# Molecular cancer screening: in search of evidence

Cancer screening with germline genetic sequencing and liquid biopsy could facilitate early cancer detection. But testing if these technologies reduce the burden of cancer mortality will require rethinking how clinical trials are run.

Sana Raoof, Caleb J. Kennedy, D. A. Wallach, Asaf Bitton and Robert C. Green

Cancer is the second leading cause of death in the United States, and the majority of cancer deaths today occur from cancers for which there are no recommended screening modalities[1]. At present, cancer screening relies largely on non-molecular technologies such as a Pap smear, mammography, colonoscopy, low-dose computerized tomography scans of people who smoke, and protein biomarkers (such as PSA). The lack of effective screening modalities for the majority of cancers raises the interesting questions of whether new molecular technologies could enhance cancer-risk stratification and screening, and what degree of evidence generation is necessary to validate and implement them in medical practice.

Germline genetic testing through next-generation sequencing can now identify pathogenic variants in cancer-susceptibility genes (CSGs) associated with substantially elevated cancer risks[2]. Sequencing and epigenetic technologies are also the basis of liquid biopsies for multi-cancer early detection (MCED) that analyze circulating tumor materials in order to identify cancer at an earlier stage than it would otherwise be detected[3]. Both testing for CSGs and MCED assess thousands of molecular targets simultaneously and can identify genetic variants or epigenetic markers that are associated with cancer in multiple tissue types (Fig. 1). Advocates for these technologies argue that early detection is beneficial, preliminary data are encouraging and randomized clinical trials that measure effects on mortality are impractically lengthy and expensive. Others maintain that randomized trials are essential to avoid premature adoption that might result in false-positive findings while exacerbating healthcare costs. As in the development of therapeutics and medical devices, newly developed molecular screening technologies are in tension with regulatory agencies seeking to ensure clinical utility and healthcare payers seeking to deploy new technologies more selectively in order to constrain costs. Is there an appropriate middle ground when it comes to evidence generation for innovative screening technologies?

## Germline genetic testing

As many as 10% of cancers are associated with monogenic cancer syndromes[4]. Where family history is suggestive of dominant inheritance, genetic testing and increased surveillance for family members who carry pathogenic variants in certain CSGs has been recommended for decades, and life-saving interventions are available. Multi-gene sequencing for CSGs has become increasingly popular within at-risk families and has been proposed for all people with cancer and even for general population screening[5]. Medical and consumer-facing laboratories currently promote population screening with panels of 30–61 CSGs. Depending on how many CSGs are evaluated, sequencing in various populations who request proactive screening has identified 1.5–7.7% of people who carry pathogenic or probably pathogenic variants of CSGs[6]. However, there is considerable debate about whether large-scale population screening for a broad panel of CSGs is prudent, due to uncertainties about the misinterpretation of variants of uncertain relevance, as well as ambiguity about the penetrance of even clearly pathogenic variants among the various CSGs, particularly in the absence of an 'enriched' family history[5]. As a consequence, some have advocated that CSG screening focus on a single condition, such as breast or ovarian cancer, for which evidence of efficacy and an acceptable cost/benefit ratio seems irrefutable[7], whereas others have advocated for larger CSG panels despite the increased likelihood of positive findings with unclear penetrance[8].

## Liquid biopsy for MCED

MCED makes use of next-generation genetic and epigenetic technologies to search for many types of cancer at once[3,9]. Most platforms are based on the detection of protein biomarkers, RNA, extracellular vesicles or circulating tumor DNA (including its epigenetic markings) that are shed into the bloodstream or urine through the active secretion of short nucleosome-associated fragments and long fragments inside vesicles, as well as through the apoptosis of cancer cells[9–11]. Methylation patterns on DNA CpG islands are used to identify early-stage cancers: hypermethylation of genes encoding tumor suppressors is a hallmark of early carcinogenesis, and the configuration of methylated DNA seems to be a sensitive means of cancer detection in clinical studies[12,13]. Many academic and commercial groups are developing early-detection tools that are in preclinical or clinical development stages and are optimized for single or multi-cancer detection, and there is widespread expectation that a simple blood test will have higher patient compliance than that of other forms of cancer screening[14,15].

MCED tests are designed to complement and not replace recommended single-cancer screening tests, and they may outperform single-cancer screens in terms of aggregate sensitivity and positive predictive value[10,11]. Two MCED tests in clinical research trials have generated positive predictive values across cancer types of 19% (DNA/protein test) and 52% (methylation-based test)[10,11], but the clinical utility of MCED is clouded by uncertainties about the accuracy of tissue of origin, questions about how frequently to test and how to follow up on positive test results, and whether clinical implementation of such tests will reduce cancer mortality in a cost-effective manner or will lead to over-diagnosis and over-treatment.

## Regulatory and payer landscape

Effective introduction of new screening and diagnostic technologies requires that inventors, implementation scientists, investors and entrepreneurs work together to develop such innovations despite the complex regulatory and reimbursement infrastructure in the United States. The US Food and Drug Administration (FDA)

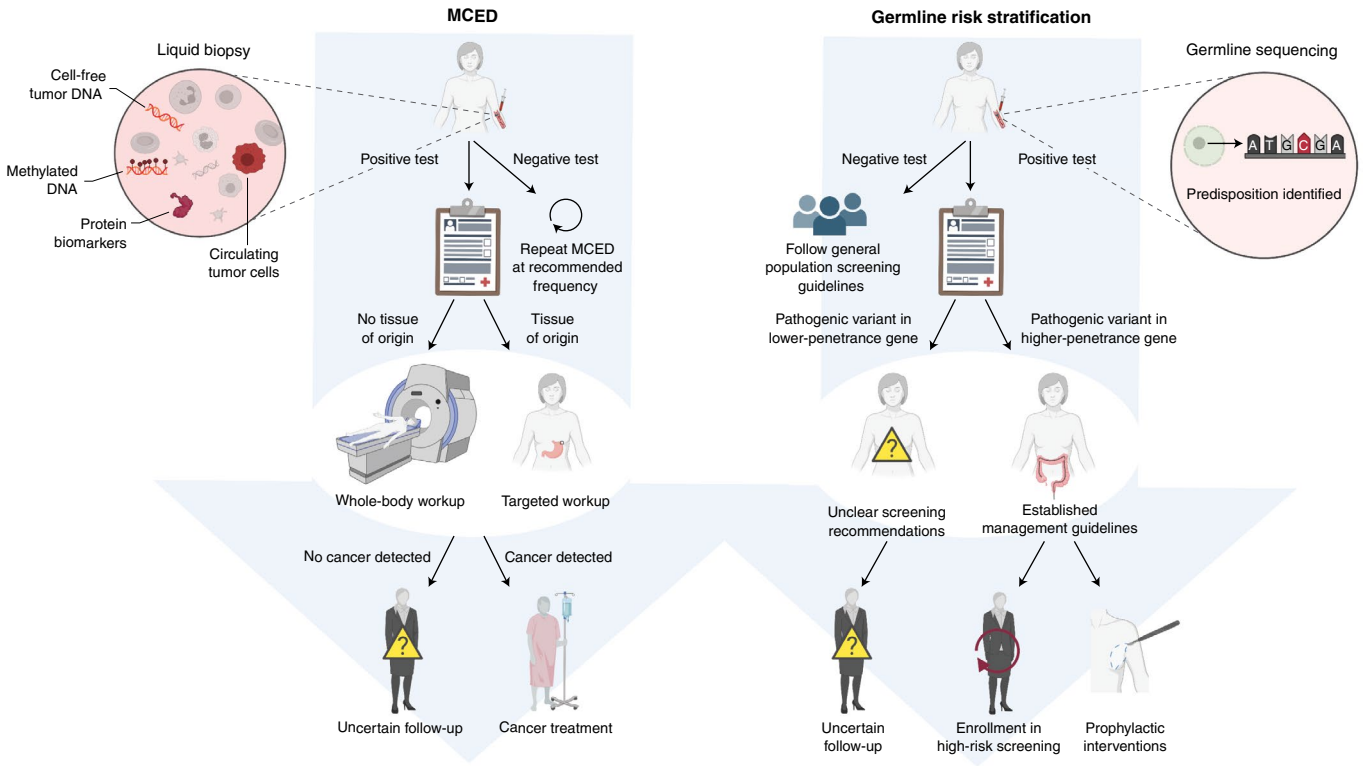


**Fig. 1 | Molecular technologies for cancer screening.** A germline risk assessment may be performed to identify people at high risk for cancer who would benefit from special surveillance programs or prophylactic interventions. Liquid-biopsy testing may be performed in screening-age adults at regular intervals to promote the early detection of multiple malignancies at once, on the basis of tumor-associated materials secreted into peripheral blood. Created with BioRender.com.

has authority over all in vitro diagnostics but has practiced enforcement discretion over laboratory-developed tests, which are also regulated by The Centers for Medicare & Medicaid Services (CMS). The FDA's decision to practice enforcement discretion has resulted in the commercialization of thousands of tests that have been launched with variable levels of technical and clinical validation. In contrast, the FDA-managed Class III designation for medical devices and premarket approval demands extensive clinical validation and evidence of medical value and is often prohibitively expensive for companies with promising science but limited financial resources.

For either path, generating revenues from test orders usually requires payer coverage, which is a formidable challenge for even well-funded companies. Among public payers, tremendous fragmentation exists in the state-by-state management of Medicaid and in the awkward dual-tier management of Medicare by regional contractors, who can make local coverage determinations, and CMS, which can make national coverage decisions. CMS has historically limited coverage for cancer screening tests to those approved through national coverage decisions and has put substantial limitations on coverage for genetic testing, typically covering diagnostic genetic tests only in affected people for tests that are expected to have an effect on treatment decisions. CMS does not cover genetic screening for cancer in unaffected people, with the exception of a specific colon cancer screening test (Cologuard). Thresholds for coverage from private payers may follow CMS or may be decided individually among over 900 US health insurance companies.

## Validating the clinical utility of screening

Molecular strategies for cancer screening such as testing for CSGs and MCED are attractive because they offer the promise of identifying, with a single assay, people who are at risk for or who already have multiple cancer types. However, understanding the clinical utility of any specific finding identified by such tests is challenging. For example, in screening for CSGs, a clinician who learns that an otherwise healthy patient without a family history of cancer carries a rare, low-penetrance pathogenic variant of *CHEK2* (which encodes a checkpoint kinase) will have little evidence upon which to offer recommendations for interventions or surveillance. Similarly, a clinician whose patient has a positive result on a test for MCED with a specific tissue of origin, but whose targeted cancer workup is negative, faces uncertainty about next steps. Did the original screening have a false-positive result? Does the screening correctly detect cancer, but the tissue of origin is incorrect? Or is the cancer actually present in the identified tissue of origin but undetectable by follow-up imaging? Screening for multiple cancers makes it more difficult to measure the clinical utility and cost-effectiveness of such tests, as many of the cancers detected have no precedent for screening interventions.

Many will maintain that the only acceptable evidence for the clinical effectiveness of multi-cancer screening

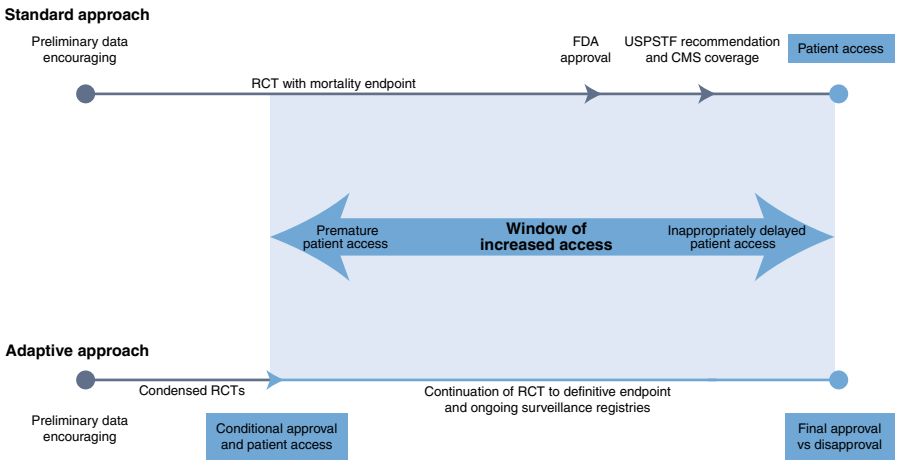


**Fig. 2 | Standard versus adaptive approach to regulation and assessment of novel cancer screening interventions.** The regulatory timeline can be accelerated through the granting of conditional approvals after randomized controlled trials (RCTs) with surrogate endpoints, contingent on continued evidence generation. This approach expedites patient access to devices that may prevent deaths from late-stage cancers but also exposes patients to the risks associated with premature implementation. USPSTF, United States Preventive Services Task Force; vs, versus.

technologies such as assessing CSGs and MCED is from randomized controlled trials with mortality endpoints[16]. But screening randomized controlled trials for CSGs or MCED would require massive enrollment, would be exceedingly expensive and could take decades to complete, especially given the inclusion of rare variants and rare tumor types that would subdivide the outcomes of screening. The dynamic world of molecular screening for cancer will probably share the validation challenges posed by the exploding digital health industry, where the conventional gatekeepers of clinical validity—specialty societies, payers, regulatory agencies and governments—are outpaced by the sheer number and scope of claims around digital health benefits[17].

## Policy and practice options

How then should clinicians proceed when faced with the proliferation of cancer screening technologies that promise to save more lives through early detection of multiple cancers than do the current battery of scopes, scans and smears? One idea is that intermediate outcomes, surrogate measures and proof-of-principle single-arm studies can be used to form a basis for approvals with a requirement for continued data collection, a strategy that the FDA accelerated in 2016 around therapeutic candidates and high-risk medical devices with the 21st Century Cures Act. For example, in MCED, one might consider a surrogate endpoint of metastatic-cancer incidence across all subtypes, as opposed to measuring stage shift, which may be confounded by increased diagnosis of early indolent lesions. Parallel review of technologies for FDA approval and CMS coverage, as occurred with the Cologuard test, could also reduce delays in the assessment of (and, ultimately, patient access to) designated breakthrough devices that have the potential for primary or secondary prevention of cancer[18]. However, parallel review typically requires that a medical-benefit category be established, usually as a result of legislative action, and there is no such category currently in place for cancer screening through genetic testing or liquid biopsy.

To accelerate implementation and ensure that the potential benefits of new cancer screening technologies will be distributed fairly across economic strata, payers and laboratories could jointly commit to coverage with evidence development[19]. Such a program could make CMS payment contingent on patient participation in clinical studies, which track test performance and clinically relevant outcomes[20]. Prospective surveillance registries could be designated as post-market requirements, especially for technologies approved on the basis of surrogate measures[21,22]. These strategies could also have the advantage of expanding clinical-utility studies into effectiveness-implementation hybrid designs under real-world conditions in which practitioner choices are not artificially bound by research protocols[23] (Fig. 2).

The downside of this adaptive assessment approach is that novel risk-stratification or screening technologies have tremendous narrative power that can be amplified in commercial and political environments and may counterintuitively cause harm through overdiagnosis[24]. Such narratives are often difficult to reverse. The ability of a regulatory agency to allow conditional approval for a screening test, or of a payer to conditionally cover costs, assumes that if the data collected were disappointing, those regulatory permissions could be withdrawn and the coverage could be ended. However, such a withdrawal is not guaranteed in an environment in which the products are backed by extraordinary investment sums and are as intuitively enticing as cancer screening or prevention. Enforcing such requirements has also been challenging: only one third of post-marketing studies evaluating high-risk therapeutic medical devices approved by the FDA a decade ago were completed and reported[25]. Politicians are already signaling a willingness to support cancer screening technologies. In December 2020, legislation was introduced in the US Congress (H.R. 8845 and S. 5051) to ensure Medicare/Medicaid coverage of MCED tests contingent on FDA approval.

Even if new modes of evaluation and regulatory approval are incorporated into the search for effective novel molecular diagnostics for cancer, important clinical implementation questions remain. Are these screening tests only for specialists, or is more widespread use in primary care warranted? If the use of these diagnostics is beneficial, should they be integrated into the already overburdened responsibility of primary care clinicians? If so, the integration of new diagnostics will require clear thinking on how to find the right combination of clinical education, patient-shared decision-making, and payment and policy changes to understand and realize optimal benefit. Regardless of whether the medical community is ready, new molecular screening technologies are being invented, refined, clinically studied and commercially promoted; liquid biopsies for MCED can now be prescribed by physicians in the United States. No matter how difficult, it is essential that an appropriate path is found toward implementation, while the guardrails of evidence-based medicine and sound health-economic decision-making are maintained. ❐

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## References

1. The American Cancer Society. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf (2020).
2. Plichta, J. K., Griffin, M., Thakuria, J. & Hughes, K. S. *Oncology* **30**, 787–799 (2016).
3. Chen, M. & Zhao, H. *Hum. Genomics* **13**, 34 (2019).
4. Yurgelun, M. B., Chenevix-Trench, G. & Lippman, S. M. *Cell* **168**, 566–570 (2017).
5. Turnbull, C., Sud, A. & Houlston, R. S. *Nat. Genet.* **50**, 1212–1218 (2018).
6. Haverfield, E. et al. *BMC Med.* (in the press).
7. Manchanda, R., Lieberman, S., Gaba, F., Lahad, A. & Levey-Lahad, E. *Annu. Rev. Genomics. Hum. Genet.* **21**, 373–412 (2020).
8. Hall, M. J., Forman, A. D., Pilarski, R., Wiesner, G. & Giri, V. N. *J. Natl. Compr. Canc. Netw.* **12**, 1339–1346 (2014).
9. De Rubis, G., Krishnan, S. R. & Bebawy, M. *Pharmacol. Res.* **136**, 35–44 (2018).
10. Lennon, A. M. et al. *Science* **369**, eabb9601 (2020).
11. Liu, M. C. et al. *Ann. Oncol.* **31**, 745–759 (2020).
12. Heyn, H. & Esteller, M. *Nat. Rev. Genet.* **13**, 679–692 (2012).
13. Luo, H. et al. *Sci. Transl. Med.* **12**, eaax7533 (2020).
14. Aravanis, A. M., Lee, M. & Klausner, R. D. *Cell* **168**, 571–574 (2017).
15. Chen, X. et al. *Nat. Commun.* **11**, 3475 (2020).
16. Bradley, S. H. & Barclay, M. E. *Br. Med. J.* **372**, m4933 (2021).
17. Mathews, S. C. et al. *NPJ Digit. Med.* **2**, 38 (2019).
18. Johnston, J. L., Dhruva, S. S., Ross, J. S. & Rathi, V. K. *Nat. Biotechnol.* **38**, 933–938 (2020).
19. American Society of Clinical Oncology. *J. Oncol. Pract.* **3**, 296–301 (2007).
20. Reynolds, I. S., Rising, J. P., Coukell, A. J., Paulson, K. H. & Redberg, R. F. *JAMA Intern. Med.* **174**, 1773–1779 (2014).
21. Resnic, F. S. et al. *N. Engl. J. Med.* **376**, 526–535 (2018).
22. Wallach, J. D. et al. *Br. Med. J.* **361**, k2031 (2018).
23. Curran, G. M., Bauer, M., Mittman, B., Pyne, J. M. & Stetler, C. *Med. Care* **50**, 217–226 (2012).
24. Srivastava, S. et al. *Nat. Rev. Cancer* **19**, 349–358 (2019).
25. Rathi, V. K., Krumholz, H. M., Masoudi, F. A. & Ross, J. A. *JAMA Netw. Open* **3**, e2014496 (2020).

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