Multi-cancer Early Detection Tests, Primary Care, and Shared Decision Making

Kevin Selby, MD, MAS; Glyn Elwyn, MD, PhD, MSc; and Robert J. Volk, PhD

"What to do you think, doc, should I get one of these tests?" I am seeing Mr. Y, a 55-year-old business school teacher with a penchant for new technologies. He is in good health, has not smoked for 20 years, and takes 1 medication for benign prostatic hypertrophy.

Mr. Y shows a direct-to-consumer advertisement for a multi-cancer early detection, or MCED, test. "What if you found cancer early enough to make a difference? Seventy-one percent of cancer deaths are caused by cancers not commonly screened for" (1). The logic is compelling: Despite recommended screening, Mr. Y might benefit from additional testing for multiple cancers. I pause. This situation, with more than one reasonable choice and considerable uncertainty due to poor-quality evidence (2), is perhaps suited for shared decision making with the 3-talk model (3). I begin with the "team talk": "This is new to me actually, so let's work together and try to decide what makes sense for you."

The MCED tests represent a significant shift in cancer screening and may arrive before most clinicians know about them. Also called "liquid biopsies," they search for very small quantities of cell-free DNA and protein biomarkers released from early-stage cancer cells into the blood, before symptoms or signs occur. Paired with machine learning, these assays use proprietary algorithms to suggest a likely tumor origin for the DNA and proteins. Some MCED tests are already commercially available as laboratory-developed tests through the Clinical Laboratory Improvement Act (CLIA), but none are currently approved by the U.S. Food and Drug Administration (FDA).

Primary care providers are accustomed to screening for individual cancers where we are aware of the risks and benefits, including follow-up diagnostic testing and treatment. For instance, colorectal cancer screening is recommended because early cancers and precancerous lesions can be removed by colonoscopy, reducing incidence and mortality. The benefit of prostate-specific antigen testing to screen for prostate cancer is less clear. It is typically reserved for people like Mr. Y, who, after a discussion, is willing to accept potential false positives, a cascade of additional tests, and possible overdiagnosis, to have a potential small survival benefit. All screening tests have risks, but the U.S. Preventive Services Task Force recommends cancer screening for 5 cancer sites among older individuals based on a rigorous appraisal of randomized trials, trends in cancer prevalence, and modeling studies.

With 1 blood test, MCEDs search for a range of cancers. The approximately 18 tests in development search for 2 to more than 50 different tumor types simultaneously, including both common culprits and others clinicians rarely come across. The tests will likely cost between $200 and $1000 and are not currently reimbursed by insurance. That could change with new legislation before the U.S. Senate to oblige Medicare to reimburse these tests if approved by the FDA (4). Because the FDA considers diagnostic accuracy and not clinical outcomes when evaluating tests, MCEDs may become widely available before we have data confirming reductions in cancer mortality or downstream harms, including overdiagnosis. Clinicians will face challenging patient questions about MCED tests. Patients may ask about false-positive rates, express anxiety before and after testing, expect help with unclear results, and be surprised by the financial costs of subsequent testing (**Figure** [5–7]). The tests will likely be heavily promoted, resulting in high expectations and demand for these new tests.

"Tell me what you know," I continue. Mr. Y replies, "Seems revolutionary, a simple blood test for so many cancers. After my colonoscopy, I'm reassured I don't have colon cancer, but here's a chance to exclude many cancers." It's no surprise to hear only the benefits. Companies, hospitals, and even physicians emphasize the positive aspects of early cancer detection and often overlook the risks.

No patient decision aids on MCEDs exist, so I draw on a sheet of paper. On one side, "Do the test now," on the other "Wait and see," to frame our "option talk." I draw his attention to potential downsides, notably, the importance of cancer prevalence and that cancer detection does not necessarily translate into lives saved. For instance, pancreatic cancer screening with sensitive imaging can yield 7.8 cancers per 1000 persons, two thirds of which are localized (8). An MCED would be expected to detect 3 of these 5 localized cancers (9). Pancreatic cancer screening is not recommended, however, because unfortunately even localized disease has a 5-year survival of only 37%, exemplifying how early detection does not necessarily mean cancer cure (8).

Given that MCEDs provide signals rather than definitive results, diagnoses will rely on many more investigations, including imaging and biopsy for confirmation. There are insufficient data to date to indicate that these early signals translate into positive clinical outcomes. In fact, the only available evidence comes from case–control studies with spectrum bias (7, 9) and uncontrolled cohort studies (6)—far-lower-quality evidence than the randomized trials with mortality outcomes we usually use to evaluate screening tests. Randomized trials are under way in the United Kingdom and United States, but the planned primary outcome is stage shift to earlier cancer detection, not cancer mortality.

I transition to the "decision talk," asking Mr. Y what seems most important to him. He hesitates. "It's going to take many years to know for certain the precise benefits and harms of this test. I might get an advanced cancer while I wait. I really value knowing I've done everything I

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Figure. Core concepts for clinicians to share with patients regarding the context, benefits, risks, and uncertainties of MCED tests in clinical care.

	Patient Questions	Having the MCED Test	Other Information Worth Sharing
Team Talk	What is it? (Context)	Blood test for traces of a cancer tumor (practical information).	Your blood is sent to a central laboratory. You will get a result in 2 weeks. Most people have no cancer signal. If there is a cancer signal, some MCED tests provide a predicted tumor origin while others require additional imaging (1).
		You are unlikely to have a clinically important cancer at this moment (low prevalence).	Although the lifetime prevalence of cancer is relatively high, the likelihood of an asymptomatic cancer at any one time is low. The absolute benefit of MCED tests is likely to be small for most individuals.
		You will have to pay for the test and may have to pay for additional testing and treatment (unintended consequences).	Because MCED testing is new, it is not covered by insurance. Further, some insurers may not cover the costs of follow-up testing (5). Your responsibility for these costs will depend on your insurance coverage.
		What about other currently recommended screening tests?	You should continue to get the other recommended screening tests even if you get an MCED test.
Option Talk	What are the benefits?	MCED tests can find cancers* (additional cancer detection).	MCED tests appear to detect cancers not detected by currently recommended cancer screening tests. However, the effect of detecting these cancers earlier is not yet clear.
		Most people will get a negative result and may feel less worried about cancer† (reassurance).	MCED tests have been calibrated with up to 99% specificity to ensure most people who do not have a cancer will have a negative result.
	What are the risks?	Some cancers are missed (false negatives)	The sensitivity for several cancer sites is less than 50%‡, which can lead to false reassurance. Some people could forgo recommended screening tests as a result.
		Some tests suggest cancer when you do not have cancer (false positives).	About 1% of people without cancer will nonetheless have a positive result. The wait for additional testing to rule out a cancer can cause anxiety.
		Results from diagnostic testing may be unclear (indeterminate results). You may need other tests (cascade testing).	Diagnostic testing following an abnormal MCED may fail to identify a cancer. Your providers may be unsure how often or how long to repeat the diagnostic tests in case a cancer becomes visible.
		The test will likely detect cancers that never would have become symptomatic and cause harm (overdiagnosis).	MCED tests detect some frequently overdiagnosed cancers, although the extent of overdiagnosis is not yet known.
	What are the things we do not yet know? (uncertainties)	MCED tests may detect cancers but not save your life (lack of outcome evidence).	It is unclear to what point MCED tests will lower cancer-related mortality.
		There are no high-quality data comparing those who got the test with those who did not (uncertainty due to lack of high-quality evidence).	Studies published to date have not been randomized or had control groups. Observational studies of cancer screening tests are subject to well-known biases (e.g., lead-time and length-time bias).
		Testing frequency (duration of protection).	It is unclear how often MCED tests should be repeated to balance risks and benefits.
Decision Talk	How to decide?	MCED tests are not part of routine care (subjective norm).	You should not feel any obligation. MCED tests are not recommended by professional societies. Patients unsure what to do should wait and not get tested now.

These points could guide discussions following the 3-talk model. MCED = multi-cancer early detection.
* Preliminary results from a study of 6662 individuals who had 1 MCED test that detected cancer in 35 participants (0.5%) (6).
† Preliminary results of 6662 individuals who had 1 MCED test that showed that 6570 had a negative result (98.6%) (6).
‡ In a case-control study of patients with cancer and healthy control participants, 1 MCED test had a sensitivity of 33% to 98%, depending on the cancer type (7). In a similar study, another MCED test detected 52% of cancers, with sensitivities between 0% and 94% for 27 different cancer types (6).

can, even if I might have a positive result and nothing found during follow-up." After some further discussion, we order the test: It is his clear preference.

Perhaps MCED tests represent a promising advance; it is too early to judge. However, these tests will arrive sooner than we might expect. We should be aware of the current gap in evidence to enable informed decisions about MCED tests. Nonetheless, patients who place strong value on the early adoption of promising technologies will likely choose to do the test, even after receiving information about the potential downstream consequences. There is an urgent need for standards-based, unbiased patient decision aids that focus on the issues that matter to patients (10).

From Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland (K.S.); The Dartmouth Institute for Health Policy and Clinical Practice, Dartmouth College, Hanover, New Hampshire (G.E.); and Department of Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, Texas (R.J.V.).

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Corresponding Author: Kevin Selby, MD, MAS, Center for Primary Care and Public Health (Unisanté), Ambulatory Care Department, Rue de Bugnon 44, 1012 Lausanne, Switzerland; e-mail, kevin.selby@unisante.ch.

Author contributions are available at Annals.org.

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