The Potential for Multi-Cancer Early Detection Testing to Save Lives and Deliver Cost Savings

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Executive Summary

Cancer kills more than 600,000 Americans each year, more than any other cause except heart disease. With almost 40 percent of people expected to develop cancer at some point during life, even Americans fortunate enough to avoid it are almost certain to see a loved one suffer from it. Almost 2 million new cases will be diagnosed in 2023. In addition to the terrible personal costs cancer imposes, it also costs our health care system more than $200 billion annually. Billions of additional dollars are lost through diminished productivity.

The United States has made progress in combating cancer over the last 30 years, with age adjusted mortality rates dropping significantly. Much of this improvement is due to a nationwide decline in cigarette smoking, more advanced medical treatments, and better screening for five types of cancer: lung, colorectal, breast, cervical, and prostate cancers. Earlier detection of cancer, which screenings help achieve, leads to better outcomes, including more lives saved.

Formidable challenges, however, remain. The risk of developing cancer soars as a person ages, with people aged 50 and older having more than 13 times the rate of cancer as people under the age of 50. The U.S. population is aging rapidly; this aging will lead to more and more cancer diagnoses. Due solely to changes in the U.S. population (primarily aging), and optimistically disregarding any inflation in medical costs, the cost of cancer treatment is expected to increase 34 percent between 2015 and 2030.

Despite improvements in screening over the last few decades, current screening has gaps. Importantly, most cancer deaths each year are from cancers for which there is no recommended screening test. Far too many cancers are detected late, when treatment is significantly more expensive and difficult but less successful.

Today, only one in seven cancers is diagnosed through screening. There is a need to supplement existing screening tests in order to increase detection of the five cancer types mentioned above. And there is a desperate need for screening for other cancer types. People unknowingly suffering from one of the "non-screened" cancers can do nothing until they become symptomatic and/or a health care provider detects the problem.

Multi-cancer early detection (MCED) is an emerging innovation that allows a simple blood draw for a patient to be tested for biological signals that can detect the presence of abnormalities suggesting cancer. Providers can generally identify the organ in which the potentially cancerous signals are originating, and can conduct follow up testing to reach a diagnosis. MCED tests vary in the signals they search for cancer, as well as in the cancers for which they test. While no screening test is perfect, MCED tests on the whole display impressive positive predictive power greater than that displayed by approved screening methods for the five cancer types for which there are currently recommended screenings that are widely recognized as effective and valuable, particularly when the analysis is confined to a dozen cancers that account for two-thirds of cancer deaths. Moreover, MCED generates few false positives relative to traditional screening tests, which eases concerns that its benefits will largely be offset by the expenses incurred by patients and providers in trying to ascertain or combat the false diagnoses.

By enabling the earlier identification of cancer in a patient, MCED has the potential to save lives, adding millions of life-years to the U.S. population. Modeling suggests that the addition of MCED tests to recommended screenings could reduce five year mortality by approximately 25 percent.[1] Additional data supports that detecting cancer at earlier stages dramatically increases survival.

Earlier identification of cancer can help achieve significant savings on treatment. It is well-established that cancer diagnosed at later stages is more expensive to treat, and that survival rates of patients decline markedly the later they are diagnosed. To provide just one example, one paper has reported that the respective costs of colon/rectum cancer treatment in the first year following diagnosis for Stage I and Stage IV cancers were $45,907 and $146,370, respectively. One study of Medicare beneficiaries showed that first-year costs for beneficiaries with Stage IV cancer were up to 7.7 times those for beneficiaries with early stage cancer. In addition, there is evidence that the costs for a given phase of treatment- such as the last 12 months of life in patients dying of cancer- are lower if the cancer was diagnosed at an earlier stage. Another study offered a conservative estimate of the annual cost savings that could be generated by early cancer detection, arriving at a total of $25.9 billion. Still another study estimated that cancer mortality within five years of diagnosis could be slashed by 15 to 24 percent if cancer could be detected earlier.

Part I of this paper provides some key background regarding cancer in the United States, and Part II offers an overview of the current status of MCED in the United States. Parts III, IV, and V discuss the detection capabilities of MCED tests, their potential to save lives, and their potential to generate cost savings, respectively. After consideration of two key concerns potentially implicated by MCED in Part VI, this paper concludes with recommendations for policymakers in Part VII. These recommendations cover:

- Congress' role in establishing MCED access pathways for Medicare beneficiaries;
- Opportunities for Texas' administrators to provide MCED coverage for at-risk state employees and retirees; and
- Texas lawmakers and publicly-supported stakeholders ensuring that data collection and cancer surveillance efforts are closely monitoring the burden of unscreened cancers and progress on driving a higher cancer detection rate statewide.

The world has an urgent need for better cancer detection. MCED is a rare innovation that can vastly expand the types of cancer being screened for, make early detection possible, be administered with virtually no inconvenience to the patient, and generate few false positives, all while delivering cost savings. Policymakers should focus on aligning public policy to take advantage of MCED, most notably by creating authority for the Centers for Medicare and Medicaid to offer Medicare beneficiaries coverage of MCED testing, provided the applicable test(s) have been approved by the United States Food and Drug Administration. Legislation was filed in Congress to this effect earlier in 2023 and deserves strong support. In addition to the Medicare legislation, similar efforts should be pursued by Texas for teachers and government employees who receive health care benefits through the state.

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[1] Earl Hubbell, et al., "Modeled Reductions in Late-stage Cancer with a Multi-Cancer Early Detection Test," *Cancer Epidemiology, Biomarkers & Prevention* (March 2021), https://aacrjournals.org/cebp/article/30/3/460/72416/Modeled-Reductions-in-Late-stage-Cancer-with-a.

Part I: Key Cancer Facts

Cancer is the second leading cause of death in the United States, behind only heart disease, and is the leading cause of death for people under the age of 65.[2] In 2020, cancer claimed the lives of 602,347 Americans.[3] That number is projected to rise to 609,820 in 2023.[4] Almost 1.96 million Americans are expected to be diagnosed with cancer in 2023, up from approximately 1.75 million in 2019.[5] Based on data from 2015 through 2017, 39.5 percent of Americans will be diagnosed with cancer at some point in their lives.[6]

A combination of factors- including a decline in smoking, increased public awareness, better screening, and improved treatments- have helped lower cancer rates and increase survival rates in the U.S. over the last few decades. The rate of deaths from cancer in the general population dropped by an impressive 27 percent from 2000 to 2020, from 196.5 to 144.1 deaths per 100,000 people.[7] The decline is even more impressive comparing changes since 1991, when the death rate from cancer peaked.[8] While the number of new cancer cases diagnosed in 2019 was actually greater than that in 1999,[9] after controlling for the aging of the American population, the (age-adjusted) rate of new cancers fell from 481.2 per 100,000 people in 1999 to 450.8 in 2019.[10]

Despite this progress, cancer continues to claim hundreds of thousands of lives annually, and treating it costs billions of dollars every year. Due to growth in, and the aging of, the American population, some sources estimate that the number of cancers diagnosed will increase by almost 50 percent from 2015 to 2050.[11] There is a pronounced relationship between aging and cancer: for people under age 20, the cancer rate is lower than 25 people per 100,000, but that rises to roughly 350 per 100,000 for people

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[2] National Cancer Institute, "Cancer Stat Facts: Common Cancer Sites" (access by clicking on the "Cancer in Context" tab), https://seer.cancer.gov/statfacts/html/common.html.

[3] Centers for Disease Control and Prevention, "Cancer Statistics at a Glance," https://gis.cdc.gov/Cancer/USCS/#/AtAGlance/.

[4] National Cancer Institute, supra n. 2.

[5] Centers for Disease Control and Prevention, "U.S. Cancer Statistics: Highlights from 2019 Incidence," https://www.cdc.gov/cancer/uscs/about/data-briefs/no29-USCS-highlights-2019-incidence.htm.

[6] National Cancer Institute, "Cancer Statistics," https://www.cancer.gov/about-cancer/understanding/statistics#:~:text=Approximately%2039.5%25%20of%20men%20and,will%20die%20of%20the%20disease.

[7] Centers for Disease Control and Prevention, "An Update on Cancer Deaths in the United States," https://www.cdc.gov/cancer/dcpc/research/update-on-cancer-deaths/index.htm.

[8] Rebecca L. Siegel, et al., "Cancer Statistics," *CA: A Cancer Journal for Clinicians* (January 2023), https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21763.

[9] According to the Centers for Disease Control and Prevention, cancer incidence rates for 2020 may be inaccurate due to the disruptions in medical care attributable to the COVID-19 pandemic. See https://www.cdc.gov/cancer/uscs/about/data-briefs/no35-USCS-highlights-2020.htm. Thus, this paper uses 2019 data on the number of new cancer cases rather than 2020 data when possible.

[10] Centers for Disease Control and Prevention, "Changes Over Time: All Types of Cancer," https://gis.cdc.gov/Cancer/USCS/#/Trends/.

[11] E.g., Hannah K. Weir, et al., "Cancer Incidence Projections in the United States Between 2015 and 2050," *Preventing Chronic Disease: Public Health Research, Practice, and Policy* (June 2021), https://www.cdc.gov/pcd/issues/2021/21_0006.htm#:~:text=Because%20of%20the%20growth%20and,adults%20aged%20%E2%89%A575%20years.

ages 45 to 49, and then soars to more than 1,000 per 100,000 for people age 60 or older.[12] Given this relationship and America's aging population, improving the diagnosis and treatment of cancer should be a national priority.

Table 1 below lists the 13 types of cancer for which each type is expected to have at least 40,000 new cases in 2023. While cancer can afflict many body organs, these 13 types of cancer are expected to account for more than four out of every five cancer diagnoses in 2023.

Table 1: New Cases of Cancer by Type, 2023 (estimated)

Cancer Type	New Cases, 2023 (estimated)[13]	Percentage of All New Cancer Cases, 2023 (estimated)
Breast (Female)	297,790	15.21%
Prostate	288,300	14.72%
Lung and Bronchus	238,340	12.17%
Colon and Rectum	153,020	7.81%
Melanoma*	97,610	4.98%
Bladder	82,290	4.20%
Kidney*	81,800	4.18%
Non-Hodgkin's Lymphoma	80,550	4.11%
Endometrial (Uterine)*	66,200	3.38%
Pancreas	64,050	3.27%
Leukemias	59,610	3.04%
Thyroid*	43,720	2.23%
Liver and Intrahepatic Bile Duct	41,210	2.10%
SUBTOTAL	1,594,490	81.42%
Other Cancers	363,820	18.58%
TOTAL[14]	1,958,310	100.00%

*Does not appear in Table 2 immediately below (i.e., on the list of top 10 cancer types by deaths)

Table 2 lists the top ten cancers in terms of deaths caused annually; there is significant overlap between the cancers listed in Tables 1 and 2.

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[12] National Cancer Institute, "Age and Cancer Risk," https://www.cancer.gov/about-cancer/causes-prevention/risk/age#:~:text=Age%20and%20Cancer%20Risk,-Advancing%20age%20is&text=The%20incidence%20rates%20for%20cancer,groups%2060%20years%20and%20older.

[13] National Cancer Institute, "Common Cancer Types," https://www.cancer.gov/types/common-cancers.

[14] American Cancer Society, *Cancer Facts & Figures 2023*, https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2023/mr6-leading-sites-2023-cff.pdf (Figure 3).

Table 2: Top 10 Cancers by Death, 2020 (actual) and 2023 (estimated)

Cancer Type	Deaths, 2020	Percentage of Cancer Deaths, 2020	Deaths, 2023 (estimated)[15]	Percentage of Cancer Deaths, 2023 (estimated)
Lung and Bronchus	136,084	22.59%	127,070	20.84%
Colon and Rectum (Colorectal)	51,869	8.61%	52,550	8.62%
Pancreas	46,774	7.77%	50,550	8.29%
Breast (Female)	42,273	7.02%	43,170	7.08%
Prostate	32,707	5.43%	34,700	5.69%
Liver and Intrahepatic Bile Duct	28,227	4.69%	29,380	4.82%
Leukemias	23,583	3.92%	23,710	3.89%
Non-Hodgkin Lymphoma	20,170	3.35%	20,180	3.31%
Brain and Other Nervous System*	18,034	2.99%	18,990[16]	3.11%
Bladder	16,682	2.77%	16,710	2.74%
SUBTOTAL	416,403	69.13%	417,010	68.38%
Other Cancers	185,944	30.87%	192,810	31.62%
TOTAL	602,350	100.00%	609,820	100.00%

*Does not appear in Table 1 immediately above.

For some cancers, screening can play an important role in identifying the cancer. According to the Centers for Disease Control and Prevention (CDC): "Screening means checking your body for cancer before you have symptoms. Getting screening tests regularly may find breast, cervical, and colorectal (colon) cancers early, when treatment is likely to work best."[17] The method of screening can vary depending on the type of potential cancer. For example, breast cancer screening is done through mammograms (a type of X-ray), while lung cancer screening in certain people with a history of smoking is done through low-dose computed tomography (CT).[18] If screening reveals concerning results, health care providers may take additional steps, such as conducting a biopsy.

The United States Preventive Services Task Force (USPSTF), a panel of medical experts, recommends the following cancer screenings (all age ranges below are inclusive):

- For breast cancer, women aged 50 to 74 are encouraged to have a mammogram every other year. Women aged 40 to 49 are encouraged to talk to their health care providers about the possibility of obtaining a mammogram.[19]

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[15] National Cancer Institute, supra n. 13.
[16] American Cancer Society, supra n. 14.
[17] Centers for Disease Control and Prevention, "Screening Tests," https://www.cdc.gov/cancer/dcpc/prevention/screening.htm#:~:text=CDC%20supports%20screening%20for%20breast,cancer%20before%20you%20have%20symptoms.
[18] Id.
[19] Centers for Disease Control and Prevention, "Breast Cancer," https://www.cdc.gov/cancer/breast/basic_info/screening.htm.

- For cervical cancer, women aged 21 to 65 are encouraged to undergo screening, although the exact screening method and the frequency of the screening can vary. Women over 65 may no longer need screening and are directed to consult with their health care provider.[20]
- For colorectal cancer, people aged 45 to 75 should undergo annual screening, and people aged 76 to 85 are encouraged to discuss screening with their health care provider.[21]
- For prostate cancer, men between the ages of 55 and 69 are encouraged to make a decision regarding prostate cancer screening based on a variety of factors, including their family history, ethnicity, and other medical conditions.[22]
- Lung cancer screening is an outlier in that the USPSTF recommends it only for a high-risk population: people aged 50 to 80 who have a smoking history of 20 pack-years and have smoked in the last 15 years.[23]

There is, however, a lack of effective screening tests for most types of cancer.[24] The gaps in current screening mean that more patients will be diagnosed with cancer at later stages, which translates into treatments that are less effective yet also more expensive.

Even with respect to the cancers that do have recommended screening tests, there is still room for improvement. Not all patients obtain recommended screenings. According to the American Association for Cancer Research, in 2015, 17 percent, 28.5 percent, 38 percent, and 96 percent of applicable screening-eligible individuals were not in compliance with screening guidelines for breast, cervical, colorectal, and lung cancer, respectively.[25] The low compliance with lung cancer screening is particularly concerning as that cancer is the leading cancer killer in the country and most lung cancers are currently diagnosed in either Stage III or IV. Five-year survival rates for lung cancer patients diagnosed later are poor (for specific numbers on lung cancer and other cancers, see table 3, discussed later in this paper). Additionally, like virtually all medical tests, existing cancer screenings can produce false negatives and false positives. For example, 95 percent of mammograms referred for further workup ultimately do not find cancer.[26]

Overall in 2017, only 14 percent of all previously undiagnosed cancers- approximately one in seven- were detected as a result of a patient undergoing a recommended screening test.[27] The remaining diagnoses were made through other means, often after the patient had become symptomatic. The

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[20] Centers for Disease Control and Prevention, "Cervical Cancer," https://www.cdc.gov/cancer/cervical/basic_info/screening.htm.
[21] Centers for Disease Control and Prevention, "Colorectal (Colon) Cancer," https://www.cdc.gov/cancer/colorectal/basic_info/screening/.
[22] U.S. Preventive Services Task Force, *Final Recommendation Statement. Prostate Cancer: Screening* (May 8, 2018), https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/prostate-cancer-screening.
[23] Centers for Disease Control and Prevention, "Who Should Be Screened for Lung Cancer?" https://www.cdc.gov/cancer/lung/basic_info/screening.htm.
[24] Centers for Disease Control and Prevention, supra n. 17.
[25] American Association for Cancer Research, *2022 Cancer Disparities Progress Report,* https://cancerprogressreport.aacr.org/disparities/chd20-contents/chd20-disparities-in-cancer-screening-for-early-detection/.
[26] USPSTF. 2016. Lehman, et al. Radiology. 2017;283(1):49-58.
[27] NORC at the University of Chicago, "Only 14% of Cancers Are Detected Through a Preventive Screening Test," https://www.norc.org/content/dam/norc-org/pdfs/State-Specific%20PCDSs%20chart%201213.pdf.

percentage of cancers that were detected by screening were 77 percent, 61 percent, 52 percent, 45 percent, and just 3 percent for prostate, breast, cervical, colorectal, and lung cancers, respectively.[28] While these screenings play an important role in cancer detection and unquestionably save lives, supplements to traditional screening are needed.

Part II: Overview and Current Status of Multi-Cancer Early Detection

Fortunately, recent innovations in cancer screening offer the potential for earlier detection that can save lives and reduce spending on cancer treatment, among other benefits. Multi-cancer early detection (MCED) testing has the ability to measure biological signals that cancer cells may create in the body;[29] specifically, MCED testing can identify signals in DNA, RNA, or proteins released by cancer cells into the blood of a person, even if that person is symptom-free.[30] Due to this ability, MCED is sometimes referred to as a liquid biopsy.

A variety of MCED tests exist. The mechanism by which a given MCED test works depends on the biomarker focus of that test: possible areas of focus include DNA methylation, cfDNA (cell-free DNA) fragmentation, gene expression, and circulating tumor cells.[31] MCED is a screening test that is designed to alert health care providers to the significant possibility that the patient may have cancer despite being symptom-free,[32] thereby allowing the provider to perform diagnostic testing (e.g., a biopsy) and, if appropriate, to offer more targeted care.

MCED tests, all of which are being developed to be used in conjunction with existing recommended cancer screenings, have several advantageous characteristics. First, they can detect signals caused by multiple types of cancer, including the many types of cancer for which no reliable screening test currently exists.[33] Development of MCED can eliminate the need to develop and administer many additional new single cancer screening tests in order to achieve the same early detection capacity. This approach - screening for many cancers at once - is the only way we can add to our existing single cancer screening paradigm to achieve maximum early detection in a way that is feasible and sustainable for patients and the health care system

Second, MCED can detect many cancers at earlier stages. As discussed below in detail, earlier detection translates to better outcomes. The chances of diagnosing cancer of whatever type at an early stage are maximized with MCED.

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[28] Id.

[29] National Cancer Institute, "Questions and Answers about MCD Tests," https://prevention.cancer.gov/major-programs/multi-cancer-detection-mcd-research/questions-and-answers-about-mcd-tests.

[30] National Cancer Institute, "Screening for Many Cancers with One Test: Uncertainty Abounds," https://www.cancer.gov/news-events/cancer-currents-blog/2022/finding-cancer-early-mced-tests

[31] See generally Tiago Brito-Rocha**,** et al., "Shifting the Cancer Screening Paradigm: The Rising Potential of Blood-Based Multi-Cancer Early Detection Tests," *Cells* (March 2023), https://www.mdpi.com/2073-4409/12/6/935

[32] National Cancer Institute, "Multi-Cancer Detection (MCD) Research," https://prevention.cancer.gov/major-programs/multi-cancer-detection-mcd-research.

[33] National Cancer institute, supra n. 29.

Third, MCED testing can be performed on a blood sample. Noncompliance with recommended screenings is a complex, multifactorial issue.[34] But this form of administration has the potential to address some of the barriers and improve patient compliance relative to more invasive tests and imaging.

Fourth, based on clinical study results publicly reported to date, MCED tests have high positive predictive value and low false positive and false negative rates. These rates are favorable relative to cancer screening tests that have already proven their value by earning positive recommendations from organizations such as USPSTF, the American Cancer Society, and medical specialty societies. These topics are discussed in greater detail below.

Fifth, MCED can often identify the organ where the tumor(s) is located. It does not simply reveal a generic cancer threat; one version had a 97 percent success rate in identifying the organ where the potential cancer signal originated.[35] This allows health care providers to offer more targeted follow-up care if the MCED results show a concern, rather than engaging in exhaustive testing to attempt to ascertain where the cancer is located.

Given these characteristics, MCED testing has the potential to build on current recommended cancer screenings by bringing earlier detection to more cancers and more patients. MCED opens up the possibility that a medical innovation could offer the dual benefits of saving lives and reducing treatment costs through greater efficiency.

Drawn by the tremendous potential of MCED, numerous companies, including GRAIL, Roche, Exact Sciences, and Natera, are developing products in that area.[36] In 2022, the National Cancer Institute's Board of Scientific Advisors approved a proposal to create a body that "will conduct rigorous, multi-center cancer screening trials and studies with large and diverse populations in a variety of health care settings."[37] More than two dozen clinical trials involving MCED are underway.[38]

Currently, no MCED test is approved by the U.S. Food and Drug Administration (FDA), although a small number have obtained "breakthrough device" designation from the FDA, an expedited and preliminary designation for tools that can treat or diagnose life-threatening or irreversibly debilitating diseases or conditions.[39] A handful of health care plans in the United States offer coverage of MCED tests, as they are laboratory-developed tests.

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[34] See, e.g., Gabriela Orsak, et al., "Return on Investment of Free Colorectal Cancer Screening Tests in a Primarily Rural Uninsured or Underinsured Population in Northeast Texas," *Pharmacoeconomics* (May 23, 2019), https://link.springer.com/article/10.1007/s41669-019-0147-y.

[35] GRAIL Press Release, "GRAIL Announces Final Results from the PATHFINDER Multi-Cancer Early Detection Screening Study at ESMO Congress 2022," (September 11, 2022), https://grail.com/press-releases/grail-announces-final-results-from-the-pathfinder-multi-cancer-early-detection-screening-study-at-esmo-congress-2022/.

[36] See National Cancer Institute, "Cancer Screening Research Network/Multi-Cancer Early Detection Evaluation," https://prevention.cancer.gov/sites/default/files/2023-02/Cancer-Screening-Research-Network-MCED-20220615.pdf

[37] National Cancer Institute, supra n. 29.

[38] Brito-Rocha, supra n. 31 (Table 3).

[39] U.S. Food and Drug Administration, "Breakthrough Devices Program," https://www.fda.gov/medical-devices/how-study-and-market-your-device/breakthrough-devices-program

And it is clear that private payors have great interest in the potential of MCED; a 2023 survey of 19 private payors- including the seven largest health plans in the United States- with 150 million enrollees found that a full 84 percent (16 of the 19) believed there could be merit in using MCED tests to screen for common cancers that currently lack a recommended screening test.[40] Moreover, all 19 payors expressed interest in the overall benefits of MCED testing, and two payors were already offering MCED pilot programs to their enrollees.[41]

Government health plans in the United States do not currently offer coverage for MCED. To be covered by Medicare, screenings for a given cancer must be (1) specifically authorized by Congress; or (2) approved by the Secretary of Health and Human Services (HHS) after a recommendation with an "A" or "B" by the USPSTF. Currently, Medicare provides coverage of screenings for only five types of cancer. Congress has authorized the Centers for Medicare and Medicaid Services (CMS), the federal sub-agency overseeing the Medicare program, to provide Medicare beneficiaries with coverage for screenings of breast, colorectal, cervical, and prostate cancers. The USPSTF recommended in 2013 that lung cancer screenings for certain high-risk populations also be covered, and this recommendation was implemented by Medicare in 2015[42] (the recommendation was revised in 2021).[43]

Legislation has been introduced at the federal level that would empower CMS to provide Medicare beneficiaries with coverage for MCED testing, provided such testing is approved by the FDA and CMS determines coverage is appropriate. H.R. 2407 was reintroduced this Congress and currently has the support of 234 bipartisan sponsors, including 107 Republicans and 127 Democrats. The Senate bill, S. 2085, currently has the support of 53 bipartisan Senators. Additionally, these bills have the support of over 524 national, state, and local stakeholders representing patients, providers, veterans, rural health, minority health, and others.[44] A similar version of this legislation (H.R. 1947, 117th Congress) was introduced in the preceding Congress and had bipartisan and majority support in each chamber, although the bill did not receive a vote.

Part III: MCED Allow for Earlier Detection of Cancers

Cancer progresses through stages. These stages can be classified in various ways, although the focus is consistently on how much (if at all) the cancer has grown and the extent (if any) to which it has spread from its initial location. For example, cancer may be classified by "Stage" numbers I through IV (or 1 through 4) with IV being the most severe. Stage 0 indicates abnormal but precancerous cells.

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[40] Julia R. Trosman, et al., "Perspectives of Private Payers on Multicancer Early-detection Tests: Informing Research, Implementation, and Policy, *Health Affairs Scholar* (July 2023), https://academic.oup.com/healthaffairsscholar/article/1/1/qxad005/7203674.

[41] Id.

[42] Centers for Medicare and Medicaid Services Press Release, "CMS Expands Coverage of Lung Cancer Screening with Low Dose Computed Tomography," (February 10, 2022), https://www.cms.gov/newsroom/press-releases/cms-expands-coverage-lung-cancer-screening-low-dose-computed-tomography.

[43] U.S. Preventive Services Task Force, *Final Recommendation Statement. Lung Cancer: Screening* (March 9, 2021), https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/lung-cancer-screening

[44] H.R. 2407 (118th Congress), https://www.congress.gov/bill/118th-congress/house-bill/2407?s=1&r=9.

Alternatively, cancer may also be classified depending on whether it is (1) in situ ("in the original place"); (2) localized; (3) regional; (4) distant; or (5) of unknown extent.[45]

Generally, the described stage of cancer in a given patient does not change after diagnosis even if the cancer spreads[46] (although re-staging can sometimes be done). For example, if a person is diagnosed with Stage I lung cancer, and the cancer subsequently goes into remission or alternatively metastasizes and spreads to distant organs, generally that patient is still referred to as having Stage I cancer.

Staging cancer is important to health care because the optimal course of treatment of a cancer may vary depending on the stage.[47] Even if the cancer spreads after diagnosis, referring to the cancer by the stage at diagnosis gives health care providers an idea of how the patient has responded to treatment.

There is significant variance among types of cancers in terms of the stage at diagnosis, as evidenced by data on Medicare beneficiaries from 2007 through 2015.[48] Lung cancer, for example, tends to be diagnosed at later stages, whereas more than 80 percent of breast cancers are detected at Stage I or II.[49] A significant number of cancer types which currently lack a recommended screening test show a pattern of at least 40 percent of diagnoses occurring at Stage III or Stage IV. These cancer types include esophagus, ovarian, pancreatic, lymphatic, and stomach.[50] These late-stage diagnoses highlight the need for better screening.

MCED can help detect cancers earlier, although the extent of the improved detection relative to the status quo is not constant for all types of cancer. In measuring the effectiveness of cancer screening tests, the following are key terms:

> *Sensitivity* measures the percentage of actually positive cases of cancer that the test identifies as positive. For example, a test that identified 15 people as having cancer out of a test population comprised of 100 people with cancer would have a sensitivity of 15 percent.
>
> *Specificity* measures the percentage of actually negative cases in the testing population that the test identifies as negative. Thus, a specificity of 98 percent means that, of 100 people who are truly negative, 98 of those people are identified as negative.
>
> There is generally a tradeoff between sensitivity and specificity. A highly sensitive test will have few false negatives, whereas a highly specific test will have few false positives.
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> *Prevalence* is the portion of the test population with the given condition at a given time.
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> *Positive predictive value* (PPV) is the probability that a patient with a positive test result actually has the disease. Conversely, *negative predictive value (NPV)* is the probability

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[45] National Cancer Institute, "Cancer Staging," https://www.cancer.gov/about-cancer/diagnosis-staging/staging#:~:text=Localized%E2%80%94Cancer%20is%20limited%20to,to%20figure%20out%20the%20stage.
[46] Id.
[47] Id.
[48] Sheila R. Reddy, et al., "Cost of Cancer Management by Stage at Diagnosis among Medicare Beneficiaries," (2022), https://www.tandfonline.com/doi/full/10.1080/03007995.2022.2047536.
[49] Id.
[50] Id.

> that a person with a negative test result is actually free of disease. PPV and NPV build upon the concepts of sensitivity and specificity by combining them with consideration of how common the relevant disease is in a given population. All else being equal, the greater the prevalence of a disease in a test population, the higher the test's PPV will be. On the other hand, when a disease has low prevalence, the positive predictive value will also be low, even if the test has high sensitivity and specificity.[51] Because PPV answers the question, "How likely is it that this positive test result is accurate?," it is arguably the most useful measurement of the effectiveness of a cancer test.

A 2021 study in the *Annals of Oncology* examining patients aged 50-79 found that the MCED testing under study had an overall sensitivity of 51.5 percent of patients with any stage of cancer. Sensitivity increased by cancer stage, rising from 16.8 percent for Stage I cancers to 40.5 percent for Stage II cancers, to 77 percent for Stage III cancers, and to 90.1 percent for Stage IV cancers.[52] The test's specificity was 99.5 percent, indicating a very low false positive rate. Crucially, the testing performed especially strongly with respect to a dozen cancer types that account for roughly two-thirds of U.S. cancer deaths, with sensitivity being 76.3 percent across all cancer stages in that context (as opposed to 51.5 percent with respect to the more than 50 types of cancer types detected). Overall, the test had a PPV of 44.4 percent.

A 2023 study based on data collected in England and Wales involving adults over the age of 18 (median age 61.9 years) who displayed symptoms potentially related to cancer found that the applicable MCED testing showed a sensitivity of 24.2 percent for stage I cancers and 95.3 percent for stage IV cancers, again with a low false positive rate.[53] The test had an overall sensitivity of 66.3 percent and a PPV of 75.5 percent.

A different MCED test was discussed in a 2018 paper. When the test was conducted on patients with cancer, the study found that the median sensitivity for detecting the cancer types was 70 percent, with a specificity of over 99 percent.[54] Subsequent MCED testing developed by the same company, Exact Sciences, had 99 percent specificity with sensitivity reaching 75 percent.[55]

MCED testing with a PPV that can reach 30 to 45 percent in an older population is a groundbreaking achievement, although those figures may appear low. Judging these numbers requires additional context. As one source has commented, "Those who are new to assessment of cancer screening often

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[51] New York State Department of Health, "Disease Screening - Statistics Teaching Tools," https://www.health.ny.gov/diseases/chronic/discreen.htm#:~:text=A%20highly%20sensitive%20test%20means,are%20few%20false%20positive%20results.

[52] E.A. Klein, et al., "Clinical Validation of a Targeted Methylation-Based Multi-Cancer Early Detection Test Using an Independent Validation Set," *Annals of Oncology* (September 2021), https://www.sciencedirect.com/science/article/pii/S0923753421020469#fig3.

[53] Brian D. Nicholson, et al., "Multi-Cancer Early Detection Test in Symptomatic Patients Referred For Cancer Investigation In England And Wales (SYMPLIFY): A Large-Scale, Observational Cohort Study," *The Lancet Oncology* (June 20, 2023), https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00277-2/fulltext.

[54] Joshua D. Cohen, et al., "Detection and Localization of Surgically Resectable Cancers with a Multi-Analyte Blood Test," *Science* (February 2018), https://pubmed.ncbi.nlm.nih.gov/29348365/.

[55] Slava E. Katerov, et al., "The Detection of Multiple Cancer Types with an Extended Set of Methylation and Protein Markers," *Journal of Clinical Oncology* (2023), https://ascopubs.org/doi/abs/10.1200/JCO.2023.41.16_suppl.3040.

are amazed that PPV is so low for cancer screening tests even when sensitivity and specificity are high."[56] But the tremendous potential of MCED can be seen by examining screening tests that are currently recommended for several cancers and are universally acknowledged as evidence-backed procedures that save lives. A 2021 paper pointed out:

> [M]ammography has an estimated positive predictive value of 4.4 percent and specificity of 90 percent, which results in 100,000 false positives for million tests; low-dose CT scans for lung cancer have a PPV of 3.8 percent, resulting in 128,000 false positives per million tests; cytology/HPV [human papillomavirus] tests for cervical cancer have a PPV of 19 percent (when including precancerous lesions) and specificity of 92.6 percent, resulting in 74,000 false positives per million tests; stool-based colorectal screening has a PPV of 1.2 percent and 87.7 percent specificity yielding 123,000 false positives per million tests; and blood tests for prostate cancer have a PPV of 30 percent and specificity of 90 percent, yielding 100,000 false positives per million tests.[57]

Seen in this full context, the predictive power and the remarkable potential of MCED testing are better appreciated.

Part IV: MCED Testing Can Save Lives

According to the World Health Organization, "Early diagnosis of cancer focuses on detecting symptomatic patients as early as possible, so they have the best chance for successful treatment. When cancer care is delayed or inaccessible there is a lower chance of survival, greater problems associated with treatment and higher costs of care."[58] If cancer is diagnosed relatively late, the range of feasible treatment options may be narrower. For example, early-stage lung cancers- which have not spread throughout the body- can often be treated through surgery.[59] The same is true of many early-stage breast cancers.[60]

The importance of early detection of cancer was highlighted by a 2020 meta-analysis which found that, with respect to seven cancers (bladder, breast, colon, rectum, lung, cervix, and head and neck), even a four-week delay in treatment was associated with increased mortality.[61] Longer delays showed a

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[56] Pamela Marcus, *Assessment of Cancer Screening: A Primer*, (November 2019), Chapter 3, https://www.ncbi.nlm.nih.gov/books/NBK550207/.

[57] Stephen Ezell, "Seizing the Transformative Opportunity of Multi-cancer Early Detection," *Information Technology & Innovation Foundation*, p. 20 (April 19, 2021), https://itif.org/publications/2021/04/19/seizing-transformative-opportunity-multi-cancer-early-detection/.

[58] World Health Organization, "Promoting Cancer Early Diagnosis," https://www.who.int/activities/promoting-cancer-early-diagnosis.

[59] Elia Ben-Ari, "Lung-Sparing Surgery Is Effective for Some with Early-Stage Lung Cancer," *National Cancer Institute* (March 9, 2023), https://www.cancer.gov/news-events/cancer-currents-blog/2023/early-stage-lung-cancer-sublobar-surgery.

[60] American Cancer Society, "Surgery for Breast Cancer," https://www.cancer.org/cancer/types/breast-cancer/treatment/surgery-for-breast-cancer.html#:~:text=Many%20women%20with%20early%2Dstage,less%20likely%20to%20need%20radiation.

[61] Timothy P. Hanna, et al., "Mortality Due to Cancer Treatment Delay: Systematic Review and Meta-Analysis," *The BMJ* (October 16, 2020), https://www.bmj.com/content/371/bmj.m4087.long.

stronger association. Moreover, delays were associated with increased mortality irrespective of the nature of the treatment provided.

Survival rates in the context of cancer treatment are typically phrased in terms of percentage of diagnosed patients surviving after five years from the date of diagnosis. These rates are consistently and substantially higher for patients diagnosed in early stages.

Table 3 below shows the 5-year survival rates for various types of cancer by stage at diagnosis for the years 2012 through 2018. The data in this table is classified according to the local/regional/distant system discussed above, rather than by stage numbers.

Table 3: 5-Year Survival Percentages, by Stage at Diagnosis, 2012-2018

	All Stages	Local	Regional	Distant
Breast (female)	91	99	86	30
Colon & rectum†	65	91	73	14
Colon	63	91	72	13
Rectum	68	90	74	17
Esophagus	21	47	26	6
Kidney & renal pelvis	77	93	72	15
Larynx	61	78	46	34
Liver‡	21	36	13	3
Lung & bronchus	23	61	34	7
Melanoma of the skin	94	>99	71	32
Non-Hodgkin lymphoma	74	86	77	67
Oral cavity & pharynx	68	86	69	40
Ovary	50	93	74	31
Pancreas	12	44	15	3
Prostate	97	>99	>99	32
Stomach	33	72	33	6
Thyroid	98	>99	98	53
Urinary bladder	77	70	39	8
Uterine cervix	67	92	59	17
Uterine corpus	81	95	70	18

Source: Reproduced from "Cancer Facts & Figures, 2023" by the American Cancer Society.[62]

An obvious pattern is evident from the above table; without exception, 5-year survival rates improve the earlier that cancer is diagnosed, with many cancer types exhibiting dramatically different survival rates based on the stage. Even moving stage of diagnosis up by one, from distant to regional, yields a much higher 5-year survival percentage for many types of cancer. Indeed, a significant reason for the improvement in the national age-adjusted mortality rate discussed earlier in this paper is the development of screenings for a few key cancer types. As noted above, many types of cancer are often diagnosed at Stage III or IV, which unsurprisingly results in relatively low survival rates. The pronounced link between stage at diagnosis and 5-year survival rate is evident in other countries as well.[63]

MCED has the potential to make screenings for over 50 types of cancer a reality, rather than just a few types. Referring back to Table 2 listed earlier in this paper, the data in it is striking in at least two respects. First, a relatively small number of cancer types accounted for a majority of the 602,347 cancer deaths in the United States in 2020, with lung cancer alone accounting for over a fifth of deaths and the top ten cancers accounting for almost seven in ten deaths. That said, more than 30 percent of cancer deaths were attributable to cancer types outside the "top ten."

Second, the five cancers that have a recommended screening test accounted for approximately 267,000 deaths (cervical cancer, not listed in Table 2, killed about 4,300 people in 2020[64]). In other words, the "non-screened" cancers accounted for 335,000 deaths, or about 56 percent of the total. But that percentage is even higher when taking into account people who die from one of the cancers with a recommended screening even though they did not meet the recommended criteria for undergoing screening. For instance, writing in 2020 based on the then-current USPSTF guidelines, one group of analysts noted, "Current lung cancer screening guidelines miss a large percentage of the high-risk population."[65]

The foregoing suggests that a multi-cancer screening tool which can detect cancers of whatever type in its earlier stages has the potential to save many lives. At least five sources support that conclusion.

- A 2020 study examined the effects on a hypothetical cohort of people aged 50-79 if people who were diagnosed after cancer had metastasized (i.e., were diagnosed at Stage IV) had instead been diagnosed at earlier stages. Under a conservative scenario, all cancers diagnosed at Stage IV were assumed instead to be diagnosed at Stage III, with a resulting 15 percent decrease in

[62] American Cancer Society, *Cancer Facts & Figures 2023*, https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2023/2023-cancer-facts-and-figures.pdf (Table 8).
[63] See, e.g., *Incisive Health*, "Saving Lives, Averting Costs," (September 2014), https://www.cancerresearchuk.org/sites/default/files/saving_lives_averting_costs.pdf?_gl=1*1ur91wz*_gcl_au*MTE0NDMxMzk3NC4xNjkwMzA2ODU0*_ga*NDEwNjk0Nzg4LjE2OTAzMDY4NTQ.*_ga_58736Z2GNN*MTY5MjIyMjkyNS41LjEuMTY5MjIyMjk2My4yMi4wLjA.&_ga=2.160985723.777648664.1692222926-410694788.1690306854.
[64] Centers for Disease Control and Prevention, "Changes Over Time: Cervix," https://gis.cdc.gov/Cancer/USCS/#/Trends/.
[65] Diane N. Haddad, "Disparities in Lung Cancer Screening: A Review," *Annals of the American Thoracic Society* (April 2020) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7175982/.

cancer-related deaths over a five-year period. In a scenario in which one-third of Stage IV cancers were assumed to have been diagnosed at each of Stage I, Stage II, and Stage III instead, the resulting decrease in cancer-related deaths in the following five-year period was 24 percent.[66]

- A 2021 study compared a base model of "usual care" with no MCED screening versus usual care supplemented with MCED screening. Several usual care plus MCED scenarios were examined, with the scenarios differing from each other in terms of the assumed progression rate of the cancers. The usual care plus MCED treatment detected the applicable cancer before usual care between 46 and 68 percent of the time. Of the subset of patients whose cancer was detected through MCED, mortality over the following five-year period was reduced by approximately 40 percent in all scenarios. And the overall five-year mortality reduction from cancer through usual care plus MCED testing (which takes into account those cancers MCED would not detect before usual care) ranged from 18.8 percent to 26.5 percent, depending on the scenario.[67]

- A 2022 study in *Pharmacoeconomics* modeled the effects of MCED supplementing ordinary care on a lifetime cohort of 100,000 people not previously diagnosed with cancer. The study found that 3,192 and 2,021 more patients would be diagnosed in stages I and II, respectively, and 1,136 and 3,704 fewer patients would be diagnosed in stages III and IV, respectively, compared to a situation in which the patients received only ordinary care.[68] Given the data on survival rates by stage at diagnosis in Table 3 above, this "stage shift" could be expected to save lives.

- Modeling used in a 2023 study found that USPSTF-recommended screenings for breast, colorectal, cervical, and lung cancer have resulted in an estimated total gain of between 12.2 and 16.2 million life-years since they were recommended.[69] Moreover, a gain of another 3.2 to 5.1 million life-years could have been achieved if there had been perfect compliance by the populations eligible for the different screenings. The study noted that MCED's benefits over just a five-year benefit (~23 million life-years) could be even larger than the maximum estimate of life-years that would have been gained by perfect compliance with the four USPSTF-recommended screenings since they were recommended.

- Researchers with Exact Sciences in a 2023 release discussed the steps necessary to achieve a proposed 20 percent reduction in cancer mortality. The researchers found that, with respect to 14 of 15 cancers studied, the majority of the hypothetical 20 percent reduction could be achieved by detecting cancer prior to Stage IV, with the remaining benefit attainable by

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[66] Christina A. Clarke, et al., "Projected Reductions in Absolute Cancer-Related Deaths from Diagnosing Cancers Before Metastasis, 2006-2015," *Cancer Epidemiology, Biomarkers & Prevention* (May 2020), https://aacrjournals.org/cebp/article/29/5/895/72197/Projected-Reductions-in-Absolute-Cancer-Related.
[67] Hubbell, supra n. 1.https://aacrjournals.org/cebp/article/30/3/460/72416/Modeled-Reductions-in-Late-stage-Cancer-with-a.
[68] Ali Tafazzoli, et al., "The Potential Value-Based Price of a Multi-Cancer Early Detection Genomic Blood Test to Complement Current Single Cancer Screening in the USA," *Pharmacoeconomics* (August 30, 2022), https://pubmed.ncbi.nlm.nih.gov/36038710/.
[69] Thomas J. Philipson, "The Aggregate Value of Cancer Screenings in the United States: Full Potential Value and Value Considering Adherence," *BMC Health Services Research* (August 2023), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10405449/.

detecting cancers just one stage earlier compared to current practice (the researchers noted that accelerated detection of lung cancer is especially important).[70]

Part V: MCED Can Generate Cost Savings

The United States spends an enormous amount of money each year treating cancer; estimates for 2020 national spending on cancer treatment are over $200 billion.[71] [72] Medical services account for roughly 90 percent of this cost and the remainder is attributable to prescription drugs.[73]

Of course, the cost of medical treatment is not the only cost of cancer. These other costs include:

- Loss of life and decreased quality of life. Even cancer patients who are fortunate enough to avoid a cancer-related death must overcome numerous challenges. To name just one example, many people whose cancer is treated find themselves facing ruinous medical bills.[74] While translating quality of life to concrete economic value is always challenging, two researchers in a 2006 paper argued that a 1 percent reduction in cancer mortality would be worth $500 billion.[75]
- Decreased productivity: This loss is experienced by workers and employers as a result of employees with cancer seeing diminished productivity, such as missing work more frequently. A 2016 study found that cancer patients missing work due to their illness alone led to a productivity loss of $8.1 billion in 2007 alone.[76] Unsurprisingly, productivity losses appear to be more pronounced for patients with later-stage cancers. For example, a study of people diagnosed with cancer from 2009 to 2019 found that the average number of days absent from work in the one-year period following diagnosis was 106 days for patients with metastatic cancer versus 46 days for patients with non-metastatic cancer.[77]
- Economic loss from premature deaths: a 2008 study estimated the loss of productivity from cancer mortality in 2000 to be $115.8 billion, with that number projected to rise to $147.6

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[70] Menggang Yu, et al., "A Flexible Quantitative Framework to Assess the Potential Contribution of Early Cancer Detection to Improved Cancer Survival," *Journal of Clinical Oncology* (June 1, 2023), https://ascopubs.org/doi/pdf/10.1200/JCO.2023.41.16_suppl.e22508?role=tab.

[71] Angela B. Mariotto, et al., "Medical Care Costs Associated with Cancer Survivorship in the United States," *Cancer Epidemiology, Biomarkers & Prevention*, (July 2020), https://pubmed.ncbi.nlm.nih.gov/32522832 (Table 6).

[72] National Cancer Institute, "Cancer Trends Progress Report," https://progressreport.cancer.gov/after/economic_burden#field_data_source.

[73] Id.

[74] Noam Levey, "She Was Already Battling Cancer. Then She Had to Fight the Bill Collectors," *NPR* (July 9, 2022), https://www.npr.org/sections/health-shots/2022/07/09/1110370391/cost-cancer-treatment-medical-debt

[75] Kevin M. Murphy, et al., "The Value of Health and Longevity," *Journal of Political Economy* (October 2006), https://www.journals.uchicago.edu/doi/10.1086/508033.

[76] Florence K. Tangka, et al., "State-Level Estimates of Cancer-Related Absenteeism Costs," *Journal of Occupational and Environmental Medicine* (January 2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4731096/.

[77] Ze Cong, et al., "Productivity Loss and Indirect Costs for Patients Newly Diagnosed with Early- versus Late-Stage Cancer in the USA: A Large-Scale Observational Research Study," *Applied Health Economics and Health Policy* (August 30, 2022), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9596506/.

billion by 2020.[78] That 2020 projection more than doubled- to $308 billion- when all productivity losses were considered (such as caregiving by family members of patients).

If MCED can accelerate the detection of cancer, it has the potential to not only save lives, but also to reduce costs. Before examining this issue, it should be emphasized that a net increase in national expenditures to save lives is not necessarily objectionable. Additional spending can be a wise investment if the benefits are significant enough. Ultimately, with MCED, as with any health care expenditure, there is a question of the tradeoffs between costs and improved health outcomes.

The costs of treating a given cancer patient depend on many variables. Of these variables, perhaps the two most important are the type of cancer and the stage at which the cancer is diagnosed. A 2020 study found that the average cost under Medicare (in 2019 dollars) for medical services to treat melanoma that was local at diagnosis was $8,800 in the twelve months following diagnosis.[79] The corresponding figures for lung cancer and pancreatic cancer were $51,400 and $79,800, respectively. Along similar lines, a 2022 study of Medicare beneficiaries found that the Year 1 cost of treating Stage I prostate cancer was $7,640, whereas the corresponding figure for Stage I stomach cancer was $81,661.[80] These are just a few examples of how costs can vary dramatically between cancer types.

Numerous studies show a consistent and pronounced pattern of treatments costs being greater the later the cancer is diagnosed. Both of the studies cited in the paragraph above also showed that the cost of treating cancer in Years 1 through 5 post-diagnosis were almost always higher the later the cancer was diagnosed. For example, the 2022 study found that the average cost of Year 1 of Stage I liver cancer treatment was $73,816, while the average Year 1 cost of Stage IV cancer was $155,515. The respective Year 1 costs of colon/rectum cancer treatment for Stage I and Stage IV cancers were $45,907 and $146,370.[81] The authors of the 2022 study pointed out that “increased cancer-related cost associated with later-stage diagnosis can be seen as early as 6 months from diagnosis . . . Across the cancer cohorts, first-year costs for beneficiaries with Stage IV cancer were 1.6 to 7.7 times that of beneficiaries with Stage I cancer.”[82]

A 2017 paper examined the net costs (approximating cancer-related costs) of breast, colorectal, lung, and prostate cancers among enrollees of four commercial health plans during the one-year period and the five-year period following diagnosis.[83] The study disaggregated the costs over these periods by the stage at diagnosis and whether the patients were over the age of 64. The study showed a strong relationship between cost and stage at diagnosis; subject to one exception,[84] for every cancer type in both age groups, one-year and five-year costs increased as the stage at diagnosis increased. For

[78] Cathy J. Bradley, et al., “Productivity Costs of Cancer Mortality in the United States: 2000–2020,” *Journal of the National Cancer Institute* (December 2008), https://academic.oup.com/jnci/article/100/24/1763/2606882?login=false
[79] Mariotto, supra n. 71 (Table 3).
[80] Reddy, supra n. 48.
[81] Id.
[82] Id.
[83] Matthew P. Banegas, et al., “Medical Care Costs Associated with Cancer Survivorship in the United States,” *Cancer Epidemiology, Biomarkers & Prevention*, (July 2020), https://pubmed.ncbi.nlm.nih.gov/32522832/.
[84] The five-year cost of prostate cancer in the underage-65 group was lower when the cancer was diagnosed at Stage II rather than Stage I.

example, the five-year costs for breast, colorectal, lung, and prostate cancers in the over-age 64 population were 3.1, 3.7, 2.6, and 2.0 times greater, respectively, when the applicable cancer was diagnosed at Stage IV rather than Stage I.

The relevant data also shows that, unsurprisingly, treatment of a cancer patient in the last year of the patient's life before he or she dies of cancer is especially expensive. A 2020 paper found a pronounced "J-pattern" in the cost of care when dividing treatment into an initial phase (the first 12 months following diagnosis), an end of life phase (the last 12 months of life), and a continuing phase (the time between the initial phase and the end of life phase).[85] Treatment of a given cancer type was initially high in the initial treatment phase, dipped in the continuing phase, and (for those patients ultimately dying of cancer) soared in the last year of life. The average annual costs during the initial, continuing, and end of life phases were $43,600, $6,400, and $109,700, respectively.[86]

Crucially, costs for medical services (as opposed to prescription drugs) were generally higher the later the stage of cancer at diagnosis had been, *even within a given phase of care*. For example, treatment in the last year of life for people dying of bladder cancer was $139,400 if they had been diagnosed when the cancer was already distant, whereas the same end of life cost for a patient whose cancer was diagnosed when it was local had a corresponding cost of only $73,300. Prescription drug spending showed the same general pattern, but subject to more exceptions. Given the very expensive last year of life for people who die of cancer and the greater costs of treatment when cancer is diagnosed relatively late, the study supports the idea that detecting cancer earlier would have the potential to reduce costs significantly.

A 2017 paper focused on the question of the costs that could be saved by early cancer detection, regardless of whether the detection was through MCED or other means.[87] That paper assumed that Stage III or Stage IV cancers would be detected at Stage I or Stage II. Based on incidence rates at stage of diagnosis for 19 cancer types (colorectal cases being divided into either colon or rectum) diagnosed in California adults and available claims payment data showing that treatment is less expensive for earlier diagnoses, the authors estimated that early cancer detection would save roughly $25.9 billion annually. They also emphasized that the estimate was conservative, and while it was imprecise given the complexity of the issue, was likely accurate within a factor of two.

A screening program conducted on uninsured and underinsured Texans in 2016 and 2017 demonstrated the impressive fiscal benefits that proper cancer screening can deliver. The program offered free colorectal cancer screening to just over 3,000 participants. As a result of this screening, 433 people had precancerous polyps removed and 12 people had potential malignancies removed. Based on the likelihood these polyps have of developing into cancer, the researchers estimated that the program saved somewhere between $3.9 and $4.8 million (2017 dollars).[88] Because the cost of the program was less than $1.6 million, the program generated significant cost savings despite its small scale. Although

[85] Mariotto, supra no. 71.
[86] Id.
[87] Zura Kakushadze, et al., "Estimating Cost Savings from Early Cancer Diagnosis," *Data* (July 2017), https://www.mdpi.com/2306-5729/2/3/30.
[88] Orsak, supra n. 34.

this screening program did not utilize MCED testing, it highlights how better screening through MCED could generate savings.

The finding that cancer treatment costs increase rapidly with later diagnosis is by no means confined to the United States. A 2014 study examining National Health Services (NHS) data in England found that treatment at Stage IV compared to Stage I was 3.7, 2.7, 1.6, and 2.8 times greater for colon, rectal, lung, and ovarian cancer, respectively.[89] The study also found that savings of more than $33 million could be attained with respect to these four cancer types if all providers could match the early detection track record of the best providers.

In summary, there is an overwhelming amount of evidence that cancer treatment costs increase with stage at diagnosis. It bears repeating that this is true even across a given phase of care (e.g., the last year of life of patients who die of cancer). To save lives and reduce costs, current cancer screening must be improved. MCED offers that improvement.

Part VI: Concerns and Questions Regarding MCED

While MCED's potential is great, there are, as with any new medical innovation, important questions to address. Two concerns repeatedly raised[90] concerning MCED's costs and benefits are the drawbacks associated with false positives and the detection of "indolent" cancers that would otherwise be undetected and harmless. These concerns are addressed below.

Are the benefits of MCED testing offset in whole or part by its reporting false positives and false negatives?

Perhaps the single biggest concern with cancer screenings is that they generate false positives and false negatives. False positives can cause tremendous anxiety in mis-diagnosed patients who are not truly suffering from cancer, and can lead them to undergo extensive follow-up testing in an attempt to learn more about the actually non-existent cancer.

It is undoubtedly true that false positives are a concern for any type of cancer screening. But one of MCED's strengths is a low percentage of false positives. The specificity of 99 percent (or more) that some MCED tests have means that, given 100 samples of true negatives, the test is correctly identifying 99 percent (or more) of them as negative. And this low rate of false positives is achieved with a test that has strong predictive power. As mentioned above, the PPVs of at least some MCED tests which search for many types of cancer are much greater than those for the existing single-cancer screening methods that are recognized as valuable in the context of colorectal, breast, prostate, and cervical cancers. Whereas PPVs for traditional screening methods- which have saved lives and helped slash the cancer mortality rate since 1991- often have a PPV below 5 percent, MCED testing can exceed a PPV of 40 percent.

Three additional points are worth recognizing. First, because MCED testing can usually point to the organ in which cancer has potentially originated, a false positive result should generally allow health

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[89] Supra, n. 63.

[90] E.g., Patricia A. Deverka, et al., "Multicancer Screening Tests: Anticipating And Addressing Considerations For Payer Coverage And Patient Access," *Health Affairs* (July 2022), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8962120/.

care providers to offer follow-up diagnostic care that is targeted and searching for confirmation of a particular cancer type. This should mitigate concerns that a false positive will necessarily result in a health care “odyssey” for the patient that is both wasteful and expensive.

Second, the problem of false positives must be viewed in the broader context of how well cancer is detected in the United States. Roughly, only one in seven cancers diagnosed in this country stems from a screening; thus, there are a tremendous number of people who stand to benefit from improved screening methods, even if some false positives are generated. Currently, the lack of recommended screening for various types of cancer is the functional equivalent of a screening test with a sensitivity of zero percent.

Third, when conducting a cost-benefit analysis of MCED testing, what might be termed “ancillary” costs must be considered. That is, costs and benefits other than the price of the test and medical costs saved, respectively, must be taken into account. False positives are an ancillary cost of MCED testing- indeed, any medical screening test whatsoever. But there are also what might be termed ancillary benefits of MCED testing that go far beyond lower treatment costs and saved lives. For example, earlier detection of cancer could likely avoid billions of dollars in lost productivity.

The issue of false negatives poses a different concern. At first glance, a person who receives a false negative result seems no worse off than if the person had never taken the screening test. But false negatives can be damaging in that they can instill a false sense of confidence in an actually cancer-stricken patient who, for example, might not obtain a subsequent screening for a number of years on the mistaken assumption that he or she is in excellent health. Such a scenario could lead to an avoidable premature death. Indeed, a number of large private payors surveyed expressed reservations about covering MCED testing due to the issue of false negatives.[91] Nevertheless, false negatives should not pose difficulty to the extent that false positives do. With false positives, wasteful follow-up costs are all but guaranteed, as health care providers search for cancer that is not actually present in a patient. In contrast, the drawbacks of false negatives- essentially, unjustified complacency about one’s health - can be managed much more efficiently through publishing guidelines and educating patients who undergo screening.

Are the benefits of MCED testing overstated in that it may detect cancers that never would have posed a health risk to the patient if they had remained undiscovered?

From the true positive results generated by MCED testing, a certain number may be “minor” in the sense that they never would have progressed to the point where they threatened the applicable patient’s life or even caused quality of life issues. This raises the possibility that the reported benefits of MCED might be inadvertently exaggerated. For example, detection of such cancers inflates the number of cancer cases detected relative to the status quo and can give the impression that MCED boosted survival rates in patients diagnosed with such cancers, when in reality nothing of practical value has been achieved. In fact, value may have been destroyed because detecting a cancer that would never have progressed to a serious risk creates the same potential for an expensive odyssey through various health care treatments that false positives can cause.

[91] Trosman, supra n. 40.

As with false positives, diagnosis of cancers that never would have posed a serious risk to the patient, and the resulting stress and unnecessary costs, are genuine concerns. There are indications, however, that at least certain types of MCED tests are better at detecting threatening cancers rather than cancers that are indolent, which allays concerns that MCED testing will lead to wasting resources on cancers that do not pose a meaningful threat. For example, a 2021 paper in *Clinical Cancer Research* conducted a follow up examination of patients with diagnosed cancer who had undergone a type of MCED testing in the previous one to three years (after being diagnosed with cancer).[92] The study found that patients whose cancers were not detected by the MCED test had overall better results than patients whose cancer had been detected, even when controlling for stage at diagnosis, age, and type of cancer. The authors concluded that the use of MCED testing may not exacerbate overdiagnosis in light of this apparent bias towards detecting more aggressive cancers. Discussing this result, another study speculated that "it is possible that by relying on circulating tumor DNA as the principal analyte, MCEDs in development will be more sensitive for cancers with lethal potential than for clinically insignificant cancers."[93] A number of other researchers have echoed the inference that MCED testing may be biased towards detecting aggressive cancers.[94] [95] [96] [97]

The idea that MCED tests are particularly good at detecting aggressive cancers accords with the leap in sensitivity of the Galleri test from 51.5 percent to 76.3 percent when the cancers tested for are confined to twelve of the top-killing cancers in the United States (as opposed to more than 50 cancers). While some potential for overdiagnosis is inherent in any screening method, there are sound reasons to believe that MCED tests minimize this problem.

Part VII: Recommendations

Policymakers should embrace the opportunity that MCED offers. This paper suggests three avenues of action. The first step, and by far the most important, is to authorize CMS to permit Medicare coverage for MCED testing. Second, Texas should explore opportunities to make MCED testing accessible to employees working for state agencies, school districts, and institutions of higher education. Third, Texas leaders should ensure that data collection and cancer surveillance efforts are monitoring the burden of unscreened cancers and progress on driving a higher cancer detection rate statewide. Each of these three steps is discussed below.

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[92] Xiaoji Chen, "Prognostic Significance of Blood-Based Multi-cancer Detection in Plasma Cell-Free DNA," *Clinical Cancer Research* (August 1, 2021), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9401481/.

[93] Eric A. Klein, et al., "The Promise of Multicancer Early Detection," *The American Journal of Medicine* (March 2023), https://www.amjmed.com/article/S0002-9343(22)00403-X/fulltext.

[94] Klein, supra n. 52 at p. 1175.

[95] Deverka, supra n. 90 (p. 3).

[96] Glenn D. Braunstein, "Criteria for Evaluating Multi-cancer Early Detection Tests," *touchREVIEWS in Oncology & Haematology* (2021), https://touchoncology.com/diagnostics-and-screening/journal-articles/criteria-for-evaluating-multi-cancer-early-detection-tests/. ,"

[97] Eric A. Klein, et al., "Dying To Find Out: The Cost of Time at the Dawn of the Multi Cancer Early Detection Era," *Cancer Epidemiology, Biomarkers & Prevention* (August 1, 2023), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10390858/.

Recommendation #1: Congress should create authority for CMS to cover MCED testing for Medicare beneficiaries.

Given MCED's ability to detect cancer earlier and the cost savings and improved health outcomes flowing from treatment of cancers at an earlier stage, the question for legislators is how best to implement MCED into public policy. The federal Medicare program, created in 1965 to provide health care coverage to older Americans, is a logical candidate. It is a government program, which avoids the concern of the government issuing mandates to private payors. While private payors are involved in Medicare, they contract with Medicare voluntarily through the Medicare Advantage program.

Additionally, Medicare covers a predominantly older population, with all Americans aged 65 and over being eligible for the program, although some younger people with certain disabilities or conditions may also be eligible for Medicare. Due to the strong link between cancer and aging, focusing on older Americans can maximize the utility of MCED.

Currently, Medicare covers screenings only for breast, cervical, colorectal, and prostate cancers, and for certain high-risk populations, lung cancer. As touched upon at the outset of this paper, the Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Coverage Act (the "Act") was filed in the current Congress (the 118th Congress) on March 30, 2023, and is under consideration for advancement into law. The bill was recently discussed by the Congressional Subcommittee on Health on September 19, 2023.

The Act is straightforward; it first makes a number of findings, one of which is that "Detecting cancer early, before it has spread throughout the body, saves lives. Cancers detected when still localized can be treated more effectively and have a 4 times greater survival rate compared to cancers found after metastasis has occurred."[98] Substantively, the bill expands the definition of "medical and other health services" covered by Medicare to include MCED screening tests that have been approved or cleared by the FDA and for which the Secretary of Health and Human Services (who ultimately oversees CMS) has determined coverage is appropriate. Thus, the bill does not mandate that CMS pay for MCED testing, but rather only permits it if a certain condition is satisfied.

It should be emphasized that obtaining FDA approval of a medical test, and subsequent approval by CMS, are by no means guaranteed. As one set of authors recently pointed out,[99] in 2021 CMS exercised its discretion to deny approval of an FDA-approved blood test for colorectal cancer screening due to concerns about its capabilities.[100] Simply obtaining FDA approval is a significant hurdle requiring persuasive evidence of the safety and efficacy of the proposed test.

Any cost-benefit analysis of Medicare coverage of MCED testing must take into account the projected escalation of cancer treatment costs due to the rapid aging of the U.S. population. A 2020 paper, updating a 2010 paper with the same lead author, estimated that the national cost of cancer care in

[98] Supra n. 44.

[99] Deverka, supra n. 90.

[100] Centers for Medicare and Medicaid Services, "National Coverage Analysis, Decision Memo: Screening for Colorectal Cancer - Blood-Based Biomarker Tests," (January 19, 2021), https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=299&type=Open&bc=AAgAAAAACAAA&.

2015 was $183 billion (in 2019 dollars).[101] *Based solely on changes in the population* (e.g., aging), the projected cost of cancer treatment in 2030 was expected to reach $246 billion (again, in 2019 dollars), an increase of 34 percent. Given the overwhelming evidence that late-stage cancers are more difficult and more expensive to treat, and that the last year of life for those dying of cancer can be particularly expensive, policymakers must find a way to utilize emerging technology to detect cancer earlier.

Recommendation #2: Texas should explore opportunities to provide MCED coverage for members of the Teacher Retirement System (TRS) and Employees Retirement System (ERS) given the potential to detect more cancers earlier among those who could most benefit.

ERS's Employees Group Benefits Program covers almost 550,000 Texans and offers, among other things, health care benefits.[102] Of that figure, about 127,000 people are retirees.[103] TRS-ActiveCare, which covers public school employees and their dependents- covers about 444,000 people in all.[104] Additionally, TRS-Care, a health care program that covers TRS retirees, has about 222,400 members.[105] Both ERS[106] and TRS[107] retirees can be eligible for Medicare.

The arguments for authorizing CMS to provide Medicare beneficiaries with coverage for MCED testing apply with equal force at the state level. Thus, Texas policymakers should consider providing MCED coverage for TRS and ERS enrollees, as determined appropriate through analysis of their at-risk population.

Additionally, the Cancer Prevention and Research Institute of Texas (CPRIT) awards grants "for a wide variety of innovative cancer-related research and product development and for the delivery of evidence-based cancer prevention programs and services by public and private entities located in Texas."[108] For example, the 2016-2017 colorectal screening program for uninsured and underinsured Texans that was discussed earlier in this paper was funded with a CPRIT grant.

One of the encouraged uses of CPRIT funds is to award grants "for cancer prevention and control programs in this state to mitigate the incidence of all types of cancer in humans."[109] CPRIT should consider investing a portion of its spending on MCED implementation research to raise awareness of the

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[101] Mariotto, supra 71.

[102] Employees Retirement System of Texas, "Whom We Serve," https://ers.texas.gov/about-ers/ers-organization/whom-we-serve

[103] Employees Retirement System of Texas, "Take a "Glance" at What ERS Has Accomplished," (March 13, 2023), https://www.ers.texas.gov/news/take-a-glance-at-what-ers-has-accomplished#:~:text=One%20in%2056%20Texans%20is,and%206%2C000%20survivors%20and%20others.

[104] Teacher Retirement System of Texas, *Popular Annual Financial Report, 2022,* https://www.trs.texas.gov/TRS%20Documents/popular-annual-financial-report-2022.pdf.

[105] Id.

[106] Employees Retirement System of Texas, "Medicare and Your State of Texas Health Plan," https://www.ers.texas.gov/retirees/life-changes/medicare.

[107] Teacher Retirement System of Texas, "FAQs: TRS-Care Medicare Advantage," https://www.trs.texas.gov/Pages/healthcare_trs-care_medicare_faq.aspx

[108] Cancer Prevention and Research Institute of Texas, "About Us," https://www.cprit.state.tx.us/about-us.

[109] Texas Health and Safety Code, Section 102.201(b)(5), https://statutes.capitol.texas.gov/Docs/HS/htm/HS.102.htm.

practical clinical and epidemiological findings discussed throughout this paper. The 2024-2025 biennial state budget appropriated roughly $600 million to CPRIT.[110]

Recommendation #3: Texas lawmakers and publicly-supported stakeholders should ensure that data collection and cancer surveillance efforts are closely monitoring the burden of unscreened cancers and progress on driving a higher cancer detection rate statewide.

Given the rapid pace of innovation in cancer screening and early detection, this paper focuses on the need to drive awareness of promising new tools, to prepare the state's key stakeholders for implementation opportunities, and to ensure access to emerging screening modalities. We must also ensure the state is collecting and analyzing comprehensive data that characterizes the landscape of cancer early detection and screening in order to identify potential gaps and opportunities for future exploration and improvements.

For example, the concept of a "percent of cancers detected by screening" (PCDS) measure has recently been surfaced by data scientists. Using annual incidence data from the National Cancer Institute, self-reported preventive screening data from the National Health Information Survey, combined with screening test efficacy rates found in published literature, and state cancer statistics collected in the Behavioral Risk Factor Surveillance System (BRFSS), it was found that only 14 percent of cancers nationwide are detected through a preventive screening test. Texas' statistics are marginally better than other states at 14.8 percent, illustrating the potential for improving this new measure and unlocking additional value from earlier cancer detection across all cancers - not just those with individual screening tests. Texas lawmakers and publicly-supported stakeholders like CPRIT and Cancer Alliance of Texas should consider annual assessments of the burden of unscreened cancers in the state in addition to the challenges with screening adherence for cancers that have screening recommendations. To the extent data capture allows or can be resourced, they should also provide an annual assessment of the burden of cancers diagnosed after metastasis (e.g., stage IV cancer) to drive awareness and progress on innovative solutions. Furthermore, policymakers and the public should have available and updated reports on facts and trends regarding disparities in late-stage cancer diagnoses (across geography, race, ethnicity, income, etc.) and related downstream impacts on cancer outcomes in the state. Lastly, opportunities should be evaluated for new data collection to better understand broader "cancer detection rates" within the state as related national efforts are underway.

Texas' All-Payor Claims Database (APCD) should also be studied to measure MCED's benefits and raise awareness of them. House Bill 2090 (87R; Rep. Burrows, et al.) created the APCD, to which insurers generally must submit claims forms. This database provides a wealth of information that is de-identified with respect to patients and contains "administrative claims information on approximately 60 percent of all covered Texans, representing nearly 100 percent of medical claims regulated by the state."[111] This

[110] House Bill 1 (88R, 2023), https://capitol.texas.gov/tlodocs/88R/billtext/pdf/HB00001F.pdf#navpanes=0 (p. I-17).

[111] UT Health Houston, School of Public Health, "TX-APCD Overview,' https://sph.uth.edu/research/centers/center-for-health-care-data/texas-all-payor-claims-database/

information allows researchers to better understand health care trends and to identify high-value and low-value treatments.

The January 2023 interim report by the Texas Select House Committee on Health Care Reform touched on this point. It summarized the testimony of a witness from the Texas Medical Association as encouraging the Legislature "to identify low and high value care as a means to reward better health outcomes under a value-based healthcare approach. Physicians, other medical providers, and hospitals get paid on whether patients achieve certain predetermined outcomes."[112] The summarized testimony pointed out that a few states have used their corresponding claims databases to examine low-value care.

Information in the ACPD, subject to the privacy protections in statute, should enable researchers and insurers to better quantify the benefits of MCED and to disseminate this information, leading to better understanding the burden of late-stage cancer diagnoses, the burden of unscreened cancers, and opportunities for value-based MCED implementation.

[112] Select House Committee on Health Care Reform, *Interim Report to the 88th Texas Legislature* (January 2023), https://house.texas.gov/_media/pdf/committees/reports/87interim/Health-Care-Reform-Committee-Interim-Report-2022.pdf (p. 53).