Blueprint for Cancer Research: Critical Gaps and Opportunities

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Abstract: We are experiencing a revolution in cancer. Advances in screening, targeted and immune therapies, big data, computational methodologies, and significant new knowledge of cancer biology are transforming the ways in which we prevent, detect, diagnose, treat, and survive cancer. These advances are enabling durable progress in the goal to achieve personalized cancer care. Despite these gains, more work is needed to develop better tools and strategies to limit cancer as a major health concern. One persistent gap is the inconsistent coordination among researchers and caregivers to implement evidence-based programs that rely on a fuller understanding of the molecular, cellular, and systems biology mechanisms underpinning different types of cancer. Here, the authors integrate conversations with over 90 leading cancer experts to highlight current challenges, encourage a robust and diverse national research portfolio, and capture timely opportunities to advance evidence-based approaches for all patients with cancer and for all communities. CA Cancer J Clin 2021;71:107-139. © 2020 American Cancer Society.

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Introduction

Recent discoveries and rapidly accumulating data are providing novel insights into the extrinsic and intrinsic causes and mechanisms in the development and progression of cancer.¹ These and earlier advances in cancer prevention, early detection, and treatment have contributed to the continuous decline in the age-standardized cancer death rate from 1991 to 2017 by a total of 29%. This translates into an estimated 2.9 million fewer cancer deaths during that interval than would have occurred if death rates had remained at their peak based on 5-year age-specific and sex-specific, population-based data.² Analyses by individual cancer type show an increase in survival for most common cancers, with the largest long term gains for hematopoietic and lymphoid malignancies. More recently, advances in treatment are also reflected in dramatic improvement in survival for metastatic melanoma of the skin and non-small cell lung cancer.³

The aforementioned data reflect real progress in the fight against cancer, but they also clearly indicate that we have not reached our goal of eliminating cancer as a major health concern. Overall, US mortality from all cancers combined declined 26% over the period from 1990 to 2015. A statistical modeling approach was then used to set the American Cancer Society (ACS) 2035 challenge goal at a 40% reduction in cancer mortality from the 2015 level.⁴ Accomplishing this reduction in cancer will clearly involve better application of today’s tools for cancer prevention, detection, treatment, and assurance of quality of life for patients with cancer, survivors, and their families.⁵,⁶ However, success also depends on a sustained research effort to develop the next generation of tools to understand, prevent, and better control all cancer types. In 2019, only about one-half of patients with cancer in the United States could be cured with existing therapies, and the remaining one-half were expected to die of their disease.⁶ In addition, while therapeutic interventions have improved significantly, chronic comorbidities often adversely affect cancer survivors and their quality of life.
Breakthroughs depend on increased understanding of the etiologic, genetic, biological, and clinical heterogeneity of cancer and the tumor cell environment. To create a snapshot of the current state, ACS research staff consulted one-on-one or in small groups with over 90 leading experts across the country to identify knowledge gaps, barriers, and research opportunities for the 20 cancers that cause the most deaths in the United States per year\(^1\) plus pediatric cancers. These cancer experts represented multiple disciplines and provided a balance of basic, translational, clinical, and cancer control perspectives. Twenty-one summary statements were prepared, from which recurrent themes emerged that were largely independent of the cancer type. These topics provide the framework for this blueprint article, the eighth in a series outlining an ACS vision for the future of the control of cancer. In contrast to the preceding blueprint articles, the information presented here was derived primarily from the comments of external experts rather than ACS staff.

Previous blueprint articles in this series have addressed important topics including the ACS 2035 challenge goals on cancer mortality reduction,\(^4\) cancer screening and early detection,\(^7\) minimizing the burden of cancer in the United States,\(^8\) equitably improving outcomes for cancer survivors and supporting caregivers,\(^9\) primary prevention of cancer,\(^10\) assessment of progress in cancer control,\(^11\) and advancing cancer health equity.\(^12\) Here, the focus is research across the cancer continuum to stimulate future investigations that will ultimately better serve all persons with cancer or those at risk for cancer. The goal is to present, in a collaborative, holistic, and thought-provoking way, the wisdom and insights of leading cancer experts and, in doing so, provide a blueprint for cancer research for the next decade. Recurring, high-impact research areas included cancer screening and early detection; precision medicine (targeted therapy and immunotherapy); tumor heterogeneity, cellular plasticity, and drug resistance; and cancer modeling. Microbiome, metabolism, epigenetics and chromatin remodeling, and metastasis were identified as emerging areas already showing clinical promise. We include health equity and access to care, smoking, survivorship, and cancer research workforce as cross-cutting issues because, in addition to being important topics for many cancer types, they affect cancer control and prevention in myriad ways. It is a daunting or perhaps impossible task to consider all that needs to be done in research to conquer the hundreds of diseases we group together under the moniker of cancer. Undoubtedly, we have left out important and exciting topics but hope that this article stimulates robust discussions and productive interactions.

### Cancer Screening and Early Detection

**State of the Field**

The aim of screening asymptomatic individuals for cancer is to detect evidence of premalignant changes or early stage, localized cancers when treatment is typically more successful, less toxic, and less costly. As detailed by Wender and colleagues in the ACS blueprint for cancer screening and early detection, there is wide recognition that detecting cancer in its early stages has demonstrated considerable success and holds even greater potential as a key component of cancer control in the future.\(^7\) Yet recommended population-based screening methods that have been rigorously tested and found to improve health outcomes are relatively few, including colorectal and cervical cancer screening for both premalignant and early invasive disease, prostate-specific antigen testing for prostate cancer, and mammography and low-dose helical computed tomography (CT) screenings for localized breast and lung cancers, respectively. For prostate cancer, there is an enduring challenge to avoid overtreatment, which prevents an unambiguous recommendation for screening; however, this does not undermine the evidence that screening is associated with a reduction in prostate cancer deaths.\(^13\)

Advances in screening and early detection have contributed greatly to the steady decline in mortality from several types of cancers.\(^14\)-\(15\) Unfortunately, despite the body of evidence supporting the effectiveness of screening for these cancer types, for a variety of reasons, many people are still not being screened in accordance with guidelines from the ACS, the US Preventative Services Task Force, and other public health and professional organizations.\(^16\)-\(19\)

Tumor biomarkers have broad clinical applications (ie, risk assessment, screening, surveillance, diagnosis, predicting treatment response, and monitoring disease progression and recurrence).\(^20\) It is beyond the scope of this article to comprehensively cover the current state of the biomarker field for cancer screening and early detection. Instead, we provide a few examples of advances and emerging technologies related to imaging, tissue and cytologic biomarkers, and liquid biopsies to highlight the expanding landscape. We also provide some context about the complexity of the biomarker pipeline and the critical role new technologies play not only in developing new screening and early detection tools but also for improving cancer risk stratification.

**Imaging biomarkers**

Imaging biomarkers encompass a broad array of anatomic (ie, size, location, calcification) and functional (tumor phenotype, rates of growth and metabolism) features. Machine learning is beginning to provide practical ways to generate imaging signatures, revealing potential opportunities for helping guide clinical decision making.\(^21\)-\(24\) A better understanding of the molecular and cellular changes accompanying tumor development is paving the way for developing innovative molecular imaging and immunomaging strategies.\(^25\),\(^26\) With additional research, we
will learn whether and how these expanded imaging capabilities lead to new or improved, evidence-based tests for cancer screening and early detection. Cellular imaging and analysis platforms, such as CellCT (VisionGate) and Totalsys (Becton Dickinson), permit capturing hundreds of morphological measurements in individual cells of clinical samples, resulting in the generation of 3-dimensional images. The ability to create high-resolution biosignatures from intact cells in sputum samples and liquid-based preparations provides complementary imaging approaches to improve upon the efficiency of lung cancer screening with low-dose CT and a Papanicolaou (Pap) test or human papillomavirus (HPV) genotyping for cervical cancer screening.

**Tissue and cytologic biomarkers**

With advances in omic technologies (genomics, proteomics, metabolomics, lipidomics, etc) and the amassing of associated large data sets have come great hope for the discovery of new tumor biomarkers that will prove useful for screening more cancer types and provide companion assays to improve existing screening strategies. The molecular biomarker repertoire for host tissues/cells is now highly diverse, including proteins, metabolites, cancer-specific mutations, high mutation burden, chromosomal translocations, epigenetic alterations, and microRNAs. In this postgenome era, there is a growing number of candidate cancer biomarkers (>1000 different molecules). However, to date, the number of biomarkers approved for clinical use remains ~25. In 2014, the US Food and Drug Administration (FDA) approved the Cologuard (Exact Sciences) test as an option for noninvasive colorectal cancer screening utilizing a multifactor analysis of markers in stool. With the advancement of metabolic profiling technologies, there have been notable efforts over the past decade to clinically exploit cancer-specific metabolism to aid in cancer detection. Thus far, translation and clinical utility have been somewhat disappointing.

Tumor biomarkers are not always host-derived. High-risk HPV is associated with the development of essentially all cervical cancers as well as a subset of oropharyngeal, anal, and genital cancers. Detection of HPV DNA in clinical specimens has become increasingly important, especially in cervical cancer screening and in the treatment of cancer precursors. Currently, there are 5 FDA-approved assays for HPV genotyping/Pap cotesting and 2 approved tests for primary HPV testing.

**Liquid biopsy**

The ability to enrich from peripheral blood, small numbers of circulating tumor cells, miniscule amounts of free tumor-derived DNA or RNA, and cancer-derived exosomes has led to the appealing concept of a liquid biopsy. Although a traditional tissue biopsy remains the gold standard for confirming a diagnosis of cancer, testing the clinical utility of these molecular surrogates in bodily fluids is a very promising area of investigation. A liquid biopsy offers many advantages over a traditional biopsy. It is minimally invasive, not generally limited in terms of sample accessibility and availability, and practical for repeat sampling, which could help clinicians during screening and surveillance as well as postdiagnosis to better understand the molecular changes occurring in a tumor over time. However, unlike traditional biopsies, a liquid biopsy does not provide morphological information, which is invaluable for diagnosis, prognosis, and distinguishing cancer from nonneoplastic diseases and benign neoplasms.

Much research in this field has focused on pan-cancer screening tests, in which a single blood draw tests for many cancers at once. CancerSEEK is a liquid biopsy test (Thrive Earlier Detection Corporation) that simultaneously measures the levels of 8 cancer-associated proteins, and, in a case-control study, this multianalyte test was able to correctly identify most (approximately 70%) patients with cancer—including cancer types for which there is no evidence-based screening tool. Although these results are encouraging, if a 30% false-negative rate is validated, it may undermine the clinical value and outcome benefits. Results from a prospective study of CancerSEEK in healthy individuals, the DETECT (Detecting Cancers Early Through Elective Mutation-based Blood Collection and Testing) study, suggest that CancerSEEK combined with positron emission tomography/CT imaging may offer a more specific approach for screening multiple cancer types. PapSEEK and UroSEEK derivatives that simultaneously detect numerous genetic alternations in DNA shed from cancer cells in fluids obtained during Pap tests and in urine samples, are being developed and tested for their clinical utility in the early detection of gynecologic and urothelial cancers, respectively.

A prospective case-control study in a cohort of more than 15,000 individuals has shown promise for the use of a liquid-biopsy test based on whole-genome bisulfite sequencing of cell-free DNA for multicancer early detection. This collaborative effort of GRAIL, Inc, the STRIVE Study (ClinicalTrials.gov identifier NCT03085888), and the Circulating Cell-Free Genome Atlas (CCGA) has led to recent validation testing, which revealed that 50 different cancer types across all stages can be identified from a single blood draw with a low (<1%) false-positive rate. Moreover, when a cancer signature is detected, the assay can identify the cancer’s tissue of origin with 93% accuracy. Additional studies are now warranted that focus on larger numbers of asymptomatic individuals to further assess the specificity and sensitivity performance of this DNA methylation-based assay.
**Biomarker pipeline**

With such a diverse repertoire of tumor biomarkers comes a multitude of potential *combinatorial* surrogates in the hope that this strategy will work better for predicting cancer risk, response to therapy, survival, etc.\(^{41-44}\) But, no matter the candidate biomarker(s) being tested for potential use in cancer care, the pipeline typically begins in a research laboratory studying features of malignant cells and the changes that occur during disease progression. As a result, biomarkers are often tested for utility in cancer diagnostics (symptoms of disease) before consideration for screening (asymptomatic) and surveillance (greater than average cancer risk) purposes. For a recent example, the FDA has approved a liquid biopsy for comprehensive tumor mutation profiling across all solid cancer types (Guardant360 CDx; Guardant Health;\(^ {45}\) related press release\(^ {46}\)). This genomic profiling strategy has also been approved as a companion diagnostic to identify patients with nonsmall cell lung carcinoma who have *EGFR* alternations to help inform personalized treatment options. Additional research is necessary to test whether profiling mutations in cell-free DNA or circulating tumor cells will prove useful for cancer screening, early detection, and improve outcomes.

The initial phase of this *retrospective* biomarker identification process is rarely followed by prospective studies in the academic setting, where the focus instead tends to be on therapeutic trials sponsored by companies. As such, building an infrastructure for funding prospective biomarker clinical trials where the patients are located (e.g., hospitals with research components) could facilitate the time from biomarker discovery to clinical utility. As new tests are developed, validated, and integrated into clinical practice, it will be critical through research to determine the best ways to increase the likelihood that these new tests will be accepted and available to all communities, and not just to those with *gold-plated* health insurance, high health literacy groups, or those who trust the health care system. There is much excitement and effort to develop new, population-based screening tools that leverage new technologies and our improved understanding of cancer. However, rigorous testing remains to determine *if* any will improve health outcome and *how* (i.e., complement or replace standard screening tests) they will be optimally integrated into cancer screening delivery and risk assessment to benefit all people.

**Knowledge Gaps and Challenges**

Even with many recent advances in cancer research, there are still critical gaps in our fundamental understanding of the cause, pathogenesis, and natural history of many different types of cancers, especially mediators of the transition from premalignant to preinvasive to invasive phenotypes.\(^ {47,48}\) For many tumor types, we can successfully detect early stage lesions; however, we are unable to distinguish with confidence which lesions will remain indolent and which will become invasive cancers. Most prostate cancers detected by screening are asymptomatic, clinically localized, and associated with limited cancer-specific mortality.\(^ {49}\) For those very slow growing lesions, active surveillance is preferable and can avoid the permanent adverse effect on quality of life that often results from curative-intent surgery or radiotherapy.\(^ {50}\) Distinguishing the many indolent prostate tumors from the minority of lethal ones remains a major clinical challenge.\(^ {51}\) Management of ductal carcinoma in situ (DCIS) of the breast is also problematic. There are an estimated 60,000 such diagnoses in the United States each year. Because mammography cannot determine which lesions are likely to progress, most patients with DCIS are treated with surgery, radiation, and hormone therapy, undoubtedly resulting in the treatment of some low-grade precancerous lesions not destined to progress to invasive cancer.\(^ {52}\) A root challenge of cancer stems from the enormous tumor heterogeneity and plasticity, with implications for early detection and screening as well as treatment response (for more information, see Tumor Heterogeneity, Cellular Plasticity, and Drug Resistance below). Although there have been significant research efforts to identify early lesions marked by certain molecular characteristics in the hope of improving risk stratification for individuals with premalignant lesions, these tumor features alone may not necessarily enable better cancer prognosis and control. However, a better understanding of host characteristics, such as tumor/tissue microenvironment and immunity, that are critical for early cancer progression may provide additional biomarkers to inform future standards of care.

Although the implementation of tools to screen for breast, lung, prostate, and colorectal cancers has unquestionably saved many thousands of lives, the information content derived from the screens themselves can be improved to the benefit of patients with cancer by research that focuses on enhanced diagnostic or prognostic accuracy and a reduction of the costs related to testing. Once there is a new screening test in hand, there are 2 notable challenges: 1) determining how best to accelerate the evaluation methodology to move more quickly on determining the efficacy of these new tests, and 2) working best practices into the cascade of events necessary for any screening test to be effective once efficacy has been demonstrated.

However, the bigger challenge for early detection is that there are no evidence-based screening tools for the vast majority of cancer types. As shown in Table 1,\(^ {14}\) looking at the next 8 most lethal cancers (solid tumors) with an annual cumulative incidence >300,000 and mortality >150,000, it is clear that substantial opportunities exist to save lives across a
range of cancer types with the development of new screening tools. When there is no screening test, tumors are often diagnosed at advanced stages, when complete surgical resection is difficult or impossible and chemotherapy or radiation are of limited benefit. Unfortunately, this pattern is more the norm than the exception across many cancer types, including pancreatic ductal adenocarcinoma and ovarian high-grade serous carcinoma, both with dismal 5-year survival rates. Additional discovery research is necessary to identify new cancer biomarkers, and additional translational research is essential to move recent advances in minimally invasive, early detection methods forward. For relatively rare cancers, there is also a need for more sophisticated approaches to risk stratify (ie, refined statistical models, including the integration of multidimensional -omic, radiologic, and established risk factor data) because even trivial false-positive proportions require follow-up that far outweighs the true-positives.

With the cancer biomarker field evolving at a rapid pace, there are numerous growing pains along the pipeline from discovery to validation to implementation. Exploratory research on biomarkers lays important groundwork for the validation process. However, a large number of candidates can create a bottleneck in the pipeline. Difficulties in preclinical and clinical validation, together with a lack of robust predictive power, have been major obstacles for translating candidate biomarkers to clinical utility. These barriers are being overcome by developing tests that rely on unique signatures and combining data from more than one class of biomolecules (eg, integrating proteomics, metabolomics, transcriptomics, and genetics).

We have proven screening tools for several common cancer types, yet many Americans are not reaping the benefits. Although the United States is a high-resource country, the uptake, equity, and effectiveness of screening are suboptimal, and socioeconomic inequalities in usage are widening. It is paramount to identify through research the most effective strategies for implementing existing screening tools for all populations at risk for cancer. If cutting-edge technology is not thoughtfully implemented into diverse populations, a significant opportunity to avert adverse outcomes is squandered.

**Research Opportunities/Priorities**

**Current screening tests need improvements**

The most commonly used screening tests for the early detection of cancer include those for breast, cervical, colorectal, lung, and prostate cancers. Each has been successfully implemented, although all have strengths and weaknesses. Screening-specific issues often center on needs for improved prognostic content, patient discomfort, which discourages use, or a need for confirmational testing. No matter the screening-specific need, it is critical to seek diagnostic solutions that are less expensive and less complex for clinicians to enable their widest application. Leading researchers in this field recommend the following areas of study for the near future:

- Focus on research to reduce the recall rates in mammography (7%-12%) and improve the ability to detect small lesions in dense breast tissue in a practical, cost-effective manner,
- Develop adjunct screening tools to provide better prognostic information for DCIS (eg, the Oncotype DX DCIS Score [Genomic Health, Inc]),
- Establish prognostic markers for aggressive prostate cancer, and
- Develop alternative or adjunct screening tools for lung cancer (ie, a minimally invasive test to inform of the biology of a lung nodule identified through imaging).

**New screening tests need to be developed**

Equally pressing, research is needed to discover new tools for cancer screening and early detection. With only 4 of the 20 most common cancer types in the United States having a proven screening method to reduce mortality by identifying early stage lesions, developing such tools for other high-incidence malignancies is urgently needed. Several high-priority research opportunities were identified in discussion with the experts that could fill current knowledge and technological gaps and pave the way for the future development of new screening approaches:

- Improve understanding of the molecular underpinnings of the earliest stages of cancer and premalignant disease;
- Determine how cellular and physical properties of the tumor microenvironment contribute to the transition from premalignant to preinvasive to invasive disease;
- Develop more sensitive and specific technologies for cancer screening, early detection, and risk stratification and
selectively invest in the most promising markers and technologies to accelerate clinical evaluation;

- Redesign clinical biomarker workflows that are practical, reliable, reproducible, and allow different analytes (circulating tumor DNA, circulating tumor cells, RNA, proteins, metabolites, etc) to be detected, quantified, and integrated in parallel from a limited amount of fluid;
- Determine how public health genomics (ie, effective and responsible translation of genomic science into population health benefits) affect precision public health related to cancer screening and early detection; and
- Explore the best ways to use artificial intelligence/machine learning and next-generation technologies, such as wearable devices, to aid in cancer screening and early detection.

**Implementation research is needed to better understand barriers to screening and rigorously test interventions**

- Determine how to increase and sustain the uptake, equity, and effectiveness of evidence-based, cancer screening tools and what is the optimal balance and integration of roles to accomplish this.
- Identify the best strategies to close the gap in the receipt of evidence-based cancer screening tests among marginalized, underserved, and never-screened populations and to increase the likelihood of follow-up after a positive screening test (such as HPV testing and/or cervical cytology, colon screening, and mammography) in rural and underserved populations.
- Overcome the issue of over-screening among some populations (eg, populations with limited life expectancy receiving cancer screening that is unlikely to provide a net benefit).
- Determine how removal or reduced insurance coverage for preventive services affects uptake of cancer screening (and modeled effects on mortality).
- Establish improved cancer screening decision support for individuals at risk of developing cancer (including a secondary malignancy from cancer treatments).

**Precision Medicine: Targeted Therapy and Immunotherapy**

**State of the Field**

Cancer therapy has traditionally focused on somewhat empirically refined combinations of radiation, surgery, and cytotoxic chemotherapy, resulting in successful outcomes for some patients, although too often accompanied by significant treatment-related toxicity, drug resistance, and debilitating, long-term sequela. Although basic science efforts began many decades prior, in the 1990s, cancer drug discovery efforts to develop better clinical agents with improved potency, specificity, durability, and reduced toxicity shifted to a more targeted approach. Robust expression of functional enzymes and receptors and adaptation to high-throughput screening led to a variety of unique antibodies, small-molecule inhibitors, and drug candidates emerging from both industrial and academic laboratories. Advances in genetics and cell biology enabled the functional validation of gene targets as drivers in different types of cancer, while advances in DNA sequencing often were able to provide clinical validation of the genetic drivers of cancer in humans. Recognition that cancer is primarily a disease of the genome has fueled a recent focus on the development of more personalized or precision treatments based largely on genomic information.

Although precision medicine has been in development for decades, recent advances in next-generation sequencing and multiple omic techniques have led the way to medicine focused less on tumor type and more on the molecular characteristics of an individual patient’s disease. Cancer treatment today may be thought of as a precise choice of best options among surgery, radiation, conventional cancer chemotherapy, targeted therapy, and immunotherapy.

**Targeted therapy**

Some have argued that the first targeted therapy dates back to the 1940s with the introduction of 131I treatment for thyroid cancer. More contemporary examples of targeted therapies are Tamoxifen, a selective estrogen receptor (ER) modulator used to prevent recurrence of ER-positive breast cancer (FDA approved in 1977), and Gleevec (Novartis), an ABL-kinase inhibitor used to treat chronic myelogenous leukemia (FDA approved in 2001). Monoclonal antibodies, as exemplified by rituximab and Herceptin (trastuzumab; Genentech Inc.) approved for lymphoma (1997) and breast cancer (1998), respectively, have been used to target extracellular receptors on cancer cells because antibodies are typically unable to penetrate cell membranes to bind intracellular targets.

As indicated in Table 2, cancer drug discovery and development have successfully exploited several classes of targets. Overall, in drug discovery, G-protein coupled receptors are the most commonly exploited targets, followed by kinases; however, for cancer, protein kinases have been the most productive target to date for small-molecule drug development. The human genome encodes about 500 protein kinases, including the 2 large families of tyrosine and serine/threonine kinases. A recent compilation indicates that, as of mid-2019, the FDA has already approved 48 protein kinase inhibitors for clinical use, with the majority directed at receptor tyrosine kinases; 43 are approved for the treatment of cancer, and many more are in preclinical and clinical testing.

A focus of the future for kinase inhibitor development, in particular, will be on further exploration of the wealth of potential targets and continued development of tunable promiscuity, in which
an individual inhibitor can target a preferred collection of kinases.81,82

**Immunotherapy**

Although research, including large-scale cancer genome projects, has shed great light on the molecular causes of cancer, detecting additional actionable targets requires a combination of DNA and RNA sequencing, immunohistochemistry, and additional multiparameter technologies. Pembrolizumab (an anti-programmed cell death protein 1 [anti–PD-1] immunotherapy), for example, was approved for microsatellite instability-high and mismatch repair-deficient cancers, making this the first drug to treat solid tumors based on biomarker prediction regardless of tumor type.83 The use of multiparameter technologies may identify a higher number of potential targets and thus drive a higher probability of matching an effective drug. Significant challenges remain in expanding the drugability of cancer targets and, even more important, the clinical relevance (drivers vs passengers) of many mutations.

Sequencing the cancer genome is a powerful tool in precision medicine, but genetic sequence alone does not reveal how genes are differentially regulated. In the section titled Epigenetics and Chromatin Remodeling (see Emerging Areas of Cancer Research, below), we expand upon how cancer development can be associated with abnormalities in complex epigenetic pathways, including DNA methylation, histone variants and modifications, and nucleosome remodeling, and we highlight promising research opportunities.

Advances in personalized medicine have paralleled the development of cancer immunotherapies. Innovations in genomics have enabled the identification of novel and specific immune targets and are driving a rational approach to immunotherapy clinical trial design.84 Personalized therapies targeting the immune checkpoints cytotoxic T-lymphocyte associated protein (CTLA-4) and PD-1 have driven a paradigm shift in the treatment of many cancers since the approval of anti-CTLA therapy (ipilimumab) for late-stage melanoma in 2011.85-90 Combinations of checkpoint blockade antibodies targeting PD-1 and CTLA-4 have demonstrated the ability of the immune system to control tumors, and anti–PD-1 antibodies alone received 9 new FDA approvals in 2018.91

The development of chimeric antigen receptor (CAR)-engineered T cells is another important breakthrough in personalized medicine. By genetically reprogramming a patient’s T-cell receptors to recognize and bind tumor antigens, CAR T-cell therapies have generated durable responses in patients refractory to standard-of-care treatments.92 Clinical trials using CAR T cells generated high response rates in leukemias and lymphomas,93-99 which fueled FDA approvals of CAR T-cell therapies for relapsed/refractory pediatric and young adult acute lymphoblastic leukemia and diffuse large B-cell lymphoma. Interest in the application of CAR T-cell therapy to solid tumors is also intensifying, with a rapidly growing number of clinical trials on solid tumors underway.100-102

CAR cell immunotherapy has also been deployed for natural killer (NK) cells. CAR-NK cells have shown significant antitumor activity in clinical settings and may have superior safety profiles compared with CAR T cells.103,104 Most CAR T-cell immunotherapies require autologous adoptive cell transfer to avoid graft-versus-host disease and may also be associated with cytokine release syndrome and neurotoxicity. Because allogeneic CAR-NK cell infusions are well tolerated, CAR-NK cells can be used off the shelf; toxicity is limited because of the short lifespan of CAR-NK

**TABLE 2. Major Targeted Cancer Drug Categories**

| TARGET | TARGET CLASS | EXAMPLES |
|---|---|---|
| **Monoclonal antibodies** | | |
| EGFR | growth factor/signal transduction | cetuximab, panitumumab |
| HER2 | growth factor/signal transduction | trastuzumab, pertuzumab |
| VEGFR | growth factor/signal transduction | bevacizumab |
| Immune cell (CD20, CD30, CD52, CTLA-4) | cell surface receptor | rituximab, ipilimumab, alemtuzumab |
| **Small molecules** | | |
| ER/AR | hormone receptor | tamoxifen, enzalutamide |
| Tyrosine kinases | intracellular enzyme | imatinib, erlotinib, crizotinib, vemurafenib, sorafenib |
| Proteasome | protein turnover/apoptosis | bortezomib |
| MTOR | cellular metabolism | sirolimus, everolimus |
| Hedgehog pathway | signal transduction (embryonic) | vismodegib |
| Histone deacetylase | gene expression | vorinostat |
| Aromatase | biosynthesis | anastrozole, letrozole |
| PARP | DNA repair | olaparib, niraparib |

Abbreviations: AR, androgen receptor; EGFR, epidermal growth factor receptor; ER, estrogen receptor; HER2, human epidermal growth factor receptor type 2; MTOR, molecular target of rapamycin; PARP, poly(ADP-ribose) polymerase; VEGFR, vascular endothelial growth factor receptor.
cells in circulation, and they are less likely to cause cytokine release syndrome because of the different spectrum of cytokines they secrete. Because CAR-NK cells kill tumor cells via CAR-dependent and CAR-independent mechanisms, CAR-NK cells may also have greater success at eliminating heterogeneous tumors. Generating sufficient numbers of NK cells for clinical applications and the lack of an efficient gene-transfer method remain barriers for NK-cell immunotherapy. Although most of the clinical results from CAR-NK cell studies are currently pending, the first large-scale CAR-NK cell trial was recently published and demonstrates feasibility, efficacy, and a promising safety profile from allogeneic cord blood–derived CAR-NK cells.

Various omic techniques have also been used to discover tumor–associated antigens (TAAs), which are presented by antigen–presenting cells to cytotoxic and helper T cells to drive an adaptive antitumor response. A higher density of tumor–infiltrating T cells is often associated with a better prognosis in solid tumors. Early TAA–derived peptide vaccines used peptide targets, which are detected by T cells and are shared by many patients with cancer. Although clinical trials of TAA peptide vaccines, in some cases, have generated increased numbers of tumor–associated cytotoxic T lymphocytes and immunoglobulins and resulted in decreased tumor volume, overall, to date, these changes have not resulted in meaningful clinical responses.

Evidence is emerging that immunotherapies targeting a specific class of TAAs, called tumor neoantigens (TNAs), will lead to greater clinical effect. Unlike TAAs, which can be expressed by some healthy tissues and during development, TNAs result from tumor–specific genetic alterations. Thus self-tolerance and adverse immune effects that limit use of TAAs are less likely. Of course, mutational load, and thus the number of neoantigens, varies between different cancers, with the highest somatic mutation frequency being found in cancers of the skin, lung, and colon.

Although there are currently no definitive biomarkers to predict patient response to immunotherapies, high tumor mutational burden, neoantigens, and mutations in DNA damage repair and mismatch repair pathways have all been proposed as predictive biomarkers based on observations that, as numbers of somatic mutations increases, so does the potential for response. Intratumoral heterogeneity and genetic variation in HLA genes involved in presentation of cancer neoantigens to T cells have also been demonstrated to influence responses to immunotherapy. Looking forward, using specific biomarkers to combine some variation of personalized peptide vaccine with immunostimulatory agents, including adjuvants, immune checkpoint inhibitors, and chemotherapy, hold great promise for leveraging personalized medicine to target the antitumor immune response.

Although the effect of cancer immunotherapy is evidenced by the 2018 awarding of the Nobel Prize for Physiology or Medicine to James P. Allison for the discovery of CTLA-4 and to Tasuku Honjo for PD-1/PD-L1, significant challenges remain. Immune checkpoint blockade is accompanied by a wide spectrum of toxicities termed immune–associated adverse events (irAEs), which includes colitis, autoimmune hepatitis, and endocrine or neurological side effects, any of which may require treatment with glucocorticoids. It remains to be seen whether irAEs are independent predictors of response to checkpoint inhibition, a reflection of longer treatment, or a combination of both. By comparison, cytokine release syndrome and neurologic events are the most significant adverse events associated with CAR T therapy.

Although trials for anti-CD19 CAR T cells have reported treatment–related deaths, no treatment–related deaths were observed in a large US multicenter trial of individuals with diffuse large B–cell lymphoma who received axicabtagene ciloleucel. Diverse strategies are currently being investigated to improve the safety profile of CAR T cells, including further modification of CAR receptors, safety switches, and the development of novel drug and intervention strategies.

Today’s patient with cancer and their oncology team have a growing war chest of available treatment options, including surgery, radiation, conventional chemotherapy, targeted chemotherapy, and immunotherapy. Somewhat modeled after the use of antibiotic combinations for the treatment of tuberculosis, the first clinically successful combinations in the 1960s and 1970s were demonstrated for acute lymphoblastic leukemia and Hodgkin lymphoma. Today, the majority of patients with cancer are treated with a combination of approaches, and the future is bright with the promise of safer and more effective combinations to treat a wide range of cancers.

Knowledge Gap and Challenges

Despite significant advances in patient management, substantial challenges persist in precision medicine as only a limited repertoire of drugs is currently approved to treat cancers associated with specific genetic mutations. The clinical relevance of many mutations remains unclear for many types of cancer. Functional genomic analyses are required to determine whether specific genes and mutations are malignant drivers or inert passengers when they are found in particular types of cancer. Furthermore, optimal profiling methodologies, the choice and timing of tumor sampling, and the effects of tumor heterogeneity remain critical issues that will affect patient management and operational efficiency in the future.

Optimism grows as more alterations are cataloged for human cancers by various omic techniques. A recent...
study of 439 patients with a range of cancers analyzed by candidate DNA sequencing indicated that almost all patients (96%) had a molecular alteration in one of 236 cancer-associated genes, with 90% of patients harboring theoretically actionable (target or pathway that may be affected by a drug or drug candidate) mutations. To frame an important gap in clinical evidence, only 20% would have been eligible for treatment with a drug approved for their particular cancer type. In contrast, a similar analysis of 91 pediatric patients with cancer determined that only 42 (46%) showed actionable mutations that changed the diagnosis or treatment plan, in part because of a higher proportion of mutations in (undruggable) transcription factors or epigenetic alterations. In addition, whereas pediatric cancers typically show lower overall rates of mutation, they often contain higher levels of structural variation (eg, translocations and gene fusions) associated with specific tumor subtypes. Nonetheless, because many of the alterations in pediatric cancers involve well known genes and pathways, hope remains that precision medicine will be accelerated for pediatric cancers to identify subsets of patients for whom the molecular characteristics of their tumors have prognostic and therapeutic implications.

One of the most studied targets relevant across all cancers is the Ras oncprotein, and it is a good representative of the class of undruggable cancer targets. Activating mutations in RAS can be found in up to about one-third of all cancers, thus inhibitors of Ras would have broad utility in many treatment protocols. Ras acts as a binary switch in critical signal transduction pathways, binding GTP for enzymatic hydrolysis and signal transmission. High intracellular concentrations of GTP render competitive inhibition a daunting challenge. This has led to recent work in the development of noncompetitive or covalent Ras inhibitors armed with good preclinical data, clinical testing is underway with early signs of promise. Although it is a very challenging target for inhibition, the effect in cancer treatment could be enormous. A second major class of therapeutic target considered to be generally undruggable is transcription factors, which may represent nearly 20% of the current library of identified oncogenes and is of particular interest in pediatric cancers. Historically, transcription factors have been difficult to target directly with small molecules because of large, interacting surfaces that enable protein or nucleic acid interactions. More recent and exciting work has examined approaches to inhibit transcription factors through selective degradation or epigenetic downregulation. The development of such methodologies for therapeutic intervention outside of enzymes and receptors could have huge benefits in medicine, with a very wide range of specific applications in cancer. Other small-molecule inhibitors that target the proteasome, heat-shock proteins, matrix metalloproteinases, BH-3 mimetics (eg, venetoclax), and targets such as these will continue to offer critical opportunities for the development of a diverse menu of inhibitors. Although fragment-based drug design and proteolysis-targeting chimeras technologies are not new drug discovery strategies, they are now proving fruitful for targeting oncogenic-driving proteins that were previously considered undruggable, including RAS. In contrast, although tumor suppressors, including the retinoblastoma protein, are functionally inactivated in many cancers, they have thus far remained refractory to drug-targeting approaches.

Research challenges for personalized immunotherapy specifically include the identification of strong cancer antigens and neoantigens, enhancing T-cell infiltration into tumors, responding to changes in major histocompatibility expression, and confronting T-cell immunosuppression. Perhaps the most immediate challenge is to find more reliable clinical biomarkers to predict responses to immunotherapy and guide treatment decisions. Mass cytometry (a technology that merges the single cell capabilities of flow cytometry with the analytical power of mass spectrometry), gene expression profiling, and next-generation sequencing have provided insights into how therapies affect tumor cells, immune cells, and the tumor microenvironment and may ultimately inform clinical trial design.

As expanded upon below (see Tumor Heterogeneity, Cellular Plasticity, and Drug Resistance), cancer cells within a tumor are highly heterogeneous, which presents challenges for achieving a durable response after cancer treatment. For immunotherapy, durability and acquired resistance remain relatively uncharted territory. Antigen presentation that reflects the entirety of mutations within a tumor remains elusive and is particularly necessary for individualized vaccine development, ie, determining how to choose which antigen is best when tumor sequencing only reveals mutations in a subset of cancer cells and only at one specific time point and how best to unveil the full spectrum of immunogenic mutations, TAA's, and the neoantigens expressed. Furthermore, because the mutational profile of residual metastatic cells may also differ, how effective will vaccination be against future metastatic disease? Knowing which patients are likely to be sensitive to immune therapy will affect our understanding of who benefits from specific treatments and why. Understanding a patient's full tumor genotype, including mutation burden and antigen presentation, immune profile, and clinical presentation, will inform which combination of targeted therapies, including immunotherapies, is best for the patient and most likely to result in durable benefit.
lead to a more durable response. To fully validate the safety and efficacy of combination treatments, appropriately powered clinical trials are needed. Unfortunately, <2% of adults with cancer enroll in active trials; last year, 40% of National Clinical Trial Network studies failed to meet patient accrual needs. Given the potential number of permutations that should be evaluated, patient numbers are likely to be rate-limiting. Although they are beyond the scope of the current article, many factors that interfere with the recruitment of participants in cancer clinical trials need to be addressed to facilitate appropriate clinical testing of compelling treatment combinations.

Analyses of clinical trials of drugs typically reveal that the primary cause of failure is most often a lack of sufficient efficacy against the intended target or in the intended population. A recent analysis of Phase 3 trials showed that 57% failed because of inadequate efficacy, whereas only 17% failed because of toxicity. With the expanded use of immunotherapy, systemic toxicity is a particularly important issue. The development of optimal imaging tools to detect irAEs will increase the detection of these events and improve their management. The identification of biomarkers for variations in gastrointestinal flora, cytokine profiles, and neutrophil activation could enable the identification of populations at higher risk for development of irAEs.

To date, advances in precision medicine and the technology driving it have allowed the collection, merging, and analysis of large clinical genomic data sets from different sources. The capability of artificial intelligence platforms to incorporate machine learning and statistical algorithms is game-changing; a technology with the potential to reliably predict which patients will respond to which treatment and for how long. The use of artificial intelligence will be essential to understand the best applications of precision medicine because, despite much progress, many barriers still exist in achieving benefits for individual patients with cancer, oncologists, and the cancer community. One important but sometimes overlooked issue is that advances in precision medicine must now extend beyond omics data and into behavioral, social, environmental, and clinical variables that influence health. When cancer therapies become truly precise, we will generate, link, and learn from data across a continuum of care and circumstances to predict response to therapy and optimize for future health.

Patient-generated data are a largely underused asset that can bring additional information to clinical practice by increasing inclusion from patients without access to clinical trials and by informing oncologists about health influences, including variables like physical activity, diet, and blood pressure—each of which is patient-reportable and often overlooked. In an ideal scenario, results obtained from various sources (medical history, genomics, proteomics, metabolomics, clinical trial, patient input, etc) would be validated and combined to allow physicians to stratify patients using sensitive and specific screening algorithms.

Sharing of big data is essential for progress in early diagnosis and accurate decision making, thus it is a crucial step in the implementation of precision medicine for cancer. What is the best way to share big data when an estimated minimum of 1000 terabytes of data per patient must be obtained, analyzed, and compared before a determination can be made of its usefulness for diagnosis and treatment? Our ability to store clinical data now largely surpasses our ability to analyze and act on those data. Progress in precision practice requires a national focus on building DNA sequencing facilities and biobanks, on finding solutions for big data storage and dissemination, and on developing methodology to integrate electronic patient records. The United States White House Precision Medicine Initiative on precision medicine includes a mission to enable a new era of medicine using research, technology, and policies that empower patients, researchers, and providers to work together toward developing individualized care. But how do we best drive collaboration between clinicians, hospitals, and comprehensive cancer centers that will ultimately allow all patients to have access to personalized oncology services?

Bioinformatics and the use of large data sets will continue to generate insight into the intersection of drug efficacy and genomics and will drive the optimization of effective treatments. Patient quality of life remains of utmost concern; balancing efficacy, toxicity, and cost (both financial and emotional) can address areas of unmet need for ongoing and future trials in precision medicine.

Research Opportunities/Priorities

Since the launch of the National Institutes of Health Precision Medicine Initiative in 2015, much progress has been made toward enabling the selection of oncology interventions and treatments on the basis of which will work best for individual patients. However, research opportunities to fully enable the potential of precision medicine cuts across the spectrum of cancers and the continuum of clinical care.

Develop new targets and new chemistry

To fill out the necessary catalog of targeted therapies to directly affect aberrant pathways across all cancers, a very broad and active discovery effort needs to remain a priority.

- Develop new cancer drug targets and diverse chemical libraries to modulate enzyme and receptor activities.
- Continue to exploit protein kinases, nuclear receptors, and G-protein coupled receptors as high-value families of target proteins.
• Continue preclinical and clinical evaluation of covalent Ras inhibitors.
• Continue to explore strategies to inhibit activity of undruggable targets, including transcription factors; accelerate work on epigenetic inhibitors for cancer treatment; and explore the viability of either directly targeting the noncoding domains of the genome (enhancer, promoters, insulators) or targeting noncoding RNAs.
• Functionally validate (drivers vs passengers) cancer targets in less common cancers or less common subtypes.
• Where not yet complete, elucidate biologically and clinically relevant subtypes for common and less common cancers to clarify potential for intervention; standardize morphological and molecular taxonomy.

**Discover new opportunities for immunotherapy**

We have seen just the beginning of immunotherapy, and although immune-modulating treatments have already transformed the clinical management of some cancer types, broadening the scope of immunotherapy is a high priority.

• Explore tumor heterogeneity to optimize antigen display.
• Develop methods to select from the full spectrum of TAA and TNA.
• Investigate antigen display by metastatic cells and a role for vaccination to prevent metastasis.
• Discover additional biomarkers (e.g., mismatch repair mutations, microsatellite instability) to identify patients who are likely to respond to immunotherapy and those who may experience serious adverse events.
• Develop monoclonal antibodies for direct cancer treatment and as site-specific carriers.
• Develop immunomodulatory approaches to increase effector T cells and decrease regulatory T cells.
• Continue clinical exploration of checkpoint inhibitors focused on expansion to different cancer types and to unresponsive patients.
• Continue efforts to increase CAR T-cell potency and efficacy and expansion of the pool of targeting antigens.
• Develop platforms and procedures to ensure that candidate patients for immunotherapy receive timely tumor tissue testing.
• Address issues of immunotherapy treatment costs, including cost trajectories and issues of cost effectiveness versus affordability.

**Accelerate evaluation of combination therapies**

Recent results from the I-PREDICT trial (ClinicalTrials.gov identifier NCT02534675) provide an encouraging, although preliminary, demonstration that combinations of targeted and immune therapies informed by tumor DNA sequencing can result in improved outcomes for a wide range of patients.158

• Improve methods for preclinical prioritization of combination therapies using in vivo and organoid systems to streamline clinical validation.
• Optimize regulatory pathways for the analysis of combination treatments.
• Reduce barriers to combination testing (i.e., facilitate cooperative agreements between pharmaceutical companies).
• Reduce barriers to patient participation (of adults) in clinical trials and integration of genomic sequencing into cancer care (e.g., insurance coverage).
• Develop and integrate interventions that reduce barriers for underserved patients and racial and ethnic minorities to improve access to precision medicine.
• Reduce disparities in health care delivery and outcomes, which may be exacerbated by multimodal or costly treatment plans.
• Explore ways to better manage comorbidities that interfere with participation by older patients with cancer.

**Data management**

A personalized approach to the management of patients with cancer requires rapid analysis and integration of tumor DNA sequence information (and perhaps also RNA and protein expression information) to inform the individualized treatment plan and facilitate integration with a wide range of patient information contained in electronic medical records. Such data flow demands have been addressed at major cancer centers, although it remains unclear how this will be operationalized at community cancer centers. Data housing, sharing, decision making, and ownership remain critical issues that will continue to accompany implementation of precision medicine in oncology. Many of the challenges noted around big data relate to infrastructure investments and operational philosophy rather than research priorities.

• Clarify the roles of public and private databases of clinical patient information to serve individual patients and provide a resource for hypothesis creation and testing in research.
• Clarify the role and rights of patients in the contribution and control of their clinical information.
• Develop analytical tools and other strategies to reduce cost and fully leverage available data for both common and rare cancers.
• Improve processes for extraction and interpretation of data from patient health records that maintain patient privacy.
• Develop ways to use data to better detect health disparities and both access to and improvement of outcomes.
• Determine how best to leverage data across multiple sources, including the use of personal health devices.
• Improve the data quality of medical health records and validation methods to fully leverage the clinical utility of big data.

Tumor Heterogeneity, Cellular Plasticity, and Drug Resistance

State of the Field

Chemotherapeutic resistance, which occurs when cancer cells evade the antitumor effects of drug(s), has been a clinical challenge for many years, and many patients’ cancers will advance in the face of emerging drug resistance. Classic mechanisms of drug resistance are numerous, including the innate and acquired ability of cancer cells to efficiently efflux a drug, chemically break down a drug, or repair DNA damage if caused by a drug. Mechanisms of chemotherapeutic resistance can also result from systemic factors, such as altered drug absorption, distribution, metabolism, and excretion. Although patients being treated with targeted cancer therapies tend to experience fewer toxic side effects that those receiving systemic DNA damaging agents, they too are vulnerable to intrinsic and acquired resistance. In addition, with advances in our ability to examine characteristics of individual tumor cells, it has become increasingly apparent that preexisting heterogeneity within the primary tumor and phenotypic evolution during cancer progression represent significant treatment and prognostic challenges, as therapy will often be directed at a biologically fluid target.

Classic cancer drug resistance initially focused on the multidrug resistance gene 1 (MDR1), encoding the membrane-associated p-glycoprotein, which is a member of the superfamily of ATP-binding cassette (ABC) transporters that normally function to transport toxic compounds across (intra and extra) cell membranes and the blood-brain barrier. Increased expression of MDR1 is a well described mechanism for resistance to taxanes, and recent studies of PARP inhibitors have shown that drug resistance to targeted therapies can result from increased expression of ABC transporters.

With a far more detailed molecular understanding of cancer cell biochemistry and biology and a wide array of cancer drugs currently being used in patients, the study of drug resistance has become an immensely important field in cancer research. In fact, addressing cancer drug resistance was one of the key recommendations for investment arising out of the Biden Cancer Moonshot Initiative (cancer.gov/research/key-initiatives/moonshot-cancer-initiative/blue-ribbon-panel/blue-ribbon-panel-report-2016.pdf). Over the past decade, research on mechanisms of drug resistance in patients with cancer has revealed a surprisingly complex spectrum of insidious alterations, which result in rescue of tumor cell growth in the presence of inhibitors. In addition, it has become apparent that multiple mechanisms of resistance can be simultaneously induced in patients’ tumors.

Table 3 provides a simplified list of some of the most common forms of cancer drug resistance seen today, starting with the well studied MDR1/ABC efflux pump, which is critical in resistance to taxanes, anthracyclines, vinca alkaloids, and, more recently, tyrosine kinase inhibitors. To date, intensive efforts to develop potent and specific inhibitors of ABC transporters to enhance cancer drug efficacy have been disappointing in the clinic.

With the growing use of targeted therapies for the treatment of cancer, a common form of acquired resistance is the appearance of mutations in the target protein that interfere with the binding ability of the inhibitor, rendering the target insensitive and resulting in pathway reactivation. A good example is the occurrence of secondary

| TABLE 3. Major Pathways of Cancer Drug Resistance |
|----------------|----------------------------------|
| PROCESSES      | RESULTS                         | EXAMPLES                                          |
| Drug transport or metabolism | Activation of efflux pumps: reduction of intracellular concentration of cancer drug due to accelerated removal | MDR1/ABC (Gottesman 2002) |
| Pathway reactivation | Mutation of target molecule: reduction of drug binding | BCR-ABL kinase resistance mutations (Gorre 2001) |
| Pathway bypass | Activation of a parallel pathway: achieve oncogenic phenotype through distinct pathway | Androgen receptor inhibitor (Arora 2013) |
| Alteration of upstream effectors: bypass site of drug inhibition | Alteration of downstream effectors: obviate drug inhibition | BCR-ABL kinase resistance mutations (Gorre 2001) |
mutations (the oncogenic mutation is the primary) in the BCR-ABL kinase in chronic myelogenous leukemia that result in resistance to imatinib.\textsuperscript{167} For several kinases, resistance mutations have been described in a gatekeeper amino acid (eg, BCR-ABL T315I), which affects the conformation of the enzyme and blocks inhibitor access to an internal hydrophobic pocket. A second strategy observed to overcome drug inhibition and pathway reactivation is through an increased level of the target protein. For example, in the context of prostate cancer treatment with androgen receptor antagonists, the receptor gene can undergo amplification\textsuperscript{173} or increased expression to overcome growth inhibition.\textsuperscript{174} This dynamic and widespread cellular response, which contributes to therapeutic resistance, has been documented in many cancer types, including breast cancer,\textsuperscript{175} melanoma,\textsuperscript{176} and glioblastoma.\textsuperscript{177}

Pathway reactivation associated with drug resistance can also result from upstream or downstream induction that effectively bypasses the block created by the inhibitor. For instance, patients who developed resistance to the B-Raf drugs vemurafenib or dabrafenib displayed several different molecular mechanisms of resistance, including mutations in NRAS, leading to MEK/ERK activation downstream of B-Raf. Thus the pathway was effectively reactivated without removal of the inhibitory block at RAF. Even in association with the same therapeutic example, treatment of BRAF melanoma can lead to drug resistance caused by complete pathway bypass through the activation of melanocortin 1 receptor and its signaling pathway through cAMP/CREB.\textsuperscript{178}

Drug resistance can also manifest when cancer cells escape chemotherapy-induced apoptosis\textsuperscript{179} and cellular senescence,\textsuperscript{180} both of which are tumor-protective mechanisms intended to prevent damaged cells from proliferating.\textsuperscript{181} Numerous other cellular processes have also been implicated in drug resistance, including epithelial mesenchymal transition,\textsuperscript{182} autophagy,\textsuperscript{183,184} cancer stem cell plasticity and dormancy,\textsuperscript{185,186} noncoding RNA dysregulation,\textsuperscript{187,188} and altered energy balance.\textsuperscript{189,190} For a greater appreciation of the roles of energy balance and other aspects of metabolism in cancer, see Metabolism and Cancer, below, in the section titled Emerging Areas in Cancer Research.

**Knowledge Gaps and Challenges**

Many of the knowledge gaps relating to cancer drug resistance center on complex interactions or processes operating at a tissue or systemic level. Malignant tumors do not consist of a homogenous mass of cancer cells but rather, of a heterogenous mixture diverse in genetic defects, patterns of gene expression, epigenetic marks, and metabolic and differentiation states. Furthermore, tumor cells will evolve over time in response to stresses and changing conditions.\textsuperscript{191,192} The mutational burden or genomic instability creates the potential for different types of tumor evolution, aspects of which have been likened to the process of Darwinian evolution.\textsuperscript{193} The accumulation of mutations over time can be a slow process, whereas larger genomic changes can result in a more rapid evolution of the tumor.\textsuperscript{135} Our limited understanding of the complexity of cellular evolutionary processes is one of the key challenges to attacking tumor heterogeneity.

The Cancer Genome Atlas has enhanced our understanding of tumor heterogeneity across different patient populations (intratumoral heterogeneity);\textsuperscript{194} however, efforts to explore variations between subpopulations of tumor cells on an individual basis (intratumoral heterogeneity) are at a much earlier stage. This is an active area of study, which is being fueled in large part by single-cell, sequencing-based technologies, including high-throughput single-cell DNA sequencing and RNA sequencing assays.\textsuperscript{195} With these tools in hand, scientists can more accurately and comprehensively assess tumor heterogeneity (in patients and experimental models), generate compelling data to support hypothesized models of tumor evolution, and identify molecular disparities between a primary tumor and metastatic lesions,\textsuperscript{196-199} all with the hope of applying new knowledge to develop more effective and precise cancer therapies.

Cellular heterogeneity exists in various degrees in different cancers. Although the processes underlying heterogeneity are not fully understood, there is evidence for several contributing factors, including variability in the mutations in different clonal lines within the tumors and differences in genomic stability resulting in aneuploidy, chromosomal events, or more subtle alterations in the DNA repair pathways.\textsuperscript{200,201} There is an emerging appreciation for the effect of epigenetic changes through DNA methylation, chromatin remodeling, and histone/protein methylation, which results in functional changes in tumor cells.\textsuperscript{202} Collectively, these events contribute to tumor cells (and sometimes foci of tumor cells) with altered and diverse functions, which impose challenges if only genome and transcript biomarkers are being factored into clinical decision making.\textsuperscript{203}

In addition to this heterogeneity of cancer cells within a tumor, there are numerous nonmalignant cell types and stromal constituents of the tumor microenvironment, including blood vessels, fibroblasts, and immune cells, that add to the heterogenous nature of a cancer and its surrounding microenvironment.\textsuperscript{192} Further adding to the complexity, adjacent nonmalignant cells can be altered by the cancer cells; and, in turn, elements of the microenvironment (eg, cytokines, growth factors, extracellular...
matrix fibers and attachment proteins) influence the biology of the cancer in many ways, including therapeutic response and resistance.\(^{204,205}\)

For years, assessment of cellular heterogeneity in situ was limited to immunostaining and fluorescent in situ hybridization approaches, both of which have limited quantitative capabilities. However, new in situ technologies are allowing researchers to assess the spatial heterogeneity of macromolecules in tumors and surrounding tumor micro-environments.\(^{192}\) For interrogating cell functions without disrupting cell attachments and adjacent tissue, technologies and techniques that show promise are variations of mass cytometry.\(^{206}\) In some methods, rare earth metals are coupled with antibodies that are used to stain tissue sections.\(^{145}\) The tissue sections are ablated and fed into a mass cytometer for the identification of molecules located specifically with cells in these sections. There is clearly the potential to significantly advance our view of the different cells within their in-situ environment.

Gaining a better understanding of tumor cell heterogeneity will require determining the cell types present and the functional consequences of their dynamic interplay. This complexity was discussed by Janes,\(^{307}\) who described technologies to determine single-cell atlases and other technologies to determine single-cell states (eg, proliferating, secretory, or stressed). For single-cell atlases, the tumors must be dissociated into single-cell suspensions using low-volume microfluidics followed by RNA-to-cDNA conversion, with subsequent sequencing.\(^{208}\) Some of the key challenges of this approach are sensitivity, throughput, and reproducibility. Once accomplished, an atlas could be assembled of the different cell types present within tumors.

Computational methods and mathematical modeling to examine tumor evolution and predict treatment resistance have become powerful methods to advance research and clinical impact.\(^{209,210}\) A particular advantage of these approaches is the ability to analyze large amounts of existing data and to identify novel and nonobvious patterns and aberrations. These data present a dynamic profile of the evolving changes within tumors and cancer cells. Computer-based assessments of these patterns could allow for unbiased recognition of some key changes. These changes could then reveal some of the critical biology playing regulatory roles in the progression of cancers and could assist in understanding the development of resistance.

As described below, emerging technologies are providing unprecedented research opportunities to study tumor heterogeneity, cellular plasticity, and treatment resistance, with the hope of leveraging these insights and discoveries for the development of personal and precise combination therapies in which a complete and durable clinical response is the norm rather than the exception.

**Research Opportunities/Priorities**

From a treatment perspective, the overarching goal is to develop the technologies and knowledge to support an accurate diagnosis that reflects the different cell types in a heterogeneous tumor, the critical signaling pathways that need to be targeted, and the most effective treatment strategies to affect a response without subsequent development of resistance and cancer relapse. Although these are challenging goals, significant progress has been made to suggest that they are tenable.

**Develop rapid techniques to screen for intrinsic resistance and monitor for the emergence of acquired resistance**

With a growing catalog of targeted agents to be used in combinations with surgery, radiation, and immune therapy, precision medicine will increasingly rely on sophisticated methods to demonstrate initial drug sensitivity and tools to monitor patients on treatment for cancer cell changes that reduce drug efficacy.

- Accelerate the development of systems for monitoring patients for the emergence of resistance (ie, liquid biopsy).
- Develop computational, artificial intelligence, in vitro methods and/or biomarker testing to predict intrinsic resistance to chemotherapy and incorporate into treatment planning for patients.

**Investigate complex pathways to drive development of rationale combination therapies to minimize the likelihood of disease recurrence**

With increasing use of a broad array of drugs targeted to different molecular entities, it has become apparent that cancer cells can use compensatory mechanisms of equivalent breadth. These complex pathways often are both the source of new drug targets and the destination of resistance mutations, thus comprehensive understanding of these cellular pathways will provide a critical framework to achieve a vision of precision medicine. Furthermore, if treatment for patients who have chronic myelogenous leukemia using multiple generations of Abl kinase inhibitors is a good paradigm, then a continued commitment to the development of significant catalogs of targeted inhibitors with overlapping specificity and distinct resistance patterns will be important. However, it is likely that chronic myelogenous leukemia is not a good model for the majority of other cancers that present with a high degree of tumor cell heterogeneity and rapidly evolve during cancer treatment and progression, creating a kind of *whack-a-mole* challenge in patient management.
Develop multiple generations of targeted inhibitors with attendant molecular details about mechanisms of resistance.

Continue to evaluate complex pathways and how they may be modified to achieve tumor resistance (ie, epigenetic regulation, apoptosis, senescence, autophagy, translational control).

Continue to develop techniques to better evaluate tumor heterogeneity and the effect of the tumor microenvironment on tumor evolution and drug resistance.

Develop a better understanding of cancer stem cells and their sensitivity to therapy and role in cancer recurrence and metastasis.

Generate a deeper understanding of factors that contribute to mutation rates, genomic instability, and immune escape in tumor evolution.

Generate a deeper understanding of the effect and mechanistic role of noncoding and microRNAs in cancer drug resistance.

### Cancer Modeling

The scope of cancer modeling is relatively wide and is covered in more detail in several reviews cited below. Here, we focus on the overall state of preclinical models and modeling needs to answer fundamental questions about the biologic complexity of cancers and to translate cancer discoveries from the research setting to the clinic. Dissemination and implementation research opportunities identified by cancer experts have been integrated throughout this research.

### TABLE 4. Examples of Animal Models in Cancer Research

| ORGANISM | COMMON NAME | ADVANTAGES | DISADVANTAGES | EXAMPLES OF SEMINAL DISCOVERIES AND USES |
|----------|-------------|------------|---------------|-----------------------------------------|
| Lower eukaryotes<sup>a</sup> | Drosophila Fruit fly | • Small genome<br>• Short generation time<br>• Inexpensive<br>• Forward genetic screening<br>• Orthologs of human oncoproteins and tumor suppressors<br>• Can physically juxtapose mutant and wild-type cells | • Rudimentary organs<br>• Dramatic structural differences from mammals<br>• Identical cell types<br>• Orthologs of human oncoproteins and tumor suppressors<br>• Can physically juxtapose mutant and wild-type cells | Identification of disrupted signaling pathways in human cancers (ie, hedgehog, Wnt, Notch, Dpp, JAK-STAT) (Miles 2017<sup>174</sup>)<br>Pharmacologic screening/drug discovery (Levinson & Cagan 2016<sup>215</sup>, Strange 2016<sup>216</sup>)<br>Tumor microenvironment (Yang 2019<sup>217</sup>) |
| | Caenorhabditis elegans Roundworm | • Small genome<br>• Short generation time<br>• Inexpensive<br>• Rudimentary organs<br>• Dramatic structural differences from mammals<br>• Somewhat more cumbersome to genetically manipulate | • Discovery of programmed cell death (apoptosis) ( Sulston & Horvitz 1977<sup>179</sup>)<br>• Importance of small, noncoding RNAs (Akay 2019<sup>219</sup>)<br>• Pharmacologic screening/drug discovery (Strange 2016<sup>216</sup>) | |
| | Danio rerio Zebrafish | • Vertebrate model<br>• Inexpensive<br>• Rapid development<br>• Tractable genetics<br>• Transparent bodies<br>• Similar immune system to humans | • Limited tools and validated reagents<br>• Duplicate genes<br>• Complex molecular manipulations<br>• Different ideal temperatures for maturing embryos and tumor metabolism | SETDB1 amplified in melanoma and a skin cancer accelerator (Ceol 2011<sup>220</sup>)<br>Antitumor drug screening and toxicity evaluation (Strange 2016<sup>216</sup>)<br>Modeling metastasis (Stuelten 2018<sup>221</sup>) and angiogenesis (Zhao 2015<sup>222</sup>) |
| Mammalian<sup>b</sup> | Mus musculus Mouse | • Small mammal<br>• Genetically similar to humans<br>• Immunocompetent and immunodeficient models<br>• Amenable to intravital imaging<br>• Ability to generate complex genetic backgrounds | • Higher costs than nonvertebrate models<br>• Lengthy cross-breeding and/or tumor latency | Preclinical testing<br>Mechanisms of treatment resistance (Kersten 2017<sup>223</sup>)<br>Testing tumor interventions<br>Cancer gene discovery and drug target validation |
| | Sus scrofa Pig | • Relevant subject size for surgery, radiation, human imaging, and development of diagnostic/therapeutic devices<br>• Genetic manipulation can speed up tumor latency times<br>• High fecundity | • Limited adoption and testing in many laboratories<br>• Spontaneous tumor latency can be ≥2 y<br>• High cost | Emerging model for pancreatic cancer (Bailey & Carlson 2019<sup>224</sup>) and NF1-associated nervous tumors (White 2018<sup>225</sup>)<br>Potential for broad preclinical applications (Watson 2016<sup>226</sup>) |

<sup>a</sup>These organisms include Xenopus oocyte models of development not detailed here.

<sup>b</sup>These organisms include canine models of naturally occurring cancer not detailed here.
blueprint; however, dissemination and implementation cancer models (including behavioral and economic)\textsuperscript{211} are beyond the scope here.

State of the Field

There is a long history of experimental or laboratory models being used for cancer research and discovery. In the early 1900s, Rous used chickens to conduct seminal work that paved the way to the discovery of SRC, the first oncogene.\textsuperscript{212} Hartwell and colleagues relied on yeast to identify the first cell cycle mutant, which led to the discovery that cancer cells are often defective at cell cycle checkpoints.\textsuperscript{213,214} There are now many animal models for studying cancer, each with advantages and disadvantages (see Table 4).\textsuperscript{215–227} Despite caveats, model organisms (and, in many cases, the simple ones)\textsuperscript{222,228,229} have been instrumental in the discovery of fundamental biological mechanisms relating to development, differentiation, cell growth, and cell death—all processes highly relevant to the biology of human cancers. Models in lower eukaryotes (flies, frogs, worms, and fish) are far less expensive to maintain than mammalian models (eg, mouse), their development time is relatively short, and their genomes are far simpler. Mammalian systems are typically better able to recapitulate a wider range of disease phenotypes than simpler models; however, mammalian models are far more costly and far more complex.

Animal models have played a major role in our understanding of the genetic basis of cancer and the role of specific genes and mutations in the development, progression, and therapeutic responses of cancers. Historically, mouse models have been the mainstay in vivo organism for identifying carcinogens, elucidating multistep processes of tumorigenesis, cancer gene discovery, and drug target validation and testing tumor interventions. Furthermore, animal models of toxicology and pharmacology remain a required component for Investigational New Drug applications submitted to the FDA, and animal-based disease models are often used for confirmation of preclinical efficacy. The repertoire of mouse models is diverse, including spontaneous tumors; viral, chemical, and physical induction; graft transplantation (ectopic, orthotopic, and patient-derived xenografts); and genetically engineered strains.\textsuperscript{230–232} The offerings continue to expand, often fueled by new technologies, such as the advent of CRISPR/cas9, which provides rapid, affordable, and precise gene editing capabilities in murine models as well as a variety of other organisms.\textsuperscript{233}

Importantly, new technologies and approaches are providing valuable cancer models that do not rely on laboratory animals. Advances in tissue culture systems and computational modeling are paving ways for future preclinical testing to be less dependent on experimental animals. Comparative oncology, which incorporates naturally occurring cancers in companion (pet) animals into studies of cancer biology and therapy, has become a powerful and attractive approach for studying some cancer types. Spontaneously occurring osteosarcoma and lymphoma in dogs are excellent examples in which scientific advancements have positively affected oncology care for pets and humans.\textsuperscript{234}

Technological advances are also leading to a broader use of human tissues in cancer research—not just to validate the biological relevance of experimental models, but as models.\textsuperscript{235} The modeling of cancer in vitro (ie, studying cells, tissues, and biological molecules outside of the living organism) has expanded in many innovative ways from the early days of growing cells on the surface of plastic dishes in poorly defined culture media. Although this 2-dimensional culturing approach is easy, inexpensive, and can be high-throughput, it fails to mimic the complexities of human cancers, which include the tumor microenvironment. Scientists are now using organoids that can be established from small tissue biopsies and maintained (sometimes genetically manipulated) in a laboratory vessel—for drug discovery, target validation, and identifying context-specific inhibitors for different tumor types.\textsuperscript{236} A recent proof-of-concept study has demonstrated that patient-derived organoids of pancreatic cancer are able to predict a patient’s response to chemotherapy.\textsuperscript{237} There is excitement that these organoids will generate preclinical data that are highly concordant with clinical studies, something that xenograft models (including those established with patient-derived tumor tissue) have struggled to achieve.\textsuperscript{238,239} Three-dimensional tissue engineering approaches,\textsuperscript{240} including cancer-on-chip,\textsuperscript{241,242} are other examples of evolving modeling approaches that are accelerating cancer discovery while providing animal-free approaches for modeling the complexity of cancers. Although very promising, organoid cultures are still limited by the availability of viable human tumor tissue and sample heterogeneity. The widespread use of human tissues in cancer modeling will require an investment in infrastructure, including live cell biobanking and training.\textsuperscript{243}

Over the past decade, there has been an expansion of large and complex omic data sets. One consequence of this trend has been a greater focus on integrative, systems biology approaches to modeling cancer. Computational systems biology, a relatively new subdiscipline, draws on concepts and expertise from experimental biology, systems biology, mathematics, statistics, and bioinformatics.\textsuperscript{244} Big data, such as those generated from genomic, epigenomic, proteomic, and metabolomic analyses, are being used to build computer simulations of intracellular and intercellular processes...
in the hope of facilitating new cancer discoveries as well as improving current and future preventative, diagnostic, and treatment options. Intense research efforts are being devoted to determining how best to integrate deep machine learning methods so that molecular patterns, hidden within the complexity of tumorigenesis and tumor heterogeneity, can be uncovered to assist with clinical decision making and how to integrate and elevate cancer research efforts beyond what is humanly possible.245–248

Knowledge Gaps and Challenges
A major challenge in modeling the biology of cancer is to create reproducible and practical systems that recapitulate the many types of cancer and the variability seen between patients with the same tumor type. Modeling is further complicated because the tumor microenvironment (composition of immune cells, other stromal cell types, and extracellular matrix)249–251 and host factors (genetics, hormones, diet, microbiome, and physical inactivity)252,253 can significantly affect the biology of cancers in individualized and complex ways. Adding to this complexity, as discussed above, tumors evolve in response to numerous environmental challenges, most notably cancer therapies.193 Faithfully modeling the complex tissue architecture and cellular interactions as well as mimicking the genotypic and phenotypic evolution that can occur during treatment remain huge challenges.

One of the biggest and most critical gaps in cancer modeling is in drug discovery, where there has been a recurrent and striking disconnect between promising preclinical data and disappointing clinical results. It has been estimated that new oncology drugs have a success rate <10% once they make it from Phase 1 clinical trials to FDA approval, with a substantial number failing due to a lack of clinical efficacy.254,255 This pattern of drug failures is undoubtedly caused by multiple factors, including caveats with preclinical models, inconsistencies between preclinical and clinical efficacy testing, and the inherent ability of cancers to adapt and survive in response to treatments. It is critical to determine how best to integrate data, including those from multiple preclinical models, to better predict clinical response.

Research Opportunities/Priorities
We now have a comprehensive catalog of the genetic mutations for 33 cancer types, including 10 rare cancers (courtesy of The Cancer Genome Atlas),256 and better appreciate the importance of molecular subtypes associated with different disease courses and outcomes. With this foundational information, we need to develop more preclinical models that capture the disease heterogeneity seen in humans, including tools to define the molecular mechanisms that control important disease phenotypes, as a starting point for identifying additional therapeutic targets. More cancer type-specific models are also necessary for establishing etiologies, studying cancer progression, testing interventions, and more. New preclinical models of metastasis—which is the leading cause of cancer deaths independent of cancer type—also are urgently needed because the current experimental systems rarely represent metastatic disease in humans.

Here, we make no attempt to comprehensively present cancer modeling opportunities or detail specific needs. The large number of cancer types, etiologic factors, and intersecting pathways that influence cancers make this virtually impossible. Instead, we provide examples in which the development of new models and the expanded use of existing models could accelerate cancer discoveries and lead to more effective translation to clinical utility.

Develop new cancer models

**Metastasis.** See this topic under Emerging Areas in Cancer Research, below, for an appreciation of the complexity and diverse modeling needs, including biologic, clinical, social, and economic aspects of metastatic disease.

**Cancer prevention.** Although controlling cancer through chemopreventive agents holds tremendous potential,257 to fulfill this promise requires additional chemoprevention models for both common and rare cancer types. In addition, improved models of primary prevention (eg, obesity) would enable improved evaluation of the intersection of genetics and exposure for cancer initiation.

**Immunotherapy.** There is need for preclinical modeling of the additional therapeutic effects of surgery, radiation, and one or more form(s) of immunotherapy.

**Tumor dormancy/quiescence.** For some cancer types, such as high-grade serous ovarian cancer,258 there can be a long period of remission followed by disease recurrence. New modeling approaches are essential for elucidating mechanisms of tumor dormancy,259 which could pave the way for the development of biomarkers to predict and monitor disease recurrence and for designing more effective therapies.

**Fundamental cellular processes (eg, autophagy, senescence and apoptosis).** Understanding fundamental mechanisms that drive the fate of cancer cells after treatment could provide insights for the development of new therapies for many cancer types.

**Continued use and integration of existing cancer models Organoids and human organs-on-a-chip.** Continue to build on promising data to support the use of these 3-dimensional systems in modeling human cancer, drug development and screening, and personalized medicine.237,240,260,261
Systems biology models. Expand the integration of systems thinking in cancer modeling through the integration of computational and mathematical analyses, including artificial intelligence and deep machine learning.

Emerging Areas of Cancer Research

We define emerging areas as those that are rapidly expanding and showing clinical promise. These topics are complex and have broad implications for cancer. Below, we focus on research opportunities and direct the reader to the cited literature for a deeper appreciation of these rapidly evolving fields and the challenges and opportunities that are manifesting in laboratories, clinics, and communities.

Metabolism and Cancer

Many aspects of metabolism affect cancer. At the cellular level, cancers reprogram their metabolism in part to efficiently obtain nutrients despite deprived microenvironments. A field that once primarily focused on the counterintuitive metabolic switch in cancer cells to aerobic glycolysis (Warburg effect), and how that affected tumor growth, has now expanded to investigate the many ways tumor cells and their surrounding microenvironment metabolically adapt to promote cancer growth and progression. Several studies have shown that drug-resistant cells are imbued with even higher levels of ATP, leading to the exploration of glycolytic inhibitors as anticancer agents. In addition, there are emerging data to indicate that extracellular levels of ATP may also be significantly elevated in proximity to tumor cells and contribute to drug resistance. Although significant knowledge gaps exist, including how metabolic rewiring of cancer cells influences their invasive behavior and response to treatment, there is hope that a better understanding of how cancers cells survive and thrive in oxygen-deprived and nutrient-deprived environments will provide insights for developing more effective cancer therapies. Rapamycin (sirolimus) and other mTOR inhibitors (eg, everolimus) are excellent examples in which basic research relating to cellular energy balance is fostering innovation that could lead to life-saving advances in cancer.

- Further explore, at the biochemical, cellular, and organismal levels, signaling networks for metabolic homeostasis and how cancer cells disrupt these pathways.
- Investigate how oncogenic viruses alter cellular metabolism and affect cancers.
- Determine key metabolic changes in immune cells within the tumor microenvironment that affect their antitumor properties.

There is a complex and incomplete understanding of the relationship between metabolism, diet, exercise, and cancer. For several decades, evidence has accumulated to suggest a role for healthy eating and physical activity in preventing cancer progression and reducing cancer risk, recurrence, and mortality in common malignancies. Yet there is a scarcity of evidence-based lifestyle interventions for patients with cancer, survivors, or those at risk of developing cancer.

- Determine how nutrition and physical activity influence cancer development, disease progression, recurrence, and survivorship and modulate health, especially in individuals with rare and recalcitrant cancers.
- Understand more completely the molecular mechanisms whereby energy intake and physical inactivity contribute to cancer development, progression, recurrence, and survivorship.
- Establish evidence-based lifestyle interventions to promote and sustain behavior change leading to healthy weight control, healthy diet, and adequate levels of physical activity, and determine how to best implement these strategies in diverse groups of individuals at risk for cancer (or cancer recurrence) and cancer survivors in both clinical and community settings.

Obesity, a global epidemic, is a risk factor for 13 different cancers and is associated with cancer-related mortality for 15 different cancers. Obesity is rarely caused by slow metabolic rate but, rather, is caused by interactions among genes, diet, physical activity, and other factors that remain poorly understood. Metabolic syndrome, the clustering of insulin resistance, obesity, and dyslipidemia, is also associated with an increased risk of developing cancer (eg, postmenopausal breast, endometrial, colorectal, and pancreatic cancer). Although the epidemiological association between obesity and many forms of cancer is clear, evidence is incomplete regarding how or why, at a biological level, obesity (with or without metabolic syndrome) can cause cancer. Equally intriguing is why many cancers are not associated with obesity. Emerging evidence from human clinical trials and preclinical (in vitro and in vivo) studies indicate a cross-talk between adipose tissue and cancers, which appears to involve numerous mechanisms varying by organ site and type of adipose tissue.

- Determine how etiologic factors related to body composition-adiposity (including the amount and distribution of adipose tissue), lean mass, and body mass index affect cancer treatment, prognosis, and survivorship.
- Conduct transdisciplinary research to establish the roles of adipose tissue in the development of obesity-related cancers and the role of obesity-associated chronic inflammation.
Develop novel biobehavioral interventions to assess mechanisms and identify new biomarkers to improve our understanding of how lifestyle factors, cancer, and host characteristics interact to influence cancer risk and carcinogenesis and how this interplay may inform precision cancer prevention.

- There is a need for cancer research career development training for physicians, dietitians, kinesiologists, nurses, and pharmacists to foster transdisciplinary research in this field.

**Microbiome**

The microbiome is a complex ecosystem of bacteria, archaea, fungi, protozoa, helminths, and viruses that live on and inside the human body. The microbiome significantly affects human health and, when imbalanced in composition (dysbiosis), has been linked to the development of cancers. Although it has been appreciated for many years that infectious agents and chronic inflammation contribute to cancer development, the concept that commensal microbes affect cancer risk, diagnosis, treatment response, and survivorship is relatively new.

Early work focused on the impact of the gut microbiome on the development of colorectal cancer, but the field is rapidly expanding to investigate microbiota from other anatomic sites and the effects on diverse cancer types. There is still much to learn about how these microbial ecosystems (in the gut and beyond, including the oral cavity, lung, skin, and pancreas) influence cancer prevention, tumor development and progression, treatment response, and cancer survivorship. The microbiome has emerged as a hot topic in cancer research, largely with the discovery that the composition of the gut microbiome can influence responses to cancer therapies, most notably immunotherapies. Numerous environmental factors, including diet, medications, surgery, smoking, and physical activity, affect the composition of the microbiome, which provides both research challenges and opportunities.

- Explore microbiome-mediated mechanisms of oncogenesis and tumor suppression, including the consequences of a given microorganism on tumor growth, metastasis, and response to therapy.
- Define mechanisms used by the human microbiota to control local and systemic immunity. Test whether microbes and their toxins, adhesins, and cell-surface proteins may serve as vaccine targets.
- Examine whether and how the microbiome composition and anatomic site facilitate antitumor immune responses and altered drug metabolism and whether these can be used as prognostic or predictive biomarkers.
- Examine how understudied microbes within the microbiome (viruses, yeast, and protozoa) influence the development of cancer and their response to therapies.
- Develop and implement safe and feasible methods of microbial manipulation in the clinical setting (eg, prebiotics and probiotics).
- Further explore how lifestyle factors (diet, exercise, alcohol consumption, etc) influence microbiota and how these changes affect adult and pediatric cancer risk, recurrence, and patient outcomes.
- Continue to investigate the diet-microbiota interplay to discover new clinical and public health approaches to cancer and other major diet-related and obesity-related diseases that affect survivors of pediatric and adult cancers.

**Metastases**

Most cancer deaths are caused by metastasis of the primary tumor, which is a highly complex biological process. Over the past few years, a far more detailed understanding of the fundamental metastatic steps, including invasion, dissemination, and colonization, has emerged. There is a basic understanding of the mechanisms underlying hallmarks of metastasis, and our knowledge is just beginning to fuel the design of novel prevention and treatment protocols. As a consequence, the treatment landscape for metastatic cancers is shifting and expanding in exciting ways. For metastatic ER-positive breast cancer, CDK4/CDK6 inhibitors have led to significant improvements in progression-free survival. A novel combination of immunotherapy and chemotherapy has shown promise in patients with metastatic pancreatic cancer. There are encouraging results for targeted tyrosine kinase inhibitors for brain metastasis with activating mutations for melanoma, breast cancer, and lung cancer. Strides have also been made for managing metastatic renal cell carcinoma by targeting vascular endothelial growth factor pathways.

A recurrent theme from the growing number of clinical trials involving patients with advanced disease is that additional research is necessary to reveal the optimal treatment sequence for combinations of targeted therapies and mechanisms governing treatment resistance of metastatic lesions. Consequently, clinical trial designs for anti-metastatic therapy are fledgling. As anticipated for a topic as complex as metastasis, cancer experts identified numerous research opportunities across the cancer research continuum:

- Establish new parameters to assess clinical trials designed for antimetastatic therapy, including chronic dormancy-related treatments and relapse prevention.

...
• Improve the detection and resolution of micrometastasis.
• Investigate psychosocial aspects of metastatic disease and how the interplay between social and biologic factors affects relapse and survival.
• Improve the management of patients with metastases at diagnosis with consideration for physical, emotional, and financial factors.

Numerous research opportunities were identified to address gaps in our fundamental understanding of metastasis, which could pave the way for new targeted approaches for preventing progression of early stage cancers and effectively treating advanced disease:

• Better define the mechanistic requirements for becoming a metastatic cell.
• Define the basis and effect of metastatic heterogeneity (genetic, epigenetic, and spatial).309,310
• Conduct targeted drug discovery research to treat or prevent metastatic lesions and residual disease.
• Elucidate the molecular underpinnings of metastatic spread (ie, within blood vessels, outside blood vessels, within lymphatics, along nerve fibers), including defining the role of collective cell migration (rather than or in addition to epithelial-to-mesenchymal transition and migration of individual cells).
• Determine the basis of metastatic potential from different tissues within a tumor (ie, colonization of metastatic cells; tumor latency and outbreak; therapeutic resistance; changes in hematopoietic cells in blood, bone marrow, and future metastatic sites; and altered immune activity and surveillance).
• Elucidate the roles of immune surveillance for the detection and elimination of disseminated micrometastases and epigenetic regulation in the induction of metastasis.

Epigenetics and Chromatin Remodeling

Epigenetics, the study of changes in gene expression that do not involve changes in DNA sequence, has revealed important cellular mechanisms to reversibly turn genes on and off.302 Chromatin is the complex of DNA, protein, and RNA that functions in tightly packing DNA and controlling access of the transcriptional machinery to different sets of genes. Epigenetic control of gene expression is exerted through enzymatic DNA methylation, histone modifications (eg, acetylation), or chromatin remodelling of nucleosomes. About one-half of human cancers have mutations in key genes that control chromatin remodelling, which can result in inappropriate expression of critical cellular control genes,303-306 thus providing opportunities for the discovery, testing, and approval of new targeted therapies. For example, targeting aberrant DNA methylation patterns by 5-azacytidine (Vidaza; Celgene Corporation) and 5-aza-20-deoxycytidine (Dacogen; Otsuka America Pharmaceutical, Inc) has been FDA approved for the treatment of myelodysplastic syndromes,307,308 and second-generation analogs are in clinical trial testing for myelodysplastic syndrome and acute myeloid leukemia.309 Although numerous studies support the involvement of histone acetyltransferase mutation or loss of function in cancer,310 clinical application of histone acetyltransferase inhibitors has yet to yield clinical success. Altered expression of histone deacetyl transferase is also linked to many cancers and has resulted in recent success as an anticancer target (eg, vorinostat).311,312

Preclinical and clinical trial results suggest that combining epigenetic therapeutics with other targeted therapies313 or with radiation314 may improve outcomes for patients with cancer, most notably lung cancer. Because only a minority of patients with cancer to date have experienced long-lasting benefits from immunotherapy, the possibility of using epigenetic reprogramming to bolster the effects of immunotherapy is an active area of investigation that is showing promise.314

With the epigenetic landscape of cancer initiation and progression becoming better appreciated, the clinical effect is now extending beyond novel, targeted therapeutics to diagnostic, prognostic, and predictive tools. For example, the DNA methylation status of individual gene promoters is increasingly being used for predicting response to therapy and overall clinical outcome (prognosis) for multiple cancer types, including glioma, melanoma, and colorectal cancer.315 Epigenetics alternations also offer hope for the identification of biomarkers to assess cancer risk.316

Despite their importance in cancers, epigenetic events (those listed above and additional histone interactions) are not separate or mutually exclusive events; rather, they form communication networks that affect gene expression. For example, histone acetylation and ubiquitination drive recruitment of DNA damage repair regulatory proteins. The development of drugs targeting additional classes of epigenetic enzymes will drive success beyond current epigenetic inhibitors and will achieve increased specificity and impact in precision medicine. Achieving the full cancer control potential of epigenetic and chromatin remodeling will also require a clearer understanding of their mechanistic roles in tumorigenesis and the development of new technologies for precise and sensitive probing of chromatin and epigenetic alternations.

• Determine the range of epigenetic targets as effective, druggable sites for the development of new chemotherapeutic agents.
• Examine the effectiveness of new epigenetic targets for the treatment of challenging cancers with fewer treatment options, such as ovarian cancer.317
• Further explore the potential for epigenetics to provide prognostic information, diagnostic tools, and treatments for a range of cancers.
• Incorporate computational approaches using machine learning to reveal epigenetic patterns in cancers to provide insights into the prognosis, diagnosis, and treatment of cancers.

Cross-Cutting Issues
Here, we define cross-cutting issues as topics that are not necessarily cancer type-specific and/or those that have effects across the cancer research and cancer control continua. Several high-impact, cross-cutting issues were identified by cancer experts, including health equity and access to care, smoking, survivorship, obesity, nutrition, and physical activity. The latter 3 topics were presented together above (see Metabolism and Cancer in the section titled Emerging Areas of Cancer Research). Because previous blueprint articles have comprehensively covered the state of the field and challenges for many of these cross-cutting issues, we focus on research opportunities and priorities.

Health Equity and Access to Care
As detailed in previous cancer control blueprint articles,7-12 a wide range of factors can have profound downstream effects on the uptake of health-promoting behaviors, access to health care, the ability to follow through with care plans, and, ultimately, health outcomes. In this series, the complexity of social determinants of health with their multiple levels of influence has also been presented within the context of health equity and access to cancer care.12 Tracking cancer disparities on a population level and conducting health disparities research continues to have strong relevance; however, there is a growing need for multilevel investigations focused on structural issues affecting care across the cancer control continuum (ie, social, physical, economic, and political factors that influence health, health behaviors, and outcomes).318 Everyone should have a fair and just opportunity to prevent cancer, receive screening and treatment, and survive cancer, regardless of sociodemographic factors, health insurance status, health care setting, and where they live. Root causes contributing to cancer health disparities, health inequities, and impediments to accessing high-quality care across the cancer continuum are interrelated and interact at multiple levels.318,319 For example, disparities in cancer incidence and mortality in a community may arise and persist because of simultaneous influences of discrimination toward racial and ethnic groups, levels of unemployment, the percentage of the population with less than a high school education, the number of primary care providers available, and the percentage of the population that is uninsured or underinsured.3,9,11,12 Thus, to accelerate health equity research, advancing from observational studies to test interventions using multifaceted approaches and greater engagement with special populations in trials is warranted. Multilevel and multi-interventional research has significant benefits, thus these resource-intense investigations merit prioritization from funders and creative collaboration efforts to leverage resources and costs.320,321

• Determine the best ways to implement existing evidence-based strategies that address access barriers related to social determinants of health.
• Gain a better understanding of barriers to high-quality and accessible health care to all populations including, but not limited to, classism and systemic racism, and develop multilevel interventions to address these contributing factors.
• Standardize data collection at the health system level to capture common variables associated with health care disparities, inequities, and access to care (ie, age, disability status, sex, gender identity, sexual orientation, income, health insurance status, employment status, years of education, housing status, and geographic information).
• Develop multilevel interventions that incorporate economic issues, such as health care costs and financial toxicity.
• Incentivize and test interventions addressing the implications of health policy, cost benefit, and cost effectiveness, such as insurance coverage for new cancer prevention and treatment modalities, changes to health insurance provisions, and evaluating value-based payment and care delivery models.
• Increase training opportunities for multilevel research theory, frameworks, intervention development, and analytic methods.

Smoking and Cancer
Research on cancer causation, epidemiology, and educational and policy interventions has contributed significantly to reducing smoking rates in the United States.14,322 However, there are information gaps and barriers that would benefit from additional research to eradicate tobacco-associated cancers.322 Although we have a good molecular understanding of how smoking causes lung cancer, we know surprisingly little at a physiological or cellular level about the mechanistic role of smoking in the many...
other types of cancers for which smoking is an associated risk factor. We also have an incomplete understanding of lung cancer in people who have never smoked, which certainly deserves research priority because as much as 20% of patients who die from lung cancer in the United States every year have never smoked or used any other form of tobacco.14

- Develop novel behavioral interventions to prevent the adoption of smoking among youth, and evaluate their effectiveness and cost benefit.
- Investigate molecular mechanisms underpinning the development of tobacco-associated cancer subtypes and their response to targeted therapies.
- Investigate molecular mechanisms of lung carcinogenesis in never-smokers beyond environmental radon exposure, including exposure to second-hand smoke.
- Examine the effects of genetic, behavioral, and chemical factors on the full range of smoking-cessation interventions.
- Establish effective methods to achieve cessation among hard-to-reach groups with high smoking rates.
- Develop sustainable tobacco-control delivery systems, such as reimbursement and virtual tobacco treatment modalities.

Survivorship
More than 15.5 million children and adults with a history of cancer were alive on January 1, 2016, in the United States.323 By January 1, 2026, it is estimated that the population of cancer survivors will increase to 20.3 million.323,324 Some survivors who complete cancer treatment have persistent symptoms and experience late effects, such as cardiomyopathy, or long-term effects, such as neuropathy or cognitive and physical disabilities, from cancer treatment. To address the myriad medical, physical, and psychosocial needs of survivors, survivorship care plans are recommended, as detailed in the Institute of Medicine report, *From Cancer Patient to Cancer Survivor: Lost in Translation.*324 Survivorship care plans should inform survivors what to expect as they transition to posttreatment life and improve care coordination among various members of the health care team.325 Given the magnitude of these numbers and the effect of cancer on multiple domains of well-being,9 we must commit to continued research to narrow the knowledge gaps and provide tangible ways to improve quality of life for cancer survivors.326 In the blueprint article by Alfano and colleagues on improving outcomes and care delivery, research, education, and policy for cancer survivors and supporting caregivers, the authors presented priority areas related to assessing needs of survivors and caregivers, facilitating personalized cancer care and referrals, and disseminating and supporting new implementation strategies—all with the goals of equitably improving survivor outcomes and supporting caregivers.9 To complement and sustain these important needs, additional research is necessary to assure that new and improved strategies will be generated, implemented, and disseminated to the growing number of cancer survivors and their caregivers.

- Develop, validate, and pilot strategies to use graphic or application-based tools to provide feedback on quality of life and other outcome information to cancer survivors.
- Identify clinically relevant metrics in cancer survivorship to aid in the development of risk-stratification tools and interventions to test models of risk-stratified care.
- Conduct dissemination and implementation science research to strengthen the evidence base for how survivorship care plans can be integrated into various survivorship care models to improve the quality and delivery of care and the quality of life for survivors with relevant outcomes metrics.
- Determine how to tailor care based on a survivor’s nutritional, physical, and psychological needs and preexisting comorbidities.
- Better understand the effects of financial toxicity on cancer survivors and effective strategies to mitigate these negative effects.
- Focus on the development of treatments with fewer short-term and long-term adverse side effects; improve surveillance tools, most notably for childhood and adolescent cancers; and establish evidence-based approaches to better manage late and long-term effects and persistent symptoms.
- Develop new technologies and interventions designed to assess risk; and tailor, stratify, and coordinate care, including process measures related to resource (human and material) use as well as intensity and economic data, to better assess outcomes in terms of clinical effectiveness, clinical benefit, and cost effectiveness to inform dissemination and policy efforts.

Cancer Research Workforce
In this blueprint, we have identified many topics and areas in cancer research that offer great promise for breakthrough discoveries. This high potential for innovation and progress, however, depends greatly on the continued strength of the US biomedical research workforce. For decades, the status of the nation’s research workforce has been monitored using independent assessments as well
as congressionally mandated reviews of research training, career paths, supply, and resources. These various reports have consistently identified serious threats to the stability of the scientific workforce and, by extension, the entire US biomedical research enterprise. Unfortunately, most of these threats persist today and, indeed, may be growing. First and perhaps foremost are the constrained resources for research, which are provided in large part by the federal government. As reported by the National Academies of Sciences, Engineering, and Medicine, after 2004, when the budget doubling ended, appropriations from the National Institutes of Health declined in constant dollars, and the success rate for R01-equivalent awards quickly decreased for both established and new investigators.\textsuperscript{327} In addition, some disciplines have had much less support in biomedical sciences, especially behavioral and social sciences, clinical sciences, and nursing.

At the same time, academic career opportunities for new investigators have continued to decline, with diminishing resources and poor transparency about the faculty job prospects for newly trained scientists. Some authors have proposed capping training positions because, for the resources and positions that are required to conduct science, there is a perceived environment of hypercompetition, which suppresses the necessary creativity, cooperation, risk-taking, and original thinking to make fundamental discoveries.\textsuperscript{328} Moreover, the representation of minorities on basic science faculties in medical schools has been static for 30 years; and, although women are equally represented among graduate students and postdoctoral fellows, among tenure-track faculty in research-intensive universities, women continue to be less represented.\textsuperscript{329} If we hope to maintain a competitive advantage in cancer research in this country and change the future of cancer for all people, we cannot continue to allow contraction of the creative workforce through loss of women and minorities. Innovative and sustained programs to address the multifaceted barriers in the workforce should be a national priority.

Finally, there is the need not only to address threats to the biomedical research workforce but also to foster developments that will promote progress. New disciplines are emerging from the combination of previously separate fields, to which the term convergence is being applied. The National Science Foundation has included convergence research among its 10 Big Ideas, stating that the great challenges today—protecting human health; understanding the nexus of food, energy, and water; and exploring the universe at all scales—cannot be addressed by a single discipline alone. They require convergence: the merging of technologies, ideas, and approaches from diverse fields of knowledge to stimulate discovery and innovation.\textsuperscript{330}

Conclusion

The 107-year-old ACS is unique among nonprofit organizations working on behalf of patients with cancer that integrates robust internal and external research programs with patient advocacy (the Cancer Action Network) and a patient care delivery group to implement our work both nationally and at the community level. This provides an unparalleled opportunity for integration and coordination across the ACS mission pillars—discovery, patient delivery, and advocacy—as we seek to develop innovative approaches to cancer that are paradigm shifting, practice changing, and policy making. Previous blueprint articles have discussed the current state and future directions for epidemiology and surveillance and the various factors associated with cancer as well as trends in incidence and mortality. Other blueprint articles have focused on how we might use current cancer screening technologies more effectively to reach larger segments of the population and critical modifications to the health care system itself to improve outcomes and deliver on the promise of health equity. Optimizing patient care delivery in most instances is focused on implementation of what we already know to save more lives from cancer.

In contrast, this blueprint article is focused on what we don't know, highlighting research challenges and opportunities important to radically changing the future of cancer. Our overall goal is to motivate a strategy to develop novel approaches for cancer prevention, interception, treatment, and improvement of quality of life for cancer survivors. Through dialogue with >90 cancer experts, themes emerged across many cancer types along with nearly 100 specific recommendations. On one hand, it is a daunting task to consider all that needs to be done in research to conquer the hundreds of diseases we collectively call cancer. However, this presents incredible potential for collaboration and clinical impact.

Fully capitalizing on these research opportunities depends on leveraging and growing our collective resources, including industry, government, academic, and foundation partnerships, to enhance the development of accessible data sets and support the Cancer Moonshot’s emphasis on rapidly translating discoveries. It also hinges on a diverse and sustainable biomedical research workforce. Encouraging the development and implementation of new collaborative models, including transdisciplinary team science and consortia and new public–private partnerships, will maximize innovation, creativity, and clinical effect.

These blueprint recommendations are built on recent discoveries, rapidly accumulating data, and the insights of experts into how cancers develop and progress. Although some recommendations and opportunities could be viewed as stand-alone needs, most are interconnected with health disparities, dissemination of cancer care, and data-sharing
as integral components. In this era, all facets of the cancer research community must unite to identify ways to break down silos, be patient-centered, and be committed to improving health outcomes for all people.

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