REVIEW SUMMARY

CANCER

Early detection of cancer

David Crosby*, Sangeeta Bhatia, Kevin M. Brindle, Lisa M. Coussens, Caroline Dive, Mark Emberton, Sadik Esener, Rebecca C. Fitzgerald, Sanjiv S. Gambhir, Peter Kuhn, Timothy R. Rebbeck, Shankar Balasubramanian*

BACKGROUND: When cancer is detected at the earliest stages, treatment is more effective and survival drastically improves. Yet ~50% of cancers are still only detected at an advanced stage. Improved earlier detection of cancer could substantially increase survival rates. Although recent advances in early detection have saved lives, further innovations and development of early cancer detection approaches are needed. The field is evolving rapidly, owing to advances in biological understanding and an increasing pace of technological progress.

ADVANCES: We highlight five challenges facing the field, current work in those areas, and where more research is needed to make early detection a reality. The first challenge is to build a greater understanding of the biology and behavior of early disease. This will help identify ways to distinguish between consequential, aggressive lesions and inconsequential lesions that will not cause harm. Such insight will be crucial to realizing the potential for early detection to inform treatment decisions and improve survival, while minimizing the risk of overtreatment. Alongside studies in human samples, better models of disease are enabling identification of early signals of tumorigenesis and clarifying the contributions of the immune system and microenvironment to tumor development.

The second challenge is determining the risk of developing cancer. How can we use germline genomic susceptibility, family history, exposures, demographic, and behavioral data to build nuanced risk models to identify who should be tested for cancer and how test results should be interpreted and followed up? Progress is being made to address this challenge through improved understanding of the genomics of cancer risk, integration of that insight with other risk factors, and the development of large-scale population cohorts where risk models can be developed and validated.

The third challenge is finding and validating biomarkers of early cancer. There is considerable difficulty in finding accurate signals of early cancer (which usually exist in very small amounts) amid the noise of normal human physiology. Although progress has historically been slow, many promising early detection markers are emerging, including circulating tumor DNA, circulating tumor cells, proteins, exosomes, and cancer metabolites. Advances in data analysis methodologies (such as machine learning) and integration across marker types in multimodal tests are also accelerating progress.

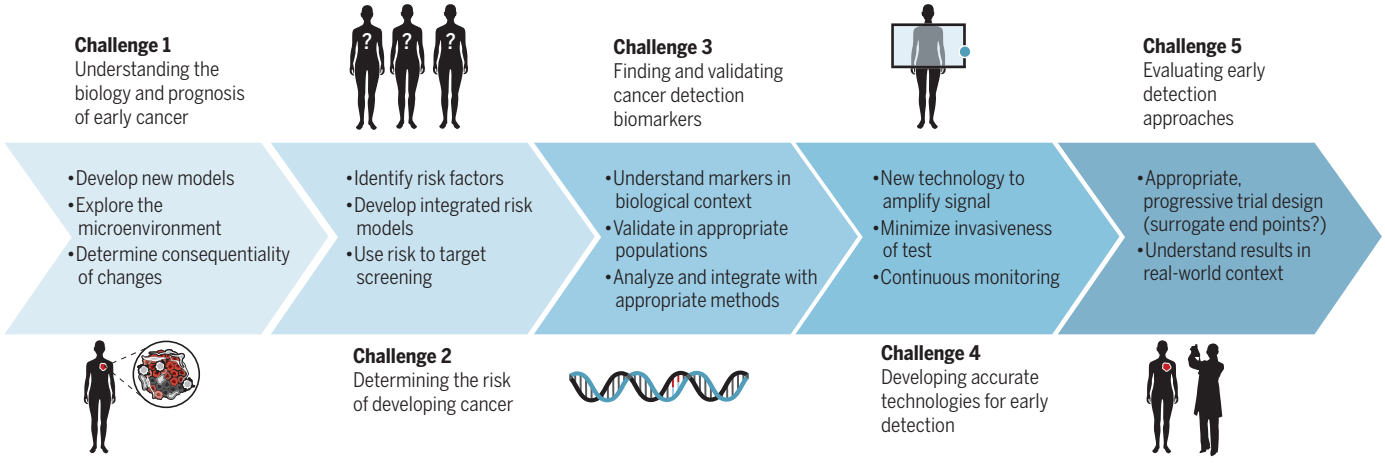
The fourth challenge is technological. It involves both the iterative improvement of existing approaches and the development of disruptive detection technologies that can very sensitively and specifically identify early biological changes, whether in tissue structure, biochemistry, or function. Powerful molecular analytical technologies and advanced imaging and histopathological methods are increasing the ability to sensitively find earlier tumors, while the use of synthetic markers may help to amplify their signal.

The fifth challenge is how to appropriately evaluate early detection approaches. Translation of biological insights into new diagnostic technologies and execution of clinical trials to validate those advances require substantial time and money. We discuss ways in which that process might be improved.

OUTLOOK: For early detection to deliver transformative progress in cancer survival, wider skill sets beyond cancer biology are essential, including engineers, chemists, physicists, technology developers, and behavioral and computer scientists. Integrated, interdisciplinary collaboration is key to bringing new ideas to address the challenges of early cancer detection. We believe that early detection of cancer is approaching a tipping point, as biological insight and technological capacity are increasing at an unprecedented rate and as public and private funders of research are increasingly willing to invest. This Review discusses the current state of the field and suggests constructive ways forward that build on current progress to deliver effective earlier detection of cancer and appropriate intervention. ■

The list of author affiliations is available in the full article online.
*Corresponding author. Email: david.crosby@cancer.org.uk (D.C.); sb10031@cam.ac.uk (S.Ba.)
Cite this article as D. Crosby *et al.*, *Science* **375**, eaay9040 (2022). DOI: 10.1126/science.aay9040

READ THE FULL ARTICLE AT
https://doi.org/10.1126/science.aay9040



The early detection of cancer—challenges and ways forward. This figure summarizes challenges that impede the early detection of cancer and the areas of current research that are helping to overcome them.

REVIEW

CANCER

Early detection of cancer

David Crosby[1]*, Sangeeta Bhatia[2,3], Kevin M. Brindle[4,5], Lisa M. Coussens[6,7], Caroline Dive[8,9], Mark Emberton[10], Sadik Esener[7,11,12], Rebecca C. Fitzgerald[13], Sanjiv S. Gambhir[14]†, Peter Kuhn[15], Timothy R. Rebbeck[16,17], Shankar Balasubramanian[4,18]*

Survival improves when cancer is detected early. However, ~50% of cancers are at an advanced stage when diagnosed. Early detection of cancer or precancerous change allows early intervention to try to slow or prevent cancer development and lethality. To achieve early detection of all cancers, numerous challenges must be overcome. It is vital to better understand who is at greatest risk of developing cancer. We also need to elucidate the biology and trajectory of precancer and early cancer to identify consequential disease that requires intervention. Insights must be translated into sensitive and specific early detection technologies and be appropriately evaluated to support practical clinical implementation. Interdisciplinary collaboration is key; advances in technology and biological understanding highlight that it is time to accelerate early detection research and transform cancer survival.

Cancer is a major global public health problem; there were 10 million deaths from cancer worldwide in 2020 (*1*). It is the second leading cause of death globally, causing one in six deaths (*2*). For nearly all cancers, the chances of survival increase significantly if the disease is detected, diagnosed, and treated at an early stage (*3*) (Fig. 1).

Early detection aims to identify consequential cancer or precancerous change at the earliest time point at which intervention could improve survival or reduce morbidity. Consequential disease will cause mortality or substantial morbidity within the individual's expected remaining life span. Early detection can take place across several windows during the transition from normal cellular activity to dysregulation to cancer; this includes not only detecting cancer itself at an earlier point in its development but also detecting precursor changes (Fig. 2). Screening, which proactively tests asymptomatic people, constitutes a subset of early detection measures. Many of the principles of early detection interact with other points in cancer care, such as detection of minimal residual disease or disease recurrence (Fig. 2). This Review focuses on early detection of primary cancers and precancerous changes in the context of both screening and symptomatic detection.

Early cancer detection research and development have produced tremendous health benefits, for example, through established screening approaches for cervical, breast, and colorectal cancers, which are now diagnosed less frequently at later stages than cancers without established screening (*4*) (Fig. 1). But many cancers, such as esophageal, pancreatic, and ovarian cancers, are still often diagnosed at advanced stages, when prognosis is extremely poor.

Although early detection confers survival advantages in all populations, ~70% of cancer deaths occur in low- and middle-income countries (*2*), often with late diagnosis. For example, the rate of late-stage breast cancer diagnosis in Black sub-Saharan African women remained well above 60% from the 1970s to 2011, whereas in the US, that rate of late diagnosis decreased from ~60% to 32% in Black women over the same period (*5*). Some cancers that have effective early detection tests, such as cervical cancer, have much higher mortality rates in low human development index (HDI) countries compared with high HDI countries (19.8 versus 3.1 deaths per 100,000, respectively), whereas other cancers without effective early detection tests differ less (e.g., stomach cancer, 5.0 versus 4.0 deaths per 100,000, respectively). Late-stage detection of cancer is a global problem that is exacerbated in resource-poor settings, demonstrating that equity is a

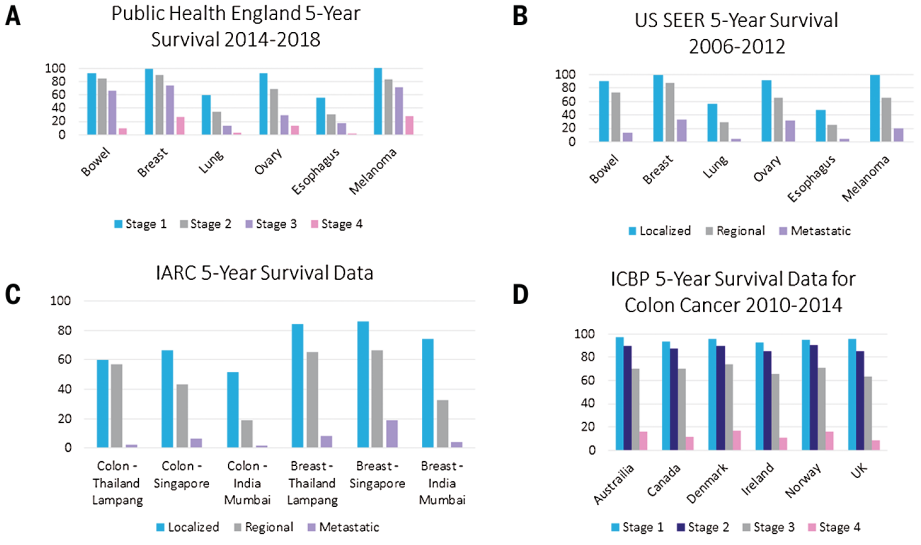


Fig. 1. Patients survive longer when cancer is detected at an early stage. Five-year survival data for bowel, breast, lung, ovarian, and esophageal cancers and melanoma by stage of diagnosis from (**A**) Public Health England (*140*) and (**B**) the US Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov). (**C**) Data from the International Agency for Research on Cancer (IARC; https://survcan.iarc.fr/indexsurvcan1.php) shows 5-year survival by stage of diagnosis for colon and breast cancers in Asian countries. (**D**) International comparison [International Cancer Benchmarking Partnership (ICBP) data; https://gco.iarc.fr/survival/survmark] across countries for 5-year survival of colon cancer shows similar trends in percentages of patients surviving early-stage disease versus late-stage disease.

[1]Cancer Research UK (CRUK), London, UK. [2]Marble Center for Cancer Nanomedicine, Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA, USA. [3]Howard Hughes Medical Institute, Massachusetts Institute of Technology, Cambridge, MA, USA. [4]Cancer Research UK Cambridge Institute, University of Cambridge, Cambridge, UK. [5]Department of Biochemistry, University of Cambridge, Cambridge, UK. [6]Cell, Developmental and Cancer Biology, Oregon Health and Science University, Portland, OR, USA. [7]Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA. [8]Cancer Research UK Lung Cancer Centre of Excellence at the University of Manchester and University College London, University of Manchester, Manchester, UK. [9]CRUK Manchester Institute Cancer Biomarker Centre, University of Manchester, Manchester, UK. [10]Division of Surgery and Interventional Science, University College London, London, UK. [11]Department of Biomedical Engineering, School of Medicine, Oregon Health and Science University, Portland, OR, USA. [12]Cancer Early Detection Advanced Research Center, Oregon Health and Science University, Portland, OR, USA. [13]Medical Research Council (MRC) Cancer Unit, Hutchison/MRC Research Centre, University of Cambridge, Cambridge, UK. [14]Department of Radiology, Molecular Imaging Program at Stanford, Stanford University, Stanford, CA, USA. [15]USC Michelson Center Convergent Science Institute in Cancer, University of Southern California, Los Angeles, CA, USA. [16]Division of Population Science, Dana-Farber Cancer Institute, Boston, MA, USA. [17]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA. [18]Yusuf Hamied Department of Chemistry, University of Cambridge, Cambridge, UK.
***Corresponding author. Email: david.crosby@cancer.org.uk (D.C.); sb10031@cam.ac.uk (S.Ba.)**
†Deceased.

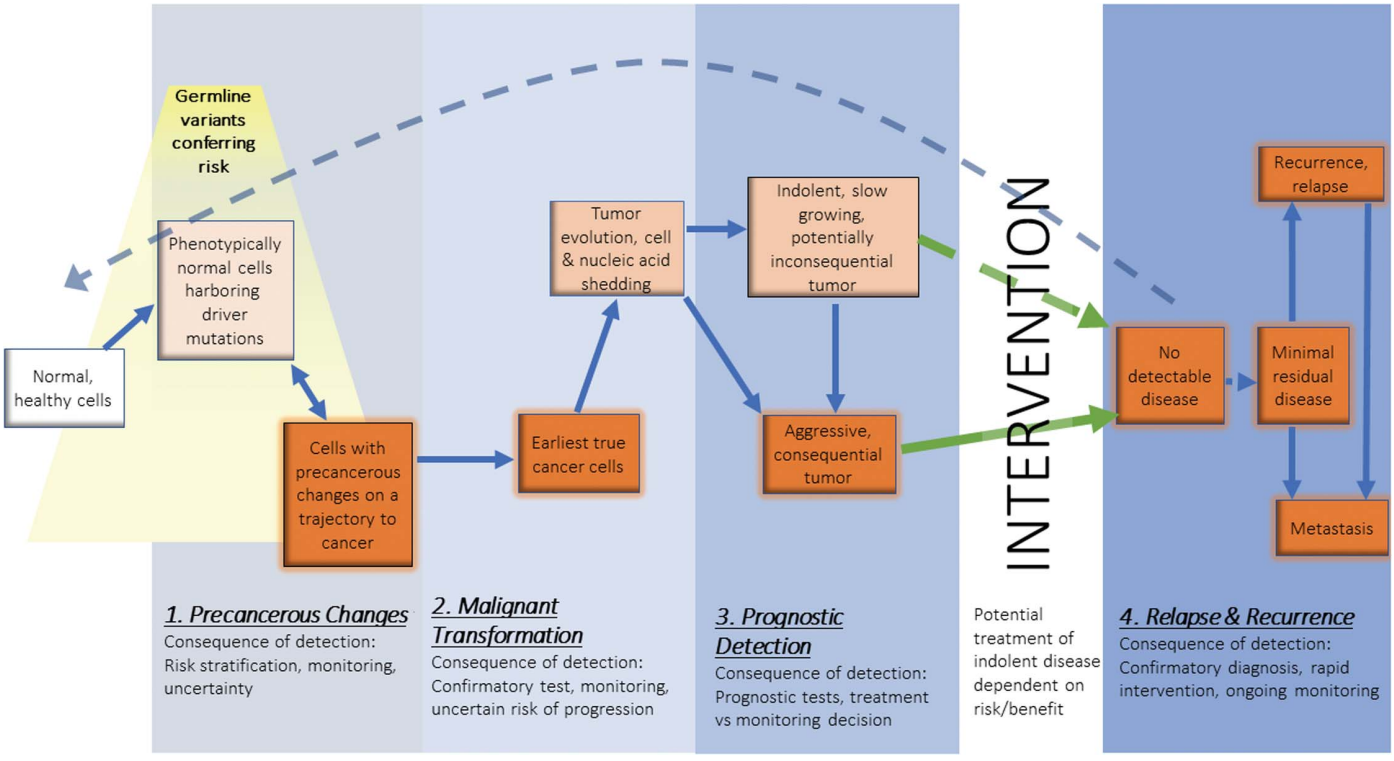


Fig. 2. Windows for early detection across the course of cancer progression. Cancer evolves through various stages, offering multiple windows for early detection. Detection at each stage presents different information and choices, with the consequences of detection dependent on the level of information provided by the subsequent test(s) and the level of certainty around whether the disease will be consequential.

considerable challenge (*6*–*8*). Patients diagnosed with later-stage cancer can miss the window for curative intervention, and expensive later-stage systemic treatments are often associated with severe side effects and worse outcomes (Fig. 1). Further research to build on early detection successes and extend these into other cancer types could transform patient outcomes.

The challenges facing early detection research fall into five broad categories. First, understanding the biology of early cancer: What should we look for, and, once found, how can we know which early lesions will progress to become aggressive, consequential disease versus indolent, inconsequential disease? Second, determining risk: There are substantial challenges in knowing which populations or individuals are at greater risk of developing cancer and therefore in deciding who should be tested and how tests should be interpreted and acted on. Third, finding and validating biomarkers: Early tumors are miniscule—discovering sensitive markers of their presence and robustly validating them presents an archetypal needle-in-a-haystack challenge. Fourth, developing accurate technologies: there is a considerable challenge in developing technologies that are sensitive enough to detect markers of early cancers and specific enough to avoid false alarms or overtreatment for inconsequential disease. Fifth, evaluating early detection approaches appropriately: The ultimate challenge is to robustly demonstrate that a new early detection approach can indeed detect cancers early and ultimately save lives. The relative scarcity of cancer in the general population can make this a difficult, prolonged, and extremely expensive process.

There is a general need for accurate early detection technologies that address the issues of cost, access and scaling, public acceptance of testing, and integration of diagnostics with public health infrastructure and decision-making. The point-of-care tools and privacy-compliant telehealth solutions that have emerged to meet the COVID-19 pandemic crisis may also help advance the implementation of early cancer detection. Early detection approaches must address, rather than exacerbate, health inequities and must achieve a positive balance of benefit to harm (through overdiagnosis, unnecessary invasive follow-up, and overtreatment for inconsequential disease). In this Review, we describe the diverse research challenges and propose ways of achieving early detection of cancer.

Challenge 1: Understanding the biology of early cancer

There is a continuum in tumorigenesis from normal to dysregulated to cancerous. A key challenge is to understand this biology so that we can predict the future trajectory of the changes we detect and determine when early disease becomes consequential and/or lethal.

The cancer continuum and transition to lethality

Cancer evolves from early inconsequential dysregulation in molecular and cellular phenotypes, to malignant transformation where critical changes in a cell's genome or epigenome culminate in a hallmark series of abnormal features that define cancer, to potentially lethal invasion and metastasis and ongoing cellular evolution and diversification (*9*). Windows of opportunity, as well as challenges, for cancer detection exist across this continuum (Fig. 2). The transition rate through these stages depends on the cancer type, therefore, understanding this timeline can help pinpoint the optimal time for detection and intervention.

Annual screening may not detect fast, aggressive cancers that develop between screening visits (*10*). Conversely, slow-growing cancers undergoing malignant transition over several years can be tracked with active surveillance and screening of at-risk populations. Some cancers follow a clear path from precursor condition to malignancy, such as polyps preceding colon cancer. However, not all precursors will progress to cancer, and not all cancers will be consequential. For example, the precancerous condition monoclonal gammopathy of undetermined significance (MGUS) has an average risk of developing into multiple

myeloma (a lethal cancer) of only 1% per year (*11*), and the risk of Barrett's esophagus developing into esophageal cancer is ~0.3% per year (*12*). We do not fully understand which lesions will progress to consequential disease and which will not.

What confers lethality and its timing? A cancer can theoretically be traced, by means of a phylogenetic tree, back to a single cell. This single cell arises from a specific set of conditions, including the tissue microenvironment and the immune system. Each organ system presents a different environment, with some mutations causing a potentially lethal tumor in one organ context but not another (*13*). The picture also changes within individuals as a result of aging. A tumor-permissive environment can be created by cellular and molecular changes in noncancerous cells during aging, such as biophysical alterations in the extracellular matrix, changes in secreted factors, and changes in the immune system (*14*). What are the transitions leading to that initial cancer cell and then the changes that engender a consequential tumor, both within the cell and its interactions with its microenvironment? The early evolution of most cancers cannot easily be observed in people owing to clinical presentation at advanced disease stages and tissue sampling difficulties when monitoring precancers. Blood cancers are an exception, where the ease of blood sampling has allowed better understanding of clonal hematopoiesis (*15*). For example, all multiple myelomas will have progressed from MGUS. Chromosomal and other mutational changes can be monitored in MGUS patients and may highlight patients who are progressing from MGUS to smoldering myeloma to malignant multiple myeloma (*16*). Clinical trials suggest that patients who undergo early detection of MGUS progression may benefit from therapeutic intervention at the stage of smoldering myeloma rather than waiting for symptomatic malignant myeloma with end-organ damage (*17*). This demonstrates how detection and molecular stratification of a preneoplastic lesion (Fig. 2) can trigger intervention before clinically observed definite malignancy. Given that not all patients presenting with multiple myeloma will have a prior clinical diagnosis of MGUS, monitoring changes in MGUS patients will not catch every case, although it does give a paradigm to study and exploit the biology of transition from precancer to cancer.

The transition from a normal state to cancer is also affected by a cell's microenvironment. The microenvironment includes host immune cells, mesenchymal support cells, vascular cells, extracellular matrix, and secreted proteins and exists in various states of hypoxia and pH. The microenvironment surrounding a would-be tumor cell can contribute to tumor progression, determining whether that cell remains localized or spreads aggressively. An early tumor may also induce detectable changes in its microenvironment, generating potential biomarkers for detection.

The immune system is a crucial regulator and indicator of the initiation and progression of early tumors (*18*). For example, the spatial positioning of tumor-infiltrating leukocytes with regard to the tumor can, in some cancer types, indicate how invasive a tumor is (*19*), and leukocyte-based biomarkers may be used to identify residual disease after therapy or to predict response to therapies (*20*). However, it is becoming clear that immune cells or their products may themselves be useful for early detection (*21*). As discussed in the Challenge 3 section below, the very small size of the earliest tumors means that any biomarkers they shed into the circulation will exist in very small amounts, impeding detection. The human immune system could act as a signal amplifier (each tumor cell being potentially exposed to many immune cells). This exquisitely sensitive apparatus could be harnessed to signal the presence of a cancer. Immune system biomarkers currently under investigation as early cancer detectors include the overall immune contexture in the peripheral circulation, autoantibodies (*22*), T cell repertoires (*23*), and leukocyte-shed exosomes.

Biological models of disease

Because we cannot easily observe the first tumor cell to emerge in humans, cancer models have been developed to probe the mechanisms underlying tumor initiation (*24*–*27*). However, there are few models of very early cancer or premalignant disease that faithfully reproduce somatic events leading to disease in immunocompetent native tissue microenvironments.

First-generation transgenic models of human cancer progression (*28*) afforded initial glimpses of tissue- and organ-specific biology of neoplastic progression. Although such studies have revealed tumor cell–intrinsic (*29*, *30*) and tumor cell–extrinsic characteristics (*9*, *31*) that support malignancy, these models have substantial drawbacks, such as rapid progression, and phenotypes that are frequently fully penetrant. Therefore, these models do not accurately recapitulate human disease.

Models of early cancer have been improved by developing immunocompetent mouse models with constitutive and conditional mutations in multiple cancer-associated genes, as well as embracing tumor microenvironment and epigenetic regulators. For example, mouse models allowing exploration of early tumorigenesis and that more closely recapitulate human disease (including immunocompetent and conditional expression models) now exist for nonmelanoma squamous cell carcinoma (*32*), pancreatic adenocarcinoma (*33*), colon cancer (*34*), and lung adenocarcinoma (*35*, *36*). Further insights will come from the next wave of model systems using approaches including circulating tumor cell patient-derived explants (*37*, *38*), patient-derived xenografts, and creation of complex organoids involving multiple cell types (*39*). However, many patient-derived xenograft models use samples from advanced human disease implanted into immunocompromised mice, which may not reflect truly early disease processes or the important role of the immune response to early lesions. With increasing sophistication, the interplay of patient-derived models and advanced nonhuman model systems can provide a path to greater understanding of early cancer biology, early detection markers, prognosis, and appropriate interventions for early cancers.

Challenge 2: Determining risk of developing cancer

Understanding whom, how, and when to test and also how test results should be interpreted requires understanding of individual cancer risk. Early detection strategies will not be of equal value to everyone. Therefore, it is important to identify the people at elevated risk of cancer and to tailor an early detection strategy to that group to maximize the benefits of early detection and minimize the harms (through over- or underdiagnosis and treatment) (*40*).

Risk models

Risk assessment models can identify individuals or populations at increased risk for a specific cancer or cancers. Risk stratification includes information about age, familial history, exposures, and lifestyle (*41*), which can be augmented by genetic screening to detect variants in genes associated with cancer. This strategy is exemplified by breast cancer risk prediction models used to stratify women into higher-risk categories and toward genetic testing for inherited cancer susceptibility (*42*, *43*). Women with inherited *BRCA1* or *BRCA2* pathogenic variants associated with increased risk of breast and ovarian cancers are candidates for chemoprevention with selective estrogen receptor modifiers, risk-reducing surgery, or enhanced breast magnetic resonance imaging (MRI) screening to enable earlier detection. Currently, very few high-risk single genes (such as *BRCA1* and *BRCA2*) trigger such action, however polygenic risk scores are being explored, which consider the risk conferred by multiple genetic variants (*44*). Better precision is needed in the identification of high-risk people who require screening for early cancer detection. Improved accuracy of risk modeling will be enabled by the discovery and use of more-informative genomic and phenotypic (e.g., breast density) markers of risk, integrated into multifactorial models that also consider, for example, family history and behavioral factors. It is crucial that risk models are evaluated by experts using the

appropriate statistical methodologies and validated in independent datasets (45).

Constructing improved risk stratification models requires data and biological samples from large cohorts, ideally in prediagnostic populations that are followed for any cancer diagnoses. Current examples include the UK Our Future Health initiative, which will follow 5 million volunteers (https://ourfuturehealth.org.uk/); Project Baseline in the US, following 10,000 volunteers (www.projectbaseline.com); the Asia Cohort Consortium, following at least 1 million volunteers (www.asiacohort.org); and the European Prospective Investigation into Cancer and Nutrition (EPIC) study, following >500,000 volunteers (https://epic.iarc.fr/). These longitudinal studies in healthy volunteers could help understand the hidden variability between healthy individuals and discover, validate, and contextualize early disease signals. Ultimately, these studies could identify factors to stratify healthy individuals into groups at risk of developing certain cancers.

Screening at-risk populations

Once validated risk models have identified the at-risk populations, these individuals can be invited to participate in screening programs, where available. Screening aims to detect early cancer by inviting asymptomatic, ostensibly healthy people for testing. Ideally, cancer screening should be minimally invasive or noninvasive, low cost, and provide minimal false negatives or positives to minimize harm and maximize benefits of screening. Several existing screening tests improve cancer-specific mortality or overall mortality, including mammography for breast cancer (46), the Pap smear for cervical cancer (47), colonoscopy for colorectal cancer (48), and low-dose computed tomography (CT) (49) for lung cancer. Although effective, these technologies are not necessarily minimally invasive, low cost, or highly sensitive and specific. Nor do these tests reach all the at-risk populations concerned. For example, in the US as of 2019, <5% of eligible individuals have been screened for lung cancer (50), owing to incomplete implementation of screening in health care systems and low individual compliance.

For screening to be successful, the follow-up diagnostic workup must be feasible and risk-appropriate. For example, breast nodule biopsy (triggered by a positive mammogram) is a low-risk outpatient procedure. Conversely, lung biopsy (triggered by a positive lung CT screen) is highly invasive and relatively high risk. The performance characteristics of the primary screening test, and the threshold set for a positive or negative test result, must be calibrated against the consequences of a positive result. Therefore, any early detection strategy should give rise to actionable, evidence-based follow-up.

Challenge 3: Finding and validating cancer detection biomarkers

A key challenge is how to detect the very small signal of the earliest cancers amid the noise of normal human biology. Two fundamental measures of a diagnostic test are sensitivity and specificity. Sensitivity is the ability of a test to correctly identify those with the condition being tested for (the true positive rate); a test with higher sensitivity will miss fewer cases (i.e., there will be fewer false negatives). Specificity is the ability of a test to correctly identify those individuals without the condition (the true negative rate); a test with high specificity does not give a positive result when the condition is not present (i.e., does not give false positives) (51). Sensitivity and specificity depend on both the technology used in the test and the biomarker(s) being measured. Two other key measures are positive predictive value (PPV), which is the probability that individuals who test positive actually have the condition, and negative predictive value, which is the probability that individuals who test negative do not have the condition (52). The target values of these parameters will depend on the intended circumstance of use of the test and on the prevalence of the particular cancer being tested for in a given population.

Challenges in biomarker validation

Many biomarkers for early cancer detection have been proposed, but few have been validated in large trials. For example, elevated prostate-specific antigen (PSA) in the blood was a candidate prostate cancer early detection biomarker. However, PSA varies greatly between individuals and within individuals as they age (or as they develop other nonmalignant prostate conditions), leading to the potential for overdiagnosis, unnecessary diagnostic workup (including invasive biopsy, which confers risk), and overtreatment of inconsequential disease (which incurs potential adverse effects without increasing survival) (53, 54). As such, PSA is not generally recommended as a primary, population-level screen (Fig. 3). Another example of a blood marker for cancer that showed promise was CA-125 for ovarian cancer; while use of this marker increased the number of early-stage diagnoses and decreased the number of late-stage diagnoses, this was not accompanied by reduction in mortality (55).

Even if validated, highly specific biomarkers can display dichotomy when taken out of context. For example, in colorectal cancer, KRAS mutations are strongly associated with disease progression (56), but in the pancreas, many neoplasms carrying KRAS mutations are not malignant (57). A useful biomarker must provide enough prognostic, actionable information to inform clinical decision-making.

Promising biomarkers

Biomarkers of early cancer include visible structural changes to tissue and biochemical changes. Minimally invasive sampling methods are preferred, especially where repeated samples from healthy and at-risk individuals are required. In practice, this includes imaging; sampling body fluids such as blood, saliva, or urine (58); and sampling tissues via swabs or brushings. Exhaled breath is another source of biomarkers, specifically volatile organic compound (VOC) signatures of cancer and associated metabolites (59).

Liquid biopsies (sampling of body fluids) can be used to identify a wide range of substances indicative of cancer, derived either from the tumor itself or from the body's response to the tumor. For example, nucleic acid fragments called cell-free DNA (cfDNA) enter the blood during cellular apoptosis or necrosis. In cancer patients, a portion of the cfDNA, called circulating tumor DNA (ctDNA), is derived from the tumor. Analysis of ctDNA has shown promise for personalized mutation profiling and monitoring of patients with advanced cancers (58, 60), in whom ctDNA levels are relatively high. A key challenge is that ctDNA and indeed all biochemical cancer biomarkers are present at extremely low concentrations in early-stage cancer. New approaches are needed to improve on current limits of detection to address this limitation.

Human genome sequencing (61, 62) has provided unprecedented insights into cancer genomes (63, 64). Although mostly focused on advanced cancer, these studies have elucidated patterns of genetic variants across cancers, some of which may also be present in early tumors. These patterns can provide a basis for detection, stratification, and treatment of cancers (65). Liquid biopsy tests based on cancer-associated mutations in ctDNA are showing promise in early detection (66). However, it is increasingly clear that phenotypically normal tissue also harbors a range of somatic mutations that might normally be considered indicative of cancer or to be drivers of cancer genesis (67). Researchers developing early detection approaches must be mindful of this—how can we define what a normal background of mutations is, as distinct from a consequential cancer signal?

Epigenetic modifications of DNA provide another source of early detection biomarkers. These include cancer-specific DNA methylation profiles (68), noncoding RNAs (69), small regulatory RNAs, and the DNA modification 5-hydroxymethylcytosine (70). One promising approach analyzes methylation patterns of cfDNA in blood (71) and is now entering large-scale prospective clinical trials in the UK (NCT03934866) and the US (NCT04241796). Another emerging technique is based on the observation that fragmentation patterns in

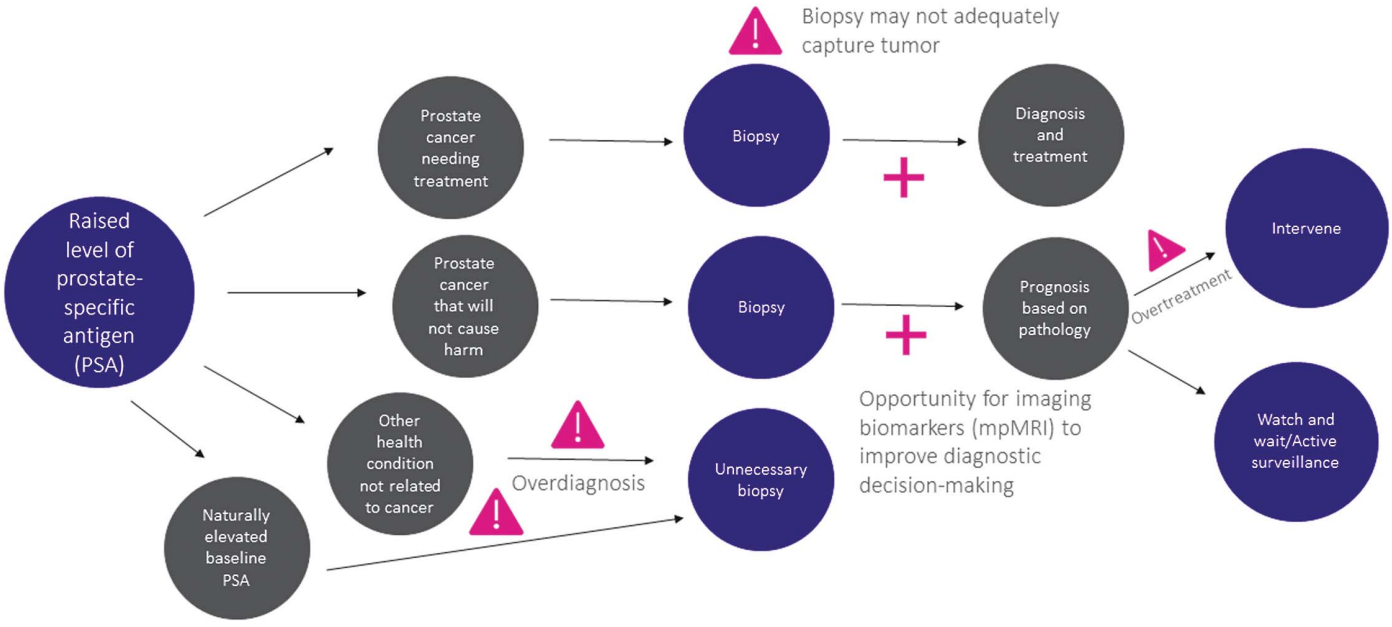


Fig. 3. Prostate cancer detection is a cautionary tale for overdiagnosis and overtreatment. There are various consequences of PSA testing when it is used as a screening tool. An elevated PSA level is not considered useful for prostate cancer screening owing to false positives and detection of inconsequential cancers that will not cause harm in an individual's lifetime. Subsequent biopsy is also imperfect because it does not always capture the tumor and may not distinguish indolent from aggressive cancers. The introduction of imaging biomarkers [e.g., multiparametric magnetic resonance imaging (mpMRI)] combined with pathology (at the junctures indicated by the red plus signs in the figure) has improved prognosis through better stratification of disease.

cfDNA differ between people with and without cancer, and between different cancer types (*72*).

Other potential detection biomarkers include circulating tumor cells (*73*), exosomes (*74*), cell fusions (*75*), metabolites (*76*), and proteins (*77*). These complement DNA sequencing for the discovery and exploitation of cancer-specific signatures (*78*–*80*). Furthermore, certain microbes may confer susceptibility to certain cancers (*81*–*84*), yielding another potential pool of biomarkers. Various types of signal modalities are in clinical use or under development for early cancer detection (Fig. 4). It is possible that multimodal testing will ultimately achieve higher sensitivity and specificity for early cancer than a test that uses a single type of biomarker.

Multimodal testing can be sequential or parallel. Sequential testing cascades from tests indicating risk to confirmatory test(s) of another modality. Although effective (e.g., colorectal cancer screening) (Fig. 5), this results in long, complex diagnostic journeys. Parallel testing integrates data from different modalities to provide the diagnostic signal, for example, detection of the same cancer through measurement of ctDNA, metabolomics, and imaging. Parallel testing has improved the accuracy of liquid biopsy tests in blood (*80*), urine (*85*), and cervical swabs (*86*). Another approach has been to profile both ctDNA mutations and serum protein biomarkers (*80*, *87*), with further improvement achieved by also adding positron emission tomography–computed tomography (PET-CT) imaging (*88*). A prominent example of a successful multimodal cancer detection test combines an assay for fecal blood with a test for known cancer-associated DNA mutations, for improved colorectal cancer screening (*89*) compared with the single fecal hemoglobin test, and is now in clinical use.

Data analytic methods

New computational tools will be vital for analyzing, integrating, and using the data generated by diagnostics. Artificial intelligence (AI) and machine learning (ML) approaches, such as support-vector machine and neural network models, can discover cancer biomarkers, detect cancer-specific signatures in high-dimensional datasets, and build prospective statistical classifiers for evaluating diagnostic performance in independent cohorts (*43*). Such approaches offer exciting avenues for progress but are also fraught with potential challenges, of which researchers should be mindful. Many AI and ML models are criticized for being "black box," that is, unable to explain why the features (e.g., biomarkers) have been selected by the model; the creation of fully interpretable models would be advantageous (*90*). AI and ML models are often developed (or trained) on datasets derived from selected populations that do not represent the real population where the AI-derived test would be used, so they cannot be extrapolated to real-life conditions (*91*). Some AI and ML models are of poor design and insufficient sample size, risking bias and overfitting (*92*). The quality of design and reporting of some trials of AI approaches can also be suboptimal, calling into question the validity of their claims. Design aspects, such as not being prospective, being at high risk of bias, lacking appropriate transparency on data and code, lacking adequate comparator groups, and deviating from existing reporting standards can jeopardize reliability (*93*). In some cases, AI and ML methodology might simply not have advantages over statistical methods such as logistic regression (*94*)—the right tools should be used for the intended purpose.

Challenge 4: Developing accurate technologies for early detection

Developing technologies with the sensitivity to detect the earliest tumors and the specificity to minimize false positives is a key challenge. The emergence of new technologies is enabling early cancer detection with increasing accuracy. One early detection goal is to detect emerging solid tumors that are susceptible to therapy and unlikely to have metastasized. This usually means prior to development of tumor microenvironments that support enhanced angiogenesis and before suppression of antitumor immunity (*27*, *31*, *95*), when the tumor is roughly a millimeter in diameter (comprising 10^5 to 10^6 cells). Most imaging technologies in clinical use or development cannot detect such tiny tumors, but new in vivo imaging instruments such as 10.5T MRI (*96*) are continuously pushing the limits.

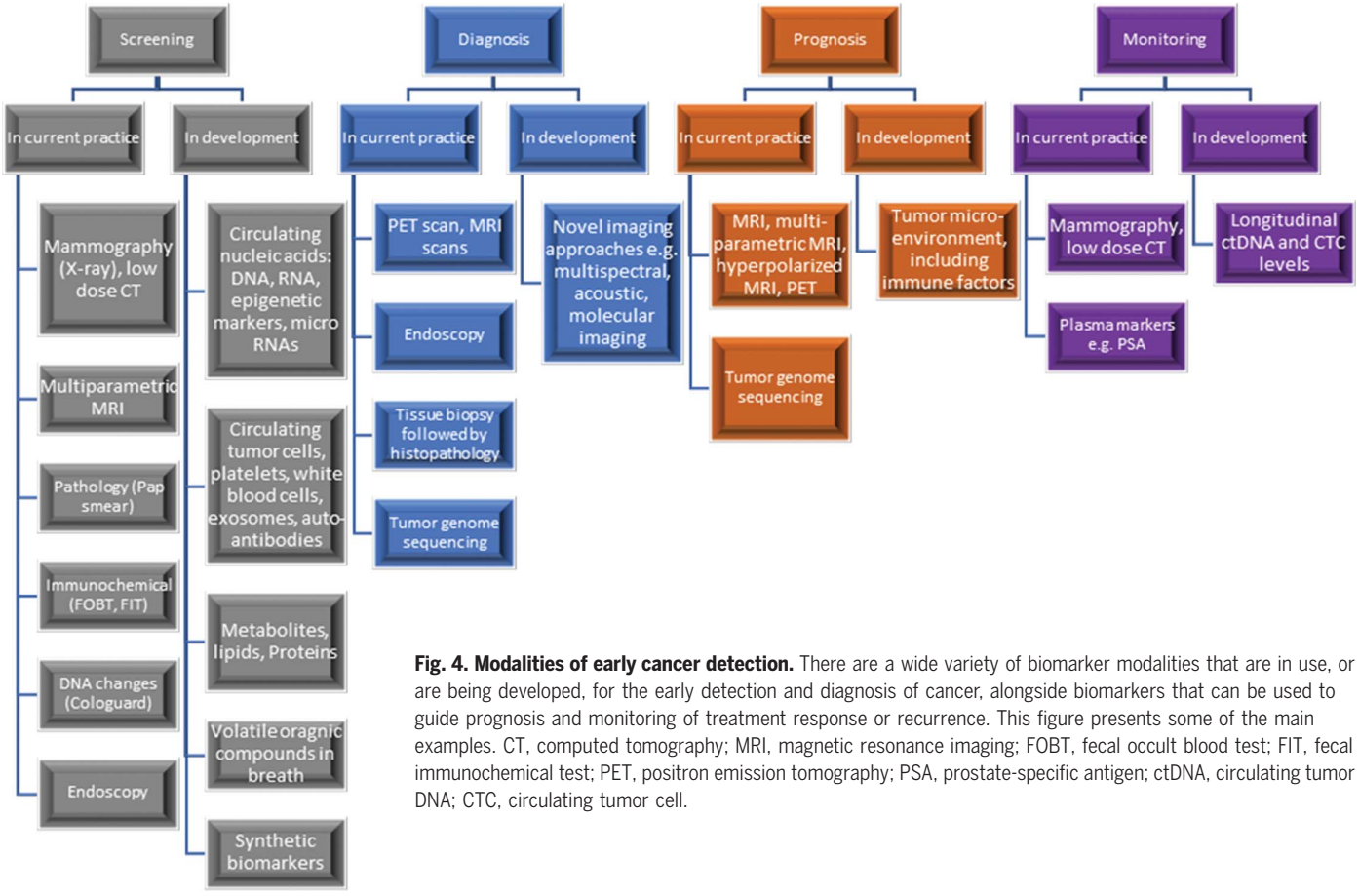


Fig. 4. Modalities of early cancer detection. There are a wide variety of biomarker modalities that are in use, or are being developed, for the early detection and diagnosis of cancer, alongside biomarkers that can be used to guide prognosis and monitoring of treatment response or recurrence. This figure presents some of the main examples. CT, computed tomography; MRI, magnetic resonance imaging; FOBT, fecal occult blood test; FIT, fecal immunochemical test; PET, positron emission tomography; PSA, prostate-specific antigen; ctDNA, circulating tumor DNA; CTC, circulating tumor cell.

New technologies

Sensitivity is being improved by recent technologies that detect tumor metabolites and other secondary products (Fig. 4) that are relatively more abundant than tumor cells. This can be augmented by highly specific probes, such as tumor-specific antibodies or peptides that are radio-labeled to increase signal. Other strategies include engineered diagnostics that are selectively activated in the presence of disease, such as molecular (*85*, *97*) and biological (*98*) sensors that profile the in vivo tumor microenvironment to generate synthetic biomarkers of disease. Activity-based diagnostics use enzyme activity to generate exogenous biomarkers that signal the presence of cancer. For instance, nanoparticles have been developed that are cleaved by dysregulated protease activity in cancer cells to generate urinary reporters (*99*), and cancer-associated enzymes can metabolize exogenous VOC probes to produce volatile reporters for noninvasive detection (*97*). New synthetic biology tools include engineered probiotic (*100*) and immune cell (*101*) diagnostics for tumor detection via amplified, activity-based readouts.

Developments in material engineering and microfabrication have yielded devices that can emulate physiological microenvironments to

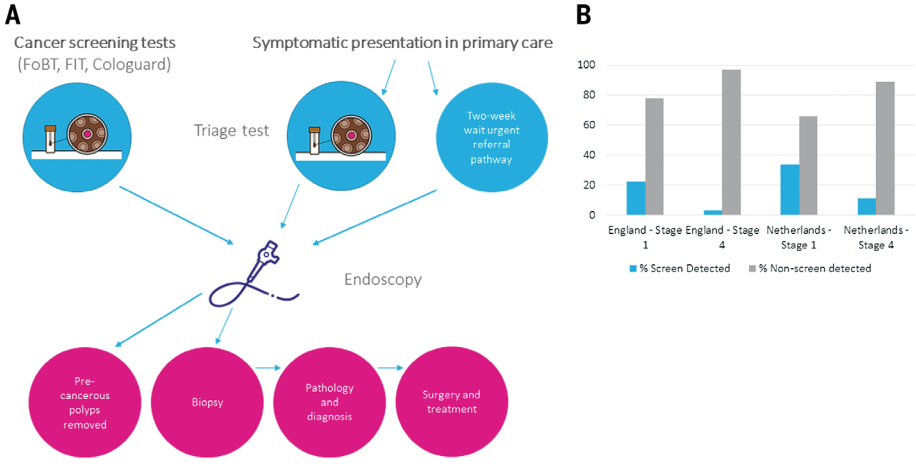


Fig. 5. Colorectal cancer screening is an early detection success story. (**A**) Screening for colorectal cancer (CRC) relies on a cascade of diagnostic tests (fecal screening to endoscopy to biopsy and histopathology) that can lead to (**B**) the detection of cancers at an earlier stage. This screening has transformed CRC into a treatable cancer with increased survival rates when the cancer is caught early (see Fig. 1). Population screening programs have relied on fecal occult blood tests (FOBTs) that measure gastrointestinal bleeding. In the UK, a FOBT was recently replaced by the fecal immunochemical test (FIT—a more accurate method of detecting blood in feces), and in the US, screening also includes the Cologuard FIT-DNA test, which looks for cancer-associated DNA mutations in the feces in addition to the FIT component. Positive results from fecal screening tests usually then cascade to endoscopic examination and, where appropriate, intervention. Most CRC, however, is still diagnosed through presentation to primary care and urgent referral routes, where symptomatic presentation is often associated with a later disease stage.

probe tumor biology and isolate circulating tumor cells (CTCs) and extracellular vesicles from patient samples. Notable examples include label-free capture of CTC clusters (*73*, *102*) and ultrasensitive detection of circulating exosomes with microfluidic chips or external hardware (*103*, *104*). Miniaturization has enabled new sensing approaches using wearables and implantable devices where personalized health data can inform the prevention or interception of certain diseases (*104*). More robust integration of device engineering with downstream molecular profiling technologies will help validate the relevance of these approaches for early detection.

Imaging technologies

Contemporary imaging technologies can only visualize tumors containing more than 10^9 cells; this will miss many of the smaller (i.e., earliest) tumors. Imaging of tissue morphology is currently used in breast cancer screening in the form of x-ray mammography, and low-dose CT is increasingly being used to detect early-stage lung cancer in high-risk groups (*105*). Although these techniques can be used for screening, as they are relatively quick and low cost, they are subject to limited resolution and also confer risk to the patient given their use of ionizing radiation. More advanced imaging modalities are not currently routinely used in primary screening owing to high cost and low availability.

Molecular imaging technologies, such as MRI (*106*) and PET (*107*), can perform early diagnosis and staging. Enhanced variations on these technologies provide the possibility of greater sensitivity, specificity, or PPV, for example, time-of-flight PET (*108*), where transit times of the photons emitted by the object generating the image signal provide a greater signal-to-noise ratio, and hyperpolarized MRI (*109*, *110*), where hyperpolarized carbon-13–containing molecules enable the collection of perfusion and metabolic information in addition to structural images.

Using imaging to examine multiple properties of a lesion can enhance the detection and classification of early lesions. For example, multiparametric MRI of the prostate provides information on prostate volume, cellularity, and vascularity; this can distinguish benign lesions from aggressive tumors requiring intervention (*111*). Imaging has the advantage of being noninvasive and easily repeatable to detect growing tumors. For example, lung cancer screening with low-dose CT repeated over time can distinguish benign lung nodules of low malignant potential from early lung cancer nodules (*105*).

Computer-assisted diagnostic systems help radiologists to interpret images (*112*). Computer-driven feature extraction can exploit differences in texture and shape that the naked eye cannot see. Digital attributes of the suspect lesion are called radiomic features and may contain indirect information about the underlying histopathology (*113*). This is an area where there is an opportunity for AI and ML to help detect cancer (*114*) and to predict risk of progression (*115*), although issues of transparency and reproducibility must be addressed (*116*). The application of AI in imaging will require large volumes of well-annotated image data, acquired under standardized conditions, representing all populations equitably, and made widely available by means of curated image repositories.

Photoacoustic imaging exposes the region of interest to pulsed laser light of a given wavelength, generating a sound that is measured by microphones or piezoelectric sensors. The level of detail and resolution of the tissue is higher than that of all other types of imaging and is free of ionizing radiation. The challenge is depth of penetration and miniaturization for clinical use (*117*). Visible light imaging through endoscopy has been a mainstay of early detection (e.g., in the colon and lung). The emerging fluorescence endoscopy technique, along with a fluorescent molecular imaging probe, has been used for enhanced detection of lesions in patients with Barrett's esophagus (*118*) and of neoplastic polyps in the colon (*119*).

Histopathology and AI

After initial detection by biomarkers and/or imaging, histopathology is a key confirmatory diagnostic and prognostic stage of the early detection paradigm. The application of ML techniques to digitized slides can increase sensitivity; reduce subjectivity and inter-reader variation; and predict prognosis, recurrence, and tumor susceptibility to treatment (*120*). In some cases, such as Barrett's esophagus dysplasia, bowel polyps, and cervical neoplasia, pathologists examine a precancerous condition with the aim of identifying the transition to early cancer. Digital pathology and AI could help improve test turnaround times and diagnostic accuracy, detecting early signs of cancer and providing data for further research (*121*). Current challenges in digital pathology include handling artifacts, overcoming sample variability, lack of binary variables where a diagnosis may require a risk score, and combining samples across multiple sites and cohorts.

Challenge 5: Evaluating early detection approaches

There are many challenges around the design and methodology of trials of early detection approaches. Trials must be carefully designed to address the relevant population and measure the appropriate end points to provide statistically robust evidence to change practice. Early detection trials differ from the better-known clinical trials for therapeutics and require specialist statistical expertise to inform study design and appropriately powered sample size. For example, the statistical power of early detection trials is affected by factors that do not exist in therapeutic trials, such as the number of times an individual is tested, the time between tests, and the ages at which testing will be performed (*122*). The end points to be considered in diagnostic trials differ from those in therapeutic trials, as do regulatory approval pathways. However, the main challenges to the delivery of early detection trials lie in their scale and interpretation.

The scale of early detection trials

Currently, regulatory or reimbursement decisions on the adoption of cancer screening tests are generally based on impact on mortality: Does the use of the screening test mean fewer deaths from cancer than in an unscreened population? Demonstrating this requires very large numbers of participants (given the comparatively low incidence rate of cancers in an asymptomatic population) and very long timelines (given the potential lag between commencement of the trial, a given individual developing cancer, and that cancer resulting in death). For example, the trials assessing low-dose CT screening for lung cancer in heavy smokers took 7 years and 53,454 participants in the US (*123*) and more than 10 years with 15,789 participants in Europe (*124*). In a more general population (lacking the greatly increased cancer risk of heavy smoking), even greater numbers of participants are needed. For example, trials assessing screening for ovarian and prostate cancers involved more than 200,000 women (*125*) and 184,000 men, respectively (*126*). This scale makes most early detection trials multicenter by default. Clinical trial networks such as those sponsored by the European Organisation for Research and Treatment of Cancer (EORTC) and the US-based National Cancer Institute (NCI) can help to facilitate and accelerate such large trials.

Another attractive option is embedding research into screening programs, taking advantage of existing screening infrastructure. This can, for example, be done using the stepped-wedge design, where observations are initially collected during a baseline period in which no participants are exposed to the intervention (i.e., the new screening test under investigation). After this baseline period, at regular intervals (or steps) participants (or groups of participants) are randomized to receive the intervention; these ascending steps continue until all participants have received the intervention (*127*).

One way to decrease the length and size of trials is to power the study to detect changes in surrogate end points (e.g., a reduction in the absolute number of late-stage diagnoses versus controls) rather than mortality (*128*). Such trials are faster and require fewer participants

to record enough events in a limited time frame. However, most health care systems, regulatory agencies, and guideline bodies still require evidence of reduced mortality before approving tests for marketing, reimbursement, or widespread use. Advice should be sought from the relevant agencies regarding acceptability of surrogate end points. Studies should be designed and powered, and end points chosen, on the basis of the objectives of the study (e.g., initial signal-finding trial versus technology validation versus confirmatory trial) and the intended circumstances of use. Early detection technology must generate the evidence that is required by regulators, advisory bodies, and payers for research to achieve clinical impact. Proper validation (*129*) and consideration of the pathway to implementation are crucial.

Interpreting trial results

Clinical trial results of early detection technologies should be interpreted taking into consideration spectrum and lead-time biases. Spectrum bias arises when tests are assessed in a population that does not reflect the intended target population (*130*). For example, comparing a study population with established and advanced disease to a healthy control population (often young and without other chronic diseases that increase variability in the general population) can confound the specificity of the test. Spectrum bias also arises when a test is developed using an at-risk population (e.g., heavy smokers) with high disease incidence but is intended for use in the general population (with lower incidence). Such a test will lose sensitivity and even specificity in the real-world target population, which has lower prevalence of disease and other confounders. This can cause false positives and even overdiagnosis.

Lead-time bias describes the time from early detection of disease to clinical presentation of signs and symptoms (when diagnosis would otherwise have taken place) (*131*, *132*). This makes survival seem longer when you detect cancer earlier by artificially moving the starting block back in time, even if early detection did not affect the point at which the individual died.

Spectrum bias can be addressed by validating markers and tests in populations that appropriately represent the population of intended use of the test. Lead-time bias is a more complex issue; currently, the method to address this bias is to conduct a trial designed to assess impact on mortality (e.g., whether there are fewer deaths overall in the screened group than in the unscreened group), however this then leads to the challenge of huge sample size and cost, as discussed above. This challenge can be addressed through careful study design. Dedicated experts in screening and diagnostic methodology must be involved, and the intended target audience for the results (e.g., regulatory and guideline-developing bodies) must be consulted when designing trials to evaluate early detection approaches. If we are to increase the glacial pace at which new early detection and screening approaches are evaluated and reach the clinic, a rethink of the evidence threshold for adoption is required. For example, success could be assessed on the basis of an absolute reduction in late-stage diagnoses (or other well-validated surrogate outcomes), with mortality data then gathered after implementation.

Conclusions

Early detection of cancer has the potential to transform patient survival and is increasingly recognized as an area of unmet need by the public, patients, policy-makers, and research funders. A sustained effort will be required to find practical, long-term solutions for many of the challenges we have described in this Review. We have suggested a framework that we believe will meaningfully accelerate progress (Fig. 6). Several contextual issues must also be carefully considered to maximize the translation of early detection research into clinical impact.

Funding programs targeting early detection have been set up by some funders of academic cancer research, such as the US National Cancer Institute (*133*, *134*) and Cancer Research UK (*135*, *136*). However, the proportion of overall cancer research funding dedicated to early detection remains disproportionately low considering the potential health benefits. More must be done, particularly in supporting validation of markers and tests (*129*). Dedicated funding would also help attract early career researchers to the field and enable them to become established. The relatively long timelines of early detection research and test development necessitate a rethink about traditional fellowship and grant models of supporting and evaluating early career researchers to incentivize them to establish a career in this field.

Furthermore, the pharmaceutical industry has invested proportionally little in early detection compared with the billions spent on drug development, often because of a historical

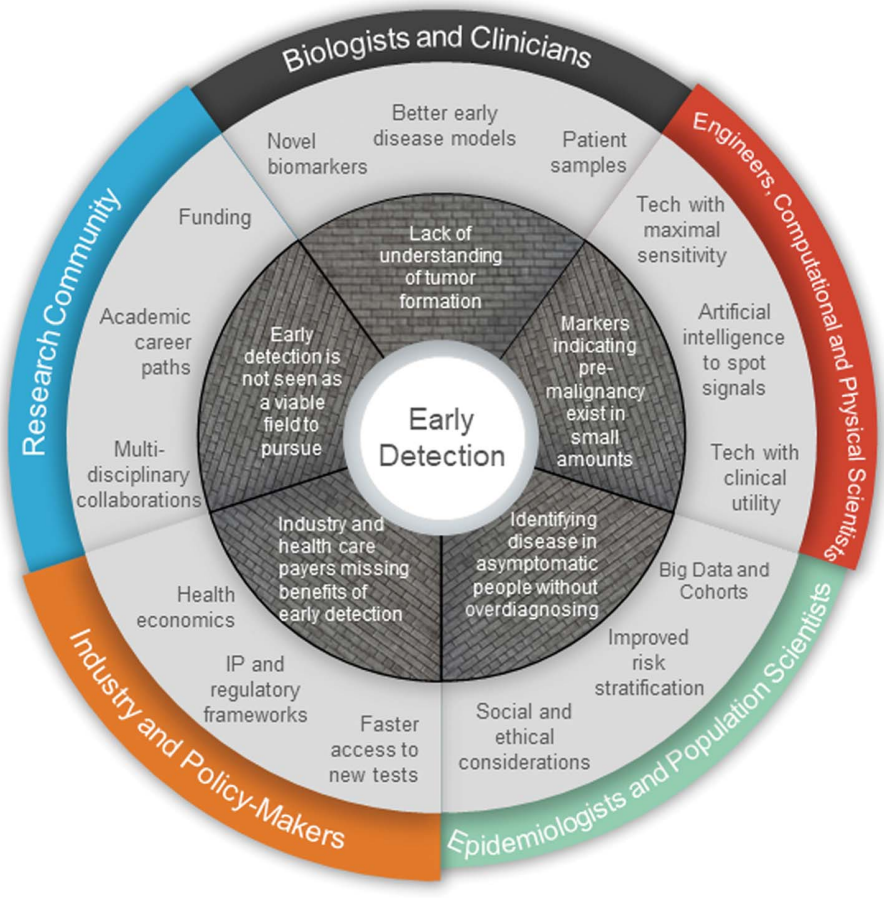


Fig. 6. Overcoming barriers to enable early detection. There are system-wide challenges (gray bricks) that must be tackled to reach the goal of earlier cancer detection. The multiple facets of these challenges require a diverse set of approaches and enablers (light gray) and communities (colored outer segments) to overcome them.

perception of an unattractive business model. However, there now appears to be an inflection (*137*) whereby investors and large corporations are increasingly willing to invest in this space (*138*, *139*). This willingness may be due to a growing realization that early detection will change the business model for cancer treatment.

An interdisciplinary culture is essential to early detection research and development, which inherently needs a convergence of biological understanding, clinical insight, technology innovation, data science, risk stratification, and health systems research. In the absence of any one of these essential components, the goal of transforming cancer survival cannot be realized. The implementation of interdisciplinarity can be fostered by research funders.

To have a meaningful impact on survival, early detection must be integrated into health care systems and must lead to evidence-based early interventions, either to prevent progression or to cure cancer. Lastly, and crucially, researchers must keep in mind that early detection should be accessible to all according to need, must not exacerbate health inequities, and must seek to do no harm (minimizing overdiagnosis and overtreatment). With the ever-increasing depth of biological insight and pace of technological innovation, we are at the tipping point for early cancer detection research and its translation to the ultimate objective of early curative interventions and increased cancer survival.

REFERENCES AND NOTES

1. H. Sung *et al*., Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **71**, 209–249 (2021). doi: 10.3322/caac.21660; pmid: 33538338
2. World Health Organization, Fact sheet: Cancer; www.who.int/news-room/fact-sheets/detail/cancer.
3. Office for National Statistics UK, Cancer survival by stage at diagnosis for England (experimental statistics): Adults diagnosed 2012, 2013 and 2014 and followed up to 2015, 10 June 2016; www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalbystageatdiagnosisforenglandexperimentalstatistics/adultsdiagnosed20122013and2014andfolloweduptо2015.
4. R. L. Siegel *et al*., Colorectal cancer statistics, 2017. *CA Cancer J. Clin.* **67**, 177–193 (2017). doi: 10.3322/caac.21395; pmid: 28248415
5. E. Jedy-Agba, V. McCormack, C. Adebamowo, I. Dos-Santos-Silva, Stage at diagnosis of breast cancer in sub-Saharan Africa: A systematic review and meta-analysis. *Lancet Glob. Health* **4**, e923–e935 (2016). doi: 10.1016/S2214-109X(16)30259-5; pmid: 27855871
6. E. Jedy-Agba *et al*., Determinants of stage at diagnosis of breast cancer in Nigerian women: Sociodemographic, breast cancer awareness, health care access and clinical factors. *Cancer Causes Control* **28**, 685–697 (2017). doi: 10.1007/s10552-017-0894-y; pmid: 28447308
7. A. M. Nelson, D. A. Milner, T. R. Rebbeck, Y. Iliyasu, Oncologic care and pathology resources in Africa: Survey and recommendations. *J. Clin. Oncol.* **34**, 20–26 (2016). doi: 10.1200/JCO.2015.61.9767; pmid: 26578619
8. I. O. Morhason-Bello *et al*., Challenges and opportunities in cancer control in Africa: A perspective from the African Organisation for Research and Training in Cancer. *Lancet Oncol.* **14**, e142–e151 (2013). doi: 10.1016/S1470-2045(12)70482-5; pmid: 23561745
9. D. Hanahan, R. A. Weinberg, Hallmarks of cancer: The next generation. *Cell* **144**, 646–674 (2011). doi: 10.1016/j.cell.2011.02.013; pmid: 21376230
10. N. Pashayan, P. D. P. Pharoah, The challenge of early detection in cancer. *Science* **368**, 589–590 (2020). doi: 10.1126/science.aaz2078; pmid: 32381710
11. R. A. Kyle *et al*., Prevalence of monoclonal gammopathy of undetermined significance. *N. Engl. J. Med.* **354**, 1362–1369 (2006). doi: 10.1056/NEJMoa054494; pmid: 16571879
12. Y. Peters *et al*., Barrett oesophagus. *Nat. Rev. Dis. Primers* **5**, 35 (2019). doi: 10.1038/s41572-019-0086-z; pmid: 31123267
13. K. M. Haigis, K. Cichowski, S. J. Elledge, Tissue-specificity in cancer: The rule, not the exception. *Science* **363**, 1150–1151 (2019). doi: 10.1126/science.aaw3472; pmid: 30872507
14. M. Fane, A. T. Weeraratna, How the ageing microenvironment influences tumour progression. *Nat. Rev. Cancer* **20**, 89–106 (2020). doi: 10.1038/s41568-019-0222-9; pmid: 31836838
15. C. J. Watson *et al*., The evolutionary dynamics and fitness landscape of clonal hematopoiesis. *Science* **367**, 1449–1454 (2020). doi: 10.1126/science.aay9333; pmid: 32217721
16. S. Manier *et al*., Genomic complexity of multiple myeloma and its clinical implications. *Nat. Rev. Clin. Oncol.* **14**, 100–113 (2017). doi: 10.1038/nrclinonc.2016.122; pmid: 27531699
17. M.-V. Mateos *et al*., Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. *N. Engl. J. Med.* **369**, 438–447 (2013). doi: 10.1056/NEJMoa1300439; pmid: 23902483
18. H. Gonzalez, C. Hagerling, Z. Werb, Roles of the immune system in cancer: From tumor initiation to metastatic progression. *Genes Dev.* **32**, 1267–1284 (2018). doi: 10.1101/gad.314617.118; pmid: 30275043
19. T. J. Honkanen *et al*., Prognostic and predictive role of spatially positioned tumour infiltrating lymphocytes in metastatic HER2 positive breast cancer treated with trastuzumab. *Sci. Rep.* **7**, 18027 (2017). doi: 10.1038/s41598-017-18266-1; pmid: 29269742
20. I. Kirsch, M. Vignali, H. Robins, T-cell receptor profiling in cancer. *Mol. Oncol.* **9**, 2063–2070 (2015). doi: 10.1016/j.molonc.2015.09.003; pmid: 26404496
21. O. J. Finn, Immune response as a biomarker for cancer detection and a lot more. *N. Engl. J. Med.* **353**, 1288–1290 (2005). doi: 10.1056/NEJMe058157; pmid: 16177255
22. I. K. Macdonald, C. B. Parsy-Kowalska, C. J. Chapman, Autoantibodies: Opportunities for early cancer detection. *Trends Cancer* **3**, 198–213 (2017). doi: 10.1016/j.trecan.2017.02.003; pmid: 28718432
23. D. Beshnova *et al*., De novo prediction of cancer-associated T cell receptors for noninvasive cancer detection. *Sci. Transl. Med.* **12**, eaaz3738 (2020). doi: 10.1126/scitranslmed.aaz3738; pmid: 32817363
24. M. DuPage, T. Jacks, Genetically engineered mouse models of cancer reveal new insights about the antitumor immune response. *Curr. Opin. Immunol.* **25**, 192–199 (2013). doi: 10.1016/j.coi.2013.02.005; pmid: 23465466
25. B. Olson, Y. Li, Y. Lin, E. T. Liu, A. Patnaik, Mouse models for cancer immunotherapy research. *Cancer Discov.* **8**, 1358–1365 (2018). doi: 10.1158/2159-8290.CD-18-0044; pmid: 30309862
26. D. Bedognetti *et al*., Toward a comprehensive view of cancer immune responsiveness: A synopsis from the SITC workshop. *J. Immunother. Cancer* **7**, 131 (2019). doi: 10.1186/s40425-019-0602-4; pmid: 31113486
27. A. K. Palucka, L. M. Coussens, The basis of oncoimmunology. *Cell* **164**, 1233–1247 (2016). doi: 10.1016/j.cell.2016.01.049; pmid: 26967289
28. D. Hanahan, E. F. Wagner, R. D. Palmiter, The origins of oncomice: A history of the first transgenic mice genetically engineered to develop cancer. *Genes Dev.* **21**, 2258–2270 (2007). doi: 10.1101/gad.1583307; pmid: 17875663
29. D. Hanahan, R. A. Weinberg, The hallmarks of cancer. *Cell* **100**, 57–70 (2000). doi: 10.1016/S0092-8674(00)81683-9; pmid: 10647931
30. F. McCormick, Signalling networks that cause cancer. *Trends Cell Biol.* **9**, M53–M56 (1999). doi: 10.1016/S0962-8924(99)01668-2; pmid: 10611683
31. D. Hanahan, L. M. Coussens, Accessories to the crime: Functions of cells recruited to the tumor microenvironment. *Cancer Cell* **21**, 309–322 (2012). doi: 10.1016/j.ccr.2012.02.022; pmid: 22439926
32. N. Oshimori, D. Oristian, E. Fuchs, TGF-β promotes heterogeneity and drug resistance in squamous cell carcinoma. *Cell* **160**, 963–976 (2015). doi: 10.1016/j.cell.2015.01.043; pmid: 25723170
33. S. R. Hingorani *et al*., Preinvasive and invasive ductal pancreatic cancer and its early detection in the mouse. *Cancer Cell* **4**, 437–450 (2003). doi: 10.1016/S1535-6108(03)00309-X; pmid: 14706336
34. K. M. Haigis *et al*., Differential effects of oncogenic K-Ras and N-Ras on proliferation, differentiation and tumor progression in the colon. *Nat. Genet.* **40**, 600–608 (2008). doi: 10.1038/ng.115; pmid: 18372904
35. E. L. Jackson *et al*., Analysis of lung tumor initiation and progression using conditional expression of oncogenic *K-ras*. *Genes Dev.* **15**, 3243–3248 (2001). doi: 10.1101/gad.943001; pmid: 11751630
36. A. L. Dooley *et al*., Nuclear factor I/B is an oncogene in small cell lung cancer. *Genes Dev.* **25**, 1470–1475 (2011). doi: 10.1101/gad.2046711; pmid: 21764851
37. S. C. Williamson *et al*., Vasculogenic mimicry in small cell lung cancer. *Nat. Commun.* **7**, 13322 (2016). doi: 10.1038/ncomms13322; pmid: 27827359
38. A. Lallo, M. W. Schenk, K. K. Frese, F. Blackhall, C. Dive, Circulating tumor cells and CDX models as a tool for preclinical drug development. *Transl. Lung Cancer Res.* **6**, 397–408 (2017). doi: 10.21037/tlcr.2017.08.01; pmid: 28904884
39. M. Breitenbach, J. Hoffmann, Editorial: Cancer models. *Front. Oncol.* **8**, 401 (2018). doi: 10.3389/fonc.2018.00401; pmid: 30338241
40. T. R. Rebbeck *et al*., Precision prevention and early detection of cancer: Fundamental principles. *Cancer Discov.* **8**, 803–811 (2018). doi: 10.1158/2159-8290.CD-17-1415; pmid: 29907587
41. M. Jansen, M. Banks, Early detection and risk stratification of gastric cancer are likely to be refined with biopsies targeted through high-resolution-enhanced imaging. *Gut* **69**, 1710–1711 (2020). doi: 10.1136/gutjnl-2019-319921; pmid: 31611299
42. A. Lee *et al*., BOADICEA: A comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. *Genet. Med.* **21**, 1708–1718 (2019). doi: 10.1038/s41436-018-0406-9; pmid: 30643217
43. J. Tyrer, S. W. Duffy, J. Cuzick, A breast cancer prediction model incorporating familial and personal risk factors. *Stat. Med.* **23**, 1111–1130 (2004). doi: 10.1002/sim.1668; pmid: 15057881
44. S. A. Lambert, G. Abraham, M. Inouye, Towards clinical utility of polygenic risk scores. *Hum. Mol. Genet.* **28**, R133–R142 (2019). doi: 10.1093/hmg/ddz187; pmid: 31363735
45. E. W. Steyerberg *et al*., Assessing the performance of prediction models: A framework for traditional and novel measures. *Epidemiology* **21**, 128–138 (2010). doi: 10.1097/EDE.0b013e3181c30fb2; pmid: 20010215
46. A. Bleyer, H. G. Welch, Effect of three decades of screening mammography on breast-cancer incidence. *N. Engl. J. Med.* **367**, 1998–2005 (2012). doi: 10.1056/NEJMoa1206809; pmid: 23171096
47. A. C. Perkins, E. N. Skinner, A review of the current cervical cancer screening guidelines. *N. C. Med. J.* **77**, 420–422 (2016). doi: 10.18043/ncm.77.6.420; pmid: 27864494
48. R. Nishihara *et al*., Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N. Engl. J. Med.* **369**, 1095–1105 (2013). doi: 10.1056/NEJMoa1301969; pmid: 24047059
49. K. L. Huang *et al*., Effects of low-dose computed tomography on lung cancer screening: A systematic review, meta-analysis, and trial sequential analysis. *BMC Pulm. Med.* **19**, 126 (2019). doi: 10.1186/s12890-019-0883-x; pmid: 31296196
50. M. Triplette, J. H. Thayer, S. N. Pipavath, K. Crothers, Poor uptake of lung cancer screening: Opportunities for improvement. *J. Am. Coll. Radiol.* **16**, 446–450 (2019). doi: 10.1016/j.jacr.2018.12.018; pmid: 30777648
51. J. Shreffler, M. R. Huecker, "Diagnostic Testing Accuracy: Sensitivity, Specificity, Predictive Values and Likelihood Ratios," StatPearls (StatPearls Publishing, 2021); www.ncbi.nlm.nih.gov/books/NBK557491/.
52. A. M. Molinaro, Diagnostic tests: How to estimate the positive predictive value. *Neurooncol. Pract.* **2**, 162–166 (2015). doi: 10.1093/nop/npv030; pmid: 31386059
53. D. Ilic, M. M. Neuberger, M. Djulbegovic, P. Dahm, Screening for prostate cancer. *Cochrane Database Syst. Rev.* **1**, CD004720 (2013). pmid: 23440794
54. D. C. Grossman *et al*., Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *JAMA* **319**, 1901–1913 (2018). doi: 10.1001/jama.2018.3710; pmid: 29801017
55. U. Menon *et al*., Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative

Trial of Ovarian Cancer Screening (UKCTOCS): A randomised controlled trial. *Lancet* **397**, 2182–2193 (2021). doi: 10.1016/S0140-6736(21)00731-5; pmid: 33991479
56. A. T. Boutin *et al*., Oncogenic *Kras* drives invasion and maintains metastases in colorectal cancer. *Genes Dev.* **31**, 370–382 (2017). doi: 10.1101/gad.293449.116; pmid: 28289141
57. M. P. di Magliano, C. D. Logsdon, Roles for KRAS in pancreatic tumor development and progression. *Gastroenterology* **144**, 1220–1229 (2013). doi: 10.1053/j.gastro.2013.01.071; pmid: 23622131
58. E. Heitzer, I. S. Haque, C. E. S. Roberts, M. R. Speicher, Current and future perspectives of liquid biopsies in genomics-driven oncology. *Nat. Rev. Genet.* **20**, 71–88 (2019). doi: 10.1038/s41576-018-0071-5; pmid: 30410101
59. S. X. Antoniou *et al*., The potential of breath analysis to improve outcome for patients with lung cancer. *J. Breath Res.* **13**, 034002 (2019). doi: 10.1088/1752-7163/ab0bee; pmid: 30822771
60. V. A. Adalsteinsson *et al*., Scalable whole-exome sequencing of cell-free DNA reveals high concordance with metastatic tumors. *Nat. Commun.* **8**, 1324 (2017). doi: 10.1038/s41467-017-00965-y; pmid: 29109393
61. International Human Genome Sequencing Consortium, Finishing the euchromatic sequence of the human genome. *Nature* **431**, 931–945 (2004). doi: 10.1038/nature03001; pmid: 15496913
62. D. R. Bentley *et al*., Accurate whole human genome sequencing using reversible terminator chemistry. *Nature* **456**, 53–59 (2008). doi: 10.1038/nature07517; pmid: 18987734
63. S. J. Jones *et al*., Evolution of an adenocarcinoma in response to selection by targeted kinase inhibitors. *Genome Biol.* **11**, R82 (2010). doi: 10.1186/gb-2010-11-8-r82; pmid: 20696054
64. T. J. Hudson *et al*., International network of cancer genome projects. *Nature* **464**, 993–998 (2010). doi: 10.1038/nature08987; pmid: 20393554
65. C. Curtis *et al*., The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. *Nature* **486**, 346–352 (2012). doi: 10.1038/nature10983; pmid: 22522925
66. N. Wan *et al*., Machine learning enables detection of early-stage colorectal cancer by whole-genome sequencing of plasma cell-free DNA. *BMC Cancer* **19**, 832 (2019). doi: 10.1186/s12885-019-6003-8; pmid: 31443703
67. I. Martincorena *et al*., High burden and pervasive positive selection of somatic mutations in normal human skin. *Science* **348**, 880–886 (2015). doi: 10.1126/science.aaa6806; pmid: 25999502
68. A. P. Feinberg, The key role of epigenetics in human disease prevention and mitigation. *N. Engl. J. Med.* **378**, 1323–1334 (2018). doi: 10.1056/NEJMra1402513; pmid: 29617578
69. Y. Long, X. Wang, D. T. Youmans, T. R. Cech, How do lncRNAs regulate transcription? *Sci. Adv.* **3**, eaao2110 (2017). doi: 10.1126/sciadv.aao2110; pmid: 28959731
70. M. Tahiliani *et al*., Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1. *Science* **324**, 930–935 (2009). doi: 10.1126/science.1170116; pmid: 19372391
71. M. C. Liu, G. R. Oxnard, E. A. Klein, C. Swanton, M. V. Seiden; CCGA Consortium, Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. *Ann. Oncol.* **31**, 745–759 (2020). doi: 10.1016/j.annonc.2020.02.011; pmid: 33506766
72. S. Cristiano *et al*., Genome-wide cell-free DNA fragmentation in patients with cancer. *Nature* **570**, 385–389 (2019). doi: 10.1038/s41586-019-1272-6; pmid: 31142840
73. A. Carlsson *et al*., Circulating tumor microemboli diagnostics for patients with non-small-cell lung cancer. *J. Thorac. Oncol.* **9**, 1111–1119 (2014). doi: 10.1097/JTO.0000000000000235; pmid: 25157764
74. S. H. Jalalian, M. Ramezani, S. A. Jalalian, K. Abnous, S. M. Taghdisi, Exosomes, new biomarkers in early cancer detection. *Anal. Biochem.* **571**, 1–13 (2019). doi: 10.1016/j.ab.2019.02.013; pmid: 30776327
75. C. E. Gast *et al*., Cell fusion potentiates tumor heterogeneity and reveals circulating hybrid cells that correlate with stage and survival. *Sci. Adv.* **4**, eaat7828 (2018). doi: 10.1126/sciadv.aat7828; pmid: 30214939
76. A. Srivastava, D. J. Creek, Discovery and validation of clinical biomarkers of cancer: A review combining metabolomics and proteomics. *Proteomics* **19**, 1700448 (2019). doi: 10.1002/pmic.201700448; pmid: 30353665
77. H. T. Tan, Y. H. Lee, M. C. Chung, Cancer proteomics. *Mass Spectrom. Rev.* **31**, 583–605 (2012). doi: 10.1002/mas.20356; pmid: 22422534
78. M. Bhardwaj *et al*., Multiplex quantitation of 270 plasma protein markers to identify a signature for early detection of colorectal cancer. *Eur. J. Cancer* **127**, 30–40 (2020). doi: 10.1016/j.ejca.2019.11.021; pmid: 31972396
79. M. Bhardwaj, A. Gies, S. Werner, P. Schrotz-King, H. Brenner, Blood-based protein signatures for early detection of colorectal cancer: A systematic review. *Clin. Transl. Gastroenterol.* **8**, e128 (2017). doi: 10.1038/ctg.2017.53; pmid: 29189767
80. J. D. Cohen *et al*., Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science* **359**, 926–930 (2018). doi: 10.1126/science.aar3247; pmid: 29348365
81. V. Gopalakrishnan *et al*., Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science* **359**, 97–103 (2018). doi: 10.1126/science.aan4236; pmid: 29097493
82. V. Matson *et al*., The commensal microbiome is associated with anti–PD-1 efficacy in metastatic melanoma patients. *Science* **359**, 104–108 (2018). doi: 10.1126/science.aao3290; pmid: 29302014
83. B. Routy *et al*., Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors. *Science* **359**, 91–97 (2018). doi: 10.1126/science.aan3706; pmid: 29097494
84. B. A. Helmink, M. A. W. Khan, A. Hermann, V. Gopalakrishnan, J. A. Wargo, The microbiome, cancer, and cancer therapy. *Nat. Med.* **25**, 377–388 (2019). doi: 10.1038/s41591-019-0377-7; pmid: 30842679
85. S. U. Springer *et al*., Non-invasive detection of urothelial cancer through the analysis of driver gene mutations and aneuploidy. *eLife* **7**, e32143 (2018). doi: 10.7554/eLife.32143; pmid: 29557778
86. Y. Wang *et al*., Evaluation of liquid from the Papanicolaou test and other liquid biopsies for the detection of endometrial and ovarian cancers. *Sci. Transl. Med.* **10**, eaap8793 (2018). doi: 10.1126/scitranslmed.aap8793; pmid: 29563323
87. Z. Hu *et al*., Quantitative evidence for early metastatic seeding in colorectal cancer. *Nat. Genet.* **51**, 1113–1122 (2019). doi: 10.1038/s41588-019-0423-x; pmid: 31209394
88. A. M. Lennon *et al*., Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention. *Science* **369**, eabb9601 (2020). doi: 10.1126/science.abb9601; pmid: 32345712
89. T. F. Imperiale *et al*., Multitarget stool DNA testing for colorectal-cancer screening. *N. Engl. J. Med.* **370**, 1287–1297 (2014). doi: 10.1056/NEJMoa1311194; pmid: 25006736
90. C. Rudin, Stop explaining black box machine learning models for high stakes decisions and use interpretable models instead. *Nat. Mach. Intell.* **1**, 206–215 (2019). doi: 10.1038/s42256-019-0048-x
91. J. Dockès, G. Varoquaux, J. B. Poline, Preventing dataset shift from breaking machine-learning biomarkers. *Gigascience* **10**, giab055 (2021). doi: 10.1093/gigascience/giab055; pmid: 34585237
92. C. L. Andaur Navarro *et al*., Risk of bias in studies on prediction models developed using supervised machine learning techniques: Systematic review. *BMJ* **375**, n2281 (2021). pmid: 34670780
93. M. Nagendran *et al*., Artificial intelligence versus clinicians: Systematic review of design, reporting standards, and claims of deep learning studies. *BMJ* **368**, m689 (2020). doi: 10.1136/bmj.m689; pmid: 32213531
94. E. Christodoulou *et al*., A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models. *J. Clin. Epidemiol.* **110**, 12–22 (2019). doi: 10.1016/j.jclinepi.2019.02.004; pmid: 30763612
95. V. Baeriswyl, G. Christofori, The angiogenic switch in carcinogenesis. *Semin. Cancer Biol.* **19**, 329–337 (2009). doi: 10.1016/j.semcancer.2009.05.003; pmid: 19482086
96. X. He *et al*., First in-vivo human imaging at 10.5T: Imaging the body at 447 MHz. *Magn. Reson. Med.* **84**, 289–303 (2020). doi: 10.1002/mrm.28131; pmid: 31846121
97. A. P. Soleimany, S. N. Bhatia, Activity-based diagnostics: An emerging paradigm for disease detection and monitoring. *Trends Mol. Med.* **26**, 450–468 (2020). doi: 10.1016/j.molmed.2020.01.013; pmid: 32359477
98. S. Slomovic, K. Pardee, J. J. Collins, Synthetic biology devices for in vitro and in vivo diagnostics. *Proc. Natl. Acad. Sci. U.S.A.* **112**, 14429–14435 (2015). doi: 10.1073/pnas.1508521112; pmid: 26598662
99. C. N. Loynachan *et al*., Renal clearable catalytic gold nanoclusters for in vivo disease monitoring. *Nat. Nanotechnol.* **14**, 883–890 (2019). doi: 10.1038/s41565-019-0527-6; pmid: 31477801
100. T. Danino *et al*., Programmable probiotics for detection of cancer in urine. *Sci. Transl. Med.* **7**, 289ra84 (2015). doi: 10.1126/scitranslmed.aaa3519; pmid: 26019220
101. A. Aalipour *et al*., Engineered immune cells as highly sensitive cancer diagnostics. *Nat. Biotechnol.* **37**, 531–539 (2019). doi: 10.1038/s41587-019-0064-8; pmid: 30886438
102. A. F. Sarioglu *et al*., A microfluidic device for label-free, physical capture of circulating tumor cell clusters. *Nat. Methods* **12**, 685–691 (2015). doi: 10.1038/nmeth.3404; pmid: 25984697
103. P. Zhang *et al*., Ultrasensitive detection of circulating exosomes with a 3D-nanopatterned microfluidic chip. *Nat. Biomed. Eng.* **3**, 438–451 (2019). doi: 10.1038/s41551-019-0356-9; pmid: 31123323
104. S. S. Gambhir, T. J. Ge, O. Vermesh, R. Spitler, Toward achieving precision health. *Sci. Transl. Med.* **10**, eaao3612 (2018). doi: 10.1126/scitranslmed.aao3612; pmid: 29491186
105. H. U. Kauczor *et al*., ESR/ERS statement paper on lung cancer screening. *Eur. Radiol.* **30**, 3277–3294 (2020). doi: 10.1007/s00330-020-06727-7; pmid: 32052170
106. J. C. Gore, H. C. Manning, C. C. Quarles, K. W. Waddell, T. E. Yankeelov, Magnetic resonance in the era of molecular imaging of cancer. *Magn. Reson. Imaging* **29**, 587–600 (2011). doi: 10.1016/j.mri.2011.02.003; pmid: 21524870
107. J. V. Frangioni, New technologies for human cancer imaging. *J. Clin. Oncol.* **26**, 4012–4021 (2008). doi: 10.1200/JCO.2007.14.3065; pmid: 18711192
108. S. Surti *et al*., Performance of Philips Gemini TF PET/CT scanner with special consideration for its time-of-flight imaging capabilities. *J. Nucl. Med.* **48**, 471–480 (2007). pmid: 17332626
109. K. Golman, R. I. Zandt, M. Lerche, R. Pehrson, J. H. Ardenkjaer-Larsen, Metabolic imaging by hyperpolarized 13C magnetic resonance imaging for in vivo tumor diagnosis. *Cancer Res.* **66**, 10855–10860 (2006). doi: 10.1158/0008-5472.CAN-06-2564; pmid: 17108122
110. J. Kurhanewicz *et al*., Hyperpolarized ^{13}C MRI: Path to clinical translation in oncology. *Neoplasia* **21**, 1–16 (2019). doi: 10.1016/j.neo.2018.09.006; pmid: 30472500
111. H. U. Ahmed *et al*., Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): A paired validating confirmatory study. *Lancet* **389**, 815–822 (2017). doi: 10.1016/S0140-6736(16)32401-1; pmid: 28110982
112. J. Katzen, K. Dodelzon, A review of computer aided detection in mammography. *Clin. Imaging* **52**, 305–309 (2018). doi: 10.1016/j.clinimag.2018.08.014; pmid: 30216858
113. H. J. Yoon *et al*., Deciphering the tumor microenvironment through radiomics in non-small cell lung cancer: Correlation with immune profiles. *PLOS ONE* **15**, e0231227 (2020). doi: 10.1371/journal.pone.0231227; pmid: 32251447
114. S. M. McKinney *et al*., International evaluation of an AI system for breast cancer screening. *Nature* **577**, 89–94 (2020). doi: 10.1038/s41586-019-1799-6; pmid: 31894144
115. M. Bahl *et al*., High-risk breast lesions: A machine learning model to predict pathologic upgrade and reduce unnecessary surgical excision. *Radiology* **286**, 810–818 (2018). doi: 10.1148/radiol.2017170549; pmid: 29039725
116. B. Haibe-Kains *et al*., Transparency and reproducibility in artificial intelligence. *Nature* **586**, E14–E16 (2020). doi: 10.1038/s41586-020-2766-y; pmid: 33057217
117. I. Steinberg *et al*., Photoacoustic clinical imaging. *Photoacoustics* **14**, 77–98 (2019). doi: 10.1016/j.pacs.2019.05.001; pmid: 31293884
118. W. B. Nagengast *et al*., Near-infrared fluorescence molecular endoscopy detects dysplastic oesophageal lesions using topical and systemic tracer of vascular endothelial growth factor A. *Gut* **68**, 7–10 (2019). doi: 10.1136/gutjnl-2017-314953; pmid: 29247063
119. J. Burggraaf *et al*., Detection of colorectal polyps in humans using an intravenously administered fluorescent peptide targeted against c-Met. *Nat. Med.* **21**, 955–961 (2015). doi: 10.1038/nm.3641; pmid: 26168295
120. K. Bera, K. A. Schalper, D. L. Rimm, V. Velcheti, A. Madabhushi, Artificial intelligence in digital pathology—new tools for diagnosis and precision oncology. *Nat. Rev. Clin. Oncol.* **16**, 703–715 (2019). doi: 10.1038/s41571-019-0252-y; pmid: 31399699

121. M. K. K. Niazi, A. V. Parwani, M. N. Gurcan, Digital pathology and artificial intelligence. *Lancet Oncol.* **20**, e253–e261 (2019). doi: 10.1016/S1470-2045(19)30154-8; pmid: 31044723
122. P. Hu, M. Zelen, Planning of randomized early detection trials. *Stat. Methods Med. Res.* **13**, 491–506 (2004). doi: 10.1191/0962280204sm379ra; pmid: 15587435
123. D. R. Aberle *et al*., Reduced lung-cancer mortality with low-dose computed tomographic screening. *N. Engl. J. Med.* **365**, 395–409 (2011). doi: 10.1056/NEJMoa1102873; pmid: 21714641
124. H. J. de Koning *et al*., Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N. Engl. J. Med.* **382**, 503–513 (2020). doi: 10.1056/NEJMoa1911793; pmid: 31995683
125. U. Menon *et al*., Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: Results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *Lancet Oncol.* **10**, 327–340 (2009). doi: 10.1016/S1470-2045(09)70026-9; pmid: 19282241
126. J. Hugosson *et al*., A 16-yr Follow-up of the European Randomized study of Screening for Prostate Cancer. *Eur. Urol.* **76**, 43–51 (2019). doi: 10.1016/j.eururo.2019.02.009; pmid: 30824296
127. L. Highfield *et al*., A non-randomized controlled stepped wedge trial to evaluate the effectiveness of a multi-level mammography intervention in improving appointment adherence in underserved women. *Implement. Sci.* **10**, 143 (2015). doi: 10.1186/s13012-015-0334-x; pmid: 26464110
128. J. Cuzick, F. H. Cafferty, R. Edwards, H. Møller, S. W. Duffy, Surrogate endpoints for cancer screening trials: General principles and an illustration using the UK Flexible Sigmoidoscopy Screening Trial. *J. Med. Screen.* **14**, 178–185 (2007). doi: 10.1258/096914107782912059; pmid: 18078562
129. G. Poste, Bring on the biomarkers. *Nature* **469**, 156–157 (2011). doi: 10.1038/469156a; pmid: 21228852
130. S. A. Mulherin, W. C. Miller, Spectrum bias or spectrum effect? Subgroup variation in diagnostic test evaluation. *Ann. Intern. Med.* **137**, 598–602 (2002). doi: 10.7326/0003-4819-137-7-200210010-00011; pmid: 12353947
131. B. S. Kramer, The science of early detection. *Urol. Oncol.* **22**, 344–347 (2004). doi: 10.1016/j.urolonc.2003.04.001; pmid: 15283894
132. T. M. Andersson, M. J. Rutherford, K. Humphreys, Assessment of lead-time bias in estimates of relative survival for breast cancer. *Cancer Epidemiol.* **46**, 50–56 (2017). doi: 10.1016/j.canep.2016.12.004; pmid: 28027488
133. National Institutes of Health, National Cancer Institute, Early Detection Research Network; https://edrn.nci.nih.gov/.
134. National Institutes of Health, National Cancer Institute, Consortium for Molecular and Cellular Characterization of Screen-Detected Lesions; https://mcl.nci.nih.gov/.
135. Cancer Research UK, Early Detection and Diagnosis Research Committee; www.cancerresearchuk.org/funding-for-researchers/applying-for-funding/funding-committees/early-detection-and-diagnosis-committee.
136. Cancer Research UK, Early Detection and Diagnosis of Cancer Roadmap; www.cancerresearchuk.org/funding-for-researchers/research-opportunities-in-early-detection-and-diagnosis/early-detection-and-diagnosis-roadmap.
137. W. N. Hait, P. F. Lebowitz, Disease interception: Myths, mountains, and mole hills. *Cancer Prev. Res.* **9**, 635–637 (2016). doi: 10.1158/1940-6207.CAPR-16-0049; pmid: 27138792
138. D. Schenkel, S. Nambi, R. Blicker, C. Lin, Liquid Biopsy: Early Detection of a Huge Investment Opportunity; www.cowen.com/insights/liquid-biopsy-early-detection-of-a-huge-investment-opportunity/.
139. Grand View Research, "Cancer diagnostics market worth $249.6 billion by 2026," February 2019; www.grandviewresearch.com/press-release/global-cancer-diagnostics-market.
140. Office for National Statistics UK, Cancer survival in England: adult, stage at diagnosis and childhood - patients followed up to 2018, 12 August 2019; www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalinengland/stageatdiagnosisandchildhoodpatientsfollowedupto2018.

ACKNOWLEDGMENTS

We dedicate this Review to our friend, colleague, and mentor Sanjiv "Sam" Gambhir. He showed us the path to early detection of cancer and taught us to always look to the horizon. We continue to walk that path in his memory. Paid editorial assistance was provided by F. Dunlevy, Axcience. We also thank A. Webb, Cancer Research UK, for editorial and logistical assistance during the preparation of this manuscript and for contributions to the figures. We acknowledge the Cancer Research UK Policy and Information Directorate for their assistance on UK cancer diagnosis and screening statistics. We also acknowledge the Early Detection, Prevention, and Infections Branch of the International Agency for Research on Cancer for their assistance on Asian cancer survival statistics. **Funding:** M.E. receives research support from the UK's National Institute of Health Research (NIHR) UCLH/UCL Biomedical Research Centre and was awarded NIHR Senior Investigator status in 2013. **Competing interests:** S.Ba. is a founder, board member, and shareholder of Cambridge Epigenetix Ltd. and a science partner and adviser to Ahren Innovation Capital. S.Bh. is a board member of Brown University and Vertex Pharmaceuticals; holds advisory roles at Chan Zuckerberg Biohub, Global Oncology Inc., Cristal Therapeutics, Glympse Bio, CEND Therapeutics, and Satellite Bio; consults for Moderna Therapeutics; and performs sponsored research for Johnson & Johnson. S.Bh. holds equity in Vertex Pharmaceuticals, Glympse Bio, CEND Therapeutics, and Satellite Bio. K.M.B. holds patents with GE Healthcare on some aspects of hyperpolarization technology and is a paid consultant for NVision Imaging Technologies GmbH and New Path Molecular Research Ltd. L.M.C. is a paid consultant for the Susan G. Komen Foundation, Cell Signaling Technologies, AbbVie Inc., and Shasqi Inc.; receives reagent and/or research support from Pharmacyclics Inc., Acerta Pharma LLC, Deciphera Pharmaceuticals LLC, Genentech Inc., Roche Glycart AG, Syndax Pharmaceuticals Inc., and NanoString Technologies; and is a member of the scientific advisory boards of Syndax Pharmaceuticals, Carisma Therapeutics, Zymeworks Inc., Verseau Therapeutics, Cytomix Therapeutics Inc., Alkermes Inc., Cell Signaling Technology, Genenta Science, and Kineta Inc.; and is a site lead for the AstraZeneca Partner of Choice Network. C.D. has received research funding and/or educational research grants from: AstraZeneca, Astex Pharmaceuticals, Bioven, Amgen, Carrick Therapeutics, Merck AG, Taiho Oncology, GSK, Bayer, Boehringer Ingelheim, Roche, BMS, Novartis, Celgene, Epigene Therapeutics Inc., Angle PLC, Menarini, Clearbridge Biomedics, Thermo Fisher Scientific, and Neomed Therapeutics. C.D. has received honoraria for consultancy and/or advisory boards from: Biocartis, Merck, AstraZeneca, GRAIL, and Boehringer Ingelheim. M.E. is an investigator, adviser, and/or lecturer to the following companies: STEBA Biotech, Sonacare Inc., and Angiodynamics Inc. R.C.F. is named on patents related to Cytosponge and associated assays, which has been licensed by the Medical Research Council to Covidien GI Solutions (now Medtronic). R.C.F. is a shareholder and consultant for Cyted Ltd., an early detection company. S.S.G. was a founder, board member, and stockholder of Earli Inc. P.K. is a named inventor on patents relating to liquid biopsy technology, which have been licensed to Epic Sciences by the Scripps Research Institute for commercial development. P.K. is a named inventor on patents relating to human performance assessment, which have been licensed to Cansera for commercial development. P.K. is a shareholder of and consultant to Epic Sciences and Cansera. P.K. receives research funding from Kite, Gilead, Amgen, and Novartis. P.K. is a member of the CRUK Early Detection committee.

10.1126/science.aay9040