SynBio for Early Intervention and Detection in Oncology (POSEIDON) program. This initiative aims to develop at-home, synthetic MCD tests that identify over 30 solid tumors at Stage I using only breath and/or urine samples [34].

Discussion

MCD testing is promising as a test for early detection of gastrointestinal cancers for which no other screening test exists and for which early detection is the only means to cure, such as cholangiocarcinoma and pancreatic adenocarcinoma. These cancers are often detected at a later stage and have a higher mortality rate than those cancers for which screening tests exist (breast, colon, lung and cervical). Although MCD testing can detect these cancers, it is not a replacement for age-appropriate and guideline-based cancer

Table 1 Overview of established multicancer detection tests -Technologies, Cancer types and key characteristics

Test Name	Technology Used	GI Cancer Types	Age (yrs)	Cancer Detection	Tumor of origin accuracy	Approval status	Notes
GRAIL/ Galleri [11–15]	DNA methylation & NGS	Esophagus Stomach Liver/Bile Gallbladder Pancreas Colorectal Anus	>20	Overall Cancer detection: Specificity 99.5% Sensitivity 52.4% Sensitivity by cancer stage: Stage I: 16.8% Stage II: 40.4% Stage III:77.0% Stage IV: 90.1% Sensitivity for all GI malignancies: 82.73% Sensitivity for foregut cancers: 83.9% High specificity and similar sensitivity across racial and ethnic groups	89%	Not FDA approved. Available for commercial use	Non-GI Malignancies: Test for 50 different cancers.
Cancer-SEEK [16–18]	NGS of Mutation and protein markers	Esophagus Stomach Liver Pancreas Colorectal	17 to 93 years. One study enrolled women 65-75yrs	Overall specificity for 8 cancers>99%. Weighted sensitivity for five GI (stage I to III) cancers is 70.4% Weighted sensitivity for foregut (stage I to III) cancers is 77.2%	63% across all 8 cancers 63.5% across 4 GI cancers	Not FDA approved Available for commercial use	Non-GI Cancers: Ovarian Lung Breast
PanTum Detect [19]	Apo10 and TKTL1 in monocytes; EDIM	Stomach Bile duct Pancreas Colorectal		No large studies. In 62 patients with known cholangiocarcinoma, pancreatic cancer or colorectal cancer, overall sensitivity was 100% Specificity 96.2%.	--	Not FDA approved. Available for commercial use	FDA breakthrough designation for ovarian and pancreatic cancer.
One Test [20–23]	Protein biomarkers AFP, CEA, PSA, CA 19−9, CA 125, CA 15−3, CYFRA 21−1 combined with AI and ML	Pancreas Colorectal cancer Liver	>18years but more suitable for age>50 years	Pre-ML performance: HCC Sensitivity 90.9%, Colorectal cancer Sensitivity 76.9%. Overall ML algorithm performance with inclusion of Age and Gender: Sensitivity: (M) 81.2%, (F) 81.7% Specificity: (M) 64.9% (F)67.5%	--	Not FDA approved but regulated as LDT by CMS and MDH under CLIA	Non-GI Cancers: Lung Prostate Breast Ovarian By imputing missing data with ML, developers report 80% specificity & sensitivity of (M)82% & (F)62%. No prospective validation
PanSeer [24, 25]	DNA methylation &NGS	Esophagus Stomach Liver Colorectal	25–90 years	Post-cancer diagnosis: sensitivity 88% Specificity 96% Pre-cancer diagnosis: Sensitivity 94.9% Specificity 96.1%	--	Not FDA approved and not available for commercial use	Non-GI Cancer: Lung Singlera has developed a GI cancer focused assay called Gutseer
OverC/ Thunder Study [26]	DNA methylation &NGS	esophageal, stomach, pancreatic, liver	50–75 years	Overall cancer types: Sensitivity 69.1 -75.1% Specificity 95.1 −98.9%	83.2%	Not FDA approved. Available for commercial use in China	Non GI cancer: Ovary

Table 1 (continued)

Test Name	Technology Used	GI Cancer Types	Age (yrs)	Cancer Detection	Tumor of origin accuracy	Approval status	Notes
SPOT-MAS [27]	DNA methylation & Fragment length patterns	Gastric, Colorectal, Liver	18–97 years	Overall cancer types: Sensitivity 72.4% Specificity 97.07% For Stage I &II cancers: Sensitivity 73.9% Specificity 62.3%	70%	Not FDA approved. Available for commercial use in Singapore	Non GI tumors: Breast, Lung
CDA [28]	Electrical biophysical signals	Esophageal Gastric Pancreatic Colorectal	>65 years	Overall cancer types: Specificity 93% Sensitivity 55%		Not FDA approved. NMPA Class III Medical Device Registration	Non GI tumor: CDA tests 27 cancer types
EpiPanGI Dx [29]	cfDNA methylation analysis	CRC, gastric, esophageal, pancreatic	age range not specified, tested in adults	prediction accuracy (ROC-AUC) of 0.85–0.95 for most GI cancers	Cancer-specific biomarker panels with AUC values of 0.98 (colorectal cancer), 0.98 (hepatocellular carcinoma), 0.94 (esophageal squamous cell carcinoma), 0.90 (gastric cancer), 0.90 (esophageal adenocarcinoma), and 0.85 (pancreatic ductal adenocarcinoma)	Research phase	Focuses on early detection of GI cancers through cfDNA methylation patterns
Caris Assure-GPSai [30]	whole exome DNA and transcriptome RNA sequencing	colorectal, gastric, esophageal, pancreatic	Age range not specified, tested in adults	Sensitivity and specificity vary by cancer type	accuracy > 93% across 21 cancer types	Available for commercial use	Utilizes comprehensive molecular profiling for cancer detection.

Table 1 (continued)

Test Name	Technology Used	GI Cancer Types	Age (yrs)	Cancer Detection	Tumor of origin accuracy	Approval status	Notes
Elypta MIRAM [31]	Metabolomic profiling of GAGome	colorectal, gastric, esophageal, pancreatic	> 18 years old	Sensitivity and specificity vary by cancer type	GAGomes predicted the putative cancer location with 89% accuracy	Research phase	Focuses on metabolomic signatures for cancer detection, utilizes urine and plasma samples
Shield, by Guardant Health/ ECLISPE Study [32]	cfDNA blood-based test	Colorectal	> 45 years old	Sensitivity for stage I, II, or III colorectal cancer was 87.5% (95% CI, 75.3 to 94.1), and sensitivity for advanced precancerous lesions was 13.2% (95% CI, 11.3 to 15.3). Specificity for any advanced neoplasia of 89.6% (95% CI, 88.8 to 90.3)	As noted previously	Commercial Use	Exclusively focused on colorectal cancer screening

CMS; Center for Medicare & Medicaid Services, LDT; Laboratory-Developed Test, MDH; Maryland Department of Health, CLIA; Clinical Laboratory Improvement Amendments, AI; Artificial intelligence, ML; Machine Learning, NGS; Next Generation Sequencing, NMPA; China's National Medical Product Administration; Food and Drug Administration (FDA)

screening. Recently, the United States Preventative Task Force Services (USPSTF) guideline was updated to recommend colon cancer screening to those at average risk at age 45 [35].

For those individuals at higher risk of cancers for which limited screening exists, including those with genetic predispositions to gastric or pancreatic cancers, MCD testing offers an alternative or adjunct to more invasive and less sensitive screening options. For instance, a patient with a BRCA gene mutation and a family history of pancreatic cancer may benefit from the blood-based MCD screen, aiding in the early detection of a cancer with a high mortality rate. MCD testing can also suggest cancers such as cholangiocarcinoma for which early detection could lead to curative transplant, but later detection may preclude treatment. MCD testing may be an option in these patient populations.

The diagnostic evaluation for positive MCD signals is not standard at this time but is based on the best medical judgment. For foregut malignancies, the diagnostic evaluation may include EGD, EGD with EUS, MRCP, or mapping gastric biopsies, which may be in addition to imaging such as CT or PET-CT. Neuroendocrine signals may warrant dotatate-PET. For some tests, no signal of origin is provided, and the diagnostic evaluation may be more generic, starting with CT of the chest, abdomen and pelvis with or without PET-CT. For those MCD tests targeting GI malignancies but that provide signal positivity for other cancers, the evaluation may need to extend beyond a GI evaluation if no cancer is identified.

Gastroenterologists may be reluctant to order MCD testing because the tests evaluate more than just GI malignancies. To mitigate this concern, the authors have created a clinic to evaluate positive MCD signals for all cancer types. This clinic is staffed with general internists who can assist with assessing various malignancies and are developing best practices for diagnostic evaluation. This can be done in concert and consultation with gastroenterologists for such signals as pancreatic and bile duct, which have nuanced approaches to diagnosis.

Limitations of MCD Testing

Determining the ideal cancer screening test for multiple cancers is a challenging endeavor due to the variability in optimal timing in detecting cancer or precancer conditions, crucial for early treatment and prevention. Furthermore, studies needed to evaluate the performance of these screening tests, especially in low-prevalence cancers, require large patient populations, which can delay the availability of conclusive results. Ultimately, the most critical measure of a screening test's effectiveness is its ability to demonstrate

a reduction in cancer-specific mortality. As MCD technology remains in the early stages of development, no definitive studies have yet demonstrated improved outcomes. Moreover, there is limited data on the frequency of adverse effects such as overdiagnosis, unnecessary procedures, and additional costs [9]. Existing studies vary significantly in methodology, target different types of cancer, and focus on disparate stages of disease. Furthermore, varying modifications introduced to MCD tests to improve performance complicate interpreting and comparing data from earlier test iterations.

In the PATHFINDER study, the false positive rate was 0.9%, but the positive predictive value was just 31%.[11] The evaluation of a positive signal, particularly when no cancer is identified, can lead to significant anxiety amongst patients and can negatively impact clinician well-being as there is a strong desire to solve the diagnostic problem. The psychological impact of a positive Grail Galleri test is currently being studied in a large cohort [36].

The cost to evaluate the positive signal can be significant as the evaluation often includes expensive and/or invasive testing such as PET-CT and endoscopy. Moreover, these tests may or may not be covered by patients' insurance, opening the door to additional financial burdens. Because MCD testing has not yet been approved by the Food and Drug Administration (FDA), many insurance companies do not cover the test nor the subsequent evaluation (all or parts). This can lead to high costs and, combined with the low positive predictive value, may not lead to a definitive diagnosis.

A limitation that is not quantifiable is the mental cost to patients. Often, the diagnostic evaluation for cancers that are detected in preclinical stages can be challenging and may be unrevealing. Knowing that a cancer signal is present but being unable to identify the inciting cancer can provoke fear and anxiety. Previous studies using tumor markers such as CA-125 for screening asymptomatic patients for ovarian cancer have lacked sensitivity and specificity and can drive similar anxiety [37]. In other instances, the cancer may require multiple invasive procedures for diagnosis, such as endoscopy, which may cause other medical complications despite being potentially non-diagnostic.

Conclusions

Facilitating shared decision-making by having risk-benefit discussions with patients is critical prior to obtaining an MCD test. The potential benefits that MCD can provide in early diagnosis of cancer must be balanced against the inherent risks that accompany this testing. This discussion must include the financial costs that can accumulate, the potential for invasive testing to obtain a diagnosis, and the potential that evaluation may not be diagnostic. The risk of a false positive test and the potential for anxiety and diagnostic uncertainty should also be discussed. MCD testing does not replace age-appropriate cancer screenings such as colonoscopy and cancer screening recommended for genetic predispositions of cancer [38]. The role of MCD is evolving, and ongoing multi-center research is necessary to provide more guidance for clinical decision-making in the years to come.

Key References

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  One of the important studies that evaluated a targeted methylation-based cell-free DNA multi-cancer early detection test designed to detect cancer and predict the cancer signal origin (tissue of origin). It was able to find that cancer was detected in a majority of the samples that were truly cancer samples, and importantly, that it did not detect cancer in any of the non-cancer samples. It was also found that the cancer signal origin was correctly predicted in all tumor samples detected as cancer. This served as an important early supporter for the role of targeted methylation cell-free DNA multi-cancer detection test.

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  This was a summary of the PATHFINDER trial, which was a prospective cohort study investigating the feasibility of MCED testing for cancer screening. This served as the key publication for reporting the findings from this study, which supports the feasibility of MCED screening for cancer and underscores the need for further research investigating the test's clinical utility.

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This large-scale clinical validation study demonstrated high specificity and accuracy of MCD for predicting cancer signal of origin, and also demonstrated its ability for detecting cancer signals across many different cancer types. Served as further support to the role for MCD testing as a complement to current guideline-directed cancer screening tests.

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  This manuscript was made regarding the design of the NHS-Galleri trial, and served to highlight the emerging collaborations that are occuring at nationwide levels in an effort to help more thoroughly investigate the role that MCD testing can play in screening asymptomatic individuals for cancer.

Author Contributions AG, KS, PK, RH, and EG all wrote parts of the main manuscript text. AG, RH, and EG prepared Table 1. PK and KS prepared Fig. 1. All authors reviewed the manuscript and approved of the final submitted version.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

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