Editorials

Multicancer Early Detection: A Promise Yet to Be Proven

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Screening is a cornerstone of cancer control and is important in primary care, for which disease prevention and early detection are fundamental tenets. Population-based screening has contributed to reduced incidence of or mortality from some cancers (e.g., cervical, colorectal). There is growing scientific and investor interest in multicancer early detection tests to screen for multiple cancers with a single test instead of using separate tests for individual cancer types[1] *(eTable A)*. Current candidate biomarkers include plasma-based assays of circulating cell-free DNA, epigenetic changes (DNA methylation), RNA, and proteins.

Well-established screening principles help explain why multicancer early detection tests are not included in current U.S. Preventive Services Task Force (USPSTF) recommendations.[2,3] Screening is a multistep process using tests or tools to identify preclinical disease. Abnormal screening results lead to invasive procedures to distinguish people with potentially lethal cancers from those with false-positive results. That diagnostic pathway should be well-defined but is unclear for multicancer early detection tests, even when a tumor of origin is suggested.

Another shortcoming of current multicancer early detection tests is their limited ability to detect precursor and early, more treatable cancers because tumor markers are less commonly expressed in the early phases of carcinogenesis.[4] Due to a lack of appropriate studies, the sensitivity and specificity of multicancer early detection tests are unclear for people with unknown disease status who would be screened in primary care. The implications of a negative result or a positive result with negative follow-up testing are unclear. The potential for harm associated with an invasive workup and treatment of false-positive results or incidental findings increases with the number of purportedly detectable cancers.

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Interest in multicancer early detection tests stems partly from limitations of currently recommended screening technologies, including a lack of effective screening tests for all but four cancers (i.e., cervical, breast, lung, and colorectal).[1,5] Consequently, highly lethal cancers, such as ovarian and pancreatic, lack effective screening strategies.[1,5-7] Limitations in the accuracy of current screening technologies lead to potentially avoidable false-negative results (or missed detection) or harms from false-positive results. Multiple encounters and separate procedures are required to screen individually for each cancer. However, the benefits of multicancer early detection–based screening (i.e., reduction in mortality and harms specific to the targeted cancer) have not been demonstrated.[1]

Screening tests are used in people who are asymptomatic for the condition of interest but are at risk of developing that condition.[3] New test evaluative processes are well-described and involve a series of studies including randomly selected people in whom the presence or absence of the disease is undetermined.[1] For cancers with USPSTF-recommended screening tests, there is the potential to conduct comparative studies that do not involve proving mortality reduction if the tests being compared detect a similar spectrum of disease and the harms are adequately documented. The benefits of any screening on health outcomes need to outweigh the harms, but no multicancer early detection test has been studied to establish whether it decreases the risk of death.[8] Although inadequate, the current best evidence on multicancer early detection tests comes from studies involving people known to have cancer, which is unsuitable for understanding sensitivity and specificity or safety and effectiveness in general populations.[9,10]

Screening is more likely to preclinically detect slower-growing, indolent, or less lethal cancers

than aggressive cancers. Screening detects precursor lesions, but relatively few become lethal in a person's lifetime. Treatment of indolent preclinical lesions, such as with thyroid cancers, only incurs the potential for harms from overdiagnosis.[11] Current multicancer early detection technologies have not been studied for the ability to distinguish indolent lesions from lethal ones.

The treatment of cancers diagnosed through screening should be more effective at preventing death than through clinical presentation. Screening and detection during the occult preclinical phase can create an illusion of benefit and the misperception of longer survival, even when treatment is not effective at improving health outcomes (lead-time bias). Epidemiologically, individual cancers are rare. For example, in 2020, there were 31.8 deaths from lung cancer per 100,000 people in the United States (0.03%).[12] Most people undergoing screening will not derive benefits but are at risk of potential harms, including death, from the screening test or subsequent downstream care. This underscores the critical importance of well-designed studies before the widespread use of multicancer early detection tests.

Some multicancer early detection tests are being directly marketed to consumers. Because of known limitations and inadequate evidence, primary care clinicians should focus on providing USPSTF-recommended, evidence-based preventive services and only use multicancer early detection tests in the context of well-designed clinical research studies and not in place of proven tests. Some clinical studies are in the planning phases. There are opportunities for methodologic developments that could shorten the discovery-to-delivery time without sacrificing rigor, addressing concerns among test developers that the current evaluation process for new screening tests is lengthy and costly.[13] However, promoting multicancer early detection tests for use before valid and rigorous evaluations are performed is similar to marketing a drug without first showing that it is safe and effective.

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eTABLE A

Multicancer Detection Tests in Development or Being Marketed in the United States

Assay	Technology	Target cancers for detection by assay: Lung	Colon/rectum	Breast	Pancreas	Liver	Esophagus	Stomach	Ovary	Prostate	Bladder	Kidney	Uterus	Head/neck	Lymphoma	Leukemia	Plasma cell	Brain	Company/developer
Adela	cfMeDIP sequencing; cfDNA fragmentomics	■	■	■	■						■	■				■			Adela Bio
Tr(ACE)	Extracellular vesicle proteins; AI				■				■		■								Biological Dynamics
Bluestar MCED	cfDNA 5-hydroxymethyl-cytosine sequencing; fragmentomics	■	■	■	■	■	■	■	■										Bluestar Genomics
OverC	ELSA sequencing	■	■		■	■	■		■										Burning Rock
MIGPSai	cfDNA/cfRNA NGS; AI	■	■	■				■				■	■						Caris Life Sciences
Delfi	cfDNA fragmentomics	■	■		■			■	■										Delfi Diagnostics
cfMethyl-Seq	cfDNA methylcytosine NGS	■	■			■		■											Early Diagnostics
MIRAM	Ultrahigh performance LC-MS glycosaminoglycans/Elypta's SKY software			■				■		■	■	■		■	■	■		■	Elypta
CancerSEEK	cfDNA NGS; protein markers	■	■	■	■	■	■	■	■										Exact Sciences
FMBT	Multi-Omics/AI	■	■	■	■	■	■	■	■	■	■	■	■						Freenome
Galleri	CpG-cfDNA NGS	■	■		■	■	■	■	■		■			■	■		■		Grail
LungLB	CTC fluorescence in situ hybridization; imaging AI	■		■		■						■							LungLife AI
Signatera	cfDNA NGS; protein markers	■	■	■	■	■			■		■		■						Natera
Sentinel-10	CpG-cfDNA quantitative polymerase chain reaction	■	■	■	■	■													Precision Epigenomics
OneTest	Circulating cancer antigens; AI	■	■	■	■	■			■	■									20/20 GeneSystems
VPAC receptor TP4303	Near infrared optical microscopy	■		■						■			■	■					Thomas Jefferson University/Intermountain Health
Acetylated polyamines	LC-MS/MS	■	■	■	■				■										MD Anderson Cancer Center
Quantum Sensor/ OncoProfiler	CTC surface-enhanced Raman scattering/machine learning	■	■	■					■									■	Toronto Metropolitan University/St. Michael's Hospital

AI = artificial intelligence; cfDNA = cell-free DNA; cfMeDIP = cell-free methylated DNA immunoprecipitation and high-throughput; cfRNA = cell-free RNA; CpG = 5'-CG-3' single-stranded linear sequence DNA site; CTC = circulating tumor cell; ELSA = enhanced linear-splinter amplification; LC = liquid chromatography; MS = mass spectrometry; NGS = next-generation sequencing.

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