Documents for the Record

Subcommittee on Health Hearing
Examining Policies to Enhance Seniors' Access to Breakthrough Medical Technologies
September 18, 2025

Majority:

1. September 17, 2025, letter to Chairman Griffith and Ranking Member DeGette from Susan G. Komen.
2. September 16, 2025, letter to Chairman Guthrie, Chairman Griffith, Ranking Member Pallone, and Ranking Member DeGette from Research America.
3. September 16, 2025, letter to Chairman Guthrie and Ranking Member Pallone from the Cancer Support Community.
4. September 16, 2025, letter to Chairman Guthrie and Ranking Member Pallone from Fight Colorectal Cancer.
5. September 16, 2025, letter to Chairman Guthrie and Ranking Member Pallone from GO2 for Lung Cancer.
6. September 16, 2025, letter to Chairman Guthrie and Ranking Member Pallone from the Ovarian Cancer Research Alliance.
7. September 16, 2025, letter to Chairman Guthrie and Ranking Member Pallone from Prevent Cancer Foundation.
8. September 18, 2025, statement from the American Cancer Society Cancer Action Network.
9. July 30, 2024, Commonwealth Beacon article entitled "Cancer early detection tests work; let's deploy them."
10. April 14, 2025, letter to Rep. Miller-Meeks from the Iowa Army of Pink.
11. September 15, 2025, letter to Chairman Guthrie and Ranking Member Pallone from the Association of Cancer Care Centers.
12. September 16, 2025, letter to Chairman Guthrie and Ranking Member Pallone from The National Grange.
13. September 16, 2025, letter to Chairman Guthrie and Ranking Member Pallone from the National Minority Quality Forum Action Network.

Minority:

1. September 14, 2025, New York Times article entitled "Trump is Shutting Down the War on Cancer" submitted by Rep. DeGette.
2. September 17, 2025, letter to Chairman Griffith and Ranking Member DeGette from the Medicare Rights Center.
3. September 17, 2025, Technical Assistance from the Department of Health and Human Services, Office of the Inspector General, to Congress.

4. September 16, 2025, Annals of Internal Medicine journal article entitled “Multicancer Detection Tests for Screening.”

September 17, 2025

The Honorable Morgan Griffith
U.S. House of Representatives
2110 Rayburn House Office Building
Washington, DC 20515

The Honorable Diana DeGette
U.S. House of Representatives
2111 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Griffith and Ranking Member DeGette:

I am writing to you on behalf of Susan G. Komen to express our support for the Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Coverage Act (H.R.842/S.339), which will provide the Medicare program the authority to cover multi-cancer early detection (MCED) tests. Representing the millions of people who have been diagnosed with breast cancer, we thank the Subcommittee on Health for their consideration of this important issue and urge swift action to advance this legislation to the House floor for passage.

Detecting cancer early improves health outcomes and saves lives. MCED tests offer the promise to expand and complement existing screenings and dramatically improve our nation's cancer early detection capabilities—which could save lives. They have the potential to revolutionize our approach to cancer screening and save costs to our health care system by identifying cancer before symptoms develop. However, patients can only benefit from advancements in cancer screenings if they are able to access and afford them.

The Nancy Gardner Sewell Multi-Cancer Early Detection Screening Coverage Act would ensure Medicare beneficiaries have coverage to fully take advantage of these innovative tests. Thanks to improved access to breast cancer treatment and early detection, breast cancer mortality in U.S. women decreased by 44% from 1989 to 2022. Despite this, an estimated 317,000 Americans will be diagnosed with breast cancer and more than 42,000 will die from the disease in 2025 alone. Age remains one of the most common risk factors for developing breast cancer. By ensuring access to FDA-approved MCED tests, this legislation will align scientific advancement with Medicare coverage and has the potential to dramatically increase the survival rates for dozens of cancer-types, including breast cancer.

Without Congressional action, access to FDA-approved MCED tests could be delayed and cost valuable time. Medicare policy must keep pace with innovation to ensure Americans have access to valuable technological advancements. Our health system must pair important new technologies with comprehensive coverage and access for all. We urge Congress to swiftly pass this legislation to ensure that Medicare enrollees have access to MCED tests once approved.

We thank the Subcommittee for their consideration of this important legislation. Given the history of this bill's outstanding bipartisan support, we urge action now and stand ready to work with you to see final passage. Should you have any questions, please reach out to Valerie Nelson, Susan G. Komen's Manager of Federal Policy & Advocacy, at vnelson@komen.org.

Sincerely,

Molly Guthrie
Vice President, Policy & Advocacy
Susan G. Komen

RESEARCH AMERICA
DISCOVERY. INNOVATION. HEALTH.

9/16/2025

The Honorable Brett Guthrie
Chair
Energy and Commerce Committee
Washington, District of Columbia 20001

The Honorable Morgan Griffith
Chair
Subcommittee on Health
Washington, District of Columbia 20001

The Honorable Frank Pallone
Ranking Member
Energy and Commerce Committee
Washington, District of Columbia 20001

The Honorable Diana DeGette
Ranking Member
Subcommittee on Health
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Dear Chairman Guthrie, Chairman Griffith, Ranking Member Pallone, and Ranking Member DeGette,

On behalf of Research!America, thank you for convening the September 18 hearing, *Examining Policies to Enhance Seniors' Access to Breakthrough Medical Technologies*. By considering legislation such as the Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Coverage Act (H.R. 842) and the Ensuring Patient Access to Critical Breakthrough Products Act of 2025 (H.R. 5343), the Subcommittee is contributing importantly to the goal of addressing inadvertent or otherwise unjustified Medicare coverage delays.

These delays are not just inefficient, they can significantly influence the direction, pace, and societal value of research-driven medical progress to the detriment of patients today and tomorrow.

Medical advances lose societal value with every delay that keeps patients from timely access to those advances. Too often, promising diagnostics and treatments face delays or barriers that prevent seniors from accessing the most advanced and effective care. These delays reverberate across the research ecosystem - discouraging investment, slowing progress, and, most importantly, costing patients and families years of health, hope, and opportunity.

Research!America's vision is for our nation to achieve the fastest possible pace of medical and public health progress. New technologies, such as multi-cancer early detection tests and other breakthrough diagnostics, have the potential to transform prevention, detection, and treatment. Yet the average six-year gap

between FDA approval and Medicare coverage for technologies requiring new reimbursement pathways represents missed opportunities for patients.

In regard to HR 842, multi-cancer early detection (MCED) tests now allow a single blood draw to screen for dozens of cancers simultaneously, an extraordinary advance in the fight against cancer. Yet these innovations can only improve outcomes if seniors can access them. Currently, Medicare-approved screening exists for only five cancers - breast, colorectal, cervical, lung, and prostate - leaving most cancers without preventive tests. Seventy percent of cancer deaths come from cancers for which no screening exists. Just as Congress acted to secure Medicare coverage for mammograms and colonoscopies, H.R. 842 removes unnecessary barriers that could delay seniors' access to MCED tests for years.

H.R. 5343 complements this effort by addressing broader coverage and reimbursement hurdles for breakthrough technologies, ensuring that patients are not left waiting years between FDA approval and Medicare access. Both bills recognize that medical innovation begins to deliver societal value when it reaches the people who need it.

We applaud your commitment to ensuring that research discoveries translate more quickly and equitably into patient benefit. When seniors can access new technologies, the impact extends well beyond individual patients: better health outcomes, reduced long-term costs, and stronger incentives for the next generation of breakthroughs.

Thank you again for your leadership and shining a light on an issue of real importance to patients, caregivers, and the research community: ensuring that the breakthroughs generated by American science can reach the people who need them most.

Sincerely,

Ellie Dehoney
Senior Vice President of Policy and Advocacy
Research!America

CANCER SUPPORT COMMUNITY
COMMUNITY IS STRONGER THAN CANCER

September 16, 2025

Dear Chairman Smith, Ranking Member Neal, Chairman Guthrie, Ranking Member Pallone, and members of the committees:

The mission of the Cancer Support Community is to uplift and strengthen people impacted by cancer by providing support, fostering compassionate communities, and breaking down barriers to care. It is our devotion to this mission that has led to our support for H.R. 842, the Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Act. We applaud the House Committees on Ways and Means and Energy and Commerce for your work on this bill this week and urge its swift passage into law.

Just last month, our organization authored an op-ed in The Hill, in which we wrote, "This policy would mark a turning point in the fight against cancer, particularly for older adults who face the highest risk and are often diagnosed in later stages. The support is overwhelming. More than 550 organizations representing cancer patients, providers, researchers and advocates have urged lawmakers to seize this moment. Congress has already thoroughly vetted this bill and cleared it for passage."

With this bill, Congress has an opportunity to continue its historic commitment to enable access to cancer screening and help improve early detection and cancer outcomes for those in our community. Your work this week is critical to that mission and there is no reason to delay passing this bill. We strongly urge your expeditious support.

Sincerely,

Sally Werner

Sally Werner, RN, BSN, MSHA
Chief Executive Officer
Cancer Support Community

September 16, 2025

Dear Chairman Smith, Ranking Member Neal, Chairman Guthrie, Ranking Member Pallone, and members of the committees:

We write today to urge swift passage of H.R. 842, the Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Coverage Act, a bill that will enable access for critical innovations in cancer screening.

At Fight Colorectal Cancer, we are fighting for a future where every person diagnosed with colorectal cancer has more time to create memories, explore treatment and live fully. One of the most critical factors in achieving that goal is early cancer detection. We are making real progress in screening more Americans for colorectal cancer and innovations in screening tools is a key part of this progress. Many cancers do not yet have the benefit of FDA approved screening tests, but we must ensure that all patients have access to new technology advancements once they are determined to be safe and effective for patients.

These principles animate our support for H.R. 842. This bill will enable Medicare beneficiaries to access multi-cancer screening tools once they have been deemed safe and effective. These tools are designed to complement existing screening technologies to help reach more people, addressing existing gaps in cancer detection. Prevention and early detection makes all the difference for colorectal cancer patients and these benefits should extend to all cancer patients as new technology comes to market. We encourage you to waste no time in passing H.R. 842 to help build a future where we are significantly improving cancer screening in the United States.

Sincerely,

Molly McDonnell
Vice President of Advocacy
Fight Colorectal Cancer

GO2 FOR LUNG CANCER
go2.org

Confronting Lung Cancer Starts Here

September 16, 2025

Dear Chairman Smith, Ranking Member Neal, Chairman Guthrie, Ranking Member Pallone, and members of the committees:

On behalf of GO2 for Lung Cancer, an organization founded by patients and survivors, dedicated to increasing survival for those at risk, diagnosed and living with lung cancer; I write today to express our strong support for H.R. 842, the Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Coverage Act and to thank you for your committees' attention to this important matter this week.

The urgency surrounding the legislation cannot be overstated. In 2025, an estimated 226,650 individuals will be diagnosed with lung cancer, and 124,730 will die from the disease. The cutting-edge MCED technology will put lung cancer—the leading cause of cancer deaths nationwide and dozens of other types in prime position for optimal early-stage screening, and that is why the legislation is so important to our community. H.R. 842 would create a meaningful pathway to allow Medicare coverage of MCED tests, and access to patients without unnecessary delay.

This is, without question, the most popular health care bill pending in Congress. It has the support of hundreds of organizations from across the patient advocacy and health care delivery spectrum and is supported by nearly 300 members of the House and more than 60 Senators.

We appreciate the committee marking up the bill and urge you to approve this legislation unanimously, and to enact it into law this year.

Thank you for your consideration of our request. Your commitment to improving healthcare outcomes for lung cancer patients, particularly Medicare beneficiaries, is invaluable and you will make a significant impact in the fight against lung cancer for your constituents and the nation. If you have any questions or require more information, please contact Elridge Proctor, Senior Director, Government Affairs at GO2 for Lung Cancer (202-669-5547, eproctor@go2.org).

With sincere regards,

Laurie Fenton Ambrose
President & CEO
GO2 for Lung Cancer

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OCRA
ovarian cancer
research alliance

September 16, 2025

Dear Chairman Smith, Ranking Member Neal, Chairman Guthrie, Ranking Member Pallone, and members of the committees:

We write today to thank your committees for your attention to H.R. 842, the Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Coverage Act this week and urge the bill's passage into law. H.R. 842 is perhaps the most consequential health care legislation currently pending in Congress. It will significantly improve the nation's cancer screening capabilities and be a major asset for women's health.

Approximately 70 percent of all cancer deaths are tied to types of the disease for which we have not had screening tools - ovarian cancer is among these. When diagnoses come too late, the change of survival is significantly reduced - and the fight a patient must endure is more costly and burdensome. Multi-cancer early detection tests can change this by expanding the number of cancers that can be found early. Now, Congress needs to act to enable access for those who need it most.

With lives being lost to cancer every day, there is no time to waste in passing this bill. It has consistently enjoyed incredible bipartisan support in Congress and has the backing of hundreds of organizations representing patients, health care organizations, clinicians, and so many others.

Thank you for your attention to this legislation this week and we call on all of Congress to pass it into law without delay.

Sincerely,

Chad Ramsey
Vice President, Policy
Ovarian Cancer Research Alliance

September 16, 2025

Dear Chairman Smith, Ranking Member Neal, Chairman Guthrie, Ranking Member Pallone, and Members of the Committees:

We write today to express our strong support for H.R. 842, the Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Coverage Act. We applaud your committees' attention to this matter this week. The Prevent Cancer Foundation is honored to lead more than 550 organizations in ongoing support for this critical legislation. That support is reflected across Congress, too, with nearly 300 supporters in the House and more than 60 in the Senate.

The Prevent Cancer Foundation is the only U.S.-based nonprofit organization solely dedicated to cancer prevention and early detection. Over the past several years, we have proudly led this groundswell of support for this bill because we know that access to multi-cancer early detection tools can change our cancer story in this country, preventing more late-stage diagnoses and reducing the toll cancer takes on families—and on the Medicare program.

Whether in our own families or among our friends, neighbors or coworkers, we all know someone who has been touched by cancer. Witnessing your colleagues share their own cancer stories at a similar markup last year was a remarkable legislative moment. We all know the profound difference between an early-stage and a late-stage diagnosis, and we understand the importance of access to tools that can make that difference. That's why support for H.R. 842 has been and remains vast.

We urge your unanimous support again and its swift passage into law.

Sincerely,

Jody Hoyos
Chief Executive Officer
Prevent Cancer Foundation

Energy and Commerce Committee

Subcommittee on Health Legislative Hearing

September 18, 2025

Statement for the Record on behalf of the
American Cancer Society Cancer Action Network

The American Cancer Society Cancer Action Network (ACS CAN) applauds the House Energy and Commerce Committee's Subcommittee on Health for holding this important legislative hearing today. ACS CAN is making cancer a top priority for public officials and candidates at the federal, state, and local levels. ACS CAN empowers advocates across the country to make their voices heard and influence evidence-based public policy change, as well as legislative and regulatory solutions that will reduce the cancer burden. As the American Cancer Society's (ACS) nonprofit, nonpartisan advocacy affiliate, ACS CAN is more determined than ever to end cancer as we know it, for everyone.

ACS CAN strongly supports the *Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Coverage Act* (H.R. 842/S. 339), which will create a pathway for Medicare to cover multi-cancer early detection (MCED) tests once the tests are approved by the Food and Drug Administration (FDA) and clinical benefit has been shown. MCED tests are innovative tests that have the potential to detect multiple cancers using a single test.

This legislation enjoys significant bipartisan and bicameral support and is currently the third most cosponsored legislation in the 119th Congress. As of September 15th, more than 295 members of the House of Representatives and 62 members of the U.S. Senate have signed on in support of the legislation.

Importance of early detection

Cancer is the second-leading cause of death in the United States, and the risk of developing and dying from cancer increases with age.[1] Of the more than 2 million new cancer cases expected to be diagnosed in 2025,[2] roughly 1.2 million new cases are

[1] American Cancer Society. *Cancer Fact & Figures 2025*. Atlanta: American Cancer Society; 2025.
[2] Id.

expected to be diagnosed in individuals over the age of 65.[3]

Almost half of all cancer deaths could be prevented with access to proven prevention and early detection interventions.[4] Cancer prevention and screening interventions are estimated to have averted about 4.75 million deaths – or 8 of every 10 averted deaths – from breast, cervical, colorectal, lung, and prostate cancers between 1970 and 2020.[5] However, these gains do not include the cancers for which no screening strategy exists at this time, which account for approximately two-thirds of deaths from cancer.[6]

Identifying and treating cancer at an early stage – before it has an opportunity to grow and spread and usually is easier to treat – can meaningfully improve clinical outcomes. Diagnosing and treating cancer early can also reduce overall health care expenditures. Research has shown that across a variety of cancer sites, being diagnosed at an earlier stage results in lower health care costs compared to being diagnosed at a later stage.[7] In the Medicare population, average total annual costs of care are up to seven times higher for Medicare beneficiaries who are diagnosed in later stages rather than earlier stages.[8]

MCED tests hold great promise for early cancer detection. These tests are designed to detect many cancers, including cancers that are currently difficult to detect at early stages, e.g., pancreatic cancer, and those cancers for which there is little chance that there will ever be a single-site screening test.[9]

Cancer is not just one disease; rather, there are many types and subtypes of cancer. MCED tests are designed to detect a common signal from many different types of cancer with a single test. MCEDs are among the groundbreaking technologies that could revolutionize cancer screening as we've known it, principally because there is little to no prospect of

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[3] Siegel, Rebecca L., et al. "Cancer statistics, 2025." *CA a Cancer Journal for Clinicians*, Jan. 2025, https://doi.org/10.3322/caac.21871.
[4] American Cancer Society. *Cancer Prevention & Early Detection Facts & Figures 2025-2026*.
[5] Goddard KAB, Feuer EJ, Mandelblatt JS, Meza R, Holford TR, Jeon J, Lansdorp-Vogelaar I, Gulati R, Stout NK, Howlader N, Knudsen AB, Miller D, Caswell-Jin JL, Schechter CB, Etzioni R, Trentham-Dietz A, Kurian AW, Plevritis SK, Hampton JM, Stein S, Sun LP, Umar A, Castle PE. Estimation of Cancer Deaths Averted From Prevention, Screening, and Treatment Efforts, 1975-2020. *JAMA Oncol*. Feb 1 2025;11(2):162-167. doi:10.1001/jamaoncol.2024.5381.
[6] Ofman JJ, Dahut W, Jemal A, Chang ET, Clarke CA, Hubbell E, Kansal AR, Kurian AW, Colditz GA, Patel AV. Estimated proportion of cancer deaths not addressed by current cancer screening efforts in the United States. *Cancer Biomark*. Jan 2025;42(1):18758592241308754. doi:10.1177/18758592241308754.
[7] McGarvey, N., Gitlin, M., Fadli, E. *et al*. Increased healthcare costs by later stage cancer diagnosis. *BMC Health Serv Res* 22, 1155 (2022). https://doi.org/10.1186/s12913-022-08457-6 .
[8] Reddy SR, Broder MS, Chang E, Paydar C, Chung KC, Kansal AR. Cost of cancer management by stage at diagnosis among Medicare beneficiaries. *Curr Med Res Opin*. 2022 Aug;38(8):1285-1294. doi: 10.1080/03007995.2022.2047536. Epub 2022 Apr 20. PMID: 35285354.
[9] Hoffman, Richard M., et al. Multicancer Early Detection Testing: Guidance for Primary Care Discussions with Patients. *Cancer*, vol. 131, no. 7, Wiley, Apr. 2025, https://doi.org/10.1002/cncr.35823.

developing even a few, let alone dozens of new screening tests in the next decade, and the potential cost and burden on the population and health services of adding many individual tests is prohibitive and undesirable. A different generation of cancer screening is needed.

ACS CAN Supports MCED Legislation

Medicare currently provides coverage of only 5 cancer screening tests. Coverage of 4 of these screening tests – breast, colorectal, cervical and prostate – are specifically statutorily mandated. Congress also allows the Secretary of Health and Human Services (HHS) to provide coverage of preventive services if they receive a grade of "A" or "B" from the U.S. Preventive Services Task Force. It is through this authority that Medicare covers lung cancer screening. Without legislation that expands coverage of screening tests, Medicare beneficiaries could experience unacceptable delays in access to MCED tests.

ACS CAN supports the *Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Coverage Act* as a way to help achieve equitable access to earlier cancer screening. This legislation will provide the Medicare program with the authority to cover MCED tests once the test has been approved by the FDA and after the Centers for Medicare and Medicaid Services (CMS) has determined the test is reasonable and necessary for the prevention or early detection of cancers and is appropriate for the Medicare population. CMS will use the existing national coverage determination (NCD) process to make a coverage determination. The legislation also makes clear that it is not disrupting the current process that allows the Secretary of HHS to cover preventive services that are recommended by the Task Force. If in the future the Task Force were to recommend MCED tests, then the Secretary could cover those tests without cost-sharing.

Importantly, the legislation clarifies that coverage of MCED tests will not impede access to existing Medicare coverage of cancer screening tests. Medicare enrollees will continue to have access to cancer screening tests for breast, colorectal, cervical, lung, and prostate cancers. The legislation specifies that Medicare could cover MCED tests on a frequency that is no less than annually.

Under the legislation, Medicare coverage of MCED tests would occur in a phased-in approach. The legislation provides that Medicare could not start covering MCED tests before January 1, 2028, which is intended to provide both the FDA sufficient time to review MCED test applications and CMS sufficient time to undergo its NCD process.

In addition, beginning January 1, 2028, the legislation would allow the Medicare program to cover MCED tests for Medicare enrollees who are 68 years old and younger. Each subsequent year, the upper age limit would increase by one year.

One of the worst feelings after a cancer diagnosis is to wonder what more could have been done had a diagnosis happened earlier; with improved access to testing, fewer patients and their clinicians will have to ask that question. We thank the Subcommittee on Health for holding this important legislative hearing and urge Congress to enact the *Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Coverage Act* this year.

CommonWealth BEACON

Cancer early detection tests work; let's deploy them

Congress must act to clear way for Medicare coverage

July 30, 2024
By Dr. Michael Constantine

IN RICHARD NIXON'S 1971 state of the union address, he called for $100 million to be allocated to irradicate cancer. This led to the National Cancer Act passed in February 1971.

In the 50-plus years since that declaration, there have been many milestones that deserve celebration. Recently, advances in immunotherapy have improved cancer survival rates in many different types of cancers at many different stages of disease giving more patients genuine hope for cure as well as the ability to live well with an advanced cancer for a long period of time.

Just recently, researchers at Mass General Brigham achieved promising trial results with a novel cell therapy for a particularly deadly form of brain cancer. Medical science continues to work to gain the upper hand in cancer care. However, each day many patients are diagnosed with late-stage cancers and these patients are a reminder that we still have more work to do to identify and fight these deadly, life altering diseases.

For those of us who are responsible for caring for patients with cancer, every day serves as a reminder of all the work still ahead. In 2024, the American Cancer Society projected the US will surpass 2 million new cancer cases for the first time ever. That means that *every day* 5,000 people and their families will learn that cancer will change their lives.

As a physician caring for cancer patients and their families every day, I bear witness to both the exciting clinical advances that are happening in cancer treatment and detection, but I also stand with patients as they navigate their cancer journey. That journey always begins with the sobering reality of a diagnosis, with every doctor wanting to be able to tell the patient that their cancer was found early and can be cured. However, too many times this is not the case. Wouldn't it be nice if we had a test that could detect cancers that are not clinically detectable, yet are forming, so we could identify those cancers and treat them in their earliest stages?
As the incidence of cancers continues to soar, advances in cancer detection tools have become just as important as the development of new treatments. Even the most sophisticated and innovative therapies have limited effectiveness when cancer progresses beyond earlier, more treatable stages.
Breakthroughs in the science of cancer screening are rapidly gaining steam, and smart public policies will ensure patients can access these innovations.

CommonWealth BEACON

Multi-cancer early detection tests are new cancer screening tools that use advanced computing power to detect the presence and likely location of a cancer, even before patients experience symptoms. Through a routine blood draw, these technologies can analyze DNA fingerprints from cancerous cells and tumors and provide physicians with the knowledge to intervene as early as possible. The early detection tests work for dozens of types of cancer, a significant addition and complement to the currently available standard screenings for just five types of cancer.

Early detection blood tests hold truly transformative potential, especially for seniors, who are the population at highest general risk for developing cancer.

The problem facing these early detection tests is that once the Food and Drug Administration approves them for widespread use, Medicare will lack the meaningful authority to provide coverage. After a test earns FDA approval, there would be an indefinite number of years before physicians and their patients could receive access. That is unacceptable. When mammograms and colonoscopies first rose to prominence, Congress had to intervene and pass legislation to ensure Medicare beneficiaries could access those screenings. Congress must now approach these early detection tests the same way for the next generation of cancer screening.

Fortunately, bipartisan legislation – the Medicare Multi-Cancer Early Detection Screening Coverage Act – is being driven forward in both chambers of Congress. The bill would create a clear pathway for Medicare to cover these tests in a timely manner so patients can benefit from advances in screening technology with ease and convenience.

In the House of Representatives, Reps. Jake Auchincloss, William Keating, Stephen Lynch, James McGovern, and Lori Trahan are among over 290 legislators who have cosponsored the legislation, and the House Ways and Means Committee, led by Rep. Richard Neal, recently advanced the bill unanimously, a major step toward passage.

The legislation has been endorsed by nearly 80 physician and nursing societies, and over 500 organizations across the country. The Massachusetts Society of Clinical Oncologists is hopeful the rest of the Massachusetts delegation will support the bill in their respective chambers.

A patient's cancer journey is often long, complex, and challenging – no matter the prognosis. Oncologists see the benefits of earlier detection every day, and multi-cancer screening holds tremendous promise to improve outcomes, reduce treatment costs, and enhance a patient's quality of life. Congress' action in 1971 to pass the National Cancer Act was the start of their commitment to go to battle to fight this war on cancer. Let's not stop now. Congress' actions on cancer early detection legislation this year can translate that potential for very early cancer detection into reality for millions of Medicare beneficiaries and their loved ones.

Dr. Michael Constantine is the president of the Massachusetts Society of Clinical Oncologists.

April 14, 2025

Representative Mariannette Miller-Meeks
504 Cannon House Office Building
Washington, DC 20515

Dear Representative Miller-Meeks,

We write to express our gratitude and support for your continued leadership on H.R. 842, the Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Coverage Act. In the 118th Congress, this bill drew more than 300 cosponsors in the House of Representative and more than sixty in the Senate. In the 119th Congress, we hope to see it become law.

As you know, age is the single biggest risk factor for developing cancer. More than half of all people diagnosed with cancer are over 65, and cancer remains the leading cause of death for Americans between the age of 65-84. Seniors cannot be last in line to access proven tools that can catch deadly cancers sooner. That is why your leadership of H.R. 842 is so critical.

Patients can currently access screening tests for just five of the hundreds of types of cancers, which is one reason why only 14% of cancers diagnosed today are found through these screenings. HR 842 would address this dramatic unmet need by allowing, rather than mandating, Medicare to cover innovative new screenings once they are approved by the Food and Drug Administration and clinical benefit has been shown. This follows Congressional precedent as similar legislation has passed in recent decades to allow Medicare coverage of mammography, colorectal cancer screening, and other life-saving early detection advancements.

Multi-cancer early detection (MCED) screenings can detect dozens of cancers in the earlier stages, when treatment is more likely to be successful as compared to later stages. Catching cancer earlier gives patients a four times greater chance of survival at half the cost burden of a later-stage diagnosis. Ensuring that seniors in Iowa, and across the country, can access these cutting-edge cancer screening tests is paramount to turning the tide in the war on cancer.

By joining this legislation as a co-lead sponsor, you've shown Iowa stakeholders that you are committed to improving cancer care by making the latest FDA-approved cancer screening tools available to those who need them most. With your leadership, we can help close the screening gap and reduce spending on late-stage cancer care within Medicare.

As you and your colleagues in Congress consider a legislative agenda for the weeks and months ahead, we hope your strong leadership on behalf of HR 842 culminates in passage of this bill to deliver a win for seniors.

Sincerely,

Above + Beyond Cancer
American Cancer Society, Cancer Action Network Iowa
American Lung Association Iowa
Ames Regional Economic Alliance
Cancer Support Community Iowa and NW Illinois
Community Liver Alliance
Easterseals Iowa
Iowa Academy of Family Physicians
Iowa Army of Pink
Iowa Bio
Iowa Community HUB
Iowa Medical Society
Iowa Nurses Association
Iowa Osteopathic Medical Association
Iowa Peace Officers Association
Iowa Pharmacy Association
Iowa Retail Federation
Iowa State Grange
Iowa State Sheriffs' & Deputies' Association
National Alliance of Mental Illness of Iowa (NAMI)
North Central States Regional Council of Carpenters
Prevent Blindness Iowa

September 15, 2025

Dear Chairman Smith, Ranking Member Neal, Chairman Guthrie, Ranking Member Pallone, and members of the committee:

The Association of Cancer Care Centers (ACCC) is pleased to lend its continued and strong support to H.R. 842, the Nancy Gardner Sewell Medicare Multi-Cancer Early Detection (MCED) Screening Coverage Act.

ACCC is a leading education and advocacy organization dedicated to the cancer care community. ACCC is viewed as a well-established and highly respected organization within the oncology industry, built from our 50+ year history of serving cancer care teams and the patients they support. ACCC's current membership base encompasses 45,000+ cancer care professionals from more than 1,700 different member organizations—in total, representing approximately two-thirds of all oncology programs and practices in the U.S.

Cancer centers throughout the country are at the heart of tremendous advances in cancer care, but they also witness the striking difference between patients whose cancers were diagnosed at earlier versus later stages. When diagnosed at a late-stage, cancer patients are more likely to undergo debilitating and expensive treatments, with lower survival rates. Fortunately, scientific advances in MCED technology have given us the opportunity to detect more cancers at earlier, more treatable stages. Yet seniors currently lack meaningful access to these transformational cancer detection tools without Congressional action.

H.R. 842 would allow seniors to access blood tests that can diagnose dozens of types of cancer from a simple blood draw. By passing this legislation, Congress can help improve outcomes for cancer patients and reduce the financial burden of cancer by preventing late-stage cancer diagnoses. There is no reason to delay action on legislation that has garnered the support of hundreds of patients and provider advocacy organizations and is cosponsored by more than two-thirds of the House and more than 60 Senators.

Thank you for your continued attention to policy that can improve the outcomes for patients with cancer. We urge you to advance this legislation expeditiously.

Sincerely,

Meagan O'Neill, MS
Executive Director
Association of Cancer Care Centers (ACCC)

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September 16, 2025

Chairman Smith, Ranking Member Neal, Chairman Guthrie, Ranking Member Pallone, and members of the committees:

We write today to express our ongoing support for H.R. 842, The Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Coverage Act and applaud your committees' attention to this matter this week. H.R. 842 will deliver meaningful progress in our nation's ability to combat cancer, particularly for those of us who live in rural communities.

The burden of late-stage cancer is particularly acute in rural America, where access to cancer screening is further away and more challenging to routinely maintain. Rural communities have higher rates of cancer incidence, late-stage diagnoses, and mortality compared with urban areas. Multi-cancer early detection (MCED) tests can change that. These tests are administered with a blood draw, meaning they can be delivered in more care centers in rural areas.

And because a higher percentage of people living in rural areas are over the age of 65 compared to their urban counterparts, H.R. 842 takes on an increased importance. Age is the biggest risk factor for developing cancer, so ensuring seniors can have access to these new cancer screening technologies without lengthy and unnecessary bureaucratic delays is only right.

Rural communities are counting on Congress to ensure they are not left behind in the fight against cancer. Thank you for your attention and we strongly urge Congress to pass it into law without any further delay.

Sincerely,
Christine E. Hamp
President
The National Grange

September 16, 2025

Dear Chairman Smith, Ranking Member Neal, Chairman Guthrie, Ranking Member Pallone and members of the committees:

The National Minority Quality Forum Action Network (NMQF AN) believes that our health care system's most important responsibility is to minimize patient risk – the risk of premature death and the risk of debilitating illness. When it comes to cancer, there is no more effective means for reducing this risk than early detection. To this end, today we write in strong support of H.R. 842, The Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Act and urge its passage.

We have been strong supporters of this legislation for years, driven in part because health inequities are particularly prominent when it comes to cancer screenings and diagnoses. Individuals who are Black, Hispanic or American Indian/Alaska Native are disproportionately diagnosed with cancer in those later, less treatable stages of the disease.

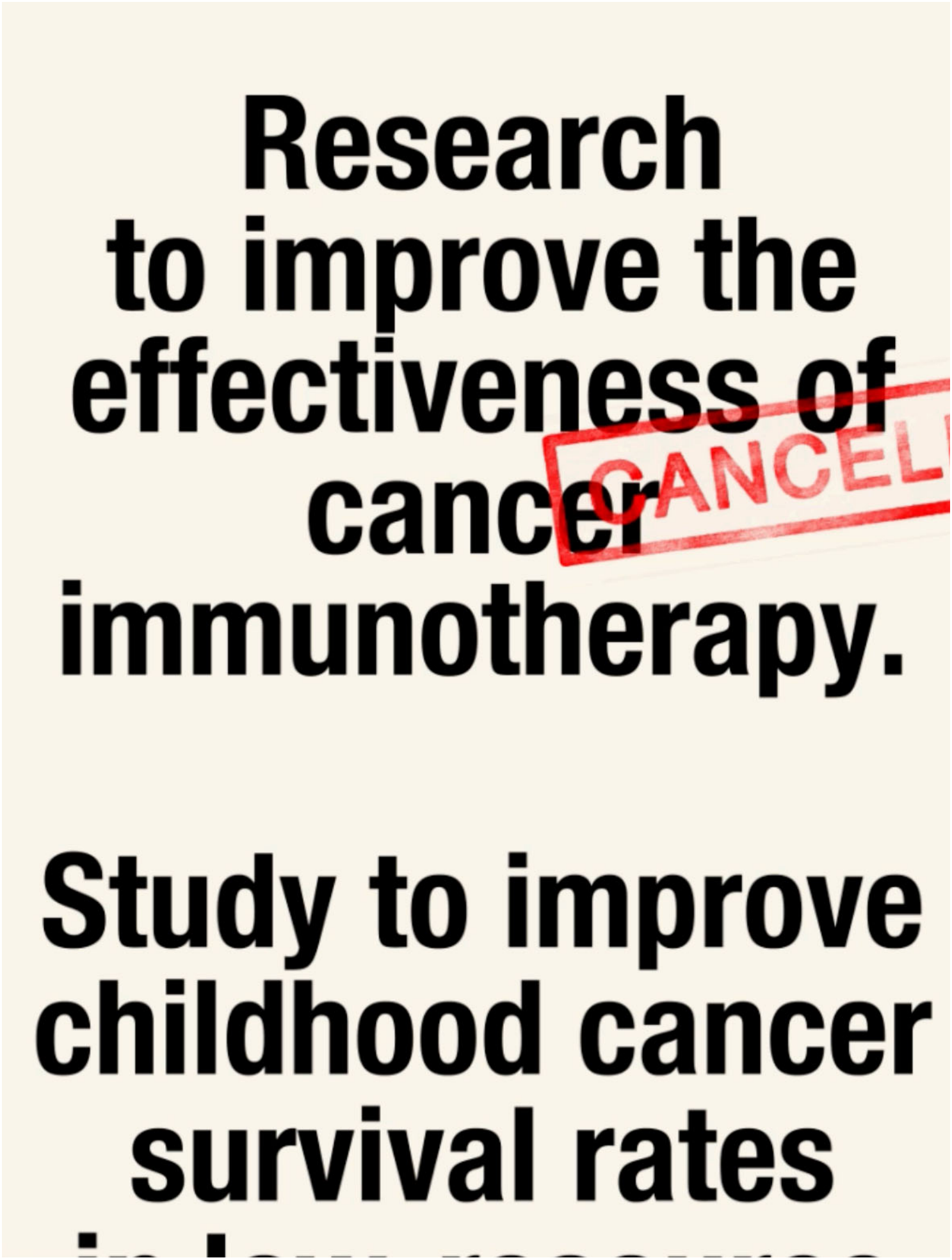
The emergence of multi-cancer early detection (MCED) tests can help turn the tide on the rates of late diagnosis. Using a blood draw, MCED tests make cancer screening more accessible for all Americans, including those in underserved and rural communities. They can reduce the burden of cancer and allow for less costly treatments.

But first, Congress must pass H.R. 842. Without it, Medicare coverage for MCED tests could be delayed for years. With this legislation, older Americans, those who are most risk to cancer, can have access to new diagnostic innovations that can make a meaningful difference in our fight against cancer.

NMQF is proud to stand with hundreds of other organizations from across the country and across the political spectrum - representing patients, health care providers and underserved communities, in endorsing this legislation. H.R. 842 has broad, enthusiastic support because it improves the state of our cancer screening capabilities and is the kind of investment that vastly improves our health care system for all Americans.

Thank you for your committees' attention to this legislation this week and we urge its immediate passage into law.

Sincerely,
Gary A. Puckrein, PhD
President & Chief Executive Officer
National Minority Quality Forum Action Network


Research
to improve the
effectiveness of
cancer
immunotherapy.
CANCEL
Study to improve
childhood cancer
survival rates

Trump Is Shutting Down the War On Cancer

America's cancer research system, which has helped save millions of lives, is under threat in one of its most productive moments.

By Jonathan Mahler

Sept. 14, 2025

Rachael Sirianni first learned her lab might be in trouble just a few weeks into the new year. A professor at the University of Massachusetts Chan Medical School, in Worcester, Sirianni focuses primarily on an aggressive form of pediatric brain cancer known as medulloblastoma. Researchers have made great strides in treating these tumors, but they are still often fatal, and even successful treatments can come with devastating side effects. Sirianni had spent the last several years working on a potentially transformative approach to treating the most malignant type of medulloblastoma and was making real progress.

Pediatric brain cancer research is expensive. UMass Chan pays for some of Sirianni's work, but most of her funding comes from the federal government. Entering 2025, she had three active grants at the National Institutes of Health that were all set to expire either this year or in 2026. She was prepared. In 2024, she submitted two new applications to continue her research. Both proposals had cleared the first hurdle at the N.I.H., earning strong scores from a panel of independent experts in the field. They were scheduled for another review at the agency in late January.

But then, in the days after Trump's inauguration, Sirianni started hearing rumors that he was planning to disrupt the N.I.H.'s grant-making process. As it turned out, he did much more than that. In late January, his administration ordered the N.I.H. to cancel meetings to consider pending grant applications.

Sirianni received her first federal research grant more than a decade earlier and had never even had an application-review meeting postponed. She scrambled to learn anything she could about the status of her proposals. This turned out to be difficult, because the new administration had ordered the N.I.H. to temporarily cease all external communications. Scientists were unsure whether they could even speak with program officers at the agency.

Sirianni, who is now 40, started college when she was 13. For more than two decades, she had spent as many as 12 hours a day in a lab, hunched over microscopes, computer monitors and lab mice. Now she was spending much of her time on the phone, talking and texting with equally anxious peers around the country. "Many of us had been in uncertain situations in the past — that's the nature of the game for academic scientists," she says. "But this was unlike anything we'd ever felt before."

Sirianni was lucky in that she had a modest buffer: When UMass Chan recruited her from the University of Texas in 2022, the school's chancellor, Michael Collins, gave her a generous start-up fund to get her new lab up and running and to pay her postdoc researchers, trainees and technicians. She had spent only half the money, so she could use what was left to help carry her and her staff through this period of uncertainty; she needed to keep the momentum going for her most promising studies and pay the researchers overseeing them.

On March 11, though, Sirianni received a troubling email from UMass Chan's administration. The disruptions at the N.I.H. were creating so much uncertainty around the school's financial future that it had to indefinitely pause all discretionary spending and freeze all hiring. The money from Sirianni's start-up fund was now effectively frozen, and she had no choice but to shrink her lab. When a researcher and her lab manager left, she was unable to replace them. Nor could

she offer positions to two undergraduates whom she had been mentoring and was planning to retain. More devastating still, she had to suspend one of her most promising pediatric brain cancer studies and eventually lay off the postdoc who was helping her run it.

‘When you remove me from the ecosystem, you are removing something that can’t be replaced.’

Rachael Sirianni

There was a sliver of hope, though: The two grants that Sirianni applied for in 2024 were pending, and they were finally scheduled for their reviews at the N.I.H. in April and May. The delay had at least allowed her to add more compelling data to one application, strengthening her case for funding.

Both proposals received strong scores from the N.I.H. program directors who analyzed and discussed them. But as of the beginning of September, neither one had been funded. “I believe I am one of only a small handful of labs in the country that specializes in drug-delivery barriers in pediatric brain cancer,” Sirianni told me when I visited her over the summer at her lab. “When you remove me from the ecosystem, you are removing something that can’t be replaced.”

Rachael Sirianni, a professor at the University of Massachusetts Chan Medical School. Her research into pediatric brain cancer was derailed by changes to federal grant programs. Matthew Monteith for The New York Times

When America declared war on cancer more than 50 years ago, there was a misguided assumption outside the scientific community that it would be only a matter of years before the disease was eradicated — that defeating cancer would be no different than building an atomic bomb or putting a man on the moon. But there would be no miracle cure: As of this writing, some 40 percent of Americans will be diagnosed with cancer at some point in their life.

What there would be, however, was decades of minor breakthroughs that would accrue over time, transforming both our understanding of the disease and our ability to treat it. One way to measure the cumulative effect of those breakthroughs is with statistics: In the mid-1970s, America's five-year cancer-survival rate sat at 49 percent; today, it is 68 percent. You can also correlate America's sustained investment in cancer research directly with these returns: According to a recent study in The Journal of Clinical Oncology, every $326 that our government spends researching cancer extends a human life by one year. Now an extraordinarily successful scientific research system — one that took decades to build, has saved millions of lives and generated billions of dollars in profits for American companies and investors — is being dismantled before our eyes.

In a matter of months, the Trump administration has canceled hundreds of millions of dollars in cancer-related research grants and contracts, arguing that they were part of politically driven D.E.I. initiatives, and suspended or delayed payments for hundreds of millions more. It is trying to sharply reduce the percentage of expenses that the government will cover for federally funded cancer-research labs. It has terminated hundreds of government employees who helped lead the country's cancer-research system and ensured that new discoveries reached clinicians, cancer patients and the American public. And the president's proposed budget for the next fiscal year calls for a more-than-37-percent cut to the National Cancer Institute — the N.I.H. agency that leads most of the nation's cancer research — reducing it to $4.5 billion from $7.2 billion. Adjusting for inflation, you have to go back more than 30 years to find a comparably sized federal cancer-research budget.

President Trump made a less ambitious attempt to defund America's scientific research system during his first term, proposing a 22-percent across-the-board cut to the N.I.H. in his inaugural budget and seeking to reduce institutions' reimbursement rates for some of their overhead expenses. Congress flatly rejected both efforts. To Republicans and Democrats, biomedical research — and cancer research, in particular — was sacrosanct.

But a very different attitude toward American science now prevails on the right wing of American politics. The Covid epidemic is largely responsible. Caught between a deadly pandemic and the government's oppressive countermeasures, many Americans sought someone to blame. A variety of vaccine skeptics, antigovernment MAGA types and wellness influencers and a discrete cohort of doctors and medical experts offered them a candidate: the scientific establishment. Their collective disaffection soon congealed into a powerful political force of its own, and a fringe movement to undermine the credibility of America's scientists went mainstream.

This force has become institutionalized in Trump's second administration. Defending the government's ongoing cuts to scientific research last May, Robert F. Kennedy Jr., a prominent vaccine skeptic who now leads the Department of Health and Human Services, told Congress that the N.I.H. was plagued by "corruption." Trump's N.I.H. director, Jay Bhattacharya, a co-author of the Great Barrington Declaration, a scientific treatise assailing America's Covid policies, made his name attacking the agency that he is now running.

Trump himself defended the cuts to biomedical research in a testy exchange with a Time magazine reporter last spring. "I could give you a list of abuse and waste and fraud," he said, "and you don't have any interest in hearing it." But neither he nor anyone inside his administration has spoken explicitly about its intention to radically rethink how America funds and directs cancer research, let alone laid out a plan for doing so.

In the absence of any such plan, it's hard not to see the ongoing dismantling of the cancer research system as collateral damage in a larger, partisan war against both the predominantly Democratic scientific establishment and the predominantly Democratic academic institutions where much of the country's biomedical research takes place. And yet the term "collateral damage" suggests a lack of agency; this has been a deliberate and targeted attack. "They have studied how N.I.H. works, studied it hard and learned it well," says Sarah Kobrin, head of the Health Systems and Interventions Research Branch at the National Cancer Institute. "And they have put sand in the gears in ways that are very effective, devastating." (The White House referred a detailed request for comment to the Office of Management and Budget, which said in a statement that the administration's "efforts to focus N.I.H. spending will establish a more sustainable and accountable fiscal path for N.I.H., while ensuring that resources are managed effectively and in a manner that best supports America's biomedical-research enterprise." An N.I.H. spokesperson said, "N.I.H. continues to invest significantly in bold and innovative cancer research.")

I spoke to 50 members of America's biomedical research establishment for this article — medical-school administrators; N.I.H.- and N.C.I.-funded researchers; former directors and current and former program officers and officials at the two agencies. As a group, they were hardly averse to change: Most acknowledged that the cancer-research system and the biomedical-research system more broadly had become too unwieldy and risk-averse. Before last year's election, both House and Senate Republicans circulated N.I.H. reform proposals on Capitol Hill, and the leaders of the National Institutes of Health and the National Cancer Institute were expecting — and even looking forward to — some new policies. "We didn't have our heads in the sand," says Michael Lauer, who retired in February as a deputy director of the N.I.H. and the agency's head of grant-making.

But no one was expecting this. "It's an absolutely unmitigated disaster," Lauer told me. "It will take decades to recover from this, if we ever do."

Frozen tissue samples and other materials used during Sirianni's research. Federal grant money supports laboratories in many ways, including supplies and facilities costs as well as staff salaries. Matthew Monteith for The New York Times

America's cancer-research system is sprawling and diffuse, beginning with Sirianni and the rest of America's tens of thousands of cancer researchers and continuing up through UMass Chan and the other research universities and cancer centers across the country that support their work. These institutions depend on the grant money their faculty members bring in to help cover their individual salaries and also to create and support their infrastructures — like the buildings that house the labs, the doctoral students and postdocs who help run

them and the supplies they need to conduct experiments. This is the economic structure that built these institutions, and it's one that they have come to rely on to function.

UMass Chan is a short drive from some of the most prestigious cancer-research centers in the world. It may not have the reputation or resources of a Harvard or Dana-Farber, but it does have 234 principal investigators doing frontline, government-funded research. When Michael Collins took over as the school's full-time chancellor in 2008, one of his priorities was to expand its research program, and he has been unambiguously successful at doing so. On his watch, the school's annual research budget has nearly doubled, to $352 million from $157 million, some $45 million of which goes toward cancer-related work. "If you have great scientists, you are going to win your share of grants," he says.

Last year was the high point of his 18-year tenure: He opened a new, $350 million, 350,000-square-foot research building, and one of his scientists was part of a duo that won a Nobel Prize. This year has been a very different story. Collins has spent much of it in urgent meetings with his finance team trying to figure out how to deal with the reality that tens of millions of dollars were suddenly disappearing from his institution's anticipated revenues.

Collins suspected that trouble was coming even before the new administration took office in Washington. One of the most important federal funding mechanisms for UMass Chan and other research institutions is what's known as their indirect cost reimbursements. In short, the government covers a portion of their facilities and administrative costs. How much institutions are entitled to receive is known as their indirect-cost rate, a fixed number that corresponds to a percentage of the direct costs associated with specific research projects.

Every institution has its own indirect rate, negotiated with the government and determined by a variety of factors, like the cost of labor in its geographic region. UMass Chan has a high indirect rate — 67.5 percent — which means it is heavily dependent on these reimbursements. As Collins is quick to point out, though, the number is misleading. Because of certain caps and other limitations, the

government reimburses the institution only for the indirect expenses associated with 44 percent of its direct costs. Those indirect expenses include the cost of administering the school's grants and the debt service on its research buildings.

During his first term, Trump tried to cap all indirect-cost reimbursements at 10 percent, which would have had dire consequences for UMass Chan. Congress not only rejected the effort but also added a rider to the budget bill preventing the administration from modifying indirect rates in the future. That same rider had been attached to every budget bill enacted since then.

Still, Project 2025 had called for the new administration to cut reimbursement rates, and Collins was worried that Trump would try again. A few days after the election, he flew down to Washington and met with Representative Lori Trahan, a Massachusetts congresswoman who sits on the committee that oversees the N.I.H., to remind her about the rider. Trahan was reassuring.

Collins's worries proved prescient. On a Friday evening in early February, the N.I.H. unilaterally amended its grant policy, ordering that all indirect-reimbursement rates be capped at 15 percent. Collins spent the weekend on the phone with his finance team, which calculated that the cut could cost UMass Chan somewhere between $50 and $60 million in expected revenues for the fiscal year. On Monday morning, Massachusetts and 21 other states sued the Trump administration to block the change. That afternoon, a federal judge in Boston issued a temporary restraining order halting the implementation of the new policy until its lawfulness had been adjudicated.

'We could lose a generation of scientists in a very short time.'

Michael Collins

Collins was safe, but not for long. Soon after, he got a call from his finance team informing him that the federal grant payments for the week were not available. There was little explanation from the government. The money simply wasn't accessible. The way the federal grant-making process works, researchers apply for funding through their respective institutions and the money is then disbursed through those institutions. Collins relies on those funds to help pay the salaries of his professors. Now he would need to find the money elsewhere to make up the difference.

Weeks passed, and there was still no money from the N.I.H., nor any clear explanation for why it had disappeared. At the same time, Collins had numerous faculty members who, like Sirianni, had grant applications pending at the N.I.H. that were completely stalled.

Already down some $30 million and with anticipated future revenues in jeopardy, Collins had to take some sort of action. In March, UMass Chan furloughed 200 employees and sent out the email to Sirianni and the rest of the school's faculty members freezing all discretionary spending. It also rescinded the offers to all 87 students whom it had admitted to its graduate school of biomedical science for the 2025-26 academic year. (The school would partly reverse this decision several weeks later, offering spots to 14 students for the current academic year and accepting the rest for the following one.)

Collins was not alone. Chancellors and medical-school deans at research institutions across the country had all had their government funding disrupted, and they were by now comparing notes during a weekly Thursday night Zoom meeting. UMass Chan had not been targeted by the Trump administration for political reasons, but other institutions had been. Harvard, Columbia, Northwestern, Cornell, Brown and the University of Pennsylvania were among those whose N.I.H. funding was cut off because the White House claimed that they had violated the civil rights of their Jewish students. Like UMass, these institutions had also received little or no warning.

In April, Collins finally got some good news: The N.I.H. had resumed meetings to discuss pending grant applications. He had his finance team run some more numbers, calculating how many proposals UMass Chan had before the agency that had already cleared the first round of N.I.H. review and had received what is considered a fundable score. They determined that the school could expect between $30 million and $40 million in new grant payments for the remainder of the fiscal year. As of the end of June, however, very few of these applications had been approved.

Michael Collins, chancellor of UMass Chan. In March, the absence of promised federal grant money forced the school to furlough 200 employees and freeze discretionary spending. Matthew Monteith for The New York Times

By that point, the N.I.H. had started resuming some payments for existing grants to UMass Chan, but the flow of money was still just a trickle — no more than a few hundred thousand dollars a week. By the middle of July, Collins was facing a research-budget shortfall for the fiscal year of $93 million. Collins told me that he planned to take stock again at the end of September, at the close of the federal government's fiscal year, and decide what additional cuts he needs to make. In the meantime, he's doing everything he can to raise money from individuals, private foundations and the state of Massachusetts. "I'm trying to get people to be worried about this," he says, "and it's hard. We could lose a generation of scientists in a very short time."

The broad framework for America's cancer-research system can be traced back many decades, to the waning days of World War II. The scientific community had played a critical role in the war effort, and President Franklin Delano Roosevelt commissioned the head of his wartime Office of Scientific Research and Development, a former M.I.T. scientist named Vannevar Bush, to draft a report — "Science: The Endless Frontier" — that would argue for carrying the partnership between government and academia into peacetime. Bush made the case that basic scientific research was critical to maintaining America's global leadership role and economic vitality, and he argued that this research should be funded by the federal government and carried out by universities.

It would be many years, though, before the government would make a large and sustained investment in fighting cancer. The individual most responsible for prodding the government into action was not a politician but a New York philanthropist and socialite, Mary Lasker. Lasker started lobbying for a sweeping government-funded effort to fight cancer in 1952, after her husband died of colon cancer, and pretty much never stopped. In 1969, she turned her lobbying campaign into a public crusade that included a series of full-page newspaper ads challenging President Richard Nixon to invest the same sort of resources and energy into fighting cancer that the government had put into the Apollo space program. Two years later, Nixon signed the National Cancer Act into law, committing $1.5 billion

— about $12 billion in today's dollars — over the next three years to fighting cancer. Thus began the War on Cancer, the most ambitious public-health initiative ever undertaken.

Before scientists could begin to figure out how to defeat cancer, they first had to learn how little they knew about its biology, starting with the fact that it was not a single disease but an infinite number of them, with hundreds of subtypes that don't just originate in different parts of the body but also behave differently in different people. The process took decades and is ongoing. Not until the late 1990s did all of the accumulated knowledge about the molecular biology of cancers begin to yield transformative treatments, in the form of targeted therapies designed to attack specific types of cancer. Since then, progress has accelerated. Between 1991 and 2022, the death rate from cancer in the United States fell by 34 percent; 4.5 million fewer people died of cancer than otherwise would have.

As scientists' understanding of the disease deepened and new paths to treat it proliferated, the cancer-research system expanded. It now reaches into just about every medical specialty, subspecialty and scientific discipline. It is diffuse but also interconnected, with researchers sharing their findings in peer-reviewed medical journals and at scientific conferences. Cancer research seldom has a clear, monetizable endpoint — it is often work, in other words, that private industry would never support. The system's extraordinary success is most clearly observed in retrospect, by looking at cancers that were fatal just a couple of decades ago and that doctors can effectively treat today. This progress is a validation of a slow but patient process that requires time — and the gradual accretion of shared knowledge — to prove its value.

'This is one of the most productive periods in the history of cancer research. At the same time, my colleagues are experiencing something between malaise and terror.'

Norman Sharpless

America's investment in cancer research has rippled out far beyond cancer. Investigating the molecular biology of one disease can naturally lead to discoveries about other ones — a phenomenon that scientists call convergence. It was cancer research that led to the creation of treatments for H.I.V. and hepatitis C, and to a vaccine for hepatitis B. When the Covid pandemic struck, technologies that had been developed for cancer enabled scientists to quickly sequence the virus and then develop a vaccine for it. The Cancer Genome Atlas, which collected and analyzed DNA samples from 11,000 cancer patients over 12 years, didn't just become a model for the mapping of other diseases; it also accelerated the evolution of the emerging interdisciplinary field of data science. America's prodigious investment in cancer research also helped jump-start the biotechnology industry, a powerful engine of medical innovation in its own right.

Sirianni's story speaks to both the short- and long-term benefits of America's cancer-research system. Her work builds on that of other drug-delivery scientists and is both costly and labor-intensive. Pediatric cancer cells can't easily be grown in vitro in a lab; they are typically harvested from operating rooms and then cultivated in lab animals — most commonly, an expensive strain of mouse. Pediatric brain cancer is also a highly specialized field, so it can take a while to train doctoral students and postdocs to become comfortable in the lab. Sirianni is targeting a specific subset of a relatively rare cancer; about 300 or so children are diagnosed with medulloblastoma every year. It is the kind of work that is unlikely to attract private investment at this early stage. And yet if she succeeds in developing a more effective method of moving therapeutic molecules into the interior of the brain to attack this particular form of cancer, she might not only save or improve the lives of many children; the technique could very well transform how doctors treat other neurodegenerative diseases like A.L.S., Alzheimer's and traumatic brain injury.

Government-funded cancer researchers across the country are engaged in work with similarly groundbreaking potential. At Ohio State University, investigators are experimenting with a so-called flash-radiation treatment that lasts just a few tenths of a second, killing cancer cells and causing significantly less harm to the

surrounding healthy tissue. At Stanford, scientists are using machine learning and mathematical modeling to more accurately predict the evolution and outcome of tumors. At Johns Hopkins, researchers recently discovered a way to detect cancer-derived mutations in the bloodstream up to three years before clinical signs or symptoms — advancing progress toward the development of a routine blood test that will be able to screen for a range of cancers. At the University of Washington and elsewhere, researchers are developing cancer vaccines. (Some, however, are mRNA vaccines, which could be threatened by Robert F. Kennedy Jr., who has already halted funding for the development of mRNA vaccines for infectious diseases.) “This is one of the most productive periods in the history of cancer research,” Norman Sharpless, who served as the director of the National Cancer Institute during the first Trump administration and for part of Biden’s presidency, told me. “At the same time, my colleagues are experiencing something between malaise and terror.”

As might be expected of any complex, multibillion-dollar entity that has been growing and evolving over decades, America’s cancer-research system has developed structural problems that need to be addressed. Because there is no mandatory retirement age for academics, the research field has aged sharply; between 1980 and 2008, the average age for an N.I.H.-funded principal investigator rose from 39 to 51, and it has slightly increased since. This has crowded out a lot of younger scientists with fresh ideas. It has also made the grant-application process enormously competitive, which means principal investigators have to spend a disproportionate amount of their time not doing research but writing grant applications. To secure funding in such a cutthroat environment, investigators are often inclined to propose safer, more incremental projects, rather than more cutting-edge ones. The top-heaviness of the research field and the time-consuming nature of the grant process is holding back progress and making it difficult to attract the most talented American students, which explains why so many postdoctoral researchers in American labs are from other countries, principally China and India.

It's perhaps no surprise that the Trump administration's attack on America's biomedical research system has been embraced by the disruption-addicted tech right. A government-run research system of sustained investment, collaboration and incremental progress no doubt looks anachronistic to a culture of individual visions, competitive silos and overnight growth — and all the more so with the leaders of various generative-A.I. companies making far-fetched promises to cure cancer in a matter of years.

Last May, in the early months of the Trump administration's cuts, the venture capitalist and Palantir co-founder Joe Lonsdale took aim at America's biomedical-research establishment in a Substack post titled "Fix the N.I.H. to Fix American Science." Lonsdale bemoaned the lack of breakthroughs to treat many cancers and proposed some of his own solutions. In addition to a sweeping regime of cuts to "underperforming labs and scientists" that "fuel mediocrity" and advance political agendas, Lonsdale called for a new federal grant-making process that would reward risk-taking and embolden visionaries. "In too many ways, the N.I.H. embodies the Soviet model that should have been left to die in the 20th century," he wrote. "Centralization, top-down ideological control of processes and an extreme conviction by the bureaucrats that they know better than anyone about everything."

A desk in a cancer-research lab at UMass Chan. Decades of federally funded efforts have led to accelerating results: Between 1991 and 2022, the death rate from cancer in the United States fell by 34 percent. Matthew Monteith for The New York Times

Dismantling a structure as large and multifaceted as America's cancer-research system is much easier than building one, but it is not without its challenges. The system was designed to be insulated from politics. Traditionally, there were only two political appointees at the N.I.H.: its director and the director of the National Cancer Institute. What's more, it's not the executive branch but Congress — which has a long history of bipartisan support for cancer research — that allocates the grant money that funds the scientists and their institutions. Tearing down the system, then, would require moving quickly and aggressively, taking control of it from the top down, clearing out civil servants and scientists while choking off the flow of money to universities and research centers.

The administration was much better prepared to accomplish this during Trump's second term than during his first. Russell Vought, the director of the White House's Office of Management and Budget and the primary architect of the attack on the biomedical-research system, spent the Biden years getting ready for this moment, drawing up a detailed plan to markedly shrink the federal government and end what he has called "the woke and weaponized bureaucracy."

He and the new administration began executing their plan on Trump's first full day in office. The first step was to effectively paralyze the N.I.H. and N.C.I. by ordering them to pause all external communications. They accomplished this via the sweeping communications ban issued by the acting head of H.H.S., Dorothy Fink. The directive compromised the agencies' ability to interact with the scientific community. But it also stopped the publication of all scientific research and, crucially, of any information in The Federal Register, in which all new opportunities for funding and all meetings to consider new grant applications have to be listed. As long as the communications pause was in effect — and the order wasn't clear about when it would end — there would be no new opportunities for cancer researchers, and all pending proposals, like Sirianni's two applications at the N.I.H., would be indefinitely delayed.

More directives followed in the days ahead, first a suspension of travel for N.I.H. employees and then a memo from the White House's Office of Management and Budget freezing grant funding from all federal agencies. Now, in addition to the ongoing pause on new cancer-research grant applications, no existing grants could be paid. All of this was unprecedented. Given the nature of the N.I.H.'s work — supporting biomedical research — new administrations usually went out of their way to make sure that transitions were as seamless as possible. "I don't ever recall a gag order or a grant freeze in my time at N.I.H.," says Lauer, the former N.I.H. deputy director who spent 18 years at the agency.

A group of nonprofits sued the administration over the funding freeze and were granted a stay in late January, ensuring that grant money would continue to flow while the case was briefed. In response, the administration withdrew the memo announcing the freeze — seemingly lifting it, per the court's order. But then the

new White House press secretary, Karoline Leavitt, announced on her social media account that the order was still in effect. No one at the N.I.H. was sure what to do. At N.C.I., the confusion was especially acute. The agency's director, Kimryn Rathmell, resigned the day of Trump's inauguration, and the president had not named an acting director to replace her, instead consolidating power at H.H.S.

The first round of layoffs came soon after, in mid-February. Some 1,200 N.I.H. employees were terminated, including 140 or so people at N.C.I. — senior leaders, scientists, grant administrators and many others. The O.M.B. order to freeze all grant payments had already disrupted the flow of money to research universities and centers. But in March, H.H.S. started formally canceling hundreds of active research grants.

This, too, was virtually unprecedented; Lauer recalled a total of two grants being unilaterally terminated by the government over the course of his career at the N.I.H. Now numerous grants that didn't comport with the administration's priorities, specifically as they concerned its D.E.I. policies, were being flagged for cancellation. At N.C.I., Sarah Kobrin, who focuses on cancer prevention, found herself trying to defend government-funded projects dedicated to increasing cancer screening in rural communities that happened to have large Black populations.

There was a more efficient way to stop the flow of money than terminating individual grants. Later in the winter, the Trump administration simply took control of the grant-payment system at H.H.S. — via Elon Musk's Department of Government Efficiency — and began freezing billions of dollars in N.I.H. funding for a group of universities that appeared on a target list compiled by the administration's new task force to combat antisemitism.

More layoffs followed in the spring. Pretty much the N.C.I.'s entire 70-person communications department, which was responsible for keeping the public and the medical and scientific communities abreast of the latest developments in the world of cancer research, was let go and not replaced. So was the N.C.I.'s acquisitions department, which purchased all the agency's office and lab supplies and issued all

its contracts. A chief surgeon at the National Cancer Institute, Steven Rosenberg, who is leading a clinical trial testing the use of immunotherapy on acutely ill patients with gastrointestinal cancer, lost two of the scientists in his lab who produced the cells with which he injected his patients.

Another way to cancel grants in bulk was to go after grant programs. The new administration terminated one of the N.C.I.'s most prestigious ones, the Outstanding Investigator Award, a seven-year grant intended to give cancer researchers with a track record of success the freedom to explore more innovative approaches in their field. It also ordered the N.I.H. to overhaul its approach to funding grants that weren't being canceled. The administration wanted half of all remaining funding for the fiscal year to be "forward-funded" — or paid out in full upfront. This would consume a large portion of the N.C.I.'s budget for the year, and translate into a significant cut to the number of new cancer-research grants that could be approved and funded. The National Cancer Institute recently informed the scientific community that it expected to be funding just 4 percent of all grant applications for the remainder of the government's fiscal year — less than half of last year's already-low 9 percent. In July, a public-policy professor at the University of Michigan, Donald Moynihan, posted an anonymous note on his Substack from an N.I.H. expert who described the abrupt shift to forward-funding as "a nuclear bomb dropped on cancer funding."

How was any of this even possible? The American people, through their representatives in Congress, had already allocated this money for research. When a president withholds congressionally appropriated funding, it is called impoundment, which Congress placed strict limits on in 1974. But Vought has insisted that the president is within his rights to refuse to disperse these funds. And he has argued that any money that hasn't been spent by the end of the fiscal year should be returned to the Treasury — a move known as a pocket rescission, which is considered illegal by the Government Accountability Office and other legal experts.

Whether the new administration's actions are legal or not, it has succeeded in blocking the disbursement of a lot of congressionally appropriated funds. Between Jan. 20 and Aug. 20, the N.I.H. paid out $4.31 billion less in grants than it did during the same period last year. The N.C.I., for its part, paid out $842 million less. And these numbers don't account for the many other billions of dollars in grants and funding that have been terminated or frozen since Trump took office.

Of course, withholding all of this money required a whole new structure inside the government. The N.I.H. no longer has two political appointees; it now has more than 20. The administration didn't so much tear down a top-down, ideologically controlled bureaucracy as it created a new one.

In the summer of 2008, my mother, who was 70 years old at the time, lost her appetite. She was a petite woman to begin with, but over the course of the next few months she lost at least 15 pounds. For a while, she refused to go to the doctor — she was also stubborn — but when she finally did, she was diagnosed with small-cell lung cancer that had spread to her liver. My mom was a lifelong smoker, so the diagnosis was devastating but not surprising. It was too late for radiation or surgery. The only option was a highly toxic course of chemotherapy. She survived for nearly a year, but her quality of life was terrible; her weekly chemo treatments left her nauseous and exhausted, unable to get out of bed or eat solid food for days. She was fully lucid and mentally sharp right up until 24 hours or so before she died, when the morphine pulled her into a state of semiconsciousness.

'Running a lab is not like running a clothing store, where if your sales are down you can bounce back. You are dealing with highly trained people and projects which, when stopped for a short time, are ruined.'

Harold Varmus

Last year, when I was suffering from a lingering respiratory infection, I went to see the pulmonologist who treated her, Daniel Libby. We talked a little bit about my mom, and he mentioned to me, almost as an aside, that if she were diagnosed today, he would be able to do a lot more for her. Over the summer, I gave him a call. Now that I was working on a story about cancer research, I was curious to hear more.

Libby told me that if he were to diagnose my mom with cancer today, her initial biopsy would include an oncogene test to see which one of the 75 known lung-cancer genes he was dealing with and what mutation could be occurring. Depending on the mutation, there might be a drug that would be effective in slowing the growth of the cancer cells. Even if there weren't, the test would provide him with actionable information about how to best treat her. Rather than chemo, he would use immunotherapy to help her immune system recognize the cancer cells and fight them off, which would probably be both more effective and much easier on her body. It's impossible to know how she would have responded to the treatment, but he estimated that she might have lived an extra six months or even a year; maybe more important, her quality of life during treatment would have been vastly better than it was during her chemo.

It's too early to predict what the ongoing dismantling of America's cancer-research system is going to cost us — what lifesaving, life-extending or life-improving treatments will be slower to develop, if they develop at all. The White House's proposed budget, with its 37-percent cut to the N.C.I., is still awaiting congressional debate, and various court battles are still playing out. In June, a Reagan-appointed federal judge in Boston, William G. Young, reversed some of the Trump administration's grant terminations in a stinging decision, writing that in his 40 years on the bench, he had "never seen government racial discrimination like this." But the administration appealed, and in late August, a 5-to-4 majority of Supreme Court justices upheld the cancellations, while leaving the door open for individual grantees to bring their own challenges.

The researchers, meanwhile, are doing what they can to continue their work. At UMass Chan, the top student in the biomedical sciences Ph.D. programs — the winner of the school's Chancellor's Award — has made plans to return home to China to run his own lab at Peking University. And Sirianni is now spending much of her time in her small office across the hall from her lab, furiously writing grant applications. For the time being, she is shifting her primary focus away from medulloblastoma, and toward other fields like traumatic brain injury. The experiments are too expensive to run, and she now has fewer researchers with the necessary expertise to help her. And pediatric cancer had very low funding rates at the N.I.H. before the Trump administration's cuts. Even if one of her new applications on a different project finds traction inside the N.I.H., though, it could take at least a year from the time of submission for the money to begin to flow. And these are just two scientists at a single institution.

Joe Lonsdale's blueprint for overhauling the N.I.H. promised a "moonshot factory that unleashes a new era of discovery." But almost eight months into Trump's second term, we have seen no proposals to replace what his administration is tearing down. The cancer-research system may be big and sprawling, but its wholesale dependence on government funding also makes it almost uniquely precarious. It doesn't take much to disrupt its normal functioning, and in the realm of science, any sort of disruption can be devastating. "Running a lab is not like running a clothing store, where if your sales are down you can bounce back," Harold Varmus, a former N.I.H. director and Nobel Prize-winning cancer researcher, told me. "You are dealing with highly trained people and projects which, when stopped for a short time, are ruined."

Other countries are seeing opportunity in the chaos. Varmus is among a number of prominent U.S. scientists who have received solicitations from the governments of France and Spain to consider relocating there. America's 80-year run as the world's leader of biomedical research — and 50-year run as the global leader of cancer research — may very well be coming to a close, and for no apparent reason. Varmus seemed as puzzled as anyone by the development. "We are great in science," he said. "Why would we want to destroy one of our greatest assets?"

Read by Eric Jason Martin Narration produced by Krish Seenivasan Engineered by Ted Blaisdell

Jonathan Mahler, a staff writer for The New York Times Magazine, has been writing for the magazine since 2001.

MEDICARE RIGHTS CENTER
Getting Medicare right

September 17, 2025

The Honorable Morgan Griffith
Chairman
Subcommittee on Health
Energy & Commerce Committee
U.S. House of Representatives

The Honorable Diana DeGette
Ranking Member
Subcommittee on Health
Energy & Commerce Committee
U.S. House of Representatives

Dear Chairman Griffith and Ranking Member DeGette:

The Medicare Rights Center appreciates your focus on bipartisan efforts to improve Medicare coverage and care. Medicare Rights is a national, nonprofit organization that works to ensure access to affordable and equitable health care for older adults and people with disabilities through counseling and advocacy, educational programs, and public policy initiatives. Each year, we provide services and resources to over three million Medicare beneficiaries, family caregivers, and professionals, including through our national consumer Helpline.

Based on this experience, we know that coverage restrictions and affordability challenges can prevent many people with Medicare from obtaining the services and medications they need to build and maintain their health. On September 18, during a hearing entitled "Examining Policies to Enhance Seniors' Access to Breakthrough Medical Technologies," the Energy & Commerce Health Subcommittee plans to review legislation intended to reduce these barriers. While we applaud this important goal, we are concerned that several of the bills to be discussed run counter to it. As outlined below, we urge you to correct these misalignments without delay.

Ensuring Patient Access to Critical Breakthrough Products Act (H.R. 5343)

This legislation would automatically allow Food and Drug Administration (FDA)-designated medical breakthrough devices to be covered by Medicare during a four-year transitional period, circumventing Medicare's ability to determine what services are "reasonable and necessary" for beneficiaries. This evaluation process is an important patient safety and consumer protection in general, and with respect to breakthrough technologies in particular. These devices, by their nature, lack complete evidence of efficacy and safety. Requiring their alignment with Medicare's "reasonable and necessary" standard is an appropriate condition for use among this population that strikes a careful balance between medical innovation and beneficiary well-being.

Importantly, a process for doing so already exists. The Centers for Medicare & Medicaid Services added a new pathway for coverage of breakthrough devices in 2024 that retains Medicare's ability to use the "reasonable and necessary" standard to ensure that safety is considered and

coverage is appropriate, while reducing needless delays. Accordingly, H.R. 5343 is both redundant and risky. Rather than establish new coverage or improve access, it would undermine current policy and safeguards, eroding the agency's ability to protect Medicare beneficiaries from harm and the program from fraud.

Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Coverage Act (H.R. 842)

H.R. 842 would allow Medicare to cover emerging blood-based cancer screenings that are FDA-approved, shown to have clinical benefit, and determined by the Secretary of the U.S. Department of Health and Human Services to be "reasonable and necessary" for the prevention or early detection of an illness or disability.

We appreciate that unlike H.R. 5343, this bill would maintain Medicare's "reasonable and necessary" authority, thereby ensuring an evidence-based, beneficiary-centered process for determining coverage parameters. However, this coverage would, without clinical basis, only reach some Medicare beneficiaries: those who attain a certain age by January 1 of the relevant year or who received a test in the prior 11 months. We strongly oppose this limitation; it would create significant barriers to care and set a dangerous precedent. We urge you to instead ensure everyone with Medicare can get the appropriate, high-quality services they need to thrive—access must not be arbitrary.

Thank you for your leadership and consideration. We look forward to continuing to work together to strengthen Medicare for all beneficiaries.

Sincerely,

Fred Riccardi

Fred Riccardi
President
Medicare Rights Center

From: Purchase, Delisa N (OIG/IO) [redacted]
Sent: Wednesday, September 17, 2025 10:40:40 AM
Subject: RE: Call on Waste Fraud Abuse in Potential Breakthrough Pathway at CMS

I wanted to send additional technical assistance on the legislation you all sent our way last week. You can review it below, please let me know if you have any questions.

1. OIG supports the goal of ensuring patients have access to technologies that can improve their health. We are concerned, however, that the draft legislation poses risk of fraud and abuse. Across Medicare benefits, our enforcement experience is that fraud follows the money, and so we expect an uptick in fraud if there is a transitional period of payment for breakthrough devices. If a reasonable and necessary standard is not practicable as a policy matter, the drafters may want to consider including additional guardrails in the conditions of the transitional period of payment (i.e., criteria that must be met for the breakthrough device to be payable by Medicare).

1. Without a “reasonable and necessary” standard for payment, it may be more difficult for the government to investigate and enforce against fraud that is likely to occur in the breakthrough device sector as more Medicare money becomes available.

1. As a general rule, no one guardrail prevents all fraud. The following conditions have been used in other contexts or could be used in the legislation to improve transparency and potentially reduce some fraud risk. There is no specific combination of guardrails that will be effective in all instances, and OIG offers the following menu of ideas:
    1. Requiring a signed physician order (to include the patient’s diagnoses related to the breakthrough device)
    2. Requiring a face-to-face encounter with the ordering physician before the device is furnished
    3. Data collection to ensure that claims submitted to CMS include data necessary for CMS to track the use of the breakthrough devices to ensure they are being used on patients who need them

4. A requirement that the manufacturer of the breakthrough device is timely pursuing the clinical trials needed to complete the FDA process, or that the manufacturers are hitting FDA milestones timely
5. A cap on the number of breakthrough devices that qualify for the transitional period of payment at any one time, or perhaps a cap on the number that will be considered each year
6. Requiring that there be evidence in Medicare claims for an enrollee that the enrollees have received other services or treatment related to the condition for which the breakthrough device is ordered
7. Authority for the Secretary to add such requirements for coverage and payment of breakthrough devices as necessary to protect against fraud and abuse
8. Site visits to the manufacturer to ensure that it is a legitimate business
9. "Enrollment" of the manufacturer in Medicare as a transparency tool so that CMS knows who owns the business, where it is located, etc. We are not aware of other requirements for manufacturers to enroll, and we recommend speaking to CMS about whether this could be operationalized. However, provider enrollment provides key protection and a screening process that helps keep bad actors out.
10. A requirement that CMS monitor the transitional payments and undertake appropriate periodic audits.

1. We expect AI to be part of many breakthrough technologies. We are already seeing considerable fraud and abuse using AI, including fraudsters using AI to fake records and orders for services. AI is being used increasingly in behavioral health, an area where we are seeing substantial fraud. It would be important to ensure that the Department can take action to prevent transitional payments for breakthrough AI technologies that are being misused.

Best,

Delisa

Annals of Internal Medicine

REVIEW

Multicancer Detection Tests for Screening

A Systematic Review

Leila C. Kahwati, MD, MPH; Matthew Avenarius, PhD; Leslie Brouwer, MS, APRN-CNP; Norah L. Crossnohere, PhD; Chyke A. Doubeni, MD, MPH; Cecelia Miller, PhD; Mariam Siddiqui, MPH; Christiane Voisin, MSLS; Roberta C. Wines, MPH; and Daniel E. Jonas, MD, MPH

Background: Screening for multiple types of cancer with a single blood test is potentially transformative.

Purpose: To assess the benefits, accuracy, and harms of screening with blood-based multicancer detection (MCD) tests in asymptomatic adults.

Data Sources: MEDLINE, Cochrane Library, trial registries, and relevant websites through March 2025.

Study Selection: Controlled studies of MCD tests (for example, cell-free DNA) in asymptomatic populations reporting cancer detection, mortality, quality of life, and harms (psychosocial, adverse events, decrease in standard-of-care screening); uncontrolled studies for harms of diagnostic evaluation; test accuracy studies.

Data Extraction: One reviewer extracted data; a second checked for accuracy; 2 reviewers independently assessed risk of bias (ROB) and strength of evidence.

Data Synthesis: No controlled studies evaluated benefits of screening. Twenty studies ($n = 109\,177$) reported accuracy for 19 MCD tests. Seven studies (5 with high ROB, 2 of unclear ROB) reported the accuracy of future cancer detection in asymptomatic persons followed for 1 year (prediagnostic performance); the rest estimated accuracy from high ROB case–control studies in clinically confirmed cancer cases and healthy, cancer-free, control participants (diagnostic performance). Across tests, sensitivity ranged from 0.095 to 0.998, specificity ranged from 0.657 to 1.0, and area under the curve (AUC) ranged from 0.52 to 1.0. Sensitivity and AUC were higher in diagnostic performance compared with prediagnostic performance studies. No other patterns in accuracy were discernible. One cohort study reported harms; however, these data were limited.

Limitations: English-language studies only. Heterogeneity precluded quantitative synthesis of accuracy; estimates from the diagnostic performance studies may not be applicable to screening.

Conclusion: No controlled studies are completed that report benefits of screening with MCD tests; evidence was judged insufficient to evaluate harms and accuracy. Accuracy varies by test and study design.

Funding Source: Agency for Healthcare Research and Quality. (PROSPERO: CRD42024570793)

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For author, article, and disclosure information, see end of text.
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Mortality from cancer has declined since the 1990s because of reduced exposures (for example, smoking), screening test availability, and more effective treatments. However, mortality for some types of cancer has not changed or has increased (1). Blood-based multicancer detection (MCD) tests offer a potentially transformative approach for screening because few effective screening tests exist for many types of cancer, particularly those typically found at advanced stages (for example, pancreatic, ovarian). The simplicity of a single blood test for multicancer screening belies their complexity, which may involve various analytic techniques (for example, next-generation sequencing), complex bioinformatics, and machine learning.

The technology underpinning many MCD tests is not new and is rooted in the "liquid biopsies" used for detecting minimal residual disease after cancer treatment. Cancer screening in asymptomatic persons is a new use case for MCD tests. Similar to other cancer screening technologies, they are intended to identify cancer at an early phase, before clinical signs or symptoms. The MCD tests use tumor- or non–tumor-derived biomarkers including cell-free DNA, proteins, or small-molecule metabolites (Table 1). Some use machine learning algorithms to analyze hundreds to thousands of biomarkers (31). Cell-free nucleic acid–based MCD tests are analyzed using genomic and epigenomic approaches (for example, methylation markers, whole-exome or targeted gene sequencing, fragmentomics), and these may be combined with other biomarkers or imaging (31–35). Results are returned qualitatively as positive or negative for a cancer signal; some tests also include a tissue-of-origin prediction to guide further diagnostic evaluation, which may include imaging, endoscopy, or other procedures. However, optimal diagnostic evaluation after a positive MCD test is not yet clear and varies by test.

No MCD tests have U.S. Food and Drug Administration (FDA) approval for multicancer screening, but

See also:

Editorial comment

Web Only
Supplement
Annals Video Summary

Table 1. Multicancer Detection Tests*

Test (Manufacturer)	Availability	Biomarker	Test Description	Cancer Types, *n*†
Commercially available for clinical use in the United States				
ARISTOTLE (2, 3) (StageZero Life Sciences)	LDT	mRNA	Quantitative mRNA gene expression profiling	9
EPISEEK (4) (Precision Epigenomics)	LDT	cfDNA	Epigenomic cfDNA methylation profiling	60
Galleri (5) (GRAIL)	LDT/BDD	cfDNA	Targeted epigenomic cfDNA methylation profiling	>50
OneTest (6) (20/20 GeneSystems)	LDT	Proteins	Immunoassay of 5–10 tumor proteins using FDA-approved kits but data analyzed with an algorithm	>20
OverC MCD (7) (Burning Rock Dx)	LDT/BDD	cfDNA	Targeted cfDNA methylation profiling	6
Qx‡ (8) (Quantgene)	LDT	cfDNA	Genomic sequencing of cancer-associated somatic mutations in cfDNA	50
Cancerguard (9, 10) (Exact Sciences)	IDE	cfDNA and proteins	Epigenomic cfDNA methylation analysis and protein classification	18–21
Commercially available for clinical use outside of the United States				
AminoIndex (11) (Ajinomoto)	Available in Japan	Amino acids	Mass spectrometry/liquid chromatography of plasma amino acids	6
OncoSeek (12) (OncoInv)	Available outside United States	Proteins	Immunoassay of 6 tumor proteins using FDA-approved kits but data analyzed with an algorithm	9
PanTum Detect (13) (RMDM)	Available in United Kingdom and in Middle East	Epitopes	Flow cytometry to identify 2 biomarkers in phagocytosed tumor cells	>50
SPOT-MAS (14) (Gene Solutions)	Available in Asia	cfDNA	Targeted and genome-wide methylation profiling, fragment length, copy number, and end-motif profiles	10
TruCheckA (15) (CancerScan UK)	Available in United Kingdom	Circulating tumor cells	Immunocytochemistry for the detection of circulating tumor cells	>70
Not available for clinical use				
Adela MCED (16–18) (Adela Bio)	RUO	cfDNA	Genome-wide epigenomic cfDNA methylation profiling	20
Avantect (19) (ClearNote Health)	Under development§	cfDNA	Genome-wide epigenomic cfDNA methylation profiling	2; more under development
CancerRadar (20) (Early Diagnostics)	Unclear; laboratory is CLIA certified	cfDNA	Genome-wide epigenomic cfDNA methylation profiling	Unclear
Carcimun (21) (Befima Diagnostix/Bioscope)	Under development	Proteomics	Detects conformational changes in plasma proteins through optical extinction measurements	16/41
Shield (22–24) (Guardant Health)	Under development‖	cfDNA	Genomic cfDNA analysis for somatic mutations with epigenomic analysis of methylation and fragmentation patterns	1; more under development
GutSeer (25) (Singlera Genomics)	Under development	cfDNA	Targeted cfDNA epigenomic methylation profiling	5 gastrointestinal cancers
MIRAM (26) (Elypta)	RUO	Glycos-aminoglycans	Mass spectrometry/liquid chromatography to measure protein-free fractions and composition of 17 glycosaminoglycans	Unclear
Panaromic (27) (Dxcover Limited)	RUO	Multiomics including DNA, RNA, proteins, lipids, and metabolites	Infrared spectroscopy	Unclear
Pan cancer test (28, 29) (Novelna)	Under development	Proteomics	Sex-specific panel of 10 proteins identified from 3072 target proteins measured using proximity extension assay	18

Continued on following page

Table 1 Continued

Test (Manufacturer)	Availability	Biomarker	Test Description	Cancer Types, *n*†
PanSeer (30) (Clinomics/ Singlera Genomics)	Unclear/laboratory is CLIA certified	cfDNA	cfDNA epigenomic methylation haplotype profiling	5

BDD = breakthrough device designation, an FDA status that expedites FDA premarket review; cfDNA = cell free DNA; CLIA = Clinical Laboratory Improvement Amendments; FDA = U.S. Food and Drug Administration; IDE = investigational device exemption, an FDA status allowing use of test within a clinical study or registry; LDT = commercially available in the United States as a laboratory developed test with no requirement for FDA review or approval; MCD = multicancer detection; mRNA = messenger RNA; RUO = commercially available for research use only.

* This list is not exhaustive; it focuses on tests that are commercially available in the United States or globally for clinical or research use, or that are not commercially available but appear to be in advanced commercial development stages for U.S. markets.

† Refers to the number of cancer types the test is designed to detect. For commercially available tests, this is the number of cancer types included in the marketing claims. For tests not yet commercially available, this is the number of cancer types included in the test development cohorts. Note that the number of cancer types evaluated by authors in external validation studies (the focus of this review) may differ from this number.

‡ cfDNA cancer signal detection is 1 component of the Qx platform; this platform also includes a personal and family health assessment, preventive cancer screening tests other than MCD tests, hereditary cancer genetic testing, full body magnetic resonance imaging, and pharmacogenomic testing.

§ Avantect is available as an LDT for pancreatic cancer or ovarian cancer screening only; the Avantect MCD test is not yet commercially available.

‖ Shield has FDA approval for colorectal cancer screening only; the Shield MCD test is not yet commercially available.

some are commercially available in the United States as laboratory-developed tests; laboratory-developed tests do not require FDA approval when conducted in a Clinical Laboratory Improvement Amendments (CLIA)–certified laboratory. Available and developing MCD tests differ in the measured analytes, analysis technology, type of cancer detected, and criteria for a positive cancer signal. For example, many use epigenomic cell-free DNA methylation profiling though they may use unique bioinformatic platforms to determine positive signals for different numbers of cancer types. Currently, no insurance providers cover MCD tests for screening (35). Some experts recommend these tests as potential supplements to, and not replacements for, standard-of-care cancer screening methods like mammography and colorectal cancer screening (35).

We conducted a systematic review to assess the benefits, accuracy, and harms of screening with MCD tests to support clinical and policy decision making by clinicians, medical professional organizations, guideline developers, health care payers, and other groups or organizations.

METHODS

This systematic review used guidance from the Agency for Healthcare Research and Quality (AHRQ)'s *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (36) and *Methods Guide for Medical Test Reviews* (37). The review protocol was registered on PROSPERO (CRD42024570793), and we reported the review using the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 statement (38). The protocol and full review report are available at the AHRQ Effective Health Care (EHC) website (39). This review included questions on screening, diagnostic test accuracy, and harms:

Screening: What is the effectiveness of screening with MCD tests on aggregate cancer detection and cancer mortality, all-cause mortality, quality of life, and functional status?

Test accuracy: What is the accuracy of MCD tests for detection of cancer?

Screening harms: What are the harms of screening with MCD tests?

Diagnostic test evaluation harms: What are the harms of additional testing or surveillance after an MCD test?

The 2 questions for harms were included to guide a search for broad evidence related to the cascade of events that occur after a positive (or negative) screening test. In addition, we specified several contextual questions, which are available in the full report (39).

Data Sources and Searches

We searched MEDLINE, the Cochrane Library, 2 trial registries, and relevant government and commercial websites between 1 January 2013 and 26 December 2024. We conducted surveillance of the literature through 31 March 2025. The complete search strategies are in **Supplement Tables 1 to 11** (available at Annals.org).

Study Selection

The inclusion criteria for evidence on benefits and harms were randomized controlled trials (RCTs) or nonrandomized controlled studies of screening tests designed to detect 2 or more types of cancer compared with no screening or standard-of-care cancer screening in asymptomatic adults without known or suspected cancer. We also included uncontrolled studies for harms of diagnostic evaluation. Eligible outcomes included cancer-specific and all-cause mortality, cancer detection and stage at diagnosis, quality of life, and functional status. Screening harm outcomes included psychosocial distress, adverse events, radiation exposure, decrease in receipt of standard-of-care cancer screening, and out-of-pocket patient costs.

For test accuracy, we selected case–control or cohort studies that evaluated sensitivity, specificity, or area under the curve in a population external to test development. Prediagnostic performance accuracy is

estimated from study designs where participants without known or suspected cancer are tested with the MCD at baseline, and then cancer status is ascertained during follow-up over time (40). Such designs can be prospective with MCD analysis at baseline or nested case–control studies that use archived blood specimens collected at baseline for analysis at the time of clinical diagnosis. We considered a minimum follow-up of 1 year for ascertaining cancer or cancer-free status as an adequate study design feature (40). In contrast, diagnostic performance accuracy is determined from diagnostic case–control study designs; sensitivity is estimated from testing persons with confirmed cancer (that is, clinical cases), and specificity is estimated from testing a separate sample of people without cancer (40).

We excluded studies reported in languages other than English and studies conducted in countries categorized as less than highly developed in the 2024 United Nations Human Development Report (41). Unpublished data, including conference abstracts or presentations, were eligible if enough details were available to determine eligibility and assess risk of bias (ROB).

Two team members used the study selection criteria to independently review titles/abstracts retrieved from the search. Two team members independently reviewed full-text articles included at title/abstract review; articles excluded by 2 reviewers were not considered further. We adjudicated full-text inclusion/exclusion conflicts through team discussion or by a third reviewer.

Data Extraction and Quality Assessment

We abstracted data from included studies using structured forms in DistillerSR (42). One reviewer abstracted data and a second checked the data for accuracy. For test accuracy, we calculated sensitivity and specificity for aggregate cancer detection (that is, any and all types of cancer) based on author-reported true positives, false positives, true negatives, and false negatives using RStudio (version 2023.6.0.421) (43).

We used QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) (14) to evaluate the ROB of test accuracy studies and tailored the signaling items for studies reporting prediagnostic or diagnostic performance (40, 44). We used the JBI Checklist for Quasi-Experimental Studies to evaluate ROB for the single study that was eligible for harms (45). Two reviewers independently assessed the ROB for each included study; disagreements were adjudicated through discussion or a third reviewer. We used TACIT (Tool for Addressing Conflicts of Interest in Trials) to evaluate conflicts of interest for the study sponsors and investigators of included studies (46). All studies were included in the review regardless of ROB rating or notable conflicts of interest.

Use of Artificial Intelligence and/or Machine Learning

We used the artificial intelligence prioritization feature in DistillerSR to prioritize titles/abstracts and full-text articles for screening and as the second title/abstract reviewer when the highest remaining citation rank score was consistently less than 0.20 (indicating a low likelihood of eligibility). We used Claude Pro (versions 3.5 and 3.7) to extract data required for TACIT; this information was reviewed by a human before finalizing the determination (46). We used 1 or more large language models as an editorial assistant to help improve the clarity or succinctness of text written by reviewers.

Data Synthesis and Analysis

We summarized data in narrative, tabular, and graphical formats but could not conduct quantitative synthesis because of clinical and methodological heterogeneity. We present data for prediagnostic performance accuracy (that is, in participants without known or suspected cancer) separately from diagnostic performance accuracy (that is, in patients with known cancer and control participants without cancer). We used guidance from the EHC program to assess the strength of evidence (47, 48). This included consideration of consistency, precision, directness, reporting bias, and study limitations. Two independent reviewers assessed strength of evidence and resolved conflicts through discussion. For accuracy, we used a modified approach because all but 2 MCD tests were evaluated in only 1 study; we generated a single, aggregated strength-of-evidence assessment.

Role of the Funding Source

This topic was selected and funded by AHRQ after nomination by the Medicaid Evidence-based Decisions Project. A representative from AHRQ provided technical assistance and comments on draft versions of the full report. However, AHRQ did not participate in the literature search, determination of study eligibility criteria, data analysis or interpretation, or preparation or approval of the manuscript for submission.

RESULTS

Our search identified 12 043 unique records (Supplement Figure 1, available at Annals.org). We did not identify any completed controlled studies of MCD tests for screening. For test accuracy, we included 20 unique studies. One of the studies included for accuracy also reported outcomes relevant to harms of screening and harms of diagnostic evaluation (49, 50). We judged 13 studies as having notable concerns for conflicts of interest (see full report for study-level details) (49, 51–62).

Test Accuracy

For test accuracy, we included 20 unique studies (published in 27 articles; 109 177 participants [range, 102 to 41 516 per study]) reporting on 19 unique MCD tests (34, 49–74). Seven studies (Table 2) reported prediagnostic performance (that is, in participants without known or suspected cancer) of 7 unique MCD tests using either a prospective cohort design (49, 52, 59,

Table 2. Characteristics of and Results From Included Prediagnostic Performance Studies

Study, Year (Reference); Country; Registry Number	Study Design; ROB; Sponsor	Study Population	Cancer Types*	Accuracy† Estimate (95% CI)
Commercially available for clinical use in the United States				
Galleri (cfDNA methylation)				
Schrag et al, 2023 (52) and Nadauld et al, 2021 (66); United States; NCT04241796 (PATHFINDER)	Prospective cohort; unclear ROB; GRAIL	6413 (64% female); ages 50 y or older; 91.7% non-Hispanic White; enrolled persons at average cancer risk and high risk, including 1622 with cancer treatment completed >3 y prior	Designed for detection of ≥50 cancer types; 19 cancer types occurred for 12 mo of follow-up	Initial test Sn: 0.29 (0.21–0.38) Sp: 0.99 (0.99–0.99) PPV: 0.38 (0.28–0.49) NPV: 0.99 (0.98–0.99) Refined test Sn: 0.31 (0.21–0.43) Sp: 1.0 (0.99–1.0) PPV: 0.43 (0.30–0.57) NPV: 0.99 (0.98–0.99) TOO prediction accuracy Primary prediction: 85% (69.9%–93.6%) Primary or secondary prediction: 97% (85.1%–99.8%)
OneTest‡ (immunoassay of proteins)				
Wen et al, 2015 (72); Taiwan; NR	Prospective cohort; high ROB; NR	41 516 (52% female); ages 20–93 y; race and ethnicity NR	Designed for detection of ≥20 cancer types; 16 cancer types occurred for 12 mo of follow-up	Sn: 0.57 (0.51–0.63) Sp: 0.89 (0.88–0.89) PPV: 0.04 (0.03–0.04) NPV: 1.0 (1.0–1.0) Test does not provide a TOO prediction
Commercially available for clinical use outside the United States				
AminoIndex (plasma amino acids)				
Mikami et al, 2019 (60); Japan; NR	Prospective cohort; unclear ROB; Ajinomoto Co. and Japanese government	10 245 (53% female); ages 24–93 y; race and ethnicity NR	Designed for detection of 7 cancer types; 7 cancer types occurred for 12 mo of follow-up	By cancer§: Breast Sn: 0.44 (0.20–0.70) Sp: 0.94 (0.94–0.95) PPV: 0.01 (0.01–0.02) NPV: 1.0 (1.0–1.0) Colorectal Sn: 0.46 (0.19–0.75) Sp: 0.91 (0.91–0.92) PPV: 0.01 (0–0.01) NPV: 1.0 (1.0–1.0) Lung Sn: 0.50 (0.07–0.93) Sp: 0.90 (0.90–0.91) PPV: 0.002 (0–0.01) NPV: 1.0 (1.0–1.0) Prostate Sn: 0.50 (0.25–0.75) Sp: 0.0.93 (0.93–0.93) PPV: 0.01 (0.01–0.02) NPV: 1.0 (1.0–1.0) Stomach Sn: 0.83 (0.52–0.98) Sp: 0.84 (0.83–0.85) PPV: 0.01 (0.0–0.1) NPV: 1.0 (1.0–1.0) Uterine/ovarian Sn: 0.50 (0.01–0.99) Sp: 0.95 (0.95–0.96) PPV: 0.002 (0–0.1) NPV: 1.0 (1.0–1.0)
SPOT-MAS (cfDNA analysis)				
Nguyen et al, 2023 (64) and Nguyen et al, 2025 (59); Vietnam; NCT05227261	Prospective cohort; unclear ROB; Gene Solutions	9024 (55% female); ages 40–79 y; race and ethnicity NR	Designed for detection of 10 cancer types; 11 cancer types occurred for 12 mo of follow-up	Sn: 0.71 (0.51–0.85) Sp: 1.0 (1.0–1.0) PPV: 0.40 (0.25–0.56) NPV: 1.0 (1.0–1.0) By stage: Stage I, II, IIIA Sn: 0.71 (0.47–0.87) Sp: 1.0 (1.0–1.0)

Continued on following page

Table 2 Continued

Study, Year (Reference); Country; Registry Number	Study Design; ROB; Sponsor	Study Population	Cancer Types*	Accuracy† Estimate (95% CI)
				PPV: 0.32 (0.18–0.49) NPV: 1.0 (1.0–1.0) Stage IIIb, IV Sn: 0.71 (0.36–0.92) Sp: 1.0 (1.0–1.0) PPV: 0.16 (0.06–0.34) NPV: 1.0 (1.0–1.0) TOO prediction accuracy Primary prediction: 52.9% (31.0%–73.8%) Primary or secondary prediction: 76.5% (NR)
Tests not commercially available				
CancerSeek (superseded by Cancerguard) (cfDNA and proteins)				
Lennon et al, 2020 (49); United States; NR	Prospective cohort; unclear ROB; multiple foundation funders	9911 (100% female); ages 65–75 y; 94.9% non-Hispanic White	Earlier version of test (5) designed to detect 8 cancer types (breast, colorectal, esophagus, liver, lung, ovary, pancreas, stomach); 15 cancer types occurred for 12 mo of follow-up	Initial test Sn: 0.30 (0.23–0.40) Sp: 0.95 (0.95–0.96) PPV: 0.06 (0.04–0.08) NPV: 0.99 (0.99–0.99) Repeat test to confirm initial positive Sn: 0.27 (0.19–0.37) Sp: 0.99 (0.99–0.99) PPV: 0.19 (0.13–0.27) NPV: 0.99 (0.99–0.99) Repeat test + PET-CT Sn: 0.16 (0.09–0.25) Sp: 1.0 (1.0–1.0) PPV: 0.28 (0.17–0.42) NPV: 0.99 (0.00–0.99) Test does not provide a TOO prediction
MIRAM (glycosaminoglycans)				
Bratulic et al, 2022 (54); The Netherlands; NR	Nested case–control; unclear ROB; multiple European government and foundation funders	281 (49% female); ages 25–84 y; race and ethnicity NR	Unclear how many different types of cancer test is designed to detect; 9 cancer types occurred for 18 mo of follow-up	AUC All cancer types: 0.65 (0.58–0.72) Stage 0-II: 0.62 (0.54–0.69) Stage III-IV: 0.73 (0.65–0.82) Test does not provide a TOO prediction
2-Protein biomarker panel				
Sekiguchi et al, 2020 (73); Japan; NR	Retrospective cohort; high ROB; Japan National Cancer Center Research and Development Fund	12 349 (36% female) ages 50–64 y; race and ethnicity NR	Evaluation of combined biomarkers limited to evaluating accuracy of 2 cancer types (colorectal, stomach) compared with concurrent upper and lower endoscopy	CEA biomarker Sn: 0.08 (0.05–0.12) Sp: 0.96 (0.96–0.97) PPV: 0.04 (0.02–0.06) NPV: 0.98 (0.98–0.98) CA19-9 biomarker Sn: 0.07 (0.04–0.12) Sp: 0.95 (0.95–0.95) PPV: 0.03 (0.02–0.04) NPV: 0.98 (0.98–0.98) Test does not provide a TOO prediction

AUC = area under the curve; CEA = carcinoembryonic antigen; NPV = negative predictive value; NR = not reported; PET CT = positron emission tomography computed tomography; PPV = positive predictive value; ROB = risk of bias; Sn = sensitivity; Sp = specificity; TOO = tissue of origin.
* Refers to all types of cancer diagnosed over duration of follow up. Cancer types were diagnosed after diagnostic work up from a positive multi cancer detection (MCD) test, from a positive standard of care screening test, or from clinically presenting signs or symptoms.
† Includes sensitivity (percentage with positive MCD result among those diagnosed with cancer over duration of follow up), specificity (percentage of those with a negative MCD result among those without cancer over duration of follow up), AUC (composite measure of sensitivity and specificity), and TOO prediction accuracy, when applicable.
‡ Results from this study are for a version of the OneTest that was a precursor to the version that is currently commercially available.
§ This test does not provide an overall cancer signal, rather it provides an individual cancer signal for each of the included cancer types.

60, 72), a retrospective cohort design (73), or a nested case–control design (54). We rated 5 of these studies (49, 52, 54, 59, 60) as having unclear ROB for lack of consecutive or random sample and no information about test thresholds. We assessed the other 2 studies (72, 73) as high ROB for lack of information about a consecutive or random sample, failure to use a predefined threshold, concerns about reference standard used, and exclusion of substantial proportions of participants from the analysis. Detailed ROB assessments are in **Supplement Table 12** (available at Annals.org). The remaining 13 studies (51, 53, 55–58, 61, 62, 65, 69–71, 74) used high ROB case–control designs to report the diagnostic performance of 12 unique MCD tests in patients with known cancer and control participants without cancer (**Appendix Table**, available at Annals.org). The use of a case–control design to estimate accuracy was the major source of bias in these studies; other sources included lack of blinding of study personnel to case/control status, limited information about predefined test thresholds, and lack of information about the inclusion/exclusion of patients throughout the testing process. In nearly all of these studies, control participants were poorly characterized.

Accuracy varied widely based on analyte and analysis approach used, the number and types of cancer for which the MCD test was designed to report, subgroups of participants, and study designs used (**Supplement Figure 2**, available at Annals.org). Sensitivity and area under the curve were generally lower in prediagnostic performance studies compared with diagnostic performance studies. No other patterns in accuracy were discernible. Of the 2 tests that are commercially available in the United States and evaluated in prediagnostic performance studies (Galleri, OneTest), the sensitivity was 0.31 (95% CI, 0.21 to 0.43) (52) for Galleri and 0.57 (CI, 0.51 to 0.63) (72) for OneTest. In these studies, the positive predictive values were 43% and 4%, respectively. Accuracy of the various MCD tests in subpopulations defined by sex, age, or cancer risk are available in additional figures in the full report (39). We graded the strength of evidence for accuracy outcomes as *insufficient* (**Table 3**).

The **Figure** depicts the types of cancer identified by studies that used prediagnostic performance designs (49, 52, 54, 59, 60, 72, 73). These were types of cancer diagnosed over the studies' follow-up periods (typically 12 months) as a result of 1) MCD test use, 2) standard-of-care cancer screening tests, or 3) development of clinical signs or symptoms prompting a diagnostic evaluation.

Harms of Screening

We identified 1 controlled cohort study (DETECT-A) that reported on an eligible harm outcome (changes in adherence to standard-of-care screening) (49, 50). Authors evaluated adherence to standard-of-care lung cancer screening by participants who received the CancerSEEK test in a subset of cohort participants ($n = 364$) compared with a control group from the same health system who were eligible to receive the MCD test but did not ($n = 2{,}548$) (50). We assessed this study as having an unclear ROB for this outcome (**Supplement Table 13**). For 1 year of follow-up, receipt of standard-of-care lung cancer screening increased in both groups and was higher in the MCD test group, but with a wide CI that included the null effect (odds ratio, 1.58 [CI, 0.47 to 5.31]) (50). We graded the strength of evidence for this outcome as *insufficient* (**Table 3**).

Harms of Diagnostic Evaluation

The DETECT-A study also reported on 2 harm outcomes relevant to diagnostic evaluation (49). We rated this study as unclear ROB for these outcomes (**Supplement Table 13**, available at Annals.org). Of the 9911 women tested, 108 had false-positive results, and the authors reported that none of these persons experienced any serious adverse events from follow-up diagnostic evaluations (49). Of the women with false-positive results, 7 did not require any further evaluation after a clinical committee review and 101 had positron emission tomography–computed tomography (PET-CT) scanning. Sixty-three women (62%) required no further diagnostic work-up after PET-CT scanning. The other 38 required further evaluation (16 [42%] noninvasive testing, 19 [50%] minimally invasive procedures to rule out cancer, 3 [8%] surgery [large colon polyps with high-grade dysplasia, in situ carcinoma of the appendix, 10-cm benign ovarian mass]) (49). All women with false-positive MCD test results who received a PET-CT scan received unnecessary radiation exposure, which averages out to a 25-mSv dosage (75). We graded these harms as *insufficient* strength of evidence (**Table 3**).

DISCUSSION

In this systematic review, we identified no completed controlled studies reporting the impact of screening with MCD tests on cancer detection, mortality, or quality of life. We found insufficient evidence on the accuracy and harms of MCD tests due primarily to study limitations and unknown or inconsistent findings. In 2001, the National Cancer Institute (NCI)'s Early Detection Research Network released a blueprint for biomarker development outlining phases spanning development (phase 1) to RCTs with disease-specific mortality outcomes (phase 5) (76). Some suggest modeling as a sixth phase for extrapolation from empirical studies (77). Few studies included in our review offer evidence beyond phase 2 (discrimination in known cancer and noncancer cases), and no studies offer evidence for phase 5.

Although evidence is either not yet available or insufficient to support widespread adoption of MCD tests, some tests are commercially available. Three tests included in this review are available with a prescription as laboratory-developed tests (OneTest, Galleri, OncoSeek). The next-generation version of the CancerSEEK test (Cancerguard) is available through an FDA investigational

Table 3. Summary of Findings and Strength of Evidence

Outcome: Strength of Evidence Grade	Study Design, Number of Studies (Total Participants, *n*)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Finding
Accuracy: Insufficient	Case–control, 13; nested case–control, 1; retrospective cohort, 1; prospective cohort, 5 (109, 177)	High*	Indirect†	Inconsistent‡	Precise for specificity§; imprecise for sensitivity and AUC§	Not detected	Sensitivity range: 0.095–0.988 (25 estimates from 17 studies); sensitivity lower in prediagnostic performance designs as compared with diagnostic performance design Specificity range: 0.657–1.0 (25 estimates from 17 studies) AUC range: 0.52–1.0 (18 estimates from 11 studies); AUC lower in prediagnostic performance designs as compared with diagnostic performance designs
Screening harms–change in receipt of standard-of-care screening: Insufficient	NRSI, 1 (2912)	High‖	Direct	Unknown (single study)	Imprecise	Not detected	Comparing participants who received MCD tests with participants who were eligible but did not receive an MCD test, the odds of receiving standard-of-care lung cancer screening increased in both groups over time; the magnitude of increase was greater in the MCD group, but this finding was not statistically significant (OR, 1.58 [95% CI, 0.47–5.31]).
Diagnostic evaluation harms–serious adverse events: Insufficient	Single-arm cohort study, 1 (9911 total study; but only reported for subgroup of 108 with false-positive results)	High‖¶	Direct	Unknown (single study)	Unable to determine**	Not detected	No serious adverse events reported among the subgroup of 108 participants who had false-positive results.
Diagnostic evaluation harms–radiation exposure: Insufficient	Single-arm cohort study, 1 (9911)	High‖¶††	Indirect‡‡	Unknown (single study)	Unable to determine**	Not detected	Unnecessary radiation exposure >10 mSv in 101/9911 (1%) of participants because of false-positive MCD test followed by PET-CT scan and further evaluation that did not find cancer.

AUC = area under the curve; MCD = multicancer detection; NRSI = nonrandomized study of intervention; OR = odds ratio; PET CT = positron emission tomography computed tomography.

* Fifteen of 20 included studies were high risk of bias (ROB) including 13 that used case control designs with limited to no information about control populations and adequacy of reference standard.

† Accuracy outcomes are indirect for establishing a clinical benefit or harm. Most estimates were obtained from diagnostic performance study designs, and these estimates may not be generalizable for screening in asymptomatic populations. Several studies were based on data in biobanks and may not be generalizable to use of MCD tests in clinical practice.

‡ All but 2 tests were evaluated by only 1 study. We could not identify any discernible patterns by analyte type (for example, cell free DNA, proteins); the only consistent pattern we could identify was lower sensitivity and AUC in prediagnostic performance designs as compared with diagnostic performance designs.

§ Individual study sample size ranged from 102 to 41 516. Few studies provided CIs around accuracy outcomes, so we calculated CIs based on raw data where possible. Precision around estimates for sensitivity and AUC varied by study and spanned a larger range of values as compared with specificity estimates, which were largely precise across most studies.

‖ Unclear ROB across multiple domains.

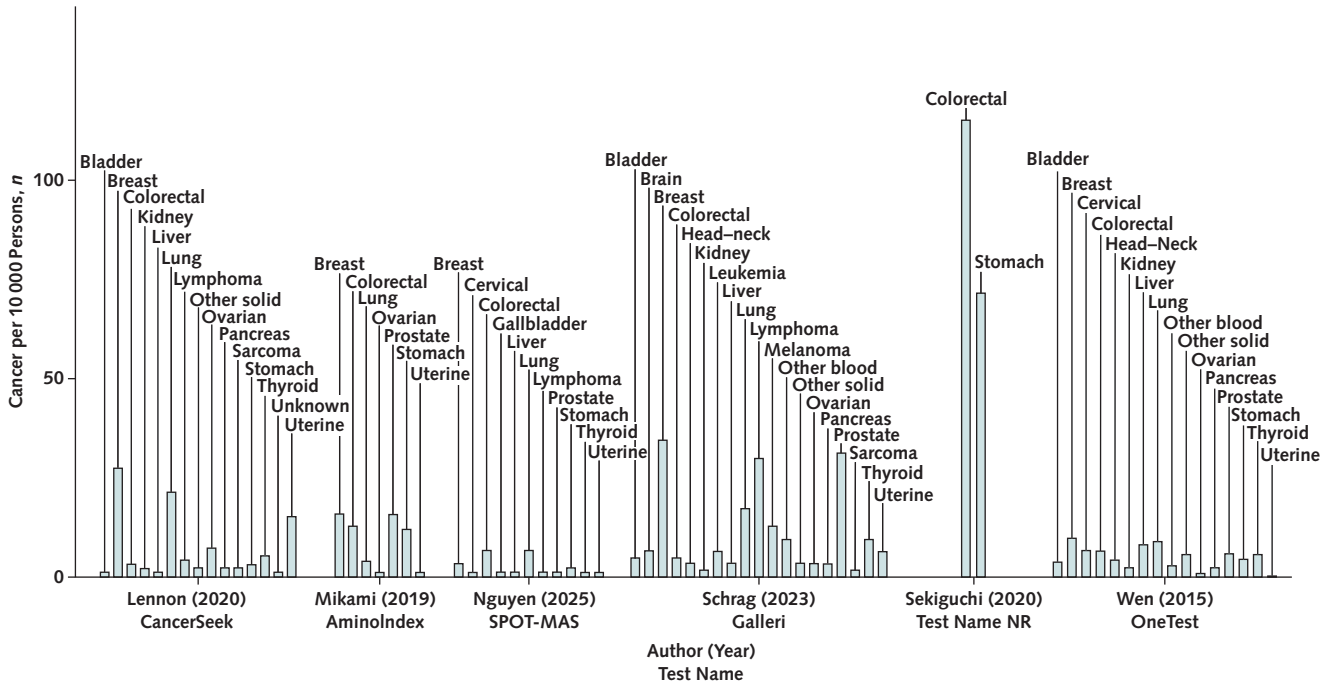
¶ Single arm analysis without a concurrent control group.

** Data provided in the study do not allow for the evaluation of precision of an effect estimate.

†† Relevance to historical comparisons of radiation exposure from medical imaging before study and exposure after study enrollment is unclear because that exposure was clinically indicated, whereas exposure from MCD testing among the 101 participants with false positive results was unnecessary.

‡‡ Radiation exposure is an indirect outcome for future adverse outcomes like secondary cancer types.

Figure. Numbers and types of cancer diagnosed in studies using prediagnostic performance designs.*



MCD = multicancer detection; NR = not reported.

* One prediagnostic performance reporting study (Bratulic and colleagues [54]) is not depicted in this figure because it used a nested case control design so the per capita number of cancer types is not comparable to the studies using cohort designs. Data from across the remaining studies were standardized to reflect the frequency of cancer among 10 000 persons. Additional notes on studies:

Lennon and colleagues (DETECT A) (49): An earlier version of the test was designed to detect 8 types of cancer (breast, colorectal, esophagus, liver, lung, ovary, pancreas, stomach) (34). The study enrolled only women; of the 96 cancer types diagnosed during follow up, 26 (27%) were detected with the MCD test. Of those, 5 (19%) were stage I, 3 (12%) were stage II, 8 (31%) were stage III, 9 (35%) were stage IV, and 1 (4%) was missing stage information. An additional 3 participants with cancer had a positive MCD test result, but these were considered as negative MCD tests because of clonal hematopoiesis of indeterminate potential.

Mikami and colleagues (60): The test was designed to detect 7 cancer types using 6 cancer signals (1 is a combined signal for uterine or ovarian cancer). Cancer types were not reported by stage at diagnosis.

Nguyen and colleagues (K DETEK) (59, 64): The test was designed to detect 10 types of cancer (breast, colorectal, esophagus, head/neck, liver/bile duct, lung, ovary, pancreas, stomach, uterine). Of the 24 types of cancer diagnosed over follow up, 17 (71%) were detected with the MCD test. Of these, 9 (53%) were localized, 3 (17%) were locally advanced, and 5 (29%) were metastatic. Specific stage information was not reported.

Schrag and colleagues (PATHFINDER) (52, 66): The test was designed to detect more than 50 types of cancer. Of 121 cancer types diagnosed during follow up, 35 (29%) were detected with the MCD test. Of those, 17 were hematologic malignancies (16 new, 1 recurrent) and 19 were solid tumors. Of the 19 solid tumors, 3 (16%) were stage I, 3 (16%) were stage II, 3 (16%) were stage III, 4 (21%) were stage IV, 1 (5%) was a local recurrence, and 5 (26%) were a distant recurrence.

Sekiguchi and colleagues (73): The analysis focused only on the accuracy in detecting stomach or colorectal types of cancer. Of the 230 types of cancer diagnosed after upper and lower endoscopy as a reference standard, 167 (73%) were early stage with no invasion past submucosa. Of these, 19 (11%) had a positive MCD test based on the lowest threshold for positivity for the 2 protein biomarkers used.

Wen and colleagues (72): The test was designed to detect more than 20 cancer types. Of the 314 types of cancer diagnosed during follow up, 179 (57%) were detected with the MCD test. Stage at diagnosis was only reported for a subset of 161 participants with 6 cancer types (breast, colorectal, liver, lung, pancreatic, prostate). Of these 161 participants, 118 (73.3%) had a positive MCD test. Of those, 14 (11.9%) were diagnosed with stage I, 23 (19.5%) were diagnosed with stage II, 19 (16.1%) were diagnosed with stage III, 40 (33.9%) were diagnosed with stage IV, and 22 (18.6%) had incomplete staging at diagnosis.

device exemption associated with a real-world evidence registry (78, 79). Thus, several considerations are relevant. No tests have published evidence on use for screening. Although a test could be accurate for identifying types of cancer, accuracy evidence alone does not mean MCD tests have a greater benefit than currently recommended screening tests. Patients may choose to screen with an MCD test for reassurance that they are cancer free. However, to minimize the risk for false positives across many types of cancer, specificity must be set high, which results in a lower sensitivity (the ability to identify persons with cancer). Furthermore, although specificity is high, given the potential use in a general population with a low prevalence of cancer, this could still result in a high rate of false positives as evidenced by low positive predictive value estimates ranging from 0.01 to 0.43, which will result in potentially unnecessary diagnostic testing.

It is unclear what stages of cancer MCD tests detect. Ideally, screening tests would detect precancerous

lesions that can be treated or removed before development of cancer. It is unclear whether MCD tests detect cancer types at later, untreatable stages or whether they detect very early-stage precancerous lesions that might never have developed into cancer. There is variability in the number and types of cancer reported, ranging from highly indolent to extremely aggressive with varying latent periods and levels of bloodstream shedding at different stages (80). The CCGA (Circulating Cell-free Genome Atlas) and PATHFINDER studies, both included in this review for test accuracy, reported that for prostate cancer, Galleri had higher sensitivity for detecting high-grade and later-stage cancer, likely reflecting more tumor shedding (81). Evidence from CCGA also demonstrates worse prognosis for tumors detected with MCD tests compared with those not detected (82). This reduces concerns about overdiagnosis, but some experts suggest MCD test–detected tumors have worse prognosis because biomarkers used preferentially identify tumors with poorer prognosis or undetected micrometastatic disease eventually leading to later recurrence after treatment of an earlier stage (83, 84). In such cases, the incidence of late-stage cancer seems reduced, but earlier treatment may not have altered the clinical trajectory. The technology underpinning MCD tests is continually evolving; however, it is unclear whether developers are designing tests to detect cancer types that will improve clinical and population health outcomes or whether the current technology is driving which cancer types are included in each test. Whether a single screening test can avoid overdiagnosis and identify a curable window across a range of many different types of cancer is best answered through empirical studies.

We found insufficient evidence after a systematic review of studies on MCD tests. However, there are challenges with obtaining the ideal evidence before widespread clinical adoption and payer coverage. Requiring an RCT of screening compared with no screening mitigates bias inherent to other study designs and outcomes. Demonstrating reductions in cancer mortality captures the collective impact of screening, diagnosis, and treatment that have been required of most single-cancer screening tests (85). Yet, trials reporting mortality require large sample sizes and take years to complete (80). Technologies for MCD tests are continually evolving such that the MCD tests evaluated in trials may change during the trials. For example, the version of the Galleri MCD test used in the PATHFINDER cohort study was refined mid-study (52). Furthermore, changes in diagnostic evaluation and treatment over time might render trial results less relevant (77, 86). Some suggest surrogate outcomes such as reduction in late-stage cancer detection and stage shift that have the potential to be reported sooner than mortality outcomes (86). Results from 2 systematic reviews evaluating breast, colorectal, lung, ovarian, and prostate cancer suggest the relationship between late-stage cancer detection and cancer mortality is moderate to strong for some types of cancer (like lung) but is not consistent across cancer types (see contextual question 1 in the full report) (87, 88). However, survival varies within a stage based on other tumor characteristics including size, grade, nodal status, and relevant prognostic markers; thus, cancer stage alone may be a poor surrogate for mortality. Some have suggested use of a "recurrence-updated stage" outcome to account for recurrence that develops during follow-up of early-stage disease to avoid biased estimates of effectiveness from the use of stage detection as an outcome (83, 84).

If MCD tests demonstrate a net benefit in empirical studies, the benefits of early detection are only achieved if patients with positive results receive prompt evaluation and high-quality cancer treatment. An effective screening test that is not coupled with policies, programs, and interventions to ensure access to diagnosis and treatment will not realize its full potential. Although some suggest that MCD tests could reduce differences in cancer-related outcomes among different sociodemographic groups by providing an accessible and acceptable screening option, unmet health-related social needs and inconsistent coverage from payers could worsen differences if people with limited or no health coverage cannot obtain the test or evaluation and treatment after a positive test or diagnosis (89, 90).

Limitations of the Evidence and of the Review Process

The most critical limitation is the absence of completed, controlled studies assessing the direct benefits of screening. Furthermore, we identified only 1 study with an unclear ROB that reported on harms, providing limited evidence about harms from using MCD tests. Most test accuracy studies were rated as high ROB inherent in the study designs used because of potential for selection and spectrum bias from use of clear-cut cases and healthy control participants. A likely result is an overestimation of discrimination accuracy (91–93). In addition, such designs are not suited for evaluating the tradeoffs between sensitivity and specificity. Only 2 tests (Galleri, Carcimun) had evidence from more than 1 study (51, 52, 61, 62); others were evaluated in single studies, limiting our ability to quantitatively synthesize findings. Even within a class of analytes (for example, cell-free DNA), accuracy is influenced by the number and types of cancer for which the test was developed, analysis technique used, thresholds for positivity, and study participant characteristics. Moreover, prediagnostic study designs used different approaches to the diagnostic work-up after a positive test, which may influence accuracy.

We used a broad search and did not limit by analyte or technology but only included English-language studies for practical reasons. We required comparative study designs to evaluate benefits and harms of screening. For accuracy, we only included data from external validation populations to improve the applicability of the findings. We did not include data from

conference posters, abstracts, or presentations from conferences if we did not have complete information on methods and population characteristics to evaluate the ROB. Lastly, we graded the strength of evidence for accuracy outcomes by generating a single, aggregated assessment across the entire body of evidence rather than separate grades for each test.

Future Research Directions

Supplement Table 14 (available at Annals.org) summarizes ongoing studies. The National Health Service (NHS)-Galleri study, an RCT with a primary outcome of stage III or IV cancer detection, has enrolled more than 140 000 participants in the United Kingdom; the estimated completion date is June 2026 (94). This trial will also report mortality outcomes after 8 years of follow-up. The NHS reviewed preliminary results from the first year of the trial and will wait for the final results before deciding on further implementation of screening with the Galleri MCD test outside of the trial context (95). The National Cancer Institute (NCI) is sponsoring the Vanguard feasibility study, a 3-arm RCT to evaluate the feasibility of a future larger trial of MCD tests, including determining diagnostic workflows after a positive screening test (96). The NCI has selected 2 MCD tests, Shield and Avantect, for use in the Vanguard trial. The data used by NCI to make these MCD test selections were not available in full-text, peer-reviewed publications through the final date of our literature surveillance. Both tests are commercially available for clinical use in single-cancer screening—Shield for colorectal (22) and Avantect for pancreatic or ovarian (97). Approval by the FDA, potential legislatively-directed Centers for Medicare & Medicaid Services coverage (98, 99), and commercial MCD test marketing may discourage patient and clinician participation in future RCTs. Future screening trials must rigorously monitor for contamination, a serious threat to validity, because commercially available MCD tests may be accessed outside of a study (35).

Additional research needs include empirical studies on 1) surrogate outcomes for cancer-specific mortality, 2) benefits and harms of MCD tests in various populations (for example, genetic predisposition, health behaviors, or environmental exposures), 3) harms and cost-effectiveness, 4) the optimal timing of use and intervals for rescreening, and 5) communicating benefits and risks for screening with MCD tests to clinicians and patients, who often overestimate benefits and underestimate risks of screening (100). Several of these needs were also identified in a workshop related to opportunities and challenges for development and adoption of MCD tests hosted by the National Cancer Policy Forum of the National Academies of Sciences, Engineering, and Medicine in October 2024 (35).

Conclusion

No controlled studies are completed that report benefits of screening with MCD tests. The evidence was judged insufficient to evaluate harms and accuracy. Accuracy varies by test and study design.

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Reproducible Research Statement: *Study protocol:* Available at https://effectivehealthcare.ahrq.gov/products/cell free dna/protocol. *Statistical code:* Available to interested readers by contacting Dr. Kahwati at LKahwati@rti.org. *Data set:* Available in Appendix C of the full report (Effective Health Care [EHC] Program [39]).

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Appendix Table. Characteristics of Included Diagnostic Performance Studies

Study, Year (Reference); Country; Registry Number	Study Design; ROB; Sponsor(s)	Study Population	Cancer Types in Validation Cohort(s)*	Accuracy† Estimate (95% CI)
Commercially available for clinical use in the United States				
Galleri (cfDNA methylation)				
Klein et al, 2021 (51); Shao et al, 2023 (63); Liu et al, 2020 (67); Tang et al, 2023 (68); United States and Canada; CCGA (third substudy) NCT02889978	Case–control; high ROB; GRAIL	4077 (55.4% female) ages 21–85 y; 81.2% non-Hispanic White; 6.8% non-Hispanic Black; 7.2% Hispanic; 1.8% Asian; 0.4% Indigenous; 2.5% Other	Included >25 cancer types: anus, bladder, breast, cervix, colorectal, esophagus, gallbladder, head/neck, kidney, liver/bile duct, leukemia, lung, lymphoma, melanoma, myeloid neoplasm, ovary, pancreas, plasma cell, prostate, sarcoma, stomach, thyroid, urothelial tract, uterine, other, multiple, and unknown primary cancers	Sn (95% CI): 0.52 (0.50–0.53) Sp (95% CI): 1.0 (0.99–1.0) TOO prediction accuracy 88.7% (95% CI, 87.0%–90.2%)
OverC (cfDNA methylation)				
Gao et al, 2023 (53); China; NCT04820868	Case–control; high ROB; Clinical Innovation Program of Shanghai Municipal, National Key Research and Development Program of China	946 (48.3% female); ages 40–75 y; race and ethnicity NR	Included 7 cancer types: colorectal, esophagus, liver, lung, ovary, pancreas, prostate	Model 1 Sn: 0.69 (0.65–0.73) Sp: 0.99 (0.98–1.0) Model 2 (designed for higher-risk populations) Sn: 0.95 (0.93–0.97) Sp: 0.75 (0.72–0.80) TOO prediction accuracy: Initial test Primary prediction: 83.2% (78.7%–87.1%) Primary or secondary prediction: 91.7% (88.2%–94.5%) Refined test Primary prediction: 79.4% (74.9%–83.5%) Primary or secondary prediction: 87.3% (83.4%–90.6%)
Commercially available for clinical use outside of the United States				
OncoSeek (protein immunoassay)				
Luan et al, 2023 (57); United States and China; NR	Case–control; high ROB; National Key Research and Development Program of China	5919 (44.5% female validation cohort 1 [V1], 50.7% female validation cohort 2 [V2]); age NR for V1, ages 17–93 y for V2; race and ethnicity NR	Included 8 cancer types: breast, colorectal, esophagus, liver, lung, ovary, pancreas, stomach	7-Marker panel (Chinese cohort) Sn (95% CI): 0.39 (0.34–0.44) Sp (95% CI): 0.94 (0.93–0.95) 6-Marker panel (U.S. cohort) Sn (95% CI): 0.52 (0.49–0.56) Sp (95% CI): 0.89 (0.87–0.91) Test does not provide a TOO prediction
Tests not commercially available				
Carcimun (optical assessment of conformational changes in plasma proteins)				
Salat et al, 2022 (61); Austria; NR	Case–control; high ROB; private funding from Berthold von und zu Zwerger	307 (43.0% female); ages NR; race and ethnicity NR	Included 17 cancer types: anal, bile duct and gallbladder, breast, carcinosis, colorectal, esophageal, kidney, liver, liver metastases, lymphoma, melanoma, neuroendocrine, ovarian, pancreatic, sarcoma, skin, stomach	Sn (95% CI): 0.89 (0.83–0.93) Sp (95% CI): 0.91 (0.84–0.95) Test does not provide a TOO prediction

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Appendix Table Continued

Study, Year (Reference); Country; Registry Number	Study Design; ROB; Sponsor(s)	Study Population	Cancer Types in Validation Cohort(s)*	Accuracy† Estimate (95% CI)
Walter et al, 2025 (62); Germany; NR	Case–control; high ROB; sponsor NR	144 (45% female); age range NR; race and ethnicity NR	Included 9 cancer types: bile duct, colorectal, esophageal, gastrointestinal stromal tumor, liver metastases, lung, pancreas, peritoneal, stomach	Sn (95% CI): 0.91 (0.81–0.97) Sp (95% CI): 1.0 (0.96–1.0) Test does not provide a TOO prediction
Multiplexed Nanomaterial-Assisted Laser Desorption/ionization for Cancer Identification (metabolomics)				
Zhang et al, 2022 (56); China; NR	Case–control; high ROB; multiple Chinese government funders	175 (43.4% female); ages 21 to 84 y; race and ethnicity NR	Included 5 cancer types: colorectal, liver, lung, stomach, thyroid	Sn: 0.84 (0.77–0.90) Sp: 0.83 (0.65–0.94) TOO prediction accuracy: Primary prediction: 77.7% (70.1%–84.1%) Primary or secondary prediction: 86.5% (79.9%–91.5%)
TOTEM (cfDNA methylation)				
Xiong et al, 2024 (58); China; NR	Case–control; high ROB; multiple Chinese government funders	322 (35% female); age 19–92 y; race and ethnicity NR	Included 2 cancer types: liver and stomach	Sn: 0.56 (NR) Sp: 0.98 (0.95–1.0) AUC: 0.87 (0.83–0.91) TOO prediction accuracy: Primary prediction: 0.76 (95% CI, NR) Primary or secondary prediction: 0.84 (95% CI, NR)
Test name NR (cfDNA methylation and genomic analysis)				
Bae et al, 2023 (71); United States, Denmark, The Netherlands; NR	Case–control; high ROB; National Research Foundation of the Republic of Korea	422 (62% female); ages 14–86 y; race and ethnicity NR	Included 7 cancer types: breast, liver, lung, ovarian, colorectal, pancreatic, bile duct	AUC (95% CI) Genome model: 0.99 (0.98–0.99) Epigenome model: 0.94 (0.91–0.96) Combined (genome and epigenome model): 0.99 (0.99–1.0) Authors report sensitivity for various levels of specificity and by cancer stage on a figure but actual values were NR. Test does not provide a TOO prediction for the external validation population.
Test name NR (6-marker cfDNA methylation panel and 3-marker protein panel AFP, CEA, CA19-9)				
Dai et al, 2023 (55); China; NR	Case–control; high ROB; multiple Chinese government and foundation funders	157 (42% female); ages 33–87 y in 1 cohort; 51 (43% female) in another cohort; race and ethnicity NR	Included 3 cancer types: colorectal, esophageal, stomach	6-Marker cfDNA panel (first validation cohort): Sn: 0.83 (0.73–0.90) Sp: 0.87 (0.76–0.93) By stage, Sn Stage I: 0.69 (NR) Stage II: 0.80 (NR) Stage III: 0.87 (NR) Stage IV: 0.80 (NR) Sp NR by stage: 6-Marker cfDNA panel (second validation cohort) Sn: 0.83 (0.59–0.96) Sp: 0.94 (0.78–0.99) 3-Marker protein panel (second validation cohort) AUC: 0.80 (NR) Test does not provide a TOO prediction
Test name NR (thermophoretic profiling of extracellular vesicle proteins)				
Liu et al, 2019 (69); China; NR	Case–control; high ROB; multiple Chinese government funders	102 (52% female); age NR; race and ethnicity NR	Included 6 cancer types: breast, liver, lung, lymph, ovary, prostate	Sn: 0.99 (0.94–1.0) Sp: 1.0 (0.80–1.0) By stage: Stage I Sn: 0.95 (0.74–1.0) Sp: 1.0 (0.80–1.0) Stage II

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Appendix Table Continued

Study, Year (Reference); Country; Registry Number	Study Design; ROB; Sponsor(s)	Study Population	Cancer Types in Validation Cohort(s)*	Accuracy† Estimate (95% CI)
				Sn: 1.0 (0.87–1.0) Sp: 1.0 (0.80–1.0) Stage III/IV Sn: 1.0 (0.91–1.0) Sp: 1.0 (0.80–1.0) TOO predication accuracy 68% (NR)
Test name NR (fragmentomic profiling of cell-free mitochondrial DNA)				
Liu et al, 2024 (74); China; NR	Case–control; high ROB; multiple Chinese government funders	479 (43.7% female); ages 23–96 y; race and ethnicity NR	Included 6 cancer types: breast, colorectal, kidney, liver, lung, ovarian	Sn: 0.95 (0.92–0.97) Sp: 0.91 (0.84–0.95) TOO prediction accuracy: Primary prediction: 87.9% Primary or secondary prediction: 96.3%
Test name NR (IgG galactosylation ratios)				
Ren et al, 2016 (70); China; NR	Case–control; high ROB; multiple Chinese government funders and Zhixianbiotech	5,704 (% female NR); ages 18 to 93 years; race and ethnicity NR	Included 12 cancer types: bladder, breast, cervical, colorectal, esophageal, kidney, liver, lung, ovary, pancreas, prostate, stomach	Sn: 0.78 (NR) Sp: 0.83 (NR) By stage: Stage I Sn: 0.75 (NR) Sp: 0.83 (NR) Other stages NR Test does not provide a TOO prediction
Test name NR (Targeted immune-related cell-free microRNA profiling)				
Wu et al, 2024 (65); China; NR	Case–control; high ROB; multiple Chinese government funders	684 (% female NR); age NR; race and ethnicity NR	Included 13 cancer types: bladder, breast, cervical, colorectal, esophagus, glioma, kidney, liver, lung, ovarian, pancreas, prostate, stomach	XGBoost model Sn: 0.82 (0.79–0.84) Sp: 1.0 (0.99–1.0) Has 1-miR-17-3p model Sn: 0.77 (0.72–0.81) Sp: 0.66 (0.60–0.71) Test does not provide a TOO prediction

AFP = alpha fetoprotein; AUC = area under the curve; CCGA = Circulating Cell free Genome Atlas; CEA = carcinoembryonic antigen; cfDNA = cell free DNA; IgG = immunoglobin G; MCD = multicancer detection; NR = not reported; ROB = risk of bias; Sn = sensitivity; Sp = specificity; TOO = tissue of origin.

* Refers to persons with cancer who were identified as cases for use in case control study designs; these persons had cancer diagnosed after clinical presentation of signs or symptoms, or through work up of positive standard of care screening tests. These cancer types were not diagnosed as a result of an MCD test.

† Includes sensitivity (percentage with positive MCD result among cancer cases), specificity (percentage of those with a negative MCD result among those identified as control participants who were free of cancer), AUC (composite measure of sensitivity and specificity), and TOO prediction accuracy, when applicable.