New Genomic Technologies for Multi-Cancer Early Detection: Rethinking the Scope of Cancer Screening

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Summary

Cancers other than breast, colorectal, cervical, and lung do not have guideline-recommended screening. New multi-cancer early detection (MCED) tests—using a single blood sample—have been developed based on circulating cell-free DNA (cfDNA) or other analytes. In this Commentary, we review the current evidence on these tests, provide several major considerations for new MCED tests, and outline how their evaluation will need to differ from that established for traditional single-cancer screening tests.

Most cancers are diagnosed too late for curative treatments. Modern systemic and targeted drugs for treating advanced cancer are expensive, and some have limited efficacy. Cancers diagnosed after distant metastasis account for 45% of cancer-related deaths within 5 years, but only 18% of diagnoses (Clarke et al., 2020). Few cancers are currently recommended for population-wide screening: breast, colorectal, cervical, and (in high-risk persons) lung cancers.

Novel, high-performance genomic technologies allow detection of signals from cancers in blood, giving rise to a new paradigm of multi-cancer early detection (MCED). Blood is inherently suited for detecting cancer biomarkers (Ahlquist, 2018), as it contains circulating tumor cells, and fragments of tumor cell-free DNA (cfDNA). MCED tests analyze genomic features of circulating cfDNA and distinguish these from background genomic signals. This multi-cancer ability aligns with an individual's risk of developing any cancer type, for which they have no control. MCED tests require us to think innovatively about the benefit/harm balance, and how it may differ from that associated with current screening paradigms targeting single cancers.

Rapid Progress in the Development of MCED Blood Tests

Table 1 summarizes features and performance of MCED tests identified from PubMed and conference abstracts as of July 2021. Most studies have only reported data from a few cancer types, while the CancerSEEK and Galleri® tests included most types.

The CancerSEEK test uses a combination of genetic mutations (in 16 genes) in cfDNA and nine protein biomarker levels in plasma. Following an initial study of 1005 participants, the DETECT-A interventional study recruited 9911 women attending for standard screening, in which the MCED test results were used clinically. Those with a positive MCED test were reviewed by a multidisciplinary panel to consider PET-CT for localizing the tumor of origin.

The Galleri test uses a targeted bisulfite sequencing methylation-based assay (>100,000 distinct regions and >1,000,000 cytosine-guanine dinucleotides). One study (Circulating Cell-Free Genome Atlas [CCGA]) was a case-control subset of a prospective cohort of 15,254 men and women. Three ongoing prospective longitudinal multi-center studies aim to validate the Galleri test performance in intended-use populations: STRIVE (NCT03085888; 99,308 women attending for mammography), SUMMIT (NCT03934866; 13,000 smokers and former smokers at high risk of lung cancer attending for low-dose CT), and PATHFINDER (NCT04241796; an interventional study that enrolled 6,662 persons, who received the test result and were managed accordingly; Beer et al., 2021).

The PanSeer test uses a similar approach to the Galleri test (covering 11,787 CpG sites across 595 genomic regions). The main study used stored blood samples from people with and without cancer nested within a longitudinal study; contrasting with studies of other tests where blood samples were collected and tested prospectively. Adela Inc. has developed an immunoprecipitation-based test to detect genome-wide methylation changes in cfDNA. Burning Rock Biotech has an MCED test based on ELSA-seq technology, and recently initiated two prospective studies (PREDICT, NCT04383353, >14,000 participants; and PRESCIENT, NCT04822792, ≈12,000 participants). Furthermore, cfDNA-based blood tests developed for single-cancer screening (e.g., Freenome and Guardant for colorectal cancer) are now being investigated for multiple cancer types.

The PanTum Detect test is fundamentally different and utilizes epitope detection in monocytes (EDIM)-based technology to detect two biomarkers, Apo10 and TKTL1, in monocytes that have phagocytosed tumor cells and migrated to the blood. Published studies were

based on newly diagnosed cases, but also included recurrent disease, so incomparable to asymptomatic individuals with cancer.

Do MCED Tests Have Sufficient Screening Performance?

Current standard-of-care screening tests each have high sensitivities for the target cancer type (80%–90%), but the false-positive rates (FPRs) of 5%–15% coupled with the relatively low incidence of individual cancer types yield modest positive predictive values (PPVs) of around 5%–10%. An MCED test targeting all cancer types will have a lower aggregate test sensitivity including low-signal cancers (e.g, 40%–50%) combined with a very low FPR (<1%), and should yield a higher PPV (≥30%). While sensitivity (percentage) is a standard performance measure of single-cancer tests, the cancer detection rate in a population (expressed as a proportion of the total diagnosed or expected) better reflects the impact of MCED tests, by combining moderate test performance and high incidence.

Table 1 shows variability in sensitivities (27%–100%). All but two studies (Lennon, 2020; Chen et al., 2020) were based on cancers diagnosed in clinics, therefore some of the high sensitivities are partly due to late-stage disease, which generally have more circulating tumor markers, compared to asymptomatic people with cancer. High sensitivities (>80%) were only seen in studies based on ≤6 selected cancer types, while studies of multiple (≥8) cancer types had lower aggregate sensitivities of 27%–62%. Sensitivities also appeared to decrease as the number of cancer types in the studies increased, highlighting the importance of large-scale studies. All tests require evaluation in populations representative of the target group for screening, because sensitivity might be higher in cancer patients recruited at diagnosis. This could explain why sensitivity in the study using the CancerSeek test, in which results were used and acted upon,

was 27% but the prior observational study reported 62%. Only one other study has used the results clinically (the Galleri test); the initial PPV of 40% (19 cancer cases among 6516 tested, Beer et al., 2021) appears consistent with prior observational studies (Klein et al., 2021).

Test sensitivities must be reported across cancer stage. The sensitivity of PanSeer appeared surprisingly similar between early- and late-stage cancers (Chen et al., 2020), given the biological expectation that tumor shedding and thus detectability increases with stage (as seen with the Galleri and CancerSEEK tests [Klein et al., 2021; Cohen et al., 2018]).

FPR varies between 0% and 4% (Table 1) across technologies. Longer follow-up can determine whether some people initially classified as false-positives are diagnosed with cancer several months later. FPRs for an MCED test must be low to avoid many thousands of people without cancer being referred for clinical investigations, thus overwhelming healthcare systems.

Using Table 1 we consider that an effective MCED test should have three features: a reasonably high aggregate sensitivity, coverage of a wide range of tumor types, and a very low FPR (ideally <1%). If any of these are absent, the test may not be a cost-effective population screening modality.

The Value of MCED Tests for Cancers Without Standard Screening

Although current screening is established for a few cancer types, together they are responsible for only approximately 25-30% of all cancer-related deaths among those age groups eligible for screening. MCED tests can provide a screening modality for lethal cancers that have no effective tests (70-75% of all cancer deaths); a major purpose of these tests. Breast, bowel, and lung cancers lead to 42,000, 51,000 and 142,000 deaths per year respectively (US 2019). However, other cancers typically lead to far fewer deaths, for example head and neck (11,000 deaths), liver

and bile duct (32,000), and bladder (18,000), therefore a randomized controlled trial (RCT) of a single test for each of these would be unfeasibly large. Furthermore, a screening test is unlikely to ever be cost-effective on a population scale for such cancers. Individuals with these less common but deadly cancers are therefore disadvantaged compared to individuals with cancers that have effective screening available.

MCED Tests and Current Standard Screening

MCED tests may have sensitivities lower than current standard screening tests, so we should also consider how MCED testing can be used alongside recommended screening programs.

An additional value of MCED testing is to find breast, colorectal, cervical, lung, and prostate cancers that are either missed by standard screenings, are detected in people who are ineligible for screening, or are detected in eligible people who decline standard screening but prefer to have an MCED test. Preliminary modeling indicates that this could be an efficient screening policy. Using current screening alone, there are an estimated 43 false-positives for every breast, colorectal, cervical or lung cancer detected in the U.S. Combining current and MCED screening yields only 14 false-positives for every cancer detected (all types) (Hackshaw et al., 2021).

MCED tests might also improve the screening performance of current tests, specifically by reducing their FPR without unduly affecting sensitivity. Research should examine whether MCED and current screening tests largely detect the same cancers in the same people. In the DETECT-A study (using CancerSEEK), test-positive cancer cases using the MCED test were not the same as test-positives using standard screening (Lennon et al., 2020). Studies can explore the

efficacy of combining MCED and established tests to produce a single risk value, as in prenatal trisomy screening which combines age, blood markers, and imaging.

Adherence to recommended screening might be reduced if people prefer the convenience of an MCED test (that has lower sensitivity), but in the DETECT-A study, participants maintained high adherence to standard screening.

4. Can MCED Tests Localize the Signal from the Primary Tumor?

MCED tests should localize the anatomic site of the primary tumor with high accuracy, ideally using the same blood sample (Ahlquist, 2018). Otherwise, diagnostic investigations among test positives may be unfocused, leading to unnecessary imaging (increasing total-body radiation exposure) and biopsies with potential harm; thus delaying definitive diagnosis and causing anxiety and frustration for patients and clinicians. Simultaneous detection and localization of cancer allows timely assessment of histological type and stage, enabling prompt treatment.

Several tests had a high level of accuracy in their ability to correctly localize the primary cancer (Table 1). However, this might vary by cancer type (Cohen et al., 2018).

5. Is Overdiagnosis a Major Concern for MCED Tests?

Overdiagnosis is an established harm of cancer screening. It is expected to be minimal for tests based on cfDNA fragments in the bloodstream, where more lethal or aggressive tumors tend to shed more tumor material (cells) and are subsequently detected. Latent or overdiagnosed cancers tend to have indolent or less aggressive behavior. The PanSeer test appeared to detect cancers four years before they were diagnosed (Chen et al., 2020), suggesting that MCED tests target clinically relevant cancers. This was also demonstrated across multiple cancer types using an

early version of the Galleri test (Chen et al., 2021). Large-scale studies of MCED tests with sufficient follow-up will determine whether overdiagnosis is minimal.

6. How Should MCED Tests Be Evaluated?

Box 1 outlines key attributes of an effective MCED blood test. Comprehensive development and evaluation of population-scale tests involve observational and interventional studies with health economics analyses. To date, decision-makers have required large (tens of thousands of participants) RCTs to determine that screening plus treatment reduces mortality just from a single cancer type. These have taken many years to complete.

Major endpoints of RCTs should reflect reduced incidence of late-stage cancers and cancer-specific mortality, and less morbidity associated with late-stage disease. Sufficiently long follow-up will overcome lead-time bias. There should be secondary analyses reporting test performance separately for cancers with and without currently recommended screening.

RCTs should be complemented by other innovative evaluation strategies. Infrastructure for real-world registries of MCED test recipients—incorporating medical records and claims data sources—can supplement RCT evidence, crucially for rare cancer types, and provide population-scale evidence of clinical utility.

Paradigm Shift

Although the concept of an MCED test (i.e., one test for multiple cancers) is relatively new, the concept of one screening test for multiple disorders is established practice for other conditions. Serum biomarkers and now noninvasive testing using fetal cfDNA from a single

maternal blood sample can detect several prenatal chromosomal abnormalities such as trisomies 13, 18 and 21, and microdeletion syndromes.

The convenience of a single blood test (that can detect numerous cancer types, whether they have recommended screening or not) that is accessible to a broad population contrasts with the resource intensiveness of implementing, coordinating, and maintaining multiple independent single-cancer screening programs. This is particularly important in lower- and middle-income countries (especially with aging populations) or geographically distant/spread populations. MCED tests for which the blood sample can be stored and shipped at ambient temperatures are the most convenient (e.g., the Galleri and CancerSEEK tests).

Healthcare providers will need to consider how to implement MCED testing with easy access for large numbers of people, administrative and IT linkage with current screening programs, and continuous monitoring of performance measures. Also, a monitoring pathway should be developed for people with a positive MCED test who have no radiological or clinical evidence of cancer.

The value of MCED blood tests will be determined by the evidence of impact on clinically relevant endpoints as well as costs. They are expected to play a major future role in reducing cancer morbidity and mortality.

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Declarations of Interest

C.A.C. is an employee of GRAIL, LLC, and holds stock in the company. **A-R.H.** is a former employee of GRAIL, and holds stock in the company, and is currently employed by Adela, Inc. **A.H.** is an investigator for an academic study (SUMMIT) sponsored by University College London that is funded by GRAIL; has received one honorarium for an advisory board meeting for GRAIL; received a consulting fee from Evidera Inc. (for a GRAIL-initiated project); and has previously owned shares in Illumina, Inc. He did not receive any compensation for his work on this manuscript. A.H. is supported by a Cancer Research UK grant to University College London (C444/A15953).

Table 1. Multi-Cancer Early Detection Blood Tests With Published Screening Test Performance (as of July 2021)

Test Name (First Author)	CancerSEEK (Cohen et al., 2018; Lennon et al., 2020)		Pantum/EDIM (Grimm et al., 2013; Saman et al., 2020)		PanSeer (Chen et al., 2020)	Galleri (Klein et al., 2021)	Not Yet Named (Li et al., 2020, Gao et al., 2021)		Not Yet Named (Shen et al., 2018)	CancerRadar (Stackpole et al., 2021)
Company Name (country)	Exact Science (U.S.)		RMDM Diagnostics/ Zyagnum AG (Germany)		Singlera Genomics (U.S.)	GRAIL (U.S.)	Burning Rock Biotech (China)		Adela (Canada)	Early Diagnostics (U.S.)
Biological Signal	Mutations & protein markers		Apo10 & TKTL1 in monocytes		DNA methylation					
Age Range, Years	17–93	65–75	19–85	All	35–85	>20	-	40–75	57–70	-
% Women	51%	100%	46%	35%	34%	55%	-	46%	61%	-
Source of Cancers	Clinic	Population	Clinic	Clinic	Population	Clinic	-	Clinic	Clinic	Clinic
No. Cancer Types	8[a]	9 (all were targeted)[b]	3[c]	3[d]	5[e]	>50	3[f]	6[g]	7[h]	4[i]
Sensitivity (No. With Cancer)	62% (1,005)	27% (96)	97% (213)	100% (62)	95% (98)[j]	52% (2823)	75% (452)	81% (351)	70-75% (137)	86% (275)
Tumor of Origin Accuracy	83%	-	-	-	-	89%	93%	82%	-	92%
FPR (No. Without Cancer)	0.9% (812)	1.1% (9815)	4.0% (74)	0% (16)	3.9% (207)	0.5% (1254)	1%–4% (290)	1.7% (288)	0% (62)	1% (204)

Sensitivity: percentage of all cancers who were test positive; False-positive rate (FPR): percentage of controls (without cancer) who were test positive.

[a]Ovarian, liver, stomach, pancreatic, esophageal, colorectal, lung, breast.
[b]Ovarian, lung, uterine, thyroid, colorectal, breast, lymphoma, kidney, unknown primary.
[c]Oral, breast, prostate.
[d:]Biliary tract, pancreatic, colorectal.
[e]Stomach, esophageal, colorectal, lung, liver.
[f]Lung, colorectal, liver.
[g]Lung, colorectal, liver, ovarian, pancreatic, esophageal.
[h]Pancreatic, colorectal, breast, lung, renal, bladder, acute myeloid leukemia. Sensitivity and FPR estimated from Figure 3 in the paper.
[i]Colon, liver, lung, stomach.
[j]Pre-diagnosis sensitivity; sensitivity was 88% at the time of diagnosis.

Box 1. Desirable Key Attributes of a Multi-Cancer Early Detection Test for Population-Wide Screening

Attribute	Impacts
Detection of cancers in most organ systems, particularly the most lethal cancers	● Cover multiple cancers, particularly those with no effective single-cancer screening test
	● Minimize overdiagnosis by preferentially detecting more lethal cancers
Accurate localization of the primary tumor to an anatomic site	● Improve diagnostic evaluation
	● Incorrect signal origin may lead to unnecessary workup of the wrong organ system
Sufficiently high sensitivity leading to a high cancer detection rate (absolute number of cancers detected)	● Detect tumors across many cancer types
	● Complements standard of care screening
	● Sensitivity needs to be high enough for early stage disease
Very low FPR	● Minimise investigations and procedures in people without cancer
	● Minimise anxiety
	● Reduce healthcare resource use and costs
Relatively high PPV	● Represents high screening efficiency in a particular population, because it reflects both cancer incidence and test sensitivity
	● PPV should be high when considering all cancers together
Convenient and accessible blood test	● Increase uptake, especially in hard-to-reach populations
	● No need for pre-test medications or preparatory procedures
	● No special equipment, staff or resources required to take the test, and blood samples can be processed and shipped at ambient temperature
	● Limited time off from work to take the test
	● Affordable test (to healthcare systems or individuals)
Demonstration of clinical utility	● Carried out using a randomized interventional trial
	● Should reduce the number of people (incidence) diagnosed with late-stage cancer and cancer-related mortality across a variety of cancers
	● Cost-effective
FPR, false-positive rate; PPV, positive predictive value.	