The Future Of Cancer Research: ACCELERATING SCIENTIFIC INNOVATION

President's Cancer Panel Annual Report 2010-2011

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

This report is submitted to the President of the United States in fulfillment of the obligations of the President's Cancer Panel to appraise the National Cancer Program as established in accordance with the National Cancer Act of 1971 (P.L. 92-218), the Health Research Extension Act of 1987 (P.L. 99-158), the National Institutes of Health Revitalization Act of 1993 (P.L. 103-43), and Title V, Part A, Public Health Service Act (42 U.S.C. 281 *et seq.*).

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The President's Cancer Panel

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The President's Cancer Panel

November 2012

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

The President
The White House
Washington, DC 20500

Dear Mr. President:

Passage of the National Cancer Act more than 40 years ago marked the start of our nation's war on cancer. In the decades since, important strides in preventing, detecting, and treating cancer have been made possible by our national investment in cancer research. Major contributors to this progress include the sharp overall decline in tobacco use among Americans, better cancer screening and early detection methods, and improved and targeted cancer therapies. As a result, more Americans are surviving longer following a cancer diagnosis than ever before. Moreover, mortality from some cancers has decreased markedly.

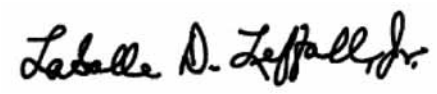
Despite these achievements, the incidence of some cancers is increasing for unknown reasons and the decline in the nation's overall cancer death rate has been slower than anticipated. Of additional concern, the number of cancer diagnoses is expected to increase sharply over the coming years as the U.S. population ages, overwhelming much of the progress that has been made. Indeed, cancer is projected to become the nation's leading cause of death over the next decade, surpassing heart disease.

Cancer is the disease most feared by Americans, and a majority of the population believes that accelerating research to improve health is a top or high priority. Yet the impediments resulting from fluctuations in funding and the current focus, priorities, and processes of cancer research have inhibited widespread reductions in incidence and mortality and limited quality of life improvements for cancer survivors. These elements of the National Cancer Program need to be examined, reimagined, and reorganized to better support innovative research with the potential to transform cancer prevention and care.

With these concerns in mind, the President's Cancer Panel (the Panel) devoted its activities in 2010-2011 to exploring opportunities to significantly improve cancer patient outcomes by fostering innovative research approaches and intensifying cancer prevention research efforts. The attached report provides the Panel's recommendations for policies and related actions to accelerate scientific innovation and achieve the transformative advances needed to dramatically decrease cancer deaths.

Mr. President, your administration has amply demonstrated its commitment to health care reform and the goal of a healthier nation. Similarly, the Panel believes that your administration now has an opportunity to lead the nation into the next era of cancer research—one that holds more potential than at any time in history for improving our understanding of cancer and learning to prevent it, find it early when it does occur, and treat all forms of the disease effectively without harmful side effects. Without your crucial support for a refocused vision for cancer research, progress toward the goal of preventing, controlling, and curing cancer will continue to proceed incrementally instead of accelerating to meet the needs of the American people.

Sincerely,



LaSalle D. Leffall, Jr., M.D., F.A.C.S.
Past Chairman

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PART II

EXECUTIVE SUMMARY

America's investment in cancer research has vastly expanded and deepened our understanding of the many diseases called cancer. Some of the genetic and environmental factors and biologic mechanisms that cause or contribute to cancer development, progression, and spread have been elucidated. This knowledge has led to the development of diverse interventions to reduce risk of cancer and more effectively treat some cancers, enabling many individuals to survive diseases that previously were almost universally fatal.

Although notable, these achievements do not obscure the fact that cancer prevention and cure remain largely elusive. Given the complex nature of cancer and the lack of screening methods to detect most types of cancer, progress against some cancers has been slower than for others. Between September 2010 and February 2011, the President's Cancer Panel (the Panel) convened four meetings to evaluate opportunities to accelerate the development of innovations with the potential to dramatically improve cancer outcomes. The Panel received testimony from 47 experts from the academic, industrial, not-for-profit, and public sectors. The speakers included basic, translational, clinical, and population science researchers and research program administrators; voluntary sector research sponsors; health and science policy specialists; representatives from the cancer advocacy community; professional and industry association representatives; and Federal Government regulators and administrators

This report summarizes the Panel's findings and conclusions based on the testimony received and additional information gathered prior to and following the meetings. The Panel's recommendations describe concrete actions that participants in the National Cancer Program can take to speed the development of advances that will propel the nation into a new era of cancer prevention and treatment.

Scope and Leadership of the National Cancer Program

The National Cancer Act of 1971 (P.L. 92-218) created the National Cancer Program (NCP) and charged the Director of the National Cancer Institute (NCI) with planning and coordinating the cancer activities of NCI and the National Institutes of Health (NIH), as well as cancer-related activities of other agencies, including those in the private sector. However, the NCI Director was not given specific legal authority to mandate or enforce actions to coordinate the NCP, and despite robust implementation plans in the early years following passage of the Act, subsequent years saw the erosion of adherence to the planning process. In 2012, more than 40 years after passage of the Act, neither the scope of the NCP nor its leadership, coordination, or participants have ever been clearly defined. As a result, the NCP lacks a national vision and priorities, and the cancer research effort continues to be fragmented and largely uncoordinated. The application and dissemination of research advances remains uneven at best.

Participants in the National Cancer Program

In addition to the issues of leadership and coordination, the full complement of entities and constituencies—not just the research and clinical enterprises—that are considered to be participants in the NCP remains unclear. It has long been the Panel's view that the NCP is not limited to cancer research and cancer care supported by government, private, and voluntary sector entities. Rather, the Panel considers the NCP to also encompass the activities of all other organizations, industries, and individuals whose actions influence the burden of cancer in the United States.

Perceptions of Cancer Risk, Cancer Research, and the National Cancer Program

Perceptions and knowledge about cancer risk, the process and benefits of cancer research, and the NCP vary substantially not only among the general public, but within the medical and research communities, and among policy makers.

According to the most currently available data, 1 in 2 men and 1 in 3 women—about 40 percent of the U.S. population—will receive a cancer diagnosis (excluding basal/squamous cell skin cancers or *in situ* cancers other than *in situ* bladder cancer) at some point in their lives. Studies suggest that people often assess their comparative risk for a given danger to be lower than average—including the risk of developing cancer—in part because they do not want to feel vulnerable. They also may misperceive their risk for specific cancers (e.g., risk of lung cancer among smokers). Research further suggests that risk perception is influenced by individuals' difficulty in using numbers and percentages.

Public support for cancer and other biomedical research to improve health is strong, and surveyed Americans have stated that we do not spend enough and that basic, health services, prevention, and regulatory research are all important to controlling rising health care costs.

The NCP lacks a clear identity and national presence. Because it is neither fully defined in statute nor a line item in the federal budget, it is poorly understood or supported by some legislators. Similarly, many in the cancer research and care communities have only a vague notion of what the NCP encompasses.

Our National Cancer Burden

In 2012, more than 1.6 million new cancer cases are expected to be diagnosed in the United States, and an estimated 577,000 Americans are projected to die of the disease. In the coming decades, changes in cancer rates related to demographic shifts in the United States are expected to offset recent mortality reductions and result in a marked increase in the

number of new cancer diagnoses made each year. Cancer is projected to become the nation's leading cause of death—surpassing heart disease—over the next decade as the U.S. population ages. Other factors also challenge efforts to make progress against the disease. Cancer is enormously complex and highly adaptable; many subtypes of the disease have distinct clinical features and susceptibilities to therapy. Many cancers still are not diagnosed until they are at advanced stages, and some resist most attempts at treatment.

Highlights of Cancer Research Progress

When the National Cancer Act was signed into law in 1971 there was widespread optimism that the significant expansion of support for cancer research would quickly yield cures. Unfortunately, progress against cancer has been far slower than anticipated. However, important advances have been made, some of which have resulted in substantial clinical benefit for patients.

Although research to prevent cancer has received far less emphasis than treatment-oriented research, it has nonetheless yielded several important benefits to date. Most notably, reduced mortality due to lung and other tobacco-related cancers (particularly among adult males) has been the direct result of intensive smoking prevention and cessation efforts over the past few decades. Epidemiologic studies and basic research have supported efforts to prevent cancer and have contributed to recently observed overall reductions in cancer incidence and mortality rates. A considerable amount of cancer prevention research has focused on vaccines, with notable successes (e.g., human papillomavirus vaccine/cervical cancer; hepatitis B vaccine/liver cancer), as well as on other preventive interventions (e.g., *Helicobacter pylori* testing and treatment of individuals at higher risk for gastric cancer). Other infectious agents, which have been associated with nearly 20 cancer types, are of growing interest as targets of vaccines and other preventive interventions.

Laboratory research over the past four decades has led to significant advances in our understanding of cancer. For example, the development and increasing availability of high-throughput technologies have enabled the sequencing of the human genome and led to the emergence of the so-called "omics"—genomics and proteomics, as well as the more nascent field of metabolomics. By providing comprehensive or near-comprehensive snapshots of the molecular make-up of normal and cancer cells, these approaches are enabling systematic characterization of the pathways and processes that are dysregulated in cancer.

Concern about the slow pace of progress against cancer has led to an increasing recognition that specific attention must be paid to the types of research activities needed to move findings from laboratory and epidemiologic studies to clinical testing and application. In many cases, the development of new technologies facilitates such translational research. For example, techniques have been developed and refined in recent decades to facilitate preclinical research on promising cancer targets and therapies.

Clinical research in the areas of surgery, chemotherapy, and radiation therapy also has contributed to important gains in our understanding of cancer and enhanced outcomes and quality of life for many cancer patients. Among these achievements are less extensive and image-guided surgical procedures; radiotherapy technologies and regimens that treat the tumor but spare normal tissue; and a growing number of targeted and personalized cancer therapies, including vaccines.

Cancer screening and early detection research has improved understanding of the cancer screening needs of various populations, assessed the efficacy of available screening tests, and stimulated imaging technology enhancements. At this time, however, population-wide cancer screening is available for only four types of cancer—breast, cervical, colorectal, and prostate—and most of these tests have notable weaknesses. Further, doubt has been raised in recent years about the extent to which routine screening decreases cancer mortality and

whether the benefits of some types of screening outweigh possible harms.

Surveillance, epidemiology, and population-based research provide information on the burden of cancer and, in the past several decades have helped uncover numerous determinants of cancer risk and outcomes. These disciplines also can inform the direction of and/or build on the results of other types of research, including basic, clinical, and applied approaches.

Modifying the Focus and Priorities of the National Cancer Program to Accelerate Innovation and Progress

The extent to which research funders are willing to accept risk (i.e., the possibility that a funded research project may fail) in order to achieve transformative innovation and progress lies at the heart of the NCP's focus and priorities. In the current era of constrained resources, most research funders are sharply risk-averse. To shift the priorities of the NCP to strongly promote innovation in cancer research and achieve more rapid reductions in the national cancer burden, action will be needed in several critical areas.

Cancer Research Funding Trends

Cancer remains the disease feared most by Americans, and the majority of Americans indicate that accelerating research to improve health—as well as rein in rising health care costs—should be a top or high priority. Americans also are concerned that the United States is losing its global competitive edge in science, technology, and innovation. Despite these widely shared perspectives, funding for biomedical research in the United States has stagnated in recent years. A lack of consistent funding threatens investments in innovation that are crucial to move beyond incremental advances in scientific knowledge and prevention and treatment of diseases such as cancer. Shifts in national priorities and an economic recession in recent years have created an environment in which NIH and NCI annual budgets have increased only marginally, if at all. The negligible growth rates are even more troubling when the increasing costs of conducting biomedical research are taken into account. Funding reductions and fluctuations not only constrain needed new research, but threaten the success of research already under way, since investigators cannot count on having funds needed to retain research staff and purchase materials. Importantly, uncertain and reduced funding are discouraging the best young scientific minds from pursuing cancer research careers and quashing the commitment of some seasoned investigators to remain in cancer or other biomedical research.

The philanthropic sector has consistently supported cancer research in the decades since passage of the National Cancer Act. Although this sector contributes only a small proportion of total cancer research funding in the United States, its role in fostering scientific innovation should not be minimized. Unfortunately, charitable donation and other funding (e.g., from for-profit entities) levels in general have decreased, and the funding base for many nonprofit organizations is in jeopardy.

Pharmaceutical companies have dramatically increased their research programs since the early 1970s. However, the ratio of R&D investment to pharmaceutical sales, which rose dramatically in the 1980s, has gradually declined. In addition, the nature of R&D research conducted by pharmaceutical companies has changed; over the past several decades investment in nonclinical and preclinical projects has suffered as more money is being spent on clinical trials and regulatory expenses.

Research Areas with Limited Emphasis

Recognition is growing that the ongoing emphases on basic and treatment research have occurred at the expense of other types of cancer research, some of which could have more immediate effects on the national and global cancer burden. Specifically, investments in translational, behavioral, and population-based research are needed to expand upon the knowledge gained through basic

and clinical investigations as well as inform development of new interventions.

More emphasis also is needed on areas of the cancer continuum beyond disease treatment, including prevention and early detection research and the long-term and late effects of treatment that often plague cancer survivors. An expanded understanding of the factors that influence cancer risk and progression is critically needed. Although some investments in such research have been made, when compared with biology and treatment research, these areas continue to comprise a much smaller component of the cancer research portfolios of most major funding organizations in the United States, Europe, and Canada. As a result, the knowledge base in these research areas is less well developed, as are the range of tools and interventions that could be developed with a more robust research investment.

Making Prevention a Research Priority

Testimony provided to the Panel emphasized that the best approach to reducing the national cancer burden is to prevent cancers from ever occurring. Most cancer research currently emphasizes drug development and surgery to achieve tumor shrinkage, improve disease management, and develop salvage therapies for advanced cancers. Although treatment advances are needed, a markedly greater emphasis on cancer prevention, early detection, and early intervention is crucial to reducing the national cancer burden.

Active areas of research related to cancer prevention have included vaccine development (e.g., human papillomavirus vaccine for cervical and other HPV-linked cancers) and chemoprevention, such as the use of tamoxifen to prevent second cancers in breast cancer survivors. While there have been successes, clinical trials and intervention development in this area have been hindered by numerous ethical concerns about administering drugs with potential side effects to ostensibly healthy, asymptomatic individuals. Such issues include weighing anticipated social benefit and risks; defining the risk status of study participants; ensuring that participant recruitment and selection is fair; and ensuring informed consent.

Recent actions represent important steps toward expanding prevention research and recognizing its importance not only in cancer, but in the nation's health as a whole. Notably, in June 2011, the Department of Health and Human Services developed the first-ever National Prevention Strategy, as required by the Patient Protection and Affordable Care Act (P.L. 111-148). Though not limited to cancer prevention, the strategy underscores the roles of virtually all federal and state/local agencies, private industry, and others in reducing the burden of disease in the United States. It also recognizes the potential savings—in health care costs, national productivity, and human suffering—that can be achieved with investments in prevention.

Changing the Focus of Biomarker Research

The United States has made considerable investments in cancer biomarker research, and this continues to be an area of intensive study. Hundreds of potential biomarkers have been discovered for possible use in drug development, and for assessing cancer risk, likely treatment response, and actual treatment response. However, most of the markers identified to date have yet to be tested sufficiently, or at all, to determine their specificity and sensitivity in clinical settings.

Greater emphasis is needed on validating the diagnostic and early-detection utility of biomarkers that have been identified compared with current emphasis on new marker discovery. Some markers already discovered may turn out to be of little or no clinical value. At the same time, new markers continue to be needed in underdeveloped areas.

Managing Cancer as a Chronic Disease

Until quite recently, cancer treatments focused almost exclusively on total and permanent eradication of disease (i.e., cure) through the use of surgery, escalating doses of cytotoxic agents, and radiation. Achieving this goal with some

consistency, however, has been possible in only a small number of cancer types (e.g., thyroid, testicular, cervical) and generally only when the disease is detected and treated in its early stages. For most cancer types, cure has been elusive. Containing cancer growth and spread for long periods of time has likewise proven to be extremely difficult, since most cancers become resistant to available therapies.

Key challenges in managing (rather than eradicating) cancer are to enable patients to live with no or minimal symptoms of disease and avoid morbidity due to toxicities that may be induced by long-term continuous or periodic maintenance treatment. Achieving these objectives would be aided significantly if aggressive and more indolent tumors could be better distinguished, since it might be possible to treat less aggressive cancers less frequently or with lower drug dosages. It can reasonably be anticipated that with continued research, effective cancer management approaches will become available to enable patients with diverse cancer types to survive for many years with a good quality of life.

Taking a Systems Approach to Cancer Treatment

A systems biology approach is needed to understand cancer in the context of the whole patient, i.e., shifting from a tumor-specific focus to one that is person-specific. Cancer exists not in isolation but as part of a hugely complex system—the human body. A key problem in cancer research as it is conducted today is the predominance of a point approach rather than a systems approach. Measuring the status of a patient's tumor or his/her symptomology at a single point in time is of limited value. Tools are needed to enable continuous monitoring to detect system changes well before they exhibit as symptoms, thereby permitting more rapid intervention to improve system function. In addition, clinicians must have a framework for evaluating and using the data generated by such tools. The goal should be health, not tumor shrinkage.

One speaker noted that thousands of cancer researchers are studying specific events (e.g., cellular transformation, metastasis), biochemical processes (e.g., cell signaling), or other tightly defined aspects of cancer. However, this work is not taking place in the context of a systems model of the problem, with researchers working in a coordinated fashion (ideally in multidisciplinary teams) toward a common goal of creating and implementing clinically effective solutions.

Rethinking Research Processes to Accelerate Progress and Encourage Innovation

Established research processes and related actions—including grant application and peer review mechanisms, publication preferences of scientific journal editors, and disincentives to participating in team science and multi-institutional collaborations—discourage innovation and slow progress against cancer. To enable the transformative research advances that will accelerate patient outcome improvements, these processes need to be reconsidered and redefined to identify problems and establish more productive approaches.

Adopting Grant Application, Peer Review, and Funding Models that Encourage Innovation

Numerous aspects of the NIH grant application and funding process discourage innovation. The lag between application submission, award notification, and receipt of funding still is exceedingly long, despite recent attempts to streamline the process. These delays may jeopardize the ability of principal investigators to hire and retain key research staff and avoid interruption or cessation of laboratory or clinical operations. Young scientists are particularly disadvantaged in the NIH grant application and peer review process, which favors established investigators over young scientists who could bring fresh perspectives to answering important cancer research questions.

Other research models have been designed specifically to encourage and fund innovative studies that hopefully will have a transformative impact on knowledge in a given field and subsequently benefit the population. Underlying all of these funding mechanisms is the critical recognition that studies exploring innovative ideas tend to have a higher failure rate than lower-risk projects aimed at incremental advances. In these funding models, however, such failures do not reflect negatively on the researcher, since much can be learned from well-designed experiments that do not yield expected results.

Ensuring Publication of Study Results

Publication of negative or inconclusive research results is rare. In many cases, such studies may not even be submitted for publication, because they do not enhance the stature of the investigator. In addition, scientific journals historically have had little interest in publishing negative results; of such studies that are submitted for publication, many are rejected. As a result, unsuccessful studies are needlessly repeated, a waste of both economic and human resources. In addition, not publishing null or negative findings increases investigators' disincentive to take on higher-risk studies that may fail because their career advancement depends heavily on the number of papers they publish. These dynamics are a function of the current academic culture.

Bolstering Drug Development

Pharmaceutical agents have made significant contributions to the progress made against cancer in the past several decades as well as in efforts to optimize the quality of life of cancer patients and survivors. New drugs will be integral to future preventive and treatment strategies; however, drug development is expensive and fraught with risk. According to some analyses, only 2 in 10 approved medications—cancer and noncancer combined—produce revenues that exceed average R&D costs. Thus, ongoing investment in R&D depends on the commercial success of a few products that must recover their own development costs and also make up for all of the rest, including those that never reach the market.

Cancer drugs comprise a substantial portion of the drugs in the pipelines of pharmaceutical and biotech companies. Although the R&D investment in anti-cancer drugs is substantial, it is associated with considerable risk. The cancer drug market is smaller than those for chronic conditions such as diabetes and hypertension and the discovery of disease subtypes continues to shrink the pools of patients that may benefit from a particular drug regimen. In addition, cancer drugs have a higher failure rate in Phase III trials than do drugs in other therapeutic areas, after substantial R&D dollars have been invested.

Reimagining the Clinical Trials System—Need for a New Paradigm

Inefficiencies in the current clinical trials system undoubtedly contribute to suboptimal oncology drug development. Recent analyses have shown that the process of activating a clinical trial is long and tedious. One study found that it requires a median time of approximately 2.5 years to open a Phase III clinical trial sponsored through the NCI Clinical Trials Cooperative Group Program, with some trials taking more than four years to achieve activation. Unfortunately, trials still face difficulty once activated. A large percentage of cancer clinical trials do not accrue adequate numbers of patients, and some fail to enroll even a single patient. A significant number of cancer clinical

trials are never completed. Failure to complete trials may not only delay or prevent potentially beneficial interventions from reaching patients, but also has troubling financial and ethical implications because of the investment of resources and involvement of patients in trials that do not yield meaningful information.

Many speakers who gave testimony to the Panel emphasized the need for the NCP to revisit the ways in which oncology trials are designed, implemented, and regulated to better meet the challenges created by advances in understanding of the molecular and genetic bases of cancer.

Addressing Organizational and Operational Issues

Several recent studies have evaluated the organization of and processes necessary to develop, launch, and conduct NCI-sponsored trials. These analyses identified organizational inefficiencies and hundreds of discrete steps and decision points required for trial activation, many of which appear to add little or no value to the process. NCI has initiated several activities in an effort to address the organizational and operational inefficiencies in its clinical trials system. Many of the changes under way are aligned with recommendations set forth in the 2010 Institute of Medicine report on the NCI Clinical Trials Cooperative Group Program as well as those in the 2005 report issued by the NCI Clinical Trials Working Group.

Designing Effective Trials

Researchers are recognizing the need to more quickly and accurately differentiate promising agents from unsafe or ineffective drugs and determine which patient populations are most likely to benefit from specific drugs. An analysis of major pharmaceutical companies in the United States and Europe found that only about 1 in 9 drugs that are taken into first-in-human studies are eventually approved; the rate is even lower for oncology drugs, which achieve approval in only five percent of cases, according to one estimate. A major challenge in drug development is the design of Phase II trials that more accurately predict success in Phase III trials, since Phase III trials account for more than two-thirds of the cost of the clinical trials process. A number of ideas for more effectively and efficiently testing interventions for cancer have been proposed, including consideration of nontraditional endpoints and use of adaptive trial designs. Also important are efforts to ensure that clinical and demographic characteristics of participants in cancer clinical trials are representative of the overall population of cancer patients.

Addressing Challenges Related to Institutional Review Boards (IRBs) and Other Regulators

Researchers are largely supportive of the goals of IRB review and most recognize the need for an oversight system, but many express frustration with the current implementation of IRB review processes. Preparing IRB submissions is time consuming and requested revisions also take time, often without adding significant value to the protocol. The burden of IRB review and the associated research costs and delays are amplified in multicenter studies that require review and approval by IRBs at each site. Cancer clinical trials also are overseen by several agencies within the U.S. Department of Health and Human Services that have different objectives and responsibilities and thus require different reporting and compliance actions. The claim that current regulatory processes result in unnecessary resource expenditures warrants attention, but perhaps more troubling is the contention that the regulatory burden leads researchers to avoid certain types of research, particularly projects that involve multi-institutional collaboration.

Promoting Productive Team Science, Multi-Institutional Collaborations, Consortia, and Partnerships

Many of the challenges facing the cancer research community cannot be adequately addressed by individual researchers in isolation but require teams with varied expertise and resources. The shift toward collaborative science was illustrated by a recent study that found that high-impact research is increasingly being published by teams rather than individuals. Collaborative scientific efforts may take several forms, including interdisciplinary team science projects, multi-institutional collaborations, consortia, and partnerships. These activities—which can involve international as well as U.S. participants—bring together people and organizations from different sectors and diverse disciplines to address a key scientific question or problem, develop needed resources or technologies, accelerate drug development, or conduct community-based research. There is, however, a need for new methods and measures to evaluate the processes and outcomes of large research endeavors.

Fortifying the Research Infrastructure to Support Transformative Innovation

Major technological advances in science made in the past decade (e.g., "-omics," computational chemistry, data-sharing capacity, digitization of scientific information) have not yet had a revolutionary effect on clinical care or clinical outcomes. Aspects of the cancer research and care infrastructure that warrant attention include the need to upgrade research facilities; further develop technologies such as imaging, data systems, and data-sharing; and expand the utility of biorepositories. With further development and support, these technologies have tremendous potential to advance the cancer research and care agenda.

Strengthening the Cancer Research and Care Workforce

The coming years hold extraordinary promise for improving our understanding of cancer and learning to prevent it, find it early when it does occur, and treat all forms of the disease effectively without significant side effects. Yet without a talented, innovative, and diverse workforce of researchers and clinicians, these much-needed advances cannot become reality.

The United States is facing critical shortages both in its research workforce and in the physician and nonphysician clinical workforce. It will not be sufficient merely to maintain current levels of research and clinical capacity. Shortages in the cancer care workforce are of great concern because they will diminish both access to and quality of care for people with cancer and may increase the burden on families of cancer patients and survivors.

Meeting the cancer research and care workforce demands of the coming decades will require creativity, foresight, and tenacity on the part of all stakeholders: government, academic institutions, scientific and medical societies, cancer advocates, quasi-governmental and private health policy organizations. Both components of the cancer workforce will be crucial to making the transformative discoveries needed to reduce America's cancer burden and ensuring that all people with or at risk for cancer benefit equally from these discoveries.

Accelerating Health Care Delivery System Improvements for Better Patient Outcomes

Several health care system characteristics discourage innovation in care, with upstream effects on translational and clinical research. These system weaknesses—such as fragmented, uncoordinated care and inequitable distribution of services—may have a negative impact on health outcomes both broadly and specifically for cancer patients/survivors.

Barriers to Health Care Delivery System Improvements

Although the United States has a wealth of health care resources, patient outcomes for most conditions lag behind those of other developed nations. Several health care delivery issues contribute to this situation. One important example of these problems is the lack of consistency, appropriateness, and equity in the application of evidence-based cancer prevention, screening, and care services across all populations. Patient care often is highly fragmented and poorly coordinated, as health services have become increasingly specialized and payment arrangements more complex. For patients with severe or multiple health conditions who take numerous prescription medications, as is the case for many people with cancer, this fragmentation of care can be especially hazardous.

Another stumbling block to the prompt delivery of cancer care advances is a lack of effective communication about cancer with key audiences. Education and communication about cancer continue to become more sophisticated and targeted, and successes, such as tobacco use prevention, illustrate the value of skills and information gained through health communications and related research that promotes dissemination of cancer research advances.

Improving Health Care Coordination, Efficiency, and Quality

Numerous health service delivery innovations are being tested to improve health care coordination, efficiency, and quality in the United States. One such initiative specific to cancer is the development of patient navigation programs to assist patients in locating needed services and managing appointments across disconnected care settings. Written cancer treatment summaries and survivorship plans, which can help patients document the cancer care they receive and plan the continuing care they will need following treatment and throughout their lives, also are important tools to support improved care coordination, communication, and efficiency.

Technological Advances with Potential to Revolutionize Health Care Delivery

Several tools and technologies—ranging from electronic health record systems to smart phones—have the potential to enable health care professionals and consumers to record, access, and exchange information that can protect or improve health. To be effective, however, these tools must be thoughtfully developed and applied. Health information technologies and electronic health records, for example, have potential to increase the efficiency, cost-effectiveness, quality, and safety of medical care. In addition to directly benefitting patient care, such technologies can support crucial surveillance and research because data can be aggregated and analyzed to gain insight into factors that influence health and disease.

Accelerating Scientific Innovation: Conclusions and Recommendations

To expand and capitalize on knowledge and technology advances achieved to date, the cancer research community now must identify and embrace strategies for accelerating the pace of scientific innovation. Only by encouraging and rewarding innovation and collaboration will critically needed transformative advances in cancer prevention and treatment be achieved.

Based on testimony received and additional exploration of these issues, the President's Cancer Panel has reached the following conclusions; these conclusions are followed by the Panel's recommendations for addressing barriers to more rapid research progress and to significant reductions in the burden of cancer on this nation.

Conclusions

Sustained Investment in Basic Science Research Is Essential to Further Increase the Understanding of Cancer

Basic research will always be needed—it is the key to transformative discoveries about fundamental cancer biology, the mechanisms by which cancer develops and spreads, and how it may be prevented. Basic science discoveries may find innovative application both in cancer and in other areas of health care.

Support for High-Impact Research Is Necessary to Drive Transformative Change in Cancer Prevention and Care

Funding instability is a critical barrier to scientific innovation. Moreover, high-risk research with the potential to result in transformative innovation and research aimed at making incremental progress currently compete for the same funds. Incremental research is safer and will pull dollars away from innovative ideas in a risk-averse climate.

The Academic Research Culture Should Emphasize the Impact of Investigators' Research on Disease Burden

The risk-averse academic research culture and its structures (promotion and tenure criteria and processes) continue to discourage innovation and collaboration. Rewards continue to be aligned primarily with independent research projects and the number of papers a scientist publishes rather than encouraging collaboration and acknowledging the impact of a researcher's work in reducing the cancer burden.

Redefined Grant Review Mechanisms and Novel Research Funding Models Have Significant Potential to Speed the Translation of Scientific Discoveries into New Standards of Cancer Care

Innovative research models; streamlined and blinded application and review processes; and grant mechanisms that reward innovation and disease impact all have significant potential to accelerate transformative innovation in cancer research that can lead to markedly improved outcomes for patients.

Expanded Research Could Lead to More Effective Long-Term Management of Cancer as a Chronic Disease

Cancer may never be eradicated entirely, but some cancers can now be managed effectively with ongoing or intermittent treatment, as is possible with certain other chronic diseases (e.g., diabetes). Increased research to improve disease control and symptom management would enable people with cancer to live more productively and with a good quality of life.

Publication of Null or Negative Research Findings Is Critical to Scientific Progress

Negative and null study results are seldom published due principally to investigator career concerns and low interest among scientific journal editors. Failure to publish such findings robs the scientific community of useful information that would inform subsequent research, prevent needless waste of resources, and accelerate progress. This information also could help cancer patients and their caregivers make more informed treatment or other cancer-related decisions.

The Best Approach to Reducing the Nation's Cancer Burden Is to Prevent Cancers from Occurring

Current research and health care delivery emphasize overwhelmingly the treatment of acute disease rather than protection and preservation of overall health. Acute, episodic care is inefficient, expensive, and difficult for patients. Preventing cancer is the best and most cost-effective way to reduce cancer incidence, mortality, and morbidity and associated human, health system, and national productivity costs. It is time for the research community and policy makers to recognize and embrace cancer prevention as one of the foremost goals of future cancer research.

Team Science and Collaborative Research Initiatives Provide Opportunities to Address Complex Cancer Research Challenges

Public-private partnerships hold enormous potential for increasing translational research investments and maximizing productivity in a resource-limited environment. Team science efforts also provide opportunities to bring nontraditional disciplines (e.g., engineering, behavioral and social sciences) to bear on cancer-related problems.

A Redesigned Clinical Trials System Has the Potential to Improve and Accelerate Oncology Drug Development

The existing clinical trials paradigm is outdated and inefficient. Traditional trial designs often are not well suited for testing emerging targeted therapies and combination regimens. In addition, due to the lack of an effective prioritization system, scarce resources and patients often are devoted to the conduct of trials likely to yield only incremental knowledge and/or benefit to patients. Drugs with potential to improve the outcomes of patients with early-stage disease may be overlooked because of the disproportionate focus of oncology trials on advanced disease.

Major Technological Advances in Science Have Not Yet Had a Revolutionary Effect on Cancer Clinical Care or Outcomes

Imaging technologies, electronic health record and other data systems, biorepositories, and communication technologies hold enormous promise for advancing the cancer research and care agendas and expanding community participation in research but need stronger support for their continued development and application.

Community Involvement in Research Design, Implementation, and Analysis Enhances the Relevance of Clinical Research

Consumer/community perspectives and expertise continue to be underutilized both in clinical trial and other research design and in study implementation and analysis.

Advances in Cancer Prevention and Care Will Not Be Achieved Without an Adequate Research and Clinical Workforce

Unless current and impending research and clinical workforce shortages are remedied, it will not be possible to make the gains in new knowledge and patient outcomes that are possible in the coming years.

Efforts Under the National Cancer Program Are Fragmented and Largely Uncoordinated

The National Cancer Program continues to be poorly defined and lacks both a national vision and a set of principles, priorities, and strategies for realizing substantial reductions in the burden of cancer borne by the American public. This ongoing deficit leads to research and patient care inefficiencies and redundancies and a lack of accountability of some stakeholders.

Recommendations

Recommendation	Responsible Stakeholder(s) and Other Entities*
1. Within fiscal limitations necessary during the nation's economic recovery: a. Support for basic research should remain strong, but funding must be better balanced to provide greater support for translational, clinical, epidemiologic, behavioral, and health services research. b. Of special importance, cancer research should shift its focus and funding across the research continuum strongly toward cancer prevention, including prevention of exposure to known carcinogens and understanding of the role of infectious agents in cancer causation and progression. c. Strategies must be devised to stabilize research funding overall and overcome the risk aversion of cancer research sponsors, which discourages innovative research.	Congress Department of Health and Human Services • National Institutes of Health • Centers for Disease Control and Prevention • Centers for Medicare and Medicaid Services • Agency for Healthcare Research and Quality • Health Resources and Services Administration Department of Defense Veterans Administration Other public sector cancer research sponsors Private and voluntary sector cancer research sponsors
2. Grant review mechanisms should be revised to encourage innovative research models, streamline application procedures, and adopt blinded peer review processes. Funding strategies should be developed that will accelerate new discoveries and their more rapid translation and assimilation into standards of cancer care.	Department of Health and Human Services • National Institutes of Health • Centers for Disease Control and Prevention • Food and Drug Administration • Centers for Medicare and Medicaid Services Department of Defense Veterans Administration Other public sector cancer research sponsors Private and voluntary sector cancer research sponsors
3. The academic research culture and its structures should be modified to more strongly encourage and reward collaboration and measurable positive impact on the national cancer burden in addition to continuing to reward basic science discoveries by individuals.	Public and private academic research organizations Scientific and medical journal editors

*The Panel recognizes that entities other than those listed may have a vital role or interest in implementation of the recommendations.

Recommendation	Responsible Stakeholder(s) and Other Entities*
4. Collaborations and partnerships, particularly between public and private sector organizations, that address questions related to cancer research and care should be actively promoted, nurtured, and monitored. Collaboration with nontraditional disciplines (e.g., engineering, mathematics, anthropology) should be encouraged.	Department of Health and Human Services • National Institutes of Health • Centers for Disease Control and Prevention • Food and Drug Administration • Centers for Medicare and Medicaid Services Department of Defense Veterans Administration Other public sector cancer research sponsors Private and voluntary sector cancer research sponsors Pharmaceutical and biotechnology industries
5. Clinical trials with potential for significantly improved outcomes or transformative change should have the highest priority; trials that are expected to demonstrate or confirm small incremental improvements should be discouraged. Innovative clinical trial designs with sound intermediate endpoints and patient protections should be developed and implemented to save research dollars and more rapidly answer key research questions. To a greater extent than currently is the case, drug trials should target early-stage disease.	Department of Health and Human Services • National Institutes of Health • Food and Drug Administration Department of Defense Veterans Administration Other public sector cancer research sponsors Private and voluntary sector cancer research sponsors
6. Widely available consumer technologies (e.g., cell phones, Internet, social media) should be incorporated into strategies for cancer communication, health literacy enhancement, outreach, navigation, patient-provider interface, and disease management, particularly for rural and other underserved populations.	Department of Health and Human Services • National Institutes of Health • Centers for Disease Control and Prevention • Food and Drug Administration • Centers for Medicare and Medicaid Services Department of Defense Veterans Administration Public relations, health communication, and telecommunications communities Behavioral and social scientists Public and private sector health care institutions and providers Universities and colleges Public health departments

*The Panel recognizes that entities other than those listed may have a vital role or interest in implementation of the recommendations.

Recommendation	Responsible Stakeholder(s) and Other Entities*
7. The development and application of innovative imaging and other technologies with potential to accelerate progress in cancer research and care should be strongly supported.	Department of Health and Human Services • National Institutes of Health • Food and Drug Administration Department of Defense Other public sector cancer research sponsors Private and voluntary sector cancer research sponsors Biotechnology and medical device industries
8. Data sharing and transparency must be improved and adequately supported. Specifically: a. Electronic health records adoption is a necessity, not an option. Additional incentives must be developed to encourage and enable EHR acquisition and implementation across the range of practice settings. Privacy and interoperability issues must be addressed more aggressively. b. Reporting of negative and null study results should be required by public, private, and other nongovernmental funders. The information should be made available via a free, online, open-access journal or database. c. Data collected about a population/community must be provided in full to that population. The participation in research of consumer communities that are interested in and willing to provide data and biospecimens should be welcomed. d. Coordination of biospecimen collection, annotation, storage, and sharing must be standardized, systematized, and expanded.	Department of Health and Human Services • Office of the National Coordinator for Health Information Technology • National Institutes of Health • Centers for Disease Control and Prevention • Food and Drug Administration • Centers for Medicare and Medicaid Services Department of Defense Veterans Administration Other public sector cancer research sponsors Private and voluntary sector cancer research sponsors Health insurance industry Scientific and medical journal editors and publishers Cancer patient/survivor advocates and consumers

*The Panel recognizes that entities other than those listed may have a vital role or interest in implementation of the recommendations.

Recommendation	Responsible Stakeholder(s) and Other Entities*
9. The views and participation of cancer patient/survivor advocates and other consumer representatives should be sought during clinical trial and other study design, and in developing and implementing public, professional, and patient education and community-based research interventions.	Department of Health and Human Services • National Institutes of Health • Centers for Disease Control and Prevention • Food and Drug Administration • Centers for Medicare and Medicaid Services Department of Defense Veterans Administration Other public sector cancer research sponsors Private and voluntary sector cancer research sponsors Academic and other medical centers Public health departments
10. A coordinated program of targeted actions must be undertaken to recruit, retain, diversify, and grow the cancer research and cancer care workforce. Specifically: a. Efforts to attract young people to careers in science and medicine must be increased and should begin at the K-12 level. b. Support for young investigators must be increased to ensure the development of the next generations of cancer researchers, including behavioral, health services, population, epidemiologic, translational, clinical, and basic scientists. Translational and physician-scientists, whose education and training is of especially long duration, are particularly in need of training support. c. Federal support for graduate medical education should not be reduced, but rather increased. Nursing and other nonphysician medical personnel training and development initiatives established by the Patient Protection and Affordable Care Act should be fully funded and actively promoted. Recruitment and retention initiatives of academic and other medical institutions and physician groups should be expanded to the extent possible. d. Mentoring should be an integral part of research and medical training at all levels. e. Increasing the diversity of the cancer research and cancer care workforce to more closely parallel that of the population is essential.	Department of Health and Human Services • National Institutes of Health • Centers for Disease Control and Prevention • Food and Drug Administration • Centers for Medicare and Medicaid Services Department of Education Department of Labor Other public sector cancer research sponsors Private and voluntary sector cancer research sponsors Academic and other cancer centers and medical centers Nursing and other nonphysician medical educational institutions State governments

*The Panel recognizes that entities other than those listed may have a vital role or interest in implementation of the recommendations.

Recommendation	Responsible Stakeholder(s) and Other Entities*
11. The Secretary of the Department of Health and Human Services should be directed to convene a trans-HHS working group to clarify the definition, mission, and vision of the National Cancer Program, define the principles and priorities for the NCP, and identify strategies for improving coordination of NCP activities to accelerate progress against cancer. The working group should solicit input from the diverse community of stakeholders whose actions affect cancer patient outcomes.	The President The Secretary, Department of Health and Human Services Department of Health and Human Services • National Institutes of Health • Centers for Disease Control and Prevention • Food and Drug Administration • Centers for Medicare and Medicaid Services • Agency for Healthcare Research and Quality • Health Resources and Services Administration

*The Panel recognizes that entities other than those listed may have a vital role or interest in implementation of the recommendations.

PREFACE

The President's Cancer Panel (PCP, the Panel), established by the National Cancer Act of 1971 (P.L. 92-218) is charged to monitor the development and implementation of the National Cancer Program (NCP) and to report at least annually to the President of the United States on impediments to the fullest execution of the Program.

Advances in biomedical science and revolutionary technologies have brought unprecedented opportunities for increasing the depth and efficiency of scientific inquiry about cancer and other human disease. Yet 40 years after declaring war on cancer, Americans still suffer cancer mortality second only to the toll taken by heart disease. Understanding of the underlying genetic and biologic mechanisms of cancer has grown rapidly, but translation of these insights into interventions that effectively prevent and treat cancer has been painfully slow. Reductions in cancer mortality and morbidity have likewise been slow and unevenly distributed among both the many types of cancer and the diverse populations of this country. The need to find ways to significantly accelerate scientific innovation and its application to reduce the burden of cancer is increasingly urgent as the United States' population ages and grows.

To more fully explore barriers and opportunities for achieving research innovations with the power to transform cancer care and dramatically improve patient outcomes, the Panel conducted a series of meetings entitled, *The Future of Cancer Research: Accelerating Scientific Innovation.* Testimony was received from 47 academic, industry, and public sector basic, translational, clinical, and population science researchers and research program administrators; voluntary sector research sponsors; health and science policy specialists; the cancer advocacy community; professional and industry association representatives; and Federal Government regulators and administrators.

Four meetings were convened between September 2010 and February 2011 at the following locations:

Meeting Date	Location
September 22, 2010	Boston, MA
October 26, 2010	Philadelphia, PA
December 14, 2010	Bethesda, MD
February 1, 2011	Atlanta, GA

In addition to verbal testimony, each speaker provided as part of the formal meeting record a brief white paper expanding on his or her remarks. A roster of meeting participants is provided in Appendix A. The recommendations in this report reflect the Panel's conclusions based on all of the testimony received, as well as on additional information gathered prior to and following the meetings.

ACKNOWLEDGEMENTS

The President's Cancer Panel is grateful to the Panel staff and support staff who provided valuable input and information for this report. This report would not have been possible without their hard work and dedication.

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Dana Young, J.D.

The Panel would like to also recognize Joe Whalen, who facilitated the September 22, 2010, Panel meeting in Boston, MA.

PART I

THE NATIONAL CANCER PROGRAM: OVERVIEW

Over the past four decades, America's investment in cancer research has yielded a vastly improved understanding of the many diseases called cancer, including some of the genetic and environmental factors and biologic mechanisms that cause or contribute to cancer development, progression, and spread. This knowledge has led to improved treatment for some cancers and enabled those afflicted to survive diseases that previously were routinely fatal. In 1975, only 50 percent of people diagnosed with cancer survived at least five years; this percentage increased to nearly 67 percent of people diagnosed in 2003.[1] The population of cancer survivors grew from 3 million in 1971 to nearly 14 million in 2012,[2] and in the past decade the psychosocial needs of cancer survivors (including those in active treatment) and their loved ones have received increased attention.

Despite these achievements, much remains to be done to control and eradicate cancer in the United States and improve quality of life for those who suffer from cancer. The following chapters highlight the early history of the nation's campaign against cancer, describe the magnitude of the national cancer burden, and note key successes to date across the cancer research and care continuum.

CHAPTER 1

Scope and Leadership of the National Cancer Program

The National Cancer Act of 1971 (P.L. 92-218; see Appendix B) created the National Cancer Program. The following sections trace the initial years of the Program and describe ongoing issues related to the scope, participants, and perceptions of the NCP.

A Brief History of the National Cancer Act

In 1970, prior to passage of the National Cancer Act, a National Panel of Consultants on the Conquest of Cancer (National Panel) was convened by a Senate resolution at the urging of the medical research lobby. It was this National Panel that first proposed establishing a national cancer program.[3] As one description[4] of the National Panel's report notes, the group considered many of the most fundamental and persistent policy issues in cancer and other biomedical research, including:

- Top-down versus bottom-up planning and direction
- How far a federal agency can and should go in coordinating related activities of other federal and state government agencies or the private sector
- How much emphasis a research agency should place on technology development and transfer
- How much to invest in basic versus applied research

The National Panel favored more centralized planning and program direction, stronger federal leadership of national activities, more active dissemination of state-of-the-art practices, and greater emphasis on applied research and development. Its report,[3] which was highly influential in the intense debate that led to the National Cancer Act, identified three components of an effective national program: a new, independent agency to coordinate cancer research and other related activities, a comprehensive national plan for a "coherent and systematic attack" on the complex problems of cancer, and increased financial resources.

I'm tempted to propose that there is a definition of the National Cancer Program which is operational, and that is that the goals are to improve survival of patients and to improve their quality of life....Where you draw the line between health care and [the] National Cancer Program, I think, is somewhat ambiguous.

– Michael Kelley, Department of Veterans Affairs

The most strident opposition to the National Panel's report and the National Cancer Act itself came from the scientific community. It centered on whether the National Cancer Institute (NCI) should become an independent national cancer authority with centralized control and jurisdiction to manage public and private sector cancer-related activities. In the final language included in the National Cancer Act, NCI was elevated within the federal organizational hierarchy but did not become an independent agency.

Further, whereas the National Panel's draft report recommended the use of large-scale planning and management techniques similar to those used by the National Aeronautics and Space Administration, the final report language referred to "administration" rather than "management" and phrases such as "centralized control" were deleted.[5] The importance of freedom in basic research was emphasized and stated explicitly. The draft language calling for a comprehensive national plan was weakened in the final report by excluding from all but loose coordination large areas of research for which neither plans nor long-term objectives could be clearly defined.[3] Moreover, the final

report language recommended the extensive use of grants to support cancer research and reliance on the scientific community for research planning as opposed to adherence to a research plan imposed by a centralized authority.

Section 407 of the National Cancer Act stated that in administering the National Cancer Program, the NCI Director should plan and coordinate the cancer activities of NCI and the National Institutes of Health (NIH), as well as those of other agencies, including those in the private sector. The legislation also gave the NCI Director other responsibilities, including encouraging and coordinating cancer research by industrial concerns; establishing or supporting large-scale production or distribution of biologic and therapeutic materials needed to further cancer research; and collecting, analyzing, and disseminating all data useful in preventing, diagnosing, and treating cancer. This latter charge was to include establishing an international data bank on the results of cancer research worldwide. In none of these areas, however, was the NCI Director given legal authority to mandate or enforce actions to coordinate the NCP.

...I don't think the national cancer plan has to do anything that's not already being done. I think its primary role should be... integration and convergence of these resources on the problem, which is improving outcomes for patients with cancer and reducing the incidence.

– Edward Benz, Jr., Dana-Farber Cancer Institute

Despite robust implementation plans in the early years following passage of the National Cancer Act, subsequent years saw the erosion of adherence to the planning process. Other than in appointments to the National Cancer Advisory Board (NCAB), no mechanism was established to involve organizations in implementing the NCP. In addition, the authority of the NCI Director to coordinate activities outside of NCI was diluted by the limits of voluntary coordination, and in the 1978 recodification of the 1971 Act, the language including other federal and non-federal organizations in the scope of the NCP was dropped.[6] Moreover, the time and attention needed to sustain the NCP planning process and Program implementation became overshadowed by the demands of running the vastly expanded NCI.

In 1994, the Subcommittee to Evaluate the National Cancer Program, convened by the NCAB at the direction of the House and Senate, recommended that strong coordination of the NCP be restored as intended in the 1971 Act, and that greater emphasis be put on translating and applying research advances for the benefit of cancer patients and all Americans.[7] Drs. Paul Calabresi and Harold Freeman, then-members of the President's Cancer Panel (PCP, the Panel), as well as Panel members Drs. LaSalle Leffall, Jr. (2002-2011) and Margaret Kripke (2003-2011), participated in this evaluation.

The PCP itself has addressed these issues, both explicitly and in the context of their ongoing impact on the national cancer burden, in several Panel reports over the past 13 years.[8-11] The perennial resistance to constraining any cancer constituency's autonomy by investing power in a single agency or group has to date obstructed the success of attempts (e.g., by the National Cancer Policy Board; C-Change) to coordinate the nation's efforts to control and cure cancer. Stakeholder groups in the cancer field continue to be fragmented, not only into broad communities—research, clinical care, advocacy—but also within each of those communities. Each subcommunity of researchers and clinicians is insular (sometimes referred to as the silo effect), with its own lexicon, internal networks, and hierarchy. As later sections of this report detail, the current research culture and career ladder still do not sufficiently embrace team science efforts. As a result, there is relatively little incentive or desire to collaborate across silos.

Further, with some exceptions (e.g., National Coalition for Cancer Survivorship, American Cancer Society [ACS], Patient Advocate Foundation, CancerCare), the cancer advocacy community remains primarily cancer site-focused. This focus promotes territorial behavior between "cancers" rather than an interest in identifying common problems and goals. In an environment

of shrinking resources, competition for attention, leadership, and funding typically discourages collaboration, though in some instances scarce resources may force groups to work together.

Participants in the National Cancer Program

In addition to the issues of leadership and coordination, the full complement of entities and constituencies—not just the research and clinical enterprises—that are considered to be participants in the NCP remains unclear. It has long been the Panel's view that the NCP is not limited to cancer research and cancer care supported by government, private, and voluntary sector entities. Rather, the NCP also encompasses the activities of organizations, industries, and individuals whose actions contribute to increasing or reducing the burden of cancer in the United States. For example, the Department of Defense (DoD) supports important cancer research programs; at the same time, as discussed in a previous President's Cancer Panel report,[12] DoD activities also have been responsible for exposing millions of people to established environmental carcinogens. In both respects, DoD is an important participant in the NCP.

Figure 1 depicts these myriad inputs that together shape the manner and extent to which cancer depletes the population and productivity of the nation. Contributors to known or suspected environmental damage that affects cancer risk—as well as those seeking to ameliorate and eliminate negative environmental influences—are part of the NCP. Similarly, the agricultural system, food industry, educators, city planners, policy makers, and the media, among others, all have influences on the extent to which the cancer burden is either exacerbated or reduced.

Perceptions of Cancer Risk, Cancer Research, and the National Cancer Program

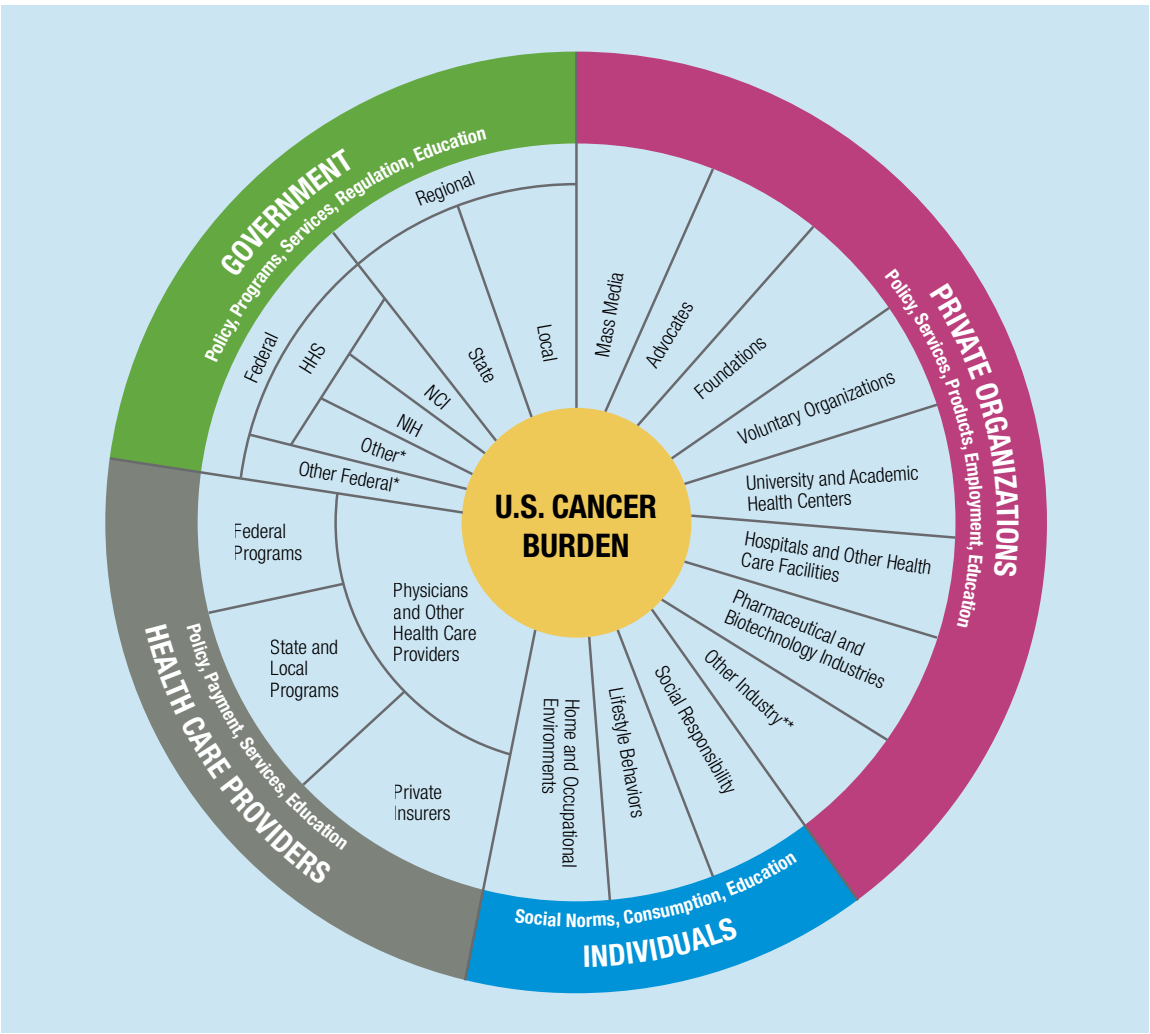
Perceptions and knowledge about cancer risk, the process and benefits of cancer research, and the National Cancer Program vary substantially not only among the general public, but within the medical and research communities and among policy makers.

According to the most currently available data, 1 in 2 men and 1 in 3 women[13]—about 40 percent of the U.S. population[14]—will receive a cancer diagnosis (excluding basal/squamous cell skin cancers or *in situ* cancers other than *in situ* bladder cancer) at some point in their lives (see also Chapter 2 and Appendix C). Studies[15-17] suggest that people generally assess their risk for a given danger to be lower than average—including the risk of developing cancer[18]—in part because they do not want to feel vulnerable.[19] They also may misperceive the comparative or absolute risk for specific cancers (e.g., risk of breast cancer compared with risk of heart disease among women;[20,21] risk of lung cancer among smokers[22, 23]). These studies also suggest that perceptions of cancer risk may vary considerably between diverse subpopulations and may be influenced by individuals' emotions and fears as well as their difficulty understanding numerical information.

A 2010 National Science Foundation study[24] showed that much of the public has little understanding of basic scientific concepts or a firm grasp of what it means to study something scientifically (i.e., the scientific process). This lack of knowledge may make it difficult to convey the need for specific studies or explain the costs associated with conducting research. In addition, while most people understand that research is required to develop new medicines, they often are unaware of the numerous other ways in which they benefit every day from biomedical research. For example, many people do not realize that extensive research is conducted to develop new imaging technologies and inform measures to protect and improve air, water, and food safety.

At the same time, public support for cancer and other biomedical research to improve health is strong. Surveyed Americans stated—upon learning that the U.S. spends less than six cents per health care dollar on biomedical research—that we do not spend enough, and that they would be willing to pay a tax to fund greater spending for

Figure 1
Components of the National Cancer Program



*Examples of federal agencies involved in cancer-related research, care, or regulation:

- Department of Health and Human Services
  - National Cancer Institute
  - National Institute for Environmental Health Sciences
  - National Center for Human Genome Research
  - Other NIH Institutes and Centers
  - Center for Disease Control and Prevention
  - National Institute for Occupational Safety and Health
  - Food and Drug Administration
  - Centers for Medicare and Medicaid Services
  - Indian Health Service
  - Health Resources and Services Administration
  - Agency for Healthcare Research and Quality
  - Agency for Toxic Substances and Disease Registry
- Office of the National Coordinator for Health Information Technology
- Environmental Protection Agency
- Department of Commerce/National Institute of Standards and Technology
- Department of Energy
- Department of Labor
- Department of Defense
- Department of Education
- Department of Housing and Urban Development
- Consumer Product Safety Commission
- Department of Veterans Affairs
- Department of Agriculture

**Examples of private sector industries affecting the national cancer burden:

- Agriculture
- Manufacturing
- Mining and drilling
- Food and beverage

Adapted from: Subcommitee to Evaluate the National Cancer Program. Cancer at a crossroads: a report to Congress for the nation. Bethesda (MD): National Cancer Advisory Board; 1994 Sep.

Figure 2

Public Perceptions of Biomedical Research Importance

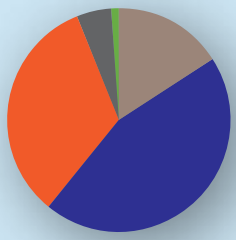
Bigger Slice of Health Dollar Should Go Toward Research

In 2010, the U.S. spent five and half cents of each health dollar on research to prevent, cure, and treat disease and disability. Do you think that this is too much, the right amount or not enough?

- **6%** Too much
- **27%** The right amount
- **51%** Not enough
- **16%** Not sure

Accelerating Investment in Health Research is a High Priority

How much of a priority is it to accelerate our nation's investment in research to improve health?



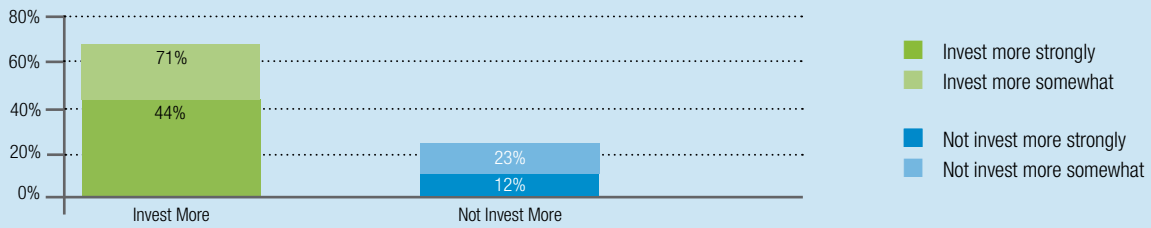
- **16%** Top priority
- **45%** High priority
- **33%** Somewhat of a priority
- **5%** Low priority
- **1%** Not a priority at all

Half of Americans Willing to Pay Tax for Research

Would you be willing to pay $1 per week more in taxes if you were certain that all of the money would be spent for additional medical research?

- **50%** Yes
- **27%** No
- **23%** Not sure

Source: Research!America. America speaks! Poll data summary, Vol. 12. Washington (DC); 2012 Jan.



Source: Robert Wood Johnson Foundation, Trust for America's Health, Greenberg Quinlan Rosner. Prevention is Central Health Care Reform Priority. Nov 2009. Cited 2012 Jun 5. Available from: http://healthyamericans.org/assets/files/TFAH-RWJFPreventionSurveyII.pdf

research (Figure 2). In addition, a majority of surveyed Americans indicated that basic, health services, prevention, and regulatory research are all important to controlling rising health care costs.[25] Further, a large majority of surveyed Americans believe it is important for the United States to maintain its world leadership in medical and health research, and that government investment in research will have an impact on the future of the nation.[26]

Taken together, the preceding paragraphs demonstrate the NCP's lack of a clear identity or national presence. Because it is neither fully defined in statute nor a line item in the federal budget, it is poorly understood or supported by some legislators. Similarly, many in the cancer research and care communities have only a vague notion of what the NCP encompasses. To the extent that a national effort against cancer is perceived by the public, it may be personified for many by the National Cancer Institute (or more broadly, the National Institutes of Health) and/or the American Cancer Society. For some, certain other well-known cancer-related organizations (e.g., StandUp2Cancer, Live**STRONG**, Susan G. Komen for the Cure) may be the face of the national fight against cancer.

In summary, more than 40 years after passage of the National Cancer Act, neither the scope of the National Cancer Program nor its leadership, coordination, or participants have ever been clearly defined. As later chapters of this report detail, the cancer research effort continues to be fragmented and largely uncoordinated, and the generation, application, and dissemination of research advances remain uneven at best.

CHAPTER 2

Our National Cancer Burden

Significant progress has been made in the ability to prevent, detect, and treat certain cancers in the decades following the passage of the National Cancer Act of 1971. Major contributors to this progress include better cancer screening and early detection methods, improved and targeted cancer therapies, and the sharp decline in tobacco use among Americans. As a result, more Americans are surviving longer following a cancer diagnosis than ever before.

In 2012, more than 1.6 million new cancer cases are expected to be diagnosed in the United States, and an estimated 577,000 Americans are projected to die of the disease.[27] In the coming decades, changes in cancer rates related to demographic shifts in the United States are expected to offset recent improvements and result in a marked increase in the number of new cancer diagnoses made each year. Cancer is projected to become the nation's leading cause of death—surpassing heart disease—over the next decade as the U.S. population ages.[28] Factors in addition to demographic changes present challenges in the push to accelerate progress against the disease. Cancer is enormously complex and highly adaptable; many subtypes of the disease have distinct clinical features and susceptibilities to therapy.[29] Many cancers still are not diagnosed until they are at advanced stages, and some resist most attempts at treatment.[30]

Figure 3 graphs cancer incidence and mortality trends for U.S. subpopulations from 1975 through 2008. These trends have important implications for national efforts to prevent and control cancer. While small reductions in cancer incidence and mortality have been observed among most racial and ethnic groups (as commonly defined), significant disparities persist for all cancer sites combined and for many cancer types. Progress in these reductions across all groups could be accelerated by applying existing cancer control knowledge related to prevention, early detection, and treatment to public health and clinical practice.[31,32]

...when we think of the national cancer plan or the National Cancer Program, we think too much of research and we think about the research infrastructure to include the universities, to include even some of the community practices. We don't think about the other aspects of the national cancer plan, and that is, how do you get the services, the things that we already know exist, to the population that actually needs those interventions.

– Otis Brawley, American Cancer Society

Cancer Data Collection Challenges

The precise number of U.S. cancer cases diagnosed each year is unknown. Many factors present challenges in the collection and analysis of such information. Cancer registry data are incomplete in some states, and about four years are needed to collect, compile, and disseminate national cancer incidence and mortality data for a given year. In addition, the growing diversity of the U.S. population challenges national efforts to identify population groups by race, ethnicity, or culture for health research and other purposes.

To develop a more robust understanding of cancer risk, progression, and outcomes among diverse populations, the Panel has recommended that actions be taken to address serious data deficiencies and develop new approaches to characterizing populations and assessing potential effects of changing demographics on cancer incidence and mortality in the coming decades.

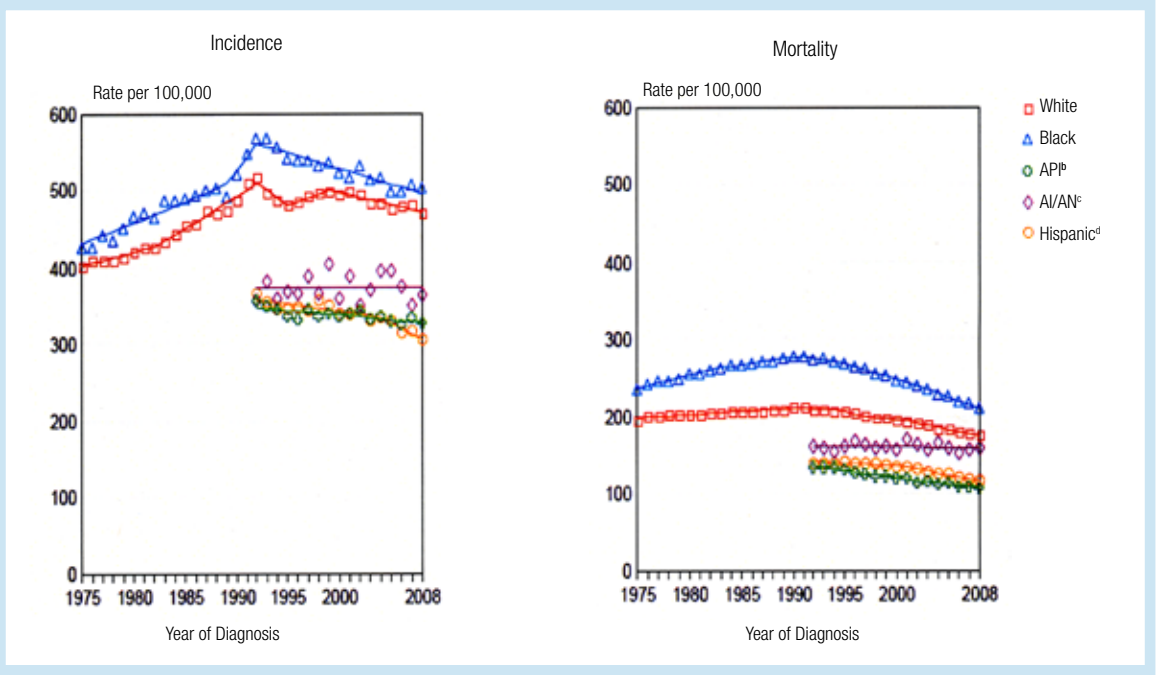
Sources: Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin. 2011;61(4):212-36.

Reuben SH, Milliken EL, Paradis LJ. America's demographic and cultural transformation: implications for cancer. President's Cancer Panel 2009-2010 annual report. Bethesda (MD): National Cancer Institute; 2011 Apr. Available from: http://deainfo.nci.nih.gov/advisory/pcp/annualReports/pcp09-10rpt/pcp09-10rpt.pdf

Figure 3

SEER Incidence and U.S. Death Rates[a]
All Cancer Sites, Both Sexes

Joinpoint Analyses for Whites and Blacks from 1975-2008
and for Asian/Pacific Islanders, American Indians/Alaska Natives, and Hispanics from 1992-2008



Source: Incidence data for whites and blacks are from the SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta). Incidence data for Asian/Pacific Islanders, American Indians/Alaska Natives and Hispanics are from the SEER 13 Areas (SEER 9 Areas, San Jose-Monterey, Los Angeles, Alaska Native Registry and Rural Georgia). Mortality data are from US Mortality Files, National Center for Health Statistics, CDC.

a Rates are age-adjusted to the 2000 US Std Population (19 age groups – Census P25-1103).
Regression lines are calculated using the Joinpoint Regression Program Version 3.5, April 2011, National Cancer Institute. Joinpoint analyses for Whites and Blacks during the 1975-2008 period allow a maximum of 5 joinpoints. Analyses for other ethnic groups during the period 1992-2008 allow a maximum of 3 joinpoints.
b API – Asian/Pacific Islander.
c AI/AN – American Indian/Alaska Native. Rates for American Indian/Alaska Native are based on the CHSDA(Contract Health Service Delivery Area) counties.
d Hispanic is not mutually exclusive from whites, blacks, Asian/Pacific Islanders, and American Indians/Alaska Natives. Incidence data for Hispanics are based on NHIA and exclude cases from the Alaska Native Registry. Mortality data for Hispanics exclude cases from Connecticut, the District of Columbia, Maine, Maryland, Minnesota, New Hampshire, New York, North Dakota, Oklahoma, and Vermont.

The following sections provide a brief overview of U.S. cancer incidence, mortality, and survival trends as they currently are understood.

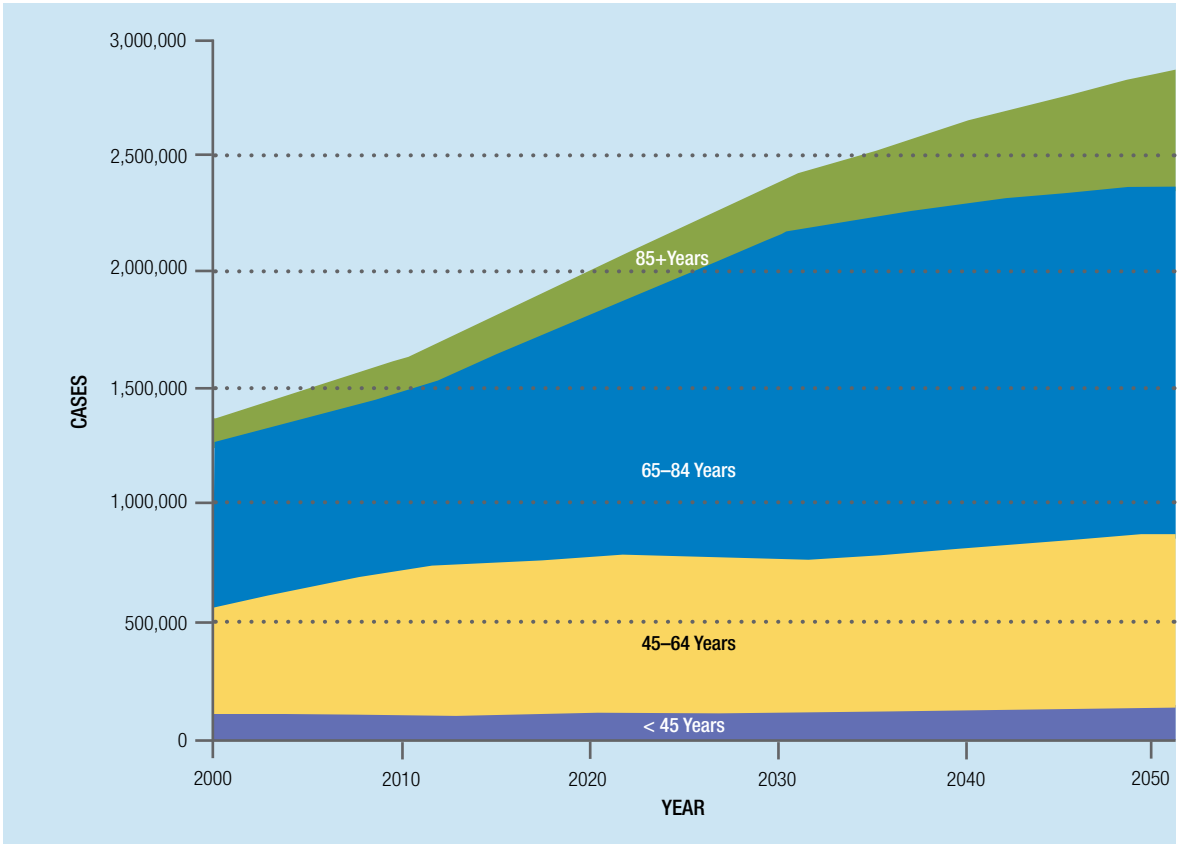
Incidence

Overall cancer incidence rates have declined slowly in the United States in recent years. From 2004-2008, the most recent five-year period for which data are available, rates declined slightly among men (by 0.6% per year) and were stable among women.[27] From 1999 to 2008, decreases were observed in the incidence of 5 of the 17 most common cancers diagnosed among men: prostate, lung, colorectal, stomach, and larynx).[33] In contrast, rate increases were observed among men for cancers of the kidney, pancreas, liver, thyroid, melanoma, leukemia, and myeloma. Among women, decreasing incidence trends were observed over the same period for 6 of the 18 most common cancers: lung, colorectal, bladder, cervical, oral cavity, and stomach.[33] Increased incidence rates were observed among women for cancers of the kidney, pancreas, liver, and thyroid, as well as for melanoma and leukemia.

Among the population as a whole, the number of new cancer cases per year is projected to nearly double from 1.3 million in 2000 to almost 3 million in 2050 as the overall U.S. population grows and as aging and diversity progress (Figure 4).[34]

Figure 4

Projected Number of Cancer Cases for 2000–2050 by Age Group Based on Projected Census Population Estimates and Delay–Adjusted SEER–17 Cancer Incidence Rates*



* Projections based on approximate single-year delay-adjusted SEER–17 incidence rates for 1998–2002 and population projections from the U.S. Census Bureau.

Source: Hayat MJ, Howlander N, Reichman MC, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) program. The Oncologist. 2007;12(1):20-37.

As noted, much of this growth in the number of new cancer cases will be attributable to the aging of the U.S. population, because most malignancies occur in older individuals. Another portion of the increase will be due to a rise in the number of cancers diagnosed among defined minority group members of all ages as defined by the Office of Management and Budget (OMB). Cancer incidence in minorities is projected to nearly double between 2010 and 2030.[35]

Mortality

Overall cancer death rates among the U.S. adult population as a whole have been on the decline since the early 1990s and rates among children have been decreasing since the mid-1970s.[31] Death rates peaked among men in 1990 and in 1991 among women. Between 1990/1991 and 2008, overall mortality rates decreased by 22.9 percent in men and by 15.3 percent in women; an estimated 1,024,400 deaths from cancer were avoided over this period.[27] These improvements are attributable primarily to reductions in tobacco use among men, increased cancer screening rates, and improved treatments for specific cancers.

From 2004-2008, the overall cancer death rate decreased by 1.8 percent per year in males and by 1.6 percent per year in females.[27] Death rates have continued to decline for the four major cancer sites (i.e., lung, colorectum, breast, and prostate). Among men, reductions in mortality for lung, prostate, and colorectal cancers (CRC) have accounted for nearly 80 percent of the total decrease in the male death rate; lung cancer alone has accounted for nearly 40 percent of the decrease. Among women, reductions in mortality for breast and colorectal cancers have accounted for 56 percent of the total decrease in the female death rate. Also notable among women, cervical cancer death rates have recently stabilized after being on the decline for decades.[31]

If you have survival or mortality information you can figure out how many people are living with [cancer]...but what are peoples' lived experiences with a disease or after they have had their cancer treated? That is really one of our top priorities right now.
– Lisa Richardson, Centers for Disease Control and Prevention

Death rates have been on the rise in recent years for some cancers, including liver cancer and melanoma in men, and liver and pancreatic cancers among women.[31] Given the complex nature of cancer as a whole and the lack of screening methods available to detect most cancer types, progress against some cancers has been slower than for others. Pancreatic, lung, liver, and brain cancers are those for which methods to detect and treat remain most inadequate.[30]

Survival

As of January 2012, there were nearly 14 million cancer survivors in the United States,[2] a nearly fivefold increase from 3 million in 1971. Fifteen percent of these survivors were diagnosed 20 or more years ago. Among those diagnosed with cancer in 2003, nearly 67 percent survived for at least five years;[1] only 50 percent of patients diagnosed in 1975 survived for five years or longer.

Advances in the treatment and early detection of cancer, combined with increased life expectancy and an aging population, are contributing to the growing population of cancer survivors.[2] Notably, refinements in treatments for Hodgkin lymphoma, chronic myeloid leukemia (CML), and cancers diagnosed among children have led to vast improvements in five-year relative survival rates among these patients.[29,32] The cancer survivor population is expected to continue to grow in the coming decades as these trends continue.

The most common cancer diagnoses among today's survivors are female breast (22%), prostate (20%), colorectal (9%), and gynecologic (9%) cancers.[36] Approximately 60 percent of cancer survivors are aged 65 years or older.[2] This percentage is expected to increase substantially over the coming years. Given the substantial costs associated with the level of care needed for older cancer patients, who often have other chronic conditions, this trend could have an enormous impact on health care delivery systems.

Continuing Disparities

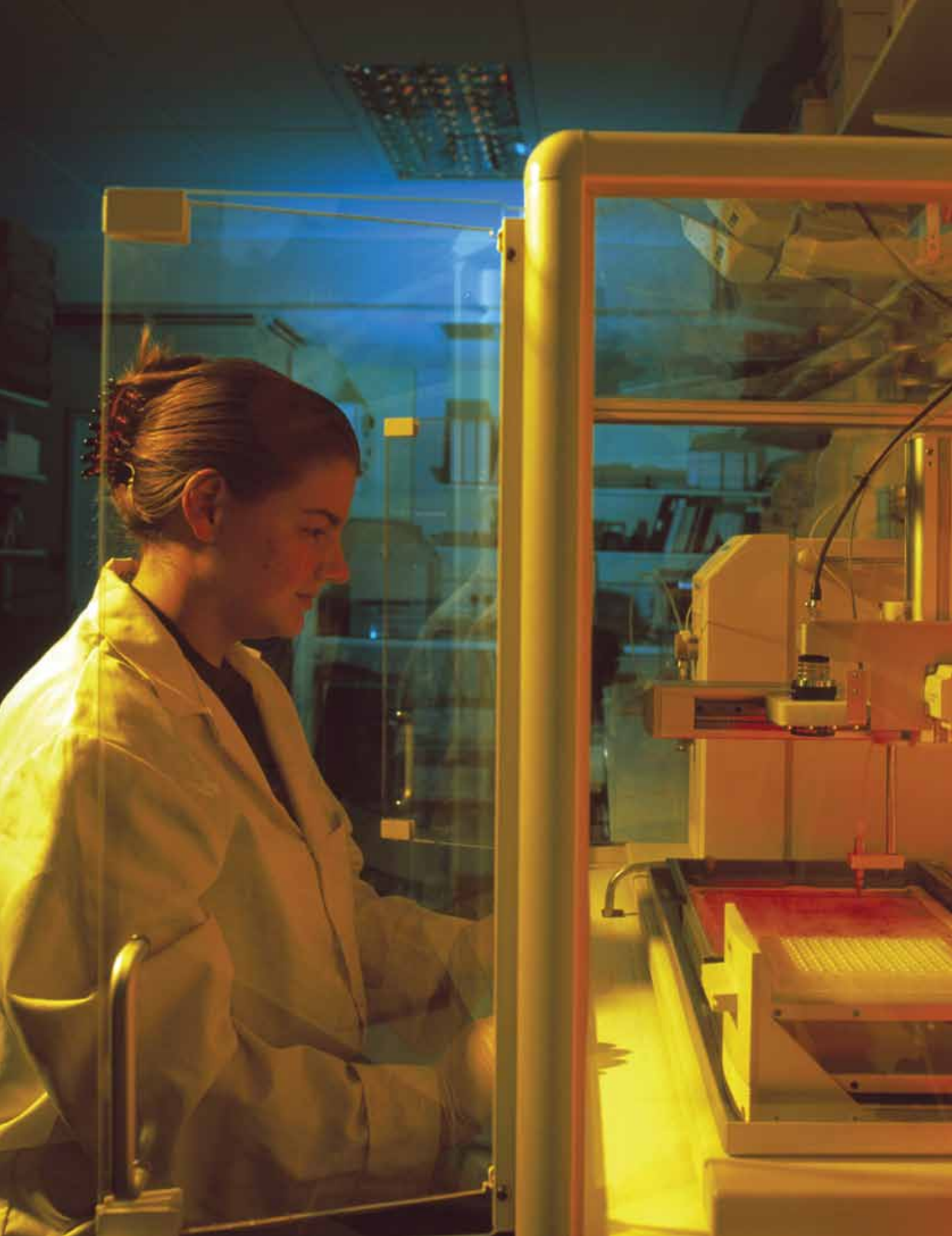
Disparities in cancer incidence, mortality, and survival across U.S. subpopulations are well documented and have been discussed extensively in previous Panel reports.[11,37] Minority and other underserved populations experience disproportionate burdens from certain cancers, are often diagnosed at later stages of disease, and frequently have less favorable odds of survival once diagnosed.[38,39]

Of all U.S. racial/ethnic subpopulations, African Americans have the highest cancer incidence and mortality rates. African American men are over 50 percent more likely than white men to be diagnosed with prostate cancer, and are more than twice as likely to die from the disease compared with all other racial/ethnic groups. Similarly, African American women are more likely than white women to die from breast cancer even though breast cancer incidence is lower among this group. Incidence and death rates for cancers linked to infectious agents—such as cancers of the stomach, uterine cervix, and liver—are generally higher among minority populations than among whites.[32]

Factors that are known to contribute to cancer disparities include differences in exposure to risk factors (e.g., tobacco use) and in access to screening and treatment modalities.[40,41] In addition, cancer risk and outcomes result from a complex interplay of numerous socioeconomic factors (e.g., education, income, wealth) along with cultural, environmental, biological, behavioral, and genetic factors. The potential effect that socioeconomic factors have on premature death from cancer is particularly compelling. One analysis has shown that 37 percent of cancer deaths in 2007 among adults aged 25-64 could have been avoided if all subpopulations had experienced the same overall cancer death rates as the most educated non-Hispanic whites.[32]

Appendix C provides 2004-2008 cancer incidence and mortality rates for selected cancer sites for major U.S. population groups, as defined by the U.S. Census.

We need to work harder to improve the enrollment of minorities and low-SES populations in research so that the research being developed and the evidence are truly representative of the populations in need and building so-called real-world evidence as opposed to just controlled-environment evidence.
– Kyu Rhee, Health Resources and Services Administration



CHAPTER 3

Highlights of Cancer Research Progress

When the National Cancer Act was signed into law in 1971, there was widespread optimism that the significant expansion of support for cancer research would quickly yield cures.[42] Unfortunately, 40 years later, cancer prevention and cure remain elusive. However, important progress has been made in recent decades, some of which has resulted in substantial clinical benefit for patients. The following paragraphs highlight some of these advances in six major types of cancer research.

Basic Research

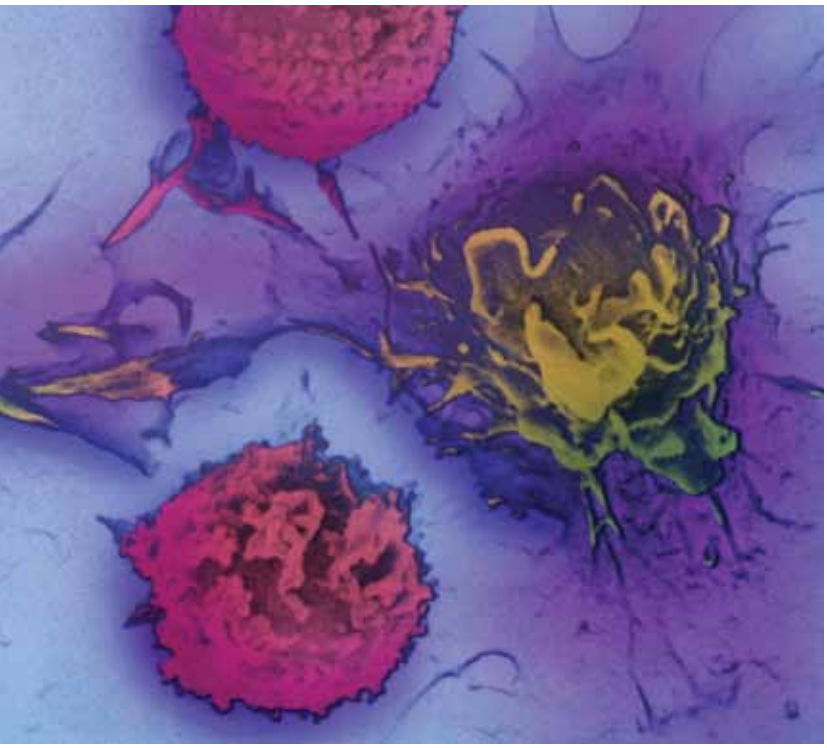
Laboratory research over the past four decades has led to significant advances in our understanding of cancer. Studies of cancer-causing viruses in the 1970s led to the identification of viral oncogenes such as v-*src* and v-*myc* that are capable of transforming normal cells into cancerous cells. Researchers eventually discovered that these viral genes were derived from genes present in mammalian cells (later called proto-oncogenes). A procedure called transfection was developed in the early 1970s, making it possible to transfer genes between mammalian cells. Researchers used this tool to confirm the presence of oncogenes in human cancers by demonstrating that DNA from these cancers could transform normal mammalian cells similar to what had been observed with viral oncogenes. In the years that followed, numerous human oncogenes were identified, including *myc* in leukemia and *erbB* in human stomach, breast, and brain cancers. Many of these oncogenes were the mammalian counterparts of viral oncogenes. Closer inspection of these genes provided insight into the many ways in which proto-oncogenes could be altered to become oncogenic. This research laid the foundation of our current understanding of cancer as a disease of the genes and led to characterization of numerous genes and cellular signaling pathways that contribute to the many diseases that comprise cancer.[43]

Speculation about the existence of genes that were "lost" (i.e., deleted) or inactivated in cancer, now called tumor suppressor genes, was confirmed by research on the rare childhood eye cancer retinoblastoma. This work spurred the identification of several additional tumor suppressor genes, which are now known to play important roles in many types of cancer, including many familial cancers. In addition, observations of the elevated DNA mutation rates in cancer cells gave way to extensive research on the cellular mechanisms that maintain the integrity of the genome and the ways in which these signaling pathways are compromised during oncogenesis. Later research found that, in addition to mutation and deletion, many tumor suppressors and DNA maintenance genes could be silenced if the regions of DNA controlling their expression were modified through the addition of a methyl group (i.e., promoter methylation).[43] Epigenetic modifications such as methylation continue to be active topics of cancer research and are also targets for potential therapeutic agents.

...when we measure what we knew about cancer 40 years ago against what we know now, the transformation is simply revolutionary.

– Harold Varmus, National Cancer Institute

More recently, the development and increasing availability of high-throughput technologies have enabled the sequencing of the human genome and led to the emergence of the so-called "omics"—genomics and proteomics, as well as the more nascent field of metabolomics. By providing comprehensive or near-comprehensive snapshots of the molecular make-up of normal and cancer cells, these approaches are enabling systematic characterization of the pathways and processes that are dysregulated in cancer.



...we'll probably never know everything we need to know to attack every cancer or prevent every cancer the way we'd like, and so research will always be part of the agenda.
– Edward Benz, Jr., Dana-Farber Cancer Institute

Research also has revealed how surrounding tissues and cells contribute to the development of cancer. Experiments in the 1990s using mice genetically engineered to lack expression of a functional interferon-gamma receptor provided support for the notion that the immune system is capable of suppressing tumor formation. These results were reinforced by observations that the growing population of people with compromised immune systems—including those infected with the human immunodeficiency virus (HIV) and organ transplant recipients on immune suppression drugs—were more susceptible than the general population to many types of cancer. Continuing laboratory research has revealed several mechanisms used by cancer cells to evade detection and destruction by the immune system, including recruitment and activation of regulatory T cells.[43] It also has become clear that the sites of metastasis are not passively determined by patterns of blood flow as was once assumed but, rather, are the result of specific interactions between tumor cells and host tissues. Knowledge also has emerged about the ability of tumor cells to recruit blood vessels to gain access to the nutrients and oxygen necessary for expansion.[44] These and other laboratory observations have paved the way for clinical interventions, some of which are described in the following sections.

Translational Research

Concern about the slow pace of progress against cancer has led to an increasing recognition that specific attention must be paid to the types of research activities needed to move findings from laboratory and epidemiological studies to clinical testing and application. In many cases, the development of new technologies facilitates translational research. Several techniques have been developed and refined in recent decades to facilitate preclinical research on cancer targets and therapies.

Researchers began growing cells in the laboratory more than a century ago,[45] but while cultured cells have made and continue to make significant contributions to biomedical research, it has been recognized that cancer cells grown in a single layer can be significantly different from those in tumors. In the 1970s, techniques were developed that allowed cells to be grown in three-dimensional cultures and scientists noted that the resulting structures more closely resembled *in vivo* tissues. Since that time, many cancer researchers have worked to develop and refine three-dimensional cell culture models for several cancer types—including those from skin, prostate, esophagus, colon, and breast—that more accurately replicate

the architecture of tumors (as well as normal tissues) and allow investigation of cancer cell interactions with the extracellular matrix and other cells. It has been suggested that these systems have potential to contribute to oncology drug development, particularly for drugs targeting the tumor microenvironment.[46]

Genetically engineered mice in which the expression of a gene (or genes) is manipulated (e.g., overexpression of transgene, expression of mutated gene, knockout) also have provided a way to investigate oncogenic processes in an intact physiological environment. Although they are imperfect mimics of human disease, in some cases, genetically engineered mice may be useful for testing potential anti-cancer drugs or drug combinations.[47-49] For example, a mouse model that lacks both *Brca1* and *p53* in mammary and skin epithelial cells develops mammary tumors that are histologically and molecularly similar to the basal-like breast cancers that form in women who carry a *BRCA1* mutation.[50] This model has been used to evaluate the efficacy of poly (ADP-ribose) polymerase 1 (PARP1) inhibitors and may also provide a model to investigate mechanisms of resistance to this drug class.[51]

In addition to facilitating discovery research, gene expression profiling and other high-throughput technologies are helping to identify subtypes of several cancers, including breast cancer, melanoma, diffuse large B-cell lymphoma (DLBCL), acute lymphoblastic leukemia, and lung cancer.[52-55] Many of these findings have clinical relevance; for example, the two major DLBCL subtypes identified through gene expression profiling are biologically distinct and are associated with significantly different survival rates. To date, distinct clinical management strategies for these subtypes have not been established,[56] but it is hoped that these findings will benefit patients in the near future.

The best lab science in the world will not cure a single patient unless it is translated into the clinic.

– George Sledge, Jr., American Society of Clinical Oncology

Other technologies and computational methods developed in recent years are increasingly being applied for diverse purposes such as drug delivery, imaging, treatment response monitoring, and prediction of biochemical, patient, and population responses to interventions. Advances in nanotechnology are beginning to yield novel methods for selectively delivering anti-cancer agents into tumor tissue and improving detection and imaging of cancer cells.[57] One of the first examples of a nanotherapeutic is Doxil®, a liposomal formulation of the chemotherapy drug doxorubicin that is used to treat ovarian cancer, multiple myeloma, and Kaposi sarcoma. Compared with doxorubicin, Doxil® remains in circulation longer and is associated with markedly less cardiotoxicity, which means that higher cumulative doses can be used and/or the drug can be used in combination with other potentially cardiotoxic drugs.[58,59] In addition to efforts to improve the pharmacokinetics of anti-cancer drugs, ligand-based nanoparticles are being used to selectively target drugs to tumor cells.[59]

Another emerging area of translational research is *in silico* research, which uses mathematical modeling to predict outcomes ranging from molecular interactions within a cancer cell to the population-level effects of a cancer control intervention.[60] For example, a series of modeling techniques that incorporated a variety of data were used to determine that screening mammography contributed to the total reduction in the rate of breast cancer deaths observed in the United States between 1975 and 2000.[61]

When we think about how we're approaching targeted therapy and the success of Gleevec® and others, I think it becomes obvious rather quickly that we have really just scratched the surface of what we can do.

– Tomasz Beer, Oregon Health & Science University Knight Cancer Institute

Clinical Research

Clinical research in the areas of surgery, chemotherapy, and radiation therapy also has contributed to important gains in our understanding of cancer and has enhanced outcomes and quality of life for many cancer patients. In the 1970s, a landmark study found that breast cancer patients undergoing breast-conserving surgery, or lumpectomy, experienced outcomes no different from those undergoing radical mastectomy. These results stimulated additional scientific examination of cancer surgery and paved the way for less invasive approaches for surgical treatment of a number of other cancers, sparing many patients from the severe disfigurement associated with more extensive surgical intervention.[62] For example, whereas treatment for prostate cancer typically required radical prostatectomy as little as 15 years ago, less invasive therapies such as brachytherapy (implantation of radioactive granules into or next to the tumor) for localized prostate cancer have been shown to have equal outcomes with fewer side effects.[63,64]

The recognition that cancer can spread to distant parts of the body via the bloodstream led to the advent of systemic therapy as an adjuvant to surgery. Trials in the 1970s and 1980s showed that chemotherapy administered either before or after surgery could improve patient outcomes.[62] The treatment of patients with no identifiable metastatic disease with systemic therapy based on the possibility of future distant metastases was a revolutionary departure from previous strategies but was shown to be effective in the case of tamoxifen treatment of breast cancer patients.[62]

More recently, technological advances also have begun to change the field of surgical oncology. Video-assisted and laparoscopic technologies are making possible less invasive approaches for some patients. Several clinical trials have concluded that colon cancer patients who underwent laparoscopic surgery for colon cancer rather than open colectomy had similar rates of recurrence but shorter surgical recovery times, fewer complications, and shorter hospital stays.[65-67]

Knowledge gleaned through basic science has been combined with new technologies to advance research on novel nonsurgical interventions for cancer. The emergence of molecularly targeted therapies is particularly notable. The development of imatinib (Gleevec®), which initially was developed as a drug to treat CML, helped to spur interest in this area. Although scientists had recognized as early as the 1960s that CML was associated with a recurring genetic mutation, it was not until the 1980s that the *BCR-ABL* fusion gene—the result of a translocation between chromosomes 9 and 22—that drives most cases of CML was identified and characterized. There was skepticism that tyrosine kinases such as BCR-ABL could be viable therapeutic targets because of the extensive involvement of this class of proteins in normal cell signaling. However, doubt gave way to widespread excitement when clinical trials clearly demonstrated the superiority of imatinib, the drug developed to target BCR-ABL, over interferon-alpha, the standard of care for CML at the time. At five years of follow-up, more than 90 percent of imatinib-treated patients had not experienced disease progression, and most patients experienced only mild to moderate side effects.[68,69] These findings illustrated that in addition to benefiting many CML patients, targeting of oncogenic mutations represents a viable therapeutic strategy for cancer, and have contributed to the fundamentally altered approach to drug development within the oncology community that has emerged in recent years.[69]

Other types of targeted therapies also are being used in patients and tested in clinical trials. Monoclonal antibodies that interact with

cancer-related targets—such as trastuzumab, cetuximab, bevacizumab, and rituximab—have benefited patients with several types of cancer, often when used in combination with standard chemotherapy.[70] In addition to focusing on targets within tumors, extensive research is ongoing to harness the immune system to eliminate or suppress the progression of cancer cells. There has been some success in this area; in 2010, the U.S. Food and Drug Administration (FDA) approved the first therapeutic cancer vaccine, sipuleucel-T, based on clinical trial results indicating that the vaccine improved survival among men with castration-resistant prostate cancer.[71]

Refinements in radiotherapy have been made possible by advances in computer and imaging technologies. Using three-dimensional conformal radiation therapy, it now is possible to shape beams to direct high doses of radiation to tumors while minimizing collateral damage to surrounding tissues. Clinical trials continue to explore ways to avoid the detrimental effects of radiation, particularly the long-term effects experienced by childhood cancer patients.[72]

Surveillance, Epidemiology, and Population Research

Surveillance, epidemiology, and population-based research provide information on the burden of cancer and in the past several decades have helped uncover numerous determinants of cancer risk and outcomes. These disciplines also can inform the direction and/or build on the results of other types of research, including basic, clinical, and applied approaches.

The National Cancer Act mandated the collection, analysis, and dissemination of information that would be useful in cancer prevention, diagnosis, and treatment. To address this mandate, in 1973 NCI established the Surveillance, Epidemiology, and End Results Program (SEER), a compilation of data from a subset of cancer registries from across the country.

SEER has since been expanded and now covers approximately 28 percent of the U.S. population, with higher percentages of many racial and ethnic minority groups represented. SEER data—which include information on cancer incidence, stage at diagnosis, first course of treatment, mortality, prevalence, and survival—are used by thousands of people each year, including researchers, clinicians, public health officials, legislators, policy makers, and the lay public.[73,74] In addition to SEER, the National Program of Cancer Registries was established by the Centers for Disease Control and Prevention (CDC) in 1992 to expand the geographic coverage of cancer registries by bolstering state-based registries.[75]

...we cannot have it take so long to bring a good idea to the population-based set of data and specimens, and then attempt to answer the questions.

– Patricia Hartge, National Cancer Institute

In the 1970s, data from SEER and other cancer registries confirmed a troubling trend that had been noted by some physicians and public health workers in previous decades—minorities (most early studies focused on African Americans) had higher cancer mortality rates than did whites.[76] In addition to spurring and enabling research on what is now referred to as cancer health disparities, these stark data mobilized advocacy groups and helped raise awareness among policy makers. In response, many agencies, including NIH and NCI, have created programs designed to illuminate the factors contributing to cancer health disparities and develop interventions to address them. Cancer registries continue to provide important insights into disparities—illustrating, for example, the widening gap in breast cancer mortality between blacks and whites following the introduction and widespread adoption of mammography[38]—but these data have limitations with respect to classification of minorities (discussed in detail in a previous Panel report).[37]

Observations made through analysis of surveillance data have stimulated a number of epidemiologic and population-based studies focused on topics ranging from environmental exposures to social and behavioral influences on health. These types of studies have identified numerous risk and protective factors for cancer. Studies in the early 20th century linked tobacco to lung cancer, and subsequent work found that smoking also increases risk of cancers of the oral cavity, esophagus, bladder, kidney, pancreas, stomach, and cervix, as well as acute myelogenous leukemia.[77] These observations spurred the development of public health programs to reduce smoking and also fueled extensive basic science investigation into the mechanisms by which tobacco induces cancer. More recently, numerous studies have suggested associations between several types of cancer and other lifestyle factors, including diet, obesity and overweight, and low physical activity.

The decades since the passage of the National Cancer Act have seen the emergence of molecular and genetic epidemiology, disciplines that investigate associations between health outcomes and molecular or genetic biomarkers. Many such biomarkers may represent innate physiologic or genetic traits, and researchers are working to identify and validate biomarkers that can serve as surrogates of some environmental exposures. Sequencing of the human genome and the development of technologies capable of identifying genetic variants (single nucleotide polymorphisms, or SNPs) in a high-throughput manner have made it possible to scan the genome for variants that may contribute to cancer risk. These genome-wide association studies (GWAS) have identified more than 150 DNA regions that are associated with one or more of two dozen specific cancers.[78]

More targeted interrogation of genetic variation has provided insight into genetic factors that influence susceptibility to occupational and environmental carcinogens. For example, variants in two genes have been found to influence mesothelioma risk in asbestos-exposed workers. Variants in one of these genes also appear to increase the risk among never-smokers of developing lung cancer due to environmental tobacco smoke exposure.[79]

As people diagnosed with cancer are living longer, the need to monitor the long-term and late effects of the disease and treatment has become apparent. Population-based research and surveillance efforts have revealed that cancer survivors are at elevated risk for neurocognitive problems, premature menopause, cardiorespiratory dysfunction, sexual impairment, infertility, chronic fatigue and pain syndromes, and second malignancies. Many survivors also experience significant negative psychosocial outcomes, including fear of recurrence, poor self-esteem, anxiety and depression, relationship difficulties, and trouble obtaining and maintaining employment and insurance coverage.[80-83] These findings have led

to efforts to identify ways to alleviate the negative long-term effects of cancer treatment. For example, the importance of fertility preservation for patients diagnosed during or before reproductive age increasingly has been recognized and steps have been taken to develop and implement procedures to increase the likelihood that survivors will be able to conceive in the future.[84] Awareness also has grown of the need for survivors to have follow-up plans to guide future health management as well as for policies to protect them from employment and insurance discrimination.[82,83]

Screening and Early Detection Research

Over the past four decades, progress has been made in understanding the cancer screening needs of various populations, assessing screening efficacy, and improving screening and early detection technologies. At this time, however, cancer screening is available for only four types of cancer—breast, cervical, colorectal, and prostate—and most of these tests have notable weaknesses. Further, as the paragraphs below detail, doubt has been raised in recent years about the extent to which routine screening decreases cancer mortality and whether the benefits of some types of screening outweigh possible harms.

Breast Cancer Screening

Breast cancer screening technology and mammographic image quality have improved significantly since the advent of screening mammography in the 1970s.[85] Digital mammography is replacing film mammography in some areas of the United States and it appears likely that digital mammography will all but replace film in the next several years. Digital mammography's advantages include the production of images that can be easily adjusted to improve the contrast between normal and abnormal tissue, the ability to magnify images for closer inspection, more convenient storage and transfer that facilitates comparisons over time, and the use of lower radiation dosages without sacrificing image quality.[86,87] One study of more than 49,000 women found that while the overall diagnostic accuracy of the two technologies was similar, the accuracy of digital mammography was higher among women under age 50, women with radiographically dense breasts, and pre- or perimenopausal women.[86]

Breast magnetic resonance imaging (MRI) screening has been shown to be effective for the early detection of cancer among high-risk women, particularly in the contralateral breast of women who have had cancer in one breast.[88,89] Because of its cost, however, it is not feasible as a screening method for the general population. Other technologies approved by FDA for diagnostic purposes (not screening) include ultrasound, scintimammography, thermography, and electrical impedance imaging.[90,91] Breast ultrasound, for example, is often used as a diagnostic tool focusing on an area of concern; it may help distinguish

between cystic and solid masses and also between benign and malignant masses.[92,93] Screening ultrasound has been limited to women with dense breasts or at higher risk for breast cancer. Its use as a screening tool in the general population is somewhat limited by the need for a well-trained, skilled operator and also by the current lack of standardized techniques and interpretation criteria. In addition, breast ultrasound does not consistently detect microcalcifications and may have a higher false positive rate than mammography alone.[87]

In February 2011, FDA approved three-dimensional mammography (digital breast tomosynthesis, or DBT) in combination with conventional mammography for routine screening and as a diagnostic tool.[94] This combined screening method delivers approximately twice the radiation dose of conventional mammography alone, but the dose remains within the limit established by FDA (3 milligray per exposure).[95] Clinical trials[96-98] have shown that DBT is more sensitive and specific than conventional mammography, resulting in fewer false negative and false positive findings. Thus, DBT may improve early detection of malignancies and reduce the need for additional radiologic diagnostic studies and biopsies that cause unnecessary anxiety and expense for patients whose lesions are found to be benign. DBT was shown to enable radiologists reviewing the images to more accurately visualize the margins and shape of masses (better distinguishing benign masses from cancerous lesions) and the number and location of microcalcifications. In addition, DBT was shown to be three times more accurate than conventional mammography alone in women with dense breast tissue. The actual benefits of DBT imaging remain to be determined as it is disseminated into the community and the breast cancer experience of women screened in this manner is followed over time.

The longstanding debate within both the medical and patient advocacy communities about the extent to which early detection via screening mammography reduces breast cancer mortality—particularly among women aged 40-49 years—flared anew in 2009 when the United States Preventive Services Task Force (USPSTF) released new recommendations for breast cancer screening.[99] The new recommendations countermanded USPSTF's 2002 recommendation for screening mammography every one to two years for women beginning at age 40 years,[100] instead recommending biennial screening beginning at age 50 and ending at age 74. The USPSTF concluded that for women under age 50 the decision to screen should be an individual one, taking into account the patient's values regarding specific benefits and harms. The Task Force further concluded that there was insufficient evidence to assess the additional benefits and harms of screening mammography in women aged 75 years or older. Some critics of the revised recommendations maintain that the USPSTF focused more on the potential harms of mammography than on its benefits, ignoring important scientific evidence supporting the mortality benefit of mammographic screening.[101] They estimate that for U.S. women currently 30-39 years old, annual screening mammography from ages 40-84 years would save 99,829 more lives than screening according to the USPSTF recommendations if all women complied,

and 64,889 more lives with the current 65 percent compliance rate.

In addition, the usefulness of older screening methods—clinical breast examination (CBE) and self breast examination (SBE)—continues to be debated. Some studies of screened populations have found little or no evidence of benefit,[86,102] while others suggest these screening methods do benefit women, albeit less than mammography.[87,103-105] Some reviews of the evidence have been inconclusive regarding CBE and SBE benefit.[106,107] Despite this ambivalent evidence, some breast cancer advocacy and survivor groups in developed countries strongly urge continuation of CBE and SBE, particularly for women who have limited access to mammography. In resource-limited countries, CBE is an important component of early detection strategies, since lacking regular mammographic screening, women with breast cancer tend to present with advanced disease and poor prognoses. Although the studies of CBE in resource-limited countries have been inconclusive, inferential studies suggest that these screening methods may help to reduce stage at diagnosis for at least some women.[108-110]

Cervical Cancer Screening

Papanicolaou (Pap) cytologic testing to detect cervical cancer and precancerous lesions has been in use for more than 50 years and remains the standard of care for cervical cancer screening in much of the world. However, between the early 1970s and mid-1990s, the causative role in most cervical cancers of persistent infection with certain human papillomavirus (HPV) strains was confirmed.[111] Following from this finding, researchers studied the efficacy and cost-effectiveness of screening women with Pap testing compared with HPV testing and conducted trials assessing the performance of combined Pap and HPV testing.[112-114]

Investigators found varying rates of test sensitivity and specificity, but the high sensitivity of HPV testing alone was found in some studies to be augmented only slightly by the addition of Pap

Cancer prevention and screening are fundamental to reducing mortality and morbidity from cancer. So primary care delivery health centers are incredibly important. They all need to have referral networks set in place to provide things like mammograms and colonoscopies and other types of interventions that are meant to screen for cancer.

– Kyu Rhee, Health Resources and Services Administration

testing, suggesting that the cost-effectiveness of cotesting needed further evaluation.[115] Though not reflected in current U.S. screening guidelines, a 2008 review of the research[116] found that HPV testing alone can safely be used for primary screening of women over age 30 years and that with appropriate triage, HPV testing does not substantially increase subsequent diagnostic testing referrals (i.e., colposcopy) and associated health care costs due to false positive test results. HPV testing also is more sensitive than cytology among younger women, but because HPV infections often clear among younger women, subsequent HPV retesting may be safer and more cost-effective than colposcopic examination following an initial positive HPV test.

As with other cancer screening tests, professionals disagree on the optimal type(s) and frequency of cervical cancer screening. Table 1 summarizes recommendations for cervical cancer screening as of March 2012.

Table 1
Summary of Recommendations for Cervical Cancer Screening

Variable	ACS–ASCCP–ASCP Draft 2011	ACOG 2009	USPSTF 2012
Age to start	21 years	21 years	21 years
Testing frequency Age 21 to 29 years (Pap alone) Age 30 years and older Pap alone Pap and HPV co-testing	Every 3 years Every 3 years Recommended but no more frequently than every 3 years	 Every 2 years Every 3 years Allowed but no more frequently than every 3 years	 Every 3 years Every 3 years Every 5 years
Age to stop	Age 65 years after three negative Pap tests or two negative HPV tests in past 3 years	Age 65–70 years after three negative tests in preceding 10 years	Age 65 years after adequate screening
After hysterectomy	Discontinue if no dysplasia or cancer	Discontinue if no dysplasia or cancer	Discontinue if no dysplasia or cancer
Screening after HPV vaccination	Same as when unvaccinated	Same as when unvaccinated	Not addressed

ACOG – American College of Obstetricians and Gynecologists; ACS – American Cancer Society; ASCCP – American Society for Colposcopy and Cervical Pathology; ASCP – American Society for Clinical Pathology; HPV – human papillomavirus; Pap – Papanicolaou; USPSTF – U.S. Preventive Services Task Force.

Sources:
Feldman S. Making sense of the new cervical cancer screening guidelines. NEJM. 2011;365(23):2145-7.
Moyer VA, for the U.S. Preventive Services Task Force. Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. Ann Int Med. 2012; 156(12):880-91.

Colorectal Cancer Screening

Colorectal cancer screening technologies and recommendations also have evolved in recent decades. American Cancer Society recommendations in 1980 called for screening with digital rectal examination (DRE), guaiac-based fecal occult blood testing (FOBT), and rigid sigmoidoscopy.[117] Since then, other organizations have recommended differing CRC screening tests as they have become available, such as high-sensitivity FOBT, colonoscopy, double-contrast barium enema, computed tomography colonography (CTC, also called virtual colonoscopy), flexible sigmoidoscopy, fecal immunohistochemical testing (FIT), and stool testing for DNA mutations. Different combinations of tests and diverse screening schedules, even for average-risk patients, have also been recommended. Table 2 arrays these varied recommendations as of 2010, including the joint American Cancer Society, United States Multisociety Task Force on CRC, and American College of Radiology guideline for screening and early detection of CRC and precancerous adenomatous polyps.[118] As shown in the table, this guideline divides the available tests into two groups—those that primarily detect cancer and those that both detect and prevent cancer.

The table also reflects the lack of consensus in the professional community regarding the best approach(es) to CRC screening. This lack of agreement has been due principally to the lack of randomized trial data on many of the CRC screening methods—particularly colonoscopy—demonstrating either reduced mortality or superiority to flexible sigmoidoscopy as an initial screening procedure.[119] However, a February 2012 study,[120] while not a randomized trial, showed that in a group of 2,600 patients followed for up to 20 years, those who had polyps removed during a colonoscopy had a 53

Table 2

Variation in Current Average-Risk CRC Screening Recommendations from U.S. Organizations

U.S. Preventive Services Task Force

- Annual screening with a high-sensitivity FOBT, or
- Flexible sigmoidoscopy every 5 years, with a high-sensitivity FOBT every 3 years, or
- Screening colonoscopy every 10 years

American Cancer Society, U.S. Multisociety Task Force on CRC, and American College of Radiology

- Tests that detect adenomatous polyps and cancer
  - Flexible sigmoidoscopy every 5 years, or
  - Colonoscopy every 10 years, or
  - Double-contrast barium enema every 5 years, or
  - CT colonography every 5 years
- Tests that primary detect cancer
  - Annual guaiac FOBT with high sensitivity for cancer, or
  - Annual FIT with high sensitivity for cancer, or
  - Stool DNA test with high sensitivity for cancer, interval uncertain

American College of Gastroenterology

- Perferred CRC prevention test recommendation for colonoscopy every 10 years
- Alternative CRC prevention tests recommended include
  - Flexible sigmoidoscopy every 5–10 years
  - CT colonography every 5 years
- Alternative cancer detection tests recommended include
  - Annual Hemoccult Sensa
  - Fecal DNA testing every 3 years

CRC – colorectal cancer; FOBT – fecal occult blood test; CT – computed tomography; FIT – fecal immunohistochemical test.

Source: Hoff G, Dominitz JA. Contrasting U.S. and European approaches to colorectal cancer screening: which is best? Gut. 2010;59:407-14.

percent lower colorectal cancer death rate compared with the general population. These findings have yet to be included in evidence reviews pursuant to screening recommendation updates.

Table 3 compares and contrasts the pros and cons of some of the most frequently used screening tools. It also should be noted that the use of CRC screening methods is influenced significantly by insurer reimbursement policies. For example, while some U.S. insurers cover CTC, the Centers for Medicare & Medicaid Services (CMS) did not cover the procedure for the more than 47 million Americans who were Medicare beneficiaries in 2011, all of whom were of screening age.[118]

Prostate Cancer Screening

Prostate cancer screening (i.e., prostate-specific antigen [PSA] testing with digital rectal examination) has changed very little since it was widely implemented in the late 1980s following publication of a seminal paper[121] on PSA as a serum marker for prostate cancer. What has changed, however, is the recognition—if not consensus—that high-risk populations (e.g., African American men, men with a strong family history of the disease) may benefit from starting screening earlier than the general population.

...the care of prostate cancer patients is among the most disparate and complicated and inefficient that you can imagine. You see an internist and you have a high PSA or they feel something on a physical exam, and then what do you do? And depending on where you get sent first, whether it be a urologist or a radiation oncologist, that may actually chart how you're going to be treated.
– Howard Soule, Prostate Cancer Foundation and The Milken Institute

At the same time, the controversy as to whether PSA screening of men at average risk leads to

Table 3

Advantages and Disadvantages of Colorectal Cancer Screening Modalities

Screening test	Frequency of testing	Advantages	Disadvantages
Fecal occult blood testing	Annual or biennial from 45–50 years	Proven reduction in cancer related mortality; proven cost-effectiveness; ready availability; not limited by health resources	High false-positive rate leading to unnecessary colonoscopy; poor detection of adenomas; frequency of testing; positive test requires further investigation
Flexible sigmoidoscopy	Once-only age 60 years	Once-only test; combined treatment and screening procedure	Examines only distal colon; cancer arising at a later age may be missed
Colonoscopy	Optimal frequency unknown	Examines entire colon; combined treatment and screening procedure	Requires extensive bowel preparation; risks associated with procedure; results are operator dependent
CT or virtual colongraphy	Optimal frequency unknown	Examines entire colon	Requires full bowel preparation; positive test requires further investigation; radiation exposure
Double-contrast barium enema	Optimal frequency unknown	Examines entire colon	Low sensitivity; positive test requires further investigation; radiation exposure

CT – computerized tomography.

Adapted from: Hawkes EA, Cunningham D. Flexible sigmoidoscopy—valuable in colorectal cancer. Nat Rev Clin Onc. 2010;7(9):488-90.

unnecessary treatment has intensified.[122] The USPSTF guideline issued in August 2008 recommended against PSA screening for men aged 75 years and older.[123]

At that time, the USPSTF concluded that the existing evidence was insufficient to assess the balance of benefits and harms of prostate cancer screening in men younger than age 75 years. Since then, however, USPSTF has further examined the evidence[124] and in 2012 issued a new recommendation statement that recommends against PSA screening for all men who do not have symptoms that are highly suspicious for prostate cancer, regardless of age, race, or family history.[125]

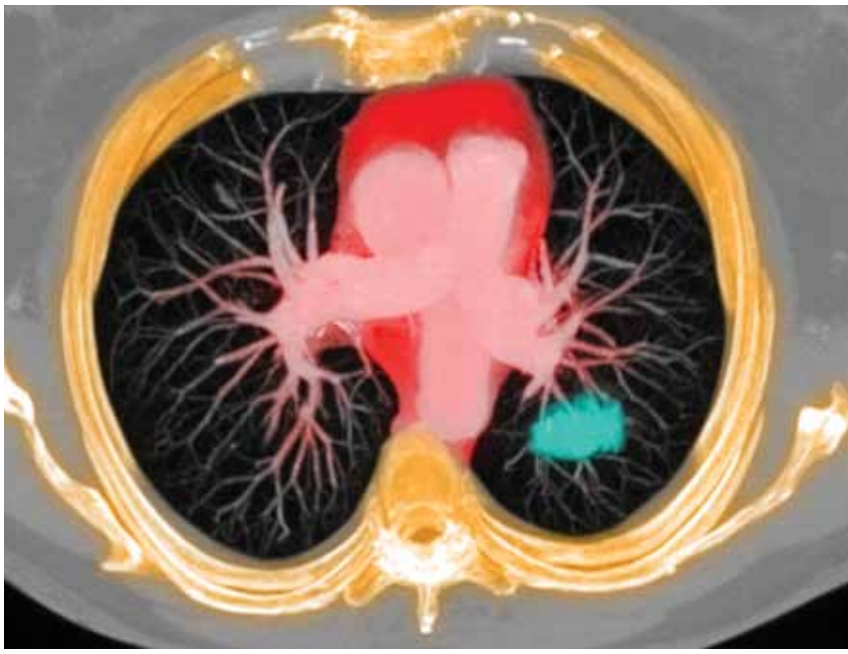
Many men with prostate cancer have an indolent form of the disease that will never become life-threatening—and the great majority of men with a diagnosis of prostate cancer die from other causes[126]—but PSA testing cannot distinguish these tumors from aggressive prostate cancers. All forms of prostate cancer treatment carry the risk of significant side effects (e.g., incontinence, impotence), so unnecessary treatment may profoundly affect patients' quality of life. Until indolent and aggressive prostate cancers can be reliably differentiated, however, a more sophisticated screening tool is unlikely to be developed.

Lung Cancer Screening

A contentious issue in the fight against lung cancer concerns the efficacy of computed tomographic (CT) screening for early-stage disease.[127] The National Comprehensive Cancer Network (NCCN), which develops cancer clinical practice guidelines, published a guideline in 2011 recommending helical low-dose CT screening for selected patients at high risk for lung cancer.[128] In addition, guidelines exist for the management of nodules detected by CT.[129] In recent years, the efficacy and risk-benefit of CT screening for lung cancer have been studied in clinical trials such as the Mayo Clinic CT screening trial[130] and the International Early Lung Cancer Action Project.[131] Though some trials have suggested potential benefit from lung CT screening, none were randomized controlled trials that showed reduced mortality.[132]

In 2011, however, preliminary results of the National Lung Screening Trial (NLST),[133,134] a randomized trial to evaluate lung CT screening in more than 53,000 smokers and ex-smokers aged 55-74 years, demonstrated not only a 20.3 percent lung cancer mortality reduction in the CT-screened group compared with an x-ray-screened group, but also an all-cause mortality reduction of nearly 7 percent. These early results, which cannot be extrapolated to other patient groups, are nonetheless promising. It should be noted that several randomized trials, including the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, have failed to find a benefit from x-ray screening for lung cancer.[135,136] The NLST final study report and ancillary papers are scheduled for publication in 2012.[137]

CT screening for lung cancer has drawbacks that will have to be considered if the final study results uphold the preliminary findings of reduced lung cancer mortality. These include cumulative effects of radiation resulting from serial screening (e.g., potentially increased breast cancer risk among women) and the need for invasive follow-up (e.g., biopsy, surgery) to confirm the benign or malignant nature of detected lung nodules.[127] In addition, to manage the increased workload that a widespread screening program would entail, tools such as computer-aided detection software will be needed to optimize radiologist productivity.[138]



I walk past a high school every day, and at 8:00 o'clock in the morning I see kids out there smoking....and I just walk past there and shake my head and say, "You know, what a tragedy we have here of something that's so preventable."

– Richard Pazdur, U.S. Food and Drug Administration

Further, the widespread adoption of CT screening for lung cancer in the United States will depend on the willingness of third-party payors to reimburse the cost of the tests.[127] It has been estimated that the cost to perform CT scans on the estimated 94 million smokers and ex-smokers in the United States would approach $30 billion annually (at an average Medicare reimbursement of $300/test).[139] Total costs of screening could be even higher, however, since CT is best at detecting nodules in the peripheral areas of the lung but is less effective in identifying centrally located nodules. For some percentage of patients, therefore, CT may need to be combined with other screening modalities such as advanced sputum testing/autofluorescence bronchoscopy,[140] which will increase total screening costs.

Prevention Research

Research to prevent cancer has received far less emphasis than treatment-oriented research, but has nonetheless yielded several important benefits to date. Epidemiologic studies and basic research have supported efforts to prevent cancer and contributed to recently observed reductions in cancer incidence and mortality rates.

Preventing Cancer through Modifiable Lifestyle Behaviors

Studies linking tobacco use and cancer led to public health programs and policy changes that have significantly reduced smoking rates in the United States.[141,142] Lower smoking prevalence has been credited with substantially reducing the incidence of certain cancer types in recent years, most notably lung cancer in men.

Lifestyle behavior changes are difficult to induce and maintain, and much research still is needed to learn how best to motivate healthier lifestyles, including lifestyle changes that are known to reduce cancer risk. In 2007, the Panel reported in detail on current knowledge and research needs related to established and suspected relationships between lifestyle factors and cancer risk;[10] this report contains the Panel's conclusions and recommendations for cancer prevention research and actions at policy, program, and individual levels.

I think everyone knows that environment, when it comes to cancer prevention, is 95 percent of the battle. So it's an area where there are huge research gaps currently. I think we have a system where if you're a hammer, you look at everything like a nail. And so we often need different disciplines to be doing this type of research…. that really requires a different type of thinking.

– Kyu Rhee, Health Resources and Services Administration

Chemopreventive Interventions

A considerable amount of the limited cancer prevention research to date has focused on chemoprevention (i.e., the prevention of cancer by pharmacological agents that inhibit or reverse the process of carcinogenesis).[143] Ideally, a chemoprevention drug should decrease incidence and mortality of the target cancer with minimal toxicity, be cost effective, and provide additional benefits.[144] At this time, however, few chemopreventive agents for cancer exist; most have significant side effects and therefore have been reserved for people with higher than average cancer risk.

Tamoxifen, a selective estrogen receptor modulator (SERM) widely used to treat both early-stage and advanced hormone receptor-positive breast cancer, is among the successes in cancer chemoprevention. Two decades ago, it was found to substantially reduce the incidence of contralateral breast cancer in women treated for breast cancer in one breast. Numerous randomized trials of adjuvant tamoxifen therapy in women with early-stage disease confirmed that tamoxifen significantly improved ten-year survival of women with estrogen receptor-positive (ER-positive) breast cancer and reduced contralateral breast cancer incidence by 47 percent.[145] Subsequent trials bore out the value of tamoxifen for primary prevention of ER-positive breast cancer in high-risk women for whom the risk-benefit profile is favorable.[146] None of the trials found a benefit of tamoxifen in ER-negative breast cancer.

Raloxifene, a second-generation SERM used to prevent and treat osteoporosis in postmenopausal women, has an antiestrogenic effect on the breast, as does tamoxifen.[144] Unlike tamoxifen, however, it does not increase the risk of endometrial cancer[144] but does increase the risk of thromboembolic disease threefold. Thus, like tamoxifen, it is reserved for women at high risk for ER-positive breast cancer. Raloxifene is not effective against ER-negative breast cancer. The Study of Tamoxifen and Raloxifene (STAR) trial[147] directly compared tamoxifen to raloxifene; raloxifene was found to be as effective as

tamoxifen (approximately 50 percent reduction in breast cancer incidence) with fewer side effects.

Research also has shown that aspirin (100 mg daily for a minimum of five years) is effective in preventing subsequent colorectal cancer incidence.[148,149] The mechanism by which aspirin confers this protection has not been proven but appears to be the reduction in precancerous adenomas, possibly by inhibition of cyclo-oxygenase (COX)-2 enzymes.[150] In addition, a review[149] of eight randomized trials of daily aspirin use versus no aspirin originally conducted to assess aspirin's effect on preventing vascular events revealed that aspirin reduced cancer deaths, again with the effect appearing only after about five years, for esophageal, pancreatic, brain, and lung cancers. The effect was more delayed for stomach, colorectal, and prostate cancers; for lung and esophageal cancers, benefit was limited to adenocarcinomas. The overall effect on 20-year risk of cancer death was consistently lower by approximately 20 percent, regardless of aspirin dose, sex, or smoking, but increased with age, peaking at age 65 years. The authors believe that these findings provide evidence for guidelines on use of aspirin and for understanding carcinogenesis and its susceptibility to drug intervention.

Addressing Cancer-Linked Infectious Agents

An estimated 15 to 25 percent of the cancer burden worldwide is believed to be attributable to infectious agents,[151-153] and research on the roles that infectious agents play in specific cancer types is of growing scientific interest. Infectious agents have been associated with nearly 20 cancer types (Table 4).

Thus far, research on the relationships between infectious agents and cancer has led to a number of preventive interventions. For example, infection with the bacterium *Helicobacter pylori* has been identified as an important risk factor for stomach cancer—individuals who are infected have nearly six times the risk for noncardia gastric cancer compared with those not infected.[154]

Table 4

Cancer-Associated Infectious Agents

Infectious Agents	Type of Organism	Associated Cancers
hepatitis B virus (HBV)	Virus	hepatocellular carcinoma (a type of liver cancer)
hepatitis C virus (HCV)	Virus	hepatocellular carcinoma (a type of liver cancer)
human papillomavirus (HPV) types 16 and 18, as well as other HPV types	Virus	cervical cancer; vaginal cancer; vulvar cancer; oropharyngeal cancer (cancers of the base of the tongue, tonsils, or upper throat); anal cancer; penile cancer; squamous cell carcinoma of the skin
Epstein-Barr virus	Virus	Burkitt lymphoma; non-Hodgkin lymphoma; Hodgkin lymphoma; nasopharyngeal carcinoma (cancer of the upper part of the throat behind the nose)
Kaposi sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV8)	Virus	Kaposi sarcoma
human T-cell lymphotropic virus type 1 (HTLV1)	Virus	adult T-cell leukemia/lymphoma
Helicobacter pylori	Bacterium	stomach cancer; mucosa-associated lymphoid tissue (MALT) lymphoma
schistosomes (*Schistosoma hematobium*)	Parasite	bladder cancer
liver flukes (*Opisthorchis viverrini*)	Parasite	cholangiocarcinoma (a type of liver cancer)

Source: National Cancer Institute. Fact sheet: cancer vaccines [Internet]. Bethesda (MD): NCI; [updated 2011 Nov 15; cited 2011 Nov 27]. Available from: http://www.cancer.gov/cancertopics/factsheet/Therapy/cancer-vaccines

A recent study demonstrated that *H. pylori* infection directly damages DNA in the nucleus of gastric epithelial cells, though the mechanism by which this occurs remains unknown.[155] *H. pylori* also is the cause of stomach ulcers.[156] Although a meta-analysis[157] of the few clinical trials conducted to date suggests that population-wide treatment for *H. pylori* would lead to only a modest reduction in gastric cancer risk, knowing the association between *H. pylori* and stomach cancer enables clinicians to target testing and treatment to higher-risk individuals (e.g., those with ulcers or a family history of stomach cancer) and those presenting with symptoms of *H. pylori* infection.

Identifying the role of infectious agents in some cancer types also has led to the development of vaccines to prevent cancer. Widespread vaccination of children in Taiwan against hepatitis B, a major risk factor for liver cancer, has dramatically reduced the large burden of liver cancer in that country.[158,159]

As noted earlier, HPV is the causative agent in most cervical cancers. Two prophylactic vaccines against the highest-risk HPV strains have been approved by FDA. The approvals were based on clinical trials indicating that the vaccines reduce HPV infection and the subsequent development of precancerous lesions and invasive cancer when administered

to girls and young women 11-26 years old before they are exposed to the virus.[160,161] The vaccine is administered in a three-dose series with the second and third doses given two and six months after the first dose.[162] However, a recent study conducted in Costa Rica suggests that two, or even one, dose of the bivalent (HPV16/18) vaccine might confer sufficient immunity.[163]

High-risk strains of HPV also are associated with vaginal and vulvar cancer and precancerous lesions in women, penile cancer in men, and anal and oropharyngeal cancers and genital warts in men and women. A state-of-the-science review regarding HPV vaccination in boys and young men concluded that males 9-26 years of age should be offered vaccination both to reduce the incidence of HPV-related disease in males and to increase immunity among males, thereby reducing the likelihood of high-risk HPV strain transmission to females.[164] In December 2011, the federal Advisory Committee on Immunization Practices (ACIP)[165] approved recommendations for routine vaccination of males 11 or 12 years old with three doses of the quadrivalent (HPV4) vaccine that protects against four of the most common high-risk HPV strains.[166] ACIP further indicated that vaccinations could start as early as age 9 years and that males age 13-21 years can be vaccinated if they have not been vaccinated previously or have not completed the three-dose series. Males ages 22-26 years may be vaccinated, and vaccination of men who have sex with men is recommended through age 26.

The full impact of HPV vaccination on overall cancer incidence and mortality has yet to be realized, as it will be possible to make such assessments only after a whole generation of young people have been vaccinated and their cancer experience is monitored over time. In addition, active HPV infection is suspected of having a role in cardiovascular disease[167] and, over time, may be found to be an agent in other health conditions.

HPV also provides a model for understanding cancer-related infectious agents and developing focused preventive approaches. Investigations of a possible link between sexually transmitted infections and cervical cancer were initiated in the latter half of the 1800s. The first reports characterizing HPV appeared in 1965 and experiments to establish the link between HPV and cervical cancer began in the early 1970s.[111]

In addition to HPV, research on the roles of other infectious agents in cancer continues to yield promising results. In October 2011, two separate research teams found high levels of *Fusobacterium*, an invasive and proinflammatory anaerobic microbe, in tumor samples collected from colorectal cancer patients.[168,169] *Fusobacteria* have previously been associated with inflammatory bowel disease[170] as well as with periodontitis, pericarditis, and thrombophlebitis.[171] Although a causative association has not been established, further research may reveal whether the bacteria are involved in tumorigenesis or early stages of colorectal cancer progression. If so, *Fusobacterium* may offer a target for antimicrobial therapy and/or vaccination to prevent colorectal cancer.

PART II

MOVING FROM INCREMENTAL ADVANCES TO TRANSFORMATIVE INNOVATION

The current focus, priorities, models, and processes of cancer research as it now is conducted have yet to achieve the significant reductions in incidence and mortality and improved quality of life for cancer survivors that the American public has sought through its investment in cancer research. All of these aspects of the National Cancer Program need to be examined, reimagined, and reorganized to better support innovative research with the potential to make possible not just incremental gains, but transformative innovation and progress in cancer prevention and care.

Including both perspectives offered by Panel meeting participants and the findings of additional information gathering, the following chapters highlight barriers constraining transformative, innovative cancer research and recent activities aimed at encouraging and enabling it.

CHAPTER 4

Modifying the Focus and Priorities of the National Cancer Program to Accelerate Innovation and Progress

The extent to which research funders are willing to accept risk (i.e., the possibility that a funded research project may fail) in order to achieve transformative innovation and progress lies at the heart of the NCP's focus and priorities. In the current era of constrained resources, most research funders are sharply risk-averse. To shift the priorities of the NCP to strongly promote innovation in cancer research and achieve more rapid reductions in the national cancer burden, action will be needed in several critical areas that are described in the following paragraphs.

Cancer Research Funding Trends

Cancer remains the disease feared most by Americans,[172,173] and the majority of Americans indicate that accelerating research to improve health—as well as rein in rising health care costs—should be a top or high priority.[25] Americans also are concerned that the United States is losing its global competitive edge in science, technology, and innovation.[26] Despite these widely shared perspectives, funding for biomedical research in the United States has stagnated in recent years. A lack of consistent funding threatens investments in innovation that are crucial to move beyond incremental advancements in scientific knowledge and prevention and treatment of diseases such as cancer.

Federal Government

In the late 1990s, then-President Clinton and the U.S. Congress committed to doubling the NIH budget over five years, resulting in an increase from $13.7 billion in 1998 to $26.7 billion in 2003. This unprecedented surge in biomedical research funding drove dramatic growth in the number of research grants awarded, bolstered infrastructure, and supported expansion of the biomedical research workforce.[174-176] However, shifts in national priorities and an economic recession in subsequent years have created an environment in which NIH and NCI annual budgets have increased only marginally, if at all (Figure 5).

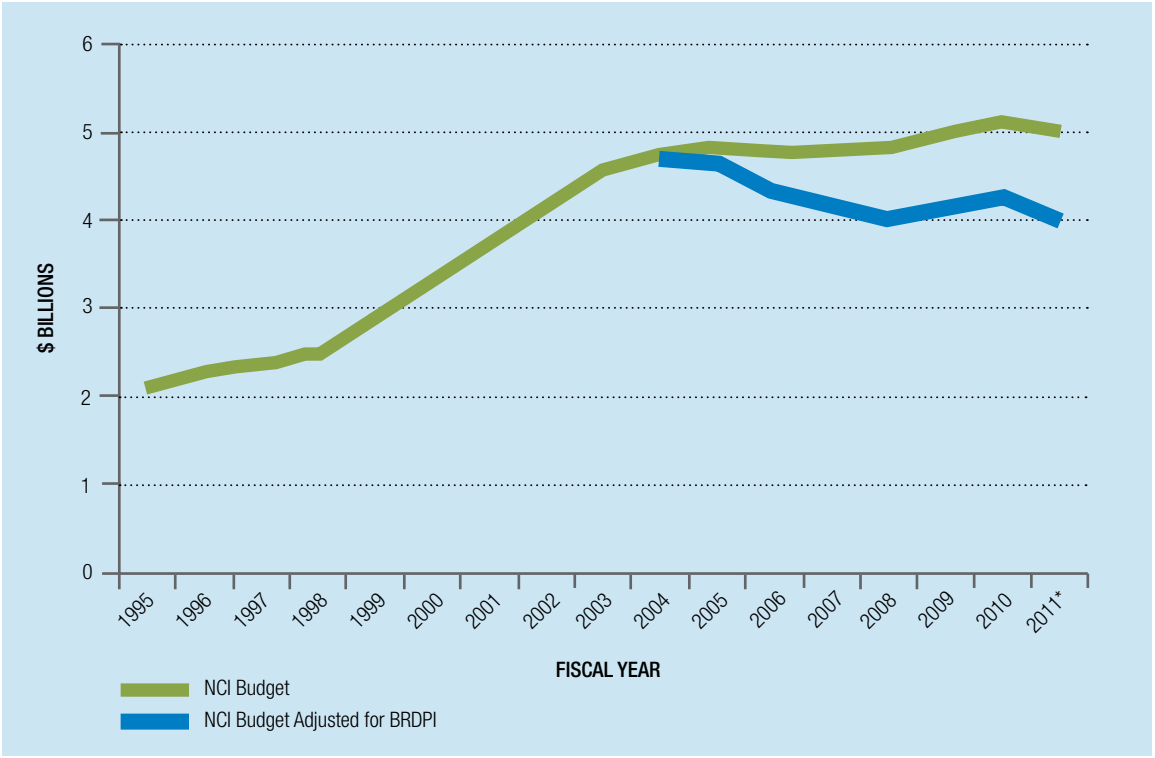
...there is always a tendency for incremental innovation to encroach and ultimately subjugate and eliminate disruptive innovation because, let's face it, it's easier, it's cheaper, and it pays back faster.

– Bernard Munos, Eli Lilly and Company (Retired)

The negligible growth rates are even more troubling when the increasing costs of conducting biomedical research are taken into account. Each year, the United States Department of Commerce Bureau of Economic Analysis provides an estimate of the Biomedical Research and Development Price Index (BRDPI), which measures changes in the weighted average of the prices of all of the goods and services (e.g., personnel costs) purchased with the NIH budget to support research. The annual change in the BRDPI theoretically indicates how much NIH expenditures would need to increase over the same time period to compensate for average increases in prices due to inflation and to maintain NIH-funded research activity.[177] Modest budget increases have failed to match the annual BRDPI every year since 2004, which has resulted in an approximately 15 percent loss in purchasing power between 2003 and 2011 (Figure 5).

Figure 5

NCI Budget, FY 1995–2011



*Budget number for fiscal year (FY) 2011 does not represent the official NCI figure and is based on the full-year Continuing Resolution for the Federal Government for FY2011 passed in April 2011.

BRDPI – Biomedical Research and Development Price Index.

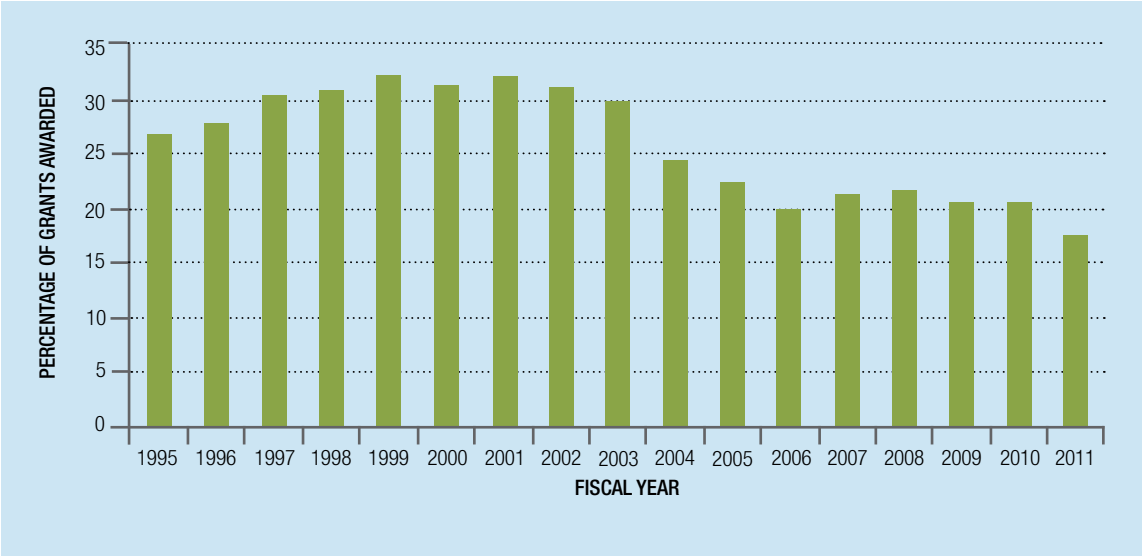
Source: NCI Fact Books, NCI Office of Budget and Finance; BRDPI-adjusted figures are calculated using the 2003 NCI budget as baseline.

NIH and NCI did benefit from funds made available through the American Recovery and Reinvestment Act of 2009 (ARRA). ARRA provided NIH with a total of $10.4 billion over the course of fiscal years 2009 and 2010. A portion of the funds was invested in infrastructure and equipment, but the majority was spent on research programs supported through the NIH Office of the Director or the various NIH Institutes and Centers.[178] NCI received over $1.2 billion in ARRA funds, allowing the Institute to spend an additional $846 million in FY2009 and $411 million in FY2010; research project grants comprised the largest portion of NCI's ARRA spending. ARRA funds also were used to supplement funding for NCI-designated Cancer Centers, kick-start the Institute's drug development platform, and fund 37 promising clinical trials of molecularly targeted therapies through the ACTNOW (Accelerating Clinical Trials of Novel Oncologic PathWays) program.[179]

Although it benefitted key initiatives, the short-lived bolus of ARRA funding was insufficient to change the cancer research funding landscape. The loss of ARRA funds in FY2011, coupled with the estimated 2.9 percent increase in BRDPI, has necessitated difficult decisions in light of the nearly 1 percent decrease in the NCI budget. NCI Director Dr. Harold Varmus announced that the funding reduction will result in about 150 fewer new research project grants (Intra-agency communication, Varmus H to National Cancer Institute staff, 2011 Apr 27), a 5 percent cut in the budgets of NCI-designated Cancer Centers, and budget cuts of 2 to 5 percent for most other existing grants and programs, including intramural programs.[180,181]

Figure 6

NCI Research Project Grant Success Rates, 1995–2011*



*Does not include projects funded through ARRA.

Sources:
Garrison HH, Ngo K. NIH research funding trends FY1995-2012 [Internet]. Bethesda (MD): Federation of American Societies for Experimental Biology; [cited 2012 Mar 13]. Available from: http://www.faseb.org/Policy-and-Government-Affairs/Data-Compilations/NIH-Research-Funding-Trends.aspx

National Institutes of Health. Research project success rates by NIH Institute [Internet]. Bethesda (MD): NIH; [updated 2011 Jun 24; cited 2012 Mar 8]. Available from: http://report.nih.gov/success_rates/Success_ByIC.cfm

The funding instability created by these budget shortfalls has multiple detrimental effects. It is difficult for funded investigators and institutions to plan and conduct their research programs if budgets can be changed from year to year. Inconsistent funding rates also make it more difficult for investigators to establish and/or maintain their laboratories and may make independent research careers untenable for some.

During the budget-doubling period, success rates for NIH grants hovered near 30 percent, meaning that 30 percent of reviewed grant applications received funding (Figure 6).[182] It has been suggested that success rates below 30 percent induce reviewers to reject high-quality proposals, force applicants to spend excess time and energy on rewriting and resubmitting applications, and create an environment averse to innovation.[183] In fiscal year 2011, the success rate for research projects was significantly below this target 30 percent threshold—17.7 percent for applications across NIH and only 13.8 percent for scientists competing for NCI funds.[182]

...it's hard to get [scientists] to think about innovation. I think we beat it out of people in our system because, too often, we only fund the things that have preliminary data [and]...will be successful because you've done so much of the work already. We want to bring it back [to] where it's a brand new idea where "I don't even [know] if it's going to work, but I want to try." That's what we try to foster.

– E. Melissa Kaime, Congressionally Directed Medical Research Programs, Department of Defense

The budgets of other federal agencies engaged in cancer research and care also have suffered in recent years. Notable among these is the Department of Defense Congressionally Directed Medical Research Programs (CDMRP). Since 1992, CDMRP has spent more than $4.1 billion on cancer research[184] focused on breast, lung, ovarian, prostate, and other cancers relevant to military members and their families. Although the addition of the lung cancer program in 2009 represents an encouraging expansion in CDMRP investment, most of the other cancer-related programs have seen their budgets frozen or decreased in the past few years.[185,186] Although CDMRP is considerably smaller than NCI in terms of scope and budget, the

The idea is that innovation can come from anyone and anywhere...
– Yun-Ling Wong, Bill & Melinda Gates Foundation

former is an important contributor to the National Cancer Program, in part because it is committed to funding high-risk/high-gain research that is needed to drive innovation and that is less likely to be funded by NIH.

Voluntary Sector

The philanthropic sector has consistently supported cancer research in the decades since passage of the National Cancer Act.[187,188] Although this sector contributes only a small proportion of total cancer research funding in the United States,[189] its role in fostering scientific innovation should not be minimized. The relative lack of bureaucracy in the small research programs of nonprofit organizations is conducive to nontraditional approaches to peer review and flexibility, both of which facilitate support of unconventional ideas. Independent grants from nonprofit organizations, such as career awards,[190-192] are valuable resources for early-career scientists needing to bridge the gap between postdoctoral work and independent scientific investigation. Some young investigators receive their first independent grants from nonprofit organizations before successfully competing for NIH-funded independent research project grants (R01). (See further discussion of early-career research training needs, p. 82.)

Unfortunately, charitable donation and other funding (e.g., from for-profit entities) levels in general are down, and the funding base for many nonprofit organizations is in jeopardy. The Internal Revenue Service recently reported a drastic decline in charitable giving—a total of approximately 20 percent between the beginning of 2008 and the end of 2009—among Americans during the recent economic recession, a decline significantly sharper than what has been observed in previous downturns.[193]

Several of the foundations that support cancer research have felt the strain of reduced giving and have, in turn, been forced to temper their research programs. American Cancer Society support for research has suffered because of budget cuts. For example, the $148.6 million in research expenditures by ACS in 2010 was considerably less than the $156.4 million and $149.8 million invested in 2008 and 2009, respectively. ACS attributes this trend to a decrease in support from the public and reduced investment income as a result of the economic challenges facing the United States. These budget cuts corresponded with a more than 12 percent decrease in the number of grants awarded between 2008 and 2010.[188] The Leukemia

and Lymphoma Society also saw decreases in contributions in 2010 compared with 2009 and, as a result, contributed only $58.7 million to research awards and grants in 2010, down from $63.5 million in 2010.[194] There are, however, some notable exceptions. Susan G. Komen for the Cure, after experiencing a moderate decrease in contributions in 2009 compared with 2008,[195] saw contributions increase from $189 million in 2009 to $203 million in 2010. The organization increased its spending on research by 7.5 percent in 2010 in addition to spending more on education and screening.[196]

Industry

Pharmaceutical companies have dramatically increased their research programs since the early 1970s. One report estimates that industry accounted for only 2 percent of cancer research funding in the United States in 1974, a figure that ballooned to 31 percent by 1997.[197] Although the magnitude of more recent investments in cancer research is difficult to ascertain, the Pharmaceutical Research and Manufacturers of America (PhRMA) estimated that the pharmaceutical companies in the United States spent $67.4 billion on research and development (R&D) for all diseases in 2010,[198] a more than 40 percent increase since 2004 and more than twice the FY2010 NIH budget. Although this certainly is an enormous investment, the ratio of R&D investment to pharmaceutical sales, which rose dramatically in the 1980s, has gradually declined. In addition, the nature of R&D research conducted by pharmaceutical companies has changed; over the past several decades, investment in nonclinical and preclinical projects has suffered as more money is being spent on clinical trials and regulatory expenses.[199]

If you go to an insurance company and say, "I want you to start to invest in something that will pay off in ten years," they [will] go, "Well, I'll be retired. I'll be gone. Forget it. I'm not going to do it."
– Donald Listwin, Canary Foundation

Variations in Research Emphases of Federal, Voluntary, and Private Sector Funders

Federal Government

Even though the balance of federally funded cancer research continues to be weighted heavily toward basic research, continued investment in basic research and supportive technologies is needed in order to build on what has been learned in recent decades. Much remains to be understood about cancer, and basic research is the source of new discoveries that may eventually lead to advances across the cancer continuum as well as to a better understanding of other human diseases. Similarly, clinical research requires ongoing investment to bring basic science advances to the bedside.

Particularly among public research funders, risk aversion is strong; unfortunately, this stance discourages innovation. As stewards of taxpayer dollars, public sector funders hesitate to fund research that is considered high risk (even if it also is potentially high reward). Research projects that fail open the funding agencies to criticism from the public and policy makers that could jeopardize already scarce funding. Notable exceptions include cancer-related research funded by the DoD CDMRP[185] and biomedical research funded by the Defense Advanced Research Projects Agency (DARPA).[200] Both agencies focus specifically on attracting and funding research proposals that have the potential for groundbreaking advances.

In an effort to spur innovation in cancer research, in January 2011 NCI launched an initiative, the Provocative Questions project,[201] to engage the research community, advocates, health professionals, members of Congress, and other constituencies in assembling a list of novel questions intended to help guide NCI and its scientific communities in efforts to control cancer through laboratory, clinical,

and population research. Based on the input received, 24 Provocative Questions (PQs) were selected for inclusion in a Funding Opportunity Announcement.[202] The Request for Applications (RFA) notes that most of the PQs fall into three broad categories. The first type of question brings ignored or neglected cancer-relevant problems back into focus. These problems typically relate to intriguing older observations or issues that cancer researchers may have taken for granted but for which satisfactory, rigorous research answers are still lacking. A second category of PQs is built on more recent findings that are perplexing or paradoxical, revealing important gaps in current knowledge. Research answers to this type of PQ have the potential to reshape several of our current key conceptions about cancer. The third category of PQs reflects problems that previously were perceived as particularly difficult to explore but which have become open to investigation because of recent scientific discoveries and technical advances. The first applications under this RFA were submitted in November 2011; funded projects are scheduled to begin in July 2012.

We picked the very visionary scientists out there, the senior clinicians, senior scientists, senior consumers as well—people living with the disease—and asked them, "What is the greatest need?" And we do this each and every year, because things change....We target those gaps and fund those underrepresented and underfunded areas, and then we target very innovative research.

– E. Melissa Kaime, Congressionally Directed Medical Research Programs, Department of Defense

Voluntary Sector

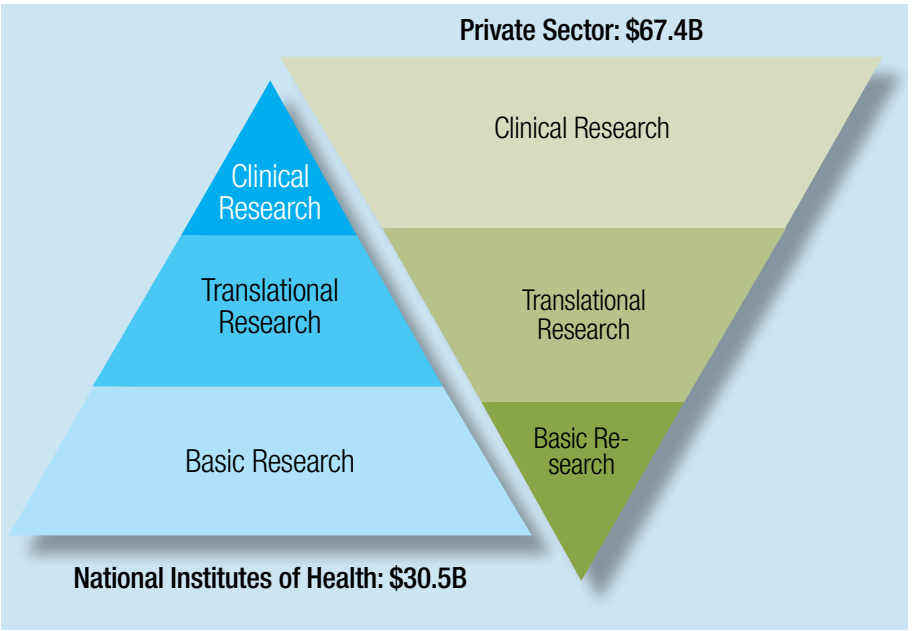
Major nonfederal cancer research funders also focus heavily on basic research. For example, of the intramural and extramural research supported by the American Cancer Society in FY2010, nearly 60 percent was devoted to basic and preclinical research (42.6% and 14.6%, respectively), with significantly less focus on epidemiology (8.8%), psychosocial and behavioral research (16.9%), and health policy/services research (9.6%).[188]

Susan G. Komen for the Cure also invests heavily in biologic and treatment-related research (23% and 35%, respectively, in FY2008-2009), although the organization's portfolio has shifted in recent years following a reprioritization. Areas of increased investment include early detection, diagnosis, and prognosis (18% in FY2008-2009); prevention (7%); and cancer control, survivorship, and outcomes (7%).[203]

Industry

The priorities of pharmaceutical and biotechnology companies, the other major source of cancer research funding, are profit driven. Because their goal is to develop revenue-producing products, they are more likely than public sector agencies to fund translational research and clinical trials compared with basic research expenditures. Figure 7 illustrates the difference in the emphases of public (specifically NIH) and private sector research and development.

Figure 7
Government and Industry Research and Development Emphases



Spending is for 2009. Private sector is estimated.

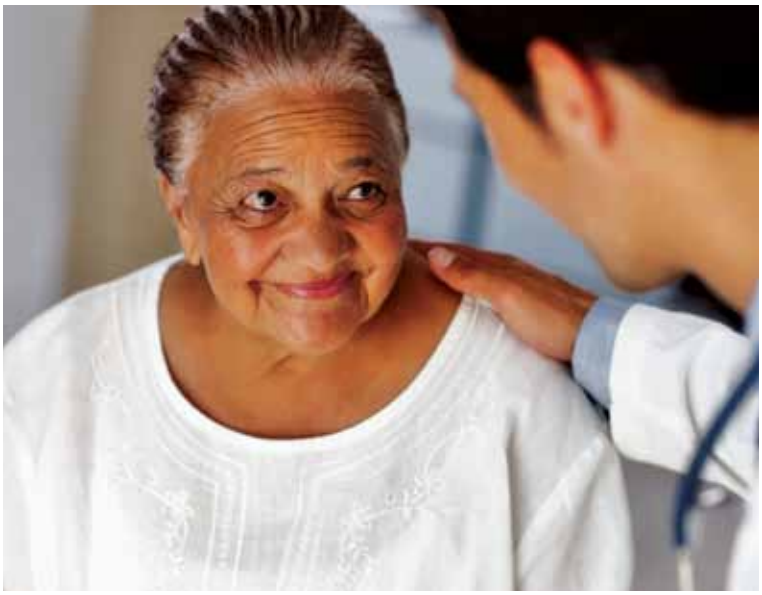
Adapted from: Pharmaceutical Research and Manufacturers of America. Chart pack: biopharmaceuticals in perspective. Washington (DC): PhARMA; 2010 Fall, slide 19.

Pharmaceutical Research and Manufacturers of America. Pharmaceutical industry profile 2011. Washington (DC): PhARMA; 2011 Apr.

It is noteworthy that many pharmaceutical companies previously had robust discovery programs, but as drug development costs have skyrocketed, many have come to rely on discoveries from federally funded basic research as the principal source of promising agents, genes, or molecules that may represent therapeutic targets. Industry now focuses more heavily on translational research and clinical trials required to gain FDA approval of new therapies.

Research Areas with Limited Emphasis

Recognition is growing that the ongoing emphasis on basic and treatment research has occurred at the expense of other types of cancer research, some of which could have more immediate effects on the national and global cancer burden. Investments in translational, behavioral, and population-based research are needed to expand upon the knowledge gained through basic and clinical investigations as well as inform development of new interventions. More emphasis also is needed on areas of the cancer continuum beyond disease treatment, including prevention and early detection research, as well as research on the long-term and late effects of treatment that often plague cancer survivors. Of particular importance is the need for an expanded understanding of the factors that influence cancer risk and progression. In this regard, a previous Panel report[12] emphasized the need to better elucidate the roles of environmental factors in cancer etiology; technologies that allow exposure assessment will contribute to this endeavor, as will investment in epidemiologic studies. Although some investments in such research have been made, when compared with biology and treatment research, these areas continue to comprise a much smaller component of the cancer research portfolios of most major funding organizations in the United States, Europe, and Canada.[189] As a result, the knowledge base in these research areas is less well developed, as is the range of tools and interventions that could be developed with a more robust research investment.



...one thing that strikes me at a meeting like this, and many other good meetings, [is] that people somehow or another always get to conversation about how important prevention is, and then we leave the meeting and we look at the statistics and how the NCI spends its money, and the needle on prevention doesn't seem to [move] all that much.

– William Hait, Ortho Biotech Oncology Research & Development

In addition, it is clear that the advances in cancer prevention and treatment that have been achieved have not reached all populations equally in this country or in other areas of the world.[37] Applied research in communications and dissemination is needed to ensure that effective interventions are optimally implemented. NCI recently launched initiatives in both of these areas,[204,205] but historically there has been little recognition that a concerted effort must be made to ensure that the fruits of biomedical research are applied equitably to achieve optimal societal benefit.

Making Prevention a Research Priority

Testimony provided to the Panel emphasized that the best approach to reducing the national cancer burden is to prevent cancers from ever occurring. As discussed earlier, however, most cancer research currently emphasizes drug development and surgery to achieve tumor shrinkage, improve disease management, and develop salvage therapies. Although treatment advances are needed, a markedly greater emphasis on cancer prevention, early detection, and early intervention is crucial to reducing the national cancer burden.

An active area of the cancer prevention research conducted to date has centered on chemoprevention and vaccines. While there have been successes (e.g., raloxifene, hepatitis B, HPV; see Chapter 3), clinical trials and intervention development in this area have been hindered by numerous ethical concerns[206-208] about administering drugs with potential side effects to ostensibly healthy, asymptomatic individuals. Such issues include weighing anticipated social benefits and risks, defining the risk status of study participants, ensuring that participant recruitment and selection are fair, and ensuring informed consent.

Cancer prevention related to lifestyle behaviors has received some attention; most notably, interventions to deter initiation of tobacco use and aid smokers' cessation attempts. As one of the Panel's previous reports[12] discussed in detail, however, relatively little research has focused on opportunities for understanding and preventing cancers related to environmental exposures.

In June 2011, the Department of Health and Human Services developed the first-ever National Prevention Strategy,[209] as required by the Patient Protection and Affordable Care Act (PPACA, P.L. 111-148). Though not limited to cancer prevention, the strategy underscores the roles of virtually all federal and state/local agencies, private industry, and others in reducing the burden of disease in the United States. It also recognizes the potential savings—in health care costs, national productivity, and human suffering—that can be achieved with investments in prevention.

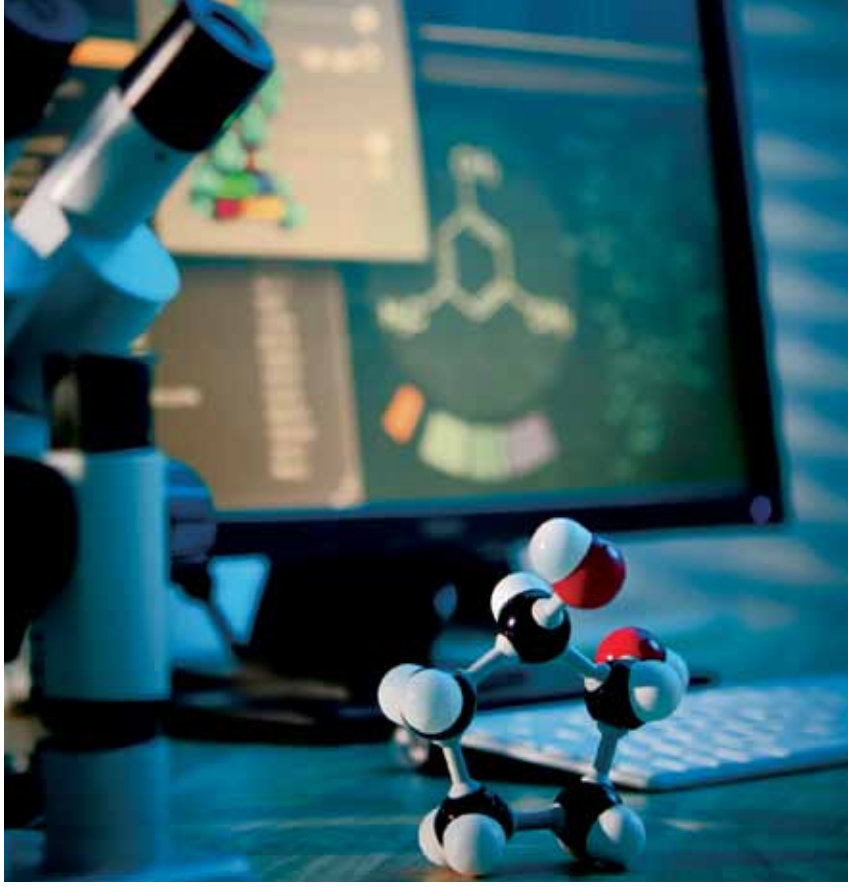
PPACA also provided funds for the creation of Clinical Preventive Services Research Centers.[210] In October 2011, three-year grants totaling $4.5

million were awarded to establish three prevention research centers that, consistent with the National Prevention Strategy, will advance the national research agenda in clinical preventive services in three specific areas: (1) health equity—to reduce disparities in the use of clinical preventive services; (2) patient safety—to better understand the risks and harms associated with clinical preventive services; and (3) health systems implementation—to improve the delivery of evidence-based clinical preventive services. These actions represent important steps toward expanding prevention research and recognizing its importance not only in cancer, but in the nation's health as a whole.

Changing the Focus of Biomarker Research

The United States has made considerable investments in cancer biomarker research, and this continues to be an area of intensive study. NCI's Early Detection Research Network (EDRN)[211] was formed in 2000 to bring a collaborative approach to the discovery and development of early detection biomarkers. A consortium of over 300 investigators and 40 private or academic institutions, EDRN is involved in both developing and validating early detection biomarkers for cancer. EDRN participants represent divergent scientific disciplines including genomics, informatics, and public health. Federal collaborators include other NCI programs, the National Institute for Science and Technology, CDC, FDA, and the Jet Propulsion Laboratory at the National Aeronautics and Space Administration, which houses the EDRN informatics center.

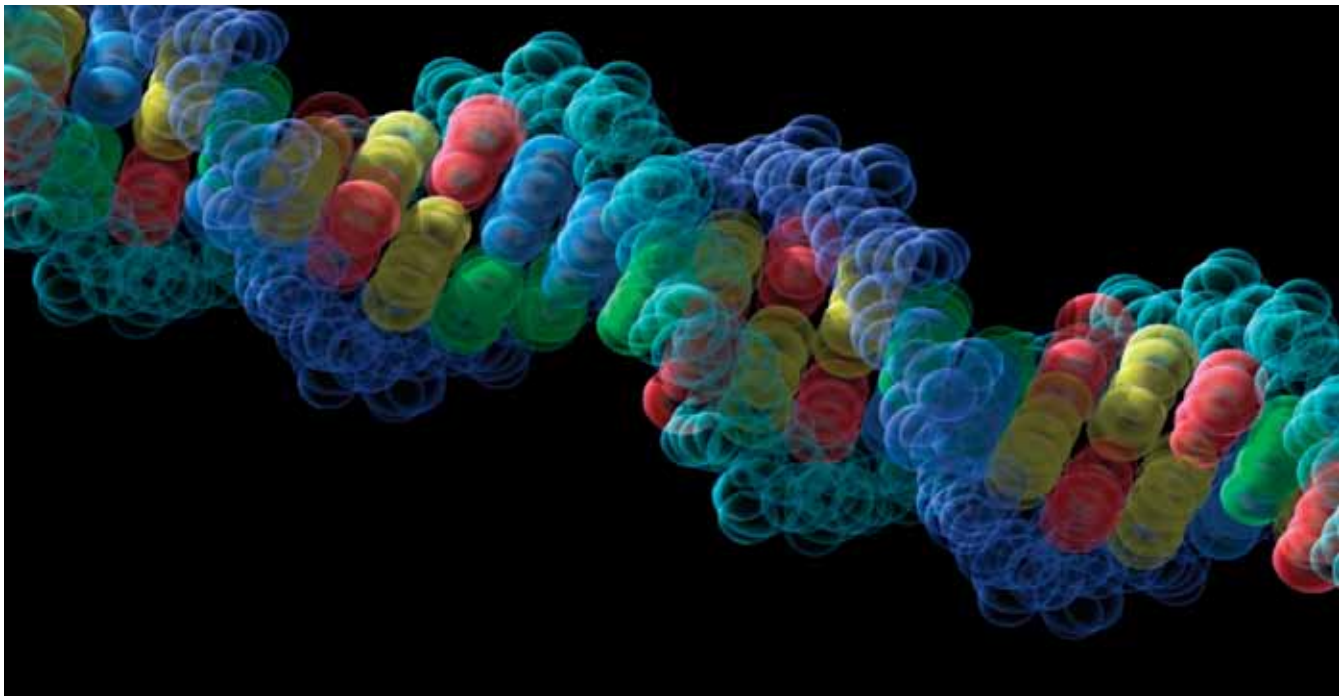
Similarly, the Foundation for the National Institutes of Health (FNIH), a nongovernmental, nonprofit organization, was instrumental in developing—and now manages—the Biomarkers Consortium, a public-private partnership of 28 companies and 34 nonprofit organizations, advocacy groups, and trade associations. Using new and existing technologies, the Consortium endeavors to discover, develop, and qualify biomarkers for disease prevention, early detection, diagnosis, and treatment.



...we really need to come up with innovative ideas between observational data and the gold standard randomized clinical trial. There needs to be something in between, and whether that's the use of biomarkers or whether that's adaptive clinical trial design, there needs to be something in between or else we're really never going to be able to realize these preventive type[s] of strategies and...get them regulatory approval.

– Scott Campbell, Foundation for the National Institutes of Health

Through these and other efforts, hundreds of potential biomarkers have been discovered for potential use in drug development and for assessing cancer risk, likely treatment response, and actual treatment response. However, most of the markers identified to date have yet to be tested sufficiently, or at all, to determine their specificity and sensitivity in clinical settings. Speakers at Panel meetings urged a greater emphasis on validating the diagnostic and early detection utility of biomarkers that have been identified compared with the current emphasis on research to discover new markers. It was pointed out that some of the markers already discovered may turn out to be of little or no clinical value. This has been the case in ovarian cancer; dozens of potential markers for the disease have been identified over the past decade, but most could not be validated.[212] At the same time, new markers continue to be needed in underdeveloped areas. For example, markers and



...we have to find ways to improve our understanding of early-life susceptibility to carcinogens in the environment. And I would suggest that the high-throughput toxicity testing assays that are currently under development...across the United States are going to be tremendously important to help us get a better understanding of cancer risks and the environment....

– Peter Grevatt, Environmental Protection Agency

metrics that measure environmental exposures that increase cancer risk are needed, particularly those related to early-life exposures to environmental carcinogens.

In addition, some biomarkers currently in use are known to be of limited specificity and sensitivity, and better markers of these diseases, particularly early-stage tumors, are urgently needed. Ovarian cancer also is an important example in this regard. CA-125, a marker for ovarian cancer, is neither sufficiently sensitive nor specific to this disease; other conditions (e.g., other gynecologic and nongynecologic cancers,[213] endometriosis[214]) can cause an elevated CA-125 level, and some women with advanced ovarian cancer may have normal CA-125 levels. Similarly, some available markers are insufficient to discern the potential lethality of the tumor. A rising PSA level, for example, may indicate the presence of prostate cancer but it cannot reveal whether the tumor is aggressive or indolent. Moreover, elevated PSA does not necessarily mean that a malignant tumor exists; it can be a sign of benign prostatic hyperplasia (enlargement), a very common noncancerous condition in older men.[215,216]

Looking for biomarkers of early-stage disease by studying late-stage tumors may not be an optimal approach, since biomarkers of early-stage disease may be different from those that characterize late-stage tumors and not just lower levels of markers of advanced disease. At this time, however, limited availability of early-stage tumor specimens and body fluids from these patients are a barrier to more rapid progress in early detection biomarker development.

Biomarkers of epigenetic changes (heritable changes that occur without changes in the DNA sequence[217]) such as DNA methylation and histone modification are being identified and may have

considerable potential to advance cancer detection and guide treatment.[218] Further, in contrast to genetic mutations, epigenetic changes (also called epimutations) are reversible. Drugs that could restore normal function to cancer cells by inhibiting enzymes of the epigenetic machinery are being researched aggressively. To date, four such drugs have received FDA approval, but it is predicted that the nascent field of epigenomics, enabled by high-throughput and next-generation sequencing technologies, will become an increasingly important tool for achieving personalized cancer detection and care.[218]

Managing Cancer as a Chronic Disease

Until quite recently, cancer treatments focused almost exclusively on total and permanent eradication of disease (i.e., cure) through the use of surgery, escalating doses of cytotoxic agents, and radiation. Achieving this goal with some consistency, however, has been possible in only a small number of cancer types (e.g., thyroid, testicular, cervical) and generally only when the disease is detected and treated in its early stages. For most cancer types, cure has been elusive. Containing cancer growth for long periods of time has likewise proven to be extremely difficult, since most cancers become resistant to available therapies.

Through many years of intensive research, several hallmark characteristics of cancer—distinct, atypical cellular capabilities acquired during tumor development—have been identified. These traits were described in 2000[219] and subsequently have become more fully understood; possible additional hallmarks, as well as enabling characteristics, also are being identified.[220] It is now known that cancer cells have the ability to switch from one acquired mechanism that promotes growth or ensures survival to another such mechanism when the first is blocked by a therapeutic agent. This ability is the basis of one form of cancer drug resistance and explains why a given therapeutic agent may have only transitory beneficial effects and also why multiple hallmark traits must be targeted simultaneously.

There is a misbehavior and disruption of the genome and its structure and its organization and its dynamics that is incredibly complex and very heterogeneous, patient to patient and group to group. And that learning is, I think, finally evolving the scientific field towards this notion of individualization and also looking [at] this as a disease of tissues and organs and organisms, as well as a disease of cancer cells. It's going to take that more holistic, comprehensive, call it a systems biology approach....

– Edward Benz, Jr., Dana-Farber Cancer Institute

Hallmark Characteristics of Cancer

Establish Hallmarks:

- Resistant to cell death (apoptosis)
- Can sustain proliferative signaling
- Insensitive to growth suppressors
- Limitless ability to replicate
- Can induce and sustain blood vessel development (angiogensis)
- Can activate tissue invasion and metastasis

Emerging Hallmarks:

- Can alter energy metabolism to fuel cell growth and division
- Able to evade immune destruction

Enabling Characteristics:

- Genome instability and mutation
- Tumor-promoting inflammation

Sources:
Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100:57-70.

Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144:646-74.

Numerous researchers are now using these insights to find ways of managing cancer as a chronic disease, either by driving the cancer into remission (i.e., little or no sign of disease, though cancer is still present in the body and relapse is possible[221]) or maintaining detectable tumors in a static state through the use of agents that target the hallmark characteristics of cancer. These approaches are to some degree being informed by the thought that eradicating most metastatic cancers is likely impossible.[222]

...we have to start to think of the patient as a system—and not 50 percent reduction of the cancer as the goal state, but health as [the] goal state.

– David Agus, University of Southern California

Enabling patients to live with no or minimal symptoms of disease and avoiding morbidity due to toxicities that may be induced by long-term continuous or periodic maintenance treatment are key challenges to managing (rather than eradicating) cancer.[223] These challenges could be met if aggressive tumors could be better distinguished from less-aggressive tumors. This would enable physicians to make better treatment decisions; for example, they could treat less-aggressive tumors with lower drug dosages.[223] It can reasonably be anticipated that with continued research, effective cancer management approaches will become available to enable patients with diverse cancer types to survive for many years with a good quality of life.

At this time, however, managing cancer as a chronic disease often means managing long-term, often complex physical and psychosocial morbidities resulting from the cancer itself or its treatment.[224] Some researchers and health care providers are exploring holistic approaches to controlling patients' cancers and treatment side effects, including targeted therapies, lifestyle modification (e.g., nutrition, exercise), and complementary therapies such as mind-body interventions. Research to evaluate the impact of such approaches to cancer management is still in its infancy. Effective cancer management also requires ongoing surveillance (e.g., screening), coordination of ongoing follow-up care (e.g., survivorship care planning, provider communication), and a diverse range of interventions such as psychosocial (e.g., stress management; employment and insurance issues), practical (e.g., transportation, household), and caregiver support.[83] In these areas, too, much remains to be learned.

Taking a Systems Approach to Cancer Treatment

A systems biology approach is needed to understand cancer in the context of the whole patient (i.e., shifting from a tumor-specific focus to one that is person-specific). Cancer exists not in isolation but as part of a hugely complex system—the human body.

One Panel meeting participant[225] maintained that a major flaw in the direction of cancer research has been the emphasis on understanding cancer as primarily a genetic aberration. Instead, cancer needs to be viewed as it relates to the system within which it lives, and intervention should be aimed at controlling the tumor by controlling the system (i.e., changing the soil affects how the seed grows).

For example, bisphosphonates—a class of drugs that prevents bone loss and is commonly used to prevent and treat osteoporosis—have been shown to reduce the risk of skeletal-related events (e.g., fracture, spinal cord compression, bone pain, hypercalcemia) that often accompany metastatic disease and can significantly diminish quality of life and potentially reduce survival. In 2002, FDA approved intravenous use of the bisphosphonate zoledronic acid to treat patients with multiple myeloma and bone metastases from any solid tumor.[226] Bisphosphonates also can be used to reduce the bone loss caused by some common cancer therapies (e.g., therapies that deplete estrogen in breast cancer patients).[227] Although the available evidence is inconsistent, bisphosphonates also may delay disease progression in some instances. A subgroup analysis of the large Phase III Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) trial[228] found that zoledronic acid reduced risk of relapse and increased survival among postmenopausal patients. In addition, the Austrian Breast and Colorectal Cancer Study Group 12 (ABCSG-12) trial[229] found that zoledronic acid was beneficial in premenopausal women whose therapy included the use of drugs that reduce reproductive hormone production.

Another bisphosphonate, sodium clodronate, has been found to improve overall survival in men with metastatic prostate cancer who are beginning hormone therapy, although no benefit was observed among men with nonmetastatic disease.[230] A 2011 study[231] found that denosumab, a monoclonal antibody, is superior to zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer. Denosumab was approved for prevention of skeletal-related events in patients with bone metastases from solid tumors.[232]

In some cases, the observed benefits of bisphosphonates may be due to the effects of the drugs on bone cells, but preclinical studies suggest that these drugs also may inhibit angiogenesis, activate antitumor immune responses, and directly inhibit cancer cells by inducing cell death and/or reducing invasive behaviors.[233] Additional research, including data from ongoing clinical trials, is needed to clarify the role of bisphosphonates as adjuvant therapies for cancer.

Panel meeting participants also noted that the mechanisms of action of many anti-cancer drugs are not known, nor is it clear in many cases that the drug actually reaches the tumor cells. A problem in treating brain cancers, for example, has been the inability of many anticancer agents to cross the blood-brain barrier. However, bevacizumab, an antibody molecule thought to be too large to breach the blood-brain barrier, produced dramatic responses in advanced brain cancer patients in Phase II trials.[234-236] The beneficial effect occurs because bevacizumab binds vascular epidermal growth factor (VEGF), lowering the interstitial fluid pressure of the tumor and reversing abnormalities in tumor blood vessels. This example, and those in the preceding paragraph, amply demonstrate how little is still known about how the human body works.

Another key problem in cancer research as it is conducted today is the predominance of a point approach rather than a systems approach. Measuring the status of a patient's tumor or his/her symptomology at a single point in time is of limited value. Tools are needed to enable continuous system (i.e., the body) monitoring to detect changes well before they exhibit as symptoms. This will allow for more rapid intervention to improve the function of the system. In addition, clinicians must have a framework for evaluating and using the data generated by such tools. The goal should be health, not tumor shrinkage.

If there's anything that we should be worried about as cancer patients and focused on, it is the problem of metastases. Nine of ten patients die as a consequence of their cancer spreading, and it's really that biology that we still know way too little about, and we're making investments all along the cascade [of steps enabling metastasis].

– Robert Urban, Massachusetts Institute of Technology

One Panel meeting speaker[237] noted that thousands of cancer researchers are studying specific events (e.g., cellular transformation, metastasis), biochemical processes (e.g., cell signaling), or other tightly defined aspects of cancer. However, this work is not taking place in the context of a systems model of the problem, with researchers working in a coordinated fashion (ideally, in multidisciplinary teams) toward a common goal of creating and implementing clinically effective solutions.

CHAPTER 5

Rethinking Research Processes to Accelerate Progress and Encourage Innovation

Established research processes and related actions—including grant application and peer review mechanisms, publication preferences of scientific journal editors, and disincentives to participating in team science and multi-institutional collaborations—discourage innovation and slow progress against cancer. To enable the transformative research advances that will accelerate patient outcome improvements, these processes need to be reconsidered and redefined to identify problems and establish more productive approaches.

Adopting Grant Application, Peer Review, and Funding Models that Encourage Innovation

This section describes aspects of the NIH grant application and funding process that discourage innovation as well as activities designed to ameliorate some of these problems, particularly in translational research. Alternative grant application, review, and funding models that encourage and support the participation of young biomedical scientists and investigators from nontraditional cancer research disciplines also are described.

NIH Investigator-Initiated Grant Applications, Peer Review, and Funding

Despite recent attempts to streamline the NIH application process, including shortened applications, improved alignment of the application with review criteria, and revised instructions for the content of each section,[238,239] the lag between application submission, award notification, and receipt of funding still is exceedingly long. These delays may jeopardize the ability of principal investigators (PIs) to hire and, in the case of "continuation grant" applications, retain key research staff and avoid interruption or cessation of laboratory or clinical operations.

The current application and review process for National Institute of Allergy and Infectious Diseases (NIAID) R01 grants is generally reflective of the revised R01 grant process across all NIH Institutes.[240] NIAID specifically notes on its Web site that for an application funded on its first try, applicants should plan on at least 21 months from "writing to award," but much longer if a resubmission is necessary, as is typically the case. The Institute further notes that, often, the longest wait is for funding, which depends on factors such as the application's score and timing of the Institute's budget for the fiscal year.[240]

...in the 40 years since the National Cancer Act, the age at which an investigator gets his/her first independent research grant has increased by almost a decade. This is not because they are training ten years longer. This is because of issues in funding that have led to loss of small grants in the middle. This kind of problem can drive young investigators to other fields. We can't afford that.
– Judy Garber, American Association for Cancer Research

Young scientists are particularly disadvantaged in the NIH grant application and peer review process, which favors established investigators over young scientists who could bring fresh perspectives to answering important cancer research questions (see additional discussion, p. 82. Most young investigators' NIH grant proposals are rejected numerous times before being accepted for funding. Typically, investigators are expected to have

It's easy to keep the old things going. It's harder to move money out of the old things and get aligned behind a set of new proposals.

– Harold Varmus, National Cancer Institute

extensive background data and to have virtually conducted the study already in order to receive funding. The protracted process of revising and resubmitting proposals can drive talented individuals to seek employment in industry or abandon careers in research entirely. Moreover, and quite importantly, these dynamics strongly discourage young investigators from proposing higher-risk research, even if the potential reward might be a transformative leap in progress.

While some changes (e.g., establishment of the NIH Common Fund's Director's Transformative Research Award Initiative[241]) have been made to address weaknesses in the peer review system that affect researchers regardless of career stage, it remains the case that some research proposals may be assessed by peer review panels that lack the necessary expertise to fully understand and provide a fair review of high-risk or unconventional proposals, or proposals related to newly emerging technologies.

Other Grant Application, Review, and Funding Models

Other research models have been designed specifically to encourage and fund innovative studies that, it is hoped, will have a transformative impact on knowledge in a given field and subsequently benefit the population. Underlying all of these funding mechanisms is the critical recognition that studies exploring innovative ideas tend to have a higher failure rate than lower-risk projects aimed at incremental advances. In these funding models, however, such failures do not reflect negatively on the researcher, since much can be learned from well-designed experiments that do not yield expected results.

The Howard Hughes Medical Institute (HHMI) Investigator Program offers one such research model that specifically encourages investigators to "push the boundaries" in their fields. A 2010 study[242] assessed the effect of incentives built into different funding mechanisms on scientific creativity. Specifically, the study compared the productivity and impact of research ideas and findings generated by HHMI-funded investigators with that of scientists with equivalent seniority and credentials (in the same subfield of research) funded by NIH investigator-initiated R01 grants. Table 5 summarizes key differences in these funding mechanisms.

The study authors conclude that, as measured by the number of high-impact publications, the HHMI investigator program—which rewards long-term success, encourages intellectual experimentation, and provides detailed evaluation and feedback to its researchers—leads to substantially higher levels of breakthrough innovation compared with NIH R01 funding. The authors emphasize that these findings do not constitute a critique of NIH and its funding policies, and acknowledge that NIH exploratory grants appear to stimulate creativity in this setting and that NIH operates under political constraints that do not encumber private foundations. They question, however, how easily and at what cost the exploratory component of the NIH portfolio could be scaled up to better encourage innovation.

Underlying the philosophy of the biomedical research grant program sponsored by the Bill and Melinda Gates Foundation is the conviction that anyone can have a good idea. With a blinded application process, young investigators are indistinguishable from more established researchers and individuals from diverse disciplines are on equal footing. Grant proposals are limited to two pages and inclusion of preliminary data related to the proposed study is discouraged. Further, instead of traditional peer review, applications can have champions (i.e., reviewers are each allowed to select one project for funding; these selections cannot be overridden by other reviewers).

Table 5

Key Characteristics of HHMI and NIH R01 Grant Mechanisms

Characteristic	HHMI Investigator Program	NIH R01 Grants
Award cycle	5 years	1-5 years; average 3.6 years
Grant renewal	Typically renewed at least once	Renewal dependent on success of initial grant project
Tolerance of project failure	High	Low
Feedback to researchers	Highly detailed	Limited depth
Focus of award	Researcher's talent	Project with predefined deliverables
Flexibility to change research direction/ resource allocation based on early results	High, encouraged	Limited

HHMI – Howard Hughes Medical Institute; NIH – National Institutes of Health.

Sources:
Azoulay P, Zivin JSG, Manso G. Incentives and creativity: evidence from the academic life sciences. Cambridge (MA): National Bureau of Economic Research; 2010.

Manso G. Motivating innovation. J Finance. 2011;66(5):1823-60.

National Institutes of Health. NIH Competing Research Project Grants (RPGs): average project period and number and percent of total awards by NIH Institutes/ Centers, fiscal year 2011, Table #211. Bethesda (MD): NIH; cited 2012 Feb 20. Available from: http://report.nih.gov/FileLink.aspx?rid=557

At the federal level, DARPA, an agency of DoD has long been a leader in supporting high-risk, innovative research with transformative outcomes (e.g., the Internet, personal and supercomputing, alternative energy technologies) that continue to change modern life;[243] in fact, its only charter is "radical innovation." DARPA typically focuses on short-term (2- to 4-year) projects conducted by small, purpose-oriented teams. Among the numerous health-related discoveries supported by DARPA are digital x-rays, advanced prosthetics development, and the Pictorial Archiving Communications System (PACS). PACS revolutionized medical image storage and sharing, making remote diagnosis possible and providing one of the most essential components of electronic health records (EHRs). DARPA has been particularly successful in facilitating the application of military-oriented research findings into products useful to the civilian population.

Like the Gates Foundation grant program, biomedical research supported by DoD's CDMRP employs a blinded application process and focuses on encouraging and funding innovative research ideas. In addition, CDMRP review groups include consumer and advocate members. Consumer reviewers evaluate research study applications for relevance to the consumer community's needs and concerns and actively participate as full members of the review panel, with full voting status.[185]

The applications are anonymous, so there's nothing that indicates what individual—what qualifications they may have, what background they have, [or] what experience they have—[the] level they have in that particular space.

– Yun-Ling Wong, Bill & Melinda Gates Foundation

Ensuring Publication of Study Results

Publication of negative or inconclusive research results is rare. As a result, unsuccessful studies are needlessly repeated—a waste of both economic and human resources. Not only are negative or inconclusive results generally not published, they may not even be submitted for publication because they do not enhance the stature of the investigator. In addition, scientific journals historically have

I am still waiting for [a] "journal of negative results" to come out. It is so important that we report back to the stakeholders the results of the research even if it was negative. So if you're going to be funding high-risk research, some of it is going to fail. Like you say, it may fail spectacularly. But, you know what? Even in that failure we're going to gain knowledge.

– E. Melissa Kaime, Congressionally Directed Medical Research Programs, Department of Defense

had little interest in publishing negative results; of such studies that are submitted for publication, many are rejected. Failure to publish null or negative findings, however, increases investigators' disincentive to take on higher-risk studies that may fail because their career advancement depends heavily on the numbers of papers they publish. These dynamics are a function of the current academic culture.

A 2011 study[244] expanding on earlier research by the authors[245] attempted to evaluate the potential impact of nonpublication on clinical oncology practice. The authors identified all abstracts describing Phase III clinical trials of systemic cancer therapy with at least 200 participants that were presented at American Society of Clinical Oncology (ASCO) annual meetings between 1989 and 2003. Of the 706 identified trials, 13 percent were published after a delay of five or more years, while more than 9 percent remained unpublished after six and a half or more years following initial presentation. Reasons for nonpublication most often cited by investigators involved in these studies included lack of time, funds, or other resources. Of the unpublished trials, 71 percent of the abstracts reported negative results. Disease site-specific oncology expert evaluators who reviewed the abstracts judged that 70 percent of the unpublished trials addressed important clinical questions and nearly 60 percent might have had clinical impact had the results been published promptly. The authors further concluded that nonpublication of clinical trials breaks an implicit contract to share research results with participants, Institutional Review Boards (IRBs), and sponsors.

Since 2007, all clinical trials (excluding Phase I trials) that are initiated in the United States must be registered in the publicly available database, ClinicalTrials.gov.[246] Trial sponsors are required to submit a summary of results within a year of trial completion; this requirement helps ensure that information on each trial's findings is available to researchers, patients, and the public even if the trial results are not published in a peer-reviewed journal.

Another strategy for ensuring that information about negative or inconclusive studies is made available has been to develop journals dedicated to publishing such results—literally, journals of negative results. In recent years, these online, open-access journals—some of which have become better established than others—have been developed in several fields including biomedicine[247] and pharmaceuticals.[248]

It is not known, however, to what extent the scientific community is aware of or consults these journals. Participants at the Panel's meetings suggested that an oncology-specific journal of negative results would be a useful resource for investigators designing new clinical trials and other cancer-related research. Conversely, it also has been suggested[249] that such journals would not attract readers and that a better approach might be to encourage medical journals to publish brief (i.e., more detailed than an abstract) reports of negative trials. Investigators might be more motivated to prepare and submit such brief reports than to write full-length reports they believe are unlikely to be published.

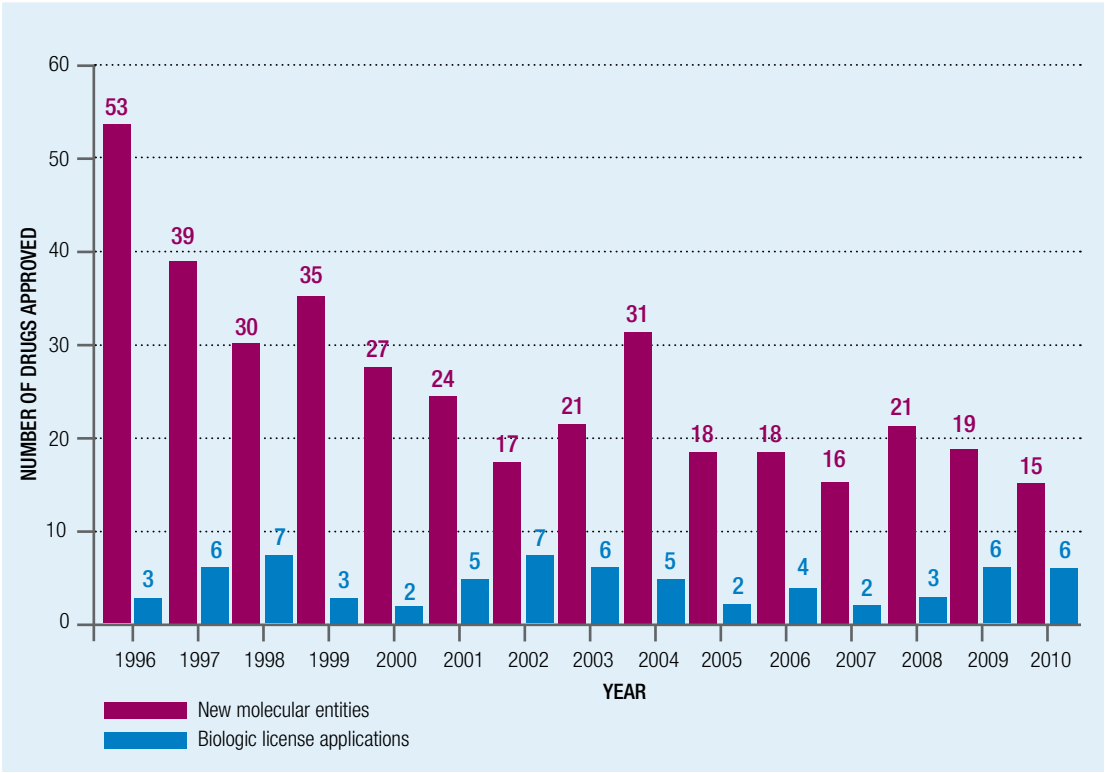
The importance of sharing negative or null results needs to be more fully appreciated, since there is much to be learned from experiments that do not have desired or expected results. Moreover, it must be recognized that while innovative research studies will have a greater percentage of failures, testing of new approaches is critical to progress. Researchers should not be penalized when studies are negative or inconclusive.

Bolstering Drug Development

Pharmaceutical agents have made significant contributions to the progress made against cancer in the past several decades and new drugs will be integral to future preventive and treatment strategies, as well as in efforts to optimize the quality of life of cancer patients and survivors. However, drug development is expensive and fraught with risk. According to some analyses,[250,251] only 2 in 10 approved medications—cancer and noncancer combined—produce revenues that exceed average R&D costs. Thus, ongoing investment in R&D depends on the commercial success of a few products that must recover their own development costs and also make up for all of the rest, including those that never reach the market. Currently, major pharmaceutical companies rely heavily on more established products, including so-called blockbuster drugs, to boost revenue: it is estimated that only 5 percent of pharmaceutical sales are driven by products launched within the last five years.[252] In addition, while technological advances have yielded unprecedented amounts of molecular information over the past several decades, the number of new molecular entities (NMEs) and biologic agents (for all indications) approved by the FDA Center for Drug Evaluation and Research has diminished significantly in the past 15 years, from a total of 56 in 1996 to only 21 in 2010 (Figure 8). The impending loss of patent exclusivity of these older drugs coupled with declining success rates throughout the drug development process is changing the

Figure 8

New Molecular Entities and Biologic License Applications Approved by the FDA Center for Drug Evaluation and Research, by Year



Source: Mullard A. 2010 FDA drug approvals. Nat Rev Drug Discov. 2011;10(2):82-85.

Table 6
Medicines in Development, 2011*

Alzheimer's and Other Dementias	98	Cardiovasular Disorders	245
Arthritis and Related Conditions	198	Diabetes Mellitus	200
Cancer	932	HIV/AIDS and Related Conditions	88
Breast Cancer	129	Mental and Behavioral Disorders	250
Colorectal Cancer	84	Parkinson's and Related Conditions	36
Lung Cancer	140	Respiratory Disorders	383
Leukemia	119	Rare Diseases	460
Skin Cancer	82		

* Reflects number of compounds in clinical trials or under review by FDA for approval through New Drug Application or Biologic License Application pathways. Medicines in development for multiple indications may appear in more than one category but are counted only once for the total (3,091). "Rare diseases" are those affecting 200,000 or fewer people in the United States.

Source: PhRMA, using data from Adis R&D Insight Database, Wolters Kluwer Health (accessed 2011 Oct 10).

...we are really witnessing the implosion of a business model, the likes of which only happens once in decades, and we're seeing it happen in front of our eyes with the pharmaceutical industry. The model started to fail, first, ten years ago with antibiotics.... [S]ince then we've also seen the industry withdrawing from CNS [central nervous system] drugs and from cardiovascular drugs. And the question is: What comes next? And my fear is that oncology is next.

– Bernard Munos, Eli Lilly and Company (Retired)

landscape of the pharmaceutical sector[252] and has led some, including one Panel speaker, to call for a change in the way companies manage their pipelines.[253,254]

Cancer drugs comprise a substantial portion of the drugs in the pipelines of pharmaceutical and biotech companies. Pharmaceutical industry data (Table 6) indicate that in 2011 there were 932 cancer-related medicines in clinical trials or undergoing FDA review—more than twice the number for all rare diseases and nearly two and one-half times more than for the next highest disease category (respiratory disorders). Most of these drugs are in early-stage (Phase I/II) clinical trials.[255] It is estimated that anti-cancer drugs account for more than 25 percent of pharmaceutical R&D budgets worldwide, and nearly 19 percent of all new targets for drugs entering the development pipeline since 2008 are within the anti-cancer category.[252] Although the R&D investment in anti-cancer drugs is substantial, it is associated with considerable risk. The cancer drug market is smaller than those for chronic conditions such as diabetes and hypertension, and the discovery of disease subtypes continues to shrink the pools of patients that may benefit from a particular drug regimen. In addition, cancer drugs have a higher failure rate in Phase III trials than do drugs in other therapeutic areas.[256,257]

The emergence of targeted therapies may be changing the landscape of cancer drug development. Despite the risks noted above, the potential revenues from these drugs, which may cost as much as $50,000 for a course of treatment—often with minimal patient benefit—entice pharmaceutical company investment. Further, in addition to the indication(s) originally approved, many companies hope they will be able to secure subsequent approval to use a drug for the treatment of other cancer types, which could lead to a huge gain in revenue if the drug is still patent protected.

Some evidence indicates that some types of targeted therapies may fare better than traditional drugs in clinical testing;[258] this seems to be particularly true for biologics such as monoclonal antibodies.[256,259] However, changes in R&D are needed to address the low rates of success for oncology drugs.

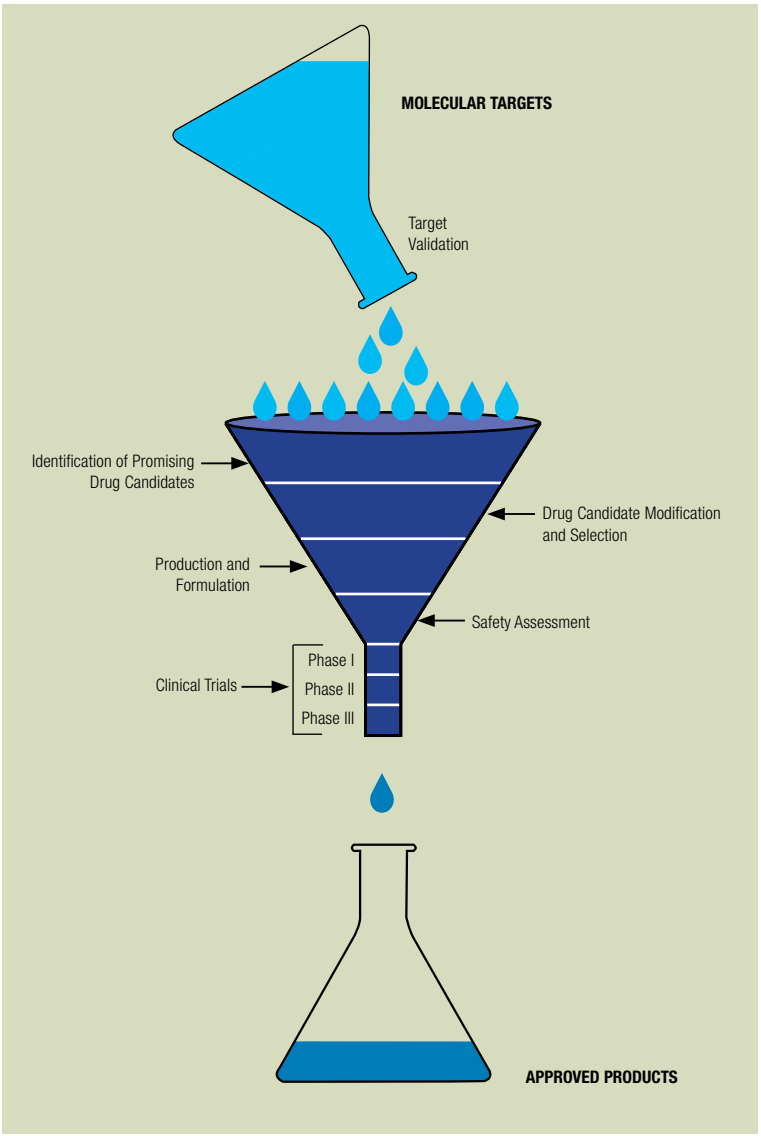
It has been asserted that the development of animal models that better mimic human cancer would help researchers more accurately predict which agents would provide clinical benefit to patients.[256,260] Enhancements to the clinical trials system with potential to improve cancer drug development are discussed in detail in the following section, but improved translational research on potential drugs and candidate targets also is needed. Unfortunately, this crucial research continues to be hampered by a persistent bottleneck, depicted in Figure 9, that occurs at the point at which promising basic science discoveries enter the product development pipeline. This bottleneck in large measure is the result of inadequate investment both in translational research and in researcher training and development (see also p. 81, Workforce Issues). The result has been an underdeveloped capacity to rapidly convert basic science findings into clinically useful products.

In addition, as knowledge has grown about the numerous paths by which cancers develop, evade immune system attacks, and spread, it has become increasingly clear that single-agent treatments are unlikely to be effective against most cancers. However, competitive pressures, along with intellectual property and patent issues, hinder the development of combined targeted agents and other innovative therapies, particularly those involving drugs and biologics that are not yet FDA approved. Therapeutic or preventive agents must be FDA approved before they can be tested in combination with other agents.[261] These regulations present an immediate roadblock to testing and codeveloping new therapeutics. Additional barriers can arise when investigators want to test in combination investigational agents that belong to different companies. Such cases raise difficult business, legal, liability, and intellectual property issues. A 2010 Institute of Medicine (IOM) workshop focused on extending the spectrum of precompetitive collaboration in oncology research to work on overcoming these issues. One workshop participant noted that reduced biomedical R&D budgets can work to encourage collaboration rather than competition and increase efficiencies.[261,262]

Reimagining the Clinical Trials System—Need for a New Paradigm

Inefficiencies in the current clinical trials system undoubtedly contribute to suboptimal oncology drug development. Recent analyses have shown that the process of activating a clinical trial is long and tedious.[263-267] One study found that it requires a median time of approximately 2.5 years to open a Phase III clinical trial sponsored through the NCI Clinical Trials Cooperative Group Program, with some trials taking more than four years to

Figure 9
The Translational Research-Product Development Bottleneck



Adapted from Winningham R, National Dialogue on Cancer Program Group.

achieve activation.[267] Unfortunately, trials still face difficulty once activated. A large percentage of cancer clinical trials do not accrue adequate numbers of patients, and some fail to enroll even a single patient.[263,268] According to one study, less than 20 percent of trials reached their minimum projected accrual within the anticipated accrual period, and nearly 40 percent of trials failed to meet accrual goals regardless of how long the trial was open;[269] as a result, a significant number of cancer clinical trials are never completed.[270] Failure to complete trials may not only delay or prevent potentially beneficial interventions from reaching patients, but also has troubling financial and ethical implications because of the investment of resources and involvement of patients in trials that do not yield meaningful information.

Many speakers who gave testimony to the Panel emphasized the need for the NCP to revisit the ways in which oncology trials are designed, implemented, and regulated to better meet the challenges created by advances in understanding of the molecular and genetic bases of cancer.[271-274] A recent IOM report also issued a call for change, maintaining that the current system for conducting cancer clinical trials in the United States is approaching a state of crisis.[270] While individual investigators can drive some of the necessary changes, in part through adoption of improved trial designs (see also p. 58), modifications also must be made to existing clinical trials operations and regulatory practices, both of which were created in a different type of research environment and have evolved in a fragmented fashion.

Addressing Organizational and Operational Issues

Several recent studies have evaluated the organization of and processes necessary to develop, launch, and conduct NCI-sponsored trials. These analyses have identified organizational inefficiencies and hundreds of discrete steps and decision points required for trial activation, many of which appear to add little or no value to the process.[263-267] NCI has initiated several activities in an effort to address the organizational and operational inefficiencies in its clinical trials system. Many of the changes under way are aligned with recommendations set forth in the 2010 IOM report on the NCI Clinical Trials Cooperative Group Program[270] as well as those in the 2005 report issued by the NCI Clinical Trials Working Group.[275,276]

NCI Clinical Trials Cooperative Group Program

NCI supports the largest network of clinical trials in the United States; the largest component of this network is the Clinical Trials Cooperative Group Program. The Cooperative Group Program has been in place for more than 50 years, and its research has resulted in notable progress in cancer treatment. However, based on a growing recognition within the cancer research community that the Cooperative Groups were not functioning optimally, the NCI Director asked the IOM to undertake a study of cancer clinical trials and the Cooperative Group Program and develop recommendations for improvement.

In its 2010 report, the IOM Committee concluded that several issues were contributing to the Program's difficulties in efficiently and effectively translating research discoveries into clinical applications. Although it focused largely on the Cooperative Groups, the IOM committee emphasized that all sectors must come together to develop a 21st century clinical trials system and laid out several recommendations within four broad goals for accomplishing this objective (Table 7).[270]

In late 2010, NCI laid out a proposal for reorganizing its clinical trials program.[277] Among the most substantive components was the call for a reduction in the number of adult Cooperative Groups from nine to a maximum of four groups (plus the sole pediatric Cooperative Group that would not be affected). In addition, alterations in the peer review process for trial prioritization were proposed to create incentives for collaboration and bring attention to the most pressing and promising scientific questions. Allowing time for input from Cooperative Groups and other stakeholders, NCI plans to release official guidelines for the new system in 2012 and begin funding groups through the system in 2014.[278] The Cooperative Groups have begun preparing for the transition: the Cancer and Leukemia Group B, the North Central Treatment Group, and the American College of Surgeons Oncology Group have announced their merger into a single group called the Alliance for Clinical Trials in Oncology;[279] the American College of Radiology's Imaging Network (ACRIN) and the Eastern Cooperative Oncology Group (ECOG) have combined to form the ECOG-ACRIN Cancer Research Group;[280] and the Radiation Therapy Oncology Group, the National Surgical Adjuvant Breast and Bowel Project, and the Gynecologic Oncology Group also have announced their intent to form an alliance.[281]

Table 7

Summary of Institute of Medicine Committee on Cancer Clinical Trials and the NCI Cooperative Group Program Goals and Recommendations

Goal I. Improve the speed and efficiency of the design, launch, and conduct of clinical trials.
1. Review and consolidate some front operations of the Cooperative Groups on the basis of peer review.
2. Consolidate back office operations of the Cooperative Groups and improve processes.
3. Streamline and harmonize government oversight.
4. Improve collaboration among stakeholders.
Goal II. Incorporate innovative science and trial design into cancer clinical trials.
5. Support and use biorepositories.
6. Develop and evaluate novel trial designs.
7. Develop standards for new technologies.
Goal III. Improve prioritization, selection, support, and completion of cancer clinical trials.
8. Reevaluate the role of NCI in the clinical trials system.
9. Increase the accrual volume, diversity, and speed of clincal trials.
10. Increase funding for the Cooperative Group Program.
Goal IV. Incentivize the participation of patients and physicians in clinical trials.
11. Support clinical investigators.
12. Cover the cost of patient care in clinical trials.

Adapted from: Institute of Medicine. A national cancer clinical trials system for the 21st century: reinvigorating the NCI Cooperative Group Program. Washington (DC): National Academies Press; 2010.

We need to reject the cynical dismissal of Cooperative Groups as out of date or not in tune with modern science and, therefore, not worthy of our respect or of our support. We need real investments in this crucial national infrastructure tied to real changes in how business is done. It's far cheaper to fix this system than it is to replace it once it disappears.

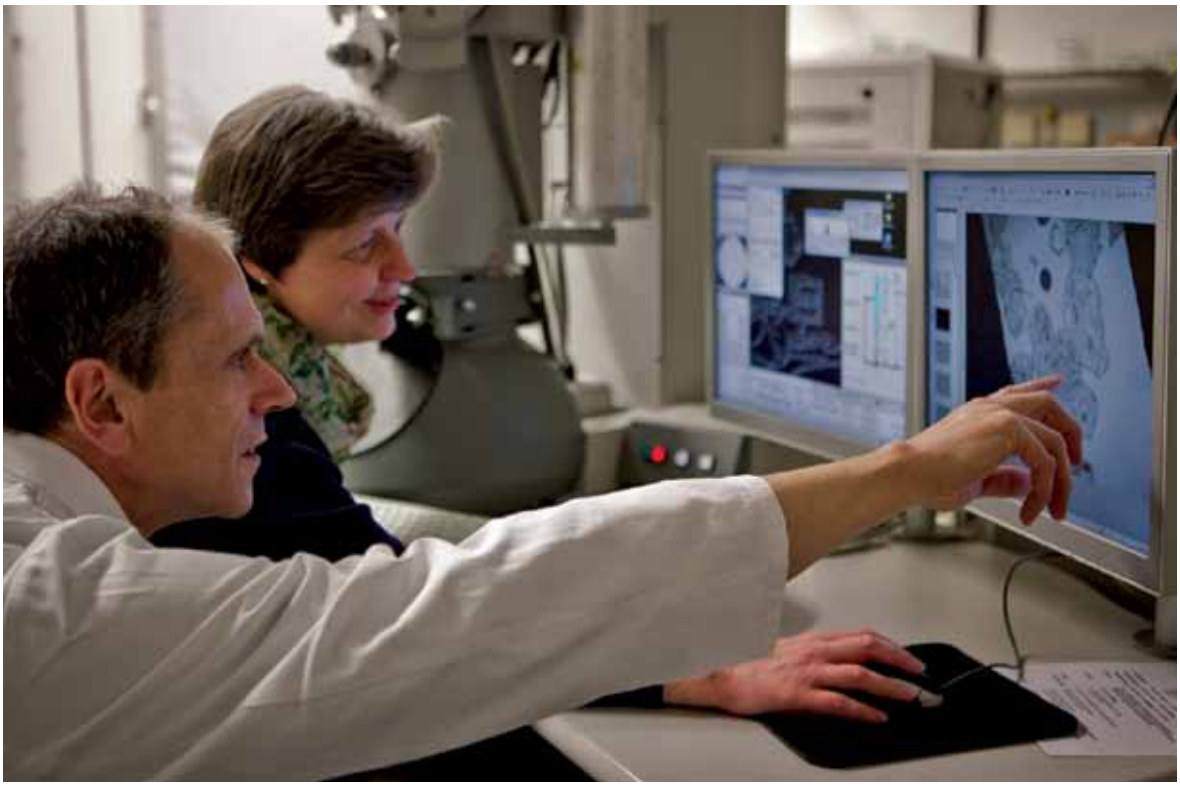
– George Sledge, Jr., American Society of Clinical Oncology

NCI Operational Efficiency Working Group

In December 2008, NCI established the Operational Efficiency Working Group (OEWG) and charged it with developing strategies to reduce the time required to activate NCI-sponsored clinical trials. OEWG assessed and developed plans for four types of trials: Cooperative Group Phase III trials, Cooperative Group trials conducted at NCI-designated Cancer Centers, early drug development trials sponsored by the NCI Investigational Drug Branch and implemented by Cooperative Groups and cancer centers, and investigator-initiated trials at cancer centers. The Working Group set the goal of reducing the time required to activate each type of NCI-sponsored trial by 50 percent. In addition to developing target timelines for activation of each type of trial, the OEWG established "drop-dead" dates, at which time trials would be terminated if they had not yet achieved activation. For example, the OEWG established 300 days as the time period in which Cooperative Group Phase III trials should progress from concept submission to trial activation and indicated that any of these trials not activated within 24 months for any reason should be terminated. OEWG called upon all of the major stakeholders in the trial activation process—Cooperative Groups, cancer centers, and NCI—to develop concrete action plans to meet these timelines and collaborate with one another. In addition, the Group's final report recommended the use of project management personnel and tools as well as additional support for protocol development (e.g., use of medical writers). The new deadlines went into effect at the beginning of 2011.[282,283] NCI also has made steps toward consolidating administrative and data management operations of the Cooperative Group system. A centralized patient registration system has been created and NCI is in the process of launching a single, electronic data management system, which will include standardized forms and tools for protocol development and data recording.[276,284] In addition, NCI has developed START (Standard Terms of Agreement for Research Trial) clauses, standard clauses that provide a starting point for contract agreements between academic, government, and industry partners and are designed to reduce the time needed for contract negotiations for clinical trials. NCI also is exploring the possibility of developing standardized Material Transfer Agreements to facilitate negotiations regarding intellectual property issues.[276] In an effort to facilitate evaluation of its entire clinical trials portfolio, including those conducted outside the Cooperative Group system, NCI has launched the Clinical Trials Reporting Program (CTRP), a comprehensive database that will contain regularly updated information about all NCI-sponsored trials. CTRP should help identify gaps in clinical research and duplicative studies, as well as facilitate trial prioritization.[285]

Designing Effective Trials

Researchers are recognizing the need to more quickly and accurately differentiate promising agents from unsafe or ineffective drugs and determine which patient populations are most likely to benefit from specific ones. An analysis of major pharmaceutical companies in the United States and Europe found that only about 1 in 9 drugs that are taken into first-in-human studies are eventually approved; the rate is even lower for oncology drugs, which, according to one estimate, achieve approval in only 5 percent of cases.[256] A major challenge in drug development is the design of Phase II trials that more accurately predict success in Phase III trials, since Phase III trials account for more than two-thirds of the cost of the clinical trials process.[251] A number of ideas for more effectively and efficiently testing interventions for cancer have been proposed, including consideration of nontraditional endpoints and use of adaptive trial designs.



Reconsidering Endpoints

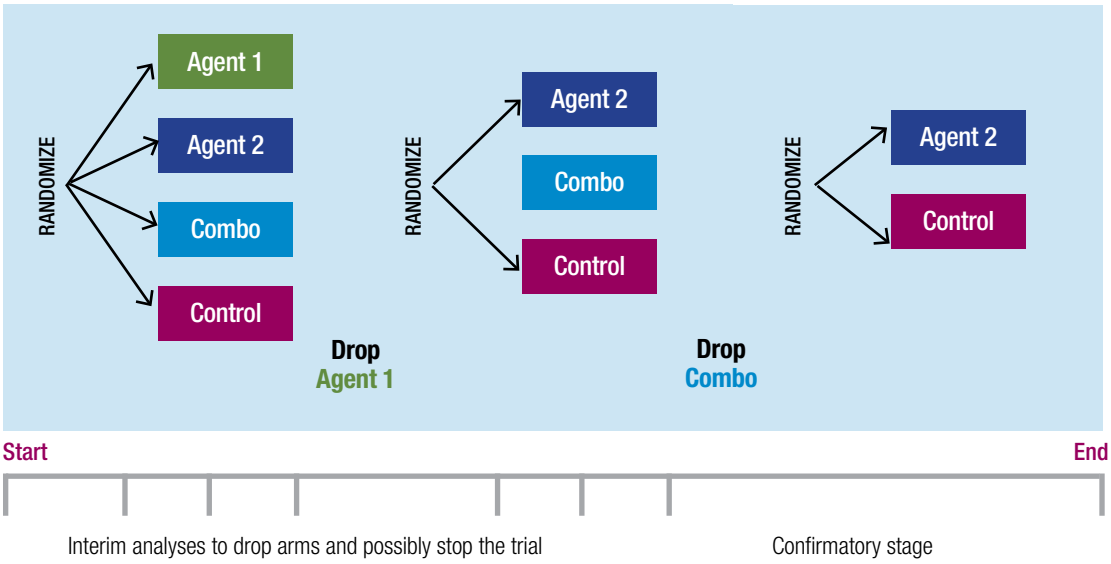
Traditional Phase II trials are single-arm trials (often using historical controls) that evaluate tumor shrinkage as the primary endpoint; this paradigm has performed reasonably well in the testing of cytotoxic agents, but many emerging molecularly targeted therapies demonstrate different mechanisms of action and may impart significant benefit to patients in the absence of tumor shrinkage. For example, some targeted therapies may be cytostatic (i.e., prevent tumor expansion) or lead to tumor necrosis that leaves minimal living tumor tissue but does not change overall tumor size. There may be circumstances in which tumor size is an appropriate trial endpoint, but experts have recently recommended that researchers consider alternative endpoints, such as progression-free survival, which may be more likely to predict patient benefit.[286,287] Functional imaging modalities—including [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), digital contrast-enhanced magnetic resonance imaging, and magnetic resonance spectroscopy—also offer potential ways to learn about the physiological and molecular effects of interventions on tumors[286] (see also Chapter 6, p. 71). It also may be informative to look beyond the tumor. One Panel speaker[225] suggested that investigators search for biomarkers that indicate the overall health of the patient rather than merely the effect of a drug directly on the tumor.

If you study late-stage cancer to find early biomarkers, you're wasting your time.

– Donald Listwin, Canary Foundation

Evaluation of drug targets may seem to be an attractive endpoint for Phase II testing, but using target molecule measurements as a surrogate for efficacy can be problematic. In some cases, the true target of a drug is unknown or a drug may have multiple targets, making it difficult to identify an informative biomarker. Even when a target is well

Figure 10
Schematic of Multiarm, Multiphase Trial



Source: Institute of Medicine. A national cancer clinical trials system for the 21st century: reinvigorating the NCI Cooperative Group Program. Washington (DC): National Academies Press; 2010.

characterized, altering it may not be sufficient to result in patient benefit. Researchers can, however, integrate molecular markers into their Phase II trial protocols, making it possible to prospectively evaluate whether the markers can predict a beneficial treatment response that may be useful in future Phase III testing and/or clinical use.[286,287]

New Approaches to Trial Design

The inability of some current Phase II trials to predict success in the Phase III setting has led some to begin Phase III testing even earlier in the drug development process, sometimes bypassing traditional Phase II evaluation altogether. However, conducting large numbers of Phase III trials will not improve the efficiency of the drug development process, as these trials are expensive and there are not enough willing, eligible patients to participate in all of the trials needed.[288] Thus, some experts have begun advocating for the use of alternative Phase II designs capable of more accurately and efficiently assessing the likelihood that an intervention will be successful in a Phase III trial.[270,286,287]

In some cases, it may be appropriate to abandon the traditional single-arm approach in favor of a randomized Phase II trial; for example, a randomized trial may be necessary for testing molecularly targeted and/or combination therapies for which robust historical controls are unavailable or expected benefits are small.[287] Efficiencies also may be gained by adopting adaptive trial designs that prospectively incorporate the ability to make changes during a trial based on interim analyses.[270] Some adaptations commonly used in modern clinical trials include stopping the trial early or extending accrual based on interim analysis; dose finding; and discontinuation of treatment arms or doses.[289]

One adaptive trial design that is being used in a small number of ongoing oncology trials is

Probably among the worst thing we've done in cancer research is we've separated out phases. So in Phase II, the focus is on tumor response; in Phase III, it's on survival, and never the twain shall meet.

– Donald Berry, The University of Texas MD Anderson Cancer Center

the multiarm, multistage trial, which has two innovative features (Figure 10).[288] First, these trials simultaneously test many promising new agents and/or combinations of agents against a single control arm. Interim analyses are used to help make decisions to discontinue testing of underperforming regimens and/or modify the number of subjects needed to demonstrate efficacy. Multiarm, multistage trials require fewer patients than would be needed for individual trials of each intervention,[288] and a simulated performance analysis indicates that such trials are an effective way of speeding up the evaluation of therapies.[290] Evaluations of ongoing trials should be informative for other clinical researchers in the coming years.

The I-SPY 2 trial is one example of an adaptive multiarm, multistage Phase II trial. The trial is testing neoadjuvant administration of novel drugs in combination with standard chemotherapy in women with locally advanced breast cancer. The trial consists of six arms—five arms in which patients are given standard chemotherapy in combination with one of five novel drugs and one control group of women who receive standard chemotherapy alone. The study integrates standard biomarkers for breast cancer (e.g., estrogen receptor, HER2) and also includes evaluation of other promising and exploratory biomarkers with the hope of being able to identify molecular signatures that will facilitate further testing of promising agents in smaller, more efficient Phase III trials. Throughout the trial, drugs will be dropped if the probability of success falls below an established threshold for all biomarker-defined patient subsets. If, on the other hand, a drug shows particular promise, it will be transitioned to a Phase III trial in which patients will be accrued as appropriate if they possess molecular signatures identified in I-SPY 2. If a drug is dropped from the trial, it may be replaced with another new drug; in all, I-SPY 2 may test up to 12 investigational new drugs, each from a different class of therapeutic agent. It is hoped that the Phase III trials stemming from I-SPY 2 will require fewer patients and have a higher likelihood of success than the average Phase III trial in oncology.[291,292]

...the gold standard randomized clinical trial is great, but it takes a heck of a long time to do it and it takes a heck of a lot of money to do it. So, especially for chronic diseases, it's going to be absolutely impossible to ever do any type of preventive randomized clinical trial. It's going to cost too much money. It's going to take too long.
– Scott Campbell, Foundation for the National Institutes of Health

Adaptive trials hold great promise, but their complexity often poses challenges that must be taken into account by researchers and sponsors. Often, multiarm trials involving multiple drugs require coordination with several industry partners. Many companies will be hesitant to include their drugs in the same trials as their competitors' drugs, but there are incentives for collaboration. Adaptive Phase II trials may provide valuable information about the likelihood that a drug will be successful in Phase III testing, which could result in substantial cost savings. In addition, trials such as I-SPY 2 that incorporate biomarkers will potentially provide insight into patient subpopulations that may be more likely to respond to a given drug, which will enhance patient selection for Phase III trials.

Adaptive trial designs also require special statistical consideration. Some statisticians advocate the use of Bayesian statistical methods for adaptive trial designs rather than the classical "frequentist" approach;[270] however, most institutions and research groups lack the expertise in Bayesian methods necessary for clinical trial planning and review. Designing these trials may also involve incorporating information on characteristics or results from prior investigations in similar patients. Regulatory challenges of adaptive trials also must be considered. FDA recently issued a draft guidance document[293] that discusses clinical, statistical, and regulatory aspects of adaptive design trials. Among other points, the document emphasizes that adaptive studies often require a lengthier planning process than traditional studies and urges early interaction between sponsors and FDA to ensure that regulatory issues are taken into account.

I'd like people to remember we are a country of ethnic minorities, and having representation in clinical trials of Asians, Afro-Americans, Hispanics is very important.

– Richard Pazdur, U.S. Food and Drug Administration

Patient Selection

The efficacy of an intervention can be influenced by a variety of clinical, biological, behavioral, and cultural factors; thus, the population in which an intervention is tested may have important implications for its effectiveness once it is disseminated for widespread use. Unfortunately, the clinical and demographic characteristics of participants in cancer clinical trials often are not representative of the overall population of cancer patients, calling into question the generalizability of trial results.

A study of more than 19,000 patients at The University of Texas MD Anderson Cancer Center found substantial differences in the clinical characteristics of clinical trial participants compared with nonparticipants. Trial participants had more extensive cancer than their nonparticipant counterparts and were more likely to have lymph node involvement and distant metastases. Among those with metastatic disease, participants were more likely than nonparticipants to have liver metastases and more metastatic sites. Participants without metastatic disease were more likely than nonparticipants to have locally advanced disease and/or extension to regional lymph nodes.[294] Other studies have confirmed the underrepresentation of early-stage cancer patients in clinical trials,[295] raising questions about the relevance of trial results to these patients. It has been noted that current regulatory structures incentivize this unbalanced approach because the testing and approval process can be expedited when drugs are tested in patients with advanced, refractory disease.[296] In addition, liability concerns may deter sponsors from testing new drugs and drug combinations in patients with early-stage cancer.[297]

Trial participation also is lower than average among elderly cancer patients, despite the fact that cancer is most common in older adults.[294,298] This is due in part to strict eligibility criteria precluding patients with certain comorbidities—that are more common among older people—from enrolling in a trial. Minorities and other underserved populations also are less likely to participate in cancer clinical trials.[298] There are indications that physicians are less likely to offer trials to minorities and elderly patients for a variety of reasons. For example, physicians may assume that minority patients harbor mistrust of the medical system.[299,300] While mistrust has been documented,[301-303] studies also have found that respectful, empathetic, and responsive interactions can help physicians build trust with patients[304] and that minority patients are just as likely as white patients to enroll in a clinical trial if given the opportunity.[305,306] Low rates of trial participation are cause for concern given the fact that the U.S. population is aging and increasingly racially and ethnically diverse, which are trends with significant implications for the national cancer burden.[37] Excluding these patients is detrimental to the generalizability of research results and likely also negatively affects trial participation rates.[299,307,308]

Pregnant women also have historically been excluded from clinical research based on concerns about fetal exposure to experimental drugs. It is estimated that 3,500 women in the United States each year receive a diagnosis of cancer during pregnancy and this number may increase as more women delay childbearing until

their 30s or 40s, when they are at higher risk for cancer.[309] However, there has been little research on cancer during pregnancy, forcing patients and their physicians to make treatment decisions using limited information. Surveillance efforts such as the Pregnancy & Cancer Registry,[310] which has compiled information on more than 200 pregnancies in women with cancer, and a few ongoing clinical trials focused on cancer in pregnant women are providing important insights. However, some clinicians and bioethicists are urging the research community to actively engage pregnant women in clinical trials unless there is a specific reason why they should be excluded, noting that failure to gather data on drug safety and efficacy in research settings is a disservice to both pregnant women and their fetuses.[311,312]

Consideration of clinical trial populations is taking on new importance as trials are becoming increasingly global in nature. Differences in ancestry and cultural factors may complicate the extrapolation of trial results from one population to another. In addition, patients in developing countries may have underlying untreated medical conditions and/or may be less likely to have received previous treatment for the disease being studied, both of which could compromise the generalizability of trial outcomes.[313]

Community Involvement

Regardless of the patient population or geographic location in which a trial is conducted, investigators benefit from involving community members early in the trial planning process. Although community-based participatory research (CBPR) has been more often integrated into public health research, clinical trialists also should be well versed in CBPR principles and appreciate how input from stakeholders in the community can enhance the relevance of clinical research. There is a growing body of literature describing methods for engaging patients in research planning and decision making.[314] A report from the Education Network to Advance Cancer Clinical Trials (ENACCT) includes several recommendations for engaging communities in clinical research, particularly in

...I think the public is willing and eager to take part in research, and as long as we're addressing important issues that the public cares about, then...they're willing to take part in research even before the onset of a disease.

– Naz Sykes, Dr. Susan Love Research Foundation

Phase III trials.[315] Soliciting input from patients and community oncologists, who treat the majority of U.S. cancer patients, is particularly important as they can provide insight into whether an intervention will be accepted by those whom it is meant to benefit and contribute suggestions for improvements. In addition to increasing the likelihood that effective treatments will be widely adopted, patients and community physicians may be more likely to participate in trials designed with community input, which has the potential to enhance accrual and speed research progress.

Some organizations have made community involvement integral to their research missions. The Dr. Susan Love Research Foundation (DSLRF) created the Army of Women (AOW) with the goal of recruiting 1 million women to partner with breast cancer researchers and participate in research studies. Since its inception in 2008, more than 365,000 women have registered with AOW and the number continues to grow. Researchers can apply for access to the AOW membership base for their studies if approved by the AOW Scientific Advisory Committee. Unlike the majority of cancer clinical trials, many AOW studies have exceeded their recruitment goals. AOW firmly believes that women should have a voice in establishing research priorities; when AOW members expressed frustration that there were not enough studies for healthy women, DSLRF teamed up with researchers at the City of Hope Beckman Research Institute to create the Health of Women study, a large, Web-based cohort that is contributing to research on risk factors for breast cancer and other diseases.[316,317]

Engaging communities and ensuring that intervention implementation is feasible are particularly important when working with minority and underserved populations that often are the last to enjoy the benefits of evidence-based interventions. To engage these communities, researchers must be willing to design interventions and studies that can be integrated into the cultural settings of target populations. Further, one Panel speaker noted that trialists also may benefit from collaborations with more traditional community-based researchers who have experience conducting research in and working with the communities of interest.[318] It is critical that communities receive the results of studies in which they are the subjects; failure to return the benefit of research to the community has been a significant source of community distrust and reluctance to participate in research.

Efforts also should be made to learn from the outcomes of clinical care provided outside the context of clinical trials; these data comprise a wealth of currently untapped information. Electronic health records will facilitate utilization of this information, but reliable mechanisms are needed to ensure the privacy of patient data (see also discussion, p. 75).

Addressing Challenges Related to Institutional Review Boards and Other Regulators

Institutional Review Boards were established to ensure that the rights and welfare of research participants are protected. The Federal Policy for the Protection of Human Subjects (45 CFR 46), better known as the Common Rule, requires that all research conducted in the United States using federal funds be reviewed and approved by an IRB. While researchers are largely supportive of the goals of IRB review and most recognize the need for some sort of oversight system, many express frustration with the current implementation of IRB review processes.[319] A common complaint is that preparation of IRB submissions is time consuming and requested revisions also take time, often without adding significant value to the protocol. The burden of IRB review and the associated costs and delays in research are amplified in multicenter studies, which often require review and approval by IRBs at each site. Multiple studies have found that revisions requested by local IRBs are often minor and unrelated to the scientific or ethical merit of the protocol (e.g., small wording/grammatical changes, addition of contact information).[319,320]

The inefficiencies of disseminated IRB review procedures have spurred calls for centralized IRBs for multisite studies, including those conducted by Cooperative Groups.[270,320] In 2001, NCI made

available a Central Institutional Review Board (CIRB) for institutions involved in NCI-sponsored clinical trials with the goal of streamlining local IRB reviews of adult and pediatric national multicenter cancer treatment trials.[321] Local IRBs of sites participating in CIRB review protocols conduct a condensed facilitated review of CIRB-approved protocols rather than a full-fledged review. Early analysis revealed that protocols were approved more expeditiously and fewer IRB staff hours were consumed at sites using the CIRB compared with sites that did not use the CIRB.[322] However, many sites remain hesitant to utilize the CIRB, in part because of concerns that they will be held legally liable for CIRB decisions.[270] To allay these concerns and promote use of central IRBs, the Office for Human Research Protections (OHRP) has proposed changes that would require domestic multisite trials to name a single IRB of record that would assume responsibility for compliance with Common Rule requirements. OHRP has also proposed an updated framework designed to better align review requirements with the level of risk of research studies, which would reduce or eliminate IRB review requirements for low-risk research.[323]

In addition to IRBs, cancer clinical trials are overseen by a number of agencies within the U.S. Department of Health and Human Services—including FDA, OHRP, the Office for Civil Rights, and, depending on the trial sponsor, NCI—before trial initiation, during the trial, and upon trial completion. The many bodies that monitor clinical trials have different objectives and responsibilities and thus require different types of reporting and actions for compliance. At times, federal regulations conflict with one another and/or with state regulations. Furthermore, review processes are serial in nature and iterative; thus, changes made in response to concerns from one agency may result in re-review by other bodies, creating more work for investigators and extending the review process.[270] Multiple bodies have recommended harmonization of guidelines and streamlining of oversight and review processes to improve the speed and efficiency of clinical trials.[270,324,325] With regard to cancer clinical trials, the IOM has called for enhanced collaboration between NCI and FDA for trials that will directly inform FDA decision making regarding approval of a drug or device.[270]

...an American investigator competing with an investigator in most parts of the world is now at a significant disadvantage....[Because of our regulations], it just simply takes me twice as long or three times as long to open a trial in my center as it does in most places around the world, and that's three months or six months or a year of accrual that I've lost....

– George Sledge, Jr., American Society of Clinical Oncology

While the claim that current regulatory processes result in unnecessary resource expenditures warrants attention, perhaps even more troubling is the contention that the regulatory burden leads researchers to avoid certain types of research, particularly projects that involve multi-institutional collaboration.[319,326] As biomedical research becomes an increasingly global endeavor, the influence of the U.S. regulatory system on international research also must be considered. Researchers involved in international studies, particularly those being conducted in developing countries, have expressed concerns about the costs associated with compliance with U.S. regulations and the inability of U.S.-based IRBs to sufficiently take into account differences in the cultures, regulations, and standards of medical care in other countries.[319] The burdens of regulatory compliance appear to be driving some sponsors to abandon U.S.-based research altogether. One analysis[313] found that one-third of all trials listed on ClinicalTrials.gov are being conducted solely outside the United States and the majority of study sites are now outside of the United States. Many of these trials are being done in developing countries where regulatory environments are less constraining. It will be important to monitor this trend to ensure that trial design and implementation are not subject to inappropriate political influences and human rights are not violated.

Promoting Productive Team Science, Multi-Institutional Collaborations, Consortia, and Partnerships

Many of the challenges facing the cancer research community cannot be adequately addressed by individual researchers in isolation but require teams with varied expertise and resources. The shift toward collaborative science was illustrated by a recent study that found that high-impact research is increasingly being published by teams rather than individuals.[327] Collaborative scientific efforts may take several forms, including interdisciplinary team science projects, multi-institutional collaborations, consortia, and partnerships. These activities—which can involve international as well as U.S. participants—bring together people and organizations from different sectors and diverse disciplines to address a key scientific question or problem, develop needed resources or technologies, accelerate drug development, or conduct community-based research.

...for starters, you have to change the metrics that are used for promotion and tenure, both in academia and also in clinical practice. Even in clinical practice, physicians are rewarded for the revenue that they bring in, and they don't get credit for enrolling patients in clinical trials where they are participating in a network, which is so important for moving things forward.

– Sharyl Nass, Institute of Medicine

As discussed in a previous Panel report,[9] participation in team science projects does not advance the career of the investigators (e.g., tenure) as do investigator-initiated independent research project grants (e.g., R01 or equivalent). Many, including the Panel, have recognized the need for incentives to encourage cancer researchers to work together rather than compete.[328,329] There has been progress in recent years. For example, in publications of team science studies, it now is possible for the contributions of all participants to be specified. While a number of team science and collaborative research initiatives have emerged in recent years, some of which are described in the following paragraphs, additional incentives are needed to promote collaboration, and more research is needed to determine the best ways to assemble, fund, and manage teams.

Federal Coordination of Team Science

Federal agencies have devoted increasing attention and resources to team science and multi-institutional collaborations in recent years. The Human Genome Project, completed in 2003, was coordinated by NIH and the U.S. Department of Energy and counted numerous government and academic laboratories from within and outside the United States among its participants. Other large-scale endeavors, such as the Clinical and Translational Science Awards,[330] the NIH Roadmap for Medical Research initiative,[331] and the newly established National Center for Advancing Translational Sciences,[332,333] illustrate NIH's desire to foster the collaborative approaches needed to address complex research questions and accelerate progress. Additionally, NIH changed its policies in 2006 to allow grant applicants to identify more than one principal investigator in order to facilitate team science.[334]

Within the cancer arena, several ongoing collaborative and multi-institutional efforts are ongoing. The Cancer Genome Atlas (TCGA), a joint effort of NCI and the National Human Genome Research Institute, is a national network of research teams working to identify the genomic changes associated with a number of different cancers.[335] NCI's Early Detection Research

Network (EDRN) brings together dozens of institutions with the goal of translating biomarker information into molecular diagnostic tests that will enable early detection and clinically useful characterization of cancer.[211] The recently established NCI Experimental Therapeutics (NExT) Program brings together researchers and resources from government and academic laboratories to drive development of cancer therapies. One component of NExT, the Chemical Biology Consortium, is a network of 12 centers that are using their collective knowledge in high-throughput methods, bioinformatics, medicinal chemistry, and structural biology to identify agents with anti-cancer potential.[336]

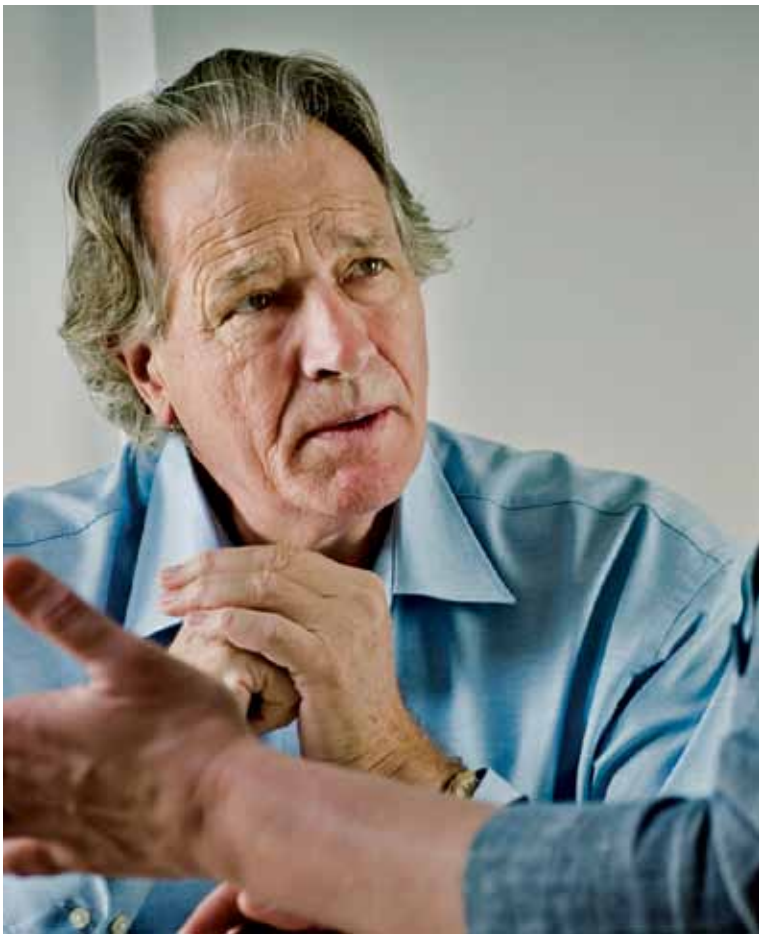
Voluntary Sector Participation

Foundations and nonprofit organizations are well poised to facilitate team science and many actively promote collaborative research. Stand Up To Cancer is using its Dream Team grants to help scientists from different institutions, disciplines, and specialties work together to answer important research questions rather than compete.[337] Foundations often partner with government agencies to promote team science. The Prostate Cancer Clinical Trials Consortium (PCCTC), a joint effort of the Prostate Cancer Foundation and the DoD CDMRP, is one such partnership.

...the relationships between public- and private-sector institutions [are]...a crucial aspect of any innovation system because public institutions and private institutions will always have different roles [and] respond to different masters, different incentives, et cetera.
– Daniel Sarewitz, Arizona State University

PCCTC, which currently comprises 13 institutions, was developed as a way to hasten the development of better therapies for prostate cancer patients through faster and more efficient Phase I and II clinical testing. Key features of the Consortium are its centralized management and frequent communication among stakeholders, which help in establishing uniform scientific priorities and addressing operational issues. PCCTC has exceeded the initial goals set forth by the CDMRP award mechanism, recruiting more than 2,600 patients to over 89 clinical trials since its inception in 2005.[338-341]

The Foundation for the National Institutes of Health (FNIH) also has facilitated productive research partnerships. FNIH is an independent nonprofit organization that raises private funds and provides a neutral forum for bringing collaborators together. FNIH oversees the Biomarkers Consortium, a 62-member public-private partnership that is working to identify, develop, and validate potential high-impact biomarkers to



enable improvements in drug development, clinical care, and regulatory decision making. FNIH also coordinates I-SPY 2, an innovatively designed clinical trial designed to test multiple drugs in patients with locally advanced breast cancer (see p. 61).

The Canary Foundation has partnered with NCI to conduct its Prostate Active Surveillance Study, which is designed to identify and validate biomarkers capable of distinguishing potentially lethal prostate cancer, which may be best treated with aggressive therapy, from nonlethal cancers for which continued monitoring without aggressive therapy may be more appropriate. The Canary Foundation is funding and overseeing the project while NCI's EDRN is providing statistical and data management support.[342,343]

Managing and Evaluating Collaborative Science

Although team science has yielded notable progress and is necessary for addressing many current scientific questions, it is not uniformly productive and cost effective, and many have expressed concern that large team science initiatives are diverting money from investigator-initiated research projects that, in some cases, may be more productive. Panel meeting speakers noted that the coordination and leadership of teams can be challenging, and as teams grow larger it may be difficult to control costs and maintain efficiency.[237,344] The nascent field of team science is beginning to develop a knowledge base to help identify determinants and facilitators of success in order to help funding agencies decide when and how to invest in large-scale collaborative science.[345]

Among the most important promoters of team science is a culture that promotes appreciation and recognition of team science and rewards team efforts and contributions. Modification of organizational structures and routines can facilitate both intra- and interinstitutional collaboration. For example, the David H. Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology (MIT) designed its new laboratory space specifically to promote transdisciplinary interaction and collaboration. Half of each floor houses laboratory space for engineers while the other half comprises laboratories devoted to life science research. All shared employee spaces (e.g., offices, conference rooms) are in the center of the building and connected with a continuous stairwell. Space is also reserved for practicing oncologists, allowing them to devote a portion of their time to research and serve as a link to the clinic for laboratory researchers.[346,347]

Although difficulties can arise in any collaboration, multi-institutional teams must contend with a special set of challenges. A study of the National Science Foundation (NSF) Information Technology Research Program (ITRP) found that having a large number of universities involved in a team project correlated with fewer outcomes (e.g.,

publications, patents, tools produced, future grants).[344,348] It may be more difficult for virtual teams to achieve the social cohesiveness that appears to support productivity. Consistent with this notion, the ITRP study found that multi-institutional collaborations were more productive if investigators had collaborated previously, and others have found that former trainees are often valuable collaborators.[348,349] Maintaining effective communication also can be more difficult when team members are geographically dispersed. Technology is increasingly critical to the success of such teams; team members must have access to communication and data-sharing tools and must also be willing and able to use them. Teams that span different countries have the additional challenge of managing the influence of cultural differences on communication and productivity.[345]

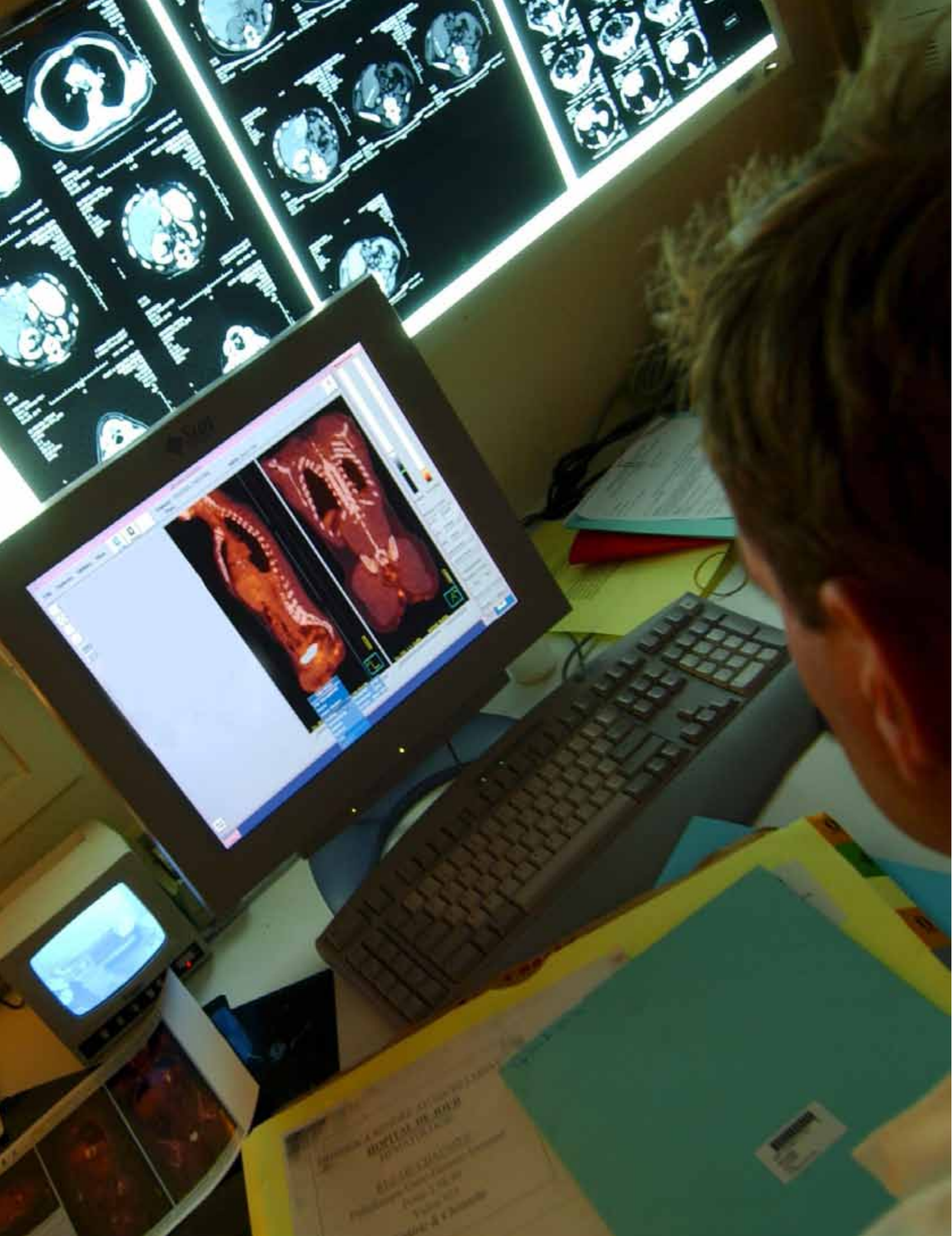
Training may help address some of the challenges of collaborative science. Students and postdoctoral fellows should be trained to participate in teams, including transdisciplinary teams, and established investigators also may benefit from training. Most researchers are not prepared for the increased management responsibilities that accompany leadership in team science. All prospective team members should be prepared for the fact that team science is often prone to conflict and requires substantial effort and trust among team members.[350]

Given the substantial investment in team science initiatives, including large investments of public funds, careful evaluation of these efforts is warranted. These data will be useful for funding agencies as well as for policy makers who hope to promote innovation and efficiency. However, evaluating research investments is complex, in part because the impact of such efforts may not be realized for many years and because innovative change often results from the convergence of many efforts. Thus, there is a need for new methods and measures to evaluate the processes and outcomes of large research endeavors.[350] NSF is contributing to this knowledge base through its Science of Science and Innovation Policy program. This program was established to promote the study of ways in which science and engineering research are translated into social and economic outcomes that inform future investments and policy.[351,352]

We were told to do this: Make a difference; measure yourself by the impact you make in the lives of people....The only way we'll be able to do that is through extensive and robust, productive collaboration.

– Robert Urban, Massachusetts Institute of Technology

As one of the few studies of multi-institutional research that has been published, the aforementioned ITRP study provides some insight that may help funding agencies build more productive teams. For example, it may be appropriate to preferentially fund teams with track records of collaboration or provide small grants that would allow teams to explore their collaborative potential and overcome barriers to working together. Multi-institutional studies also should have adequate budgets for communication and coordination, including funds for travel and workshops if necessary.[344,348]



CHAPTER 6

Fortifying the Research Infrastructure to Support Transformative Innovation

Major technological advances in science made in the past decade (e.g., "-omics," computational chemistry, data-sharing capacity, digitization of scientific information) have not yet had a revolutionary effect on clinical care or clinical outcomes. The following paragraphs highlight several areas in which the cancer research and care infrastructure remains limited.

Upgrading Research Facilities

Many cancer research laboratories and clinical facilities need modernization and have needed to be updated for years. In an increasingly constrained fiscal environment, funding for such capital-intensive projects is exceedingly scarce; facility modernization or the construction of new facilities may be difficult without a major monetary donation(s) from an individual (often, a bequest), family foundation, or corporation (for which a donation may be advantageous from a tax perspective and in generating good will in the community).

Recognizing the need to upgrade research facilities to support state-of-the art biomedical research, the American Recovery and Reinvestment Act of 2009 provided a bolus of $1 billion for improvements to extramural research facilities, $300 million for shared instrumentation, and $500 million for construction, repairs, and improvements to NIH facilities.[353]

Using Technology Infrastructure to Facilitate Innovation

Imaging technologies and data systems that facilitate data collection and sharing have advanced in recent years, but further development is needed for these tools to more effectively support research innovation.

Imaging

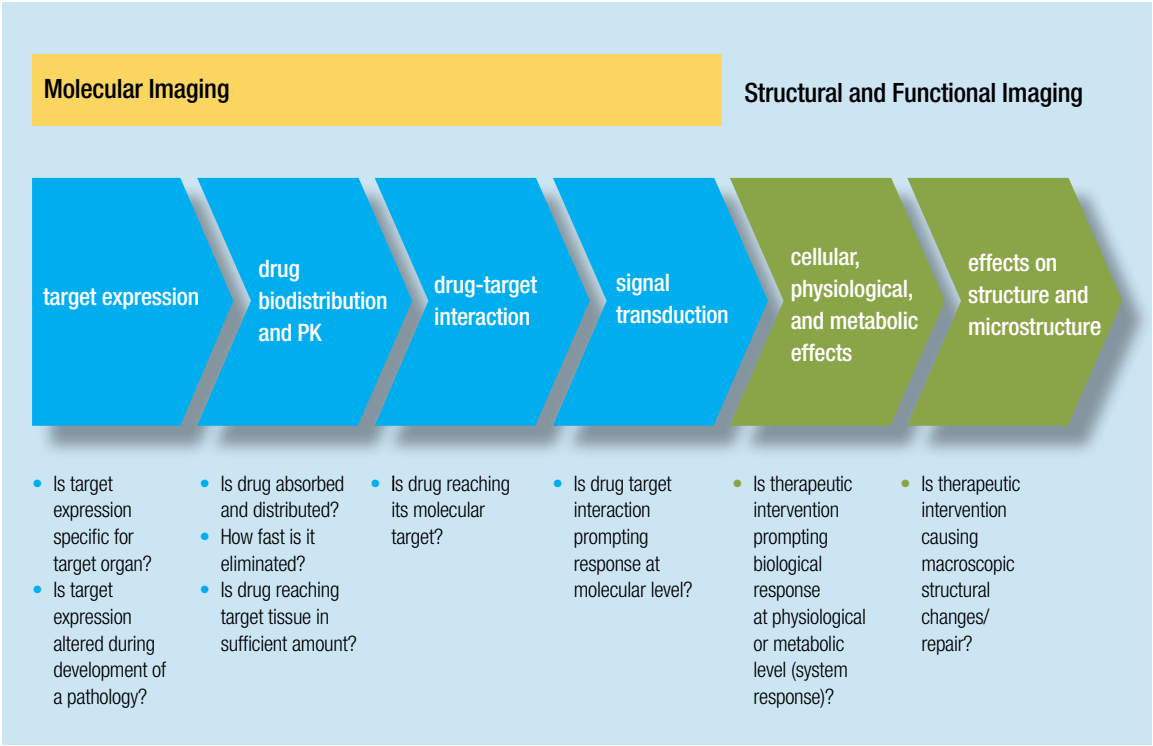
Imaging has significant potential to enable transformative innovation in research and clinical care, but progress depends on investment in the infrastructure necessary to optimize imaging modalities and integrate them into basic, translational, and clinical research. Historically, imaging modalities have measured anatomical and morphological features. These approaches—which can be used in clinical settings for screening, diagnosis, and monitoring, as well as to guide surgical and locoregional treatment—have made and likely will continue to make invaluable contributions to medicine as available technologies are improved. They likely will be complemented by emerging functional and molecular imaging technologies, which can provide windows into the physiological, cellular, and molecular characteristics of patients and their tumors. Imaging approaches are well suited for following patients or animal models over time, which provides an advantage over more invasive data collection approaches (e.g., surgical biopsy).

...there is so much fruit that is ready to be picked, but we don't have the ladders to reach it....we just don't have the kinds of resources that assist investigators getting from the bench to things that could be tested, whether it's prevention or whether it's therapy or whatever you talk about. There has been an enormous investment, and yet it isn't sufficient to really make things happen.
– James Doroshow, National Cancer Institute

Functional imaging methods measure physiological changes, such as changes in metabolism, blood flow, or chemical composition. One technique that has been clinically validated is FDG-PET, which allows measurement of tumor metabolism, as a means to predict response to imatinib (Gleevec®) in patients with gastrointestinal stromal tumors. Diffusion-weighted MRI (DW-MRI)

Figure 11

Information Relevant for Drug Discovery and Development Provided by Molecular, Functional, and Structural Imaging



PK – pharmacokinetics.

Adapted from: Rudin M. Noninvasive structural, functional, and molecular imaging in drug development. Curr Opin Chem Biol. 2009;13:360-71.

can be used to evaluate the diffusion of liquid in tumors, and there is increasing interest in using this approach to monitor the development of tumor necrosis as well as the effects of therapy on several cancer types.[354] In addition to clinical applications, functional readouts such as this can be used in validated model systems to evaluate the activity of experimental drugs and/or potential pharmaceutical solutions to drug resistance.[355]

Molecular imaging—defined as the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in living systems[356]—can be used to study the molecular underpinnings of cancer in laboratory settings and also can play a role in intervention development and testing. Figure 11 illustrates ways in which molecular imaging can contribute to multiple steps in the drug development process.[357] Optical and nuclear imaging techniques can be used to assess whether a target of interest is present or altered; in some cases, probes can provide information on the activity of a molecular target. Once a candidate drug is developed, molecular imaging can be used to assess its biodistribution and how it is metabolized (pharmacokinetics) as well as to determine whether it reaches its target. PET is the most commonly used imaging approach for these types of measurements. Imaging also can be used to provide molecular readouts of drug activity (e.g., activity of downstream signaling pathways, changes in protein-protein interactions). This information can aid in making determinations about drug efficacy and/or investigating mechanism(s) of action. In addition to research applications, molecular imaging has potential to play a pivotal role in clinical management of cancer patients by assisting in diagnosis, staging, assessment of therapeutic targets, monitoring of therapy, and evaluation of prognosis.[356,358]

However, despite the existence of numerous potential imaging agents, translation of molecular imaging approaches to clinical application has proven difficult.

Several factors have impeded progress in imaging research and application development. Imaging research requires sophisticated instrumentation, which is usually very expensive. In the case of PET, researchers also must have access to a resource capable of generating radiopharmaceuticals. In addition, highly trained personnel and transdisciplinary teams that include expertise in material science, chemistry, physics, pharmaceutical development, biology, and medicine are needed to design, synthesize, and test imaging modalities and agents in preclinical and clinical settings.[359,360] Generation of imaging probes is expensive and risky, and the revenue potential of these agents is considerably lower than that of most drugs. In addition, biomarkers and imaging assays must be validated through comparison with more established readouts (e.g., histology, immunohistochemistry) and association with clinical endpoints must be demonstrated. Standardizing measurement processes also can be a major issue given the variety of imaging platforms used across institutions. Regulatory factors also may pose challenges, although FDA has acknowledged that imaging is a key enabling technology in the effort to identify biomarkers capable of guiding treatment decisions.[357]

Although resource-intensive, investment in imaging infrastructure will likely help drive innovation in both cancer research and clinical care. In addition to the benefit provided by novel imaging approaches, the burden of cancer could also be lessened through efforts to minimize the potential detrimental effects of current imaging modalities. In the United States, exposure to medical radiation has doubled in the past three decades. In a recent report, the Panel recommended immediate action to reduce radiation exposure from medical sources through more informed decision making, reduction of duplicate tests, and implementation of radiation-lowering techniques.[12]

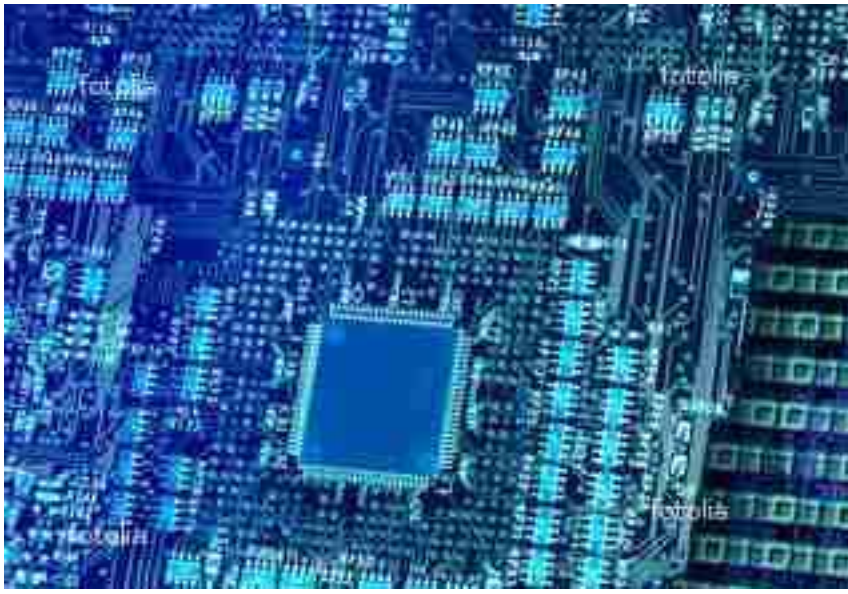
Data Systems and Data Sharing

Knowledge about biology and disease is being accumulated at an unprecedented pace, with large volumes of data being generated via high-throughput technologies and other research tools. It is generally accepted that taking full advantage of this knowledge is predicated on making data widely available for use by the research community, but this has proven challenging. Barriers to data sharing include a research culture that places high value on independent investigators; lack of appropriate venues for data exchange; incompatibility of data sets, data elements, definitions, and systems; and ethical and privacy considerations.

Since 2003, NIH has required all investigator-initiated applications with direct costs greater than $500,000 for any single year to include a data-sharing plan.[361] There have been some notable successes in the effort to integrate data, but the creation and adoption of the tools and

...we have to work together to provide shared tools, and if that means a database of information, if that means a biorepository—whatever that might mean for our particular area of work, we need to work together to do it because we cannot do it alone.

– Chandini Portteus, Susan G. Komen for the Cure



We are going to need some kind of federated system that leaves data in place until they are needed for a specific purpose, and then and only then will they move. It needs strong policy and governance—policies that will have to be developed—but there are examples in other countries that show that this can be done.
– Charles Friedman, Department of Health and Human Services

infrastructure needed to achieve widespread sharing have run into a number of roadblocks. NCI has invested heavily in informatics support for cancer research through efforts such as the cancer Biomedical Informatics Grid® (caBIG®). caBIG focused on the creation of open-access, interoperable tools for research and the creation of a framework—called caGrid—designed to link institutions conducting cancer research.[362] It also promoted the development of standards for data exchange and application interoperability, which have been adopted for products developed within academic institutions and commercially; however, with some exceptions, adoption of caBIG® software and infrastructure has been limited, and the goal of creating a framework for data sharing among cancer researchers has not been achieved.[363] Efforts are now under way to look at the lessons learned from caBIG, build on its successes and reshape the vision for cancer research informatics. The National Informatics Program will focus on developing core resources that serve the whole cancer research enterprise and integrate those tools into legacy systems to meet current and future needs.[364]

Progress with integration is occurring within some pockets of the research community. One of the features of the TCGA initiative is a centralized repository that compiles data generated by participating laboratories and makes these data freely available for analysis by other researchers.[335] Numerous publications have resulted from use of this resource by non-TCGA investigators.[365] Data sharing and collaboration are central to the goals of the Clinical and Translational Science Award (CTSA) program launched by NIH in 2006. Several CTSA awardees are developing platforms to support integration, repurposing, and classification of data within and among institutions.[366,367] The National Institute of Allergy and Infectious Diseases also has created a Web-based warehouse called ImmPort (Immunology Database and Analysis Portal), which integrates data generated by NIAID-supported researchers with other relevant data extracted from a variety of public databases. Efforts have been made to ensure that all ImmPort data—which are generated via a wide range of methodologies, from SNP genotyping microarrays to clinical trials—are interoperable with other external resources.[368]

Sharing and integration of human data are of particular interest because of the potential of these data to yield insights that may directly influence patient outcomes. Several groups—including those involved with ImmPort and the Human Studies Database Project—are working to develop a common conceptual scheme and principles that will facilitate large-scale sharing of human study designs and results. This will allow aggregation and meaningful analysis of existing data and also help inform the design of new studies.[369,370]

Patient medical records also are a rich source of information for clinical, epidemiological, and population-based research. Historically, researchers have had to review charts manually, a cumbersome and time-consuming process.

The transition to electronic health records has the potential to substantially enhance the efficiency and scale of in-human research efforts by facilitating data sharing and integration as well as identification of patients potentially eligible for clinical trials. However, the value of EHRs for research is predicated on the presence of data of interest within the system and the ability to extract and compile those data. This is easiest to do when data are entered in standardized, structured formats with standardized nomenclature and definitions. Some organizations—such as the Geisinger Health System, Kaiser Permanente, and the Mayo Clinic—have integrated research functionality into their EHR systems but EHR developers generally do not build research capacity into the architecture of their systems.[371]

The lack of interoperability between systems is also a limitation for multi-institutional studies, although some researchers have developed ways to overcome this problem to some extent. The Electronic Medical Records and Genomics Network, a seven-institution consortium supported by the National Human Genome Research Institute and the National Institute of General Medical Sciences (NIGMS), is testing the ability and feasibility of using EHR systems to investigate gene-disease relationships among diverse populations of patients treated at different institutions.[372] The group recently reported that it was able to successfully identify patients with one of five conditions at each of five participating institutions using different EHR systems; however, they noted that pertinent information—such as racial/ethnic background and exposure to environmental factors (with the exception of tobacco use)—was often lacking or not easily extracted from the records.[373] Past reports of the President's Cancer Panel have emphasized the need to capture such information in a format that is amenable to analysis.[12,37]

In addition to issues related to standardization and interoperability, which are common to all data types, use and sharing of clinical and human research data requires consideration of privacy. Protecting the privacy of human research subjects has become more challenging with the advent of EHRs and other electronic data management resources, which are more easily disseminated, mined, and linked to other data sources than are paper-based records. Much of the discussion surrounding privacy and EHRs focuses on deidentification of data prior to their dissemination for secondary uses such as research. Current standards for deidentification of clinical data are set forth in the U.S. Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. HIPAA states that in order to be shared without patient consent, health information must be either deidentified using the Safe Harbor method, which involves the removal of 18 identifiers enumerated in the Privacy Rule, or an expert must certify that steps taken to deidentify data have resulted in a very small risk that an individual could be identified.[374,375]

We have to look at privacy issues so that patients' genetic [information] will not [put them] at risk but will be beneficial to them, and they won't be afraid to have information in their medical records or available overall.

– Judy Garber, American Association for Cancer Research

Most organizations utilize the more straightforward Safe Harbor method, but this approach does not fully eliminate the possibility of reidentification, particularly for patients in geographic regions with relatively small populations.[376,377] In addition, some of the data suppressed by Safe Harbor may be pertinent to epidemiologic and population-based studies. Expert determination of reidentification risk, sometimes referred to as the Statistical Standard, may allow the inclusion of data that would be excluded under Safe Harbor and also may provide a more quantifiable estimate of the risk of reidentification. Relatively few methodologies for applying the Statistical Standard have been published, although it has been shown that this approach can result in reidentification risk that is equal to or less than that of Safe Harbor.[378] One Panel speaker noted that mechanisms are needed to train experts in deidentifying data and broad discussion is needed to determine acceptable levels of risk with respect to deidentification.[18]

Issues of privacy are further complicated by the collection of genetic data through research and clinical diagnostic tests. The unique nature of genomic DNA sequences means that individuals—along with their associated clinical information—could potentially be identified within an otherwise deidentified data set by a user with prior knowledge of their genomic sequences. Many of the issues related to sharing of human data, and genetic data in particular, are illustrated by genome-wide association studies, which are used to identify genetic factors that influence health and disease. GWAS collect information on markers of genetic variation (SNPs) throughout the genomes of participants. There is widespread recognition in the scientific community of the benefit of making the tremendous amount of information yielded by GWAS broadly available to researchers. Since 2006, investigators have been required to submit data generated via GWAS conducted or funded by NIH to the database of Genotypes and Phenotypes (dbGaP), a resource developed and maintained by the National Library of Medicine.[379,380] All data submitted to dbGaP are deidentified (i.e., not associated with any of the 18 Safe Harbor identifiers enumerated in the HIPAA Privacy Rule) and, to circumnavigate the risk of research participants being identified by their DNA sequences, NIH originally included only aggregate data (representing groups of study participants) in the publicly accessible domain of

dbGaP. However, when a 2008 study demonstrated that it is possible to identify individuals within aggregate genetic data sets,[381] dbGaP and other databases implemented more restrictive data access policies.[382]

There has been much discussion within the scientific community about the best way to balance the privacy of patients with the desire to make biomedical data as accessible as possible for research.[374,383] Among the recommendations that have been made are to maintain open access to types of data for which the risk of reidentification is low (e.g., gene expression data), while requiring researchers to formally request access to data—such as SNP sequences—that are associated with higher risk. Database managers have also been urged to establish clear policies and procedures for assessing credentials of potential data users and create user agreements that explicitly define acceptable use of data.[374]

There is also a realization that the privacy concerns created by large-scale genomic databases are not adequately addressed by traditional informed consent procedures. Some ethicists have begun promoting a new model of consent that allows research subjects to exercise a certain degree of control over how their information and biological materials are used;[384,385] however, such an approach would involve considerable regulatory and logistical changes. At the very least, research participants should be made aware of the risks associated with contributing genetic material for research.

Expanding and Improving the Utility of Biorepositories

Biospecimens—body tissues and fluids—are crucial to the conduct of biomedical research and research progress. These specimens must be numerous and varied, properly collected and preserved, and annotated (accompanied by descriptive information about the patients from whom they have been collected). In addition to tumor specimens, samples of normal tissue are urgently needed for research on tumorigenesis and tumor microenvironment.

Unfortunately, difficulties in obtaining, preserving, annotating, and sharing biospecimens have been an ongoing stumbling block impeding research progress. Despite a long-recognized need for standardized specimen preservation, annotation, and related terminology, such standards do not yet exist. Market research conducted by NCI[386] revealed that researchers commonly limit the scope of their research to what can be done with available samples and that a considerable percentage question their own data because they lack confidence in the quality of the specimens they are using. Moreover, the lack of sufficient sample material for iterative studies means that many experiments are not reproducible.

The geographic and organizational dispersion of existing biosamples complicates efforts to make these resources readily available to researchers who need them. Further, issues of specimen and related intellectual property ownership, incompatible information technology (IT) systems, and responsibility for costs associated with distribution and administration are among other factors that have made adequate sharing of available biospecimens problematic.

...the centers who collect these [tissue] samples feel a great sense of ownership. A great sense of ownership leads to potential intellectual property, and there's definitely a sense of control over those samples. As patients become, increasingly, activists in this field, I do hope that that equation changes somewhat.

– Louise Perkins, Multiple Myeloma Research Foundation

The lack of high-quality, clinically annotated human specimens is the number-one limiting factor of translational research in the United States today; in fact, around the world.

– Carolyn Compton, National Cancer Institute

Informed consent for the use of donated specimens also varies. Access to biospecimens became considerably more difficult with the 2002 implementation of the HIPAA Privacy Rule.[387] Under the Common Rule, patients can give consent for future research use of biological samples or information stored in databases, so long as there is IRB oversight and future uses are described in sufficient detail to allow informed consent. For example, a consent form may specify that the sample tissue will be kept for research to learn about, prevent, or treat the type of cancer that affects the donor.[324] However, such language is too general to comply with requirements of the Privacy Rule, which specifies that the use or disclosure of personal health information must include a description of each purpose of the requested use or disclosure. In essence, the Privacy Rule does not permit an individual to grant authorization for nonspecific research using stored biosamples. This requirement forces researchers to recontact sample donors to obtain consent for every research project for which the samples might be used.[388-391] In some cases, patients may no longer be living and no relatives can be reached who could provide consent. Despite the fact that a donor wanted a sample to be used for research purposes, as one Panel meeting speaker pointed out, one can have a "platinum-grade" specimen and never be able to use it if appropriate consent was not obtained.[392]

A 2009 IOM examination of HIPAA's effects on the conduct of research recommended that "the discordance between the Privacy Rule and the Common Rule be eliminated through guidance explicitly stating that future research may go forward if the authorization describes the types or categories of research that may be conducted with the personal health information stored in a biospecimen bank or database, and if an IRB or Privacy Board determines that the proposed new research is not incompatible with the initial consent and authorization and poses no greater than minimal risk to the privacy of individuals."[324]

Proposed changes[393] to the Common Rule would modify consent requirements for biospecimen use. Currently, research using existing biospecimens (clinical or from prior research) can be done without consent by stripping the specimens of identifiers. Under the proposed reform, the donor's written consent must be obtained for the use of all specimens, even those that have been stripped of identifiers. This consent could take the form of a short form that gives open-ended consent for a variety of biospecimens for most research uses.

Among the efforts under way to improve the availability and quality of biospecimens, the Multiple Myeloma Research Foundation established and funds a repository of multiple myeloma specimens.[394] The samples are sent to the tissue bank from a consortium of 13 academic centers. The tissue bank was launched in 2004; as of late 2010, it held 2,800 purified multiple myeloma tumor samples, most of which had peripheral blood samples from the same patients. The tissue bank also provides the material for whole-genome and -exome sequencing studies.

On a broader scale, NCI has attempted to address many of the biospecimen issues noted above through a state-of-the-science document, Best Practices for Biospecimen Resources,[395] which is made available to the research community. However, NCI is not a regulatory agency and cannot require or enforce adherence to these practices. Through its Biospecimen Research Network (BRN) and Innovative Molecular Analysis Technology for Cancer initiative, NCI is working to communicate a more scientific understanding of what constitutes a high-quality specimen and employ new technologies to help address some of the current biobanking issues. The BRN also is building evidence-based standard operating procedures for biobanks in the United States and worldwide.

Concurrently, through its Cancer Human Biobank (caHUB) initiative, NCI is planning specialized tissue and data procurement using evidence-based protocols and a comprehensive quality control program. The caHUB core functions will play a critical role in supporting translational research both within and outside of NCI. The caHUB infrastructure includes the development of policies and procedures for tissue procurement and processing, patient accrual, data handling, and pathology review. caHUB also is developing a system of data services to manage the flow of clinical and specimen handling data needed to support cutting-edge research and continuous practice improvement.[396]

The administration of drugs intraoperatively [or] preoperatively, the different physiologic stresses, physical stresses, that occur in a pathology suite—they all have the ability to change the specimen, which is still viable until you freeze it or fix it, until you suspend its biological activity.

– Carolyn Compton, National Cancer Institute

It is important to note, however, that biorepositories are able to answer only the questions they are set up to answer. The type and number of samples and processes used to collect and store them may vary by tumor type, which influences what can be done with them and the types of questions that can be answered. Biorepositories and associated standards for collecting and storing tissue are important, but the needs of discrete research projects are both varied and specific. Moreover, even if perfect standards are designed and adopted, this will not address the issue of tissue heterogeneity—a biological rather than technical issue—including heterogeneity within individual tumors.

CHAPTER 7

Strengthening the Cancer Research and Care Workforce

The coming years hold extraordinary promise for improving the current understanding of cancer and learning to prevent it, find it early when it does occur, and treat all forms of the disease effectively without significant side effects. Yet, without a talented, innovative, and diverse workforce of researchers and clinicians, these much-needed advances cannot become reality.

The United States is facing critical shortages in both its research workforce and physician and nonphysician clinical workforce. As the sections below detail, it will not be sufficient merely to maintain current levels of research and clinical capacity. To improve the ability to expand and capitalize on scientific discoveries, rapidly deliver such discoveries in the form of new treatments and other interventions to benefit patients with cancer, and meet the needs of a growing population of cancer patients and survivors, the research and care workforce must grow.

The Cancer Research Workforce

An Aging Workforce

Like the general population, the nation's cadre of highly skilled scientists is aging. It is projected that by 2020 NIH-funded investigators over age 68 could outnumber scientists under age 38 (Figure 12). The average age of NIH-funded scientists is 51 years.[397]

The workforce of basic biomedical researchers numbers approximately 120,000 personnel with doctoral degrees; they are distributed primarily between academia (62,000), industry (29,000), and government and nonprofit organizations (12,000).[398] The median age of this workforce in 2006 was 52.3 years.

Clinical scientists, as defined by the U.S. Congress in the Clinical Research Enhancement Act of 2000 (P.L. 110-148), are those whose research involves interactions with patients, use of diagnostic clinical materials or data, or populations in any of the following areas:

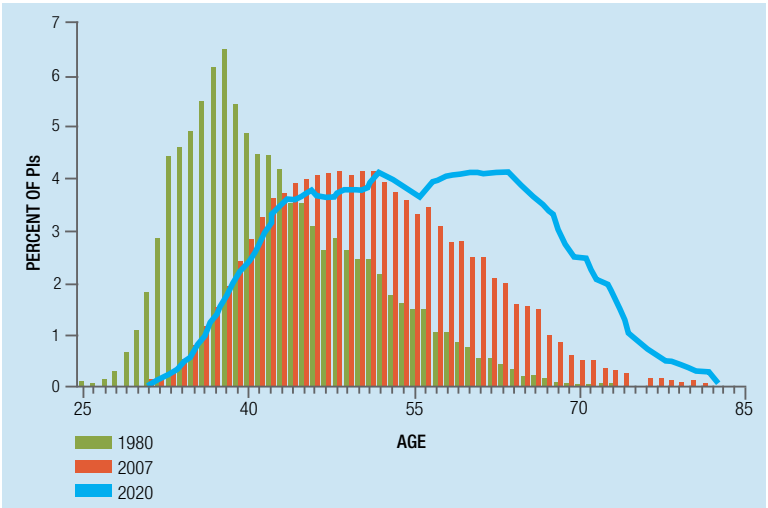
- Disease mechanisms (etiopathogenesis)
- Bidirectional integrative (translational) research
- Clinical knowledge, detection, diagnosis, and natural history of disease
- Therapeutic interventions, including clinical trials of drugs, biologics, devices, and instruments
- Prevention (primary and secondary) and health promotion
- Behavioral research
- Health services research, including outcomes and cost-effectiveness
- Epidemiology
- Community-based trials

The breadth of this definition—which includes translational, therapeutic, prevention, and health services research, among others—makes it difficult to accurately determine the size of the clinical research workforce. Nonetheless, it is generally appreciated that the clinical research enterprise has for years been underdeveloped.[398] This segment of the research workforce also is aging; the median age of medical school faculty in 2009 was 52 years.[399]

To make this workforce that's going to...do innovative research, do translational research, care for patients in a much more sophisticated way than we currently do...[we should] ask the question: Are we still, as a country, the beacon for those kids, people, young people around the world who want to be leaders in cancer research, in training in oncology, and doing the things that we need?

– William Hait, Ortho Biotech Oncology Research & Development

Figure 12
Age Profile of NIH Investigators



Source: Kaiser J. The graying of NIH research. Science. 2008;322(5903):848-9.

The behavioral and social science research workforce, which includes basic, translational, and clinical scientists, was estimated at more than 108,000 in 2006. The largest proportion of these doctorate-level workers is employed in academia, followed by industry, government, and other sectors.[398] Relative to the basic biological sciences workforce, a greater percentage of these scientists is employed in industrial, government, and other sectors.[398] The median age of behavioral and social scientists in 2006 was 55.4 years.[398]

As these data show, significant portions of the research workforce, regardless of specialty, are nearing retirement age. The Institute of Medicine notes that the recent economic downturn has likely deterred some researchers from retiring until their retirement portfolios regain some of their lost value.[398] Though this dynamic has the benefit of keeping the workforce from shrinking as fast as it otherwise might, it also means that these researchers continue to be awarded grant funding that might otherwise go to younger investigators, thereby accelerating their professional advancement.

Supporting Young Investigators

To maintain the critical cadre of biomedical scientists, young researchers are needed to take the place of veteran investigators as they retire. But to increase the research workforce, a far greater number of new scientists is needed to explore and answer critical questions in cancer prevention, early detection, diagnosis, treatment, and survivorship.

As noted earlier, young scientists are particularly disadvantaged in the NIH grant application and peer review process; the current system favors established investigators over young scientists who could bring fresh perspectives to answering important cancer research questions. Some awards targeting young investigators have been established by NIH, NCI, and other research funders (see Appendix D), but more are needed. As of 2007, the average age at which investigators received their first NIH R01 grant (or equivalent) was 42.6 years.[397] Figure 13 shows the steep decline in NIH research awards to principal investigators aged 35 years and younger from 1970 through 2003. In academia, investigators who fail to win independent research funding after a period of years are unlikely to ever become tenured and may come to be perceived as a liability to the institution, both financially and in terms of the institution's reputation.

Most young investigators' NIH grant proposals are rejected numerous times before being accepted for funding. The process of revising and resubmitting proposals, particularly with the long lag time between each submission and notification of peer review results, can be so discouraging that talented individuals may seek employment in industry or abandon careers in research entirely. With the serious decline in cancer (and most other biomedical) research support, fewer and fewer highly meritorious grant applications are being funded. Moreover, and quite importantly, these dynamics strongly discourage young investigators from proposing higher-risk research, even if the potential reward might be a transformative leap in progress.

To level the playing field for young scientists applying for their first R01 grants, NIH established a minimum number of awards to be made to first-time applicants in FY2007—in essence, a quota—that, as shown in Figure 14, contributed to the increase in new R01 awardees that year.[400,401] However, an analysis of the peer review scores of first-time applicants compared with scores of established investigators revealed a bias against young investigators among peer reviewers, most of whom were established scientists, and a backlash against the quotas.[402] NIH subsequently revised the policy to indicate that new investigators applying for new R01s should be supported at rates comparable to those of established investigators rather than setting a target number of awards.[403] Since these changes were implemented, new investigators and established investigators submitting new grant applications have had nearly equivalent success.[400,402]

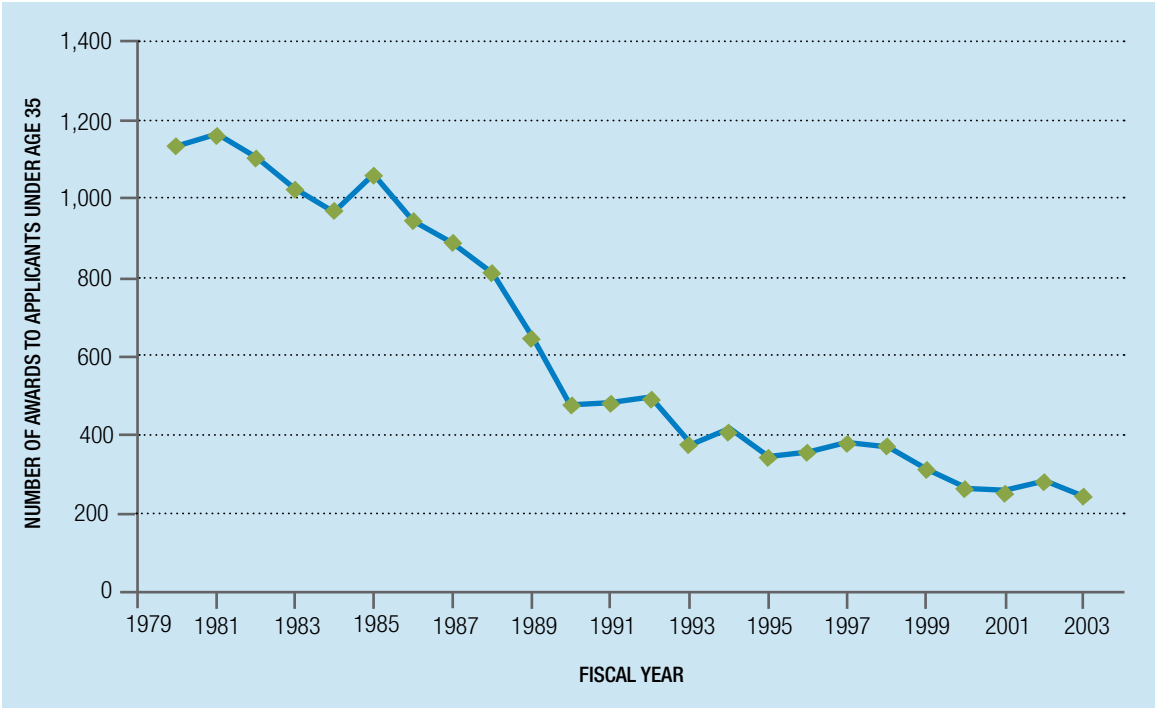
I know young people who are very excited about science, but when they are trying to make decisions in college, they see one pathway where after they graduate with a bachelor's degree they can go into investment banking and have a pretty good chance of making some pretty good money and a good career and so on in a relatively short time.

When they look at research, they see "I have to invest ten years of my life and if I do that the chances of me landing an academic tenure track position is very low, and even if I do that there's 10 percent funding success for established people in those tenure track positions." So they see it as almost like going down a pathway where they almost have to win the lottery in order to be successful in their career.

– Sharyl Nass, Institute of Medicine

Figure 13

Number of NIH Research Awards Made to PIs 35 Years of Age and Younger



Source: NIH Office of Extramural Research. In: National Research Council. Bridges to independence: fostering the independence of new investigators in biomedical research. Washington (DC): National Academies Press; 2005.

We invest in human capital by funding young investigators. I would say to anybody involved in funding research today [that] there is a crisis out there, and we are liable to lose a generation of researchers, especially physician scientists who want to have career[s] in academic medicine....

– Howard Soule, Prostate Cancer Foundation, The Milken Institute

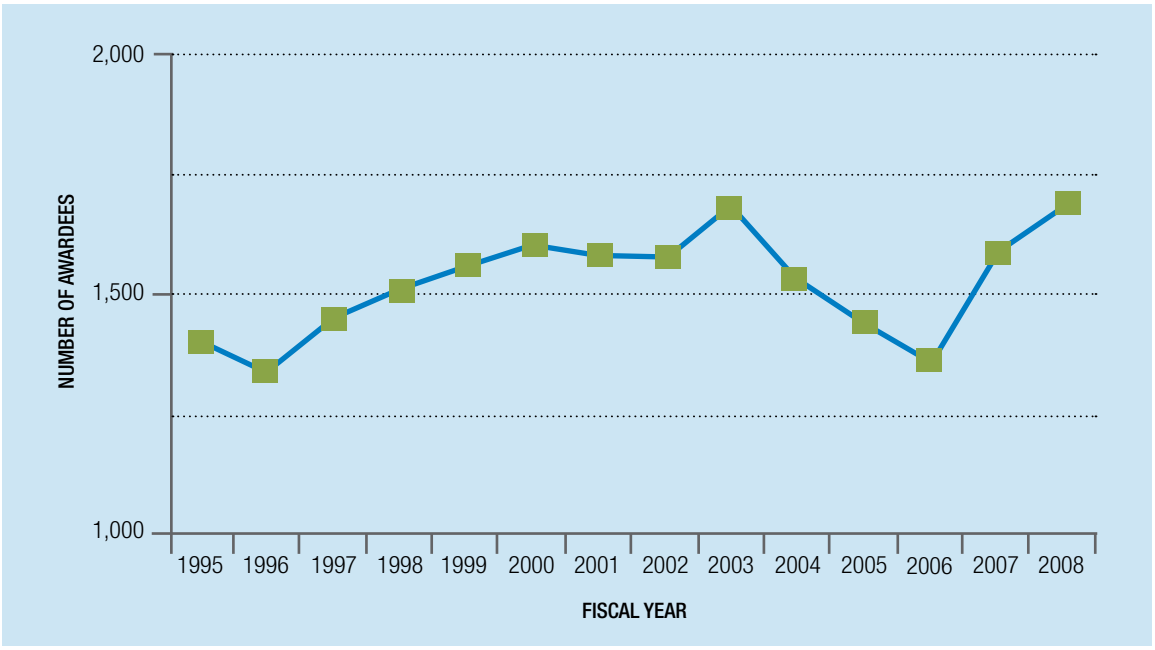
Physician-scientists (M.D./Ph.D.), who are essential to bridging the gap between basic and clinical science, require special support. Training for these dual-degree scientists takes approximately eight years. A key barrier faced by many M.D.s with an interest in research is cost; most M.D.s graduate from medical school with high levels of educational debt (averaging $145,020 in 2010[404]) that may prevent them from entering research training. In addition to the weight of previously accumulated educational debt, potential M.D./Ph.D.s must consider the long period of training and the uncertainty of success, particularly in the current economic and research funding environment.[398]

One author suggests that international medical graduates (IMGs) may be an overlooked source of physician-scientists, since most IMGs have minimal, if any, debt and many are eager to remain in the United States once they complete their postdoctoral training.[405]

The NIH Medical Scientist Training Program (MSTP), established in 1964, funds research training leading to the M.D./Ph.D. degree.[406] The program has been highly successful in attracting outstanding physicians into research, and these graduates have proven more successful at winning NIH R01 funding than applicants with either an M.D. or Ph.D. only.[407] MSTP graduates may receive training not only in the biological sciences, but also in the chemical and physical sciences, social and behavioral sciences, economics, epidemiology, public health, computer science, bioengineering, biostatistics, and bioethics. A 2010 study[408] of MSTP graduates found that many were conducting

Figure 14

NIH First-Time R01 Equivalent Awardees, 1995-2008



Source: Kaiser J. Zerhouni's parting message: make room for young scientists. Science. 2008;322(5903):834-5.

translational and patient-focused research as well as basic research and adding research strength to major clinical departments in medical schools across the country.

Current economic constraints notwithstanding, an IOM committee on the research workforce recommended that MSTP support be increased in a phased manner by 20 percent, which would raise the number of training slots from 911 to about 1,100.[398] To improve health resource accessibility, IOM further recommended that the increase be accomplished by increasing the number of MSTP programs rather than increasing the size of existing programs. Examples of other federal and nonfederal training support programs for physician-scientists are included in Appendix D.

Bringing New Disciplines into Cancer Research

Behavioral and social scientists and nontraditional cancer research participants such as engineers, mathematicians, and physical scientists need to be brought more fully into the cancer research workforce. A 2011 IOM report on research training[398] notes that only 1 percent of NIH research training support is allotted to the behavioral and social sciences, despite the growing importance of these disciplines to the nation's health. The report surmises that the lack of support may in part be due to the lack of an NIH Institute focused exclusively on basic behavioral and social science research. The report authors recommend that: (1) training programs in basic behavioral and social sciences that cross-cut disease categories and age cohorts be established at NIGMS in collaboration with the NIH Office of Behavioral and Social Sciences Research; (2) training programs in basic and traditional behavioral and social sciences that bear on specific diseases and age cohorts be housed in all of the relevant Institutes and Centers; and (3) behavioral and social science training relevant to biomedical and health science research be included consistently in the MSTP.

Through a number of collaborations and team science initiatives, nontraditional disciplines have begun to be applied to cancer research questions, particularly in translational research. Examples of these activities are described in Chapter 5, pp. 66-68. Efforts such as these hold great promise for bringing new perspectives and innovative approaches to bear on complex cancer prevention, detection, diagnosis, and treatment problems.

...whatever we wind up doing in terms of tweaking the system and finding mechanisms by which we can give out money...we [must] always look very quickly upstream to the youngest brilliant people who are coming out and make sure that there are very clear mechanisms by which they, too, can assure themselves that this is sustainable....

– Robert Urban, Massachusetts Institute of Technology

The Cancer Care Workforce

As the implications of the impending oncology workforce shortage have become clearer, efforts have been made to better quantify the shortfall and identify existing and potential strategies to address it. An IOM workshop on oncology workforce issues concluded that this shortage is of great concern because it will diminish both access to and quality of care for people with cancer and may increase the burden on families of cancer patients and survivors.[409] IOM workshop participants further noted that cancer care shortfalls are likely

...never has the knowledge been higher. We have targets. We have treatments, and there's a lot of hope, but I fear that there's a slowdown of progress because the resources are diminished....I'm very concerned about the future, especially as it affects human capital. Without people, we get nowhere.

– Howard Soule, Prostate Cancer Foundation, The Milken Institute

to affect poorer communities disproportionately since more affluent communities will be able to outbid others for scarce human resources; this scenario raises important social justice issues that also must be addressed. The Patient Protection and Affordable Care Act contains numerous provisions aimed at increasing the numbers, distribution, and diversity of physicians, nurses, and other medical personnel needed to provide cancer and other medical care to the population.[410]

As the population ages, the number of new cancer cases is expected to increase dramatically. An NCI-sponsored study projected that the number of cancer patients/survivors in the United States will skyrocket by 55 percent between 2005 and 2020.[411] The study also indicated that oncology-related medical visits are expected to increase from 38 million in 2005 to 57 million in 2020. Moreover, the population of cancer survivors is expected to grow by 81 percent by 2020; currently, 68 percent of oncologist visits are for patients one or more years postdiagnosis.[412]

Oncologists and Other Physicians

According to one estimate, by 2015 the shortage of physicians of all kinds will number 62,900 doctors; by 2025, the shortage is projected to more than double to 130,600.[413] Much of the unmet need will be for primary care and internal medicine physicians. More than 60 other reports issued in the past decade by universities, state governments, private foundations, and medical societies also have identified physician shortages in already underserved areas and in many specialties.[414] Primary care providers are critical to improving cancer patient outcomes since they typically are the gatekeepers to cancer care, including cancer clinical trials. As the health care system evolves—ideally, toward a more patient-centered approach and better coordination of care—the primary care physician's role can be expected to expand (see also Chapter 8).

Although the nation's supply of physicians has fluctuated considerably over the past several decades, the Federal Government has remained a strong supporter of graduate medical education (GME). This support is provided through the Medicare program, which in 2010 provided $9.5 billion to teaching hospitals toward the training of approximately 100,000 medical residents.[415,416] It is of great concern that GME program cuts have been seriously considered in Congress as part of national budget deficit reduction efforts.[412] Reduced support for GME would mean fewer postdoctoral training positions for medical graduates, thereby cutting the nation's capacity to train new physicians at a time when physician shortages are escalating. Since it takes about a decade to educate and train a new doctor, constraining the training pipeline of new physicians now will have significant long-reaching detrimental effects that cannot easily or quickly be reversed.

At the same time, there is a growing discussion as to whether the GME program as it currently is structured and administered should be modified to meet society's changing needs for medical expertise (reflecting regional differences and disparities); better emphasize collaboration, communication, and transitions in care; and provide quality care at lower cost.[417] Several members of Congress have requested that the IOM undertake an independent review of the governance and financing of the GME system, including inequities in funding across states based on their needs and capacity, with report completion requested by the third quarter of 2012.[418]

An undersupply of primary care physicians board-certified in internal medicine is of special concern to the cancer care workforce because doctors often become certified in internal medicine before going on to specialize in oncology.

A 2007 workforce study by the American Society of Clinical Oncology[412] projected that the demand for oncologists' services will significantly exceed capacity by 2020—demand is expected to increase by 48 percent, yet the number of visits the workforce can provide is expected to increase by only 14 percent. Over half of currently practicing oncologists are aged 50 years and older. One speaker at a Panel meeting noted that the expected gap between supply and demand in 2020 could prove to be much larger than baseline projections suggest if younger physicians have lower lifetime productivity than their predecessors and/or if visit rates increase due to changing practice patterns or demand for services.[419]

There is some migration of academic oncologists to community practice. An Association of American Medical Colleges study[420] found that half of oncology graduating fellows start out in academic settings immediately after completing training, with the remainder going into private practice. About three to seven years later, however, many academic oncologists reevaluate their careers. Due to a lack of success in acquiring research grants, the strains of raising a family, or both, many leave academic institutions and pursue community practice. The study found that the reverse is not true; private practice oncologists seldom move into academic settings.

Expanding the Expertise of Oncologists and Other Physicians

To keep pace with new scientific knowledge about cancer and limit the effects of physician shortages, it has been suggested that oncologists and other physicians may need to become more knowledgeable in aspects of treatment not previously part of or central to their roles. For example, one report[421] on the looming shortage of oncologists available to treat the growing population of older Americans, who are at highest risk for cancer, concludes that in the coming years, primary care physicians will need to learn to treat cancer.

...do we think as a nation that...young people have valued a career in research, cancer research, clinical research, whatever research it happens to be, as something really exciting and rewarding for a career's work? And my guess is that that's changing in the wrong direction.

– William Hait, Ortho Biotech Oncology Research & Development

In addition, because treatment choices increasingly may be guided by individual patients' genetic characteristics, it has been recommended that education in genetics be incorporated into oncology and other training.[329,422] Further, both primary care physicians and community oncologists need to have a better understanding of clinical trials so they can accurately explain to patients the benefits and risks of trials as a treatment option and be effective participants in research to improve the quality of cancer care.

The Nonphysician Clinical Workforce

The nonphysician workforce includes but is not necessarily limited to nurses (including oncology nurses and nurse practitioners [NPs]), physician assistants (PAs), radiation and imaging technologists, radiation physicists, oncology and other social workers, patient navigators, and community health workers. These members of the oncology care team, who care for cancer patients and survivors and participate in cancer screening and prevention activities, have a direct effect on patient outcomes. Their importance in bringing the fruits of cancer research to patients should not be underestimated. Moreover, it is becoming increasingly clear that to help offset physician shortages and contain health care costs, nonphysician providers must take over some of the routine care for which they are appropriately trained but that now is provided primarily by physicians.[415,423]

Nurses

Nurses interact with oncology patients across the continuum of care from prevention and early detection through treatment and survivorship. Oncology nurses administer complex chemotherapies and supportive care drugs, educate patients and their families, and help them cope with physical and emotional effects of cancer and cancer treatment. Nurse scientists have a key role in developing supportive care interventions. The top recommendation of a 2011 IOM report was that nurses be allowed to practice to the full extent of their education and training.[424]

Estimates of the nursing workforce shortage in the United States vary—from a shortage of 260,000 nurses by 2025[425] to as many as 1 million full-time nurses by 2020.[421,426] A major factor driving the projected nurse shortage is aging of the nursing workforce—the largest age group of registered nurses (RNs) was projected to be between 50 and 60 years old in 2010, and many are expected to retire by 2025.[427] In addition, there are too few nurse training programs, resulting in a narrowing pipeline of new nursing students.[421] In 2011, U.S. nursing schools turned away more than 75,000 qualified applicants because of insufficient clinical teaching sites, numbers of faculty, clinical sites, classroom space, and clinical preceptors, as well as other budget constraints.[428]

A recent survey found that nearly 60 percent of nursing schools have full-time faculty vacancies and another 17 percent need additional faculty but are not actively hiring, often because they have insufficient funds.[429] The vast majority of these schools require or prefer candidates to have doctoral degrees, but persuading nurses to pursue Ph.D. degrees to teach and conduct research is difficult because doctorate- and master's-prepared clinical nurses can earn more in health care administration or as nurse practitioners or nurse anesthetists.[409,430]

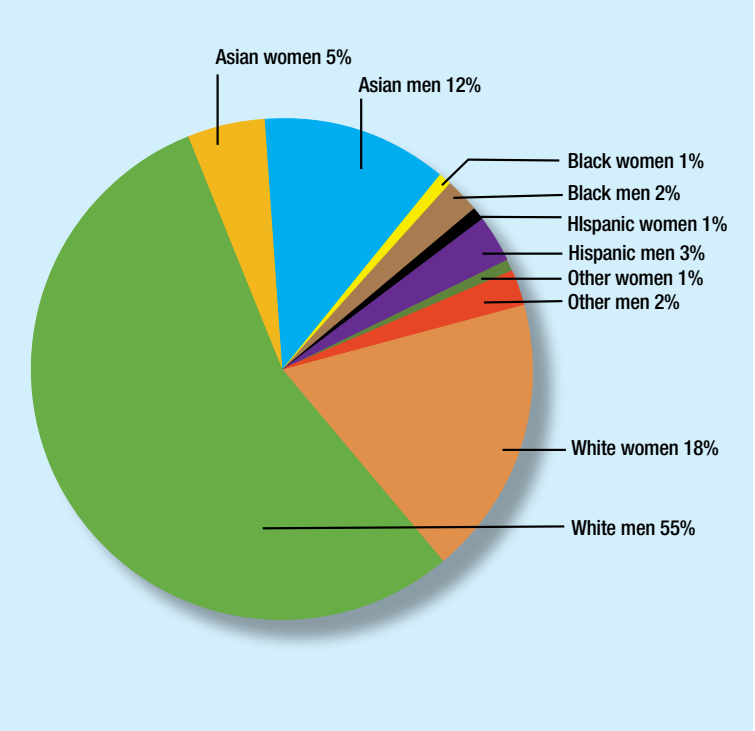
Advance practice nurses (e.g., oncology nurses, NPs) and nurse scientists have made significant contributions to the development of interventions for symptom and side effect management, psychosocial and behavioral issues, and health promotion in diverse practice settings. The Association of American Cancer Institutes notes that the multidisciplinary approach to high-quality cancer care would be difficult to sustain without nurse clinicians, educators, administrators, and scientists.[421]

Other Nonphysician Providers

Similarly, PAs are becoming increasingly important members of cancer care teams, and some PAs choose oncology as their area of specialization. A study[431] of collaborative practice arrangements found that oncology practices that integrated nonphysician practitioners (NPPs), specifically NPs and PAs, into their practices were more productive and physicians, NPPs, and patients all reported high levels of satisfaction. Likewise, patients reported high satisfaction with all aspects of the collaborative care received. The investigators concluded that the integration of NPPs into oncology practice offers a reliable means of addressing increasing demand for oncology services without adding physicians.

Shortages of other health care professionals who provide cancer care—radiation and imaging technologists, laboratory personnel, pharmacists, social workers, and other public health workers—also will affect cancer care quality across the entire care continuum. For example, shortages of radiation and imaging technologists have the potential to delay patients' treatment and interrupt disease monitoring. The population of oncology social workers, which may number no more than about 1,000 nationwide,[432] help patients cope with cancer-related depression and myriad other psychosocial issues; they also frequently serve as patient navigators and are active in cancer screening and assessment activities. The shrinking cadre of oncology social workers, coinciding with the growing social work needs of increasing numbers of older cancer patients, has the potential to translate into a significant toll in human, personal, and economic costs.[432]

Figure 15
Scientists and Engineers in Science and Engineering Occupations: 2006



Note: Hispanic may be any race. Other includes American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, and multiple race.

Source: National Science Foundation, Division of Science Resources Statistics. Women, minorities, and persons with disabilities in science and engineering: 2011. Arlington (VA): NSF; 2011. Special Report NSF 11-309. Available from: http://www.nsf.gov/statistics/wmpd/pdf/nsf11309.pdf

Cross-Cutting Workforce Issues

Workforce diversity, recruitment, and retention issues are important concerns for strengthening the cancer research and care workforce.

Workforce Diversity

A 2011 report[433] by the National Academy of Sciences, National Academy of Engineering, and Institute of Medicine (NAS/NAE/IOM) notes that minorities are seriously underrepresented in science and engineering (S&E) occupations, yet they are the most rapidly growing segment of the population. As Figure 15 shows, the S&E workforce remains largely white and male.

....we do not want to know who you are. We don't want to know your institution, because no matter how much you think, "Well, that's not going to bias me," always you will be biased.... So we just take that away completely. [The application is] one page, and we do not allow preliminary data.
– E. Melissa Kaime, Congressionally Directed Medical Research Programs, Department of Defense

According to the NAS/NAE/IOM report, underrepresented minorities comprised just 9.1 percent of all college-educated Americans in academic and nonacademic S&E occupations in 2006. To match their share of the overall U.S. population (28.5% in 2006), participation in S&E by these populations would have to triple. The NAS/NAE/IOM report further notes that underrepresentation of this magnitude in the S&E workforce stems from underproduction of minorities academically prepared in S&E at every level of postsecondary education. Moreover, representation diminishes further at each level up the academic ladder. In 2007, graduate school students from underrepresented minorities comprised 17.7 percent of those earning S&E bachelor's degrees, 14.6 percent of those earning S&E master's degrees, and only 5.4 percent of students earning S&E doctoral degrees.[434]

In 2008, among S&E doctorate holders employed full-time as full, associate, or assistant professors in four-year colleges or universities, women were less likely than men to have been supported by federal grants or contracts, and underrepresented minority women were the least likely to have had such support (Figure 16).

At NIH, the predominant federal funder of biomedical research in the United States, the racial/ethnic imbalance in grant awards to PIs is clear; Table 8 arrays the race/ethnicity of NIH-funded PIs in Fiscal Years 2000-2006.

A 2011 NIH-commissioned study [435] of investigator-initiated (R01) grant applications over the same period of years (FY 2000-2006)

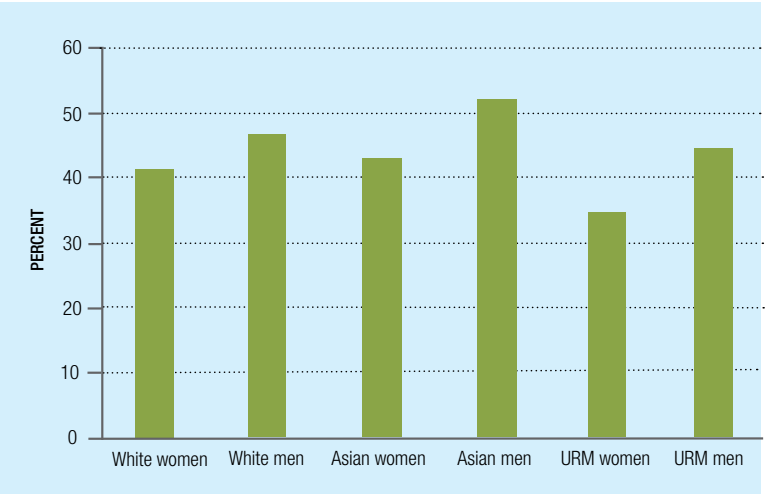
found that African American researchers received less R01 grant funding than did white applicants. Even after controlling for applicants' background, country of origin, training, previous research awards, publication record, and employer characteristics, this review of more than 83,000 applications submitted by 40,000 researchers determined that black/African American applicants were 13 percent less likely to receive R01 funding compared with whites. Asian applicants were found to be 4 percent less likely to receive funding compared with their white counterparts. Moreover, the study found that black/African American and Asian applicants resubmitted applications more times before being awarded R01 grants compared with white applicants. At the same time, black/African American and Hispanic applicants were significantly less likely than white investigators to resubmit unfunded applications. Responding to the findings, NIH developed and is implementing a framework[436] for action to:

- Increase the number of early career reviewers, including those from underrepresented populations; a New Early Career Reviewer program will encourage promising junior faculty to participate in peer review panels.
- Examine the grant review process for conscious and unconscious bias and develop interventions to remediate identified problems.
- Improve support for grant applicants; this may include providing additional technical assistance in grant preparation and encouraging more extensive and effective mentoring of junior faculty.
- Gather experts through two high-level advisory boards formed by the NIH Director to identify other possible action steps to address this issue.

Consistent with the NIH-wide patterns noted above, non-Caucasian U.S. citizens and permanent residents remain significantly underrepresented in the cancer research workforce as a whole relative to their proportion of the general population.

Figure 16

Percentage of Full-Time Faculty Members with Science and Engineering Doctorates Who Received Federal Support, 2008*



URM – underrepresented minority.

*Faculty members at four-year institutions.

Source: National Science Foundation, Division of Science Resources Statistics. Women, minorities, and persons with disabilities in science and engineering: 2011. Arlington (VA): NSF; 2011. Special Report NSF 11-309. Available from: http://www.nsf.gov/statistics/wmpd/pdf/nsf11309.pdf

As described by a speaker at one Panel meeting, NCI offers a wide range of cancer research training grants for individuals from underrepresented groups beginning at the high school level and continuing through to a first independent research grant (R01 or equivalent), though additional funding is needed to reach and support a greater number of potential cancer researchers from these populations.[437]

Through its Continuing Umbrella of Research Experiences (CURE) program,[438] NCI provides several mentored training experiences as well as exposure to the peer review process through participation in mock review sessions. Mentors can be particularly valuable for trainees from underrepresented groups who still are unlikely to encounter many researchers in their fields who "look like them." NCI further encourages trainees, once established as competitive independent

Table 8

Principal Investigators on NIH Research Grants, by Race/Ethnicity, FY 2000-2006

Fiscal Year	White (%)	African American (%)[a]	Hispanic (%)[b]	Other (%)[c]
2000	86.2	1.3	2.9	11.4
2001	85.7	1.3	2.9	12.1
2002	85.2	1.5	3.1	12.4
2003	84.4	1.6	3.3	13.2
2004	83.5	1.7	3.3	14.1
2005	82.8	1.7	3.5	14.8
2006	82.1	1.8	3.5	15.4

a African American race data may contain individuals reporting Hispanic ethnicity, as well as individuals reporting more than one race.
b "Hispanic" includes Hispanic race, plus individuals reporting Hispanic ethnicity (for these individuals the data include individuals who are represented in one or more of the racial groups).
c Includes Asian, Native Hawaiian or Pacific Islander, and American Indian or Alaska Native.

Source: Kington, R. Deputy Director, National Institutes of Health, Presentation to Committee; 2008 Jun 11.

scientists, to themselves become mentors. Research training grants also are targeted at women scientists returning to the workforce after a period of family-related absence and to disabled individuals pursuing cancer research careers.

Diversity in the cancer care workforce also needs strengthening. The Panel has previously reported extensively on these issues, and readers are directed to those reports[8,11,37,439,440] and the Panel's recommendations for increasing diversity in the cancer care workforce.

Recruitment and Retention

Preparing and inspiring young people to consider careers in science and medicine are most successful when outreach and core academics start at the K-12 grade levels.[441] It is essential that grade school children achieve competence in fundamental mathematics and science. Likewise, middle school students need a strong foundation in science and mathematics to prepare them for high school curricula in these areas. Without adequate preparation at these early stages, students are highly unlikely to ever enter the biomedical research and medical training pipelines. As one measure to address this issue, the IOM has recommended that NIH and the Department of Education work together to provide incentives to attract biomedical and behavioral science trainees to teach middle and high school science.[398]

Mentoring

As noted above, mentoring is recognized as a key factor not only in science career advancement, but in retaining talented scientists and medical personnel in the workforce. Moreover, lack of effective mentoring has been identified as an important reason trainees decide not to pursue research careers. Among other benefits, mentors provide trainees with the perspective that comes from research experience, assist trainees in making contacts and learning research processes and procedures at their institutions, and help young

scientists home in on their areas of greatest interest and plan career trajectories. As Table 9 suggests, effective mentoring requires considerable time and effort. The NIH K24 award for mentors has been successful in developing the careers of clinical scientists, and it has been suggested that its use be extended to include the basic sciences.[398] Other support for mentors is limited, however, and more support mechanisms for mentors are needed to encourage established scientists to make this investment in the next generation of researchers. Prospective mentors also may benefit from training on how to be an effective mentor.

Table 9

Key Characteristics of Effective Mentor/Trainee Relationships

Mentor	Trainee
Shows that research is interesting and rewarding	Learns different options and how to weigh them
Provides opportunities for laboratory experiences	Identifies appropriate institutions and laboratories
Provides expertise in research area and techniques	Learns to narrow field of study
Introduces the trainee to the scientific community	Enhances research knowledge and skills; builds positively on strengths
Helps the trainee understand scientific organizations, their relationships, and various aspects of their function	Identifies potential advisors and collaborators
Provides needed resources and information	Learns scientific organizations and their functions
Acts as a sounding board for professional and personal matters	Brings new perspectives and values to the research community
Provides encouragement	Builds personal bonds and good interpersonal/interprofessional relationships
Offers personal attention and guidance	Builds self-confidence
Helps trainee contend with academic barriers; provides advice about thesis and authorship issues	Counteracts isolation; develops social support and publication competence
Provides advice about balance between home and laboratory	Learns to evaluate abilities realistically
Provides advice about career options	Learns good communication skills
Provides help with self-promotion and professional survival	Builds professional competence; learns career mobility and forecasting

Adapted from: National Cancer Institute Center to Reduce Cancer Health Disparities. The CURE paradigm: enhancing workforce diversity. Bethesda (MD): NCI; 2011. NIH Publication 11-7945.

Work/Life Balance

The stresses of traditional research and medical care professions are influencing the career choices of both men and women. Both sexes increasingly are demanding a better balance of work and personal life and are less willing to work the often grueling schedules that are common among professionals in these fields.[442,443] Some researchers are leaving academia for jobs in industry, government organizations, or nonprofit groups, while some clinician-scientists are choosing specialties such as dermatology, pathology, ophthalmology, and radiology that allow more manageable lifestyles than oncology research and more controllable schedules than oncology care.[444]

Issues Specific to Women Scientists

Reports[326,445] have examined the loss of highly trained women scientists, especially during the career transition from postdoctoral fellow to faculty or tenured positions. At NIH, only 29 percent of the tenure-track PIs and 19 percent of tenured PIs (the NIH equivalent of assistant and full professors, respectively) were women in 2007.[445] These percentages have been virtually unchanged for a decade.

The reasons for women's attrition from academic research are numerous but fall into two general categories: family obligations (including plans to have children) and confidence issues.[446-448] For example, women's greater family caregiving role and associated need for work schedule flexibility may be seen as a lack of commitment that puts them at a disadvantage for promotion. Inadequate child and elder care options may limit women scientists' professional travel and hamper participation in the informal networking that helps solidify professional relationships. Women who leave research to have children may find reentry difficult and be unable to recover their career momentum. Some attempts to accommodate family obligations, such as extending the tenure track, are actually looked upon negatively.[449,450] As a 2006 report on women in academic science and engineering[446] notes, anyone lacking the work and family support traditionally provided by a "wife" is at a serious disadvantage in academia—about 90 percent of the spouses of women faculty are employed full time, while less than half of the spouses of male faculty work full time.

Confidence issues may manifest as a lower belief in the likelihood of achieving tenure among women scientists compared with male counterparts that in turn may translate into a reduced willingness to repeatedly submit and resubmit applications for independent grant funding.[445] In addition, women—especially minority women—are rarely in leadership positions in science, particularly at the highest levels; this lack of successful role models has been cited as a factor in women's departure from academia.[446]

Table 10

First-Year Support for Doctoral Students in the Biomedical Sciences

Field	Percent		
	Full Support	Partial Support	No Support
Biochemistry, Biophysics, and Structural Biology	96	3	1
Biomedical Engineering and Bioengineering	86	7	7
Cell and Developmental Biology	97	1	2
Genetics and Genomics	93	4	4
Immunology and Infectious Disease	95	4	1
Integrated Biomedical Sciences	97	1	2
Microbiology	96	2	2
Neuroscience and Neurobiology	96	3	1
Nutrition	88	10	2
Pharmacology, Toxicology, and Environmental Health	94	4	2
Physiology	96	2	2
Total	95	3	2

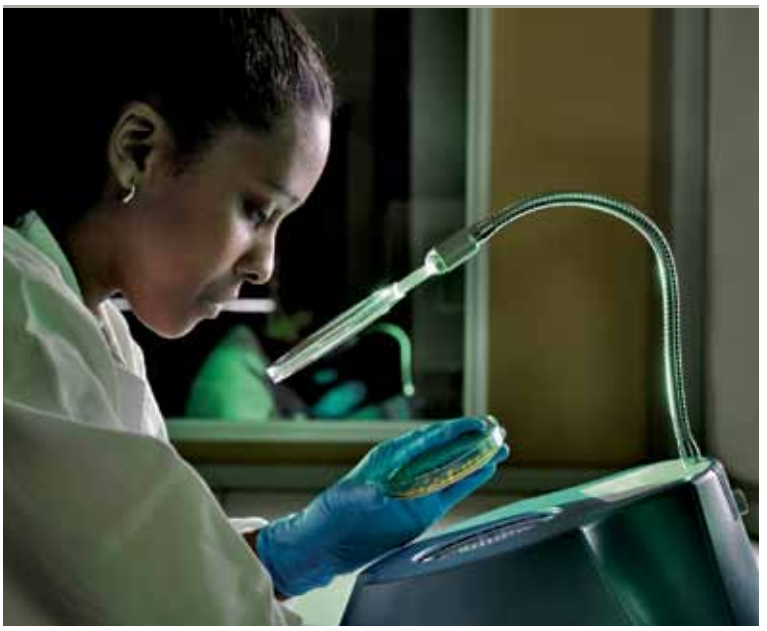
Source: National Research Council. A data-based assessment of research-doctorate programs. Washington (DC): The National Academies Press; 2010.

Even after achieving faculty positions, women's success is affected by other barriers to advancement in academic science that have yet to be adequately addressed. For example, studies at MIT and elsewhere have noted that women faculty often are underpaid relative to men.[451,452] Women faculty also are less likely than men to have opportunities to serve on meaningful department and university committees or participate in collaborative efforts, more likely to feel professionally isolated, and more likely to have their research devalued by colleagues.[453,454]

Taken together, these factors affecting female researchers result in a tragic loss of scientific talent at a time when it is greatly needed.

Training Costs

The cost of research training and other advanced education in the life sciences is significant, but an average of 95 percent of Ph.D. candidates in biomedical sciences receive full support while in graduate school (Table 10), many through the NIH National Research Service Award program,[455] which provides tuition coverage and a stipend, or other NIH grants. In addition to federally funded support, a limited number of non-federal programs exist under which individuals who are or will be conducting biomedical research in specified areas can receive financial support during their training. For example, the Howard Hughes Medical Institute, ACS, and Susan G. Komen for the Cure offer biomedical research training opportunities.[456-458] However, Ph.D. trainees in the behavioral and social sciences and graduate



students in the clinical sciences tend to have fewer financial support options and are much more likely to be self-supported.[398]

Rather than grants or stipends, some trainees may receive full or partial repayment or forgiveness of their student loan expenses. For example, NIH offers loan repayment to intramural researchers doing AIDS research, general research (including Accreditation Council for General Medical Education fellows), and clinical research for individuals from disadvantaged backgrounds.[459] Researchers outside NIH can qualify for loan repayment if they are or will be conducting clinical, pediatric, health disparities, or contraception and infertility research. As with the intramural program, loan repayment also is available to clinical researchers from disadvantaged backgrounds. The National Health Service Corps offers repayment of medical school loans in exchange for a two-year full-time (or four-year half-time) commitment to practice in a medically underserved area.[460] Similar programs for physicians are available to military personnel[461] and to those who commit to practicing at an Indian Health Service or other Indian health program priority site. Some states have loan repayment or loan forgiveness programs for health service providers, including physicians, nurses, nurse practitioners, physician assistants, and social service workers, and a few such programs may exist outside of government.

Table 11

Selected Strategies for Expanding the Oncology Research and Care Workforce

- Conducting outreach to high schools
- Conducting national advertising campaigns that emphasize the positive aspects of oncology professions (including job opportunities)
- Offering internships for students with an interest in either laboratory or clinical research that include preceptors or mentoring
- Providing trainees with grant writing assistance and mock peer review experiences
- Facilitating strong mentor/trainee relationships; encouraging faculty from underserved populations and female faculty to serve as mentors and role models for trainees
- Recognizing and validating alternative career paths in research (e.g., cancer-related research conducted outside of academic settings, new product invention and development, teaching secondary school science, careers in intellectual property law)
- Allowing more flexible work schedules that enable scientists and clinicians to better balance work and family life without promotion penalty
- Creating more appealing, collaborative, and inclusive work cultures
- Developing opportunities for partially retired workers to stay in the workforce
- Facilitating the reentry of women scientists following a period of absence
- Developing in-house programs that encourage and facilitate workers' development of oncology-specific advanced training or movement into faculty positions
- Ensuring that faculty compensation is competitive and equitable
- Improving startup packages for new faculty
- Seeking donors to endow chairs to help retain talented researchers at their institutions
- Expanding loan repayment and salary support mechanisms for researchers and clinicians in training

Sources:

Institute of Medicine. Ensuring quality cancer care through the oncology workforce: sustaining care in the 21st century. Workshop summary. Washington (DC): National Academies Press; 2009.

Association of American Cancer Institutes Oncology Workforce Initiative. 2010 Oncology workforce report. Pittsburgh (PA): AACI; 2010.

National Cancer Institute. The CURE paradigm: enhancing workforce diversity. Bethesda (MD): NCI; 2011. NIH Publication No. 11-7945.

Institute of Medicine. Research training in the biomedical, behavioral, and clinical research sciences. Washington (DC): National Academies Press; 2011.

Mason MA, Goulden M, Frasch K. Keeping women in the science pipeline. Presented at Focus on Workplace Flexibility. Washington (DC); 2010 Nov 29-30. Available from: http://workplaceflexibility.org/images/uploads/program_papers/mason_-_keeping_women_in_the_science_pipeline.pdf.

Committee on Maximizing the Potential of Women in Academic Science and Engineering, National Academy of Sciences, National Academy of Engineering, Institute of Medicine. Beyond bias and barriers: fulfilling the potential of women in academic science and engineering. Washington (DC): National Academies Press; 2006.

Recruitment and Retention Strategies

Meeting the cancer research and care workforce demands of the coming decades will require creativity, foresight, and tenacity on the part of all stakeholders: government, academic institutions, scientific and medical societies, cancer advocates, and quasi-governmental and private health policy organizations. Both components of the cancer workforce will be crucial to making the transformative discoveries needed to reduce America's cancer burden and ensuring that all people with or at risk for cancer benefit equally from these discoveries. Numerous strategies are being considered or tested to increase the number of people who choose oncology research or care as a career. These strategies include but are not limited to those listed in Table 11.

...we have to be sure that we keep intact the training of young people, cancer centers where much of the work is done, [and] the collaborative enterprise, which we try to emphasize. We have to pay attention to the health of many disciplines. And we think about how many of our dollars are used to support the facilities and administrative infrastructure of the institutions at which these activities occur....

– Harold Varmus, National Cancer Institute

CHAPTER 8

Accelerating Health Care Delivery System Improvements for Better Patient Outcomes

Several health care system characteristics discourage innovation in care, with upstream effects on translational and clinical research. The following sections describe these system weaknesses as well as selected initiatives to improve health care coordination both broadly and specifically for cancer patients/survivors. In addition, this chapter highlights several recent technological advances with untapped potential to revolutionize health care delivery.

Barriers to Health Care Delivery System Improvements

Although the United States has a wealth of health care resources, health care outcomes lag behind those of other developed nations.[462] A number of health care delivery issues contribute to this situation; some of these fundamental problems and efforts to ameliorate them are discussed in this section.

Impact of a Patient Rescue Imperative

The cancer care system continues to be influenced strongly by the high societal value placed on avoiding death at almost any cost. This imperative or perceived duty to save endangered life where possible with little regard for the cost of doing so has been referred to as the Rescue Rule.[463,464]

Hospice care still is misunderstood by many patients as "giving up" and by providers as a professional failure. As a result, much of the cost of cancer care is incurred in the last weeks of life as additional treatments with curative intent—often known to be futile—are attempted in accordance with the wishes of the patient or family. Though open to differing interpretations, one study of deceased Medicare patients[465] found an unexpectedly high number of surgeries performed in the last year of life, and most of these procedures occurred during the last month of life. Nearly a third of the elderly Americans studied had received surgical interventions during the last year of life; compared with the patient sample as a whole, those who had undergone surgery were most often younger, male, nonwhite, and had more comorbidities. The authors acknowledge that many factors may have influenced the findings. Nonetheless, they suggest that the results should prompt clinicians to carefully consider a patient's goals when assessing the need for surgical intervention at the end of life and ensure that such interventions help extend life and reduce suffering.

...[with] the cultural value of rescue, end-stage and late-stage situations are places that we're tempted to pour resources because we feel morally, not [based on evidence] but morally, we have to try and bring back people from imminent death.

– Arthur Caplan, University of Pennsylvania

Our society is uncomfortable with discussions about cessation of active treatment and about death, yet these conversations must take place at public policy and personal levels if a better balance between cancer therapies and cancer prevention, wellness, and quality of life is to be achieved. At the same time, access to quality cancer treatment must be readily available and affordable for people who need it. Currently, the predominant research emphasis—driven in significant measure by the rescue imperative—toward the development of high-cost salvage therapies and technologies reduces the level of clinical cancer research funding that could be allocated to efforts to improve cancer prevention, early detection, and palliative and supportive care interventions.

Health care delivery is moving toward value-based payment systems (i.e., reimbursement based on

Hospice Care and Palliative Care

Hospice care is end-of-life care provided by health professionals and volunteers who provide medical, psychological, and spiritual support. The goal of hospice care is to help people who are dying have peace, comfort, and dignity. Caregivers try to control pain and other symptoms so the dying person can remain as alert and comfortable as possible. Hospice programs also provide services to support patients' families. Usually, a hospice patient is expected to live six months or less. Hospice care can take place at home, at a hospice center, in a hospital, or in a skilled nursing facility.

Palliative care is appropriate for anyone with a serious illness, beginning early in the course of the disease and in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy. Palliative care relieves symptoms and treatment side effects and improves quality of life without curing disease.

Sources:
National Library of Medicine. MedlinePlus: hospice care [Internet]. Bethesda (MD): NIH; [updated 2011 Dec 11; cited 2012 Jan 4]. Available from: http://www.nlm.nih.gov/medlineplus/hospicecare.html

National Library of Medicine. MedlinePlus: palliative care [Internet]. Bethesda (MD): NIH; [updated 2011 Dec 12; cited 2012 Jan 4]. Available from: http://www.nlm.nih.gov/medlineplus/palliativecare.html

World Health Organization. WHO definition of palliative care [Internet]. Geneva (CH): WHO; [cited 2012 Jan 3]. Available from: http://www.who.int/cancer/palliative/definition/en

patient outcomes), which is at odds with the rescue mentality. It may be perceived as health care rationing by those who favor exhausting all possible treatment options, regardless of the likelihood of benefit. In addition to incurring increased costs, cancer patients who pursue treatment with curative intent that has little or no possibility of benefit often are denied the physical, psychosocial, and spiritual care they could receive in a hospice setting.

...if we simply apply what we currently know—the rational application of what we currently know to the population—there is the possibility that over the next 15 years or so we can save more than 2.5 million men from dying and more than 1.25 million women from dying from cancer....

– Otis Brawley, American Cancer Society

It is important to emphasize that palliative care services are not the same as hospice care (see sidebar) and should not—as they now largely are—be reserved only for terminal patients and their families. This misperception of palliative care often keeps physicians from referring patients for these services and may make patients hesitant to ask for them. Palliative and supportive care services are of benefit to cancer patients and their families from the point of diagnosis onward.[466]

Inequitable Resource Distribution and Failure to Apply What Is Known

Many Americans have unfavorable cancer-related health outcomes because the services they need are geographically, financially, or culturally inaccessible and/or because, while needed services are accessible, they may not be recommended by the health care provider. Evidence-based cancer prevention, screening, and care services still are not being provided consistently, appropriately, or equitably across all populations. These major health care delivery system failures, on which the Panel has reported extensively over the past decade,[9,10,12,37,82,439,440] are often driven to varying degrees by local and regional economics and market forces; national, state, and private payor reimbursement policies; insufficient health services and personnel; and bias, among other factors.

Fragmented, Uncoordinated Care

As health services have become increasingly specialized and payment arrangements have grown more complex, the care provided to individual patients has become highly fragmented and poorly coordinated. Fragmentation is pervasive at every level—national, state, community, practice—of the health care system.[467] No national entity or set of policies guides health care provision; at the state level, numerous agencies provide various aspects of care. Community providers typically practice autonomously and there seldom is clear accountability for the patient's total care. The system also is oriented toward treating episodes of acute illness with costly interventions rather

than emphasizing prevention and chronic disease management. For patients with severe or multiple health conditions who take numerous prescription medications, as is the case for many people with cancer, this fragmentation of care can be especially hazardous. Too often, poorly coordinated care equals poor-quality care.

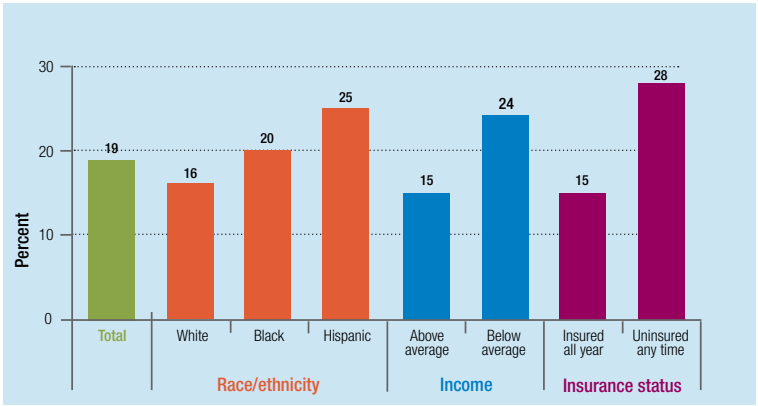
Among the hallmarks of fragmentation are poor communication between physicians and other care providers who are treating the same patient, needless repetition of tests and procedures (Figure 17), and the requirement that patients—many of whom are severely ill—travel to numerous locations to receive care. It is not uncommon for the patient, out of necessity, to become his or her own case manager—responsible for ensuring that test results and medical records are transmitted between health care providers and care settings (Figure 18) and that providers confer with one another so that care is provided as prescribed and potentially dangerous medical and medication errors are avoided. As Figures 17 and 18 show, such problems are more pronounced among minority, lower income, and uninsured populations but are prevalent even among those with more resources and robust health insurance coverage.

Limited Clinical Trial Participation, Reimbursement, and Referral

It is widely acknowledged that the dramatic improvements in childhood cancer survival achieved over the past few decades have in large measure resulted from the participation of most newly diagnosed children in trials (and parents' willingness to try experimental therapies) as well as collaboration both within the oncology community and with industry to best serve the relatively small population of children with cancer. Similarly, such collaboration and enhanced patient accrual are crucial for treatment trials addressing adult cancers.

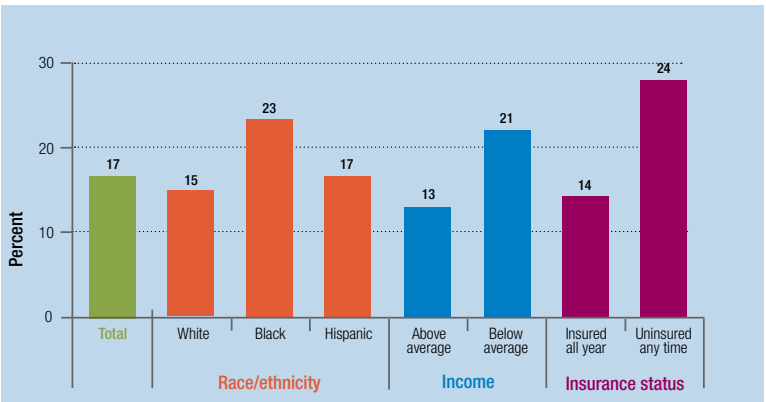
Unfortunately, overall adult cancer patient referral to clinical trials by community oncologists in the United States remains low; only 3-5 percent of

Figure 17
Duplicate Medical Tests by Race/Ethnicity, Income, and



Source: Commonwealth Fund Commission on a High Performance Health System. Why not the best? Results from the Commonwealth Fund national scorecard on U.S. health system performance, 2011. New York: Commonwealth Fund; 2011 Oct. Available from: http://www.commonwealthfund.org/Publications/Fund-Reports/2011/Oct/Why-Not-the-Best-2011.aspx?page=all

Figure 18
Test Results or Medical Record Not Available at Time of Appointment, by Race/Ethnicity, Income, and Insurance Status, 2010



Source: The Commonwealth Fund Commission on a High Performance Health System. Why not the best? Results from the Commonwealth Fund national scorecard on U.S. health system performance, 2011. New York: Commonwealth Fund; 2011 Oct. Available from: http://www.commonwealthfund.org/Publications/Fund-Reports/2011/Oct/Why-Not-the-Best-2011.aspx?page=all

...we make it very difficult for people who are not being treated in large centers to participate in research. We try to build networks with private practices of people who want very much to be part of research, but it's almost impossible for them to support the research costs of a clinical trial in a practice office or even in a small hospital. There are patients who are often quite willing to participate who can't travel, for all kinds of reasons, to the major centers and we can't bring them in because it's impractical. There need to be ways to improve that.

– Judy Garber, American Association for Cancer Research

adults with cancer participate in clinical trials.[468,469] Moreover, patients still are most likely to participate in a trial when standard treatment options have failed, rather than receiving first-line therapy in a trial. This situation is a critical impediment to accelerating progress against cancers most prevalent in adults. (See pp. 62-63 for additional discussion of current and anticipated clinical trial patient selection issues and p. 110 for discussion of increasing awareness of clinical trials and patient accrual through the use of consumer technologies.)

Many insurers still limit access to clinical trials by excluding coverage for "experimental" or "investigational" therapies, although the study sponsor typically provides the drug or other agent under investigation at no cost to the trial participants. Many states have laws or agreements with insurance providers in place that mandate reimbursement for the same routine care administered in clinical trials that would be provided for standard cancer treatments,[470] but coverage requirements vary substantially in scope, standards, and conditions.[471,472] Patients who receive reimbursement for treatment on clinical trials may still accrue higher out-of-pocket costs compared with those receiving standard treatment (e.g., additional imaging and other testing). In addition, insurers may refuse to cover the cost of drugs or other measures needed as a result of adverse events unique to the research or other events (e.g., infections) that ordinarily would be covered.[472] Patients on clinical trials also may incur non-care-related costs associated with traveling to receive care, such as child care expenses. Starting in 2014, the Patient Protection and Affordable Care Act will require health insurance plans nationally to cover the cost of routine patient care costs associated with approved clinical trials.[471]

As previous Panel reports[9,37,82,439] have discussed, primary care and community oncology providers may fail to offer clinical trials as a treatment option for numerous reasons including concern about trial risks compared with standard care, poor understanding or mistrust of clinical trials and clinical research, lack of awareness of available trials or how to identify appropriate trials for the patient's condition, concern about losing patients, inadequate reimbursement for the consultation and paperwork associated with enrolling patients onto trials, and overt or unconscious bias (e.g., assumption that the patient cannot or will not adhere to treatment regimen).

Education and Communication Issues

Education and communication about cancer continue to become more sophisticated and targeted, and there have been notable successes (e.g., tobacco use prevention). Yet inadequate communication about cancer with key audiences continues to be a stumbling block to more rapid deployment of cancer research and care advances.

Public Education and Communication

There still is much to learn about how to increase public awareness—and convert awareness into lasting action—among diverse American populations. Areas requiring greater public education and communication emphasis include understanding cancer as a disease, understanding personal cancer risk, dispelling persistent myths and cultural taboos about cancer, and understanding recommended screening schedules and the pros and cons of screening (see Chapter 3, p. 21).

Educational efforts to date, particularly with regard to cancer risk factors, recommended screening, and possible preventive measures, have been complicated by changing messages from

government health agencies and other sources. Further, literacy, health literacy, numeracy, and language issues in both the native and second languages of diverse population groups affect the development of understandable and culturally appropriate messages and materials in all media. The Panel has discussed these issues as they affect cancer research and care in previous reports.[10,37]

Cancer advocacy organizations have been important providers of cancer education to the general public and to newly diagnosed individuals and their loved ones. In recent years, in addition to using their Internet Web sites to provide cancer information, advocacy groups have developed social media presences (e.g., Facebook, Twitter) to build extensive informal online networks and extend the reach of their educational efforts far beyond what could be accomplished with radio, television, or print media—at a fraction of the cost.

Researchers, Cancer Care Providers, and Policy Makers

In addition to the general public, researchers, cancer care providers, and policy makers can benefit from targeted education and communication training that will help them better contribute to improving patient outcomes. For example, cancer researchers' work can be enriched considerably by cross-training and collaboration with scientists from other disciplines, community clinicians, and advocates. Cultural competency training can help researchers better design, implement, and interpret studies. Investigators also can benefit from communication skills training, which will facilitate clear and productive discussions with funders, policy makers, and the public. In addition, investigators need to be skilled in communicating health and scientific information to patients whose health and numeric literacy is limited.[473]

Similarly, health care providers need excellent communication and collaboration skills to work effectively with patients/families and coordinate patient care (including conversations about poor prognoses, end-of-life wishes, and the nature and benefits of palliative care). Clinicians also need better tools for facilitating patient decision making, and many would benefit from training to better understand the clinical trials process and its value. Like researchers, many care providers would benefit from training on the communication of information to lay audiences, particularly patients with limited literacy. As clinical practices convert from paper records to EHR systems, providers need initial and ongoing training on the selection and use of EHR technology.

We think that if we can educate the public before they get diagnosed with a disease about the importance of taking part in research, then when they do get diagnosed with a disease it's probably going to be a lot easier to get them involved in clinical trials.

– Naz Sykes, Dr. Susan Love Research Foundation

Lastly, the vast majority of policy makers have relatively limited backgrounds in science or medicine, yet they have the responsibility of making numerous policy decisions that must be based on scientific evidence and best medical

practices. Taken together, these decisions affect every American by facilitating or limiting the expansion of scientific and medical knowledge that will in turn affect other health care services. Thus, the scientific, medical, and advocacy communities have an obligation to provide policy makers at all levels with the most accurate and unbiased information possible in forms that are readily understandable and promote reasoned discussion.

Improving Health Care Coordination, Efficiency, and Quality

Numerous health service delivery innovations are being tested to improve health care coordination, efficiency, and quality in the United States. A number of these initiatives are highlighted in the following paragraphs. Some are of benefit to the general population, including cancer patients/survivors, while others are specific to people with cancer.

Health Service Delivery Innovations to Improve Care Coordination

Numerous efforts are under way to improve health care coordination and quality in the United States. In addition, mechanisms exist specifically to improve the coordination of cancer care. The paragraphs below highlight a number of these efforts.

Patient-Centered Medical Homes

Patient-Centered Medical Homes (PCMHs) have been developed and refined over the past decade to improve health care coordination and quality for populations that historically have not had a regular source of primary or other health care.[474] Individuals without regular sources of care are more likely to receive care in emergency rooms, are often diagnosed with cancer and other diseases at advanced stages, and may have difficulty accessing appropriate care once diagnosed. Compared with patients who lack medical homes, individuals in PCMHs have been shown to have fewer problems accessing their medical records as needed and experience fewer medication, medical, and laboratory errors. They are more likely to receive reminders for preventive and follow-up care and written instructions for managing care at home.[475]

Comparative Effectiveness Research

Comparative effectiveness research (CER) generates and synthesizes evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or improve the delivery of care.[476] Unlike clinical trials, CER makes head-to-head comparisons of alternative interventions in populations representative of clinical practice and is becoming an increasingly important tool in attempts to contain health care costs and provide the best-quality care.

Patient Protection and Affordable Care Act Provisions to Improve Care Coordination

Several provisions of PPACA support innovative efforts to improve the quality and coordination of health care and contain health care cost escalation:

- The Center for Medicare and Medicaid Innovation is charged with identifying, developing, testing, and disseminating alternative models of organizing, delivering, and paying for care provided to Medicare beneficiaries and Medicaid enrollees. Innovative models will be tested to improve all aspects of patient care, including safety, effectiveness, patient-centeredness, timeliness, efficiency, and equity—the domains of quality in patient care as defined by the Institute of Medicine. The Center also focuses on improving health by encouraging healthier lifestyles (including use of preventive

...most excitingly, we have some opportunities under the Affordable Care Act...to focus more on demonstrations, pilots, and promotion of innovation in cancer treatment....
– Barry Straube, Centers for Medicare and Medicaid Services

care) and reducing cost by promoting preventive medicine, better recordkeeping, coordination of health services, and reduced waste, inefficiency, and miscommunication.

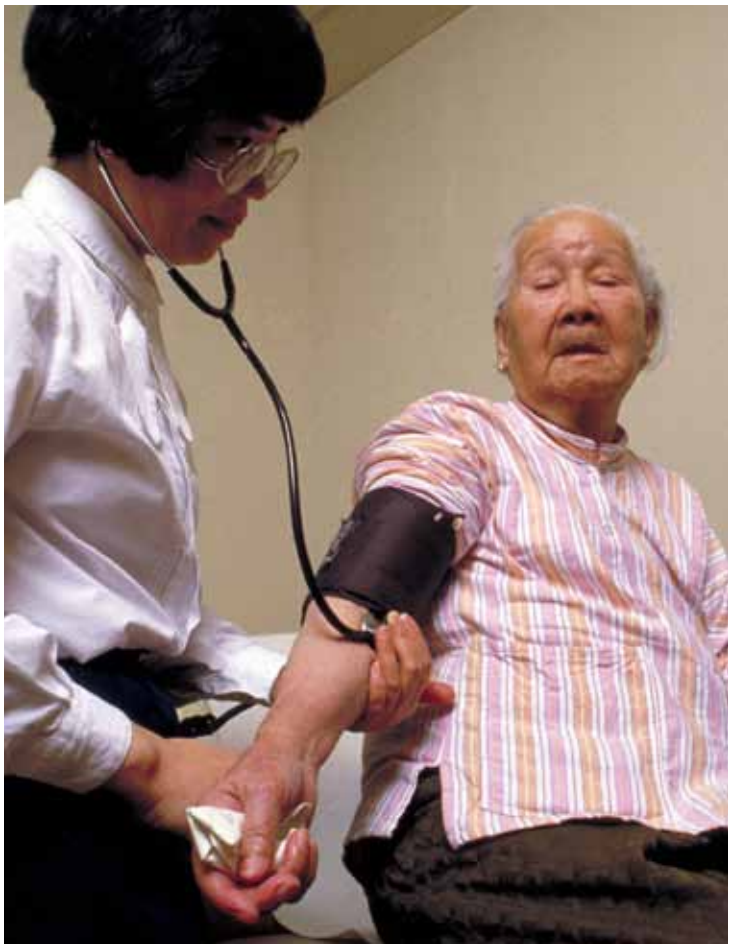
- Accountable care organizations (ACOs) are voluntary groups of physicians, hospitals, and other health care providers that assume responsibility for the care of a clearly defined population of Medicare beneficiaries. If an ACO is successful in delivering high-quality care or improving care and reducing the cost of that care below what otherwise would have been anticipated, it shares in the savings.[477] Compared with medical homes, which may focus somewhat more heavily on care coordination and patient satisfaction, ACOs coordinate care to achieve their objectives but also focus strongly on cost containment. It has been suggested that marrying these approaches may help create an optimally integrated and cost-effective health care delivery system.[478]
- The Patient-Centered Outcomes Research Institute (PCORI) is an independent, not-for-profit, private research organization dedicated to supporting and promoting clinical CER. Its mission is to help people make informed health care decisions, and improve health care delivery and outcomes by producing and promoting high-integrity, evidence-based information that comes from research guided by patients, caregivers, and the broader health care community. PCORI addresses a widespread concern that patients and their support communities do not have the information they need to make choices that are aligned with their desired health care outcomes and their values and preferences. Outcomes studied will include survival, function, symptoms, and health-related quality of life.[479]

Cancer-Specific Strategies to Improve Coordination and Quality of Care

Cancer Patient Navigation

The U.S. health care system has become so fragmented and complex that even well-educated, insured, affluent individuals experience significant difficulties finding and obtaining needed health services when cancer is diagnosed or suspected. For those with fewer resources, the need for assistance in navigating the system is particularly acute. Patient navigators assist patients with locating needed services and making, coordinating, and keeping appointments across disconnected care settings (e.g., primary care, tertiary care). They also help locate and arrange assistance with financial and nonmedical support needs (e.g., child care, transportation assistance) that are needed to enable patients to obtain care. Importantly, navigators often are crucial to bridging cultural and language barriers that can delay cancer screening, prevent prompt diagnosis of suspicious screening results, and derail adherence to treatment regimens.[480]

The first major program to measure the effectiveness of patient navigation (PN) in decreasing disease stage at diagnosis began at Harlem Hospital in New



York in 1990. That program served as a catalyst for numerous similar efforts in other health systems and medical centers.

While evidence[481-483] indicates that navigation programs have increased patients' timely access to and satisfaction with care, navigation programs have not been rigorously studied to determine their benefit relative to cost. Despite growing interest in PN among health policy makers, this lack of cost-benefit evidence has been a barrier to more widespread adoption of and reimbursement for PN services.[484]

With partial funding from ACS and the Avon Foundation, NCI funds and directs grants to establish, operate, and evaluate nine navigation intervention programs for diverse underserved populations.[485-487] Rigorous evaluation of navigation intervention effectiveness and cost-effectiveness are critical components of the program, as is documentation on aspects of the program that may be implemented for specific cancers and other diseases. In addition, the Patient Navigation Outreach and Chronic Disease Prevention Act of 2005 (P.L.109-18, reauthorized by PPACA), authorized grants for the development and operation of demonstration programs to provide patient navigator services to improve health care outcomes for people with cancer and other chronic diseases. These grants are administered by the Health Resources and Services Administration.[488] Other cancer-focused patient navigation programs are sponsored by ACS, CMS, CDC, and others.

Cancer Treatment Summaries and Survivorship Care Plans

Many cancer patients still are discharged from active treatment without receiving either a record describing the treatment they received (e.g., types of treatment[s] administered with dosages, dosing schedule, total duration of treatment, side effects, contact information for all treatment providers) or a written plan for the periodic testing and other follow-up care they will need for the rest of their lives.[82,489] Survivorship care plans also provide survivors with information about possible late effects of their treatment, symptoms or signs that may indicate a recurrence or second cancer, medications needed, and resources that may be of help. This lack of information has been particularly problematic for adult survivors of childhood cancers, some of whom may know little about the treatment they received or even the details of their diagnoses. Appendix E outlines components of a survivorship care plan recommended by the President's Cancer Panel and subsequently adapted by the Institute of Medicine.

Moreover, some cancer patients travel away from home to receive treatment at cancer centers or other medical facilities. When treatment ends, they typically return to the care of community oncologists, primary care providers, and/or other providers (e.g., oncology nurses, nurse practitioners, physician assistants, physical and rehabilitation therapists). All of these providers will need the survivor's treatment and follow-up care information in order to provide effective ongoing care. Table 12 lists the numerous advantages of adopting treatment summaries to improve care coordination, communication, and efficiency.

Table 12

Objectives of Adoption of Oncology Treatment Summaries

Adoption of a treatment summary could improve three interrelated aspects of cancer care delivery:

Care Coordination (between providers) is especially important because:

- Cancer survival has improved.
- Cancer treatment is increasingly complex.
- Society is increasingly mobile and patients transition across practice sites.
- Unexpected events—hurricanes and other disasters—happen.
- More fragmentation occurs as care teams include many subspecialized members.

Communication (between patients and providers) is especially important because:

- It is a prerequisite for shared decision making.
- More complex treatments and preference-sensitive options now exist.
- Patients desire it.

Efficiency (document tracking, recordkeeping for patients, providers, systems, and research) is especially important because:

- It limits time spent reviewing/obtaining/providing medical records.
- It facilitates tracking of processes and outcomes of care for quality improvement initiatives.
- It facilitates document storage, retrieval, copying, and transmission.
- It facilitates tracking of care for public health and research data collection-e.g., cancer registries.

Adapted from: Schrag D, Donaldson M. The cancer treatment plan and summary: re-engineering the culture of documentation to facilitate high quality cancer care [commissioned paper]. In: Implementing Cancer Survivorship Care Planning/A National Coalition for Cancer Survivorship and Institute of Medicine National Cancer Policy Forum Workshop, the Lance Armstrong Foundation, and the National Cancer Institute. Hewitt M, Ganz PA, rapporteurs. Washington (DC): National Academies Press; 2007.

Over the past several years, as the benefits of treatment summaries and survivorship plans have appeared more evident, a number of cancer-related organizations (e.g., Minnesota Cancer Alliance, American Society of Clinical Oncologists, National Coalition for Cancer Survivorship, American Cancer Society, Oncology Nursing Society, Live**STRONG,** Children's Oncology Group)—both individually and through collaborations that include academic institutions—have developed templates to help patients document the cancer care they receive and plan the continuing care they will need following treatment and throughout their lives.[490] However, these instruments still are not being used routinely, largely because many patients and primary care providers are unaware of them.[491] Further, some oncology professionals consider them too complex. As community experience in using the templates accumulates, users of treatment summary and survivorship care plans have begun to tailor them for use in local populations and care settings.[492] The benefits and impact on patient outcomes of treatment summaries and survivorship care plans have yet to be assessed through rigorous empirical investigation.[493]

Technological Advances with Potential to Revolutionize Health Care Delivery

A number of tools and technologies—ranging from electronic health record systems to cell phones—have potential to enable health care professionals and consumers to record, access, and exchange information that can protect or improve health. To be effective, however, these tools must be thoughtfully developed and applied.

Status of Electronic Health Records in the United States

In the United States, only about 10 percent of office-based physicians and 2.7 percent of hospitals reported having comprehensive EHR systems in 2010 and 2009, respectively. Larger proportions of physicians and hospitals reported using some form of EHR and use of EHRs has been increasing over the past several years, but small practices and critical-access, small, medium-sized, public, nonteaching, and rural hospitals reported lower levels of EHR adoption, a disparity that appears to be widening. Several barriers to EHR adoption have been reported, including inadequate capital for initial investment and maintenance costs, the time and effort required for implementation, concerns about choosing a system, and resistance from physicians. Federal interest and investment in electronic health systems have intensified in recent years. Most notably, the American Recovery and Reinvestment Act of 2009 (ARRA, P.L. 111-5) included $19 billion for promotion of the adoption and use of health information technology, with emphasis on EHRs. The ARRA initiatives are designed to address many of the commonly cited barriers to EHR adoption and use, although it is still too early to ascertain the extent of their impact.

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Technologies for Information Management and Collaboration

As digital methods of information management and communication have become increasingly affordable and widely used, many potentially transformative applications in medicine have emerged, including electronic health records and a number of telemedicine tools.

Many have touted the potential of health IT and EHRs to improve the efficiency, cost-effectiveness, quality, and safety of medical care,[494-496] and one Panel speaker noted that the sheer volume of data generated through modern diagnostic tests necessitates the adoption of EHRs. Several features of EHR systems could benefit cancer patients as well as those at risk for cancer. For example, EHRs often include automated notifications related to cancer screening (e.g., Papanicolaou screening, mammography), and researchers are testing ways to use patient information within EHRs to tailor guidelines for cancer screening based on an individual's risk factors.[497] EHRs also can facilitate coordination among the myriad providers involved in caring for cancer patients from diagnosis to posttreatment surveillance,[498] although the current lack of interoperability among EHR systems may limit this benefit for providers who are not within the same integrated health care system.

In addition to directly benefitting patient care, EHRs have potential to aid in surveillance and research as data can be aggregated and analyzed to gain insight into a variety of factors that influence health and disease. Health services research could particularly benefit. For example, an analysis of one clinic's EHR data found that two-thirds of low-risk women were screened for cervical cancer more often than recommended, with resulting false-positive results leading to unnecessary physical, financial, and psychological burden for several.[499] Studies such as these that document the impact of deviating from evidence-based guidelines could inform efforts to improve adherence and may also help refine guidelines based on clinical outcomes.

However, realization of these benefits depends largely on widespread willingness among the public to share data. Importantly, individuals from all demographic groups must be willing to participate so that data sets are adequately representative.

Other technologies are being used to link health care professionals with each other and their patients. These efforts—collectively termed "telemedicine"—utilize a variety of media, including text, video, still images, and audio. For individuals living in low- and middle-income countries, as well as those in rural and/or remote areas of high-income countries, telemedicine has the potential to provide access to quality medical care that would not otherwise be available.[500] Telemedicine also has potential to significantly change health care delivery in more industrialized regions and is being utilized and studied as a way to diagnose and manage health issues more conveniently and cost-effectively.[501,502]

Telemedicine is being tested and used for various applications in oncology, including diagnosis, treatment, and supportive care. One of the more sophisticated telemedicine applications is NCI's TELESYNERGY®, a system that allows for broadcast-quality videoconferencing and the sharing of diagnostic-quality radiology and pathology images.[503,504] The University of Kansas (KU) has developed an extensive telemedicine program that links patients and their health practitioners in rural areas of Kansas with KU oncologists.[505] The telemedicine clinics use an interactive televideo unit as well as peripheral devices (e.g., electronic stethoscope) that allow the remote physician to examine patients in collaboration with an onsite nurse. This service relieves patients from traveling long distances, which is particularly burdensome given the physical and emotional toll cancer has on patients and their caregivers. Evaluations of video consultations for oncology patients indicate

[In our study] patients were actually very satisfied with videoconferencing as a way to interact with their physicians. We found no difference in terms of attention that patients felt that physicians were paying to them. We found no difference in terms of the quality of the explanation, which is a key part of the physician-patient interaction. We did find...a small, slight difference—in the overall rating of the virtual visit compared to a face-to-face visit, but nonetheless [ratings were] very high....generally, the people who are not onboard on a lot of this technological enablement of patient-physician relationships are physicians...

– Ronald Dixon, Massachusetts General Hospital

...public Wi-Fi and mobile devices are erasing the digital divide. When we include mobile in our definition of Internet users, the differences between African American and white adults disappear.

– Susannah Fox, Pew Internet & American Life Project

that they are relatively well accepted by patients and feasible, but additional research is needed on clinical outcomes.[506] Telemedicine also can link specialists in high-income countries with populations in low- and middle-income nations and thus has implications for global health. For example, researchers also are testing whether photographs taken with mobile phones may allow off-site physicians to assist in screening for cervical and skin cancers within low-resource countries.[507,508]

Consumer Tools and Technologies

Access to and use of the Internet, mobile phones, and other consumer technologies have increased dramatically in recent years. In 1995, only about 5 percent of American adults had Internet access. Currently, about 79 percent of American adults and more than 90 percent of teenagers and adults under 30 years of age use the Internet.[509] Of Americans who are online, 8 of 10 use the Internet to look for health information (e.g., specific disease information, treatment options, prescription drug information).[510] Many health and advocacy organizations are taking advantage of widespread Internet use. Army of Women members frequently disseminate "call to action" emails with clinical trial information via the Internet and social networking outlets, which spurs AOW membership and study recruitment.[316] The Health of Women study initiated by DSLRF and the City of Hope Beckman Research Institute is the first completely online research cohort. Women periodically complete short online questionnaires focused on issues related to breast cancer risk. DSLRF is working toward using mobile phones to collect data, which appears to be particularly effective for women in African American and Hispanic communities.[316]

Americans also increasingly are using mobile technologies. Eighty-three percent of American adults have cell phones and one-third of U.S. adults are smartphone users.[511] A growing cohort of the American population is mobile-only in terms of Internet usage. Mobile access also is changing Internet users, making them more likely to gather and share information online.[510] The expansion of mobile technologies has led to the emergence of mobile health (mHealth) initiatives focused on areas such as patient communication, point-of-care documentation, disease management, and education.[512] Phone-based interventions have yielded positive results among various populations, including those of low socioeconomic status and ethnic minorities. Information relayed includes education messages as well as medication and appointment reminders. NCI has launched SmokefreeTXT a free mobile service designed for teens who want to quit smoking. Teens can sign up online or from their mobile phones to receive information and encouragement via text message.[513]

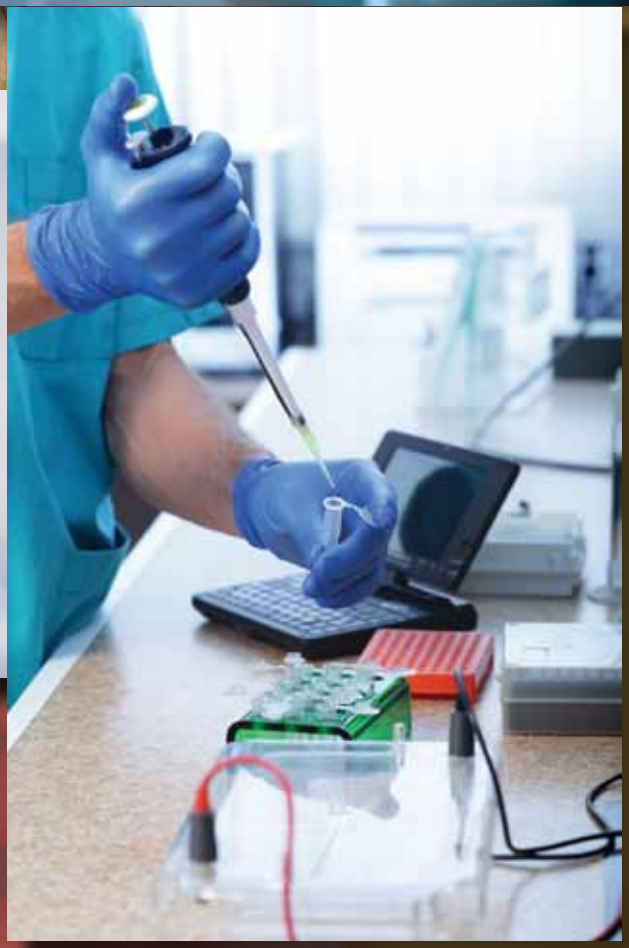
Some recently developed tools allow individuals to digitally manage their own health information. These personal health records (PHRs) have been envisioned as tools to enhance patient-provider

communication and empower patients to manage their own health. Some PHRs are linked to external resources for health information (e.g., MedlinePlus, Healthwise, WebMD) and could thus serve as a vehicle for patient education.[514,515] Health care consumers express strong interest in having access to and control of their health information, but only 7 percent of U.S. adults report using PHRs.[515]

What we are seeing not just in health but in news and politics and other sectors is that the social network sites are becoming the default front page for many Americans, especially younger Americans. Their first stop is a social network site. And the way that this pertains to cancer research and health in general is that if you want to reach people, your best bet is to reach them through the social networks.

– Susannah Fox, Pew Internet & American Life Project

Modern health care consumers have unprecedented access to information, which provides tremendous opportunities to enhance health education and disease management. Health professionals should be cognizant of the ways in which people use the Internet and PHRs and make efforts to optimize access to high-quality information. For example, important information should be found easily using search engines such as Google and posted to the Internet in formats that are easily accessible via mobile devices. However, the Internet also can accelerate the spread of misinformation, and there is concern among physicians and ethicists that patients may become overwhelmed if they have access to detailed, highly technical information via PHRs.[516,517]



PART III

CONCLUSIONS AND RECOMMENDATIONS

The past four decades of investment in cancer research have yielded important gains in understanding the complex nature of cancer. These discoveries have in turn led to cancer detection methods and treatment strategies that have enhanced cancer patient survival, most notably among children. Yet cancer remains a fearsome specter for all Americans, and for too many, a harsh and harrowing reality. With an aging population at increasing risk for cancer and the incidence of some cancers rising for unknown reasons, bold steps are required to address the urgent need for more effective and affordable cancer prevention and treatment interventions.

To capitalize and expand on accumulated knowledge and technologic advances achieved to date, the cancer research community now must identify and embrace strategies for accelerating the pace of scientific innovation. Only by encouraging and rewarding innovation and collaboration will critically needed transformative advances in cancer prevention and treatment be achieved.

Based on testimony received and additional exploration of these issues, the President's Cancer Panel has reached the conclusions outlined in the following section; these conclusions are followed by the Panel's recommendations for addressing barriers to more rapid research progress and significant reductions in the burden of cancer on this nation.

Conclusions

1. Basic research will always be needed—it is the key to transformative discoveries about fundamental cancer biology, the mechanisms by which cancer develops and spreads, and how it may be prevented. Basic science discoveries may find innovative application in both cancer and other areas of health care.

2. Funding instability is a critical barrier to scientific innovation. Moreover, high-risk research with the potential to result in transformative innovation and research aimed at making incremental progress currently compete for the same funds. Incremental research is safer and will pull dollars away from innovative ideas in a risk-averse climate.

3. The risk-averse academic research culture and its structures (promotion and tenure criteria and processes) continue to discourage innovation and collaboration. Rewards continue to be aligned primarily with independent research projects and the number of papers a scientist publishes rather than encouraging collaboration and emphasizing the impact of a researcher's work in reducing the cancer burden.

4. Innovative research models, streamlined and blinded application and review processes, and grant mechanisms that reward innovation and disease impact all have significant potential to accelerate transformative innovation in cancer research that can lead to markedly improved outcomes for patients.

5. Cancer may never be eradicated entirely, but some cancers now can be managed effectively with ongoing or intermittent treatment, as is possible with certain other chronic diseases (e.g., diabetes). Increased research to improve disease control and symptom management will enable people with cancer to live more productively and with a good quality of life.

6. Negative and null study results are seldom published due principally to investigator career concerns and low interest among scientific journal editors. Failure to publish such findings robs the scientific community of useful information that can inform subsequent research, prevent needless waste of resources, and accelerate progress. This information also may help cancer patients and their caregivers make more informed treatment or other cancer-related decisions.

7. Current research and health care delivery emphasizes overwhelmingly the treatment of acute disease rather than protection and preservation of overall health. Acute, episodic care is inefficient, expensive, and difficult for patients. Preventing cancer is the best and most cost-effective way to reduce cancer incidence, mortality, and morbidity and associated human, health system, and national productivity costs. It is time for the research community and policy makers to recognize and embrace the prevention of cancer as one of the foremost goals of future cancer research.

8. Public-private partnerships hold enormous potential for increasing translational research investments and maximizing productivity in a resource-limited environment. Team science efforts also provide opportunities to bring nontraditional disciplines (e.g., engineering, behavioral and social sciences) to bear on cancer-related problems.

9. The existing clinical trials paradigm is outdated and inefficient. Traditional trial designs often are not well suited for testing emerging targeted therapies and combination regimens. In addition, due to the lack of an effective prioritization system, scarce resources and patients often are devoted to the conduct of trials likely to yield only incremental knowledge and/or benefit to patients. Drugs with potential to improve the outcomes of patients with early-stage disease may be overlooked because of the disproportionate focus of oncology trials on advanced disease.

10. Imaging technologies, electronic health record and other data systems, biorepositories, and communication technologies hold enormous promise for advancing the cancer research and care agendas and expanding community participation in research but need stronger support for their continued development and application.

11. Consumer/community perspectives and expertise continue to be underutilized in both clinical trial and other research design and in study implementation and analysis.

12. Unless current and impending research and clinical workforce shortages are remedied, it will not be possible to make the gains in new knowledge and patient outcomes that are anticipated in the coming years.

13. The National Cancer Program continues to be poorly defined and lacks both a national vision and a set of principles, priorities, and strategies for realizing substantial reductions in the burden of cancer borne by the American public. This ongoing deficit leads to research and patient care inefficiencies and redundancies and a lack of accountability among some stakeholders.

Recommendations

Recommendation	Responsible Stakeholder(s) and Other Entities*
1. Within fiscal limitations necessary during the nation's economic recovery: a. Support for basic research should remain strong, but funding must be better balanced to provide greater support for translational, clinical, epidemiologic, behavioral, and health services research. b. Of special importance, cancer research should shift its focus and funding across the research continuum strongly toward cancer prevention, including prevention of exposure to known carcinogens and understanding of the role of infectious agents in cancer causation and progression. c. Strategies must be devised to stabilize research funding overall and overcome the risk aversion of cancer research sponsors, which discourages innovative research.	Congress Department of Health and Human Services • National Institutes of Health • Centers for Disease Control and Prevention • Centers for Medicare and Medicaid Services • Agency for Healthcare Research and Quality • Health Resources and Services Administration Department of Defense Veterans Administration Other public sector cancer research sponsors Private and voluntary sector cancer research sponsors
2. Grant review mechanisms should be revised to encourage innovative research models, streamline application procedures, and adopt blinded peer review processes. Funding strategies should be developed that will accelerate new discoveries and their more rapid translation and assimilation into standards of cancer care.	Department of Health and Human Services • National Institutes of Health • Centers for Disease Control and Prevention • Food and Drug Administration • Centers for Medicare and Medicaid Services Department of Defense Veterans Administration Other public sector cancer research sponsors Private and voluntary sector cancer research sponsors
3. The academic research culture and its structures should be modified to more strongly encourage and reward collaboration and measurable positive impact on the national cancer burden in addition to continuing to reward basic science discoveries by individuals.	Public and private academic research organizations Scientific and medical journal editors

*The Panel recognizes that entities other than those listed may have a vital role or interest in implementation of the recommendations.

Recommendation	Responsible Stakeholder(s) and Other Entities*
4. Collaborations and partnerships, particularly between public and private sector organizations, that address questions related to cancer research and care should be actively promoted, nurtured, and monitored. Collaboration with nontraditional disciplines (e.g., engineering, mathematics, anthropology) should be encouraged.	Department of Health and Human Services • National Institutes of Health • Centers for Disease Control and Prevention • Food and Drug Administration • Centers for Medicare and Medicaid Services Department of Defense Veterans Administration Other public sector cancer research sponsors Private and voluntary sector cancer research sponsors Pharmaceutical and biotechnology industries
5. Clinical trials with potential for significantly improved outcomes or transformative change should have the highest priority; trials that are expected to demonstrate or confirm small incremental improvements should be discouraged. Innovative clinical trial designs with sound intermediate endpoints and patient protections should be developed and implemented to save research dollars and more rapidly answer key research questions. To a greater extent than currently is the case, drug trials should target early-stage disease.	Department of Health and Human Services • National Institutes of Health • Food and Drug Administration Department of Defense Veterans Administration Other public sector cancer research sponsors Private and voluntary sector cancer research sponsors
6. Widely available consumer technologies (e.g., cell phones, Internet, social media) should be incorporated into strategies for cancer communication, health literacy enhancement, outreach, navigation, patient-provider interface, and disease management, particularly for rural and other underserved populations.	Department of Health and Human Services • National Institutes of Health • Centers for Disease Control and Prevention • Food and Drug Administration • Centers for Medicare and Medicaid Services Department of Defense Veterans Administration Public relations, health communication, and telecommunications communities Behavioral and social scientists Public and private sector health care institutions and providers Universities and colleges Public health departments

*The Panel recognizes that entities other than those listed may have a vital role or interest in implementation of the recommendations.

Recommendation	Responsible Stakeholder(s) and Other Entities*
7. The development and application of innovative imaging and other technologies with potential to accelerate progress in cancer research and care should be strongly supported.	Department of Health and Human Services • National Institutes of Health • Food and Drug Administration Department of Defense Other public sector cancer research sponsors Private and voluntary sector cancer research sponsors Biotechnology and medical device industries
8. Data sharing and transparency must be improved and adequately supported. Specifically: a. Electronic health records adoption is a necessity, not an option. Additional incentives must be developed to encourage and enable EHR acquisition and implementation across the range of practice settings. Privacy and interoperability issues must be addressed more aggressively. b. Reporting of negative and null study results should be required by public, private, and other nongovernmental funders. The information should be made available via a free, online, open-access journal or database. c. Data collected about a population/community must be provided in full to that population. The participation in research of consumer communities that are interested in and willing to provide data and biospecimens should be welcomed. d. Coordination of biospecimen collection, annotation, storage, and sharing must be standardized, systematized, and expanded.	Department of Health and Human Services • Office of the National Coordinator for Health Information Technology • National Institutes of Health • Centers for Disease Control and Prevention • Food and Drug Administration • Centers for Medicare and Medicaid Services Department of Defense Veterans Administration Other public sector cancer research sponsors Private and voluntary sector cancer research sponsors Health insurance industry Scientific and medical journal editors and publishers Cancer patient/survivor advocates and consumers

*The Panel recognizes that entities other than those listed may have a vital role or interest in implementation of the recommendations.

Recommendation	Responsible Stakeholder(s) and Other Entities*
9. The views and participation of cancer patient/survivor advocates and other consumer representatives should be sought during clinical trial and other study design, and in developing and implementing public, professional, and patient education and community-based research interventions.	Department of Health and Human Services • National Institutes of Health • Centers for Disease Control and Prevention • Food and Drug Administration • Centers for Medicare and Medicaid Services Department of Defense Veterans Administration Other public sector cancer research sponsors Private and voluntary sector cancer research sponsors Academic and other medical centers Public health departments
10. A coordinated program of targeted actions must be undertaken to recruit, retain, diversify, and grow the cancer research and cancer care workforce. Specifically: a. Efforts to attract young people to careers in science and medicine must be increased and should begin at the K-12 level. b. Support for young investigators must be increased to ensure the development of the next generations of cancer researchers, including behavioral, health services, population, epidemiologic, translational, clinical, and basic scientists. Translational and physician-scientists, whose education and training is of especially long duration, are particularly in need of training support. c. Federal support for graduate medical education should not be reduced, but rather increased. Nursing and other nonphysician medical personnel training and development initiatives established by the Patient Protection and Affordable Care Act should be fully funded and actively promoted. Recruitment and retention initiatives of academic and other medical institutions and physician groups should be expanded to the extent possible. d. Mentoring should be an integral part of research and medical training at all levels. e. Increasing the diversity of the cancer research and cancer care workforce to more closely parallel that of the population is essential.	Department of Health and Human Services • National Institutes of Health • Centers for Disease Control and Prevention • Food and Drug Administration • Centers for Medicare and Medicaid Services Department of Education Department of Labor Other public sector cancer research sponsors Private and voluntary sector cancer research sponsors Academic and other cancer centers and medical centers Nursing and other nonphysician medical educational institutions State governments

*The Panel recognizes that entities other than those listed may have a vital role or interest in implementation of the recommendations.

Recommendation	Responsible Stakeholder(s) and Other Entities*
11. The Secretary of the Department of Health and Human Services should be directed to convene a trans-HHS working group to clarify the definition, mission, and vision of the National Cancer Program, define the principles and priorities for the NCP, and identify strategies for improving coordination of NCP activities to accelerate progress against cancer. The working group should solicit input from the diverse community of stakeholders whose actions affect cancer patient outcomes.	The President The Secretary, Department of Health and Human Services Department of Health and Human Services • National Institutes of Health • Centers for Disease Control and Prevention • Food and Drug Administration • Centers for Medicare and Medicaid Services • Agency for Healthcare Research and Quality • Health Resources and Services Administration

*The Panel recognizes that entities other than those listed may have a vital role or interest in implementation of the recommendations.

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Appendices

Appendix A

Roster of President's Cancer Panel Meeting Participants
The Future of Cancer Research: Accelerating Scientific Innovation

Meeting Date	Location
September 22, 2010	Boston, MA
October 26, 2010	Philadelphia, PA
December 14, 2010	Bethesda, MD
February 1, 2011	Atlanta, GA

Meeting Participants	
David Agus, M.D.	Center for Applied Molecular Medicine Keck School of Medicine of the University of Southern California
Peter Alperin, M.D.	Archimedes, Inc.
Margaret Anderson, M.S.	FasterCures/The Center for Accelerating Medical Solutions
John Auerbach, M.B.A.	Association of State and Territorial Health Officials Massachusetts Department of Public Health
Tomasz M. Beer, M.D., F.A.C.P.	Oregon Health & Science University Knight Cancer Institute
Edward J. Benz, Jr., M.D.	Dana-Farber Cancer Institute
Donald A. Berry, Ph.D.	The University of Texas MD Anderson Cancer Center
Otis W. Brawley, M.D.	American Cancer Society
Scott Campbell, Ph.D.	Foundation for the National Institutes of Health
Arthur L. Caplan, Ph.D.	Center for Bioethics University of Pennsylvania
Bruce Chabner, M.D.	The National Cancer Advisory Board's Ad hoc Working Group to Create a Strategic Scientific Vision for the National Cancer Program and Review of the National Cancer Institute Massachusetts General Hospital Cancer Center

Carolyn Compton, M.D., Ph.D.	National Cancer Institute
Jonathon N. Cummings, Ph.D.	The Fuqua School of Business, Duke University
Gwen Darien	National Cancer Institute Samuel Waxman Cancer Research Foundation
Ronald F. Dixon, M.D.	Virtual Practice Project at Massachusetts General Hospital
James Doroshow, M.D.	National Cancer Institute
Susannah Fox	Pew Internet & American Life Project
Charles Friedman, Ph.D.	Office of the National Coordinator for Health Information Technology Office of the Secretary U.S. Department of Health and Human Services
Judy E. Garber, M.D., M.P.H.	American Association for Cancer Research Dana-Farber Cancer Institute
Michael A. Goldstein, M.D.	Beth Israel Deaconess Medical Center
Peter Grevatt, Ph.D.	Environmental Protection Agency
William Hait, M.D., Ph.D.	Ortho Biotech Oncology Research & Development, A Unit of Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Patricia Hartge, Sc.D.	National Cancer Institute
Brandon Hayes-Lattin, M.D.	Lance Armstrong Foundation Oregon Health & Science University Knight Cancer Institute
E. Melissa Kaime, M.D.	Department of Defense Congressionally Directed Medical Research Programs
Michael Kelley, M.D., F.A.C.P.	Department of Veterans Affairs Veterans Health Administration
Margaret L. Kripke, Ph.D.	President's Cancer Panel The University of Texas MD Anderson Cancer Center
Julia I. Lane, Ph.D.	Science of Science & Innovation Policy National Science Foundation
LaSalle D. Leffall, Jr., M.D., F.A.C.S.	President's Cancer Panel Howard University College of Medicine
Donald J. Listwin, LL.D.	Canary Foundation
Bradley Malin, Ph.D.	Vanderbilt University School of Medicine
Bernard Munos, M.S., M.B.A.	Eli Lilly and Company
Sharyl J. Nass, Ph.D.	Institute of Medicine National Academy of Sciences

Richard Pazdur, M.D.	Center for Drug Evaluation and Research U.S. Food and Drug Administration
Louise M. Perkins, Ph.D.	Multiple Myeloma Research Foundation
Chandini E. Portteus	Susan G. Komen for the Cure
Raj K. Puri, M.D., Ph.D.	Center for Biologics Evaluation and Research U.S. Food and Drug Administration
Kyu Rhee, M.D., M.P.P., F.A.A.P., F.A.C.P.	Health Resources and Services Administration
Lisa Richardson, M.D., M.P.H.	Centers for Disease Control and Prevention
Abby B. Sandler, Ph.D.	President's Cancer Panel National Cancer Institute
Daniel Sarewitz, Ph.D., M.S.	Arizona State University
Ellen V. Sigal, Ph.D.	Friends of Cancer Research
George W. Sledge, Jr., M.D.	American Society of Clinical Oncology Indiana University Simon Cancer Center
Howard R. Soule, Ph.D.	Prostate Cancer Foundation The Milken Institute
Barry M. Straube, M.D.	Centers for Medicare and Medicaid Services
Naz Sykes	Dr. Susan Love Research Foundation
William J. Todd	Georgia Cancer Coalition
Robert G. Urban, Ph.D.	David H. Koch Institute for Integrative Cancer Research Massachusetts Institute of Technology
Harold Varmus, M.D.	National Cancer Institute
Nina Wallerstein, Dr.P.H.	Center for Participatory Research University of New Mexico School of Medicine
Yun-Ling Wong, Ph.D.	Bill & Melinda Gates Foundation

Appendix B

The National Cancer Act of 1971

[PUBLIC LAW 92-218]
[92ND CONGRESS, S. 1828]
[DECEMBER 23, 1971]

AN ACT

To amend the Public Health Service Act so as to strengthen the National Cancer Institute of Health in order more effectively to carry out the national effort against cancer.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled.

SHORT TITLE

SECTION 1. This Act may be cited as "The National Cancer Act of 1971."

FINDINGS AND DECLARATION OF PURPOSE

SEC. 2. (a) The Congress finds and declares—

(1) that the incidence of cancer is increasing and cancer is the disease which is the major health concern of Americans today;

(2) that new scientific leads, if comprehensively and energetically exploited, may significantly advance the time when more adequate preventive and therapeutic capabilities are available to cope with cancer;

(3) that cancer is a leading cause of death in the United States;

(4) that the present state of our understanding of cancer is a consequence of broad advances across the full scope of the biomedical sciences;

(5) that a great opportunity is offered as a result of recent advances in the knowledge of this dread disease to conduct energetically a national program against cancer;

(6) that in order to provide for the most effective attack on cancer it is important to use all of the biomedical resources of the National Institutes of Health; and

(7) that the programs of the research institutes which comprise the National Institutes of Health have made it possible to bring into being the most productive scientific community centered upon health and disease that the world has ever known.

(b) It is the purpose of this Act to enlarge the authorities of the National Cancer Institute and the National Institutes of Health in order to advance the national effort against cancer.

NATIONAL CANCER PROGRAM

SEC. 3. (a) Part A of title IV of the Public Health Service Act is amended by adding after section 406 the following new sections:

SEC. 407. (a) The Director of the National Cancer Institute shall coordinate all of the activities of the National Institutes of Health relating to cancer with the National Cancer Program.

(b) In carrying out the National Cancer program, the Director of the National Cancer Institute shall:

(1) With the advice of the National Cancer Advisory Board, plan and develop an expanded, intensified, and coordinated cancer research program encompassing the programs of the National Cancer Institute, related programs of the other research institutes, and other Federal and non-Federal programs.

(2) Expeditiously utilize existing research facilities and personnel of the National Institutes of Health for accelerated exploration of opportunities in areas of special promise.

(3) Encourage and coordinate cancer research by industrial concerns where such concerns evidence a particular capability for such research.

(4) Collect, analyze, and disseminate all data useful in the prevention, diagnosis, and treatment of cancer, including the establishment of an international cancer research data bank to collect, catalog, store, and disseminate insofar as feasible the results of cancer research undertaken in any country for the use of any person involved in cancer research in any country.

(5) Establish or support the large-scale production or distribution of specialized biological materials and other therapeutic substances for research and set standards of safety and care for persons using such materials.

(6) Support research in the cancer field outside the United States by highly qualified foreign nationals which research can be expected to inure to the benefit of the American people; support collaborative research involving American and foreign participants; and support the training of American scientists abroad and foreign scientists in the United States.

(7) Support appropriate manpower programs of training in fundamental sciences and clinical disciplines to provide an expanded and continuing manpower base from which to select investigators, physicians, and allied health professions personnel, for participation in clinical and basic research and treatment programs relating to cancer, including where appropriate the use of training stipends, fellowships, and career awards.

(8) Call special meetings of the National Cancer Advisory Board at such times and in such places as the Director deems necessary in order to consult with, obtain advice from, or to secure the approval of projects, programs, or other actions to be undertaken without delay in order to gain maximum benefit from a new scientific or technical finding.

(9) (A) Prepare and submit, directly to the President for review and transmittal to Congress, an annual budget estimate for the National Cancer Program, after reasonable opportunity for comment (but without change) by the Secretary, the Director of the National Institutes of Health, and the National Cancer Advisory Board; and (B) receive from the President and the Office of Management and Budget directly all funds appropriated by Congress for obligation and expenditure by the National Cancer Institute.

(c) (1) There is established the President's Cancer Panel (hereinafter in this section referred to as the 'Panel') which shall be composed of three persons appointed by the President, who by virtue of their training, experience, and background are exceptionally qualified to appraise the National Cancer Pro-

gram. At least two of the members of the Panel shall be distinguished scientists or physicians.

(2) (A) Members of the Panel shall be appointed for three-year terms, except that (i) in the case of two of the members first appointed, one shall be appointed for a term of one year and one shall be appointed for a term of two years, as designated by the President at the time of appointment, and (ii) any member appointed to fill a vacancy occurring prior to the expiration of the term for which his predecessor was appointed shall be appointed only for the remainder of such term.

(B) The president shall designate one of the members to serve as Chairman for a term of one year.

(C) Members of the panel shall each be entitled to receive the daily equivalent of the annual rate of basic pay in effect for grade GS-18 of the General Schedule for each day (including traveltime) during which they are engaged in the actual performance of duties vested in the Panel, and shall be allowed travel expenses (including a per diem allowance) under section 5703(b) of title 5, United States Code.

(3) The Panel shall meet at the call of the Chairman, but not less often than twelve times a year. A transcript shall be kept of the proceedings of each meeting of the Panel, and the Chairman shall make such transcript available to the public.

(4) The Panel shall monitor the development and execution of the National Cancer Program under this section, and shall report directly to the President. Any delays or blockages in rapid execution of the Program shall immediately be brought to the attention of the President. The Panel shall submit to the President periodic progress reports on the Program and annually an evaluation of the efficacy of the Program and suggestions for improvements, and shall submit such other reports as the President shall direct. At the request of the President, it shall submit for his consideration a list of names of persons for consideration for appointment as Director of the National Cancer Institute.

NATIONAL CANCER RESEARCH AND DEMONSTRATION CENTERS

SEC. 408. (a) The Director of the National Cancer Institute is authorized to provide for the establishment of fifteen new centers for clinical research, training, and demonstration of advanced diagnostic and treatment methods relating to cancer. Such centers may be supported under subsection (b) or under any other applicable provision of law.

(b) The Director of the National Cancer Institute, under policies established by the Director of the National Institutes of Health and after consultation with the National Cancer Advisory Board, is authorized to enter into cooperative agreements with public or private nonprofit agencies or institutions to pay all or part of the cost of planning, establishing, or strengthening, and providing basic operating support for existing or new centers (including, but not limited to, centers established under subsection (a)) for clinical research, training, and demonstration of advanced diagnostic and treatment methods relating to cancer. Federal payments under this subsection in support of such cooperative agreements may be used for (1) construction (notwithstanding any limitation under section 405), (2) staffing and other basic operating costs, including such patient care costs as are required for research, (3) training (including training for allied health professions personnel), and (4) demonstration purposes; but support under this subsection (other than support for construction) shall not exceed $5,000,000 per year per center. Support of a center under this section may be for a period of not to exceed three years and may be extended by the Director

of the National Cancer Institute for additional periods of not more than three years each, after review of the operations of such center by an appropriate scientific review group established by the Director of the National Cancer Institute.

CANCER CONTROL PROGRAMS

SEC. 409. (a) The Director of the National Cancer Institute shall establish programs as necessary for cooperation with State and other health agencies in the diagnosis, prevention, and treatment of cancer.

(b) There are authorized to be appropriated to carry out this section $20,000,000 for the fiscal year ending June 30, 1972, $30,000,000 for the fiscal year ending June 30, 1973, and $40,000,000 for the fiscal year ending June 30, 1974.

AUTHORITY OF DIRECTOR

SEC. 410. The Director of the National Cancer Institute (after consultation with the National Cancer Advisory Board), in carrying out his functions in administering the National Cancer Program and without regard to any other provision of this Act, is authorized—

(1) if authorized by the National Cancer Advisory Board, to obtain (in accordance with section 309 of title 5, United States Code, but without regard to the limitation in such section on the number of days or the period of such service) the services of not more than fifty experts or consultants who have scientific or professional qualifications;

(2) to acquire, construct, improve, repair, operate, and maintain cancer centers, laboratories, research, and other necessary facilities and equipment, and related accommodations as may be necessary, and such other real or personal property (including patents) as the Director deems necessary; to acquire, without regard to the Act of March 3, 1877 (40 U.S.C. 340, by lease or otherwise through the Administrator of General Services, buildings or parts of buildings in the District of Columbia or communities located adjacent to the District of Columbia for the use of the National Cancer Institute for a period not to exceed ten years;

(3) to appoint one or more advisory committees composed of such private citizens and officials of Federal, State, and local governments as he deems desirable to advise him with respect to his functions;

(4) to utilize, with their consent, the services, equipment, personnel, information, and facilities of other Federal, State, or local public agencies, with or without reimbursement therefor;

(5) to accept voluntary and uncompensated services;

(6) to accept unconditional gifts, or donations of services, money, or property, real, personal, or mixed, tangible or intangible;

(7) to enter into such contracts, leases, cooperative agreements, or other transactions, without regard to sections 3648 and 3709 of the Revised Statutes of the United States (31 U.S.C. 529, 41 U.S.C. 5), as may be necessary in the conduct of his functions, with any public agency, or with any person, firm, association, corporation, or educational institution; and

(8) to take necessary action to insure that all channels for the dissemination and exchange of scientific knowledge and information are maintained between the National Cancer Institute and the other scientific, medical, and biomedical disciplines and organizations nationally and internationally.

SCIENTIFIC REVIEW; REPORTS

SEC. 410A. (a) The Director of the National Cancer Institute shall, by regulation, provide for proper scientific review of all research grants and programs over which he has authority (1) by utilizing, to the maximum extent possible, appropriate peer

review groups established within the National Institutes of Health and composed principally of non-Federal scientists and other experts in the scientific and disease fields, and (2) when appropriate, by establishing, with the approval of the National Cancer Advisory Board and the Director of the National Institutes of Health, other formal peer review groups as may be required.

(b) The Director of the National Cancer Institute shall, as soon as practicable after the end of each calendar year, prepare in consultation with the National Cancer Advisory Board and submit to the President for transmittal to the Congress a report on the activities, progress, and accomplishments under the National Cancer Program during the preceding calendar year and a plan for the Program during the next five years.

NATIONAL CANCER ADVISORY BOARD

SEC. 410B. (a) There is established in the National Cancer Institute a National Cancer Advisory Board (hereinafter in this section referred to as the 'Board') to be composed of twenty-three members as follows:

(1) The Secretary, the Director of the Office of Science and Technology, the Director of the National Institutes of Health, the chief medical officer of the Veterans' Administration (or his designee), and a medical officer designated by the Secretary of Defense shall be ex-officio members of the Board.

(2) Eighteen members appointed by the President. Not more than twelve of the appointed members of the Board shall be scientists or physicians and not more than eight of the appointed members shall be representatives from the general public. The scientists and physicians appointed to the Board shall be appointed from persons who are among the leading scientific or medical authorities outstanding in the study, diagnosis, or treatment of cancer or in fields related thereto. Each appointed member of the Board shall be appointed from among persons who by virtue of their training, experience, and background are especially qualified to appraise the programs of the National Cancer Institute.

(b) (1) Appointed members shall be appointed for six-year terms, except that of the members of first appointed six shall be appointed for a term of two years, and six shall be appointed for a term of four years, as designated by the President at the time of appointment.

(2) Any member appointed to fill a vacancy occurring prior to expiration of the term for which his predecessor was appointed shall serve only for the remainder of such term. Appointed members shall be eligible for reappointment and may serve after the expiration of their terms until their successors have taken office.

(3) A vacancy in the Board shall not affect its activities, and twelve members thereof shall constitute a quorum.

(4) The Board shall supersede the existing National Advisory Cancer Council, and the appointed members of the Council serving on the effective date of this section shall serve as additional members of the Board for the duration of their terms then existing, or for such shorter time as the President may prescribe.

(c) The President shall designate one of the appointed members to serve as Chairman for a term of two years.

(d) The Board shall meet at the call of the Director of the National Cancer Institute or the Chairman, but not less often than four times a year and shall advise and assist the Director of the National Cancer Institute with respect to the National Cancer Program.

(e) The Director of the National Cancer Institute shall designate a member of the staff of the Institute to act as Executive Secretary of the Board.

(f) The Board may hold such hearings, take such testimony, and sit and act at such times and places as the Board deems advisable to investigate programs and activities of the National Cancer Program.

(g) The Board shall submit a report to the President for transmittal to the Congress not later than January 31 of each year on the progress of the National Cancer Program toward the accomplishment of its objectives.

(h) Members of the Board who are not officers or employees of the United States shall receive for each day they are engaged in the performance of the duties of the Board compensation at rates not to exceed the daily equivalent of the annual rate in effect for GS-18 of the General Schedule, including traveltime; and all members, while so serving away from their homes or regular places of business, may be allowed travel expenses, including per diem in lieu of subsistence, in the same manner as such expenses are authorized by section 5703, title 5, United States Code, for person in the Government service employed intermittently.

(i) The Director of the National Cancer Institute shall make available to the Board such staff, information, and other assistance as it may require to carry out its activities.

AUTHORIZATION OF APPROPRIATIONS

SEC. 410C. For the purpose of carrying out this part (other than section 409), there are authorized to be appropriated $400,000,000 for the fiscal year ending June 30, 1972; $500,000,000 for the fiscal year ending June 30, 1973; and $600,000,000 for the fiscal year ending June 30, 1974.

(b) (1) Section 402 of the Public Health Service Act is amended by adding at the end thereof the following:

(b) Under procedures approved by the Director of the National Institutes of Health, the Director of the National Cancer Institute may approve grants under this Act for cancer research or training—

(1) in amounts not to exceed $35,000 after appropriate review for scientific merit but without the review and recommendation by the National Cancer Advisory Board prescribed by section 403(c), and

(2) in amounts exceeding $35,000 after appropriate review for scientific merit and recommendation for approval by such Board as prescribed by section 403(c)."

(2) Section 402 of such Act is further amended—

(A) by inserting "(a)" immediately after "Sec. 402."; and

(B) by redesignating paragraphs (a), (b), (c), (d), (e), (f), and (g) as paragraphs (1), (2), (3), (4), (5), (6), and (7), respectively.

(3) Section 403(c) of such Act is amended by striking out "In carrying out" and inserting in lieu thereof "Except as provided in section 402(b), in carrying out."

REPORT TO CONGRESS

SEC. 4. (a) The President shall carry out a review of all administrative processes under which the National Cancer Program, established under part A of title IV of the Public Health Service Act, will operate, including the processes of advisory council and peer group reviews, in order to assure the most expeditious accomplishment of the objectives of the Program. Within one year of the date of enactment of this Act the President shall submit a report to Congress of the findings of such review and the actions taken to facilitate the conduct of the Program, together with recommendations for any needed legislative changes.

(b) The President shall request of the Congress without delay such additional appropriations (including increased authorizations) as are required to pursue immedi-

ately any development in the National Cancer Program requiring prompt and expeditious support and for which regularly appropriated funds are not available.

PRESIDENTIAL APPOINTMENTS

SEC. 5. Title IV of the Public Health Service Act is amended by adding after part F the following new part:

PART G—ADMINISTRATIVE PROVISIONS DIRECTORS OF INSTITUTES

SEC. 454. The Director of the National Institutes of Health and the Director of the National Cancer Institute shall be appointed by the President. Except as provided in section 407(b)(9), the Director of the National Cancer Institute shall report directly to the Director of the National Institutes of Health."

CONFORMING AMENDMENTS

SEC. 6. (a) (1) Section 217 of the Public Health Service Act is amended (A) by striking out "National Advisory Cancer Council," each place it occurs in subsection (a), and (B) by striking out "cancer," in subsections (a) and (b) of such section.

(2) Sections 301(d), 301(i), 402, and 403(c) of such Act are each amended by striking out "National Advisory Cancer Council" and inserting in lieu thereof "National Cancer Advisory Board".

(3) Section 403(b) of such Act is amended by striking out "National Cancer Advisory Council" and inserting in lieu thereof "National Cancer Advisory Board".

(4) Section 404 of such Act is amended—

(A) by striking out "council" in the matter preceding paragraph (a) and inserting in lieu thereof "National Cancer Advisory Board", and

(B) by striking out "COUNCIL" in the section heading and inserting in lieu thereof "BOARD".

EFFECTIVE DATE

SEC. 7. (a) This Act and the amendments made by this Act shall take effect sixty days after the date of enactment of this Act or on such prior date after the date of enactment of this Act as the President shall prescribe and publish in the Federal Register.

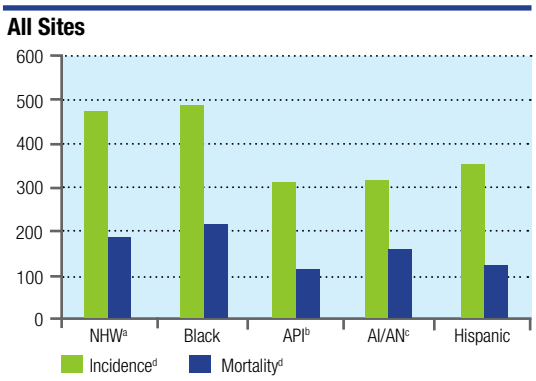
(b) The first sentence of section 454 of the Public Health Service Act (added by section 5 of this Act) shall apply only with respect to appointments made after the effective date of this Act (as prescribed by subsection (a)).

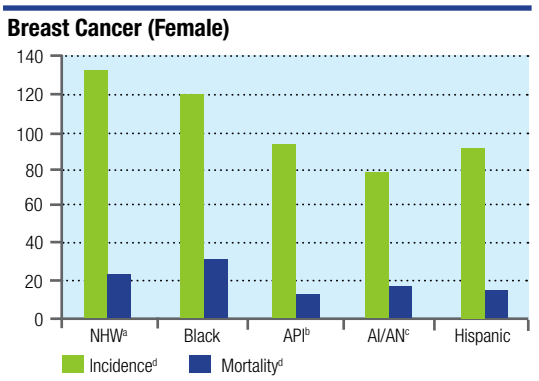
(c) Notwithstanding the provisions of subsection (a), members of the National Cancer Advisory Board (authorized under section 410B of the Public Health Service Act, as added by this Act) may be appointed, in the manner provided for in such section, at any time after the date of enactment of this Act. Such officers shall be compensated from the date they first take office, at the rates provided for in such section 410B.

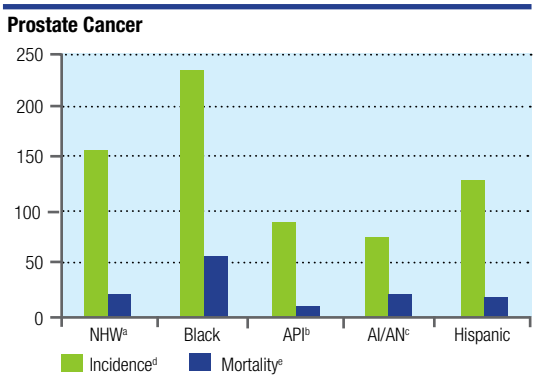
Approved December 23, 1971.

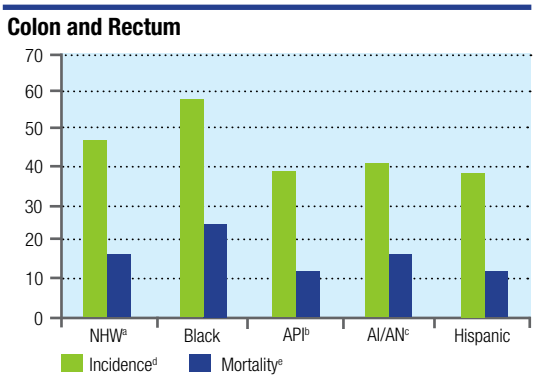
Appendix C

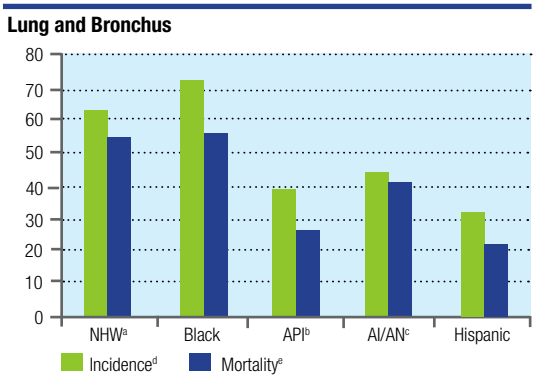
U.S. Cancer Incidence and Mortality Rates By Population, Selected Cancer Sites (per 100,000 Population), 2004-2008

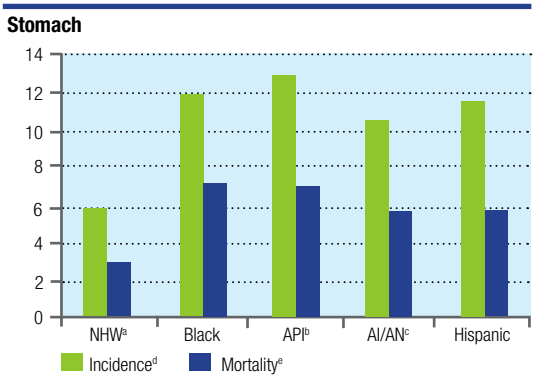


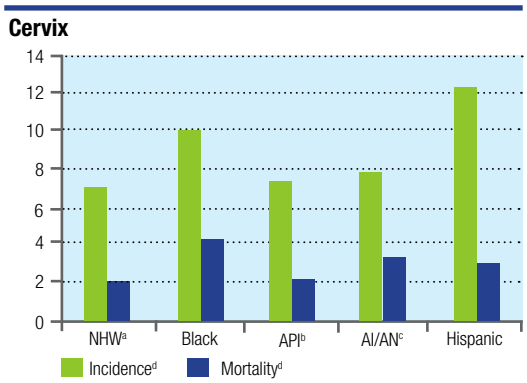


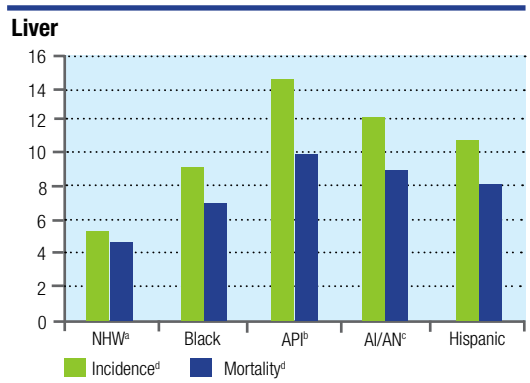


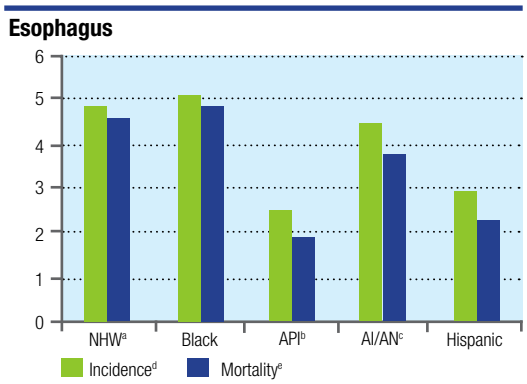


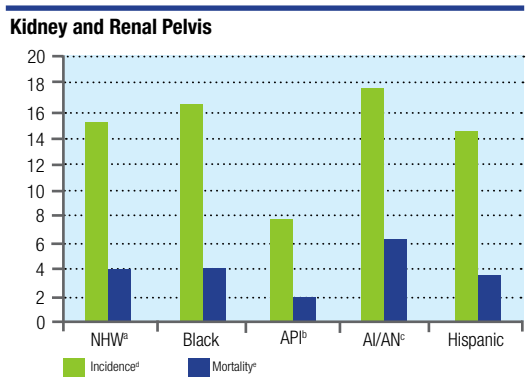


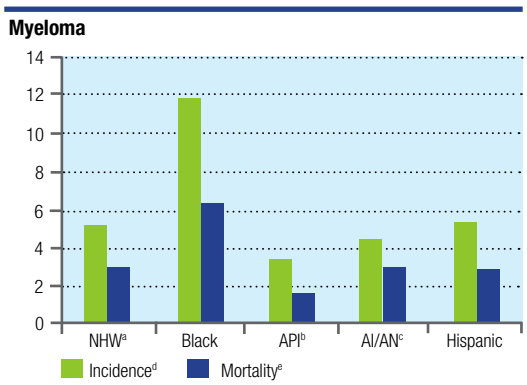


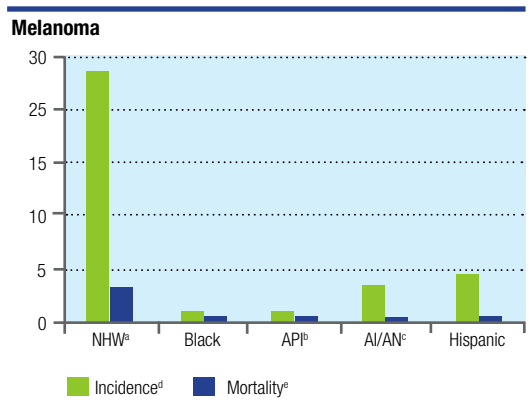












a Non-Hispanic white.
b Asian/Pacific Islander.
c American Indian/Alaska Native.
d Incidence data are from the 17 SEER areas: San Francisco (SF), Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey (SJM), Los Angeles (LA), Alaska Native Registry, Rural Georgia, California (excluding SF, SJM, and LA), Kentucky, Louisiana, and New Jersey.
e Mortality data used in calculating the rates are analyzed from U.S. mortality files provided by the National Center for Health Statistics, Centers for Disease Control and Prevention.

Source: Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, et al., editors. SEER cancer statistics review, 1975-2008, National Cancer Institute [Internet]. Bethesda (MD): http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER Web site, 2011. Accessed 14 Nov 2011.

Appendix D

Examples of NIH and Other Young Investigator Awards

NIH:

NIH Director's New Innovator Award Program – designed to stimulate highly innovative research and support promising new investigators. These are different from traditional NIH grants in important ways—preliminary data are not required, but may be included; no detailed, annual budget is requested in the application; and there is increased emphasis on the applicant's creativity, innovativeness of the research, and potential of the project. *https://commonfund.nih.gov/newinnovator/*

NIH Pathway to Independence Award – facilitates early-stage basic scientists to make a timely transition from a mentored postdoctoral research position to a stable, independent research position earlier than is currently the normal transition time (e.g., NCI-specific program is called the Howard Temin Pathway to Independence Award). *http://www.cancer.gov/researchandfunding/cancertraining/outsidenci/K99/*

NIH Director's Pioneer Award Program – designed to support individual scientists of exceptional creativity who propose pioneering and possibly transforming approaches to major challenges in biomedical and behavioral research. Investigators at all career levels are eligible, and those at early to middle stages of their careers are especially encouraged to apply. *https://commonfund.nih.gov/pioneer/*

NIH Director's Early Independence Award – intended to support exceptional junior investigators who wish to bypass traditional postdoctoral training and directly pursue independent research after completing the terminal research degree or clinical residency. *http://grants.nih.gov/grants/guide/notice-files/NOT-RM-11-009.html*

NCI Transition Career Development Award – supports the transition of postdoctoral fellows to faculty positions (e.g., NCI Transition Career Development Award, which supports transition of investigators from the mentored state to the independent stage). *http://grants.nih.gov/grants/guide/pa-files/PAR-09-089.html*

NCI Center to Reduce Cancer Health Disparities Continuing Umbrella of Research Experiences (CURE) Awards – prepares qualified individuals for careers that have a significant impact on the health-related research needs of the nation. This NCI-sponsored award is specifically designed to promote career development of racially and ethnically diverse individuals who are underrepresented in health-related science and for those who are committed to a career in cancer health disparities, biomedical, behavioral, or translational cancer research. CURE's career development awards include:

- NCI Mentored Career Development Award to Promote Diversity
- NCI Mentored Clinical Scientist Award to Promote Diversity
- Mentored Patient-Oriented Research Award to Promote Diversity
- NCI Transition Career Development Award to Promote Diversity

http://crchd.cancer.gov/diversity/cure-overview.html

Cancer Prevention, Control, Behavioral, and Population Sciences Career Development Award – provides support for salary and research costs for up to five years for individuals with health professional or science doctoral degrees who are not fully established investigators and want to pursue research careers in the cancer prevention, control, population, and/or behavioral sciences. *http://grants.nih.gov/grants/guide/pa-files/PAR-09-078.html*

Ruth L. Kirschstein National Research Service Award for Individual Postdoctoral Fellows – provides up to three years of aggregate support at the postdoctoral level, including stipends, tuition and fees, and fellowship expenses. *http://grants.nih.gov/training/nrsa.htm*

Ruth L. Kirschstein National Research Service Award Institutional Training Grants – the primary means of supporting pre- and postdoctoral research training programs at institutions since 1974. This grant offsets the cost of stipends, tuition and fees, and training-related expenses for appointed trainees. *http://grants.nih.gov/training/nrsa.htm*

Other:

AACR-The ASCO Cancer Foundation Young Investigator Translational Cancer Award – provides funding to physician-scientists during the transition from a fellowship program to a faculty appointment. *http://www.aacr.org/home/scientists/aacr-research-funding/junior-faculty-grant-recipients/aacr-the-asco-cancer-foundation-young-investigator-translational-cancer-research-award-.aspx*

AACR Gertrude B. Elion Cancer Research Award – open to tenure-track scientists at the level of assistant professor who completed postdoctoral studies or clinical research fellowships no more than four years prior to the start of the grant term. *http://www.aacr.org/home/scientists/aacr-research-funding/junior-faculty-grant-recipients/aacr-gertrude-b-elion-cancer-research-award.aspx*

The Doris Duke Clinical Scientist Development Award – provides grants to junior physician-scientists to facilitate their transition to independent clinical research careers. *http://www.ddcf.org/Medical-Research/Program-Strategies/Clinical-Research/Clinical-Scientist-Development-Award/*

Burroughs Wellcome Fund Career Award for Medical Scientists – provides "bridge" funding for physician-scientists in postdoctoral/fellowship training and the early years of faculty service. *http://www.bwfund.org/pages/188/Career-Awards-for-Medical-Scientists/*

Susan G. Komen for the Cure Career Catalysts Research Grant – provides support for breast cancer researchers who are in the early stages of their faculty careers. *http://ww5.komen.org/uploadedFiles/Content/ResearchGrants/GrantPrograms/FY12_CCR_RFA.pdf*

Alliance for Cancer Gene Therapy Fund for Discovery Grant – supports young investigators seeking to advance cell and gene therapy research into the causes, treatment, and prevention of all types of cancer. *http://www.acgtfoundation.org/grants.html*

Appendix E

Recommended Survivorship Care Plan Elements

Upon discharge from cancer treatment, including treatment of recurrences, every patient should be given a record of all care received and important disease characteristics. This should include, at a minimum:

1. Diagnostic tests performed and results.
2. Tumor characteristics (e.g., site(s), stage and grade, hormone receptor status, marker information).
3. Dates of treatment initiation and completion.
4. Surgery, chemotherapy, radiotherapy, transplant, hormonal therapy, or gene or other therapies provided, including agents used, treatment regimen, total dosage, identifying number and title of clinical trials (if any), indicators of treatment response, and toxicities experienced during treatment.
5. Psychosocial, nutritional, and other supportive services provided.
6. Full contact information on treating institutions and key individual providers.
7. Identification of a key point of contact and coordinator of continuing care.

Upon discharge from cancer treatment, every patient and his/her primary health care provider should receive a written follow-up care plan incorporating available evidence-based standards of care. This should include, at a minimum:

1. The likely course of recovery from treatment toxicities, as well as the need for ongoing health maintenance/adjuvant therapy.
2. A description of recommended cancer screening and other periodic testing and examinations, and the schedule on which they should be performed (and who should provide them).
3. Information on possible late and long-term effects of treatment and symptoms of such effects.
4. Information on possible signs of recurrence and second tumors.
5. Information on the possible effects of cancer on marital/partner relationship, sexual functioning, work, and parenting, and the potential future need for psychosocial support.
6. Information on the potential insurance, employment, and financial consequences of cancer and, as necessary, referral to counseling, legal aid, and financial assistance.
7. Specific recommendations for healthy behaviors (e.g., diet, exercise, healthy weight, sunscreen use, immunizations, smoking cessation, osteoporosis prevention). When appropriate, recommendations that first-degree relatives be informed about their increased risk and the need for cancer screening (e.g., breast cancer, colorectal cancer, prostate cancer).
8. As appropriate, information on genetic counseling and testing to identify high-risk individuals who could benefit from more comprehensive cancer surveillance, chemoprevention, or risk-reducing surgery.
9. As appropriate, information on known effective chemoprevention strategies for secondary prevention (e.g., tamoxifen in women at high risk for breast cancer; aspirin for colorectal cancer prevention).
10. Referrals to specific follow-up care providers (e.g., rehabilitation, fertility, psychology), support groups, and/or the patient's primary care provider.
11. A listing of cancer-related resources and information (e.g., Internet-based sources and telephone listings for major cancer support organizations).

Source: Institute of Medicine. From cancer patient to cancer survivor. Washington (DC): The National Academies Press; 2006. Adapted from the President's Cancer Panel; 2004.

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