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Seizing the Transformative Opportunity of Multi-cancer Early Detection

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Blood-based multi-cancer early detection (MCED) technologies hold the promise to revolutionize America's cancer-screening paradigm, dramatically expanding the range of detectable cancers and identifying them at earlier stages when cancers are more treatable. Policymakers should provide a supportive regulatory and coverage environment.

KEY TAKEAWAYS

- Multi-cancer early detection approaches merge emerging biological and information technologies—including next-generation gene sequencing, artificial intelligence, and big data—in a revolutionary new approach to cancer detection.

- MCED can detect signals for dozens of different types of cancers with a very high rate of accuracy, a low false-positive rate, and the ability to trace the detected cancer to its likely tissue of origin with a high degree of confidence.

- MCED holds the potential, over time, to transform America's cancer-detection paradigm from one in which most cancers are detected when patients present symptomatically to one in which they can be screen-detected in advance.

- If U.S. enterprises are to lead in this fast-emerging, intensely globally competitive technology field—and if citizens are to enjoy the benefits—then policymakers will need to get the regulatory and coverage environment right.

- Congress should pass the Medicare Multi-Cancer Early Detection Screening Coverage Act, which authorizes the Centers for Medicare & Medicaid Services to use an evidence-based process to cover blood-based MCED tests.

INTRODUCTION

Cancer remains one of humanity's most intractable diseases, and is expected to surpass heart disease as the leading annual cause of American fatalities by 2030. The individual, social, and economic costs cancer inflict are enormous, meaning the need for both effective cancer screening and therapeutic options remains paramount. Fortunately, a new slate of biological and informational technologies—including genome sequencing, big data analytics, artificial intelligence/machine learning (AI/ML), and nanotechnology—are enabling breakthrough innovations in cancer detection and treatment.

In detection, blood-based approaches hold the potential to screen for signals of over 50 cancers simultaneously with a very high rate of accuracy and the ability to trace the detected cancer to its likely tissue of origin with a high degree of confidence. Multi-cancer early detection (MCED) screening holds the promise to radically expand the number of cancers for which there are available screening options and to broaden cancer detection to the asymptomatic population. It heralds a potential paradigm shift from trying to treat cancer in later stages to detecting and treating the disease in its earliest ones. But if the promise of multi-cancer early detection screening approaches is to be realized, policymakers will have to get the regulatory and coverage policies right to support deployment and uptake of this transformative technology.

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This report begins by examining the social and economic costs cancer inflicts. It discusses the importance of early cancer detection and moves on to an exploration of how MCED technologies work, evidence of their effectiveness to date, the benefits they are capable of providing, and why it's important the United States remain the global leader in this field. It then analyzes the regulatory and coverage environment before concluding by providing recommendations for how policymakers can enact policies enabling this transformative technology to flourish, including by passing legislation creating a pathway to ensure timely Medicare coverage of MCED screening exams.

## THE INDIVIDUAL, SOCIAL, AND ECONOMIC COSTS OF CANCER

Cancer refers to a group of diseases characterized by the uncontrolled growth and spread of abnormal cells.[1] It remains one of America's, and global societies', greatest health challenges. Cancer is responsible for almost one in six deaths globally.[2] The global cancer burden is expected to surpass 20 million new yearly cases by 2025.[3] Cancer is the second-most common cause of death in the United States, exceeded only by heart disease, although cancer is expected to become the leading cause of American fatalities by 2030. Likewise, among adults ages 35 to 70, while cardiovascular disease remains the leading cause of mortality globally, "mortality from cancer will probably become the leading cause of death" in the near future.[4] Experts predict the year 2021 will see 1.9 million new cancer cases diagnosed in the United States, with over 600,000 Americans expected to perish from the disease, which translates to about 1,650 deaths per day.[5] Approximately 1 out of every 200 Americans

receive a cancer diagnosis each year. For Americans born today, one in two women, and one in three men, are likely to develop cancer at some point in their lifetimes (with one in five perishing from them).[6] One in eight U.S. women will be diagnosed with breast cancer in their lifetimes.[7] One reason cancer rates are increasing is because cancer is primarily a disease of old age, and as Americans live longer in general, the likelihood of their developing a cancer grows. In the United States, 60 percent of all cancer cases diagnosed are in people above age 65, while 80 percent of all cancers in the United States are diagnosed in people 55 years of age or older.[8] Americans ages 65 and older are more than seven times more likely than younger Americans to be diagnosed with cancer.[9] Seventy percent of all American cancer deaths occur with people ages 65 or older.[10] Yet, despite being more prevalent in the older population, cancer is actually the leading cause of death for Americans under age 65.[11] In the United States, health experts predict that breast, prostate, and lung cancers will account for the most new cases diagnosed among American men and women in 2021. (See figure 1.) However, in terms of cancer fatalities, lung cancer is now the leading cause of death for American men and women alike, second is prostate cancer for men and breast cancer for women, followed by colorectal and pancreatic cancer. (See figure 2.)

Figure 1: Estimated new U.S. cancer cases, 2021 (by cancer type, both sexes combined)[12]
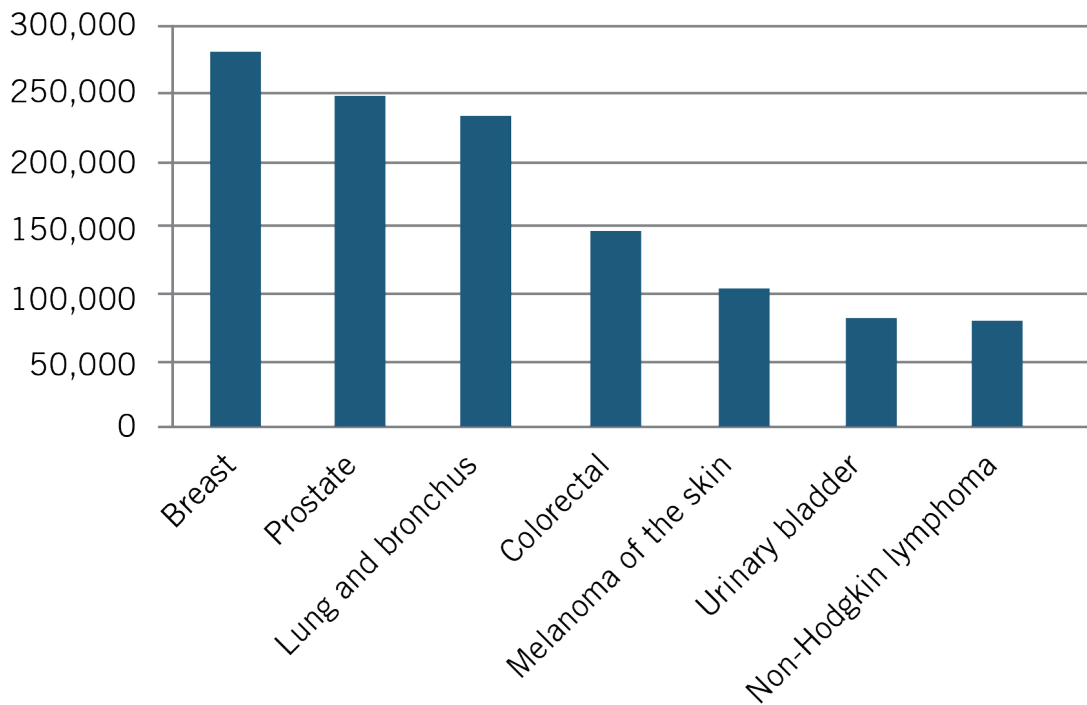
**Figure 2: Estimated U.S. cancer fatalities, 2021** [13]
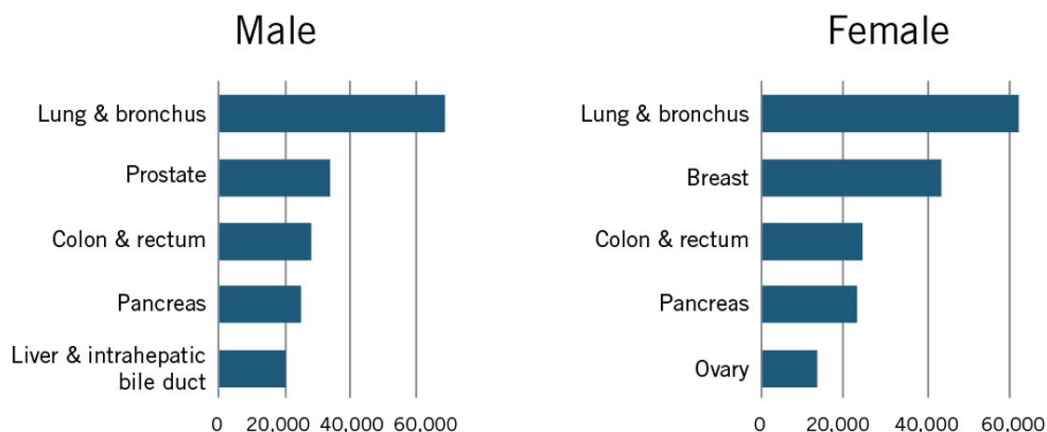
Fortunately, American cancer fatality rates have decreased over the past half-century, largely the result of a combination of more-effective screening approaches, an overall decrease in smoking in the population, and more-effective treatment and therapeutic options. For some of the most common cancers—lung, colorectal, breast, and prostate—reductions in smoking and improvements in screening have led to 36 percent fewer deaths than would have occurred otherwise.[14] Americans' deaths from cancer have fallen from 193.9 per 100,000 population in 1950 to 152.5 today.[15] Since peaking in the early 1990s (at 215 per 100,000 population), U.S. cancer death rates have declined by 27 percent.[16] This decline translated into more than 2.9 million fewer cancer deaths from 1991 to 2017.[17] And breakthrough therapies such as Avastin and Herceptin for breast cancer, Keytruda for lung cancer, and Yervoy for melanoma help explain why American citizens enjoy the highest cancer survival rates in the world. For instance, over 99 percent of U.S. women suffering from localized breast cancer are still living five years later.[18] One study estimates that approximately 73 percent of survival gains in cancer are attributable to new treatments, including medicines.[19] Moreover, as Lichtenberg explains, "During the period 2000–2011, the premature (before age 75) cancer mortality rate … declined by about 9 percent…. In the absence of pharmaceutical innovation during the period 1985–1996, the premature cancer mortality rate would have increased about 12 percent during the period 2000–2011."[20]

Yet, as Azra Raza, a professor of medicine and director of the MDS Center at Columbia University, writes, "Cancer is still beating us … I have been studying and treating cancer for 35 years, and here's what I know about the progress made in that time: There has been far less than it appears."[21] She points out that, for all this progress, overall cancer death rates are not dramatically different from what they were in the 1930s, before they began increasing alongside the rise in smoking. Indeed, while the age-adjusted death rate per 100,000 U.S. population from heart disease fell by roughly two-thirds from 1950 to 2010, the similar rate for cancer just barely decreased. (See figure 3.) As. Dr. Bert Vogelstein, a professor of oncology at Johns Hopkins University, explains, part of this disparity can be attributed to the fact that the heart disease research community has largely focused on early detection and prevention, "whereas the oncology community has been more focused on curing advanced disease."[22] Or, as Raza puts it,

"We now invest a lot of effort into finding minimal residual disease. Why not apply the same rigor and focus to finding minimal initial disease?"[23]

Figure 3: Age-adjusted rate of death per 100,000 population[24]
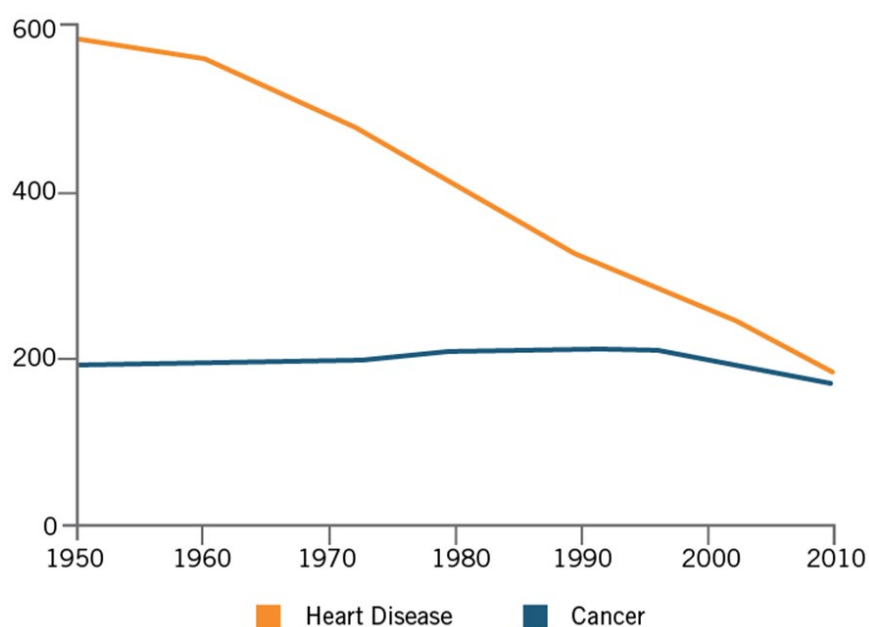
Thus, despite some progress, cancer still afflicts millions annually and imposes tremendous costs on the U.S. health care system, as well as the broader economy. Cancer is the second-most-costly disease in the United States.[25] Cancer accounts for an estimated 5 to 11 percent of the annual total U.S. health care budget.[26] In 2017, cancer care cost the United States an estimated $177 billion (an increase of approximately 39 percent since 2010), equivalent to 1 percent of U.S. gross domestic product (GDP).[27] Medicare—the federally administered health care program that covers more than 60 million seniors and persons with disabilities—shoulders roughly one-third of this cost annually.[28] The United States invests about $27 billion annually on cancer screening tests.[29]

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More than $94 billion in earnings were lost in the United States in 2015 due to cancer deaths.[30] A 2008 study estimated that the value of life lost from all cancer deaths in the year 2000 totaled $960.6 billion and predicted that the total value of life lost in 2020 from cancer deaths in the United States would reach $1.5 trillion.[31] The tremendous costs cancer imposes conversely suggest tremendous benefits if cancers could be detected earlier when treatments are more likely to succeed and as more-effective treatments and therapeutics for cancer are invented. In fact, Murphy and Topel, considering the benefits of increased longevity and improved quality of life, find that a 1 percent reduction in mortality from cancer could deliver roughly $500 billion in net present benefits, while a cure (if one could be achieved) could deliver $50 trillion in present and future benefits.[32] Similarly, Lakdawalla et al. examined trends in survival after cancer diagnosis from 1988 through 2000 and argued that improvements in

treatments led to approximately 24 million more life years for patients, at an economic value of $1.9 trillion.[33] Their research finds that the overwhelming amount of economic value produced from investments in cancer research and development (R&D) made by the public and private sector have flowed to patients, with health care providers and pharmaceutical companies appropriating 5 to 19 percent of the total economic value created, with the rest accruing to patients.[34]

THE IMPORTANCE OF EARLY CANCER DETECTION

Earlier cancer detection generates significant health and economic benefits, as the two following sections attest.

Health Benefits

Cancer is most effectively and efficiently treated when it is caught early, when it is localized, and before it has metastasized to distant parts of the body. As one report explains, "Survival rates improve dramatically when cancer is diagnosed early and the disease is confined to the organ of origin before it has had a chance to spread, and the cancer is more likely to be treated successfully."[35] Early detection, especially resulting from effective cancer screening protocols, is paramount to reducing mortality from cancer. As the American Cancer Society explains, "Screening is known to reduce mortality for cancers of the breast, colon, rectum, cervix, lung (among current or former heavy smokers), and probably prostate."[36] Overall, patients' survival rates are 5 to 10 times greater when cancer is detected at an early stage rather than at a late stage.[37] When cancer is diagnosed after it has spread, the five-year cancer-specific survival rate is 21 percent, compared with 89 percent when the cancer is diagnosed early and still localized.[38] According to a study by Clarke et al., "Projected Reductions in Absolute Cancer–Related Deaths from Diagnosing Cancers Before Metastasis, 2006–2015," detecting cancers with distant metastases at earlier stages could potentially reduce cancer-related five-year mortality by at least 15 to 24 percent.[39] The study found that detection of multiple cancer types earlier than stage IV could reduce at least 15 percent of cancer-related deaths within five years, affecting not only cancer-specific but all-cause mortality. Stage IV cancers represented 18 percent of all estimated diagnoses but 48 percent of all estimated cancer-related deaths within five years. Assuming all stage IV cancers were diagnosed at stage III, 51 fewer cancer-related deaths would be expected per 100,000, a reduction of 15 percent of all cancer-related deaths. Assuming one-third of metastatic cancers were diagnosed at stage III, one-third diagnosed at stage II, and one-third diagnosed at stage I, 81 fewer cancer-related deaths would be expected per 100,000, a reduction of 24 percent of all cancer-related deaths.[40]

Earlier detection of cancers saves both lives and costs for health care systems and economies more broadly.

The importance of early detection becomes even clearer when examining its impact on survival rates for certain forms of cancer. Well more than 90 percent of women diagnosed with breast cancer at the earliest stage survive their disease for at least five years, compared with about 15 percent for women diagnosed with the most-advanced stage of disease. More than 80 percent of lung cancer patients will survive for at least one year if diagnosed at the earliest stage, compared with around 15 percent for those diagnosed with the most-advanced stages of the disease.

Unfortunately, only about 15 percent of lung cancers are diagnosed at the localized stage, when clinical intervention can markedly improve patient outcomes.[41] Ninety percent of women diagnosed with earliest-stage ovarian cancer survive their disease for at least five years, compared with around 5 percent for women diagnosed with the most-advanced stage of disease. And more than nine in ten bowel cancer patients will survive the disease for more than five years if diagnosed at the earliest stage.[42]

Earlier detection makes all forms of cancer intervention more effective than when cancers are diagnosed at later stages. As Dr. Vogelstein notes, patients with stage III colorectal cancer, if they have micrometastases (i.e., a very small micro-metastatic disease, even if already spread to other organs), given chemotherapy, can recover almost 50 percent of the time; whereas if the cancer becomes visible and bulky (visible metastases), the recovery rate is close to nil. This also holds true for the newest, most cutting-edge interventions, such as targeted immunotherapies (i.e., immune checkpoint inhibitors) and CAR-T-based (chimeric-antigen receptor T cell) therapies: Recovery rates are far higher in patients with low tumor burdens than with high.[43] Indeed, in quite many cases, these technologies mean that patients with localized (i.e., Stage I-II) solid tumors are potentially curable. As Raza writes (about what this evidence makes clear):

> What we need now is a paradigm shift. Today, the newest methods generating the most research and expense tend to be focused on treating the worst cases—chasing after the last cancer cells in end-stage patients whose prognoses are the worst. We need instead to commit to anticipating, finding, and destroying the first cancer cells.[44]

Unfortunately, only five types of cancer—breast, cervical, colorectal, prostate, and "high-risk" lung—have guideline-recommended screening options available today, whereas the vast majority of cancers, including blood, head and neck, pancreatic, ovarian, and liver cancers, have no guideline-recommended screening tests available.[45] The five types of cancer with guideline-recommended screening options represent approximately 40 percent of the total cancer incidence in the United States, yet only 15 to 20 percent of cancer diagnoses when test performance and compliance are accounted for, according to an analysis of 2006 to 2015 data from the National Institutes of Health's (NIH) Surveillance, Epidemiology, and End Results (SEER) Program.[46] Overall, about 70 percent of all U.S. cancer deaths occur in cancers with no recommended screening options.[47] This is a global story: Of the 9.5 million cancer fatalities recorded globally in 2017, the vast majority had no screening test available to detect the cancer prior to the onset of signs or symptoms. (See figure 4, where cancers with screening tests available are shown in orange, and those that do not are in blue.)

Figure 4: Global cancer fatalities, by type, 2017[48]
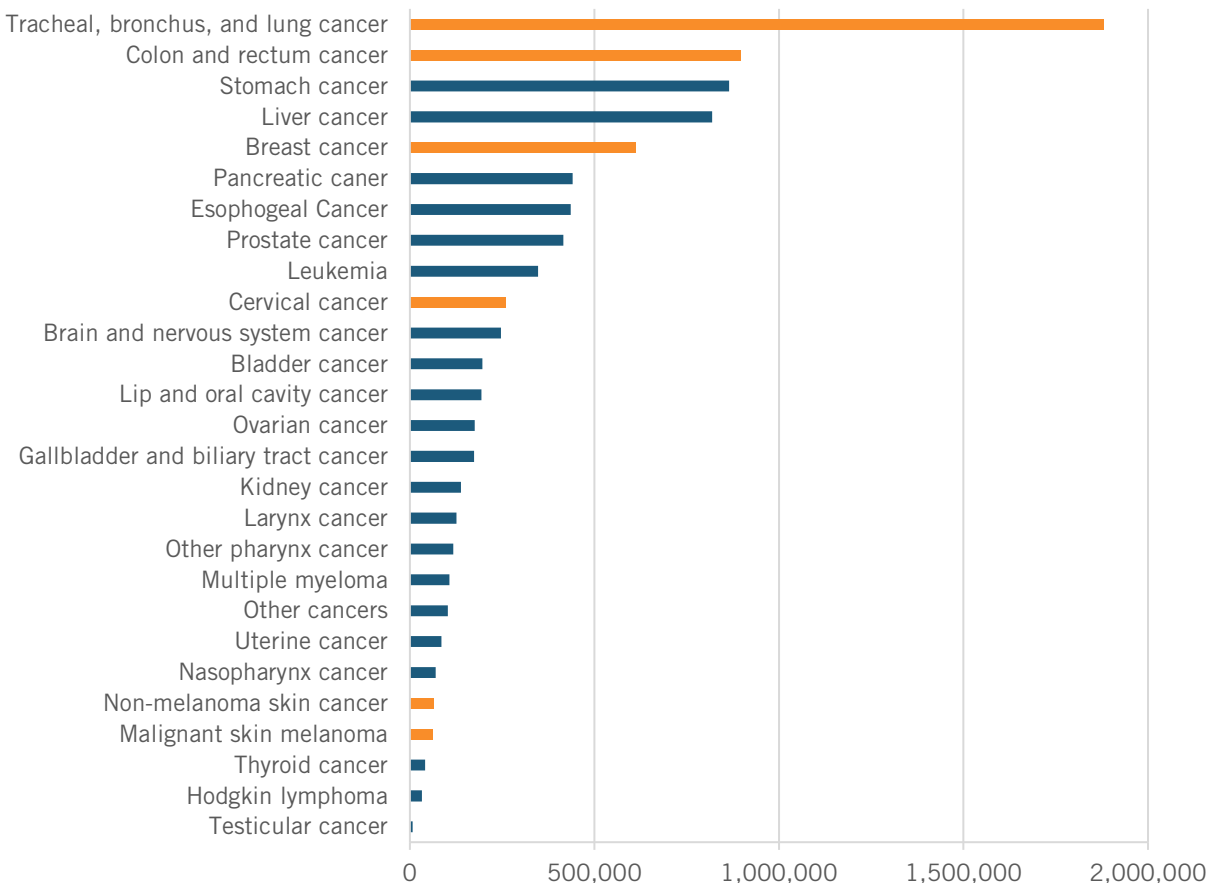
However, effective screening can deliver tremendous benefits: Since the pap smear test was introduced, the cervical cancer death rate in the United States has declined by about 70 percent.[49] The first U.S. trial of breast-cancer screening, launched in 1963, reduced mortality by 25 percent in its first 18 years.[50] And analysts estimate that, since 1998, the number of U.S. breast cancer deaths prevented due to mammography increased from 384,000 to 614,000.[51]

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According to a 2016 study by Seabury et al., "Quantifying the Gains in the War on Cancer Due to Improved Treatment and Earlier Detection," an examination of the 15 most-common types of cancers found that the three-year cancer-related mortality of cancer patients fell by 16.7 percent from 1997 to 2007, with advances in early detection responsible for 4.5 percentage points of that decline (in other words, 27 percent of the decline) and advancements in treatment for a reduction of 12.2 percentage points.[52] As the authors wrote, "Cancer detection has seen significant breakthroughs, such as digital mammograms and the development of genetic profile tests."

Their study found that the relative importance of treatment and detection in reducing mortality varied across cancer types. Improvements in detection contributed to reduced mortality rates for all 15 types of cancers studied, but were most significant for thyroid, prostate, and kidney cancer.[53] Improved early detection accounted for 60 percent of the reduction in the three-year mortality rate for prostate cancer and just about half the reduction for kidney and renal pelvis cancers.[54] Earlier detection of colorectal cancer accounted for 42 percent of the gain in colorectal cancer survival rates from 1997 to 2007, abetted by the fact that the percentage of adults receiving recommended screening for colorectal cancer rose from 44 to 65 percent from 2000 to 2010. (That figure stood at 68.8 percent as of 2018.)[55] Overall, the study estimates that the benefits of earlier detection (for this suite of 15 cancers) during the years 1997 to 2007 generated $19 billion in societal value (even without considering the benefits of having identified patients before they developed malignancies).[56]

Economic Benefits

Earlier and better screening yields economic benefits as well. The 2018 report "Medical Care Costs Associated With Cancer in Integrated Delivery Systems" examined the costs associated with treating cancer from January 1, 2000 to December 31, 2008 in a population of over 45,000 patients diagnosed with one of the four most-commonly diagnosed cancers in the United States (breast, colorectal, lung, and prostate) who were members of one of the four health care plans within the Cancer Research Network. The report shows significant potential economic savings from earlier cancer detection, and that mean total one-year costs for lung cancer ranged from $50,700 (stage I) to $97,400 (stage IV) among patients ages <65 years and from $44,000 (stage I) to $71,200 (stage IV) among patients ages ≥65 years. For colorectal cancer patients under age 65, the five-year cost of treatment for a patient with stage IV cancer was $205,100, compared with $65,000 for a stage I patient. (For individuals over 65 diagnosed with colorectal cancer, the five-year total costs ranged from $67,900 for a stage I patient to $141,000 for stage II patients). Similar trends were apparent for lung and prostate cancer, with the five-year total costs for a stage I lung cancer patient under the age of 65 estimated at $93,800 and for a stage IV patient at $200,300; for prostate cancer, five-year total costs for the under-65 stage I prostate patient stood at $51,800 compared with $72,300 for a stage IV patient.

Overall, the report observes "higher costs among patients diagnosed with advanced versus earlier-stage disease in the fee-for-service setting." It concludes by noting that "net costs of care were highest for patients aged <65 years with advanced-stage cancers, suggesting that early detection and prevention strategies are key to curtailing high long-term costs associated with late-stage disease." The report "emphasizes the need for continued effective cancer screening" especially "to reduce the number of invasive colorectal and late-stage female breast cancer diagnoses."[57] The study's message is clear: Earlier detection of cancers saves both lives and costs for health care systems and economies more broadly.

Similarly, a 2017 study, "Estimating Cost Savings for Early Cancer Diagnosis," sought to examine the cost savings from early cancer diagnosis for 19 cancers, assuming that all stage III and IV cases were detected at stage I or II instead (using current incidence rates for these cancers). As the report notes, "In many cases, it is much less costly to treat cancer when it is diagnosed earlier."[58] In part, that's because cancer patients' costs of care in the last year of life are sizably higher than during early stages. The study concluded that earlier diagnosis of those cancers could generate $26 billion in cost savings annually, equivalent to 17 percent of total

estimated yearly expenditures on cancer treatment.[59] For breast, lung, prostate, and colorectal cancers, and melanoma, which are the top-five cancers in the United States by incidence, with an estimated 859,110 new cases in 2017 (accounting for 50.9 percent of the 1,688,780 cancer cases diagnosed that year), the study estimated $10.7 billion in savings from earlier diagnosis (about 41.5 percent of cost savings from all cancers).[60]

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Those findings also concord with a 2016 study which examined the cost of breast cancer coverage across various stages of the disease. The study concluded that "the costs were higher for patients whose cancer was more advanced at diagnosis, for all cumulative 6-month periods (months 0–6, 0–12, 0–18, and 0–24)." It found that the average costs per patient (as allowed by insurance companies) in the year after diagnosis were $60,637, $82,121, $129,387, and $134,682 for disease stage 0, I/II, III, and IV, respectively, and the costs allowed per patient in the 24 months after the index diagnosis were $71,909, $97,066, $159,442, and $182,655, for those four stages. As the study concluded, "The cost difference based on the stage at diagnosis was largely driven by the cost of chemotherapy and noncancer treatments."[61] Across the broader U.S. health care system, treatment of metastatic cancer may be as much as two times more costly than treatment of cancer before it metastasizes.[62]

THE PROMISE OF MULTI-CANCER EARLY DETECTION TECHNOLOGIES

MCED screening represents a groundbreaking technology now in the advanced stages of development that is poised to contribute to a step change in cancer screening and care. MCED represents perhaps the most sophisticated application of the emerging technique of liquid biopsy: the detection of cancers using biomarkers circulating in human fluids (e.g., blood), such as circulating tumor cells and circulating cell-free tumor DNA (ctDNA).[63] As Dr. Catherine Marinac, a member of the Faculty of Medicine at the Dana-Farber Cancer Institute, notes, "The blood is a very rich source of information about cancers in the body, because tumors shed a lot of information into the bloodstream, including cells, circulating tumor DNA, and other molecules that we can collect and analyze."[64] The World Economic Forum has identified liquid biopsy as one of the world's top-10 emerging technologies, although scientists have known since the 1960s that there exists free-floating DNA in blood and have long dreamed of the potential to identify cancers through blood analysis.[65] In fact, the first DNA-based blood test for cancer in the United States was actually commercialized in 2014 by Guardant Health.[66] Since then, extensive research has demonstrated that tumor-derived somatic alterations in DNA can be detected in the plasma of cancer patients in the form of cell-free DNA.[67]

Early cancer detection represents an increasingly competitive and growing global industry, with firms such as AnchorDx, ArcherDx, Burning Rock Biotech Limited, Exact Sciences Corporation, GRAIL, Freenome, Foundation Medicine, GENECAST (South Korea), Guardant Health, Laboratory for Advanced Medicine, and Singlera Genomics (China), among others, competing in the space.[68] These companies are using a variety of approaches; some competitors are developing blood-based tests optimized to identify specific types of cancers (such as colon or pulmonary cancers), while others are developing tests that can screen for multiple cancers simultaneously. Analysts

estimate that the market for such next-generation cancer detection technologies stands at $6.2 billion as of 2020, and that it will grow to $16.7 billion by 2025 (an estimated compound annual growth rate of 21.9 percent over that period).[69]

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Now, an increasing number of competitors, such as South Korea's Genecast and the United States' GRAIL and Thrive Earlier Detection (acquired in October 2020 by Exact Sciences) are taking the potential of liquid biopsy a significant step further by developing tests that can simultaneously screen for signals of dozens of cancers—the vast preponderance of which currently enjoy no effective screening technique—with a potentially high degree of accuracy, opening a new frontier of MCED possibility. As Dr. Chetan Bettegowda of Johns Hopkins University explains, MCED introduces the potential "to transform the concept of cancer screening from an organ-by-organ, site-by-site, to a whole system, patient, individual approach."[70] It also introduces the possibility to screen for cancers in the asymptomatic population. This matters greatly, for, as Dr. Norman "Ned" Sharpless, director of the National Cancer Institute at the National Institutes of Health, notes, "The most common way people are diagnosed with a cancer is when they present to a doctor with a new symptom [subsequently identified as cancer]."[71] Of these, the vast majority are discovered at the latest stage, stage IV. In fact, out of every 100,000 cancers diagnosed in clinical settings, stage IV cancers account for approximately 170, compared with 100 for stage III, 75 for stage II, and 50 for stage I.[72]

In June 2020, the National Cancer Institute commented on results from a test called "CancerSEEK" developed by a team of researchers led by Nickolas Papadopoulos, Ph.D., of the Johns Hopkins University School of Medicine that sought to access the feasibility of a blood test that could detect cancers before symptoms develop.[73] Their study (which enrolled 10,006 women ages 65 to 75 with no known cancer) sought to detect alterations in 16 genes associated with cancer, in pieces of circulating tumor DNA in the bloodstream and to measure the blood levels of nine proteins overproduced by some cancer types. Of the over 10,000 women participating in the study, 26 eventually received a diagnosis of cancer first detected by the CancerSEEK test; 14 of them were in organs such as the ovaries, kidney, and lymphatic system, for which no approved screening tests exist.[74] Commenting on the test, Dr. Papadopoulos observed, "So, can such a [blood] test be performed safely, without triggering a large number of futile, invasive follow-up tests based on the test results? Yes."[75] Dr. Papadopoulos and his Johns Hopkins University colleagues Kenneth W. Kinzler and Bert Vogelstein founded Thrive Earlier Detection to further develop and commercialize the CancerSEEK technology.[76]

Elsewhere, Menlo Park, California-based GRAIL Inc. has developed an MCED blood test which has demonstrated in clinical studies the ability to detect cancer signals from more than 50 types of cancer, across all stages, and localize the cancer signal with a high degree of accuracy, from a single blood draw.[77] It's important to note that MCED approaches such as GRAIL's and Thrive's/Exact's are envisioned as complements, not substitutes, to currently recommended cancer screening guidelines (for breast, cervical, colorectal, prostrate, and "high-risk" lung cancers).

Both GRAIL's and Thrive's approaches seek to identify cancers from ctDNA moving through the human bloodstream. Every cell contains DNA and RNA, the nucleic acids providing the genomic blueprint for all organisms. DNA is a double-stranded molecule composed of complementary pairs of nucleotide bases known as base pairs; it is organized into long strands called chromosomes, and the DNA sequences encoded by these nucleotide bases within each chromosome constitute genes. Cancer is often called a disease of the genome, as changes in the genome are a hallmark of the disease. Cancerous mutations reflect alternations to DNA sequences that can occur as a result of defective processes in the repair of damaged DNA, errors during DNA replication, or exposure to environmental toxins. Accordingly, genomic sequencing makes it possible to identify alterations in both DNA sequences and chromosomal structure that occur with cancer and thus to distinguish between a cancerous cell and a healthy cell.[78] Interestingly, as Dr. Vogelstein notes, "There are a relatively small number of genes, maybe only a couple of dozen, that play a key role in most cancer types. It turns out there are common threads that facilitate relatively reasonable ways to use these mutations as biomarkers to detect multiple cancer types."[79]

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DNA methylation refers to an epigenetic process (that occurs by the addition of a methyl (CH_3) group to DNA) that modifies the function of genes and affects their expression.[80] Gene expression and cellular function are controlled by methylation patterns through segments of DNA, meaning methylation represents an essential step in the process of cellular differentiation, what directs a cell to evolve into kidney, liver, or heart tissue, for instance. There are nearly 30 million methylation sites across the human body, making them "a ubiquitous and rich signal for detecting cancer."[81] Moreover, each cell type in the human body has a unique methylation pattern, or "fingerprint," which enables evaluation of abnormal methylation patterns to identify the site of the disease. Changes in methylation can be indicative of early-stage tumorigenesis, with abnormal methylations being either hyper- or hypo-methylated.[82] Abnormal methylation may cause genes to become overexpressed, resulting in excessive protein production; underexpressed, resulting in reduced protein production; or silenced, sometimes triggering changes in cellular function that can lead to diseases such as cancer. For instance, Exact Sciences has leveraged these biological processes in its development of its proprietary QuARTS (Quantitative Allele-specific Real-time Target and Signal Amplification) technology, which efficiently amplifies and quantifies two separate methylated DNA markers (NDRG4 and BMP3) along with seven distinct KRAS point gene mutations as part of its DNA biomarker detection system.[83] In other words, the ability to identify and detect methylation patterns in the human body has opened new pathways to create innovative new cancer screening tests.

Cells shed nucleic acid fragments (cfNA) coming from virtually all cell types in the body, including normal cells, diseased cells, cancerous cells, and microbes such as parasites, bacteria, and viruses, into the bloodstream.[84] Advanced next-generation sequencing techniques can be used to sequence these cfNA fragments, and their exact sequences can be used to determine the location within the human genome where they originated. As the article "Next-Generation Sequencing of Circulating Tumor DNA for Early Cancer Detection" explains:

ctDNA is a fundamentally different type of cancer "biomarker" than most that have been used for cancer detection. Most importantly, ctDNA detection leverages the hallmarks of cancer as a disease of genomic alterations and is thus a direct measurement of the tumor. As such, it has the potential to be more specific to the presence of the tumor than other surrogate and downstream measurements of proteins and metabolites.[85]

Thus, as GRAIL notes, "sequencing cfNAs provides a direct measure of genomic changes, which are involved in virtually all cancers; therefore, the technology has great promise for development of a highly specific test for the early detection of multiple types of cancer in a single blood test."[86] As part of its clinical development program, GRAIL assembled "the largest linked datasets of genomic and clinical data in the cancer field" and applied machine learning analytics to determine which of three different next-generation sequencing approaches—mutations, chromosomal alterations, or methylation patterns—would provide the optimal method of detecting cancer.[87] (GRAIL's clinical trial has enrolled over 145,000 participants.) The company trained its machine learning algorithms to distinguish patterns of cancer from non-cancer while filtering out technical and biological noise, enabling it to distinguish genetically heterogeneous cancer cfNA from other cfNA that are indicative of non-cancerous conditions.[88] The company reported that its research found that, while each of the sequencing approaches proved capable of detecting cancer, methylation profiling yielded significantly better results for cancer detection and that a targeted methylation approach (focusing on the 1 million or so most-informative methylation sites) demonstrated superior performance and greater efficiency than whole-genome methylation.[89]

Elsewhere, a *Nature* article notes that researchers throughout the world are similarly starting to develop these types of Artificial Intelligence (AI)-driven, methylation-based cancer classification systems. As *Nature* explains:

> Full-genome methylation analysis checks for small hydrocarbon molecules attached to DNA. The addition of such methyl groups is one of the mechanisms behind epigenetics—when the activity of genes is altered without any mutation to the underlying genetic code—and different types of cancer show different patterns of methylation.[90]

Researchers throughout the world are applying such methylation approaches to cancer detection. For instance, researchers at the German Cancer Research Center in Heidelberg, Germany, have developed an AI-driven, methylation-based classifier originally trained to sort medulloblastomas into subtypes, which they have now expanded to cover all of the approximately 100 known cancers of the central nervous system. The methylation-based classified developed by the team in Germany now recognizes about 150 different cancer entities, and is helping to make more-accurate cancer diagnoses—their algorithm found that 12 percent of the brain tumors studied had actually been misdiagnosed by pathologists. [91]

In March 2020, in an *Annals of Oncology* article, "Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA," GRAIL published clinical test data from its Circulating Cell-free Genome Atlas (CCGA) study.[92] The study found that an earlier version of the company's cancer detection technology, Galleri, could, through a single blood draw, detect cancer signals from more than 50 cancer types across all stages, with a very low

false positive rate of 0.7 percent, and moreover that when a cancer signal is detected, it can be linked to the cancer signal of origin (i.e., where in the body the cancer is coming from) with 93 percent accuracy.[93] The test's detection rate for a pre-specified set of 12 cancers that collectively account for nearly two-thirds of all U.S. cancer deaths annually was 67.3 percent across stages I–III, while the test's overall detection rate for all cancer types was 43.9 percent across stages I–III.[94] Assuming test performance replicated across the asymptomatic population, a multi-cancer test with a stage I–IV sensitivity of 55 percent and a specificity (i.e., accurate detection rate) of 99.3 percent, applied to a similar population with a 1.3 percent incidence rate per year of cancer, would achieve a positive predictive value (PPV) of 43 percent.[95] This figure, the PPV, which represents the probability that a patient with a positive (abnormal) test result actually has the disease, is perhaps the most significant in considering the merits and effectiveness of various cancer screening approaches.

A December 2020 article in *Cancer Epidemiology, Biomarkers, and Prevention* presented data modeling the potential impact of adding an annual MCED blood test to existing standard of care cancer screenings.[96] It estimated a potential reduction in late-stage (stage III and IV) cancer diagnoses of more than half of those in the U.S. population ages 50–79. The model estimated this decrease in late-stage diagnoses could translate to a reduction in five-year cancer deaths by 39 percent among those detected earlier, equating to an overall reduction of all five-year cancer deaths by 26 percent.[97]

The Technologies Underpinning Multi-cancer Early Detection Technologies

MCED systems leverage a range of emerging biological and information technology (IT)-based tools, including genomics/gene sequencing, big data analytics, and AI/ML. This section examines each in turn.

Genomics/Gene Sequencing

Historically, medical treatment was dictated by what worked for the average person, thereby making it reliant on a general approach.[98] But increasingly, researchers are finding that human differences play a key role in both the nature of diseases and the effectiveness of treatments thereof. This understanding gave rise to the field of genomics, the study of a person's unique genes (i.e., their genome), including interactions of those genes with each other and with the person's environment.[99] The incorporation of genetic data increasingly drives disease screening and drug development, in the latter case allowing for treatments to be tailored for particular groups, and even individuals. That especially matters, as understanding increasingly grows that cancers are individual-specific, and that there is no "one-size-fits-all" rule when it comes to treatment.[100]

The largest contributing factor to the feasibility of using genetic data in the development of diagnostics and treatments (for cancer and other diseases) is the increasing utility and cost-effectiveness of genetic-sequencing technologies.[101] The Human Genome Project (HGP), a $2.7 billion initiative, created the first reference sequence of the human genome in June 2000 after 13 years of work. HGP researchers have estimated the first genome sequencing cost between $500 million and $1 billion.[102] Since 2000, genome sequencing has become cheaper and faster by orders of magnitude, in significant part because of improvements in computing power. Today, modern gene-sequencing machines can sequence an entire human genome in under an hour, for under $300—and the cost is expected to fall even further in coming years.[103] Critically, the HGP

has been as important in mapping the cancer genome as it has been in mapping the human genome.

Moreover, the maturation of genomics has accompanied somewhat-related disciplines that have likewise exerted a beneficial impact on disease detection and drug development. Many of the technologies and techniques developed in pursuit of sequencing the human genome have spurred the development of the "omics" revolution (often referred to as "multi-omics") which includes advancements in fields such as proteomics (the study of proteomes, which are sets of proteins produced by an organism); transcriptomics (the study of an organism's RNA transcripts, which are responsible for the expression of genes); and metabolomics (the study of an organism's metabolites.)[104] For instance, GRAIL observed that its "multi-omics technology platforms, include … [its] technology related to interrogating mutations, chromosomal alterations, and RNA."[105] Similarly, Exact Sciences notes that its Oncotype DX® portfolio of breast, colon and prostate cancer tests applies advanced genomic science to reveal the unique biology of a tumor in order to optimize cancer treatment decisions.[106] Collectively, these advancements have made available a previously untapped wealth of data to biopharmaceutical researchers to help them better understand human biology and guide the development of both new drugs and detection mechanisms for diseases.[107]

Big Data/Artificial Intelligence/Machine Learning

Recent years have seen explosive growth in the amount of life-sciences data, especially as a result of modern gene-sequencing technologies, which can produce gigabytes of information from even just a single experiment.[108] For instance, the Cancer Genome Atlas, launched in 2006, has collected information on tens of thousands of samples spanning 33 cancer types. Its dataset now exceeds over 2.5 petabytes of genomic, epigenomic, transcriptomic, and proteomic data (1 petabyte equals 1 million gigabytes).[109] Meanwhile, "advances in tissue labelling and automated microscopy are generating complex imaging data faster than researchers can possibly mine them," creating tremendous opportunities to apply intelligent systems to these datasets to identify trends and patterns.[110]

The increasing application of AI-based systems to disease detection and drug discovery represents a genuine revolution in the approach to modern medicine.

AI refers to a field of computer science devoted to creating computing machines and systems that perform operations analogous to human learning and decision-making.[111] Machine learning is a branch within AI that focuses on designing algorithms that can automatically and iteratively build analytical models from new data without explicitly programming a solution.[112] Machine learning essentially represents the process of teaching a computer to carry out a task, rather than programming it to carry out that task step by step, such that at the end of training, a machine-learning system will be able to make accurate predictions when given data.[113] Machine learning is well suited to analyzing unstructured data—such as an image of a cluster of cells—unlocking a vast new resource for a wide variety of new and valuable applications to improve disease detection and drug development. That's especially important because such unstructured data constitutes 80 percent of all clinical data in the United States.[114]

An important development in machine learning has been deep learning.[115] Deep-learning algorithms use statistical techniques to develop a model to solve problems from large, complex datasets with very little guidance from programmers. Computer scientist Amit Karp writes that "deep learning relies on simulating large, multilayered webs of virtual neurons, which enable a computer to learn to recognize abstract patterns."[116] It is called "deep" because it automatically generates multiple layers of abstractions of the data and uses these abstractions to identify patterns. A deep-learning system is "trained" using a mathematical function to determine how accurate its latest prediction is compared with what was expected. This function generates a series of error values, which in turn can be used by the system to calculate how the model should update the value of each link in the neural network, with the ultimate aim of improving the accuracy of the network's predictions. Over many training cycles, deep-learning systems grow to generate ever-better predictions.[117]

AI and big data have already made substantial contributions in life-sciences innovation, touching every phase of drug and diagnostic tool development from discovery, clinical research, and U.S. Food and Drug Administration (FDA) review, to FDA post-market safety monitoring.[118] Already, AI systems are matching or exceeding human-level performance in analyzing unstructured medical data, often in dramatically shorter amounts of time. For example, researchers at University of California, Los Angeles (UCLA) and NantWorks have developed an AI-powered device that can detect cancer cells in just a few milliseconds—hundreds of times faster than previous methods.[119] Elsewhere, researchers at Google have developed a machine learning system that can, with 89 percent accuracy, identify in medical scans when breast cancer has metastasized, compared with a human accuracy rate of 73 percent.[120] In 2019, cancer biologist Neil Carragher at the University of Edinburgh used deep-learning techniques on a breast-cancer dataset from the Broad Bioimage Benchmark Collection to train a deep neural network that previously had seen only general images, such as of animals or cars. By scanning for patterns in the breast-cancer data, the model learned to discover certain cellular changes that could be useful for drug discovery. Moreover, because the software wasn't told what exactly to look for, it found features that researchers hadn't ever previously considered.[121] A team from the University of Texas Southwestern Medical Center in Dallas, Texas, developed an AI algorithm called ConvPath that classifies cell types from lung cancer pathology slides. The algorithm distinguishes between cell types based on their appearance in pathology images and converts the pathology image into a "map" that shows the spatial distributions and interactions of tumor cells and lymphocytes in tumor tissue. The algorithm achieved an overall classification accuracy of 92.9 percent in training datasets.[122] Similarly, the biotech start-up Berg has used AI to analyze large amounts of oncological data to create a complete model of how pancreatic cancer functions.[123] Based on this model, Berg identified specific metabolic processes that contribute to pancreatic cancer's rapid growth and developed a drug, currently in phase II trials, that targets these processes to make cancer cells more responsive to chemotherapy.[124]

Elsewhere, Kyun Hyun Sung, a radiologist at UCLA is building an AI-based system called FocalNet designed to help physicians better classify prostate cancer. Sung and his colleagues collected 400 pre-operative MRI scans of patients undergoing prostate-removal surgery and input those images along with the tumors' Gleason scores (a rating of malignancy, as determined by a pathologist) into the AI tool and trained the system to spot patterns in the MRI scans that matched the pathology-based scores.[125] The computer successfully identified 79.2 percent of significant cancer lesions (as determined by pathology), compared with a group of radiologists,

each with at least 10 years of experience reading more than 1,000 images annually, that managed a success rate of 80.7 percent.[126]

In summary, AI-enabled machine learning has become an increasingly prevalent tool in the biomedical community. With a high degree of accuracy, it's enabling the identification of the presence of cancers from ctDNA circulating in the bloodstream and the ability to connect that identification to the tissue of origin, just as it's facilitating the identification of cancerous cells based on an examination of images or facilitating the identification of cellular or metabolic processes as a basis for new drug development. As such, the increasing application of AI-based systems to disease detection and drug discovery represents a genuine revolution in the approach to modern medicine in general, and to cancer detection in particular.

The Benefits of Multi-cancer Early Detection Screening

Blood-based, MCED technologies are poised to bring a multitude of benefits to individual patients, health care systems, and even entire economies more broadly.

Earlier Detection

As noted, the most significant potential benefits of MCED technologies are: 1) to screen for a higher number of cancers—the vast majority of which currently have no recommended screening guidelines—and make this testing available to the asymptomatic population; and in so doing, ideally; 2) to detect cancers much earlier when odds of treatment success and long-term survival are (in general) much higher. Again, the first point is critical, as 70 percent of U.S. cancer deaths occur from cancers for which there are no guideline-recommended screenings—and it is simply not feasible to spend decades in developing and testing new screening approaches for every single individual cancer. In this regard, it's instructive to think about how to improve a nation's overall cancer detection rate (CDR). Of the 1.2 million cancers expected to have been diagnosed in U.S. adults ages 50 to 79 in 2020, only about 16 percent were diagnosed in whole or part through one of the five single-cancer screening tests (led by mammography, which detected approximately144,000, or 9 percent, of those cancers). Multi-cancer early detection approaches could make significant contributions to increasing the cancer detection rate in the general population, ideally at earlier stages when, for most cancers, treatment options and potential prognoses are far better.

America should aspire to a future wherein, within 10 years, 75 percent of cancers are screen-diagnosed, with roughly half that amount provided by MCED and single-cancer screening tests each.

As Dr. Vogelstein observes, the current system which detects cancers predominantly at late stages when patients show up at clinics manifesting physical symptoms is highly unsatisfactory. Whereas just about 20 percent of all cancers are detected through screening today, it appears to be technologically feasible, and we need to aspire to, a system in the next 5 to 10 years wherein we reverse that, with three-quarters of cancers being screen-detected and just one-quarter symptom-detected, and where roughly half the screen-detected diagnoses are provided by MCED technologies and half by single-cancer screening methods.[127]

Physical Patient Benefits

For patients, there are several potential additional ancillary benefits of MCED screening. First, MCED (and liquid or blood-based biopsies in general) represents a non-invasive procedure (beyond a blood draw). Moreover, as noted, many cancers present as unspecified pains in certain parts of the body, which can even be difficult to physically biopsy, so MCED expands the range of cancers for which earlier detection is physiologically possible. Second—and again, to be absolutely clear, experts view MCED screening as a complement to and not a substitute for current cancer screening guidelines—the ease of MCED approaches (a simple blood draw) could bolster the availability of and adherence to cancer screening guidelines. The practical and logistical ease of such testing could also benefit those living in rural or remote communities who may experience more difficulty in seeing doctors for physical screening exams or more difficulty in accessing specialized screening services, such as for mammography or low-dose computerized tomography (LDCT).

Closing the COVID-19-Induced Cancer Screening Gap

Another benefit of MCED technologies is that they offer a pathway to catch up on the gap in U.S. cancer screenings caused by the coronavirus crisis. Indeed, hundreds of thousands of cancer screenings were missed or deferred as a result of COVID-19's impact on the U.S. health system in 2020. A survey by the Prevent Cancer Foundation of more than 1,000 respondents found that about 35 percent of Americans have missed routine cancer screenings due to COVID-19 fears.[128] These missed cancer screenings are delaying diagnoses and causing some patients to arrive in worsened condition when they do get tested. For instance, according to Quest Diagnostics, the mean weekly number of newly diagnosed breast cancer patients fell by nearly 52 percent for March and early April 2020, compared with figures before the pandemic.[129] In an analysis of its roughly 32 million Medicare Advantage and commercial members, United Health counted nearly one million fewer mammograms and colorectal and cervical cancer screenings compared with the same period in 2019. Meanwhile, cancer-care provider 21st Century Oncology reported that 18 percent of its newly diagnosed breast-cancer patients through August 2020 had an advanced stage of the disease, compared with 12 percent for all of 2019.[130] William Cance, chief medical and scientific officer of the American Cancer Society, observes that due to the COVID-19 pandemic, "[w]e undoubtedly will have delays in diagnoses, and more advanced cancers."[131] Similarly, as National Cancer Institute Director Dr. Ned Sharpless notes, "There's really almost no way that [delaying screenings] doesn't turn into increased mortality."[132]

The disruption COVID-19 has wreaked on America's cancer screening paradigm only further emphasizes the pressing need to introduce new and effective approaches to cancer screening in the country.

In fact, according to the National Cancer Institute, missed screenings and other pandemic-related impacts on cancer care could result in about 10,000 additional deaths from breast and colon cancer (which together account for about one-sixth of all cancer deaths) alone over the next 10 years.[133] The Institute's research found that a 75 percent decrease in screening for those two cancers over a six-month period resulted in deferred or delayed care that alone would be enough to produce a 1 percent increase in excess deaths for those two tumor types over the next decade.[134] Dr. Sharpless notes that even that estimate was conservative, as it does not consider

other cancer types or for the additional nonlethal morbidity from upstaging, and it assumes a moderate disruption in care that completely resolves after just six months.[135] The disruption COVID-19 has wreaked on America's cancer screening paradigm only further emphasizes the pressing need to introduce new and effective approaches to cancer screening in the country, especially ones that could be carried out in a time of social distancing.

Addressing Racial and Socioeconomic Disparities in Cancer Screening

Another area where MCED approaches could deliver a patient benefit pertains to equity, in terms of cancer screenings and, potentially, end results. For instance, in their 2009 study, "A Matter Of Race: Early- Versus Late-Stage Cancer Diagnosis," Virnig et al. used data from the SEER cancer registry database for the period 1992 through 2003 to provide population-based cancer surveillance for 12 U.S. geographic areas. That study found that African Americans were diagnosed at more-advanced stages than whites for all four cancers with then-widely recommended screening procedures (female breast, colon, rectum, and cervix).[136] The study further found that African Americans were diagnosed at more-advanced stages than whites for 11 of 13 cancers, with an annual incidence of 5.0 per 100,000 or greater as well as for 15 of 16 tumor types with low annual incidence. Overall, African Americans were diagnosed at more advanced stages than whites for 31 of 34 tumor sites.[137]

MCED approaches could play an important role in reducing socioeconomic and racial disparities in cancer screening adherence and potentially cancer mortality rates.

A (2005) report commissioned by Pfizer, "Racial Differences in Cancer: A Comparison of Black and White Adults in the United States," confirmed the trend that African Americans generally receive cancer diagnoses at later stages. It notes:

> Five-year relative survival is lower in blacks than whites, 53% compared with 64%, respectively. Part of this disparity is because blacks are less likely to be diagnosed in the more survivable local stage. Among women, 40% of blacks and 50% of whites are diagnosed in the local stage. Among men, early diagnosis occurs in 54% and 58% of blacks and whites, respectively.[138]

The report confirms that diagnosis of cancer at the earliest (localized) stage is associated with higher survival rates. Among black men, five-year relative survival rates decline from 92 percent to 31 percent and 16 percent for those diagnosed in the local, regional, and distant stages, respectively. The corresponding rates for black women are 83 percent, 50 percent, and 15 percent.[139] (However, the report finds that five-year relative survival rates among blacks are lower than those among whites regardless of stage of diagnosis.) Regarding the early detection of lung cancer, the report notes that black adults are less likely to be diagnosed than white adults (15 percent vs. 18 percent) in the local stage.[140] Likewise, breast cancer in black women is less likely to be diagnosed in the local stage compared with white women (54 percent vs. 65 percent), contributing to higher mortality.[141] Regarding prostate cancer, the report found similarly high levels of diagnosis in the local/regional stage (91 percent for blacks and 94 percent for whites), but that blacks were 50 percent more likely than whites to be diagnosed in the less survivable distant stage (9 percent vs. 6 percent).[142] And a lower percentage of colorectal cancer in blacks was diagnosed in the local stage compared with whites (37 percent

vs. 41 percent in men, and 37 percent vs. 39 percent in women). As of 2020, African Americans still have the highest mortality rates of any racial or ethnic group for most cancers. And, while Hispanic men and women are less likely to be diagnosed with cancer than non-Hispanic whites overall, cancer is the leading cause of death among Hispanic Americans.[143]

The extent of cancer screening also varies considerably by state. For instance, the percentage of adults ages 50 to 75 who reported being up to date with colorectal cancer screening in 2016 ranged from 75.3 percent in Massachusetts to 59.9 percent in Mississippi.[144] Likewise, the percentage of female Medicare enrollees ages 65 to 74 that received an annual mammography screening in 2017 was 39 percent in Mississippi, compared with 54 percent in Massachusetts.[145] To be sure, there's a clear distinction between differences in the medical availability of cancer screenings across states and the differences in patients' partaking of those screenings across states. However, as Otis Brawley, Bloomberg distinguished professor of Oncology and Epidemiology at Johns Hopkins University, notes, many of the disparities in the differences among states in death rates from cancer pertain to socioeconomic factors, such as access to transportation, access to doctors and medical facilities, and affordability of care. In fact, he notes that for women diagnosed with breast cancer, the fatality rate is half in Massachusetts what it is in Mississippi.[146]

Certainly there exist a wide range of factors that inform and cause racial, geographic, and socioeconomic disparities in cancer screening rates and in cancer fatalities. However, differences in access to cancer screening do appear to be one causal factor.

Addressing Concerns About Multi-cancer Early Detection Screening

Some have raised potential concerns about MCED approaches, including that they might lead to overdiagnosis, might produce diagnoses for which there are no treatments, and that their use might add to overall health care system costs. This section addresses each of these potential misgivings in turn.

Minimizing Overdiagnosis and False Positive Returns

One of the potential concerns with MCED technologies pertains to their potential to detect indolent cancers, which are those that progress slowly and do not pose an imminent threat to a patient's health. Some have called these the types or stages of cancers that Americans will increasingly die "with," rather than "from." In other words, it's vitally important that MCED technologies be attuned (or optimized) to identifying particularly the invasive, fastest-growing, most-lethal cancers. In this regard, it's fortuitous that scientific research appears to indicate that indolent, less-aggressive cancers are less likely to shed ctDNA into the bloodstream and that it tends to be the more-aggressive, faster-growing cancers that are shedding the most ctDNA into the bloodstream, conferring better ability for MCED tests to discriminate between indolent and aggressive cancers.[147] For instance, according to GRAIL, its MCED test, Galleri, "detected the strongest signals for the most aggressive cancers, while detection of signals for indolent cancer types was low."[148] That finding is partially based on research from the company showing that detected cancers appear to have a prognosis, in terms of survival rates, similar to what was expected, based on 2006–2015 SEER data, whereas cancers not detected by Galleri had a more favorable prognosis than would be expected. As GRAIL explains, "This suggests that some indolent cancers are unlikely to be detected by Galleri, and Galleri could potentially reduce the potential harms from treatment of over-diagnosed cancers."[149] In general, scientific research

appears to connect the aggressiveness of cancers to tumor fragmentation rates, suggesting that cancer-detection technologies focused on these fragmentation rates may preferentially detect aggressive cancers. If it is in fact the case that MCED tests do perform this way, that will help mitigate the concern around over-diagnosis.

While avoiding overdiagnosis will be crucial to the success of MCED tests, the far greater challenge American (and global) society confronts is the underdiagnosis of cancers.

Closely related to the challenge of minimizing overdiagnosis is minimizing the return of false positives. While this will certainly be a challenge to be addressed with MCED screening, the reality is that it's a challenge with the current single cancer-screening paradigm already. The $27 billion America expends on cancer screening yields about 9 million positive results annually; of these, only 204,000 turn out to be actual cancers, while 8.8 million end up being false positives.[150] The (cumulative) screening tests recommended for a 60-year-old U.S. female with a history of smoking (thus suggesting screening for breast, colon, cervical, and lung cancers) yield a 37 percent likelihood of at least one false positive result.[151]

Based on the performance of an earlier version of GRAIL's Galleri, in its second CCGA sub-study, and extrapolating to a population aged 50 to 79 representative of 2006 to 2015 SEER data, the test achieved an estimated 43 percent positive predictive value, and the specificity would translate to 7,000 false positives per million tests. That's actually better performance than the five screening tests currently recommended by the U.S. Preventive Services Task Force (USPSTF): mammography for breast cancer, cytology/HPV tests for cervical cancer, colonoscopy and stool-based screenings for colorectal cancer, PSA blood tests for prostate cancer (on an individualized basis), and low-dose CT scans for lung cancer (in high-risk patients). For example, mammography 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 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.[152] In other words, multi-cancer early detection tests appear to at least be comparable to other cancer screening procedures in terms of their positive predictive value.

To be sure, optimizing MCED systems to avoid overdiagnosis and to increase their positive predictive value and lower false positives will be crucially important to the success of MCED screening tests. However, as Dr. Vogelstein noted, "America now suffers from a massive under-diagnosis problem."[153] Indeed, as this report shows, the far greater challenge American (and global) society confronts is the underdiagnosis of cancers, and the potential to make quite significant progress in that area should not be sacrificed out of fears of overdiagnosis, which the scientific evidence to date suggests can be limited by MCED technologies, especially as they iteratively and continually learn over time, which is likely to further improve their accuracy.

Diagnoses for Cancers Lacking Treatments

Some have raised concerns that MCED tests may lead to patients receiving a diagnosis for a form of cancer for which there are no effective medical treatments or therapeutics, such as pancreatic cancer. Yet this concern is misplaced for several reasons. First, patients deserve the right to receive forthright information about the state of their physical health, no matter how dire the diagnosis may be. Second, "a review of practice guidelines and the literature shows that nearly all early cancers have effective treatments, even if watchful waiting is recommended for some, such as nonaggressive early prostate cancers."[154] But, third, and more to the point, patients unfortunately receive a diagnosis that they have an incurable cancer (whether of a particular type or at a particular stage) all the time, and it matters little whether that news is delivered after receiving the results of a physical biopsy, or whether that knowledge is delivered earlier as a result of a specific liquid biopsy test or a broader MCED test.[155]

Patients individually, and society broadly, need more data, not less, about the prevalence of cancer.

Beyond this, one reason it has been difficult to develop treatments for certain cancers, such as pancreatic cancer, is that they are very difficult to diagnose at an early stage, and as such it's difficult to identify patient populations against which clinical trials for possible therapeutics can be run. If MCED tests were deployed more widely across the population, and proved to deliver on their potential to identify cancers emerging at earlier stages, they could contribute to the identification of populations against which clinical trials could be run. It's even conceivable in the future that, once such patient populations are identified, human or AI-based systems will be able to identify trends or patterns, suggesting certain biomarkers that could become targets for drug therapies or to identify trends or patterns among such patient populations that could be indicative of environmental or physical conditions that lead to the onset of such diseases. To be sure, the developers of MCED tests are focused on screening and diagnostics and are not making claims that their technologies can predict disease onset or identify biomarkers. But nevertheless, the point stands that a greater base of knowledge about patient populations with certain cancers at certain stages can provide a further platform on which innovation can occur to address some of these diseases, especially ones for which there are currently no effective treatments. In this regard, patients individually, and society broadly, need more data, not less, about the prevalence of cancer; especially when, as noted previously, AI combined with modern big data analytics methods are proving increasingly helpful in identifying biomarkers and developing therapeutics.

Of course, it's vital to recognize that, for all, the end goal is to reduce mortality from cancers, not simply to detect them. And it is true that the earlier detection of cancer may not change mortality for a specific individual or in cases where effective interventions are lacking. But, in most cases, it would certainly increase an individual's odds; and, moreover, not screening for a cancer because there may not be an effective treatment for that cancer simply is not a desirable or ideal approach.

More Cancer Diagnoses Will Only Exacerbate Health Care System Costs

Some have raised concerns that more-accurate cancer diagnoses will in turn lead to greater demand for cancer care, and that this will only exacerbate growing health care costs, especially if many of the diagnoses occur for citizens over the age of 50, many of whom are on Medicare. To

be sure, it is likely that if MCED testing is deployed across a large number of individuals, some cancers that would have been diagnosed otherwise will be detected by MCED tests. The potential increased cost of greater demand for cancer care from these additional cancers, however, would be offset by the dramatically expanded potential to diagnose cancers earlier, when, as noted previously, the costs of treatment are lower (and the odds of enhanced survival, and thus that individual's ability to return to productive enterprise, are higher).And though MCED is viewed as a complementary tool to existing guideline-recommended cancer screenings, it should be noted that blood-based tests themselves also introduce a potentially more economical cancer screening method, at least as compared with the costs of X-rays or MRIs. In these ways, MCED actually holds the potential to strongly align the interests of individuals and society—here meaning the government, when it's a payer (and taxpayers, individual or corporate, because they are always ultimately the payer)—by identifying cancers at an earlier stage and controlling health care costs in that way.

Across the broader U.S. health care system, treatment of metastatic cancer may be as much as two times more costly than treatment of cancer before it metastasizes.

Indeed, there is some evidence that effective cancer screening initiatives can decrease health system costs and generate positive returns on investment. For instance, a study by Homan et al. examined the impact of Missouri's Show Me Healthy Women (SMHW) program, an initiative designed to heighten awareness and uptake of breast cancer screening benefits in the state. Specifically, the study sought to estimate breast cancer treatment and health care services costs by stage of diagnosis among Missouri's Medicaid beneficiaries and assess the SMHW program impact. The study, of about 1,400 women, concluded that "a significantly higher proportion of SMHW participants were diagnosed at an early stage resulting in lower unadjusted expenditures and cost savings over time for Medicaid."[156] This study, akin to the ones referenced previously, affirmed the significant cost savings from being able to detect breast cancers earlier. That concords with the finding, as noted previously, that across the broader U.S. health care system, treatment of metastatic cancer may be as much as two times more costly than treatment of cancer before it metastasizes. Similarly, a study by Orsak et al. sought to examine the return on investment, in terms of reduced costs attributed to cancer prevention, of a colorectal cancer screening outreach program providing education and free screenings in a primarily rural Northeast Texas region targeting the uninsured and underinsured. The study found that, for fiscal years 2016 and 2017, the program delivered an average return of $1.46–$2.06 for every tax dollar spent. This translates into an estimated cost avoidance of $165,080 per avoided case and estimated cost avoidance of $245,601 among early-stage cancer cases detected, resulting in potential savings ranging from $3.89 million to $4.83 million.[157]

Beyond all this, an important point is that cost is not the key issue; cost benefit is the key issue. If we spend more money to treat cancers once detected, we spend more money, but if we can save lives cost effectively, then that is exactly what our health care system is supposed to do. If saving money is the paramount concern, then let's not conduct heart health exams and let's ban open heart surgery.

Why Multi-cancer Early Detection Should Be a Priority for the United States

There are several reasons leadership in early cancer multi-detection should be considered a priority for the United States, from both a domestic and international perspective.

Domestic Considerations

As explained, the first reason MCED should be a priority for the United States is its potential to considerably improve health care outcomes for American citizens thanks to the earlier detection of cancers, and the second is actually MCED's potential to help manage long-term health care system costs through the earlier detection of cancers. More widespread availability of MCED testing could also address equity issues related to cancer screening and care.

Another reason is that Americans desire greater access to cancer screening opportunities. For instance, in a survey of 1,400 Americans conducted by Lake Research, when asked how important early detection is in America's fight against cancer, 85 percent responded "very important" and 10 percent responded "important." When asked how important they thought it is for early detection tests to be developed for cancers that don't currently have available screenings, 81 percent responded "very important" and 13 percent "important" (none responded "not important"). If such screening becomes safe and effective, 91 percent responded that it would be a high priority to make such tests available to patients, and 95 percent responded that they believe such tests should be covered by Medicare.[158] Such broad public support for MCED screening represents another reason policymakers and health care providers and stakeholders should prioritize making such tests available to the public, if and when they are confirmed by the U.S. FDA as safe and efficacious.

International Considerations

As noted, the World Economic Forum identified liquid biopsies as one of the top-10 emerging technologies of 2020, and competitors in the field (especially of liquid biopsy, but also MCED) are emerging worldwide. As noted, South Korea's Genecast is developing ctDNA liquid biopsy tests that "can be applied to diagnosis, prognosis, prediction, treatment decision, treatment monitoring, and recurrence testing through accurate analysis of cancer genes." Genecast contends it can detect the "the most common mutations in non-small cell lung cancer with up to 0.01% sensitivity."[159]

Global competition for leadership in the field of liquid biopsy broadly, and MCED specifically, in terms of both production and adoption, has become increasingly fierce.

China has identified the biopharmaceutical industry as one in which it seeks global leadership, with the country's 11th Five Year Plan identifying "providing bioinformatics services for individualized diagnosis and treatment" as one of its key priorities.[160] Similarly, a 2019 report prepared for the U.S.-China Economic and Security Review Commission on China's biotechnology development efforts observes that "many [Chinese] companies are interested in liquid biopsy for cancer diagnostics."[161] For instance, it cites Singlera Genomics, which is developing proprietary technology for analysis of ctDNA and closed a $60 million series A round in early 2018.[162] Another company, HaploX Biotechnology, raised a $32 million funding round it intends to use for two major sequencing projects in the areas of lung cancer and colorectal cancer.[163]

As that report (among others) notes, China's strengths in genome sequencing—as the country is now the world's leader in genome sequencing capacity—gives its companies the potential to become increasingly viable players in the field of precision diagnostics and development of accurate, cost-effective, DNA-related diagnostic tests.[164] And as David Cyranoski notes in *Nature*, the Chinese government "has promised to add several precision drugs and molecular-diagnosis products to the national medical-insurance list, ensuring that companies' research costs will be recouped if they lead to such a product."[165] China understands both that scale and first-mover advantages matter, especially when getting into systems that start to incorporate AI technologies that are continually learning and improving by being trained on large datasets, and that committing the government as a procurer of such early detection technologies will build companies and markets, and allow for reinvestment into the next generation of R&D and product innovation in the field.

Apart from industry-level competitiveness in developing next-generation liquid biopsy-based and MCED tests is the issue of which nations will lead in making these tests available to their citizens most rapidly, and so be among the first countries to enjoy the patient and economic benefits MCED can bring. In November 2020, the United Kingdom's National Health Service (NHS) partnered with GRAIL to test Galleri in a program involving 165,000 British citizens (140,000 citizens over the age of 50 without any suspicions of cancer and 25,000 citizens ages 40 or over with indications of cancer) that seeks to validate the clinical and economic performance of the technology.[166] If the first stage goes positively, the NHS will seek to roll out the test to approximately one million British citizens in 2024–2025, and potentially to a larger population thereafter.

The point here is that global competition for leadership in the field of liquid biopsy broadly, and MCED specifically, in terms of both production and adoption, will become increasingly fierce. And as the Information Technology and Innovation Foundation (ITIF) noted in its report, "Reforming Regulation to Drive International Competitiveness," a nation's regulatory policies—especially with regard to expeditious regulatory approval approaches once products are confirmed to be safe and effective, as well as alignment with federal procurement procedures—can have a significant impact on the competitiveness of U.S. firms and industries.[167] In this particular instance, this suggests that the decisions the federal government faces with regard to approval and Medicare coverage of MCED screening tests will have a profound impact both on Americans' health and the ability of the industry to thrive in both domestic and international competition.

THE REGULATORY AND COVERAGE ENVIRONMENT FOR MCED

This section examines the regulatory and Medicare coverage reimbursement environment for MCED screening.

Regulatory Environment

The U.S. FDA has responsibility for evaluating the safety and efficacy of drugs and medical devices (which MCED tests are evaluated as). As ITIF noted in its report, "How the Prescription Drug User Fee Act (PDUFA) Supports Life-Sciences Innovation and Speeds Cures," the FDA is generally regarded as a world-leading drug/device evaluation agency, in part due to the contributions PDUFA has made in terms of helping provide a stable funding steam for the agency (enabling it to acquire the personnel and resources needed to make accurate and timely safety and efficacy evaluations) and in the performance goals the legislation sets for the agency.[168] In

fact, PDUFA, and its sister legislation, MDUFA (the Medical Device User Fee Act) have played an important role in helping innovative drugs and medical devices reach patients faster in the United States than in Europe or elsewhere. For instance, one study found that "the median time for approval for new cancer medicines in the United States was just six months—and that new anticancer medicines are typically available in the United States before they are in Europe."[169] One reason for this is the willingness of both Congress and the FDA to embrace innovative approaches to accelerate evaluation of potential breakthrough therapies. Specifically, in PDUFA V in 2012, the FDA created an expedited program for accelerated drug approvals: the "breakthrough-therapy" designation, which helps expedite the development and review of drug and biological products for serious or life-threatening diseases or conditions when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies.[170] Similarly, the FDA's Breakthrough Devices Program, which emerged from the agency's Expedited Access Pathway program, aims to speed the development and assessment of devices that promise a more effective treatment or diagnosis for life-threatening or irreversibly debilitating conditions.[171] As of May 2020, the FDA had granted 298 breakthrough device designations since the program's inception.[172] In May 2019, GRAIL received a breakthrough device designation from the FDA for its MCED test.[173] GRAIL's and other companies' MCED tests will need to receive final approval from the FDA before they can be broadly adopted.

Another area where the FDA's efforts are to be commended is in creating regulatory pathways to facilitate the emergence of innovative IT-based medical devices, software, and digital technologies. For instance, the agency has created a Digital Health Unit. The agency is also trying to be thoughtful about how to regulate medical devices that incorporate AI, recognizing that by their nature they can be programmed to continually innovate and improve. In a 2019 discussion paper, "Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device," the agency noted, "The traditional paradigm of medical device regulation was not designed for adaptive AI/ML technologies, which have the potential to adapt and optimize device performance in real-time to continuously improve healthcare for patients."[174] In response, the FDA has proposed a framework that introduces a "predetermined change control plan" in pre-market submissions that requires commitments from manufacturers on transparency and real-world performance monitoring for AI and machine learning-based software as a medical device, as well as periodic updates to the FDA on what changes were implemented as part of the approved pre-specifications and the algorithm change protocol.[175] In other words, the FDA would issue device pre-market authorizations or clearances that include change protocols permitting autonomous updates. Additionally, the FDA's (pilot) Pre-certification Program would move from individual product review to a firm-based review of software as or in a medical device. The FDA is to be commended for thinking innovatively about regulating novel medical devices, whether smart electrocardiogram (ECG) devices or MCED tests, that incorporate AI/ML elements which permit optimized device performance in real time to continuously improve health care outcomes for patients.

The Evolution of the Medicare Coverage Environment for Cancer Screening

As medical science's understanding of cancer has evolved over the past half century, so has the evolution of recommended cancer screening guidelines. Only five types of cancer—breast, cervical, colorectal, prostate, and "high-risk" lung—have guideline-recommended screening options available today, meaning there's tremendous potential to develop effective screening

options for many other types of cancers. Moreover, with persons over 65 accounting for 60 percent of newly diagnosed malignancies and 70 percent of all cancer deaths, this issue becomes even more important for Americans on Medicare—and that's why ensuring that Medicare recognizes MCED screening as a covered benefit will be so vital to helping detect cancers in America's seniors earlier when treatment options are better.

Launched in 1966, Medicare is a program administered by the Centers for Medicare and Medicaid Services that helps pay for health care services for citizens over the age of 65, certain younger people with disabilities, and individuals with end-stage renal disease.[176] When Medicare was launched, it initially covered only acute health care situations (e.g., sicknesses or hospitalizations). However, over time, Medicare added a range of covered benefits (within specified patient parameters) for preventive services, such as for cardiovascular disease (i.e., Medicare Part B covers cardiovascular screening blood tests once every five years), diabetes (up to two screenings per year), hepatitis C, and HIV.[177] Today, in terms of cancer, Medicare provides covered screening benefits for cervical and vaginal cancer, colorectal cancer, lung cancer (LDCT, once each year), mammograms, and prostate cancer.

As medical science's understanding of cancer has evolved over the past half century, so has the evolution of recommended cancer screening guidelines.

However, Medicare does not cover cancer screening as a preventive benefit except where Congress has explicitly amended Medicare laws to provide such coverage. Cancer screening was for the first time added as a statutorily covered Medicare benefit when the Omnibus Budget Reconciliation Act (OBRA) of 1989 added coverage for pap smear tests (and pelvic exams) to examine for cervical and vaginal cancers. A year later, OBRA of 1990 added a benefit for mammography to examine for breast cancer. Specifically Section 4163 of the 1990 OBRA explicitly added coverage for "screening mammography," defined as "a radiologic procedure provided to a woman for the purpose of early detection of breast cancer." Importantly, each of these covered benefits applies only to the modality specified, such that Medicare provides a covered benefit for mammograms (i.e., a radiological procedure) but not for other potential modalities of breast cancer screening.

Seven years elapsed before Congress again expanded statutorily covered cancer screening benefits in Medicare, with the Balanced Budget Act of 1997 adding prostate and colorectal cancer screening benefits.[178] Importantly, instead of specifying a modality for colorectal cancer screening, the legislation was crafted to provide flexibility in terms of the types of colorectal cancer screening tests covered, including:

> (A) Screening fecal-occult blood cancer test; (B) Screening flexible sigmoidoscopy; (C) In the case of an individual at high risk for colorectal cancer, screening colonoscopy; (D) Such other tests of procedures, and modifications to tests and procedures under this subsection, with such frequency and payment limits, as the Secretary determines appropriate, in consultation with appropriate organizations.[179]

The expansiveness of the covered benefit for colorectal screenings has proven to be prescient, for today it allows for Medicare to provide benefits for colorectal cancer screening modalities that didn't exist in the late 1990s. For instance, home-based stool DNA tests such as Exact Sciences'

Cologuard can detect microscopic amounts of blood in stool samples and check for certain DNA changes and mutations found in cancerous tumors or precancerous polyps, indicating the potential presence of colon cancer. Recognizing that DNA changes and mutations may differ between colon cancers, the stool DNA test targets multiple DNA markers, which has helped other such tests achieve high detection rates of early-stage colon cancer.[180] The Centers for Medicare & Medicaid Services (CMS) is also now in the process of evaluating for coverage approval several potential blood-based biomarker screening tests for colorectal cancer.[181] In other words, by not limiting itself to particular modalities, the 1997 Balanced Budget Act provided a constructive pathway for innovative colorectal cancer screening approaches to emerge in future years and receive Medicare coverage.

In 2008, the Medicare Improvements Patients Providers Act (MIPPA) proscribed a new pathway through which Medicare can provide coverage of new preventive services under certain conditions. It charged the United States Preventive Services Task Force, an independent, volunteer panel of national specialists in prevention and evidence-based medicine, with evaluating proposed preventive screenings and assigning each recommendation a letter grade (an A, B, C, or D grade or an I statement) based on the strength of the evidence and the balance of benefits and harms of a preventive service, with services receiving an "A" or "B" rating being eligible to become a Medicare-covered benefit.[182] Recommendations made by the USPSTF also have considerable implications on private health insurance coverage. That's because of an Affordable Care Act provision requiring that private insurance plans cover recommended preventive services without any patient cost-sharing. (The required preventive services come from recommendations made by four expert medical and scientific bodies—USPSTF, the Advisory Committee on Immunization Practices, the Health Resources and Services Administration's (HRSA's) Bright Futures Project, and HRSA and the Institute of Medicine (IOM) committee on women's clinical preventive services).[183]

Ensuring that Medicare recognizes MCED screening as a covered benefit will be vital to helping detect cancers in America's seniors earlier when treatment options are better.

Among the USPSTF's first charges was evaluating low-dose CT as a preventative screening for lung cancer. In 2002, the National Cancer Institute launched the National Lung Screening Trial (NLST), a multi-year study comparing low-dose CT to X-rays in 53,000 people ages 55 to 74 at heightened risk for lung cancer. In 2004, the USPSTF issued an "I" recommendation for lung cancer screening with LDCT, chest X-ray, sputum cytology, or a combination of these tests, meaning it found that "evidence is insufficient to recommend for or against routinely providing [the service]."[184] In 2011, the results of the NLST study were released in the *New England Journal of Medicine*, finding that LDCT resulted in a 20 percent reduction in lung cancer mortality and a 6.7 percent decrease in all-cause mortality.[185] A 2013 study in *Cancer* found that low-dose CT scans held the potential to reduce the number of lung cancer deaths in the United States by as much as 20 percent per year—saving the lives of about 12,250 people, equivalent to 7.6 percent of the total lung cancer population in the United States.[186] Acknowledging these findings, in 2013, USPSTF issued a "B" recommendation on LDCT screening for those ages 55 to 80 at elevated risk for lung cancer.[187] Yet, in May 2014, the Medicare Coverage Advisory Committee (MEDCAC) found low to intermediate confidence that there existed adequate evidence that the benefits of annual LDCT screening outweighed the

harms and voted against recommending national Medicare coverage for annual screening for lung cancer with LDCT in high-risk individuals.[188] However, in November 2014, CMS reversed course and announced that it would after all cover the cost of low-dose CT scans for individuals between the ages of 55 and 74 who smoke, or who quit within the last 15 years, and who have a smoking history of 30 pack-years.[189] While ultimately the process did arrive at inclusion of low-dose CT as a covered Medicare benefit in 2015 for adults 55–77 at high risk for lung cancer, Laurie Fenton Ambrose of the Lung Cancer Alliance notes that "lung cancer screening for the at-risk public … was encumbered by the timing of these final policy determinations, despite its scientific validation in 2010."[190]

Evaluating the benefits and harms of cancer screening procedures is essential, even more so in cases where the cancer screening method itself can have deleterious consequences for patients. For instance, in South Korea, thyroid ultrasound screening guidelines in the early 2010s caused a tenfold increase in thyroid cancer incidence; since 2015, when the Korean Committee for National Cancer Screening Guidelines recommended against the screening approach, incidence of the disease in South Korea has been fairly flat.[191] Similarly, chest X-rays for lung or breast cancer introduce radiation to the patient. Meanwhile, the more extensive colorectal screening procedures can themselves induce harms such as bowel perforations, intestinal bleeding resulting in hospitalizations, and adverse events from anesthesia.[192] It's all the more important to weigh the benefits and harms of cancer screening tests—beyond the traditional concerns of overdiagnosis, false positives, and psychological effects—when the tests themselves may introduce new physical harms to the patient.

And in fact that's all the more reason new human liquid- or blood-based tests, whether Cologuard or related stool DNA-based colorectal screening tests or MCED tests, are needed more than ever, because they can present a complementary way to screen for cancers without those physical harms. That's also why it's imperative that policymakers create a pathway—as soon as MCED screening tests receive FDA safety and efficacy approval—to get them to the public, which can benefit from them on a timely basis. Once the tests have been validated as safe and effective, Americans, especially ones who rely in part or in full on federal support for health care, shouldn't have to wait a half decade or longer to enjoy access to such tests. And one important way Congress can achieve that, as it has done several times in the past, is to specify that MCED screening becomes a covered Medicare benefit.

Policy Recommendations

This report offers the following policy recommendations.

Provide a pathway for Medicare coverage of multi-cancer early detection screening tests. Building on previous congressional action to create Medicare coverage for cancer screenings including mammography and colorectal screening, on March 16, 2021, U.S. Representatives Terri Sewell (D-AL), Jodey Arrington (R-TX), Raul Ruiz (D-CA), and Richard Hudson (R-NC) introduced the Medicare Multi-Cancer Early Detection Screening Coverage Act.[193] Companion legislation has been introduced in the Senate by Senators Bennet (D-CO), Crapo (R-IH), Cardin (D-MD), and Scott (R-SC).[194] The Act addresses the misalignment between advances in science and Medicare coverage by permitting Medicare coverage of multi-cancer screening. The Act creates the authority for the CMS to use an evidence-based process to cover blood-based MCED tests and future test methods once approved by the FDA, while maintaining CMS's authority to use an

evidence-based process to determine coverage parameters for these new types of tests. It affirms that multi-detection tests are designed to complement, not replace, existing screening methods, noting that beneficiaries receiving a multi-cancer detection test would still have full access to other recommended screening exams. The Act would ensure Medicare beneficiaries are eligible to benefit on a timely basis from MCED screening technologies. Importantly, like the Balanced Budget Act's treatment of colorectal screening, the legislation does not specify particular modalities for multi-cancer detection tests, noting that such tests may include: "(1) a genomic sequencing blood or blood product test that includes the analysis of cell-free nucleic acids. (2) Such other equivalent tests (which are based on urine or other samples of biological material) as the Secretary determines appropriate."[195]

Boost National Institutes of Health funding. Achieving far greater early detection of cancers is critical in the fight against the disease, but gains will also need to continue to be complemented with new drugs and therapies as well. As Dr. Bert Vogelstein observes, "The key to reducing cancer deaths is to combine earlier detection with improved therapeutics."[196] An important component of that is increased federal funding for basic life-sciences research—for instance, into understanding the fundamental processes by which diseases develop and are transmitted, or identifying novel biomarkers that signal the presence of a disease—which creates a platform for innovation that leads not only to the discovery of new medicines, but to new tests, procedures, and equipment.[197] One reason cancer mortality rates have declined by 25 percent over the past two decades is in part NIH-supported breakthroughs such as genomic analysis of tumors, precision medicine (e.g., treatment of a tumor by targeting a specific mutant gene that drives it), and use of immunotherapy with checkpoint inhibitors. Indeed, R01 applications to NIH's National Cancer Institute increased by almost 50 percent between 2013 and 2018.[198] However, NIH data shows that the average age of Ph.D. applicants at the time they win their first grant approval increased from 34 in 1970 to 42 in 2015.[199] That in part signals a lack of funding for promising research and researchers.

Public and private investment in life-sciences research is strongly complementary.[200] And, while it is true that NIH funding increased 64 percent between 1990 and 2019, NIH funding as a share of GDP peaked in 2003 and declined through 2015. In fact, NIH funding as a share of GDP in 2019 remained 12 percent below 2003 levels. The Biden administration should work with Congress to at least restore NIH funding to 2003 levels as a share of GDP, which would entail boosting NIH funding by $11.6 billion per year, and then maintain regular, steady increases—ideally 2 to 3 percentage points faster than the nominal rate of GDP growth—thereafter. Of note in this regard, the Biden campaign platform calls for $300 billion in increased innovation funding over four years, including a call for "major increases" in NIH funding (however, the Biden administration has not enumerated a specific amount in this regard).[201]

Within NIH, the National Cancer Institute's proposed budget for the 2022 fiscal year includes a funding increase of $1.17 billion, plus an additional $194 million for the Cancer Moonshot, which plans to address cancer treatment, obesity, and survivorship.[202] In his campaign, President Biden affirmed he would sustain the Cancer Moonshot program, which he led as Vice President during the Obama administration, and which aims to double the rate of progress in the prevention, detection, diagnosis, and treatment of cancer.

Increase investment in America's biomedical STEM talent. The United States needs to invest more in biomedical science, technology, engineering, and mathematics (STEM) talent. As one study finds:

> The lack of a biomanufacturing workforce that is well trained in [current good manufacturing procedures and analytics] and that could populate clinical and industrial manufacturing settings is seriously hampering the progress and translation of cell therapies. Significant investment in developing such a workforce—both at the level of 2-year community or technical colleges or standard 4-year universities—is critically needed.[203]

Congress should take several steps to address this. First, Congress should expand the Manufacturing Engineering Education Program from its current $15 million annual funding. In its FY 2021 budget request, the Department of Defense (DOD) asked for Congress to at least double the program's funding.[204] Congress should oblige. Further, Congress should direct DOD to develop a competition for biomedical manufacturing programs.[205] In addition, Congress should expand funding for the National Science Foundation's (NSF's) Advanced Technical Education program and target the funds to the development of centers focused on industry skill needs. Increasing linkages with industry for doctoral STEM students can improve the quality of research and education. To increase these linkages, Congress should appropriate $20 million per year for the establishment of an NSF-Industry Ph.D. Fellows Program to support an additional 1,000 Ph.D. students in STEM fields.[206] The new NSF-industry program would work by enabling industry to contribute $20,250 toward each fellowship, in whatever field(s) each company chooses. NSF would match industry funds dollar for dollar.[207]

Support data-driven life-sciences Innovation. As this report has shown, the advent of big data and AI is likely to facilitate life-sciences innovation in both the discovery of new disease screening mechanisms and new drug therapies. It represents one of the many approaches being taken to try to improve R&D productivity in the biopharmaceutical industry.[208] For instance, as of November 2019, at least 43 biopharma companies were using AI for drug discovery, including by partnering with AI start-ups.[209] But achieving the full promise of data-driven life-sciences innovation will require Congress to take several steps to address a number of obstacles.

First, Congress should direct the Department of Health and Human Services (HHS) to implement a unique patient identifier, as originally intended by the Health Insurance Portability and Accountability Act (HIPPA). Though electronic health record usage is commonplace, health care providers do not have an accurate and efficient method of matching patients' records across different systems.

Second, policymakers should enforce the publication of data from clinical trial results by directing agencies such as the FDA and NIH to be more aggressive about penalizing noncompliance. The FDA's finalized rule for penalizing noncompliance went into effect in January 2018, but according to a January 2020 report by researchers at the University of Oxford, compliance with the rule is poor, and not improving.[210]

Third, Congress should direct HHS to create a model for data trusts that facilitates data sharing among biopharmaceutical stakeholders involved with data-driven drug development. This model

could be adapted from data trusts being developed in other countries, such as the United Kingdom.

Fourth, policymakers should increase the availability of new kinds of data, such as biometric, lifestyle, and environmental data, from nontraditional sources. This could be supported by fully funding NIH to accelerate the development of the All of Us Research Program's million-person research cohort.

Fifth, policymakers should direct the FDA to develop best practices for data collection in health care to ensure equitable outcomes, such as strategies to increase coverage of underrepresented populations.

Overcoming these obstacles should be a priority for policymakers because enabling data-driven life-sciences innovation would not only accelerate access to more effective and affordable treatments for Americans, but help maintain the competitiveness of the U.S. biopharmaceutical industry.

CONCLUSION

Multi-cancer early detection leverages newly emerging biological and information technologies to usher in a transformative paradigm shift in cancer screening approaches. With February 4, 2021, marking the 50th anniversary of the "War on Cancer" proclaimed by President Richard Nixon, and initiated in the landmark 1971 National Cancer Act, it's time to add a new front to the battle, one that dramatically expands the nation's ability to screen for and detect cancer at its earliest stages before it has metastasized and spread throughout the body. To be sure, innovative drugs and therapies to treat cancers will remain indispensable, but MCED offers the opportunity to complement the nation's strength in therapeutic treatments with the ability to detect cancers at earlier and more-treatable stages. Not only could this produce tremendous quality and longevity of life benefits, but earlier detection of cancers makes economic sense for the nation as well both in terms of the documented cost savings from earlier versus later treatments as well as the productivity impact from both treating and returning citizens to productive work and saving many years of lost life. Cancer has proven to be a relentless and wily enemy. To defeat it, we're going to need to embrace equally creative solutions and radically new approaches, such as how checkpoint blockading and cancer immunotherapy transformed cancer therapy—despite the intense early resistance the approach encountered. MCED heralds the potential to mark a significant breakthrough in the war against cancer, to dramatically enhance patients' lives by detecting cancers earlier, and to put the nation's cancer response on a more-sustainable economic footing. It's time for policymakers to boldly embrace this opportunity.

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ENDNOTES

1. American Cancer Society (ACS), "Cancer Facts & Figures 2020," 1, https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf.

2. World Health Organization, "Early cancer diagnosis saves lives, cuts treatment costs," news release, February 3, 2017, https://www.who.int/news/item/03-02-2017-early-cancer-diagnosis-saves-lives-cuts-treatment-costs.

3. Soumita Ghose, Vivek Radhakrishnan, and Sanjay Bhattacharya, "Ethics of Cancer Care: Beyond Biology and Medicine," *Cancer* Vol. 13, 911 (2019), 8; N. Faiza et al., "The dire need for primary care specialization in India: Concerns and challenges," *J Family Med Prim Care* Vol. 5, Issue 2 (2016): 228, https://doi.org/10.4103/2249-4863.192382.

4. Gilles R Dagenais et al., "Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): a prospective cohort study," *The* Lancet Vol. 395, Issue 10226 (March 7, 2020): 785–794, https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)32007-0/fulltext.

5. American Cancer Society, "Facts & Figures 2021 Reports Another Record-Breaking 1-Year Drop in Cancer Deaths," news release, January 12, 2021, https://www.cancer.org/latest-news/facts-and-figures-2021.html.

6. Honor Whiteman, "'1 in 2 people will develop cancer in their lifetime'," *Medical News Today*, February 4, 2015, https://www.medicalnewstoday.com/articles/288916.

7. *The Atlantic*, "People vs. Cancer Summit," November 18, 2020, https://peoplevcancer.theatlantic.com/.

8. Whiteman, "'1 in 2 people will develop cancer in their lifetime'."

9. Cancer Action Network, "New Legislation Aims to Increase Early Cancer Detection in Medicare," news release, December 3, 2020, https://www.fightcancer.org/releases/new-legislation-aims-increase-early-cancer-detection-medicare.

10. Nathan A Berger et al., "Cancer in the Elderly" *Transactions of the American Clinical and Climatological Association* Vol. 117 (2006): 147–155, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1500929/.

11. Dr. Norman "Ned" Sharpless, Director, National Cancer Institute, National Institutes of Health, "Remarks at 'People v. Cancer Summit'" (AtlanticLIVE, November 18, 2020), https://www.youtube.com/watch?v=xIEisUiYNwM.

12. Presentation of Judy Hoyos, Executive Vice President, Prevent Cancer Foundation, "Webinar on the Multi-Cancer Early Detection Screening Coverage Act," March 10, 2021, https://tinyurl.com/yhoexce3.

13. Ibid.

14. Azra Raza, "Cancer is Still Beating Us—We Need a New Start," *The Wall Street Journal*, October 4, 2019, https://www.wsj.com/articles/cancer-is-still-beating-uswe-need-a-new-start-11570206319.

15. "Deaths by cancer in the U.S. from 1950 to 2017 (per 100,000 population)," Statista, https://www.statista.com/statistics/184566/deaths-by-cancer-in-the-us-since-1950/.

16. Rebecca L. Siegel, Kimberly D. Miller, and Ahmedin Jemal, "Cancer statistics, 2019," *CA: A Cancer Journal for Clinicians* Vol. 69, Issue 1, (2019): 7–34, https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21551.

17. American Cancer Society, "Cancer Facts & Figures 2020," 1.

18. Susan G. Komen Foundation, "The Who, What, Where, When and Sometimes, Why.," https://www.komen.org/breast-cancer/facts-statistics/survival-rates/; Monique Ellis, "The most

successful cancer drugs in 2019," *Proclinical*, March 13, 2019, https://www.proclinical.com/blogs/2019-3/the-most-successful-cancer-drugs-in-2019.

19. Seth A. Seabury et al., "Quantifying Gains in the War on Cancer Due to Improved Treatment and Earlier Detection," *Forum for Health Economics & Policy*, Vol. 19, Issue 1 (November 2015), https://www.degruyter.com/view/journals/fhep/19/1/article-p141.xml.

20. Frank R. Lichtenberg, "The Impact of Pharmaceutical Innovation on Premature Cancer Mortality in Canada, 2000-2011" (working paper no. 212139, National Bureau of Economic Research, June 2015), http://www.nber.org/papers/w21239.

21. Raza, "Cancer is Still Beating Us—We Need a New Start."

22. Remarks of Dr. Bert Vogelstein, "Webinar on the Multi-Cancer Early Detection Screening Coverage Act" (March 10, 2021), https://tinyurl.com/yhoexce3.

23. Raza, "Cancer is Still Beating Us—We Need a New Start."

24. Mingyang Song et al., "Cancer prevention: Molecular and epidemiologic consensus," *Science* Vol. 361, Issue 6409 (September 2018): 1317–1318, https://science.sciencemag.org/content/361/6409/1317/tab-pdf.

25. Anita Soni, "Top Five Most Costly Conditions among Adults Age 18 and Older, 2012: Estimates for the U.S. Civilian Noninstitutionalized Population," Statistical Brief #471 (Agency for Healthcare Research and Quality, April 2015), https://www.meps.ahrq.gov/data_files/publications/st471/stat471.pdf.

26. Matthew P. Banegas et al., "Medical Care Costs Associated With Cancer in Integrated Delivery Systems," *Journal of the National Comprehensive Care Network* Vol. 16, No. 4 (April 2018): 402–409, https://pubmed.ncbi.nlm.nih.gov/29632060/.

27. Zura Kakushadze, Rakesh Raghubanshi, and Willie Yu, "Estimating Cost Savings from Early Cancer Diagnosis," *Data* Vol. 2, Issue 30 (September 2017), https://www.researchgate.net/publication/319475610_Estimating_Cost_Savings_from_Early_Cancer_Diagnosis; Angela B. Mariotto, "Projections of the Cost of Cancer Care in the United States: 2010–2020," *Journal of the National Cancer Institute* Vol. 103, Issue 2 (January 2011): 117–128, https://academic.oup.com/jnci/article/103/2/117/2568866.

28. Andrew Shooshtari, Yamini Kalidindi, and Jeah Jung, "Cancer Care Spending and Use by Site of Provider-Administered Chemotherapy in Medicare," *The American Journal of Managed Care* Vol. 25, Issue 6 (June 2019), https://www.ajmc.com/view/cancer-care-spending-and-use-by-site-of-provideradministered-chemotherapy-in-medicare.

29. Joshua J. Ofman and Azra Raza, "Taking Early Cancer Detection to the Next Level," *Scientific American*, November 1, 2020, https://www.scientificamerican.com/article/taking-early-cancer-detection-to-the-next-level/.

30. Farhad Islami, MD et al., "National and State Estimates of Lost Earnings From Cancer Deaths in the United States," *Journal of American Oncology* Vol. 5, Issue 9 (2019), https://jamanetwork.com/journals/jamaoncology/article-abstract/2737074.

31. K. Robin Yabroff, "Estimates and Projections of Value of Life Lost From Cancer Deaths in the United States," *Journal of the National Cancer Institute* Vol. 100, Issue 24 (December 17, 2008): 1,755–1,762, https://academic.oup.com/jnci/article/100/24/1755/2606867.

32. Kevin Murphy and Robert Topel, "The value of health and longevity," *Journal of Political Economy* (2006), 114:871–904, https://www.nber.org/papers/w11405.

33. Darius N. Lakdawalla, "An Economic Evaluation of the War Against Cancer," *Journal of Health Economics* Vol. 29, Issue 3 (May 2010): 333–346, https://www.sciencedirect.com/science/article/abs/pii/S0167629610000214?via%3Dihub#!.

34. Ibid.

35.   Kakushadze, Raghubanshi, and Yu, "Estimating Cost Savings from Early Cancer Diagnosis," 2.

36.   American Cancer Society, "Cancer Facts & Figures 2020," 1.

37.   Alexander M. Aravanis, Mark Lee, and Richard Klausner, "Next-Generation Sequencing of Circulating Tumor DNA for Early Cancer Detection," *Cell* Vol. 168, Issue 4 (2017): 571–574, https://pubmed.ncbi.nlm.nih.gov/28187279/.

38.   "GRAIL Announces Validation of Its Multi-Cancer Early Detection Test Published in Annals of Oncology," *Biospace*, news release, https://www.biospace.com/article/releases/grail-announces-validation-of-its-multi-cancer-early-detection-test-published-in-annals-of-oncology/. Citing: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data, Nov 2018 Sub. Includes persons ages 50–79 diagnosed 2006–2015. "Early/Localized" includes invasive localized tumors that have not spread beyond organ of origin, "Late/Metastasized" includes invasive cancers that have metastasized beyond the organ of origin to other parts of the body.

39.   Christina A. Clarke, "Projected Reductions in Absolute Cancer–Related Deaths from Diagnosing Cancers Before Metastasis, 2006–2015," *Cancer Epidemiology, Biomarkers, and Prevention* Vol. 29, Issue 5 (May 2020), https://cebp.aacrjournals.org/content/29/5/895.

40.   Ibid.

41.   Ronald Piana, "The Ongoing Challenges of Lung Cancer Screening," *The ASCO Post*, May 25, 2017, https://ascopost.com/issues/may-25-2017/the-ongoing-challenges-of-lung-cancer-screening/.

42.   Cancer Research UK, "Why is early diagnosis important?" https://www.cancerresearchuk.org/about-cancer/cancer-symptoms/why-is-early-diagnosis-important.

43.   Remarks of Dr. Bert Vogelstein, "Webinar on the Multi-Cancer Early Detection Screening Coverage Act."

44.   Raza, "Cancer is Still Beating Us—We Need a New Start."

45.   U.S. Preventive Services Task Force (USPSTF), "Recommendations," https://www.uspreventiveservicestaskforce.org/uspstf/topic_search_results?topic_status=P. Screening includes methods with a USPSTF A, B, or C rating (breast, colon, cervical, prostate, and lung).

46.   Joshua J. Ofman and Azra Raza, "Taking Early Cancer Detection to the Next Level," *Scientific American*, November 1, 2020, https://www.scientificamerican.com/article/taking-early-cancer-detection-to-the-next-level/.

47.   Ibid.

48.   Presentation of Bert Vogelstein, "Webinar on the Multi-Cancer Early Detection Screening Coverage Act."

49.   American Cancer Society, "History of Cancer Screening and Early Detection," https://www.cancer.org/cancer/cancer-basics/history-of-cancer/cancer-causes-theories-throughout-history11.html.

50.   Natasha Gilbert, "An uncertain diagnosis," *Nature* Vol. 579 (March 26, 2020), https://media.nature.com/original/magazine-assets/d41586-020-00841-8/d41586-020-00841-8.pdf.

51.   Doug Rix, "Cancer screening; What's new, what's coming and what you should consider," *SSWire*, February 3, 2020, https://www.swissre.com/reinsurance/life-and-health/reinsurance/cancer-risks/cancer-screening-what-you-should-consider.html.

52.   Seth A. Seabury et al., "Quantifying Gains in the War on Cancer Due to Improved Treatment and Earlier Detection," *Forum for Health Economics & Policy*, Vol. 19, Issue 1 (November 2015), https://www.degruyter.com/view/journals/fhep/19/1/article-p141.xml.

53.   Ibid., 150.

54. Ibid.

55. Djenaba A. Joseph, MD et al., "*Vital Signs*: Colorectal Cancer Screening Test Use–United States, 2018," Centers for Disease Control and Prevention, https://www.cdc.gov/mmwr/volumes/69/wr/mm6910a1.htm.

56. Seabury et al., "Quantifying Gains in the War on Cancer Due to Improved Treatment and Earlier Detection," 153.

57. Banegas et al., "Medical Care Costs Associated With Cancer in Integrated Delivery Systems," 408.

58. Kakushadze, Raghubanshi, and Yu, "Estimating Cost Savings from Early Cancer Diagnosis," 2.

59. Ibid., 13.

60. Ibid.

61. Helen Blumen, Kathryn Fitch, and Vincent Polkus, "Comparison of Treatment Costs for Breast Cancer, by Tumor Stage and Type of Service," *American Health Drug Benefits* Vol. 9, Issue 1 (February 2016): 23–32, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4822976/.

62. Based on stage II and stage IV breast, colorectal, lung cancer, and metastatic/non-metastatic pancreatic cancer: Banegas et al., "Medical Care Costs Associated With Cancer in Integrated Delivery Systems"; Stacey Costa Byfield et al., "Healthcare costs, treatment patterns, and resource utilization among pancreatic cancer patients in a managed care population" *Journal of Medical Economics* Vol.16, Issue 12 (December 2013): 1379-1386, https://pubmed.ncbi.nlm.nih.gov/24074258/.

63. Catherine Alix-Panabières, "Perspective: The future of liquid biopsy," *Nature*, March 25, 2020, https://www.nature.com/articles/d41586-020-00844-5.

64. Dr. Catherine Marinac, Member of the Faculty at Dana-Farber Cancer Research Institute, "Remarks at 'People v. Cancer Summit'" (AtlanticLIVE, November 18, 2020), https://www.youtube.com/watch?v=xIEisUiYNwM.

65. Tim Peacock, "Grail's $1 Billion Bet on the Perfect Cancer Test," *MIT Technology Review*, June 5, 2017, https://www.technologyreview.com/2017/06/05/4591/grails-1-billion-bet-on-the-perfect-cancer-test/.

66. Antonio Regalado, "Bankrolling the 10 Breakthrough Technologies: Liquid Biopsy," *MIT Technology Review*, November 23, 2015, https://www.technologyreview.com/2015/11/23/164959/bankrolling-the-10-breakthrough-technologies-liquid-biopsy/.

67. Chetan Bettegowda et al., "Detection of Circulating Tumor DNA in Early- and Late-Stage Human Malignancies," *Science Translational Medicine* Vol. 6, Issue 4 (February 19, 2014), https://stm.sciencemag.org/content/6/224/224ra24.short.

68. Alex Antoniou, "Jeff Bezos Backed Grail To Disrupt Cancer Detection," *HealthBrew*, "Jeff Bezos Backed Grail To Disrupt Cancer Detection," September 25, 2020, https://www.healthbrew.org/articles/jeff-bezos-backed-grail-to-disrupt-cancer-detection.

69. BCC Research, "Liquid Biopsy Research Tools, Services and Diagnostics: Global Markets," April 2019, https://www.bccresearch.com/market-research/biotechnology/liquid-biopsy-research-tools-services-diagnostics.html.

70. U.S. Department of Health and Human Services Food and Drug Administration, Center for Devices and Radiological Health, "Public Workshop: Detecting Circulating Tumor DNA for Cancer Screening" (FDA, March 9, 2020), 19, https://www.fda.gov/medical-devices/workshops-conferences-medical-devices/public-workshop-detecting-circulating-tumor-dna-cancer-screening-03092020-03092020.

71. Dr. Norman "Ned" Sharpless, "Remarks at 'People v. Cancer Summit."

72. Remarks of Hans Bishop, Chief Executive Officer, GRAIL, Inc., "Webinar on the Multi-Cancer Early Detection Screening Coverage Act."

73. National Institutes of Health, National Cancer Institute, "Study Examines Whether Blood Test Can Identify Early Cancers," June 2, 2020, https://www.cancer.gov/news-events/cancer-currents-blog/2020/cancerseek-blood-test-detect-early-cancer.

74. Ibid.

75. Ibid.

76. Thrive, "Meet the Team," https://thrivedetect.com/meet-the-team/.

77. M. C. Liu et al., "Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA," *Annals of Oncology* Vol. 31, Issue 6 (March 2020): 745–759, https://www.annalsofoncology.org/article/S0923-7534(20)36058-0/pdf.

78. Cristian Tomasetti, Lu Li, and Bert Vogelstein, "Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention" *Science* Vol. 335, 6631 (March 2017): 1330-1334, https://pubmed.ncbi.nlm.nih.gov/28336671/.

79. Remarks of Dr. Bert Vogelstein, "Webinar on the Multi-Cancer Early Detection Screening Coverage Act."

80. Theresa Phillips, Ph.D., "The Role of Methylation in Gene Expression," *Nature,* 2008, https://www.nature.com/scitable/topicpage/the-role-of-methylation-in-gene-expression-1070/.

81. Joshua J. Ofman, Megan P. Hall, and Alexander M. Aravani, "GRAIL and the quest for earlier multi-cancer detection" *Nature*, 2018, https://www.nature.com/articles/d42473-020-00079-y.

82. Ibid.

83. Exact Sciences Corporation, "DNA Biomarker Detection," https://www.exactsciences.com/innovative-science/screening.

84. Gabriel D. Dakubo, *Cancer Biomarkers in Body Fluids Principles* (Springer International Publishing, 2016), https://www.springer.com/gp/book/9783319015798.

85. Alexander M. Aravanis, Mark Lee, and Richard D. Klausner, "Next-Generation Sequencing of Circulating Tumor DNA for Early Cancer Detection," *Cell* Vol. 168 (February 9, 2017), https://pubmed.ncbi.nlm.nih.gov/28187279/.

86. Ofman, Hall, and Aravani, "GRAIL and the quest for earlier multi-cancer detection."

87. Ibid.

88. Ibid.

89. Ibid.

90. Neil Savage, "Another set of eyes for cancer diagnostics," *Nature* Vol. 579 (March 26, 2020), S14, https://media.nature.com/original/magazine-assets/d41586-020-00847-2/d41586-020-00847-2.pdf.

91. Ibid., S15.

92. M. C. Liu et al., "Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA."

93. GRAIL, "GRAIL Announces Validation of its Multi-Cancer Early Detection Test Published in Annals of Oncology," news release, March 30, 2020, https://grail.com/press-releases/grail-announces-validation-of-its-multi-cancer-early-detection-test-published-in-annals-of-oncology/.

94. Ibid.

95. M. C. Liu et al., "Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA," 754.

96. Earl Hubbell et al., "Modeled reductions in late-stage cancer with a multi-cancer early detection test," *Cancer Epidemiology, Biomarkers, and Prevention* (December 16, 2020), https://cebp.aacrjournals.org/content/early/2020/12/12/1055-9965.EPI-20-1134.

97. GRAIL, Inc., "New Research Suggests Multi-Cancer Early Detection Blood Test Could Reduce Late-Stage Cancer Diagnoses by More Than Half," news release, December 16, 2020, https://grail.com/press-releases/new-research-suggests-multi-cancer-early-detection-blood-test-could-reduce-late-stage-cancer-diagnoses-by-more-than-half/.

98. "What Is Precision Medicine?" U.S. National Library of Medicine, accessed July 22, 2019, https://ghr.nlm.nih.gov/primer/precisionmedicine/definition.

99. National Institutes of Health, National Human Genome Research Institute, "A Brief Guide to Genomics," https://www.genome.gov/about-genomics/fact-sheets/A-Brief-Guide-to-Genomics.

100. Elisa Port, Chief of Breast Surgery, Mount Sinai Health System, "Remarks at 'People v. Cancer Summit" (AtlanticLIVE, November 18, 2020), https://www.youtube.com/watch?v=xIEisUiYNwM.

101. Joshua New, "The Promise of Data-Driven Drug Development" (ITIF, September 2019), 8, https://itif.org/publications/2019/09/18/promise-data-driven-drug-development. Note, the FDA considers the drug development lifecycle to have five stages, with the "preclinical research" coming before the clinical research stage.

102. "The Cost of Sequencing a Human Genome," National human Genome Research Institute, accessed July 22, 2019, https://www.genome.gov/27565109/the-cost-of-sequencing-a-human-genome/.

103. Emily Mullin, "The Price of DNA Sequencing Dropped From $2.7 Billion to $300 in Less Than 20 Years," *One Zero*, February 18, 2020, https://onezero.medium.com/the-price-of-dna-sequencing-dropped-from-2-7-billion-to-300-in-less-than-20-years-f5e07c2f18b4; "DNA Sequencing Costs: Data," National Human Genome Research Institute, accessed July 22, 2019, https://www.genome.gov/27541954/dna-sequencing-costs-data/; Bradley J. Fikes, "Focus: new Machines Can Sequence Human Genome in One Hour, Illumina Announces," *The San Diego Union-Tribune*, January 9, 2017, https://www.sandiegouniontribune.com/business/biotech/sd-me-illumina-novaseq-20170109-story.html; Megan Molteni, "Now You Can Sequence Your Whole Genome for Just $200," *Wired*, November 11, 2019, https://www.wired.com/story/whole-genome-sequencing-cost-200-dollars/.

104. E. Mathé et al., "The Omics Revolution Continues: The Maturation of High-Throughput Biological Data Sources," *Yearbook of Medical Informatics* No. 1, (August 2018): 211–222, https://www.ncbi.nlm.nih.gov/pubmed/30157526.

105. Sinisia Bratulic, Francesco Gatto, and Jens Nielsen, "The translational status of cancer liquid biopsies" *Regenerative Engineering and Translational Medicine* Vol. 25 (2019) 25: 1-41, https://link.springer.com/article/10.1007/s40883-019-00141-2.

106. Exact Sciences Corporation, "Exact Sciences Announces Fourth Quarter 2020 Results," news release, February 16, 2021, https://investor.exactsciences.com/investor-relations/press-releases/press-release-details/2021/Exact-Sciences-Announces-Fourth-Quarter-2020-Results/default.aspx.

107. New, "The Promise of Data-Driven Drug Development," 9.

108. Esther Landhuis, "Deep Learning Takes on Tumors," *Nature*, Vol. 580 (April 23, 2020), https://www.nature.com/articles/d41586-020-01128-8.

109. National Institutes of Health, National Cancer Institute, "The Cancer Genome Atlas Program," https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga.

110. Landhuis, "Deep Learning Takes on Tumors," 552.

111. Daniel Castro and Joshua New, "The Promise of Artificial Intelligence" (Center for Data Innovation, October 2016), 2, http://www2.datainnovation.org/2016-promise-of-ai.pdf.

112. Ibid., 2.

113. Nick Heath, "What is deep learning? Everything you need to know," *ZDNet*, August 7, 2018, https://www.zdnet.com/article/what-is-deep-learning-everything-you-need-to-know/.

114. "Accelerating Clinical trials Through Access to Real-World Patient Data" (InterSystems), accessed July 26, 2019, https://www.intersystems.com/isc-resources/wp-content/uploads/sites/24/Accelerating_Clinical_Trials_Through-_Access_to_Real-World_Patient_Data_WP.pdf.

115. Castro and New, ""The Promise of Artificial Intelligence," 3.

116. Amit Karp, "Deep Learning Will Be Huge—and Here's Who Will Dominate It," *Venture Beat*, April 2, 2016, http://venturebeat.com/2016/04/02/deeplearning-will-be-huge-and-heres-who-will-dominate-it/.

117. Heath, "What is deep learning? Everything you need to know."

118. New, "The Promise of Data-Driven Drug Development," 2. Note, the FDA considers the drug development lifecycle to have five stages, with the "preclinical research" coming before the clinical research stage.

119. Yueqin Li, "Deep learning enables scientists to identify cancer cells in blood in milliseconds," UCLA news release, August 21, 2019, https://newsroom.ucla.edu/releases/deep-learning-identifies-cancer-cells-in-blood.

120. Yun Liu et al., "Detecting Cancer Metastases on Gigapixel Pathology Images," March 8, 2017, https://arxiv.org/abs/1703.02442.

121. Landhuis, "Deep Learning Takes on Tumors," 552.

122. UT Southwestern Medical Center, "New software tool uses AI to help doctors identify cancer cells," news release, December 9, 2019, https://www.utsouthwestern.edu/newsroom/articles/year-2019/ai-identifies-cancer-cells.html.

123. Laura Lorenzetti, "This Company Wants to Cure Pancreatic Cancer Using AI," *Fortune*, April 22, 2016, http://fortune.com/2016/04/22/berg-pacreatic-cancer-artificial-intelligence/.

124. Ibid.

125. Savage, "Another set of eyes for cancer diagnostics," S15.

126. Ruiming Cao, "Joint Prostate Cancer Detection and Gleason Score Prediction in mp-MRI via FocalNet," *IEEE Trans Med Imaging* Vol. 38, Issue 11 (November 2019): 2496–2506, https://pubmed.ncbi.nlm.nih.gov/30835218/.

127. Remarks of Dr. Bert Vogelstein, "Webinar on the Multi-Cancer Early Detection Screening Coverage Act."

128. Adrianna Rodriguez, "People 'afraid to go to doctors': A third of Americans miss cancer screenings, survey suggests," *USA Today*, July 28, 2020, https://www.usatoday.com/story/news/health/2020/07/28/coronavirus-pandemic-americans-keep-canceling-cancer-screenings-survey/5524899002/.

129. Anna Wilde Mathews and Mike Cherney, "Covid-19 Outbreaks Led to Dangerous Delay in Cancer Diagnoses," *The Wall Street Journal*, October 15, 2020, https://www.wsj.com/articles/covid-19-outbreaks-led-to-dangerous-delay-in-cancer-diagnoses-11602756013.

130. Ibid.

131. Ibid.

132. Ibid.

133. Norman E. Sharpless, "COVID-19 and Caner," *Science*, Vol. 368, Issue 6497 (June 2020): 1290, https://science.sciencemag.org/content/368/6497/1290.

134. Jo Cavallo, "How Delays in Screening and Early Cancer Diagnosis Amid the COVID-19 Pandemic May Result in Increased Cancer Mortality: A Conversation With NCI Director Norman E. 'Ned' Sharpless, MD," *The ASCO Post*, September 10, 2020, https://ascopost.com/issues/september-10-2020/how-delays-in-screening-and-early-cancer-diagnosis-amid-the-covid-19-pandemic-may-result-in-increased-cancer-mortality/.

135. Ibid.

136. Beth A. Virnig et al., "A Matter Of Race: Early- Versus Late-Stage Cancer Diagnosis," *Health Affairs* Vol. 28, Issue 1 (2009): 160–168, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2766845/pdf/nihms78588.pdf.

137. Ibid.

138. Pfizer, "Racial Differences in Cancer: A Comparison of Black and White Adults in the United States" (Pfizer, 2005), 2, https://pfe-pfizercom-d8-prod.s3.amazonaws.com/products/Racial_Differences_in_Cancer.pdf.

139. Ibid., 6.

140. Ibid., 29.

141. Ibid., 16.

142. Ibid., 21.

143. The National Minority Quality Forum, "National Minority Quality Forum Urges Action in Multi-Cancer Early Detection," news release, December 4, 2020, https://www.nmqf.org/nmqf-media/mced.

144. Centers for Disease Control and Prevention, "Use of Colorectal Cancer Screening Tests by State," https://www.cdc.gov/cancer/dcpc/research/articles/use-colorectal-screening-tests-state.htm.

145. County Health Rankings and Roadmaps, "Mammography screening" (accessed December 1, 2020), https://www.countyhealthrankings.org/explore-health-rankings/measures-data-sources/county-health-rankings-model/health-factors/clinical-care/quality-of-care/mammography-screening.

146. Otis Sharpley, Bloomberg Distinguished Professor of Oncology and Epidemiology, Johns Hopkins University, "Remarks at 'People v. Cancer Summit'" (AtlanticLIVE, November 18, 2020), ttps://www.youtube.com/watch?v=xIEisUiYNwM.

147. Oliver Venn et al., "Tumor Shedding into Cell-free DNA (cfDNA) is Associated with High-mortality Cancers," (poster presented at: The Biology of Genomes Meeting, May 7-11, 2019, Cold Spring Harbor, New York), https://grail.com/wp-content/uploads/2019/05/BOG_2019_Tumor_Fraction_Venn_Poster_Final-1.pdf; A similar statement was made by Dr. Catherine Marinac, "Remarks at 'People v. Cancer Summit.'"

148. M. C. Liu et al., "Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA."

149. Ibid.

150. Ofman and Raza, "Taking Early Cancer Detection to the Next Level."

151. Constance D. Lehman et al., "National Performance Benchmarks for Modern Screening Digital Mammography: Update from the Breast Cancer Surveillance Consortium" *Radiology* Vol. 283, Issue 1 (December 5, 2016), https://pubs.rsna.org/doi/full/10.1148/radiol.2016161174; U.S. Food and Drug Administration, "PMA P130017: FDA summary of safety and effectiveness data," August 11, 2014; Joy Melnikow et al., "Screening for Cervical Cancer With High-Risk Human Papillomavirus Testing" *Journal of the American Medical Association* Vol, 320, Issue 7 (2018): 687-705, https://jamanetwork.com/journals/jama/fullarticle/2697703; Paul F. Pinsky et al., "Performance of Lung-RADS in the National Lung Screening Trial: a retrospective assessment" *Annals of Internal Medicine* Vol. 162, Issue 7 (April 2015): 485-491, https://pubmed.ncbi.nlm.nih.gov/25664444/.

152. Constance D. Lehman et al., "National Performance Benchmarks for Modern Screening Digital Mammography: Update from the Breast Cancer Surveillance Consortium" *Radiology* Vol. 283, Issue

1 (2017): 49-58, https://pubs.rsna.org/doi/pdf/10.1148/radiol.2016161174; Jane J. Kim, "Screening for Cervical Cancer in Primary Care: A Decision Analysis for the US Preventive Services Task Force" *Journal of the American Medical Association* Vol. 320, Issue 7 (2018): 706-714, https://jamanetwork.com/journals/jama/fullarticle/2697702; U.S. Food and Drug Administration, "Premarket Approval (PMA): Cologuard," https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P130017; Exact Sciences Corporation, "Cologuard: Colorectal cancer (CRC) is the most preventable yet least prevented form of cancer," https://www.cologuardhcp.com/crc-screening-unmet-need/crc-landscape; Paul F. Pinsky et al., "Performance of Lung-RADS in the National Lung Screening Trial: a retrospective assessment" *Annals of Internal Medicine* Vol. 162, Issue 7 (2015): 485-491, https://pubmed.ncbi.nlm.nih.gov/25664444/; Paul F. Pinsky and Christine D. Berg, "Applying the National Lung Screening Trial eligibility criteria to the US population: what percent of the population and of incident lung cancers would be covered?" *Journal of Medical Screening* Vol. 19, Issue 3 (2012): 154-156, https://pubmed.ncbi.nlm.nih.gov/23060474/.

153. Remarks of Dr. Bert Vogelstein, "Webinar on the Multi-Cancer Early Detection Screening Coverage Act."

154. Ofman and Raza, "Taking Early Cancer Detection to the Next Level."

155. A patient receiving a false positive for a cancer that is not treatable would hopefully receive an all-clear diagnosis upon further physical examination.

156. Dr. Sherri G. Homan et al., "Breast Cancer Population Screening Program Results in Early Detection and Reduced Treatment and Health Care Costs for Medicaid," *Journal of Public Health Management Practices* Vol. 27, Issue 1 (2019): 70–79, https://pubmed.ncbi.nlm.nih.gov/31592983/.

157. 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* Vol. 4 (2020): 71–77, https://link.springer.com/article/10.1007/s41669-019-0147-y.

158. Lake Research Partners, "Public Support for MCED Questionnaire," September 2020, https://irp-cdn.multiscreensite.com/167e816a/files/uploaded/MCED.Topline.2020.10.22.pdf.

159. Genecast, "Liquid Biopsy for Cancer Diagnostics," https://www.igenecast.com/.

160. Robert D. Atkinson, "China's Biopharmaceutical Strategy: Challenge or Complement to U.S. Industry Competitiveness?" (ITIF, August 2019), https://itif.org/publications/2019/08/12/chinas-biopharmaceutical-strategy-challenge-or-complement-us-industry.

161. Mark Kazmierczak et al. "China's Biotechnology Development: The Role of US and Other Foreign Engagement" (Gryphon Scientific, February 2019), https://www.uscc.gov/sites/default/files/Research/US-China%20Biotech%20Report.pdf.

162. Singlera Genomics, "Singlera Genomics Raises $60 Million in Series A+ Financing," news release, March 27, 2018, https://www.prnewswire.com/news-releases/singlera-genomics-raises-60-million-in-series-a-financing-300619990.html.

163. *GenomeWeb*, "Chinese Firm HaploX Biotechnology Raises $32M in Financing," January 3, 2018, https://www.genomeweb.com/informatics/chinese-firm-haplox-biotechnology-raises-32m-financing.

164. *Dark Daily*, "Why China Is Now the World Leader in Genome Sequencing Capacity," https://www.darkdaily.com/why-china-is-now-the-world-leader-in-genome-sequencing-capacity-062810/; Kazmierczak, et al. "China's Biotechnology Development."

165. David Cyranoski, "China's bid to be a DNA superpower," *Nature,* June 22, 2016, https://www.nature.com/news/china-s-bid-to-be-a-dna-superpower-1.20121.

166. GRAIL, Inc. "GRAIL and UK Government to Make Galleri Multi-Cancer Early Detection Blood Test Available to Patients," news release, November 26, 2020, https://grail.com/press-releases/grail-and-uk-government-to-make-galleri-multi-cancer-early-detection-blood-test-available-to-patients/.

167. Joseph P. Kennedy, "Reforming Regulation to Drive International Competitiveness" (ITIF, March 2015), http://www2.itif.org/2015-reforming-regulation-drive-international.pdf.

168. Stephen J. Ezell, "How the Prescription Drug User Fee Act (PDUFA) Supports Life-Sciences Innovation and Speeds Cures" (ITIF, February 2017), http://www2.itif.org/2017-pdufa-life-sciences-innovation.pdf.

169. Samantha A. Roberts, Jeff D. Allen, and Ellen V. Sigal, "Despite Criticism of the FDA Review Process, New Cancer Drugs Reach Patients Sooner in the United States Than in Europe," *Health Affairs 30*, no. 7 (2011): 1375–1381, http://content.healthaffairs.org/content/30/7/1375.full.pdf+html.

170. Ezell, "How the Prescription Drug User Fee Act (PDUFA) Supports Life-Sciences Innovation and Speeds Cures," 13.

171. Jacob Bell, "FDA Breakthrough Devices Program nears 300 designations," *MedTech Dive*, May 27, 2020, https://www.medtechdive.com/news/fda-breakthrough-devices-orteq-archerdx-terumo-thermedical-helius-photopharmics/578562/.

172. Ibid.

173. "Grail's multi-cancer blood test gets FDA breakthrough status," *PM Live*, May 14, 2019, http://www.pmlive.com/pharma_news/grails_multi-cancer_blood_test_gets_fda_breakthrough_status_1287854.

174. The U.S. Food and Drug Administration, "Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) - Discussion Paper and Request for Feedback" (U.S. FDA, April 2019), https://www.fda.gov/media/122535/download.

175. U.S. Food and Drug Administration, "Artificial Intelligence and Machine Learning in Software as a Medical Device," https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device.

176. Medicare.gov, "What is Medicare?" https://www.medicare.gov/what-medicare-covers/your-medicare-coverage-choices/whats-medicare.

177. Medicare.gov, "Is my test, item, or service covered?" https://www.medicare.gov/coverage/preventive-screening-services.

178. Congressional Research Service, "Medicare Coverage of Clinical Preventive Services" (CRS, March 2010), 8, https://crsreports.congress.gov/product/pdf/R/R40978/6.

179. Federal Register, "Balanced Budget Act of 1997," 42 CFR Part 400, https://omlc.org/news/jan98/BBA1997.txt.

180. Colorectal Cancer Alliance, "Stool DNA," https://www.ccalliance.org/screening-prevention/screening-methods/stool-dna.

181. Centers for Medicare & Medicaid Services, "Proposed Decision Memo for Screening for Colorectal Cancer - Blood-Based Biomarker Tests (CAG-00454N)," https://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?NCAId=299&bc=AAgAAAAACAAA&.

182. U.S. Preventative Services Task Force, "About the USPTF," https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf.

183. Kaiser Family Foundation, "Preventive Services Covered by Private Health Plans under the Affordable Care Act," August 4, 2015, https://www.kff.org/health-reform/fact-sheet/preventive-services-covered-by-private-health-plans/.

184. U.S. Preventative Services Task Force, "Final Recommendation Statement: Lung Cancer: Screening" (USPSTF, May 15, 2004), https://www.uspreventiveservicestaskforce.org/uspstf/document/RecommendationStatementFinal/lung-cancer-screening-2004.

185. Stacey Butterfield, "Lung cancer screening guideline debated," *ACP Internist*, March 2014, https://acpinternist.org/archives/2014/03/lung-cancer.htm; Denise R. Aberle, "Results of the Two Incidence Screenings in the National Lung Screening Trial," *New England Journal of Medicine* Vol. 369 (September 5, 2013): 920–931, https://www.nejm.org/doi/full/10.1056/NEJMoa1208962.

186. Jessica Firger, "CT Scans for Lung Cancer May Save More Lives," *EveryDayHealth*, February 25, 2013, https://www.everydayhealth.com/lung-cancer/ct-scans-for-lung-cancer-may-save-more-lives.aspx.

187. U.S. Preventative Services Task Force, "Final Recommendation Statement: Lung Cancer: Screening" (USPSTF, December 31, 2013), https://www.uspreventiveservicestaskforce.org/uspstf/document/RecommendationStatementFinal/lung-cancer-screening.

188. Zosia Chustecka, "Panel Says No to Medicare Coverage for Lung Cancer Screening," *Medscape*, May 1, 2014, https://www.medscape.com/viewarticle/824427.

189. Howard LeWine, M.D., "Medicare says it will cover lung cancer scans for long-time smokers," *Harvard Health Publishing,* November 11, 2014, https://www.health.harvard.edu/blog/medicare-says-will-cover-lung-cancer-scans-long-time-smokers-201411117511; Centers for Medicare & Medicaid Services, "Decision Memo for Screening for Lung Cancer with Low Dose Computed Tomography (LDCT) (CAG-00439N)," https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=274.

190. Piana, "The Ongoing Challenges of Lung Cancer Screening."

191. Rix, "Cancer screening; What's new, what's coming and what you should consider."

192. Jennifer M. Croswell, David F. Ransohoff, and Barnett Karmer, "Principles of Cancer Screening: Lessons from History and Study Design Issues," *Semin Oncology* Vol. 37, Issue 3 (June 2010): 202–215, https://pubmed.ncbi.nlm.nih.gov/20709205/.

193. U.S. Representative Terri Sewell, "Reps. Sewell, Arrington, Ruiz, and Hudson Introduce Bipartisan Legislation to Ensure Access to Innovative Multi-Cancer Screening Technologies for Medicare Beneficiaries," news release, March 16, 2021, https://sewell.house.gov/media-center/press-releases/reps-sewell-arrington-ruiz-and-hudson-introduce-bipartisan-legislation-0.

194. Senator Michael Bennet, "Bennet, Crapo, Colleagues Introduce Legislation to Ensure Medicare Beneficiaries Receive Coverage for Cancer Detection Technologies," news release, December 17, 2020, https://www.bennet.senate.gov/public/index.cfm/2020/12/bennet-crapo-colleagues-introduce-bipartisan-legislation-to-ensure-medicare-beneficiaries-receive-coverage-for-cancer-detection-technologies.

195. Congress.gov, "H.R. 8845: The Medicare Multi-Cancer Early Detection Screening Coverage Act of 2020."

196. Remarks of Dr. Bert Vogelstein, "Webinar on the Multi-Cancer Early Detection Screening Coverage Act."

197. Dr. Everett Ehrlich, "An Economic Engine: NIH Research, Employment, and the Future of the Medical Innovation Sector" (United for Medical Research, 2011), 3, http://www.eyeresearch.org/pdf/UMR_Economic%20Engine_042711a.pdf.

198. National Institutes of Health, "Research Portfolio Online Reporting Tools (RePORT)," https://report.nih.gov/.

199. Robert D. Atkinson et al., "Leadership in Decline: Assessing U.S. International Competitiveness in Biomedical Research" (ITIF and United for Medical Research, May 2012), 8, http://www2.itif.org/2012-leadership-in-decline.pdf; National Institutes of Health, National Institute on Aging, "R01 teams and grantee age trends in grant funding."

200. Stephen Ezell, "Ensuring U.S. Biopharmaceutical Competitiveness" (ITIF, July 2020), 45–46, http://www2.itif.org/2020-biopharma-competitiveness.pdf.

201. Robert D. Atkinson et al., "President-Elect Biden's Agenda on Technology and Innovation Policy" (ITIF, November 2020), 15, http://www2.itif.org/2020-biden-tech-innovation-policy.pdf.; "THE BIDEN PLAN TO ENSURE THE FUTURE IS 'MADE IN ALL OF AMERICA' BY ALL OF AMERICA'S WORKERS," joebiden.com https://joebiden.com/made-in-america/.

202. "Will cancer be a winner in the U.S. election?" *The Lancet* Vol 21, Issue 3 (October 2020): 153, https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(20)30548-9/fulltext

203. Isabelle Rivière and Krishnendu Roy, "Perspectives on Manufacturing of High-Quality Cell Therapies," *Molecular Therapy* Vol. 25, Issue 5 (May 2017): 1067–1068, https://www.sciencedirect.com/science/article/pii/S1525001617301715.

204. United States Department of Defense, "Department of Defense Fiscal Year (FY) 2021 Budget Estimates" (Department of Defense, February 2020), https://comptroller.defense.gov/Portals/45/Documents/defbudget/fy2021/budget_justification/pdfs/03_RDT_and_E/RDTE_Vol3_OSD_RDTE_PB21_Justification_Book.pdf.

205. American Institute of Physics, "Final FY19 Appropriations: STEM Education," news release, March 8, 2019, https://www.aip.org/fyi/2019/final-fy19-appropriations-stem-education.

206. Stephen J. Ezell and Robert D. Atkinson, "Fifty Ways to Leave Your Competitiveness Woes Behind: A National Traded Sector Competitiveness Strategy" (ITIF, 2011), http://www2.itif.org/2012-fifty-ways-competitiveness-woes-behind.pdf.

207. Robert D. Atkinson and Merrilea Mayo, "Refueling the U.S. Innovation Economy: Fresh Approaches to Science, Technology, Engineering and Mathematics (STEM) Education" (ITIF, 2010), 156, http://www.itif.org/files/2010-refueling-innovation-economy.pdf.

208. Peter Tollman et al., "Unlocking Productivity in Biopharmaceutical R&D" (Boston Consulting Group, January 2016), https://www.bcg.com/en-us/publications/2016/unlocking-productivity-in-biopharmaceutical-rd---the-key-to-outperforming.aspx; Massachusetts Institute of Technology (MIT) Startup Exchange, "Improving R&D Productivity in the Biopharmaceutical Industry," https://startupexchange.mit.edu/node/17406.

209. Simon Smith, "43 pharma companies using artificial intelligence in drug discovery," *BenchSci*, June 24, 2020, https://blog.benchsci.com/pharma-companies-using-artificial-intelligence-in-drug-discovery.

210. Nicholas J DeVito, Seb Bacon, and Ben Goldacre, "Compliance with legal requirement to report clinical trial results on ClinicalTrials.gov: a cohort study" *The Lancet* Vol. 395 (2020): 361–369, https://doi.org/10.1016/S0140-6736(19)33220-9.