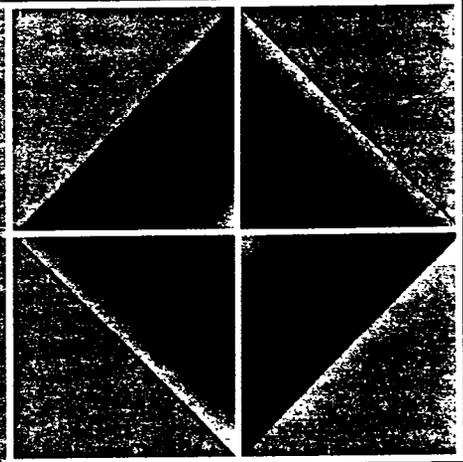


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Cancer at a Crossroads: A Report to Congress for the Nation



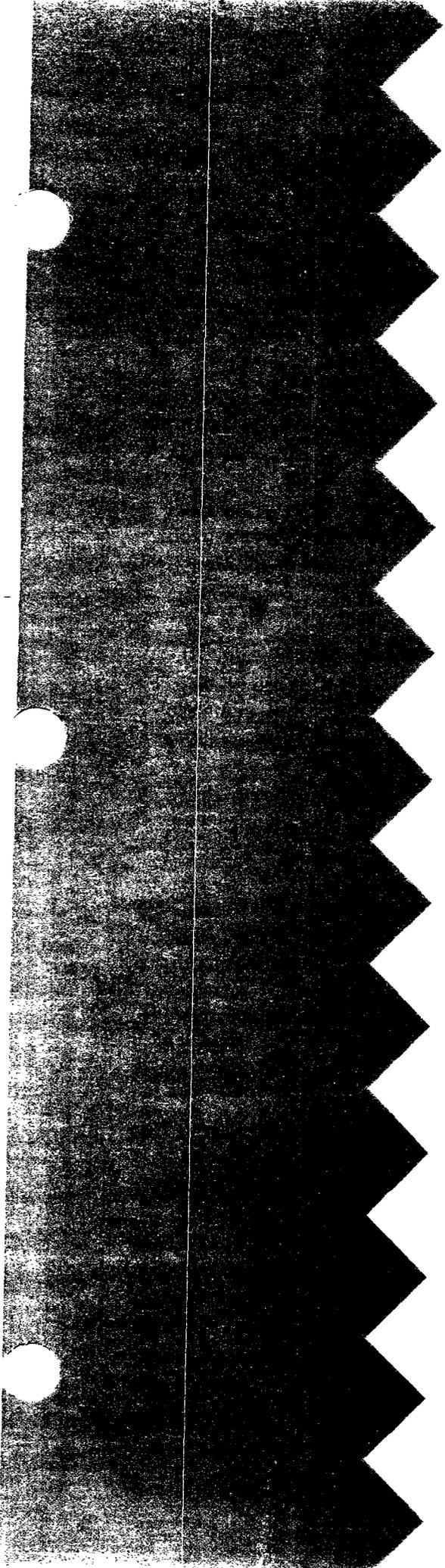
The Subcommittee
to Evaluate the
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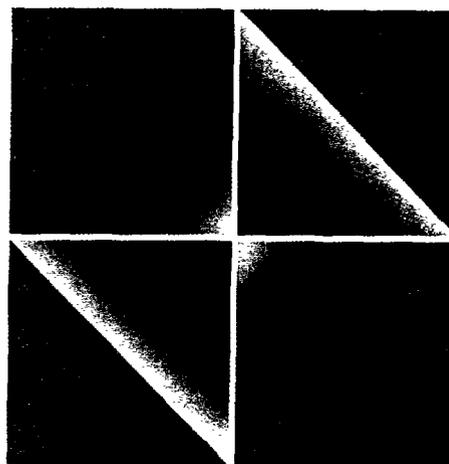
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Cancer at a Crossroads: A Report to Congress for the Nation



The Subcommittee
to Evaluate the
National Cancer
Program

NATIONAL CANCER ADVISORY BOARD
SEPTEMBER 1994



From the Chairman:

It is with great pleasure that I transmit this report. ***Cancer at a Crossroads: A Report to Congress for the Nation***, by the National Cancer Advisory Board (NCAB) Subcommittee to Evaluate the National Cancer Program (NCP). This evaluation was undertaken at the request of both the House of Representatives and Senate Appropriations Subcommittees on Labor, Health and Human Services, Education, and Related Agencies to assess the achievements of the NCP, identify barriers to reducing the burden of cancer, and make recommendations for future research and Program directions.

From the outset, it was this Subcommittee's firm belief that the National Cancer Program comprises not just the cancer research community, but government at all levels, business and industry, the total health care system, and every individual citizen. Unless all of these constituents recognize their potential to minimize the impact of this affliction and take appropriate actions, cancer will continue to ravage our population. The Subcommittee has concluded that the strongest strategy for a renewed War on Cancer includes three essential elements: 1) applying currently available knowledge about cancer prevention and care to all segments of the population; 2) increasing support for translational research that develops basic cancer knowledge into preventive strategies, new technologies, and effective treatments; and 3) increasing support for basic cancer research to ensure the continued flow of new discoveries that lead to better cancer prevention and care.

The Congress requested that the Subcommittee draw together diverse constituencies and scientific disciplines to recommend future directions for the National Cancer Program. As confirmed by the membership roster contained in the report, the individuals who gave so generously of their valuable time to this endeavor are among the most respected professionals in cancer prevention and control, epidemiology, environmental carcinogenesis, molecular biology, drug and vaccine development, clinical investigation, and patient care, including therapy and rehabilitation. In addition, other advocates and critics of the NCP, including cancer survivors, parents of children with cancer, representatives of the insurance and pharmaceutical industries, and public health experts brought their personal testimony, special insights, and individual perspectives to bear throughout the Subcommittee's discussions. Despite hectic schedules, all of these individuals devoted many hours to attend meetings, prepare draft reports, review comments from outside reviewers, and participate in final editing sessions. I am deeply grateful for their participation, dedication, willingness to evaluate divergent viewpoints, and profound commitment to the eradication of this dreadful disease.

The Subcommittee's work also benefited from exceptional staff support. Specifically, the project could not have been completed without the invaluable assistance of Executive Secretary Cherie Nichols, Chief, Planning, Evaluation, and Analysis Branch, Office of Program Operations and Planning, National Cancer Institute, her staff, and the NCI Committee Management Office. Consultants to the project were Suzanne Reuben, President, Progressive Health Systems and Jay Bell, Director, James Bell Associates. Logistical support was provided by Tina Mastrian, NOVA Research Company.

It is the sincere hope of all those involved in producing this report that the Congress, on behalf of the people, will use this document to guide priority setting, policy decisions, funding appropriations, and legislative action that will help to relieve the suffering and eliminate the devastation caused by cancer.

Respectfully,



Paul Calabresi, M.D.
Chairman
Subcommittee to Evaluate
the National Cancer Program
National Cancer Advisory Board



Table of Contents

Preface	1
NCAB Subcommittee to Evaluate the National Cancer Program	3
Executive Summary	5
Cancer at a Crossroads	9
The State of the National Cancer Program	9
A Three-Stage Approach to Progress	10
Developing and Delivering Cancer Care: Centers, Groups, and Community-Based Programs	13
Maintaining Balanced Support for the National Cancer Program.. ..	13
Barriers to Success Against Cancer	14
Challenges for the National Cancer Program	14
Recommendations	15
I. Application of Research—Bringing the Benefits of Current Knowledge to All of the People	17
Cancer, Lifestyle, and Public Policy	17
Cancer Care Access	18
Education and Training of Health Care Providers	20
Recommendations for Application of Research	21
II. Translational Research-Bridging the Gap Between the Laboratory and the People	23
The Role of Translational Research	23
Examples of Translational Research	23
Challenges to Progress	24
Recommendations for Translational Research	26
III. Basic Cancer Research-Maintaining Excellence, Accelerating Progress	29
The Status of Basic Cancer Knowledge	29
Approaches to Accelerating Progress	29
Recommendations for Basic Cancer Research	33
Appendices	
A. Excerpts From House of Representatives and Senate Appropriations Subcommittee Reports: Requests for an Evaluation of the National Cancer Program	A-1
B. Summary--Measures of Progress Against Cancer	B-1
C. Meetings of the President's Cancer Panel	C-1
D. Executive Summary of the President's Cancer Panel Special Commission on Breast Cancer	D-1
E. Measurable Outcomes, Assigned Responsibility, and Priority for National Cancer Program Recommendations	E-1

Preface

This report concludes a three-phase evaluation of the National Cancer Program, as requested by the Congress (see Appendix A). The evaluation methodology, approved by the Congress, was intended to assimilate the viewpoints of varied constituencies having either direct involvement in the National Cancer Program or a secondary relationship to the Program.

In Phase I, six panels of experts were convened to identify advances in basic, clinical, and applied cancer research over the past decade, the potential of these advances to reduce the national cancer burden, and challenges for the future. Summaries from the products of their review, the *Measures of Progress Against Cancer* reports, are included as Appendix B to this document.

During Phase II, information was collected and testimony heard on the current status and recommended future directions of the National Cancer Program through the framework of the

President's Cancer Panel (PCP). The report of the PCP Special Commission on Breast Cancer was also used as a resource for the current evaluation. (See Appendices C and D.)

In the final phase of the evaluation, the materials developed and collected in Phases I and II were integrated by a subcommittee of the National Cancer Advisory Board appointed to: assess progress against cancer; identify gaps, shortfalls, and opportunities in cancer research, prevention, detection, diagnosis, treatment, control, and rehabilitation/supportive care; define barriers to further progress; and provide recommendations for the future directions of the National Cancer Program. A compilation of the Subcommittee's recommendations, indicating suggested measurable outcomes, parties responsible for implementation, and priorities, is included as Appendix E. This report, reflecting the work of the Subcommittee from September 1993 through September 1994, is transmitted to the Congress with the concurrence of the full National Cancer Advisory Board.

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more advanced disease, and have lower survival rates and access to health care than the more affluent. The elderly have the highest cancer incidence and mortality, yet they are frequently not offered, nor do they seek, optimal cancer care. The uninsured, who may have no access to health care other than that available from emergency rooms or free clinics, seldom receive preventive or early diagnostic services. Even those with insurance and access frequently do not receive state-of-the-art care. Capitated health care delivery systems often create a barrier to effective cancer care by pitting patient needs against the providers' financial interests. We must tear down the barriers to cancer prevention, early detection, treatment, and control in all of the neighborhoods where our people live and all too often die of cancer.

Current laws, policy, and regulation thwart our efforts to reduce the national cancer burden. Regulations regarding clinical trial design, the approval process for additional uses of established cancer therapies, and excessive documentation create disincentives for industry to undertake anticancer drug and technology development. As a result, many promising investigative cancer treatments and devices will never reach the public. Lack of appreciation of the potential hazards of environmental and food source contaminants, and laws, policies, and regulations protecting and promoting tobacco use worsen the cancer problem and drive up health care costs.

Failure to support **translational research** severs the essential bridge connecting basic science discoveries to improvements in cancer prevention and care. Through translational research, basic research findings become specific cancer care products and services. Opportunities to translate basic science advances are hampered by insufficient numbers of funded translational research studies and trained investigators; economic and program cutbacks by health care providers, pharmaceutical and biotechnology

companies; and declining patient care revenues. Much translational research has been supported by third party payments. Under a reformed health care system based on managed care and capitated payments, explicit support for translational research through support for qualified clinical trials will be an absolute necessity. Without this way of paying for patient costs associated with clinical research, the clinical research performed in this country will be reduced both in amount and importance. All of these issues must be addressed to avoid further erosion of support for essential translational research.

For the first time in cancer research history, we are poised to make major inroads into our understanding of the multistep process of cancer onset and spread. The ongoing revolution in molecular and cellular biology has created **unprecedented opportunities in basic science research** for advancing the fight against cancer, led to discovery of genetic links to cancer, and given rise to the biotechnology industry. These exciting discoveries and the opportunities for their application to cancer are the result of our significant public investment in untargeted, basic biomedical research. Inadequate resources now jeopardize continued basic science discoveries and undermine the creativity and morale of cancer researchers. Failure to respond will result in lost lives and will endanger this country's ability to maintain its superb talent base and world leadership in the creation of new cancer-related knowledge.

To address these issues, this Subcommittee to Evaluate the National Cancer Program advises the Congress to:

- Include in any health care reform plan, as part of the core benefit package, universal access to cancer care coverage that includes quality preventive, diagnostic, treatment, and rehabilitative/supportive services, including services provided in qualified clinical trials.

Executive Summary

In five years, cancer will surpass heart disease as the number one cause of death. One in three people in this country will be diagnosed with cancer, and one in five will die from it. Many lives are prematurely lost from insufficient knowledge of how a healthy cell becomes a cancer. The resulting health care costs, lost productivity, and personal tragedy are staggering. If this nation fails to address these six major issues, we will not prevail in our War on Cancer:

1. **Current health care reform proposals are devastating to the War on Cancer by denying resources for research and quality cancer care.**
2. **The National Cancer Program suffers from an absence of national coordination of cancer-fighting efforts in the public, private, and voluntary sectors.**
3. **Many people in this country, especially the poor, elderly, and uninsured, receive inadequate cancer care.**
4. **Current laws, public policy, and government regulation undermine cancer prevention, treatment, and control efforts.**
5. **Failure to support translational research hinders rapid development of cancer-fighting advances.**
6. **Current investment is insufficient to capitalize on unprecedented opportunities in basic science research.**

Health care reform, with universal cancer care coverage written in statute, is a necessity for all people. Rhetoric is no substitute for adequate cancer prevention and care. Cost control and health care funding provisions that (a) reduce cost by limiting use, thus compromising quality cancer care, (b) fail to cover patient care deliv-

ered in qualified clinical trials.’ and (c) fail to consider medical research costs are unacceptable. Revitalizing the commitment to the War on Cancer through responsible health care reform is a crucial mandate from the people to the Administration and the Congress. Any enacted national health care reform legislation, whether incremental or comprehensive, must address these critical needs.

An **absence of coordination** of the National Cancer Program (NCP) results in research and service gaps and costly duplication of effort. The original 1971 National Cancer Act established the NCP and mandated that the Director of the National Cancer Institute (NCI), with the advice of the National Cancer Advisory Board, plan and develop an expanded, intensified, and coordinated cancer research program encompassing the NCI programs, related programs of other research institutes, *and other Federal and non-Federal programs*. Several years later, the responsibility for other Federal and non-Federal programs was removed from the authorities of the NCI Director and included in the general authorities of all national research institutes. This Subcommittee believes strongly that the original legislation characterized correctly the broad scope of NCP research-related activities. It is the Subcommittee’s view that the NCP extends beyond research to its application to the people and includes all nonresearch, nongovernmental, and community constituents whose actions impact the cancer problem. Better coordination and collaboration among all public, private, and voluntary agencies with cancer-related activities are critical if we are to reduce the burden of cancer.

Many people in this country receive **inadequate cancer care**, especially the poor, the elderly, and the uninsured. The poor have a higher incidence of many cancers, are diagnosed with

1. “Qualified clinical trials” are defined on page 18.

- Reestablish the 1971 legislative authority for coordinating the National Cancer Program: implement coordination of research and cancer care activities throughout the public, private, and voluntary sectors.
- Stabilize and strengthen the research infrastructure and cancer care delivery system, including NCI-designated Cancer Centers, Community Clinical Oncology Programs (CCOPs), and Clinical Trials Cooperative Groups.
- Change government policies and industry practices that undermine cancer prevention and control and inhibit the development of new cancer-fighting technologies and therapies.
- Provide support and structure to develop and disseminate knowledge and techniques needed to effectively deliver quality cancer care and education to culturally and economically diverse populations.
- Strengthen essential mechanisms, funding, and other support for research to translate basic science advances into promising cancer-fighting technologies.
- Intensify support for basic research to identify the mechanisms of cancer onset and spread, which are the foundation for future cancer preventive and therapeutic advances.

The attached full report of the Subcommittee presents in detail these key issues and additional recommendations. The highest priorities for the Program as a whole are described in the introduction, *Cancer at a Crossroads* (pages 9-15). More detailed recommendations associated with applying our current cancer knowledge and continuing essential translational and basic research are found in Chapters I-III. In addition, a compilation of the Subcommittee's recommendations, indicating suggested measurable outcomes, parties responsible for implementation, and priorities, is included as Appendix E.

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Cancer at a Crossroads

The United States Congress, the Administration, and the nation stand at a crossroads of unprecedented challenge and opportunity to reduce this nation's enormous cancer burden. The alarming statistics are that **one in three people in this country will be diagnosed with cancer during their lifetime; every minute, another person in the United States dies of cancer; in 1994, 1.2 million new cancer cases will add to the more than eight million people in this country alive today who have already been diagnosed; and within five years, cancer will surpass heart disease as the leading cause of death.** While 50 percent of people diagnosed with cancer can expect to live for five years or more, their quality of life issues remain inadequately addressed and opportunities for prevention go unrealized. The estimated annual cost of cancer to the United States, excluding incalculable psychosocial costs, approached \$100 billion in 1990. Individuals with cancer and their families suffer economic losses that include reduced earnings and both life savings and life goals sacrificed to finance cancer care costs.

The State of the National Cancer Program

The National Cancer Act of 1971, which declared the War on Cancer, mandated that: "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."

The NCP has been a highly successful investment. As detailed in the *Measures of Progress Against Cancer* reports (see Summary, Appendix B), there have been breathtaking advances in

the fundamental understanding of how a healthy cell becomes a cancer cell. The application of new technology has allowed for earlier diagnoses and has produced superior and less toxic treatments. The biotechnology industry has emerged with an array of new approaches to the treatment of cancer and other diseases. A basic infrastructure of cancer research and cancer care delivery is in place through the Cancer Centers, Community Clinical Oncology Programs (CCOPs), and Clinical Trials Cooperative Groups. Whereas 25 years ago there were few doctors with expertise in cancer care, now there are well-trained medical, radiation, and surgical oncologists, and oncology nurses available to deliver the best treatments.

The eradication of cancer has been an elusive goal. Although the rapidity with which basic research is unraveling the mysteries of cancer is phenomenal, we still have much to learn to create improved prevention and treatment technologies for the many different cancers and reduce the total burden of cancer. Without new knowledge, we will have the same preventive and treatment approaches tomorrow that we have today. In addition, current and new knowledge must be applied adequately and equally to all of the people.

Federal and State cancer research and care programs are not well coordinated and at times work at cross-purposes. Realigning and streamlining these programs and processes must be among the highest priorities in the effort to re-engineer government and private sector cancer activities. Support for cancer research has not kept up with potential opportunities and the United States is in jeopardy of slowly dismantling its research base. The conduit of knowledge from the laboratory to the people, the translational researcher, is an endangered species. Health care reform as currently proposed will obstruct the access of people with cancer to

state-of-the-art cancer care and will devastate the clinical research program.

The nation can be proud of the progress that has been made, though it has been slower than expected in 1971 by then-President Nixon, the Congress, and the public. Despite this progress, however, it is clear that research advances alone cannot reduce cancer mortality, pain, and suffering, nor should they be expected to do so. The great strides made in understanding the disease still pale in comparison to the problem. It is disturbing that since 1971 the overall incidence of cancer has increased 18 percent, and the mortality rate has grown by 7 percent. Tobacco use and inadequate health care access account for much of this alarming and wholly unacceptable increase, but other contributing factors remain undiscovered or unconfirmed. Much remains to be done.

A Three-Stage Approach to Progress

The NCP encompasses the cancer effort from basic cancer research through its application to the public. The future success of the NCP is dependent on the entire community, as illustrated in Figure 1. Working together, these parties must take responsibility for health-promoting laws and public policy, and for bringing cancer-fighting advances to the nation. Individuals must take responsibility to reduce cancer risk factors (e.g., unhealthful diet, smoking) over which they have control.

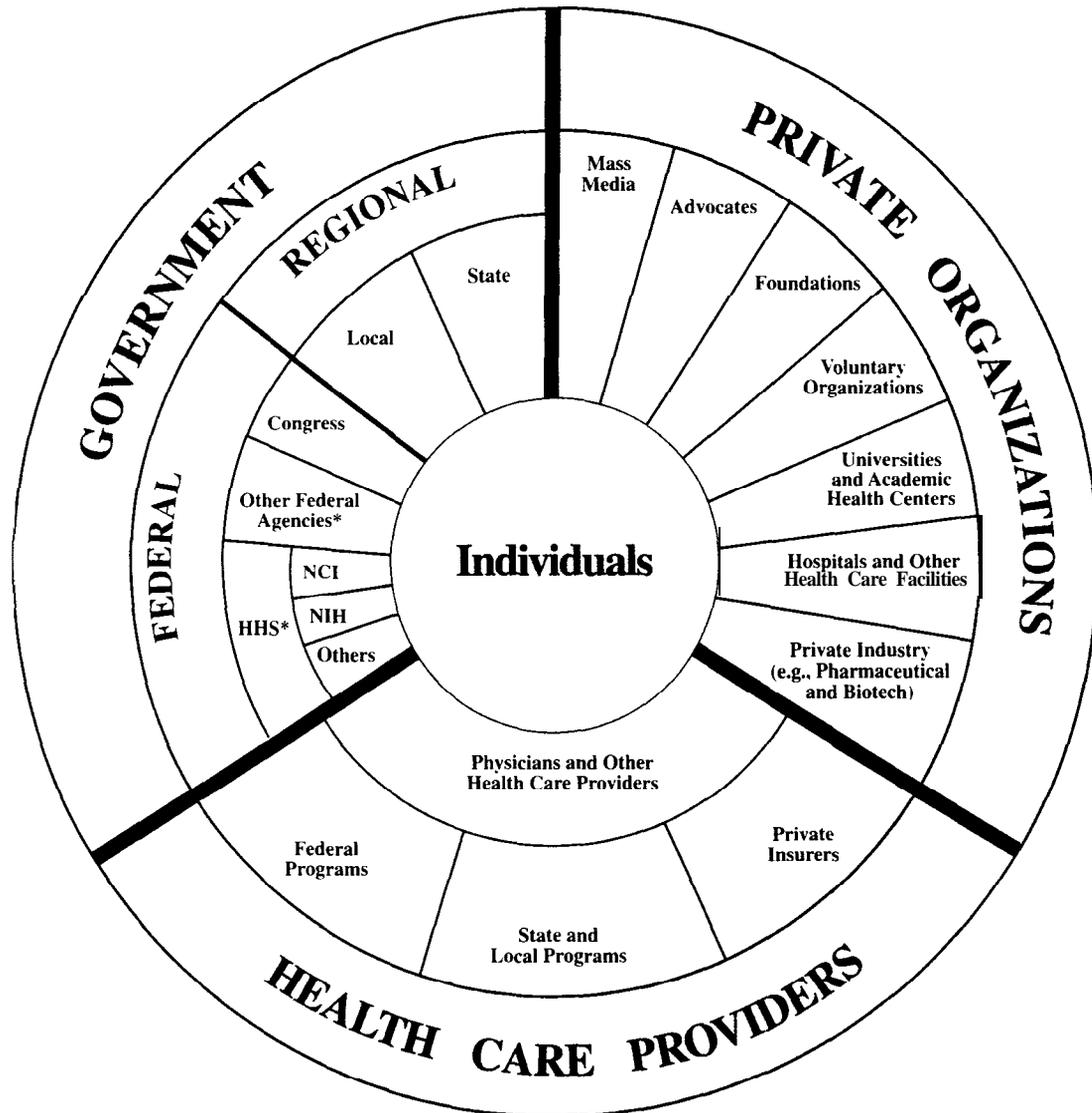
Bringing cancer research advances to the public involves three interdependent stages -basic research, translational research, and application of research (Figure 2). Application of research findings has the most direct impact on the people. In this stage, findings that have advanced beyond basic and translational investigation undergo final study in a defined population, and if warranted, dissemination to the general public. This is also the stage least influenced directly by the efforts of the research commu-

nity. Researchers can prove that tobacco causes a substantial portion of cancer cases, but they cannot control tobacco use and the tobacco promoting actions of other participants—including those inside the Federal government who enact laws and make policy on advertising, agriculture, taxes, and foreign trade. Researchers can develop new cancer treatments, but they cannot guarantee the people's access to and insurance coverage for these therapies. Key participants in the application of research are: private firms such as pharmaceutical and biotechnology companies that bring new technologies to the market; legislative, regulatory, and provider groups that control their use; providers and public and private third party payers that enable individuals to receive health care; and the media and public who must respond to the new opportunities in cancer prevention and care.

The opportunity for application of research is most immediately dependent on translational research—the bridge connecting basic research to its application. This is the stage at which basic science discoveries are first tested in humans and fundamental research becomes a product or service. This realm of research also establishes safety and possible efficacy for more generalized use. The key players are the translational researchers, research financiers, individuals who enroll in research trials, and firms, regulatory agencies, and third party payers that determine whether promising technologies reach the application stage.

The foundation and engine of the development process is basic, untargeted research. Investigators in many disciplines pursue enhanced basic knowledge of biology and human behavior. The key participants in this stage are the basic scientists and sponsors who fund their work, and the institutions and investors that maintain the necessary basic research infrastructure of facilities, personnel, equipment, and supplies.

FIGURE 1: COMPONENTS OF THE NATIONAL CANCER PROGRAM

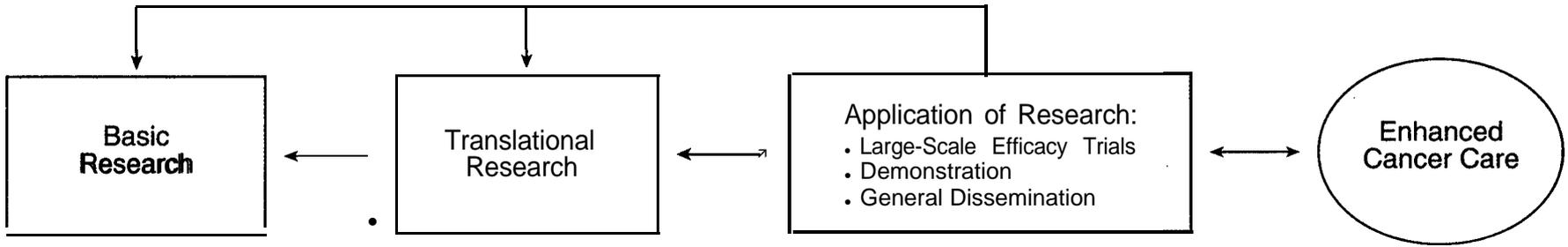


* *Examples of Federal Agencies Involved in Cancer-Related Research, Care, or Regulation:*

- ◆ 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
 - Centers for Disease Control and Prevention
 - National Institute for Occupational Safety and Health
 - Food and Drug Administration
 - Health Care Financing Administration
 - Indian Health Service
 - Health Resources and Services Administration
 - Agency for Health Care Policy and Research
 - Agency for Toxic Substances and Disease Registry
- ◆ 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

**FIGURE 2: BRINGING CANCER ADVANCES TO THE PUBLIC—
STAGES OF RESEARCH AND DEVELOPMENT**

DEVELOPMENT STAGES



WHO IS RESPONSIBLE?

- Universities, Other Private Organizations
- NIH, Other Federal Agencies

- Universities, Other Private Organizations
- NIH, Other Federal Agencies
- Public and Private Insurers, Other Health Care Providers

- Universities, Mass Media, Industry, Other Private Organizations
- NIH, Other Federal Agencies
- Public and Private Insurers, Other Health Care Providers
- Individuals

WHAT ACTIVITIES?

- Laboratory Research
- Epidemiology

- Preclinical Research
- Phase I/II Trials (Developmental)
- Cancer Control Research

- Phase III/IV Trials (Large-Scale Efficacy)
- Demonstration Studies
- Population Studies
- Epidemiology

- Clinical Practice Standards
- Medical Education
- Public Education
- Universal Health Care Coverage



Developing and Delivering Cancer Care: Centers, Groups, and Community-Based Programs

The National Cancer Institute's Cancer Centers Program has become a primary vehicle for accomplishing the goals of the NCP. The Subcommittee believes an enhanced and expanded Centers Program is necessary to achieve an appropriate geographic and demographic distribution of state-of-the-art multidisciplinary cancer care nationwide. As hubs of regional cancer care, Cancer Centers can provide essential guidance to the NCI and to the leadership of the NCP. The NCI's designated Comprehensive Cancer Centers can provide the vital network supporting an enhanced effort to understand the scientific basis of cancer and implement translational research through Phase I and Phase II clinical trials. Multidisciplinary research groups at Clinical and Comprehensive Cancer Centers have demonstrated the capability to rapidly implement high-quality, high-priority clinical trials to speed laboratory findings to patient care and cancer control.

Centers also contribute significantly to the NCP through public education efforts, outreach and training programs for community physicians, and training of the next generation of cancer scientists and cancer care providers. Increasingly, Centers are contributing to the understanding of and provision of services for the psychosocial aspects of cancer, psychiatric and psychologic support, long-term quality of life assessment strategies, and family support services. Further, Centers are now spearheading cancer prevention research and community outreach efforts.

The Subcommittee also recognizes that, because of the size and geographic distribution of the existing Cancer Center network, most people do not receive cancer care at these premiere institutions. Instead, most cancer care is delivered in a community setting. The CCOPs and the national Clinical Trials Cooperative Groups, therefore, are also essential to a successful NCP,

since they are responsible for developing, testing, and disseminating new advances to oncologic practice. With the inevitable increasing emphasis on outpatient treatment due to cost, patient comfort, and convenience considerations, it is extremely important that the role of community oncology is preserved and ties to Cancer Centers strengthened. New and broader mechanisms (e.g., level of care designations such as those used to define trauma center capacities) are necessary to ensure that quality cancer care reaches all of the people.

Maintaining Balanced Support for the National Cancer Program

Researchers dedicated to ending cancer misery find themselves on a funding rollercoaster propelled by ever-strengthening political winds. Research priorities must be based on opportunities for real scientific progress, not on who has the loudest voice, the most signatures, the worst disease, or the most dollars. Allowing politics to dictate narrow scientific direction is counterproductive to the goal of preventing and curing cancer.

To maintain stability and avoid waste, the portfolio of NCP activities must maintain a balance among application of research, translational research, and basic research, with emphasis appropriately placed on common cancers. Excessive earmarking and targeting leads to the same inefficiency and waste of time and money that accompanies rapid funding shifts. New opportunities in application and research can be realized only with careful planning and stable financing. Additional program mandates without additional resources will predictably lead to frustration of the Congress, the research community, and the population.

The resources for the NCP come from the many sources shown in Figure 1. To maintain and accelerate progress, additional funds are required. Funding for cancer care and research at the expense of another Federal health care or science program creates a resource-shifting

“shell game” that subverts the War on Cancer and is deceptive to the people.

Barriers to Success Against Cancer

New knowledge, strategies, and tactics for continuing the fight against cancer are needed more urgently than ever. Without them, the casualties, suffering, and burden of cancer will not be abated. In defining the six major issues enumerated in the Executive Summary, this Subcommittee’s review of the cancer problem in the United States identified three significant barriers:

- Ineffective coordination and inconsistent legislation, policy, and regulation that thwart implementation of existing knowledge
- Lack of access to effective cancer care and education among the poor and other special populations
- Funding constraints and resource shifting that affect training, outreach, treatment, and research of all types

Challenges for the National Cancer Program

The major challenges in reducing mortality and the burden of cancer will be to:

- Bring the benefits of current cancer prevention and cancer care knowledge to all of the people
- Bridge the gap between the laboratory and the individual through translational research
- Maintain excellence and accelerate progress in basic research to expand the knowledge needed to develop new treatment and prevention strategies and technologies

These barriers must be overcome; these challenges must be met. The battle against cancer will not be won without the motivated and earnest participation of all those with a stake in the outcome—health care payers, industry, government, academia, providers, advocates, communities, and each individual.

Recommendations

1. Establish a Presidentially led plan for overall coordination of the National Cancer Program that includes appropriate Cabinet-level representation, criteria for broad participation in Program planning and activities, and reestablishment of the 1971 legislative authority for national coordination of NCP cancer-related research activities of government, industry, and voluntary sectors.
2. Perform a detailed evaluation of cancer research programs and priorities, including questions of value, purpose, function, and duplication, under the direction of the Director, NCI, with representation from other Federal research agencies. The portion of the National Cancer Program review encompassing the intramural program should take into account the recent NIH evaluation, *Report of the External Advisory Committee of the NIH Director's Advisory Committee*, on the Intramural Research Program.
3. Provide sufficient funding to maintain a balanced portfolio of basic, translational, and applied research. Eliminate excessive earmarking and redirection of funds.
4. Expand the number and broaden the scope of NCI-designated Cancer Centers and community-based oncology programs to enhance their capacity to conduct research, expand outreach activities and research dissemination, and improve their geographic and demographic distribution nationwide.



I. Application of Research-Bringing the Benefits of Current Knowledge to All of the People

Unless proven advances in cancer prevention and care are made available to our people in all walks of life, the cancer burden will never be markedly reduced. Bringing existing knowledge and technologies to all of the people will achieve the greatest and most rapid impact on cancer incidence, suffering, and death. For example, employing recent improvements in cancer pain management would relieve patient suffering today. If all women received annual Pap smears, cervical cancer deaths could be dramatically reduced within five years. Breast cancer mortality could be reduced substantially in approximately ten years if all women received appropriate screening and proper treatment. If all tobacco use ceased today, there would be immediate reductions in heart disease, bronchitis, and other smoking-related diseases, though reductions in tobacco-related cancer incidence and death would not be evident for over a decade.

Reducing the cancer burden requires heightened awareness of and commitment to shared responsibilities for change by society, its institutions, and individuals. Providing cancer education and cancer care falls primarily to public and private sector organizations and individual providers outside the realm of research. Tested, effective cancer prevention and cancer care are available for widespread application. Research still is needed, however, on how best to apply current knowledge and technologies to diverse populations. Epidemiologic and population-based studies require access to comprehensive, compatible cancer data (e.g., NCI's Surveillance, Epidemiology, and End Results [SEER] Program; National Cancer Data Base of the Commission on Cancer, American College of Surgeons; the American Cancer Society; Centers for Disease Control and Prevention [CDC]; and State cancer databases). These data must include information about special populations,

especially regarding cultural and socioeconomic variables.

Some people in this country have higher cancer mortality and lower survival than others. For example, populations in poor, underserved, and high-incidence cancer areas suffer and die disproportionately. Among the principal determinants of this disparity in survival and mortality are factors related to physical and social environments and differences in access to early diagnosis and treatment. Accordingly, applying what is already known about cancer prevention, detection, treatment, and rehabilitation requires culturally targeted population interventions and policies that promote environmental and lifestyle changes, universal health coverage for cancer care, and cancer-related education and training of health care providers.

Cancer, Lifestyle, and Public Policy

Lifestyles reflect the relationship of populations to their physical and social environment, the nature of which is often beyond the individual's control. The way we live is dictated substantially by laws, government policies, educational institutions, and advertising that influences individual values, desires, and actions. While individuals have a responsibility to change high-risk behavior, government and society have responsibilities to identify and prevent workplace and environmental hazards, restrict advertising of unsafe products, require accurate product labeling, and provide culturally targeted education about cancer risk and prevention. Epidemiologic research indicates that many aspects of lifestyle leading to high cancer risk are linked to low socioeconomic status.

A large proportion of cancer deaths are believed to be related to lifestyle factors such as tobacco use and diet. Other cancers may be tied to

occupational and environmental exposures and infectious agents. Culturally targeted education, directed particularly toward the young and their parents, is critical to reducing cancer risk, since tobacco use and dietary habits are nearly always formed in the early years of life. Education on the need for cancer detection through routine self-examinations and those by health care providers is also essential. In addition, continued research is needed on cancer etiology relative to environmental and occupational hazards. Information on risks and benefits must be communicated to the people so that each person can make informed choices.

Cancer Care Access

If the people are to benefit from advances across the continuum of cancer care, they must have both financial coverage for and access to the providers of cancer-related preventive, diagnostic, treatment, and supportive services. Over 38 million people have no health insurance at all; 50 million are uninsured at some time during the year. Eighty million more have health insurance insufficient to cover the costs of a catastrophic illness such as cancer.

The problem of access is severe among the 35 million poor. African-Americans represent one-third of the poor although they comprise only 12 percent of the United States population. The poor, who typically experience substandard living conditions, lower educational levels, risk-promoting lifestyles, and insufficient access to

health care, have a higher incidence of many cancers, are diagnosed with more advanced disease, and have lower survival rates than the more affluent. Even the poor on Medicaid may fare no better than the uninsured.

Similarly, the elderly, who have the highest cancer incidence and mortality rates, lack coverage under Medicare for certain cancer prevention services, and are not covered for care provided in qualified clinical trials.² They are frequently not offered, and do not seek, state-of-the-art cancer care. Many of the elderly are unaware of available cancer care services or how to obtain cancer-related information.

In all of these groups, thousands have preexisting conditions, including cancer, that render them uninsurable under the current health care system, or eligible only for hopelessly unaffordable coverage. Anecdotal evidence indicates that even those with insurance may delay seeking diagnostic and other medical care for fear of employment discrimination, future uninsurability, and financial ruin should cancer be discovered. Achieving the goal of coverage for and access to affordable, comprehensive health care that includes cancer prevention and cancer care services will require health care reform that guarantees universal cancer care coverage.

Access to effective cancer services and technologies is unequal across population groups

2. The Subcommittee adopted the definition of a qualified clinical trial as recommended by the Cancer Leadership Council (National Coalition for Cancer Survivorship, Candlelighters Childhood Cancer Foundation, Susan G. Komen Foundation, Cancer Care, Inc., National Alliance of Breast Cancer Organizations, US-TOO, and Y-Me). Qualified clinical trials are defined as those in which the following conditions exist:

- (a) Treatment is being provided pursuant to a clinical trial approved by the NIH in cooperation with the NCI, any of its Cancer Centers, Clinical Trials Cooperative Groups, or Community Clinical Oncology Programs; the FDA in the form of an Investigational New Drug (IND) exemption; the Department of Veterans Affairs; or a qualified nongovernmental research entity as identified in the guidelines for NCI Cancer Center support grants; and
- (b) The proposed therapy has been reviewed and approved by a qualified institutional review board (IRB); and
- (c) The facility and personnel providing the treatment are capable of doing so by virtue of their experience or training; and
- (d) The patients receiving the investigational treatment meet all protocol requirements; and
- (e) There is no clearly superior, noninvestigational alternative to the protocol treatment; and
- (f) The available clinical or preclinical data provide a reasonable expectation that the protocol treatment will be at least as efficacious as the alternative.

and geographic localities. Cancer care resources, equipment, and providers must be appropriately distributed in communities. In most communities and States, and in most health plans, however, no individual or entity is responsible for ensuring cancer care. Culturally tailored education and outreach services are needed so that individuals learn about and accept available tests and treatments. Empowering individuals to take responsibility for their health is especially important in populations with high cancer incidence and mortality. Often, these populations also are underserved and may hold cultural beliefs that discourage active participation in the health care system. Specific strategies are needed to help the poor with cancer navigate the health care system. Even the well-insured and well-educated frequently experience problems accessing needed health services. Few people begin to understand the complexities of cancer care until they or a family member are diagnosed with the disease.

Critical to effective cancer care is patients' freedom to choose the most appropriate provider. Protecting the option to select "point of service" is especially critical under managed care plans, since the most effective treatment for a patient's problem may be available only from an individual or institutional provider outside the plan. Payment mechanisms must be in place to ensure patients' access to these providers.

The term "Cancer Center" can be particularly confusing to the patient because it has been adopted by institutions and organizations ranging from NCI-designated Comprehensive Cancer Centers to physicians' private offices. This confusion, and possible deception, can be clarified by a carefully defined and structured system to designate the level of expertise available at the various types of Cancer Centers. Such a system could be modeled on the existing national trauma center designation scheme and would help providers and patients identify the most appropriate cancer care resources.

Information technologies now exist to extend the reach of state-of-the-art diagnostic services and cancer treatment management by linking rural and community hospitals to major Cancer Centers, improving patient access to quality care, and enhancing local providers' expertise. With the NCI's Cancer Information Service and Physician Data Query (PDQ) database, patient and physician access to state-of-the-art cancer care information in Spanish or English is now as close as the telephone or facsimile machine. In addition, national organizations such as the American Cancer Society and many other grassroots and patient/survivor organizations operate information and referral services. Though use of these information systems continues to increase, access is still limited to people who use a fax, phone, or computer to obtain information. Information dissemination approaches that help patients, particularly the poor, identify and access cancer care resources are also needed.

Frequently, differences in cancer care occur because existing practice standards are not uniformly applied, or because standards have not been established. For example, up to 90 percent of cancer pain would be alleviated if Agency for Health Care Policy and Research (AHCPR) pain management guidelines were followed. Safety and other laws and regulations, such as the Mammography Quality Standards Act of 1992, help ensure that patients receive safe and effective services in appropriate settings. To ensure that advances in cancer care are incorporated into clinical practice nationwide, standards of care must be developed, implemented, and evaluated where they do not exist, are not uniformly applied, or are not widely known by the consumer. Poor quality care can be worse than none. Appropriate utilization means that patients receive the best care possible, but do not receive unwarranted care or unproven care outside the context of a clinical trial.

Education and Training of Health Care Providers

Cancer education and training of physicians and other health care providers are essential if advances in prevention, diagnosis, treatment, and control are to benefit people with cancer and at-risk individuals. Even the well-insured will not get the most effective care if health care providers are unaware of or unable to employ state-of-the-art prevention, detection, diagnosis, and therapy. For example, a large percentage of women aged 50-69 do not get regular breast cancer screening. For these women, routine screening with mammography and clinical breast examination and appropriate treatment of detected abnormalities are known to reduce breast cancer mortality by 30 percent. Lack of physician recommendation is the most frequently cited reason among surveyed women for not getting mammograms. Information services (e.g., NCI's PDQ) and practice standards can help inform patients and cancer care providers about available research studies and help them distinguish established therapies from unproven or ineffective approaches.

Basic education of cancer care providers must place greater emphasis on cancer prevention and control. Medical schools must add cancer causation, prevention, early detection, diagnosis,

treatment, and control to organ-oriented curricula. Similarly, better cancer education is needed in the basic preparation of nurses, social workers, physical and occupational therapists, and other health care providers.

Continuing education is critical to update health care providers' knowledge and skills in cancer detection, diagnosis, treatment, and supportive care. Primary care physicians should be well informed and able to counsel patients about cancer prevention and detection; however, they are not and cannot be expected to be knowledgeable in detailed aspects of cancer management and treatment. This is best done by clinical oncologists. Managed care systems that assign most cancer care to primary care physicians will prevent subscribers from receiving state-of-the-art care.

All aspects of cancer care for minority and underserved populations will be improved if more health care providers are recruited from and encouraged to establish practices in these communities. Financial assistance or incentives may be needed to enable qualified individuals to receive the necessary training and establish cancer programs in minority and underserved communities.

Recommendations for Application of Research

- I-1. Include as part of the core benefit package under any health care reform plan, universal access to state-of-the-art cancer care that includes preventive, diagnostic, treatment and rehabilitative/supportive services, and access to qualified clinical trials. Managed care plans must allow subscribers access to the expertise available at NCI-designated Cancer, Centers.
- I-2. Increase the use of established early detection and diagnostic tools and programs, e.g., Pap smears for cervical cancer, and screening mammography for breast cancer.
- I-3. Apply current knowledge about cancer prevention and care to culturally and economically diverse populations, including the poor, elderly, rural populations, cancer survivors, ethnic and racial minorities, and low literacy populations. Improve methods of communicating cancer prevention and control information to these groups and the general public.
- I-4. Change tobacco-related policies, apply current knowledge on tobacco interventions to prevent children and young adults from starting to smoke, and decrease tobacco use among current smokers. Specifically:
 - (1) Create an environment that makes it undesirable to use tobacco.
 - (2) Enforce existing laws and enact new legislation and regulations to make tobacco products unavailable to minors.
 - (3) Increase tobacco product taxes to reduce demand.
 - (4) Provide subsidies or other financial incentives for tobacco education for children and other high-risk groups.
 - (5) Eliminate tobacco subsidies to reduce the tobacco supply.
 - (6) Eliminate tobacco company tax deductions for tobacco product advertising.
 - (7) Withdraw Federal funding from cancer research organizations that accept tobacco industry support.
 - (8) Reduce secondhand smoke exposure by prohibiting smoking in all public buildings.
 - (9) Prohibit tobacco exports to prevent broader exposure to known carcinogens.
- I-5. Examine and change laws and regulatory policies and practices, including those related to the environment and food supply, that contribute to the cancer problem and frustrate cancer prevention and control efforts.
- I-6. Strengthen support for evaluation, implementation, and access to new cancer care technologies and therapies.

Recommendations for Application of Research (continued)

- I-7. Improve the cancer care delivery system and strengthen the Cancer Centers Program:
- (1) Develop standards and a review process for formally designating levels of care provided at NCI-sponsored, academic, and community cancer care facilities.
 - (2) Establish and support **NCI Cancer Centers** with a principal focus on cancer control issues in high-incidence and high-mortality cancer areas. The review process for such centers should place greater emphasis on cancer control activities and application of research findings. Revitalized and expanded Cancer Prevention Research Units (**CPRUs**) may be an established mechanism through which such programs might be developed.
 - (3) Facilitate cooperative efforts in which established NCI-designated Cancer Centers work with community hospitals and other facilities involved in cancer control, and/or design a new kind of center that focuses on cancer control as its primary mission.
- I-8. **Provide** support for clinical trials of new treatments. This includes support from health care payers for outpatient and inpatient clinical care costs incurred in the conduct of clinical trials, outcomes research, and quality of life studies.
- I-9. Develop and conduct clinical research to identify differences in culture and biology in minority and underserved populations that may affect success in cancer prevention, detection, treatment, supportive, and terminal care,
- I-10. Modify, coordinate, and expand existing data collection systems to improve the conduct of research; collect data on the efficacy of cancer control measures in diverse populations.
- I-11. Increase attention to cancer prevention, detection, diagnosis, treatment, supportive care, and survivorship issues in basic medical and other health professional, curricula. Emphasize cancer topics in continuing education for practicing health care providers.
- I-12. Provide educational support or loan forgiveness to develop or support cancer care providers, with emphasis on underrepresented minority health care providers who will practice in designated underserved areas and areas with disproportionately high cancer incidence, suffering, and mortality.
- I-13. Continue support and expansion of public cancer information systems (e.g., Cancer Information Service), making special efforts to reach rural, culturally diverse, and other health care providers among whom these systems currently may be underutilized.

II. Translational Research-Bridging the Gap Between the Laboratory and the People

The Role of Translational Research

An unparalleled opportunity now exists to apply rapidly to clinical practice the knowledge gained from basic research. The essential bridge connecting basic science to enhancements in cancer prevention and care is translational research. Translational research moves basic research findings into technology development and initial human trials, and returns questions of toxicity and efficacy to the laboratory. Translational research is conducted by physician-scientists and other investigators possessing a broad base of knowledge and expertise in basic science, epidemiology, clinical oncology, and clinical investigation. The breadth and scope of knowledge required for translational research are both its strength and its vulnerability. For the National Cancer Program to achieve optimal translation of basic science knowledge to specific cancer prevention and care products and services, a solid and stable mechanism that supports dynamic interaction between the laboratory and human research is required.

Examples of Translational Research

Translational research focuses on cancer by studying the disease from the defective cell to the physical and emotional burden experienced by the individual, and by bringing novel multidisciplinary approaches to cancer prevention, diagnosis, treatment, and supportive care.

A major thrust to improve screening technologies is more and more promising. To illustrate, utilizing knowledge of defective genes that cause colon cancer requires translational research-to develop a practical test to detect the mutated or absent genes, to determine the reliability of the detection tests and their power to predict cancer risk, and to define appropriate surveillance studies for people with the missing

or abnormal genes. New knowledge gained from basic research may enable translational researchers to devise intervention strategies to prevent the occurrence of clinically evident cancer in those with the mutated gene or to halt the progression of the disease. Establishing national health care policy that protects against insurance and employment discrimination and providing psychosocial support for people with the missing or mutated genes are other aspects of translating the scientific discovery to application.

Other aspects of translational research include establishing resources such as tumor tissue banks and developing molecular tests to predict treatment outcome and prognosis of individual cancer patients. Treatment could then be individualized based on the biological characteristics of the person's cancer. Comparing tumor molecular and cellular characteristics in patients for whom a specific treatment is effective with those in patients for whom the identical treatment is not successful will lead to novel treatment strategies and more effective resource allocation.

Translational research also includes developmental clinical trials of cancer therapies and cancer prevention agents, diagnostic procedure assessments, and prosthesis development to reduce disfigurement or disability that cancer treatment may cause. The Phase I and II developmental trials conducted by translational investigators provide products to be tested in large-scale Phase III efficacy trials. The Phase III randomized trials conducted by NCI, the national Clinical Trials Cooperative Groups, CCOPs, Cancer Centers, and industry are the final step to assess whether preventive or therapeutic interventions **or techniques are effective** and merit widespread application. The translational researcher is critical to the conduct of the

Phase I and II trials and the scientific design and planning of Phase III trials.

The status of knowledge in translational and clinical research has been described in the ***Measures of Progress Against Cancer*** reports. Appendix B summarizes some of these advances. Success in implementing the Subcommittee's recommendations for translational research should be measured by increased availability of new approaches and products that benefit the cancer patient and people at risk for cancer. Interim progress measures include increases in the number of people with cancer who have access to novel therapies within clinical trials, and increases in the number of translational investigators, research grants, and publications.

Challenges to Progress

Translational researchers are becoming an endangered species in part because they have the greatest difficulty in competing for research support. Translational research is often characterized as too clinical and applied for the basic scientist and too basic for the clinical investigator or pharmaceutical company. Since both clinical and basic science expertise are necessary, a substantial period of time is required to train a translational scientist. As a result of past and current support difficulties, a diminishing number of senior translational scientists are available to train and serve as role models for the next generation of researchers. Without the reasonable likelihood of a stable career, investigators will not enter the field and the transfer of knowledge from the laboratory to the people will be delayed needlessly. The current funding structure has led many young people to conclude that such a choice is "academic suicide." Our success in cancer research in the 21st century depends on today's support for research career development.

The current research and health care climate is proving particularly difficult for individuals and institutions wishing to conduct translational

research. Traditionally, much translational research has been partially supported by investigators' clinical care revenues. Shorter average hospital stays and other cost-cutting measures by health care providers have reduced substantially this source of revenue, and this trend is expected to intensify under managed care. Critical support from the pharmaceutical and biotechnology industries is diminishing rapidly due to health care reform pressures. Constrained funding of NIH and other biomedical research grants has created difficulty for all investigators and has increased the tension between clinical and laboratory-based investigators.

Financial support for patient care related to clinical trials is a major source of concern. Some insurance companies have expressed a willingness to support patient care costs for Phase III trials but not for Phase I and II trials, which are the backbone of translational research. The funding problem will be exacerbated with the changes in health care financing, particularly under capitated insurance systems that will discourage participation in research. It is critically important that all proposed new cancer prevention and treatment protocols are validated scientifically through rigorously conducted human trials. Future health care policy must resolve the problems in funding these essential trials. A concerted effort among the Federal government, health care providers, pharmaceutical companies, insurers, and patients will be required.

There is a need to balance disease-targeted and concept-targeted translational and clinical research. Basic mechanisms of cancer induction and progression are shared among different tumor types. Common tumors should certainly be a major focus of research; however, overemphasis on specific tumor sites may be counterproductive to achieving the fundamental understanding of cancer necessary to attain effective prevention and treatment strategies.

Translational investigators and industry face barriers that impede the delivery of new cancer prevention and care. Chief among these are the Federal drug and device approval processes that, despite some improvement, delay new drug testing and discourage pharmaceutical and biotechnology companies from developing new agents and technologies and conducting Phase I and II trials in the United States. The high cost of developing new diagnostic and therapeutic modalities reduces industry interest in new product development. This is particularly critical for anticancer drugs due to potential safety issues and a limited market. The current relationship between industry and government does not ensure a balanced return on investment for either partner for the successful development of a new clinical modality (e.g., financial reward for industry/investors: improved, lower-cost treatment: or profits returned to support further research).

In addition, the practice of expediting developmental Phase I and II clinical trials by using many clinical sites, each with only a few patients, reduces investigators' knowledge of treatment efficacy and toxicity. Though such arrangements may improve access for people with cancer, unexpected problems may arise as more patients receive the treatment in subsequent expanded Phase II and Phase III trials.

This complex situation interrupts the flow of knowledge between the laboratory and people. Translational investigators and stable support for translational and clinical research are urgently needed to bring the revolution in our understanding of cancer biology to cancer prevention, early diagnosis, treatment, and supportive care.

Recommendations for Translational Research

- II-1. Conduct research on internal (endogenous) factors influencing cancer development:
 - (1) Conduct studies to identify hereditary and genetic abnormalities associated with cancer development, and investigate the role of carcinogen metabolism in cancer susceptibility. Target screening and prevention programs to individuals with the highest risk of developing cancer.
 - (2) Establish the role of hormones in the etiology and prevention of certain cancers.

- 11-2. Conduct research on external (exogenous) factors related to cancer prevention and causation:
 - (1) Develop cancer risk assessments for occupational and environmental carcinogens, based on sound epidemiologic evidence, potency of the carcinogen, and prevalence of human exposure.
 - (2) Establish the role of diet and nutrition in the etiology and prevention of cancer, and continue work toward standardized dietary guidelines across Federal agencies.
 - (3) Establish the relationship between infectious agents and cancer development, and investigate immunization and/or antibiotic therapies.
 - (4) Establish the role of external hormones (e.g., from plant or environmental sources) in the etiology and prevention of certain cancers.

- 11-3. Develop effective strategies and methodologies for encouraging individuals to avoid behavior that increases cancer risk and to adopt health-promoting practices.

- 11-4. Develop technologies to improve cancer detection and treatment:
 - (1) Further develop and define the appropriate utilization of less invasive and more precise diagnostic procedures. These range from imaging devices and blood tests for early detection of cancers, to biochemical and molecular characterization of the cancer tissue to predict tumor behavior.
 - (2) Further develop and define the appropriate utilization of new **treatment**-related tumor imaging, radiation therapy, and minimally invasive surgical procedures and technology. Examples include laser therapy, cryotherapy, thermal therapy, computer-assisted radiation therapy, and particle therapy.
 - (3) Analyze cost-effectiveness of new and/or expensive technologies prior to widespread implementation.

Recommendations for Translational Research (continued)

- 11-5. Develop agents for cancer prevention and treatment:
- (1) Support chemoprevention studies, including the identification of novel uses of chemopreventive agents, through basic and epidemiologic investigations.
 - (2) Develop novel strategies such as cancer vaccines to prevent the development of cancer and to treat cancer recurrence and metastasis.
 - (3) Conduct preclinical developmental research on novel therapies such as chemotherapeutic agents, radiation modifiers, biotherapy, gene therapy, and immunotherapy.
- II-6. Develop methodologies and technologies to better predict and improve cancer patient outcomes:
- (1) Develop surrogate or intermediate endpoints (i.e., outcomes other than cancer development or mortality) to predict incidence and mortality and speed the development of new preventive and therapeutic approaches by reducing the length of clinical trials.
 - (2) Further develop and define the appropriate utilization of predictive and prognostic indicators, e.g., tumor markers and clinical characteristics that might alter therapeutic strategies.
 - (3) Pursue research to identify the reasons for different outcomes among patients who receive the same treatment. Such knowledge will lead to more effective prevention and control measures and to novel treatments.
 - (4) Further develop and define the appropriate utilization of measures that eliminate or reduce acute and late treatment toxicity. Developing strategies to reduce acute toxicity (e.g., infection, hair loss), prevent long-term complications (e.g., organ dysfunction, secondary malignancy), and increase treatment efficacy requires the use of appropriate animal models.
- 11-7. Improve grant administration and peer review processes to strengthen support for translational research:
- (I) Using the peer review process, phase into the Cancer Centers Program an additional \$60 million per year (i.e., an average of approximately \$1 million per NCI-approved Comprehensive and Clinical Cancer Center) to support translational investigation.
 - (2) Modify the peer review system for translational research grants to ensure fair review and provide a reasonable probability of success for an individual who wishes to pursue a translational research career.
 - (3) Establish an NIH Clinical Research Initial Review Group (IRG). Revise the composition of existing IRGs to enable translational research to compete on equal footing with basic science research.

Recommendations for Translational Research (continued)

- II-8. Encourage research and development firms to enter into cooperative agreements with the Federal government to conduct cancer research. Create a mechanism to examine and refine laws and regulations for drug and device approval. Current laws and regulatory practices inhibit adequate return on investment in cancer research for people with cancer, academic centers, industry, and investors.
- II-9. Streamline the FDA approval process for Phase I and early Phase II studies. Alternative review processes should be more efficient, yet remain as safe as they are now.
- II-10. Provide support for clinical trials of new treatments, screening, and diagnostic approaches. This includes support from health care payers for outpatient and inpatient clinical care costs incurred in the context of Phase I and II trials.
- II-1 1. Support activities to evaluate scientifically the possible efficacy of complementary (also known as unconventional or alternative) therapies.

III. Basic Cancer Research-Maintaining Excellence, Accelerating Progress

The Status of Basic Cancer Knowledge

The creation of an enormous body of new knowledge about the cellular, biochemical, and molecular alterations that lead to the uncontrolled growth of cancerous cells is one of the greatest achievements of the National Cancer Program since enactment of the National Cancer Act in 1971. This information, particularly recent advances in molecular biology and genetics, provides a wealth of new opportunities for intervening in the processes of cancer development, growth, and progression. Unless we seize these opportunities to develop new knowledge, we will have the same treatments and preventive approaches tomorrow that we have today.

As described in the *Measures of Progress Against Cancer* reports, the revolution in molecular biology and the creation of the biotechnology industry have resulted in large part from NCP investment in untargeted, fundamental, biological research sponsored by diverse agencies and organizations. This investment has produced benefits in many other diseases besides cancer, such as AIDS, immunodeficiency diseases, and cystic fibrosis.

The cancer problem remains formidable, however, and many lives are prematurely lost to this disease. The cause of many cancers still is not understood, and our picture of how normal cells become cancerous is incomplete. Only a few of the genetic alterations leading to the formation of the most prevalent cancers have been identified, and the molecular mechanisms of cancer progression and metastasis are not fully understood. Cancer cells are genetically unstable, and transformation from a normal cell to a cancer cell is believed to result from successive and accumulating genetic defects. A single tumor may contain several distinct cell types which are susceptible to different treatments. Tumor

biology refers to the growth and life history of the tumor, including blood vessel development necessary for tumor growth. Host-tumor interactions include the body's immune system and hormone responses to the tumor, and mind/body interactions that may promote or impede cancer development and spread. Microorganisms are associated with the development of cancer by disrupting normal cellular function or inducing an abnormal immune response. Lastly, the basis for differences in cancer risk and outcome among individuals and population subgroups remains largely unexplored.

Approaches to Accelerating Progress

The many advances in cancer research must now be translated into direct benefits for cancer patients, but it is imperative that this not be done at the expense of continued progress and investment in basic research. There is danger of losing sight of the efforts required to continue the basic discoveries that, when translated and applied, become tomorrow's new weapons against cancer.

Maintaining excellence and accelerating progress in basic research requires keeping the major focus on nontargeted research, streamlining the Federal research grant administration process, making a long-term commitment to basic biomedical research funding, fostering creativity, and providing stable support of the research infrastructure so that research will not be compromised by health care reform.

The Federal research grant administration process, encompassing the peer review process, has become cumbersome, inefficient, and an impediment to scientific excellence. Investigators spend as much as 30 percent of their time preparing lengthy grant applications, responding to regulations, and preparing administrative documentation. Though some administrative

time and expense are necessary, the current system siphons excessive dollars and time into efforts that do nothing to promote progress against cancer. Redesigning the system to reduce its administrative burden would return dollars to the conduct of research and minimize funds needed to capitalize on the most promising opportunities in basic cancer research.

Fundamentally, peer review strengthens biomedical research and accelerates advancement of scientific knowledge. Unfortunately, funding constraints have adversely affected the peer review system, which no longer functions as intended to develop consensus on scientific merit to inform funding decisions. Grant applications, including continuation grants, that would be fundable given greater resources are frequently rejected for inconsequential reasons. Currently, only about 17 percent of NCI's traditional R01 grant applications can be funded, a percentage so low that many excellent proposals must be rejected. Many young investigators submit worthy applications for three years before receiving an award. It is often necessary to demonstrate that the work has already largely been done before an application is considered fundable. Even the most senior investigators must often resubmit amended applications and struggle to maintain project continuity and staffing. The situation also causes great frustration among Initial Review Group (IRG) members who see many excellent projects go unfunded and spend excessive time reviewing new and resubmitted applications at the expense of their own research. As a result, many senior scientists are reluctant to serve on IRGs. The Subcommittee supports in principle the current NIH initiative to review and re-engineer the peer review process.

Basic research funding has not kept pace with escalating costs of laboratory- and population-based studies. In addition to overall national budget constraints, earmarking of funds in response to special interest groups and changes in health care financing and cost control have

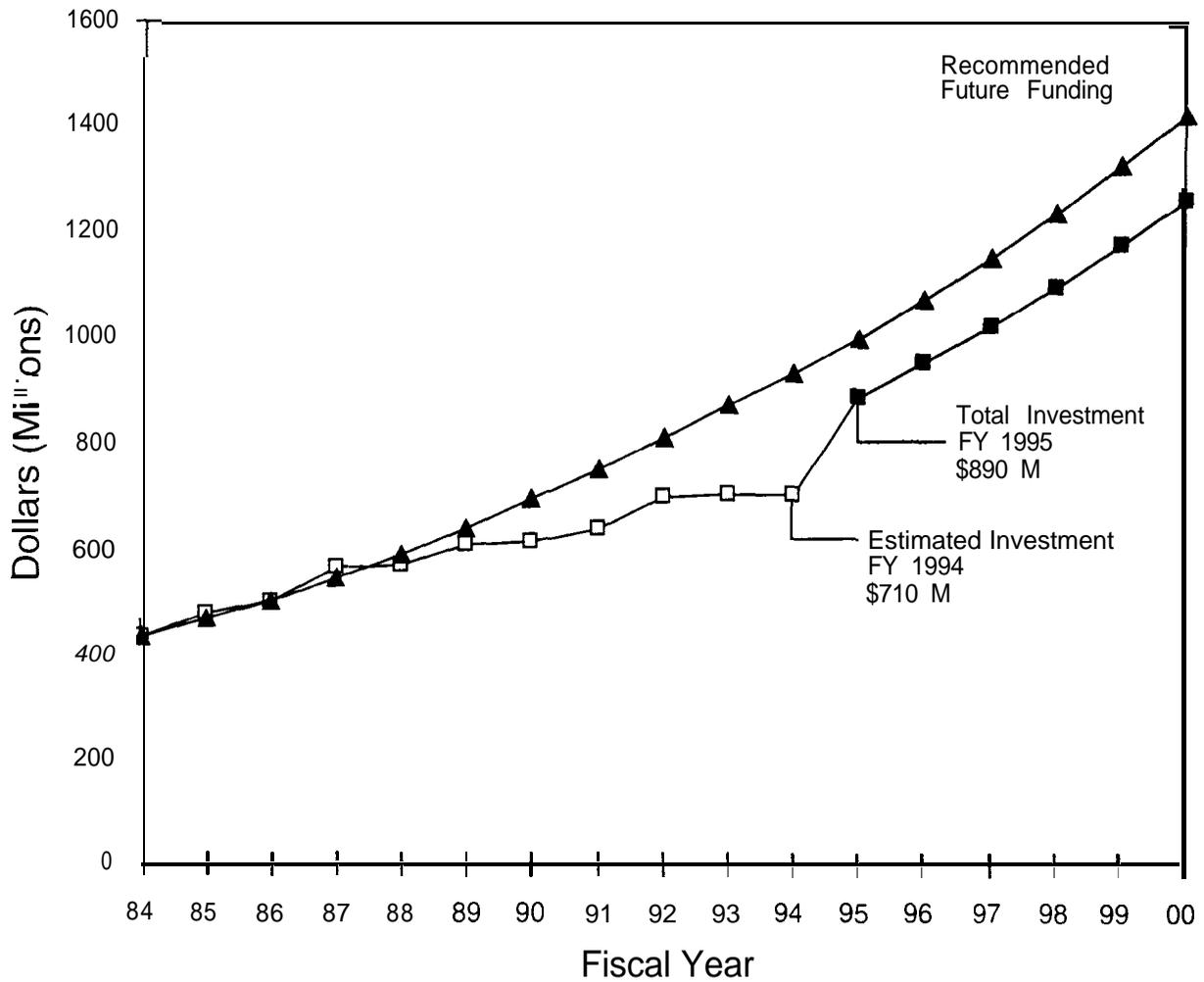
served to limit available funds. Molecular studies require sophisticated equipment and materials, and epidemiologic research requires the study of large numbers of people over long periods of time. These are expensive but necessary endeavors. Cost-cutting measures driven by health care reform are shrinking the discretionary funds upon which academic health centers have relied to subsidize basic cancer research. Similarly, funds for refitting or rebuilding outdated laboratory facilities are available only through philanthropic gifts; institutions are no longer able to support capital projects that are not revenue producing. Federal and private sources of funds have not increased to maintain total funding levels. Although some savings could be realized by streamlining the grant administration and peer review processes, these gains are not enough to augment current funding support for essential research.

To take advantage of scientific opportunities and stabilize basic cancer research, at least \$890 million should be expended for NCI investigator-initiated research grants in FY 1995. In addition to yearly adjustments for inflation using the Biomedical Research and Development Price Index, this amount should rise 3 percent annually for the next five years.

Figure 3 illustrates the actual and recommended future funding pattern for investigator-initiated cancer research grants (R01, P01, R37, and R29). As shown, the actual expenditures from FY 1984 through FY 1993 are well below the desired amounts based on 3 percent real annual growth (over inflation). This funding gap would close substantially with the recommended \$890 million total investment in FY 1995 for investigator-initiated research. Three percent real increases in the five years through FY 2000 will keep the funding gap from enlarging, as occurred in the early 1990s.

Real progress and new ideas in cancer research usually come from unexpected and unpredictable directions. Although it seems logical to

FIGURE 3: RECOMMENDED FUNDING FOR NCI INVESTIGATOR-INITIATED* CANCER RESEARCH GRANTS' FISCAL YEARS 1995-2000



A 3 Percent Actual or Desired Growth in Current Dollars Beginning in Fiscal Year 1984

□ Actual Funding, Fiscal Years 1984-1994

■ Recommended Funding, Fiscal Years 1995-2000

* R01, P01, MERIT (R37), FIRST (R29).

† Increases in funding are also necessary for all other Federal institutions engaged in cancer-related research.

target funds to specific cancers that affect large numbers of individuals or to problems that are urgently in need of solution, this is not always the shortest path to progress. In fact, excessive targeting of specific areas for research can be counterproductive. It can distract scientists, disrupt research programs, and divert funds from more productive lines of research. Therefore, it is essential to resist the temptation to target research funds to specific areas that are important but may not be ready to yield useful information. In many cases, basic research is the best investment to lead to progress against specific cancers, because it facilitates identifying the right questions to address.

The creativity of individual investigators is the driving force behind advances in cancer research and the major source of scientific progress and productivity. Creativity cannot be mandated; rather, it must be fostered by providing a supportive environment that maximizes the possibility of its occurrence. Providing an environment conducive to research creativity might include reducing the amount of time scientists spend on paperwork associated with the funding process and compliance with regulations, maximizing opportunities for interactions among scientists, making it easier to pursue new

avenues of research and high-risk research, providing a stable source of support insulated from political forces, and providing opportunities for training and mentorship. The basic research of today will provide the foundation for tomorrow's advances in the War on Cancer. Maintaining and encouraging the flow of innovative ideas and laboratory advances has become a preeminent challenge confronting cancer research.

At present, morale among cancer researchers is low, and anxiety over research funding is high. This climate is not conducive to creativity and productivity and actively discourages bright young people from pursuing careers in cancer research. These potential warriors in the quest to conquer cancer see first-rate researchers who are unable to work in their field for lack of funding. Failure to address this problem will result over time in the loss of our talented pool of cancer researchers and will erode our ability to generate the scientific base upon which future advances in cancer prevention and patient care depend. Every effort must be made to preserve the community of cancer researchers, foster the spirit of creativity and innovation, maintain the momentum of discovery, and accelerate progress in basic research.

Recommendations for Basic Cancer Research

- III-1. Increase the pool of funds for investigator-initiated grants. R01, R29, R37, and PO1 grants provide the most appropriate and **efficient** mechanisms for providing support for investigator-initiated research. At least \$890 million should be available in FY 1995 for NCI investigator-initiated grants, with 3 percent real annual growth (e.g., adjusted for inflation using the Biomedical Research and Development Price Index) through FY 2000. Increases in funding are also necessary for all other Federal institutions engaged in cancer-related research.
- 111-2. Preserve the infrastructure that supports academic research. A stable pool of funds is required to support research and education of basic and clinical researchers. Enable new construction, renovation, and conversion of outdated research facilities.
- 111-3. Restructure the grant administration process:
- (1) Revise the application process to reduce time spent in writing and reviewing grant applications.
 - (2) Increase the funding period of individual research grants.
 - (3) Decrease the time between application and funding (currently 9-12 months).
 - (4) Explore mechanisms for quickly identifying the most meritorious grant applications while still providing young scientists sufficient feedback to enable them to improve their unsuccessful grant submissions.
- 111-4. Develop a full understanding of the molecular and cellular basis for cancer development and progression.
- (1) Continue development of technologies and tools, such as human genome mapping, x-ray crystallography, nuclear magnetic resonance analysis, and three-dimensional protein modeling using super computers, that support this critically important research.
 - (2) Improve understanding of genetic instability and differences among cancer cells (e.g., variations in drug resistance and tendency to metastasize) and how these factors contribute to disease progression and cancer treatment failure.
- 111-5. Conduct epidemiologic and laboratory investigations to determine the causes of cancer, including the interactions between hereditary, environmental, (including lifestyle and occupational), dietary, infectious, and hormonal risk factors.
- 111-6. Expand knowledge of cell cycle control, tumor biology, and host-tumor interactions and how they affect responses to treatment.

Recommendations for Basic Cancer Research (continued)

- 111-7. Expand basic knowledge of tumor virology/microbiology, including isolation and characterization of existing and/or new microorganisms associated with cancer initiation, and of mechanisms by which these microorganisms contribute to tumor formation.
- III-8. Encourage collaboration between basic scientists and translational and clinical researchers to accelerate cancer prevention, detection, and treatment technology development.
- 111-9. Speed scientific progress and foster creativity by facilitating scientific interaction and collaboration through novel use of information technology and shared instrumentation and resources.

Appendix A Excerpts From House of Representatives and Senate Appropriations Subcommittee Reports: Requests for an Evaluation of the National Cancer Program

Excerpt from the Fiscal Year 1993 House Report 102-708, House Appropriations Subcommittee on Labor, Health and Human Services, and Education:

NATIONAL CANCER INSTITUTE

Mission.—The National Cancer Institute (NCI) conducts and supports basic and applied cancer research in early detection, diagnosis, prevention, treatment and rehabilitation. NCI provides training support for research scientists, clinicians and educators, and maintains a national network of cancer centers, clinical cooperative groups, and community clinical oncology programs, along with cancer prevention and control initiatives and outreach programs, to rapidly translate basic research findings into clinical practice.

Research Program Review.—The Committee notes that since the initiation of the expanded war on cancer in 1971, more than \$23 billion has been appropriated for cancer research at the NCI. While the Institute is to be congratulated on many breakthroughs in molecular biology and other basic cancer research areas, the Committee must express its impatience with the lack of overall progress. In 1971, 336,000 Americans died of cancer and the age-adjusted death rate from cancer was 162 per 100,000. This year more than 500,000 Americans will die of cancer and the mortality rate will have increased by 8 percent. While there have been declines in deaths from certain cancers, particularly those affecting children, rates among the elderly, the poor and minorities continue to rise. The Committee is encouraged by the openness of the Director to consider new approaches to research on cancer. His emphasis on prevention and research affecting minorities and the elderly is welcomed by the Committee. As a next step, the Committee encourages the Director to reach beyond the current cancer establishment as part of a fundamental review of the research program sponsored by the Institute. The Committee looks forward to testimony from the Director on his views regarding the need for such a review and the best mechanism for carrying out such a study. The Committee believes this review must be separated from any debate about specific funding levels if it is to be effective.

Excerpt from the Fiscal Year 1993 Senate Report 102-397, Senate Appropriations
Subcommittee on Labor, Health and Human Services, Education and Related Agencies:

Review of our National Cancer Program

Twenty-one years ago, Congress and the President committed this Nation on a course to aggressively address an epidemic called cancer. Since 1971, our National Cancer Program has facilitated significant progress against many of the over 100 diseases we call cancer. Overall survival rates have improved from 38 percent to over 52 percent, and nearly 70 percent of children diagnosed with cancer survive, specifically, childhood leukemia once had a mortality rate of 95 percent; today 73 percent of children diagnosed with the disease survive. Further, the impact of our investment in cancer research can be felt across the spectrum of diseases. Progress in cancer research positioned us to respond to the AIDS epidemic with regard to identifying the virus that causes AIDS and developing drugs to fight it; it enabled us to identify human genes, such as the CF gene and develop therapies to fix the defect; and it developed the technology to build the supercomputer which has expedited drug and vaccine development for many diseases.

The time is right to assess the achievements of the National Cancer Program, to reinvigorate our National Cancer Program, and to put forth a new plan to carry us into the next century. The Committee recommends that the Director review the establishment of a knowledgeable and independent panel to undertake an evaluation of the achievements of our National Cancer Program relative to the investment to date: the opportunities which exist in our research effort; a plan for future research across the broad spectrum from basic biology to applications; cancer control efforts including the distribution and quality of preventive services, screening, diagnosis and treatment, aftercare, and rehabilitation; and the barriers to state-of-the-art cancer treatment which are detrimental to our ability to adequately address cancer in some populations, particularly minority and older Americans. The Committee expects recommendations to be made with regard to how to address those research and program gaps.

Further, the Committee recommends that the President's cancer panel convene an ad hoc group, to assist in deliberations, which should reflect the following constituencies and scientific disciplines: prevention and control, molecular biology, vaccine development, epidemiology, clinical investigation, environmental carcinogenesis, virology, drug development, and rehabilitation, as well as representatives from outside the scientific community including cancer survivors, parents of children with cancer, insurance and pharmaceutical industry, and public health experts.

Appendix B Summary-Measures of Progress Against Cancer

INTRODUCTION

Relieving the burden of cancer in this country is NCI's ultimate goal, which it strives to accomplish through its support of a national biomedical research program on the causes, prevention, detection, diagnosis, treatment, and control of cancer. Since the National Cancer Program (NCP) was established by the passage of the National Cancer Act in 1971, much interest and debate among scientists, policymakers, legislators, and the public has focused on the extent of progress that has been made against cancer. The most direct measures of the NCP's success are reductions in cancer rates, and progress has been made. Most importantly, reductions in mortality and improvements in survival rates have been observed for certain types of cancer. However, the age-adjusted mortality rate for cancer has not changed significantly over the past 30 years although certain age-specific rates are declining. While cancer incidence, mortality, and survival statistics do reflect the direct population impact of the disease, these measures do not reflect the wealth of knowledge that has grown from the investment in cancer research nor the potential of this knowledge to reduce the future cancer burden. Other measures are necessary to demonstrate advancement of the NCI's goal through our growing understanding of the prevention, development, detection and treatment of cancer and its psychosocial consequences.

Congressional interest to evaluate the NCP and assess progress has been building since the Congress dedicated the War on Cancer in 1971 and began the significant infusion of resources into the program. In FY 1993 the House and Senate Appropriations Committees requested that NCI assess the achievements of the NCP, identify barriers to reducing the burden of cancer, and make recommendations for future research and program directions.

For the first phase of the evaluation, six expert panels were convened to identify advances in basic and clinical cancer research in the most recent decade. They were also charged to describe the potential of the new scientific knowledge for preventing cancer, reducing morbidity and

mortality, and improving survival and quality of life. Each panel was comprised of six to eight members of the extramural community and a chair who was a member of one of NCI's Boards of Scientific Counselors. Scientific areas addressed were: **Molecular Medicine: Mechanisms of Cancer Induction and Progression—Endogenous and Environmental Exposures; Cancer Prevention: Early Detection and Diagnosis; Cancer Treatment; and Cancer Control.**

Each of the panels identified the advances in basic, clinical, and applied research with the greatest potential for reducing the cancer burden in this country. Six volumes of the *Measures of Progress Against Cancer* reports relate their findings. The chairs of the six panels then identified those advances having a broad, cross-cutting significance in understanding the biology and etiology of cancer and individual advances having a far-reaching impact on detection, diagnosis, treatment, control, and prevention. These achievements, together with a statistical overview of cancer in the United States and a discussion of future challenges are described in *Measures of Progress Against Cancer: Consolidated Report*.

This appendix highlights the advances identified for each scientific area using excerpts from the *Consolidated Report* and the individual panel reports. Also provided here are updated versions of two appendices included in the original reports: 1) Environmental and Genetic Factors in Carcinogenesis, and 2) Selected Investigative Strategies for Reducing the Burden of Cancer.

Copies of the individual panel reports and the *Consolidated Report* are available from:

Planning, Evaluation and Analysis Branch
NCI/NIH
31 Center Drive, MSC 2590
Bethesda, MD 20892-2590
Phone: (301) 496-5515
Fax: (301) 402-1225.

MOLECULAR MEDICINE

New developments in molecular genetics have driven the majority of advances in medicine, especially oncology, during the past decade. The ability to clone and express individual genes from tumor cells, as well as normal cells, has permitted the identification of specific genetic changes associated with human cancers and has greatly enhanced understanding of the cancer process. This growing understanding of the genetic basis for cancer has led to a turning point in the development of cancer therapy and prevention. Strategies are now being designed to specifically intervene in the cancer process at the molecular level.

Molecular Technology

Biomedical research has experienced a decade of unprecedented discovery. Much of this growth in knowledge is directly related to developments in molecular technology that allowed the study of cells at the genetic level and the manipulation of genes and gene products in normal and malignant cells. Technological advances that have stimulated this explosion of knowledge have occurred in structural biology, molecular biology, gene transfer, creation of transgenic animal models, flow cytometry, recombinant biological therapies, and medicinal chemistry. Collectively, these technologies have ushered in the era of molecular oncology.

Cancer Susceptibility Genes

One of the most dramatic advances in medicine during the past decade has been the identification of specific cancer susceptibility genes that can be used to recognize "high-risk" individuals. The cloning of these genes is a process still in its infancy, and currently, only a handful have been cloned: the retinoblastoma (*Rb*) tumor suppressor gene, the adenomatous polyposis coli (*APC*) gene, the *p53* tumor suppressor gene, and the ataxia-telangiectasia (*AT*) gene. The *BRCA1* gene has been localized to chromosome 17q, and its cloning is imminent. The availability of these molecular markers potentially shifts the detection of individuals with inborn cancer susceptibilities from the review of individual patient family histories to the screening of large numbers of individuals who may be at risk and can benefit from preventive strategies.

Identification of Specific Genetic Alterations in Cancer: Implications for Diagnosis

Over the last decade, many genes have been identified that become abnormal and contribute to the process of tumor development. The changes in these genes in tumor cells not only help us understand how tumors form, but also provide a tool for distinguishing normal cells from tumor cells. These tools also make it possible to detect tumors at earlier stages and to detect minimal numbers of tumor cells remaining after therapy that were previously undetectable. These new molecular insights are already affecting the way cancer patients are treated, both at the time of diagnosis and at relapse, if it occurs, by influencing decisions about therapeutic options that can reduce morbidity and improve cure rates. There is also great potential that this information will lead to the development of useful screening tests in the near future.

Genetic Alterations in Cancer: Implications for Therapy

Two developments during the past decade have dramatically changed the opportunity for developing therapy that is both selective and effective: 1) the characterization of changes within cancer cells that give rise to the disease process within each organ site and within each patient; and 3) the ability to direct therapy toward these specific and unique changes within the cancer cell. These events, in turn, have made possible the following advances in cancer therapy: development of molecular surrogate endpoints for evaluation of treatment response, duration of remission, and survival; use of dominant changes in cancer cells as identifiers for patterns of response to therapy, duration of remission, and survival; and use of differentiation induction agents, biological response modifiers, and chemotherapy resistance and sensitization genes as forms of therapy. As a result, therapy has become more specific, less toxic to the normal tissues of the body, and ultimately more effective.

Molecular Immunology and Immunotherapy: T Cell Recognition and Therapy

Studies in basic molecular immunology are revolutionizing our approach to cancer immunotherapy and the development of anticancer vaccines. In the past decade, progress in our understanding of the host's immune response to foreign or altered proteins, such as those associated with cancer cells, has continued to accelerate at

a dramatic pace. A number of novel immunotherapy strategies have been developed in preclinical animal models for cancer. Most of these advances are based on the enhanced understanding of the molecular events of immunologic recognition, in particular T cell recognition and activation. In addition, technical advances in high-efficiency gene transfer as well as molecular engineering are enabling the development of immunotherapy approaches, which include tumor vaccines/active immunotherapy, adoptive immunotherapy, and novel uses of monoclonal antibodies. A number of these approaches have now reached an early clinical trial stage in humans.

Molecular Therapeutics

Advances in basic cell biology and biochemistry have made major contributions to our understanding of the mechanisms of action of cancer chemotherapeutic drugs. This type of information is forming the basis for new directions in rational drug discovery. Three drugs, each with a different cellular target, highlight our increase in knowledge in this area during the past 10 years—camptothecin, the epipodophyllotoxins, and Taxol. Knowing the specific targets for these three drugs has allowed the development of screening assays, which in turn may lead to the discovery of new compounds that have similar mechanisms of action. Our understanding of cytokines and growth factors is also expanding rapidly, and there should be a major increase in the application of biologicals in the treatment of malignancies. New drugs are also being sought to reverse the problem of multidrug resistance in tumor cells as the mechanisms of multidrug resistance have been elucidated.

Molecular Controls of Cell Growth: Implications for Therapy

Because cancer can be viewed as an abnormality of cellular growth control, the discovery and characterization of many of the components of normal cellular growth control mechanisms represent a major advance in our ability to understand the carcinogenic process and to formulate therapeutic strategies targeting growth control mechanisms. The genes and gene products that are important to cell growth control can be functionally categorized into a number of groups: peptide growth factors, growth factor receptors, guanosine triphosphate (GTP)-binding proteins, tyrosine kinases and phosphatases, nuclear transcription factors, steroid hormone

receptors, cell cycle-related proteins, and tumor suppressor genes. Many of the proteins in each of these groups are potential targets for therapeutic intervention.

MECHANISMS OF CANCER INDUCTION AND PROGRESSION-ENDOGENOUS AND ENVIRONMENTAL EXPOSURES

Recent advances in knowledge of the mechanisms of carcinogenesis have been crucial to the progress of our overall understanding of cancer. Much of this progress has been made possible by the application of nontargeted basic science research, including advances in molecular genetics and biotechnology. The availability of these new concepts and techniques has enabled scientists to begin to formulate a “unified theory” of cancer etiology. It is now clear that cancer is initiated and promoted through a progressive, multistep process involving multiple genetic changes arising from exposure to endogenous or environmental agents.

Environmental Carcinogenesis

Studies during the past 10 years have clarified the importance and interplay of genetic and environmental factors in the etiology of human cancer. Epidemiologic studies have indicated that about one-third of human cancer in the United States is related to the use of tobacco products and another third may be related to dietary factors. The contribution of viruses, ultraviolet radiation from the sun, and hormonal factors to cancer risk is also becoming increasingly understood and offers insight for prevention. The processes through which environmental carcinogens exert their effects on normal cells and contribute to the cancer process are being identified.

DNA Damage and Repair

During the last decade, scientists have begun to understand the consequences of cellular DNA damage occurring as a result of exposure to carcinogens or to cancer therapy with alkylating agents or ionizing radiation. The processes responsible for DNA repair have been found to be defective in certain inherited disorders, many of which are associated with a predisposition to cancer (e.g., xeroderma pigmentosum). Studies have now shown that there is a direct link between defective DNA repair mechanisms and abnormal expression of normal regulatory genes—both oncogenes and tumor suppressor genes.

With the understanding of the genetic defect in the DNA repair disorders, preventive measures can be undertaken to reduce cancer incidence in these individuals. Ironically, active DNA repair mechanisms within cancer cells can reduce the effectiveness of some chemotherapeutic agents, particularly alkylating agents. Researchers are currently working to develop ways to inhibit the repair process in cancer cells to improve treatment efficacy.

Elucidation of the Step- Wise Process by Which Normal Cells Transform into Cancer Cells

The mechanisms by which cancer develops have become more clearly understood within the past 10 years. It is now known that cancer is a genetic disease and that a tumor cell arises as the result of a multi-step process (that may require many years) in which specific changes or mutations occur in genes that control cell growth. When a single cell acquires the appropriate mutations in these genes, the cell is released from normal growth constraints and is thus able to form a tumor. The understanding of how human cancer cells differ from normal cells is illustrated by studies of cancers of the colon and rectum, which show that cells of these tumors commonly exhibit four specific genetic changes as well as others not yet identified. Experiments also indicate that genetic mechanisms are involved in metastasis, an important breakthrough in our understanding of tumor progression.

Positive Regulators of Cell Growth

By the early 1980s certain genes, called oncogenes, were discovered to stimulate abnormal cell growth although the functions of these genes were unknown. It is now known that oncogenes are often growth factors, growth factor receptors, genes that are turned on by growth factors, or signaling molecules in growth factor-activated pathways. Oncogenes are mutated forms of normal genes involved in positive growth control regulation. The mutations allow cells to bypass the normal cell growth controls. The cloning and characterization of oncogenes allowed molecular biologists to identify other related genes that maintain normal cell growth and division.

Tumor Suppressor Genes and Growth Regulation

During the last decade, there has been a revolution in our understanding of negative regulation of cell growth and the critical changes in this regulation that result in cancer development. Virtually all of the known genes and factors involved in negative growth control have been identified

and cloned during the past 10 years. Studies of tumor suppressor genes (e.g., *Rb* and *p53*) and diffusible negative growth factors (e.g., TGF β and retinoids) have shown the importance of negative regulation in normal growth control. A balance of the positive and negative pathways is required for the precise growth regulation necessary for normal growth and development. Research in this area is now being translated to significant advances in cancer screening, diagnosis, and therapy.

Epidemiologic Studies in Cancer Etiology

Epidemiologic studies conducted in the past 10 years have demonstrated the significance of genetic susceptibility, the importance of identifying at-risk individuals and the specific genes involved, and the role of viruses in a large proportion of cancers. Knowledge of the role of hormones in cancer has also increased, and studies have indicated that it may be possible to alter cancer risk favorably through the use of hormones. Great advances have been made in our understanding of the role of diet in the etiology of cancer, including studies of colon cancer establishing that low-fat, high-fiber diets reduce risk of this cancer. Evidence is also strengthening the link between other lifestyle factors, including alcohol consumption and tobacco use, and increased risk for several types of cancer. Identification of risk factors for cancer is important to develop strategies to reduce risk, select populations for preventive programs, and also to elucidate the mechanisms of cancer induction and progression.

Inheritance of Cancer Predisposition

In the past 10 years, a number of genes associated with heritable mutational effects have been molecularly characterized, including genes for retinoblastoma (*Rb*), Wilms' tumor (*WT*), adenomatous polyposis coli (*APC*), neurofibromatosis, and Li-Fraumeni syndrome (*p53*). An early onset breast cancer gene, *BRCA1*, has been linked to chromosome 17q21 and its molecular characterization is close at hand. Understanding the functions of the genes that are responsible for these mutational effects provides insight into the spontaneously occurring cancers, since mutations for many of these genes have now been characterized in those tumors as well. Advances in the molecular genetic definition of mutational defects leading to cancer have provided practical opportunities for molecular diagnosis of the disease and insights into the molecular and cellular functions that are disrupted in cancer.

CANCER PREVENTION

The evolving understanding of the molecular mechanisms of carcinogenesis is creating unprecedented opportunities for advances in cancer prevention based on the identification of specific molecules and the targeted modulation of their effects. Indeed, with the accumulation of this basic knowledge, cancer prevention has moved from the conceptual realm into the realm of clinical practice. Increasingly, scientific findings suggest that elements of environment and lifestyle can be altered to reduce cancer risk.

Tobacco

Approximately one-third of all cancer deaths are attributable to tobacco use, making it the leading preventable cause of cancer mortality in the United States. The most significant advances over the last decade include the established and accepted quantification of the hazards of smoking and other methods of tobacco use; demonstration that environmental tobacco smoke is a cause of lung cancer in nonsmokers; and identification of successful interventions for prevention and cessation of smoking and tobacco use. The quantification of the hazards of smoking and other tobacco use, such as smokeless tobacco, has led to laws limiting exposures to environmental tobacco smoke and to societal changes associated with unprecedented reductions in rates of cigarette smoking.

The Nutrition, Diet, and Cancer Prevention Connection

Significant progress has been made during the past 10 years in advancing knowledge of the connection between nutritional status, dietary intake of foods, and cancer. Significant advances include: 1) identification, through epidemiological, clinical, animal, and laboratory research, of specific positive and negative nutritional and dietary factors related to cancer; 2) conduct of the first prospective and clinical intervention trials documenting connections between diet, nutrition, and cancer; 3) refined targeting and matching of nutrients to specific cancers (e.g., increased fiber intake to reduced incidence of colon cancer); and 4) heightened public awareness of the role of nutrition and diet in cancer risk and prevention.

Chemoprevention

One of the foremost new investigative approaches for controlling cancer is chemoprevention, which is designed

to work as an adjunct to established cancer treatment and control. Chemoprevention is defined as the use of selected synthetic, chemical, or natural agents to reverse, suppress, or prevent the carcinogenic process. Significant advances in the past decade include: 1) identification of chemopreventive agents such as 13-cis-retinoic acid, tamoxifen, and finasteride; 2) implementation of the first human cancer prevention clinical trials; and 3) establishment of screening systems for the identification of chemopreventive agents. Preclinical and clinical studies are under way to evaluate new chemopreventive agents. More than 1,000 agents, from more than 20 chemical classes, have shown preclinical chemopreventive activity. Based on the outcome of screening systems, the NCI currently sponsors more than 40 clinical chemoprevention trials.

Hormonal Factors in Reproductive Cancers

Cancers developing in reproductive tissues such as the breast, ovary, endometrium, and prostate account for approximately 30 percent of all cancers. These tissues are dependent upon an interactive network of various hormones (estrogens, progestins, and androgens) for their structural and functional development. In recent years, investigators have shown that there is a relationship between the level and duration of hormone exposure and tumor development in these hormonally sensitive tissues. The use of oral contraceptives can protect women against ovarian cancer but is associated with increased risk for breast cancer when used by young women for long periods of time. The safest patterns of use to get maximum protection against ovarian cancer with the lowest risk of breast cancer must be determined. Postmenopausal estrogen replacement therapy has been associated with increased risk for both breast and endometrial cancer. Randomized trials will be necessary to determine the optimum patterns of hormone use for women in various age and risk groups.

Virus-Related Cancers

There has been great difficulty in establishing a cause and effect relationship between a suspected cancer virus and a specific form of cancer. The relationship is not a simple one: there may be several cofactors and interactions with other chemical or physical factors. There is now evidence that these viruses are necessary but not in themselves sufficient to cause these cancers—additional events occur

in the chain of carcinogenesis. Epidemiological data have demonstrated a causative link between specific viruses and certain types of cancer (e.g., the hepatitis B virus has been associated with hepatocellular cancer and the human papillomavirus with cervical cancer). The development and use of vaccines against some viruses is being pursued and could substantially reduce the incidence of the cancers with which they are associated.

Biomarkers and Intermediate Endpoints of Cancer

Biomarkers and intermediate endpoints of cancer are potential predictors of disease and can be considered as “signposts” that occur as tissues progress toward cancer. Increased research efforts have resulted in preliminary identification of biomarkers and intermediate endpoints, and clinical trials are in developmental stages. Biomarkers can take various forms, including abnormal cell products or biochemical parameters. In some instances, intermediate endpoints are nonmalignant or premalignant lesions that can be detected during physical examination. Biomarkers and intermediate endpoints are important in the field of prevention in two ways. As predictors of increased risk, they help identify individuals who are likely to develop cancer and for whom justifiable interventions exist. Secondly, they are a cost-effective means of assessing the likely efficacy of a chemopreventive or dietary intervention by providing endpoints that can be measured in a relatively short period of time.

Occupational and Environmental Carcinogens

The elimination or reduction of exposure to carcinogenic agents is a priority in the prevention of cancer. We are just beginning to understand the full range of health effects resulting from the exposure to occupational and environmental agents and factors. In general, advances have been made over the past decade in: 1) identifying probable environmental risks; 2) developing methods for monitoring exposure and effects; and 3) educating the public about effective prevention measures. Researchers have identified many probable environmental and occupational risks, including exposure to the sun, radon, pesticides and other synthetic chemicals, urethane, molds and other food and beverage carcinogens, and second-hand smoke.

ADVANCES IN EARLY DETECTION AND DIAGNOSIS

Many advances in basic science during the past decade have contributed to improvements in the accuracy and efficiency of cancer diagnosis and early detection. As a result, it is now possible to learn more about tumors at an earlier stage: to monitor tumor behavior and response to treatment with greater precision; to more reliably detect recurrence of cancer; and to design targeted cancer screening programs.

Morphologic Imaging

In the past 10 years, the development and maturation of new noninvasive imaging methods that permit generation of accurate morphological images of internal organs and tissues have greatly improved the diagnostic process. Imaging methods include sound waves, or ultrasound (US); transmitted x-rays, or computerized tomography (CT); magnetically resonating atomic nuclei, or magnetic resonance imaging (MRI); and direct vision through fiber-optic devices (endoscopy). These techniques provide information about a cancer more rapidly and with greater accuracy. Such information is used in determining treatment and prognosis, monitoring treatment efficacy and detecting disease relapse.

Functional Imaging

The 1980s saw the refinement of noninvasive imaging methods that can provide functional information about human tissues and monitor potential toxic effects of anticancer therapies. Techniques include conventional nuclear medicine methods that employ radiotracers that are metabolized organ specifically (e.g., Technetium phosphonate compounds to diagnose early bone metastases). There have also been important advances in positron emission tomography (PET), single photon emission computerized tomography (SPECT), and magnetic resonance spectroscopy (MRS). These imaging modalities provide functional images of biological processes, measure energy requirements of biochemical processes in normal and cancer tissues, and provide novel information on tumor viability, extent, and response to therapy.

Image-Guided Intervention

A major task in oncology is to obtain tissue samples from tumors to confirm the malignancy, diagnose the exact

tumor type, document metastatic disease, and measure various biological parameters at the cellular or subcellular levels. Before the 1980s, excisional biopsy—often requiring open surgical procedures—was the predominant method used for these purposes. Over the past 10 years, image guidance using x-ray fluoroscopy, radiography (mammography), endoscopy, ultrasound, CT, and MRI have enabled the precise placement of biopsy needles within a few millimeters of any suspected tumor site in the body. These techniques are progressively replacing more invasive surgical alternatives.

Identification and Use of Serologic Tumor Markers

Research in the 1980s led to an increase in both the number and availability of tumor markers that can be used to identify the presence of specific cancers. Serologic tests that can detect tumor markers may prove to be useful in cancer screening and diagnosis and improve outcomes through earlier initiation of treatment. Many new target sites on tumor cells have been found that are either specific to a particular malignancy or associated with a group of tumors. Greater clinical application of tumor markers will lead to improved diagnosis, prognosis, and treatment of individual patients and will allow diagnostic and treatment interventions to be targeted to highly specific subgroups. Clinical applications of tumor markers include: serum PSA for prostate cancer, and serum CA 15-3 for breast cancer.

Cellular Analysis in Cancer Diagnostics

Cellular analytic techniques can be used to determine diagnosis and prognosis and to manage treatment for many tumors. The essence of this advance is the combination of elements permitting analysis of tumor cell characteristics that distinguish them from normal cells. These elements include: 1) procedures for tissue procurement, such as fine needle aspiration or stereotactic needle biopsy; 2) assay technology, including immunohistochemistry techniques; 3) development of new monoclonal antibodies and nucleic acid probes that can be used with intact cellular samples; and 4) development of hardware and software for flow and image cytometry. These techniques are being applied frequently to common cancer sites.

Markers of Carcinogenesis

The revolution in DNA technology during the 1980s has driven fundamental research and provided probes and technologies that enable earlier and more accurate cancer

diagnosis. Basic research in the molecular genetics of cancer has led to the discovery of prognostically distinct subtypes of what were previously considered single, homogeneous disease entities. New genes have also been identified during the past decade as a consequence of molecular genetic analysis of human tumors. These discoveries, while providing new insight into the pathogenesis of neoplasia, have provided an armamentarium of DNA probes to detect specific tumor types. New technologies of the past decade such as Southern blotting and PCR have also been rapidly translated into cancer diagnostics. These methods will be useful to screen populations for cancer susceptibility as appropriate markers become available.

Multistage Carcinogenesis

The process of **carcinogenesis** rather than extent of **cancer** has become the focus of early detection. Using colorectal cancer as a model, solid tumors are now thought to progress through a series of genetic changes that lead to tumor progression. Enhanced understanding of tumor biology has led to the identification of potential markers of the preclinical process of carcinogenesis. The phase of cancer promotion, during which genetic changes begin to affect cell proliferation and differentiation, is now recognized as the most rational target for both early detection and for cancer control through biochemical intervention. Markers of carcinogenesis already have found a role in verifying the presence of malignancy, identifying heterogeneous tumor prognosis, and monitoring of minimal residual disease.

Data Analysis to Determine Clinical Utility of Multiple Tumor Markers

In the 1980s, multiple “tumor-specific” or “tumor-associated” antigens that could be used to separate normal from malignant tissue, and one malignancy from another were identified. Sophisticated analytic techniques have been applied to identify the independent clinical utility of multiple tumor-related factors in predicting the clinical outcome of patients. Examples of these techniques include multivariate analysis, overview (meta) analysis, and dynamic monitoring analysis. These techniques have been successfully applied to almost every known malignancy and permit efficient use of diagnostic and/or therapeutic modalities in those groups of patients most likely to benefit.

CANCER TREATMENT

The most significant advance in cancer treatment during the past 10 years is the greater number of patients and types of cancer for which cures or significant improvements in survivorship can be achieved. The quality of life of the six million cancer survivors in the United States has also improved during recent years through treatment advances that are more effective, less toxic and more conserving of function.

Conservation of Organ and Limb Function Through Advances in Surgical Techniques

Dramatic changes in the primary surgery for solid tumors have evolved from a methodical, stepwise application of the scientific method in randomized clinical trials. Many women with early stage breast cancer now choose conservation surgery in conjunction with radiation treatment. In patients with soft tissue and bone sarcomas of the extremities, limb-preserving operations are now routine. Adoption of technological advances, such as laparoscopy, in performing standard cancer operations also allows use of less invasive surgery to reduce treatment-related morbidity. Investigations have shown that preoperative chemotherapy and radiotherapy can be used to prolong survival and also to reduce tumor size, permitting less extensive surgery. This approach is being used to treat laryngeal carcinoma, where preoperative chemotherapy and radiation spare an important function.

Radiation Therapy

Advances in the delivery of radiotherapy have made dose intensification and more precise localization of radiation possible, thus sparing normal tissue and reducing the morbidity and complications of treatment. This advance has been made possible by progress in computerized imaging and magnetic resonance imaging techniques, the recent introduction of new computer technology for treatment planning, and computer-driven treatment delivery systems. Through the use of particle-beam and three-dimensional (3-D) conformal radiotherapies, radical surgery at selected tumor sites will increasingly be replaced by the combination of radiotherapy and conservation surgery or radiotherapy alone.

Adjuvant/Neoadjuvant Therapies

During the 1970s and 1980s, the concepts of adjuvant and neoadjuvant chemotherapy evolved. Adjuvant therapy

consists of treating residual disease after surgery or radiation therapy while neoadjuvant therapy involves treatment of the tumor prior to surgery or radiotherapy. The use of adjuvant/neoadjuvant therapies has resulted in increased cure rates, extended disease-free time, and decreased morbidity in some tumors. Favorable results have been observed for most nonhematologic pediatric cancers and testicular, colon, anal, esophageal, laryngeal, and breast cancers.

New Drug Development

Approaches to new drug development have changed significantly during the past decade. Screening systems have been introduced that focus on human, rather than murine, cell lines or tumors. These approaches facilitate the rapid evaluation of new agents and also offer the possibility of developing unique agents with different modes of action and selectivity for human tumors. New cellular targets have been identified and have significantly expanded the cancer treatment base, with an increased focus on novel classes of anticancer drugs such as differentiation agents, anti-angiogenesis agents, antimetastatic agents, and agents that can overcome mechanisms of resistance. This marks a fundamental shift in the drug development process from the empirical identification of drugs that kill cancer cells to the rational development of agents that inhibit discrete steps in the pathogenesis of malignancy.

Cytokines in Cancer Therapy

Advances in cytokine research have led to the establishment of human cytokines as the fourth component to the conventional therapeutic armamentarium of surgery, radiation therapy, and chemotherapy. New therapeutic applications have been designed using cytokines alone (e.g., interferon therapy of hairy cell leukemia) or as adjunct treatments to reduce the morbidity and toxicity of traditional cancer therapies (e.g., hematopoietic growth factors to reduce the incidence of febrile neutropenia associated with myelosuppressive regimens). Several cytokines also have important uses for nonmalignant disease states.

Bone Marrow Transplantation

Chemotherapy in conventional doses may fail in some patients due to the persistence of residual tumor cells that may be drug resistant. Clinical research has shown that

increasing the dose intensity of chemotherapy or whole body irradiation to myeloablative levels can eradicate these cells. Infusions of bone marrow progenitor cells have been used to “rescue” the patient after high-dose therapy by repopulating ablated marrow. These progenitor cells can be derived from the bone marrow or blood of the patient (autologous) or from another donor (allogeneic). Adding cytokines to the treatment regimen further reduces some of the morbidity associated with dose-intensive therapy. There is also evidence that allogeneic bone marrow transplants have an added tumor-fighting capability since they carry immunocompetent cells that can recognize and destroy residual malignant cells that survive treatment.

Molecular Mechanisms Applied to Therapeutics

In the last decade, as the mechanisms of tumor induction, progression, and survival have been elucidated, new targets for treatment have been identified. The mechanisms underlying inherent and acquired drug resistance, a major obstacle to improving therapy in many common tumors, have been shown to involve activation of multidrug resistance genes and processes that affect drug transport into and out of the tumor cell. One strategy to overcome expression of the multidrug resistance phenotypes has been the use of drugs such as verapamil to alter drug transport. The critical research findings that expression of oncogenes or loss of suppressor genes can lead to abnormal cell proliferation and differentiation offer a number of potential targets for specific inhibition. Certain oncogenes, such as the *myc* oncogene family, have already become targets of drug discovery programs.

Enhanced Quality of Life in Cancer Survivors

The quality of life of the six million cancer survivors in the United States is seriously affected by the morbidity and treatment of the disease. Physical problems may require rehabilitation, but impairments may also be emotional, social, or vocational. Expanded knowledge about quality of life enhancement has decreased the morbidity of cancer therapies and increased treatment compliance. Evidence that some limited surgical procedures yield equal survival compared with more radical surgery has made an important contribution to cancer treatment. Understanding the pathophysiology of nausea and vomiting, pain, and metabolic processes, such as those involved in hypercalcemia, has grown. Advances in

knowledge about the usefulness of counseling, support groups, and behavioral techniques for symptom control have led to psychosocial interventions that improve the quality of survival and may actually extend it.

CANCER CONTROL

The aim of cancer control research is to identify the most promising methods for reducing the cancer burden in defined populations and develop systematic strategies for translating them into practice. The past 10 years have seen steady progress in cancer control research.

Public Health Advances in Tobacco Control in the United States

During the past 10 years, there have been significant advances in several areas that are enabling further progress in controlling tobacco use in the United States. Consensus was reached on the essential elements of effective control programs: the first randomized community-based trials of comprehensive tobacco control programs were undertaken; the health consequences of environmental tobacco smoke were firmly established, resulting in more regulations and policies limiting smoking in worksites and public buildings; and nicotine replacement therapy was identified as a technique to aid smoking cessation.

Screening and Early Detection of Breast Cancer and Cervical Cancer

The 1980s saw significant progress in public and health care provider acceptance and use of screening as a means of reducing mortality associated with breast and cervical cancer. This progress was made possible by cancer control research demonstrating efficacy of screening and detection procedures. During the past decade, guidelines for breast cancer detection/screening were promulgated and widely adopted. Insurance coverage of mammography and Pap tests has been legislated by most States, and the Congress included coverage for these as a Medicare benefit. When important new information became available on risk factors associated with cervical cancer, guidelines for cervical screening were modified to include older women and emphasize the importance of screening for at-risk groups of all ages.

Strategies for Reaching Special Populations

Health professionals and the public have become increasingly aware of "special populations" who have special needs and are at higher risk for some cancers than the general public or who have not equally benefited from advances in cancer prevention, detection, diagnosis, and treatment. During the past decade, NCI established the National Black Leadership Initiative on Cancer, the National Hispanic Leadership Initiative on Cancer, the Appalachia Leadership Initiative on Cancer, initiatives directed to Native Americans and Native Pacific populations, and programs targeting populations with low levels of income, literacy, and/or education. Culturally appropriate interventions have increased access to screening, detection, early diagnosis, treatment, and psychosocial support for members of special populations.

Increased Public and Patient Interest and Activism in Cancer Prevention, Control, Quality of Life, and Survivorship

Cancer has an enormous impact on the psychological, interpersonal, social, and economic well-being of millions of Americans. Major gains were made in the last decade toward increasing public awareness of, interest in, and adoption of behaviors consistent with proven cancer prevention and control measures. For example, decreases in the use of tobacco should result in fewer cases of cancer, and earlier screening using mammography should result in more successful treatment of women with breast cancer. Quality of life issues for cancer patients, survivors, and their families have been elevated to the forefront of national consideration among organizations involved in cancer research, education, and advocacy.

The Health Care Delivery Setting as a Primary Channel for Individual Behavior Change

During the 1980s, a variety of strategies for enhancing state-of-the-art cancer prevention, early detection, and treatment for patients in community settings were evaluated. These studies have led to a growing recognition that the health care delivery system must be altered to maximize and sustain behavior change (among physicians and lay persons). Research findings indicate that dissemination of new information is most successful when it occurs through health care delivery channels accepted by the target audience. For the physician, acceptance of new treatment information is most likely when he or she

participates in the research that produces it; for the patient, prevention and early detection guidelines are most likely to be followed when initiated by the physician in the context of regular health care.

Expanded Knowledge Concerning Relationships Between Diet/Food/Nutrition and Cancer

Ongoing epidemiological and prevention studies are producing data that suggest a significant relationship between diet, nutrition, and cancer. If the evidence from these studies continues to support the assumption that dietary intervention can reduce cancer risk, then applications of these findings can eventually contribute to the primary prevention of diet-related cancers. Educational approaches—including improvements in food package labeling and the National 5-A-Day Program, which encourages Americans to eat five or more servings of fruits and vegetables every day—are already helping consumers to reduce their intake of harmful ingredients and increase their consumption of beneficial foods. Intervention research is now focusing on strategies to change the shopping, cooking, and eating habits of the general public.

Crosscutting Issues

Since the early 1980s, a number of lines of intervention research have emerged that promise great benefit to the general public. Among these are tobacco control, for which the theoretical base has been developed and methods for studying and evaluating interventions have grown in both scope and sophistication. Similarly, a strong base for intervention research in chemoprevention has emerged in conjunction with clinical research initiatives. Finally, research in improving the delivery of treatment and early detection through health services strategies has defined a third major intervention area.

Nationwide statistics on incidence, morbidity, survival, and death rates for specific cancer sites are crucial to identify high-risk populations, monitor changes in risk factors, and measure the effects of large-scale interventions. Since the 1970s, the major surveillance resources contributing such data for cancer control research have included surveys conducted by the National Center for Health Statistics and the NCI's Surveillance, Epidemiology, and End Results (SEER) program, which now covers 14 percent of the U.S. population through 11 regional cancer registries. During the 1990s, data from the SEER

program will contribute to special studies focusing on topics such as patterns of care, cancer-related health care costs, and the relationships between screening and treatment practices.

In the 1980s, many communication and information dissemination programs initiated in the 1970s came into their own, and major new programs of communication with the public and health professionals began to realize their full potential. As a result, today there are many advanced communication and information resources on cancer available to the public and health professionals that are regularly and rapidly updated. Additionally, there have been sustained public and professional informational and educational programs. Together, these efforts have resulted in significant advances in the knowledge base of the general population and among health care providers.

CHALLENGES FOR THE FUTURE

The past decade of cancer research was a period of unprecedented expansion of knowledge, technology, and applications that will reduce the burden of cancer in this country. As the National Cancer Program moves into the next decade and beyond, it is poised to extend the gains that have been made. The future can be viewed with optimism, but with an understanding that special challenges remain. Support for investigator-initiated research should remain the highest priority for the National Cancer Program. A crucial link in the research infrastructure that merits attention as a special challenge is the need to train and support investigators from multiple disciplines to focus on cancer and thereby guarantee that an adequate number of researchers are available to move cancer science forward.

The immediate challenge for basic research is to fill the remaining gaps in understanding the mechanisms of cancer induction and progression. The elucidation of the roles of cancer-causing agents or exposures, and the mechanisms underlying the multistep progression of cancer has rapidly led to basic and population-based research, research that has already identified critical genetic changes involved in cancer development for some tumors. Researchers are now using this knowledge to develop novel prevention and treatment approaches as

well as methods to screen populations at risk of developing cancer. This area of investigation must be broadened so that risk factors and genetic changes can be identified which can be used to design effective prevention and treatment strategies for each of the more than 200 cancer types.

In addition to these scientific and technological challenges, clinical research progress depends on continuing cooperation of the government, academia, and the private sector to ensure development and clinical evaluation of new approaches to prevention, early detection and diagnosis, and treatment. After innovative treatments, technologies, and prevention techniques are developed through basic and clinical phases of investigation, it is also critical to meet the challenge to ensure that all Americans have access to appropriate population-based, culturally sensitive applications of cancer research.

One of the most formidable challenges for cancer research today is the responsible application of the advancing knowledge base and technologies into widespread medical practice. Introducing evolving medical technologies where technical capability may out-pace evaluation of appropriate use or development of required follow-up interventions may be problematic. For example, ethical and societal issues must be considered in using genetic screening to evaluate individual cancer risk, where the ability to assess risk must be accompanied by the availability of interventions that enable individuals to understand and manage their risk through behavioral modification and medical intervention.

Cancer	Estimated 1994 Incidence/Mortality	Epidemiologic or Etiologic Factors	Familial Syndromes	Key Gene Abnormalities	Tumor Biology and Prognostic Factors
ENVIRONMENTAL AND GENETIC FACTORS IN CARCINOGENESIS					
Breast	182,000/46,000 (plus 25,000 <i>in situ</i>)	<p>Reproductive/Hormonal Estrogen exposure/metabolism DES Hormone replacement therapy Oral contraceptives Dietary intake?</p> <p>Fat Dietary intake Metabolism Obesity Total calories</p> <p>Ethnic/Racial?</p> <p>Environment/Occupational Pesticides Heterocyclic amines Radiation at time of breast proliferation (for Hodgkin's disease, scoliosis, TB)</p> <p>Geographic Northeast U.S. Long Island, NY</p> <p>Protective Factors Dietary fiber Calcium/Vitamin D Dietary antioxidants (Vitamin A) Physical activity Lactation</p>	<p>Li-Fraumeni</p> <p>Early Onset Breast, Ovarian</p> <p>Hereditary Non-Polyposis Colorectal Cancer (HNPCC)?</p> <p>Ataxia-Telangiectasia (AT) heterozygotes (?)</p> <p>Proliferative breast disease kindreds</p>	<p><i>p53</i> (17p13)</p> <p><i>BRCA-1</i> (17q21.1 complex) <i>HER-2/neu(erbB-2)</i> (17q21.1)</p> <p><i>NM23</i> (17q21.2) <i>TIMP-2</i> (17q25)</p> <p><i>MSH-2</i> (2p16) <i>MLH-1</i> (3p21.3-23)</p> <p><i>AT gene</i> (11q22-23)</p> <p>Cyclin D₁ (11q13: <i>PRAD-1/bcl-1</i>) Cyclin E</p> <p><i>c-myc</i></p> <p>Maspin gene</p>	<p>Growth Kinetics S phase fraction <i>HER-2/neu(erbB-2)</i> <i>erbB-3</i> Protein Tyrosine Phosphatase (PTP1B) Cathepsin D and B Heat shock proteins Cyclins D₁, E</p> <p>Nuclear Matrix Proteins</p> <p>Invasion/Dissemination > 10 positive nodes Angiogenesis/b-FGF Low <i>NM23</i> expression Collagenase Low maspin expression</p> <p>Drug Disposition Multidrug resistance (<i>MDR</i>) Glutathione-S-transferase</p>
Ovary	24,000/13,600	<p>Hormonal Estrogens Ovulation Fertility drugs</p> <p>Fat Dietary intake Metabolism Obesity</p> <p>Vitamin A</p> <p>Protective Factors Oral contraceptives (5yrs.) Tubal ligation Hysterectomy</p>	<p>Hereditary Non-Polyposis Colorectal Cancer (HNPCC)?</p> <p>Breast-Ovarian</p>	<p><i>MSH-2</i> (2p16) <i>MLH-1</i> (3p21.3-23)</p> <p>17q complex <i>BRCA-1</i> <i>HER-2/neu(erbB-2)</i></p> <p>Ovarian cancer minim31 deletion unit (17q22)</p> <p>6q <i>p53</i> <i>Rb</i></p> <p><i>c-myc</i> (8q24) <i>c-fms</i> (5q31)</p>	<p><i>HER-2/neu(erbB-2)</i> <i>c-myc</i> <i>c-fms</i> <i>MDR</i> Collagenase Angiogenesis: b-FGF, Vascular Endothelial Growth Factor (VEGF)</p>

Cancer	Estimated 1994 Incidence/Mortality	Epidemiologic or Etiologic Factors	Familial Syndromes	Key Gene Abnormalities	Tumor Biology and Prognostic Factors
ENVIRONMENTAL AND GENETIC FACTORS IN CARCINOGENESIS (continued)					
Cervix	15,000/4,600 (plus 55,000 <i>in vitro</i>)	HPV (types 16, 18) Herpes viruses (HSV-2, HHV-6) HIV Tobacco Folate deficiency Oral contraceptives Vitamins A & C (Protective)	Not identified	Human Papilloma Virus (HPV) oncoproteins E5, E6 and E7 interactions with p53 and Rb tumor suppressor proteins and with growth factor (EGF) receptors	Immunosuppression <i>c-myc</i> <i>MDR</i> Glutathione-S-transferase
Prostate	200,000/38,000	Hormonal Testosterone Estrogen (<i>in utero</i>) ? Black vs. White (genetic, hormonal) Dietary Vitamins A & D Animal fats Vasectomy (>20 yrs) ? Farming/Pesticides Metallothioneins Physical Activity (protective)	Not clarified--- higher incidence in men from families with women who develop breast cancer (? related to <i>BRC-1</i>)	<i>vpc</i> <i>ras</i> <i>p53</i> <i>Rb</i> <i>bcl-2</i> <i>DCC</i> 11p11 2-13 metastasis suppressor gene Chromosomes 8, 10, 16	Growth Kinetics Nuclear Matrix Proteins Invasion/Dissemination Angiogenesis Collagenase E-Cadherin
Bladder	51,200/10,600	Tobacco Chemicals/dyes—chlorination byproducts Phenacetin-containing analgesics Alkylating agents (cytoxan) Cytochrome P450s	HNPCC	<i>MSH-2</i> <i>MLH-1</i> 9q <i>p53</i> 18q <i>Rb</i> 7q (<i>MDR</i>), (<i>erbB-1</i>) “Clonal Progression” Model	Invasion/Dissemination Autocrine Motility Factor Collagenase Angiogenesis (urine b-EGF levels)
Kidney	27,600/11,300	Tobacco Analgesics ? Diuretics Obesity	von Hippel-Lindau Disease Hereditary Papillary Renal Cell Cancer Wilms' Tumor Beckwith-Wiedemann Syndrome	3p26 (VHL) deletions 11p13-15 (WT) 11p15.5 (IGF-2 gene) <i>Rb</i> <i>p53</i> ? <i>DCC</i> ? 11q11 2-13	AMF Angiogenesis <i>MDR</i>

Cancer	Estimated 1994 Incidence/Mortality	Epidemiologic or Etiologic Factors	Familial Syndromes	Key Gene Abnormalities	Tumor Biology and Prognostic Factors
Non-Hodgkin's Lymphoma	45,000/21,200	<p>Immunosuppression Genetic Iatrogenic (transplant) AIDS</p> <p>Viral Cofactors EBV ? HHV-6 HTLV-1</p> <p>Occupational Pesticides, herbicides Organic solvents, gases Nitrates</p> <p>Hair Dyes (dark dyes, >20 yrs)</p> <p>Bacterial Cofactors <i>Helicobacter pylori</i> associated with low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue (MALT)</p>	<p>Genetic Immunodeficiency Syndromes Wiskott-Aldrich Severe combined immunodeficiency (adenosine deaminase) (Common variable immunodeficiency)</p> <p>Ataxia-telangiectasia</p>	<p><i>bcl-1</i> (11q13) <i>bcl-2</i> (18q21) <i>bcl-6</i> (3q27) <i>c-myc</i> (especially involved in translocation to immunoglobulin genes) <i>p53</i> <i>Rb</i> 6q21-23 and q25-27 losses AT gene (11q22-23)</p>	<p>Immunosuppression Histologic/cell lineage features</p>
Brain	17,500/12,600 (plus 8,000 <i>m.situ</i>)	<p>Pesticides Organic solvents Metals ? EMF (including cellular phones?) Ionizing radiation</p>	<p>von Hippel-Lindau Li-Fraumeni NF 1 (neurofibromas) NF 2 (meningioma, acoustic neuroma, schwannoma)</p> <p>Nevroid Basal Cell Carcinoma (medulloblastoma)</p>	<p>VHL gene (3p26) <i>p53</i> NF1 (17q11) NF2 (22q12) Chromosome 7: (<i>erbB-1</i>, <i>MDR</i>) <i>HER-2/neu</i> (<i>erbB-2</i>) <i>c-myc</i> <i>N-ras</i> <i>gli</i> Chromosome 10 (losses) <i>N-myc</i> (Neuroblastoma) <i>trk</i> (Neuroblastoma)</p>	<p>Angiogenesis (b-FGF, TNF-α, VEGF, IL-8) TGF-β <i>MDR</i> PET scan glucose metabolism TIMP-2 loss</p>
Melanoma	32,000/6,900	<p>Sunlight/sunburn UVA – sunlamps</p>	<p>Cutaneous Malignant Melanoma/ Dysplastic Nevi Syndrome (CMM/DNS) Xeroderma pigmentosum</p>	<p>Chromosome 1p36 ? <i>MTS1</i> (9p21)</p>	<p>Immunosuppression <i>MM23</i> loss Angiogenesis (b-FGF, VEGF, IL-8)</p>

Courtesy of Dr. Judith Karp, Special Assistant to the Director, NCI.

Cancer	Vaccine Candidates	Prevention Trials	Early Detection Modalities	Established Therapies	Investigative Treatment Modalities
SELECTED INVESTIGATIVE STRATEGIES FOR REDUCING THE BURDEN OF CANCER					
Breast	Recombinant Vaccinia/CEA TAG-72 Mutant genes or gene products (<i>p53, HER-2/neu</i>) Cytokine gene-transfected tumor cells or Tumor Infiltrating Lymphocytes (TILs) Mucins Melanoma Antigen E (MAGE) genes	Tamoxifen 4-HPR Dietary fat reduction Early Phase Trials Vitamin D ₃ analogs? DFMO Piroxicam Oltipraz CAI	Mammography Stereotactic Biopsy Novel imaging: Digital mammography MRI/RODEO Metabolic imaging (PET, MRS) Electron paramagnetic resonance Monoclonal antibodies (MoAb) Interferon-induced antigen shedding	Conservation surgery plus radiation Adjuvant Chemotherapy Hormonal Combination	Neoadjuvant Therapy New Drugs Taxol Other tubulin-directed agents (Navelbine) Anthracyclines Protein kinase antagonists (flavopiridol, staurosporine derivative) Perillyl alcohol (Isoprenylation inhibition) Anti-Metastasis/ Anti-An&genesis Suramin CAI TIMP-2 Dose-Intensive Therapies + CSFs Marrow Transplant (including MDR-transfected stem cells) Immunoconjugates/toxins ²¹² Bi Anti- <i>HER-2/neu</i> B ₃ -PE38 DAB ₃₈₉ -anti EGF Gene Therapy "Suicide Vectors"

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Cancer	Vaccine Candidates	Prevention Trials	Early Detection Modalities	Established Therapies	Investigative Treatment Modalities
SELECTED INVESTIGATIVE STRATEGIES FOR REDUCING THE BURDEN OF CANCER (continued)					
Ovary	Mutant genes or gene products (<i>p53, HER-2/neu, ras</i>) Cytokine gene-transfected tumor cells TAG.72	Dietary fat reduction Retinoids?	CA 125 Urinary gonadotropin fragment (UGF) Transvaginal ultrasound OncoScint®-radiolabeled antibody	Adjuvant Taxol (for refractory ovarian cancer) Taxol + Cisplatin (first-line therapy for advanced ovarian cancer)	Neoadjuvant New Drugs Taxol Taxotere Camptothecins Anti-Metastasis/ Anti-Angiogenesis CAI Anti-VEGF Biomodulation IL-2 +/- LAK + IFN IFN + cytotoxics Immunoconjugates B ₁ -PE40 Photodynamic Therapy Gene Therapy "Suicide Vectors"
Cervix	HPV oncoproteins (E6, E7) L1 capsid protein	Retinoids Beta-carotene Folate Niacin Interferon-alpha (cervical dysplasia)	Bethesda Classification System: Pap Smear Cervicography	Brachytherapy	Neoadjuvant Therapy New Drugs Taxol Taxotere Camptothecin Biomodulation Retinoids + Interferon Neutron Beam Therapy

Cancer	Vaccine Candidates	Prevention Trials	Early Detection Modalities	Established Therapies	Investigative Treatment Modalities
SELECTED INVESTIGATIVE STRATEGIES FOR REDUCING THE BURDEN OF CANCER (continued)					
Prostate	Recombinant vaccinia/ <i>ras</i> or Prostate-Specific Antigen (PSA) Cytokine gene-transfected tumor cells	Finasteride (Proscar) Early Phase Trials: DFMO DHEA Analog Oltipraz Genistein	PSA Transrectal ultrasound Digital rectal exam	Hormonal Radiation Nerve-sparing surgery	New Drugs Isoprenylation inhibitors (lovastatin, phenylacetate, limonene) Protein kinase antagonists (flavopiridol, staurosporine derivatives) Antimetastasis/Antiangiogenesis Suramin TNP 470 TIMP-2 Radiation Proton Beam 3-D conformal Immunoconjugates/MoAb B ₁ -PE 40 Differentiation Retinoids Phenylacetate Gene Therapy GM-CSF-transfected tumor cells
Bladder	Mutant genes or gene products Cytokine gene-transfected tumor cells	DFMO MESNA 4-HPR CAI	<i>p53</i> DNA (urine) Autocrine Motility Factor (urine) Cytochrome p450 activity h-FGF (urine)	Intravesicular Adjuvant Therapy Cytotoxics BCG (intravesicular + percutaneous)	Neoadjuvant Combination (M-VAC) New Drugs Taxol Taxotere Anti-metastasis CAI Immunoconjugates TGF-n-PE-40 Photodynamic Therapy Gene Therapy

Cancer	Vaccine Candidates	Prevention Trials	Early Detection Modalities	Established Therapies	Investigative Treatment Modalities
SELECTED INVESTIGATIVE STRATEGIES FOR REDUCING THE BURDEN OF CANCER (continued)					
Kidney	Cytokine gene-transfected tumor cells	None yet	DNA polymorphism analysis for chromosome 3p26 deletion (VHL gene)	IL-2	New Drugs Camptothecins Demethylation 5-aza-2'-deoxycytidine Phenylacetate Anti-Metastasis CAI Immunomodulation IL-2 +/- LAK +/- Interferon IL-6 Tumor Infiltrating Lymphocytes (TIL) Gene Therapy TIL transfections GM-CSF gene-transfected tumor cells
Lung	Mutant <i>p53</i> and <i>ras</i> peptides MAGE genes	ASSIST: Smoking cessation and prevention Retinoids Vitamin E Selenium Folate Vitamin B12 Niacin CAI	Sputum immunocytology Bronchial epithelial growth factors (Gastrin-Releasing Peptide) X-my	Adjuvant Cisplatin+VP-16 +/- radiation	Neoadjuvant Cisplatin combinations Radiation New Drugs Taxol Camptothecin Protein kinase antagonists (flavopiridol, staurosporine derivatives) Photodynamic Therapy Gene Therapy
Colorectal	Recombinant vaccinia/CEA Autologous—irradiated tumor cell or cell fragments Mutant genes or gene products (<i>ras</i> , <i>p53</i>) Cytokine gene-transfected tumor cells	Diet & Micronutrient Fiber, low fat, vitamins, calcium, beta-carotene DFMO CAI Anti-Inflammatory Piroxicam Sulindac Aspirin	<i>ras</i> DNA (stool) Sigmoidoscopy Interferon-induced antigen shedding OncoScint® with CT Radiolabeled antibodies	Adjuvant 5FU/Levamisole (colon) 5FU/radiation (rectal)	New Drugs Camptothecins Radiation Proton Beam (rectal) Biomodulation Leukovorin + Interferon + 5FU Immunoconjugates B ₁ -PE40

Cancer	Vaccine Candidates	Prevention Trials	Early Detection Modalities	Established Therapies	Investigative Treatment Modalities
Pancreas	Mutant <i>p53</i> and <i>ras</i> peptides	None	None	None	<p>Neoadjuvant Leukovorin + Interferon + 5FU</p> <p>New Drugs Isoprenylation inhibitors (lovastatin, phenylacetate, limonene)</p> <p>Anti-Metastasis CAI</p> <p>Immunoconjugates MoAb + Interferon</p>
Gastric	Recombinant vaccinia/CEA Mutant <i>p53</i> and <i>ras</i> peptides Mucins	Micronutrient replacement (beta-carotene, vitamin E, selenium) Anti- <i>H. pylori</i> antibiotics (plus Bismuth)	<i>H. pylori</i> direct detection or antibodies	None	<p>Neoadjuvant/Adjuvant Leukovorin + 5FU + cisplatin Intraperitoneal adjuvant therapy</p> <p>New Drugs Camptothecins</p> <p>Biomodulation Leukovorin + 5FU + Interferon</p>
Non-Hodgkin's Lymphoma	Mutant genes Viral products Anti-idiotypes	None	Cell surface differentiation antigens	Combination chemotherapy	<p>New Drugs Taxol Camptothecins Nucleoside analogs (fludarabine, DCF, 2-CDA)</p> <p>Biomodulation Interferon Anti-IL-6, Anti-IL-10, IL-4, IL-12</p> <p>Immunoconjugates Humanized anti-Tac DAB₄₈₆-IL-2 toxin Anti-CD19 antibodies (B4 coupled to ricin)</p> <p>Marrow Transplant (with MoAb or drug purging)</p>

SELECTED INVESTIGATIVE STRATEGIES FOR REDUCING THE BURDEN OF CANCER (continued)

Cancer	Vaccine Candidates	Prevention Trials	Early Detection Modalities	Established Therapies	Investigative Treatment Modalities
SELECTED INVESTIGATIVE STRATEGIES FOR REDUCING THE BURDEN OF CANCER (continued)					
Brain	Mutant genes or gene products (<i>p53</i> , <i>ras</i> , <i>erbB</i> genes)	None	CT MRI PET	Multimodality chemoradiotherapy, surgery	New Drugs Temozolamide Phenylacetate Protein kinase antagonists (staurosporine derivatives) Anti-Angiogenesis Anti-VEGF Interferon Suramin Stereotactic surgery (with implants) Radioimmunoconjugates (MoAb to EGFR) Proton Beam Boron Neutron Capture Therapy Photodynamic Therapy Gene Therapy "Suicide Vectors" Antisense IGF-1
Melanoma	Cytokine gene-transfected tumor cells MAGE B7 MART (Melanoma antigen recognized by T cells) Autologous irradiated tumor cells or cell fragments	Educational strategies regarding sun exposure New CCSP skin cancer trials-4	None	Interferon α	Radiation Proton Beam (Ocular) Biomodulation IL-2 +/- LAK +/- Interferon Anti-Angiogenesis CAI Interferon Immunoconjugates R24 MoAb +/- IL-2 Gene Therapy TIL + TNF, or TIL-2 + TNF Cytokine gene-transfected tumor cells

Appendix C Meetings of the President's Cancer Panel

July 1991	Cancer and Poverty <i>Highlighting issues related to socioeconomic factors</i>
September 1991	Training in Science <i>The challenge of attracting and retaining qualified candidates to biomedical science</i>
December 1991	Breast Cancer Research: Progress and New Perspectives <i>Advances in detection, diagnosis, treatment, and prevention of breast cancer</i>
February 1993	Cancer Research and Technology Transfer in the 1990's: Old Tools, New Tools <i>Integrated approaches to the transfer of basic and clinical research</i>
June 1992	Cancer in Minority Populations: Opportunities and Obstacles <i>Special challenges facing minority and underserved populations</i>
October 1992	The Role of Voluntary Organizations in the NCP <i>Interaction and cooperation among general and special interest groups</i>
November 1992	Prostate Cancer <i>Meeting the challenge of prostate cancer, progress in screening and treatment</i>
April 1993	Breast Cancer Specialized Program of Research Excellence (SPORE) at the University of California, San Francisco and the Relationship With Area Breast Cancer Patient Organizations <i>Translational research within the SPORE</i>
July 1993	Cancer and the Family <i>Impact on family, family counseling, and cultural, ethnic, and socioeconomic influences</i>
September 1993	Evaluating the National Cancer Program: An Ongoing Process <i>Assessment of the achievements of the Program during the last decade</i>
November 1993	Cancer Statistics: Chronic Disaster Areas <i>Outreach issues in areas and among populations where cancer mortality is excessive</i>
January 1994	Role of Government in the Cancer Research Mission <i>Interactions and responsibilities of government agencies in cancer research and its applications</i>

Appendix D Executive Summary of the President's Cancer Panel Special Commission on Breast Cancer

EXECUTIVE SUMMARY

Overview

Breast cancer is a large and growing public health problem in the United States. During the decade of the 1990s, it is estimated that nearly 2 million women will have been diagnosed with the disease and that 460,000 women will have died of it. Between 1950 and 1989, the incidence of breast cancer increased by 53 percent. The magnitude of this problem and its constant increase over time understandably result in considerable anxiety among all women.

Some improvements in breast cancer detection and treatment have occurred over the past few decades. Yet even these modest improvements are not uniformly applied throughout the population. Most current therapies (surgery, radiation therapy, and chemotherapy) are non-specific in their effects and frequently diminish quality of life. Although women diagnosed with early-stage breast cancer have a 5-year survival rate of 93 percent, there is no period of time after which a woman who has been treated for breast cancer can be assured that it will not recur. At this time, there are no proven methods of preventing breast cancer.

Advances in basic science have raised the realistic hope that more specific methods can be developed to treat or prevent breast cancer.

Breast cancer advocates – women with breast cancer, their families, friends, and supporters – demand that breast cancer become a national priority. There is a widespread sense of urgency that more can and must be done to address the problem of breast cancer in this country. There is growing public demand for even greater levels of funding of a national breast cancer program and an outcry for the development of cure and prevention.

Recommendations

The goals of the President's Cancer Panel Special Commission on Breast Cancer recommended breast cancer program are:

1. To make substantial progress in developing effective methods to cure and to prevent breast cancer, and
2. To make current and future proven methods of early detection, treatment, and prevention universally available.

The National Institutes of Health and other involved federal agencies must receive research funding of no less than \$500 million per year for this program until these goals are achieved.

Specific recommendations made by the commission are outlined below.

Causes and Prevention

- Research into breast cancer causes and prevention must receive high priority.
- Investigator-initiated inquiry should remain the mainstay of research funding.
- Genetic, hormonal, environmental, dietary, and other causes of breast cancer must be identified through basic and epidemiologic research; this knowledge is the foundation needed to develop effective preventive strategies.
- Knowledge gained through research must be translated into clinically effective methods of prevention, early detection, and treatment.

Earlier Detection and Diagnosis

- Early detection should be improved by further refining x-ray mammography, developing newer imaging methods using non-ionizing radiation, and identifying breast cancer biomarkers that can be detected in a blood test.
- Improved access to early detection must include prompt diagnostic work-up and treatment referral for patients in whom breast abnormalities are identified.

Treatment Strategies

- Women must be empowered to be active participants in their decisions about breast cancer screening and, if diagnosed with the disease, about their treatment options.
- Patients, their families, and breast cancer experts want and deserve less invasive, disfiguring, and toxic treatments than surgery, radiation, and chemotherapy.
- High priorities for new and more specific treatments include: therapy directed at hormones and hormone receptors, tumor growth factors or growth factor receptors; inhibitors of angiogenesis and metastasis; immunologic therapy; and gene therapy.
- Methods should be developed to overcome resistance to hormonal and chemotherapeutic agents.
- Diagnostic decisions, treatment options, and recommendations should be provided in an interdisciplinary setting.

Psychosocial Effects

- Current methods of psychosocial support should be available to all breast cancer patients and their families.
- More effective supportive care interventions for breast cancer patients and their families must be developed.

Access

- Current and future methods of early detection, treatment, and prevention should be universally available as soon as their efficacy is demonstrated.
- United States health care delivery system reforms must ensure the removal of financial barriers to access.

- Research is required to understand and remove the non-financial barriers to universal use of effective means of combating breast cancer.

Public Policy

- Federal regulations should limit the proliferation and use of unproven treatments, prognostic markers, prevention methods, and technologies, except within the confines of a well-defined clinical trial.
- Clinical testing of new detection, treatment, and prevention methods should be supported cooperatively by third-party payors, industry, academic centers, and the National Cancer Institute.
- Research costs for clinical trials should be carefully delineated and paid by industry or the National Cancer Institute, while patient care costs should be covered by third-party payors.
- The 1992 Mammography Quality Standards Act should be implemented immediately.
- Federal agencies should coordinate their breast cancer programs through an interagency breast cancer task force.

A Partnership of Breast Cancer Advocates and Breast Cancer Scientists

- This partnership must continue in a way that promotes the shared objective of finding effective prevention and cure of breast cancer.
- Breast cancer advocates should be integrated into decision-making regarding the optimal use of breast cancer research funding.

Information and Empowerment

- Women in the United States should be provided with accurate, up-to-date, and culturally sensitive information about the risks of breast cancer and how it is best detected.
- Women diagnosed with breast cancer should be provided with accurate, up-to-date, and culturally sensitive information about their treatment options.
- The National Cancer Institute should provide leadership in the development and distribution of culturally sensitive breast cancer educational materials and special materials for women with low levels of literacy.
- Women should be empowered both psychologically and financially to take responsibility for their own breast health, including adopting healthy lifestyles, practicing breast self-examination, following recommended guidelines for breast cancer screening, and immediately obtaining diagnostic and treatment services when breast abnormalities are observed.

Past investments in basic science and breast cancer research have brought us to a point where numerous opportunities exist to advance our ability to prevent and treat breast cancer. The enormity of the impact of breast cancer on the mental and physical well-being of women in the United States and their families requires that we as a society devote the resources needed to achieve the most rapid progress possible.

Appendix E Measurable Outcomes, Assigned Responsibility, and Priority for National Cancer Program Recommendations

Recommendation	Measurable Outcome ¹	Responsible NCP Component ²	Priority ³
OVERARCHING RECOMMENDATIONS			
1. Establish a Presidentially led plan for overall coordination of the National Cancer Program that includes appropriate Cabinet-level representation, criteria for broad participation in Program planning and activities, and reestablishment of the 1971 legislative authority for national coordination of NCP cancer-related research activities of government, industry, and voluntary sectors.	<ul style="list-style-type: none"> Completed coordination plan for the National Cancer Program Established criteria for participation in NCP planning and activities Enacted legislation for coordination of cancer-related research Annual reports to Congress by overall coordinator of NCP on status of implementation of the Subcommittee's recommendations 	<ul style="list-style-type: none"> Congress and Executive 	Immediate
2. Perform a detailed evaluation of cancer research programs and priorities, including questions of value, purpose, function, and duplication under the direction of the Director, NCI, with representation from other Federal research agencies. The portion of the National Cancer Program review encompassing the intramural program should take into account the recent NIH evaluation, <i>Report of the External Advisory Committee of the Director's Research Committee</i> , NIH, on the Intramural Research Program.	<ul style="list-style-type: none"> Strengthened cancer research program Saved resources from eliminating unnecessary duplication Completed inventory of Federal cancer research expenditures Review of evaluation by the National Cancer Advisory Board (NCAB) and recommended corrective action if warranted 	<ul style="list-style-type: none"> Director, NCI Federal Research Agencies NCAB 	Immediate
3. Provide sufficient funding to maintain a balanced portfolio of basic, translational, and applied research. Eliminate excessive earmarking and redirection of funds.	<ul style="list-style-type: none"> Increased funding for cancer research with: <ul style="list-style-type: none"> appropriate percentage for nontargeted, investigator-initiated research balanced portfolio based on scientific opportunity 	<ul style="list-style-type: none"> Director, NCI Congress and Executive 	Initiate
4. Expand the number and broaden the scope of NCI-designated Cancer Centers and community-based oncology programs to enhance their capacity to conduct research, expand outreach activities and research dissemination, and improve their geographic and demographic distribution nationwide.	<ul style="list-style-type: none"> Modified and expanded Cancer Centers Program <ul style="list-style-type: none"> application guidance review criteria performance data Increased number of Cancer Centers in underserved areas Increased percentage of population with access to Cancer Centers Increased percentage of providers linked formally to NCI Cancer Centers 	<ul style="list-style-type: none"> Director, NCI Congress and Executive 	Initiate

- 1 Intermediate, observable effect
- 2 As outlined in Figure 1, page E-10
- 3 *Immediate*: Substantial progress toward completion in 1 to 2 years; *Initiate*: Major new effort to be started in 1 to 2 years; *Ongoing*: Continued and increased support of current efforts.

Recommendation	Measurable Outcome ¹	Responsible NCP Component ²	Priority ³
APPLICATION OF RESEARCH			
I-1. Include as part of the core benefit package under any health care reform plan, universal access to state-of-the-art cancer care that includes preventive, diagnostic, treatment and rehabilitative/supportive services, and access to qualified clinical trials. Managed care plans must allow subscribers access to the expertise available at NCI-designated Cancer Centers.	<ul style="list-style-type: none"> • Health benefits package that provides universal access and covers full spectrum of state-of-the-art cancer care • Increased percentage of individuals participating in qualified clinical trials • Established provisions to ensure freedom of choice of cancer care provider 	<ul style="list-style-type: none"> • Congress and Executive • Regional Government • Health Care Providers 	Immediate
I-2. Increase the use of established early detection and diagnostic tools and programs, e.g., Pap smears for cervical cancer, and screening mammography for breast cancer.	<ul style="list-style-type: none"> • Increased percentage of people screened appropriately according to their risk • Increased percentage of people with positive screenings who receive appropriate follow-up care 	<ul style="list-style-type: none"> • Health Care Providers • Government • Private Organizations • Individuals 	Ongoing
I-3. Apply current knowledge about cancer prevention and care to culturally and economically diverse populations, including the poor, elderly, rural populations, cancer survivors, ethnic and racial minorities, and low literacy populations. Improve methods of communicating cancer prevention and control information to these groups and the general public.	<ul style="list-style-type: none"> • Increased percentage of economically and culturally diverse populations receiving current cancer information in usable form • increased number of proven methods for cancer communications • Decreased cancer risk-promoting behaviors 	<ul style="list-style-type: none"> • Government Agencies • Health Care Providers • Private Organizations • Individuals 	Immediate
-4. Change tobacco-related policies, apply current knowledge on tobacco interventions to prevent children and young adults from starting to smoke, and decrease tobacco use among current smokers. Specifically: <ol style="list-style-type: none"> 1. Create an environment that makes it undesirable to use tobacco. 2. Enforce existing laws and enact new legislation and regulations to make tobacco products unavailable to minors. 3. Increase tobacco product taxes to reduce demand. 4. Provide subsidies or other financial incentives for tobacco education for children and other high-risk groups. 5. Eliminate tobacco subsidies to reduce the tobacco supply. 6. Eliminate tobacco company tax deductions for tobacco product advertising. 7. Withdraw Federal funding from cancer research organizations that accept tobacco industry support. 8. Reduce secondhand smoke exposure by prohibiting smoking in all public buildings. 9. Prohibit tobacco exports to prevent broader exposure to known carcinogens. 	<ul style="list-style-type: none"> • Reduced incidence of tobacco smoking to 15 percent or less • Reversed trend of increases in teen smoking • Decreased percentage of people exposed to second-hand tobacco smoke • Reduced incidence of use of smokeless tobacco and other tobacco products • Enacted legislation to eliminate tobacco subsidies and exports and tax deductions for tobacco product advertising • Federal funding withdrawn from cancer research organizations that accept tobacco industry support • Increased tobacco product taxes • Decreased availability of tobacco products to minors • Established financial incentives for tobacco education 	<ul style="list-style-type: none"> • Government • Private Organizations • Health Care Providers • Individuals 	Immediate

1 Intermediate, observable effect

2 As outlined in Figure 1, page E-10

3 *Immediate*: Substantial progress toward completion in 1 to 2 years; *Initiate*: Major new effort to be started in 1 to 2 years; *Ongoing*: Continued and increased support of current efforts.

Recommendation	Measurable Outcome ¹	Responsible NCP Component ²	Priority ³
APPLICATION OF RESEARCH (continued)			
I-5. Examine and change laws and regulatory policies and practices, including those related to the environment and food supply, that contribute to the cancer problem and frustrate cancer prevention and control efforts.	<ul style="list-style-type: none"> • Regulations changed based on identified carcinogens 	<ul style="list-style-type: none"> • Government 	Ongoing
I-6. Strengthen support for evaluation, implementation, and access to new cancer care technologies and therapies.	<ul style="list-style-type: none"> • Increased number of quality standards/practice guidelines issued for new technologies/therapies • Increased utilization of new technologies/therapies used according to standards/guidelines 	<ul style="list-style-type: none"> • Private Organizations • Health Care Providers • Government 	Initiate
<p>I-7. Improve the cancer care delivery system and strengthen the Cancer Centers Program Specifically:</p> <p>1. Develop standards and a review process for formally designating levels of care provided at NCI-sponsored, academic, and community cancer care facilities.</p> <p>2. Establish and support NCI Cancer Centers in high-incidence and high-mortality cancer areas. The review process for such centers should place greater emphasis on cancer control activities and application of research findings. Revitalized and expanded Cancer Prevention Research Units (CPRUs) may be an established mechanism through which such programs might be developed.</p> <p>3. Facilitate cooperative efforts in which established NCI-designated Cancer Centers work with community hospitals and other facilities involved in cancer control, and/or design a new kind of center that focuses on cancer control as its primary mission.</p>	<ul style="list-style-type: none"> • Increased percentage of cancer care providers with appropriate accreditation • Increased number of Cancer Centers within areas of high cancer mortality oriented to cancer control • Increased percentage of Cancer Centers budget spent on outreach/cancer control • Increased percentage of cancer care facilities linked to Cancer Centers 	<ul style="list-style-type: none"> • NCI, other NIH/Federal Agencies • Health Care Providers 	Immediate
I-8. Provide support for clinical trials of new treatments. This includes support from health care payers for outpatient and inpatient clinical care costs incurred in the conduct of clinical trials, outcomes research, and quality of life studies.	<ul style="list-style-type: none"> • Increased percentage of clinical trials' participants with full coverage for health care costs associated with treatment • Increased percentage of trials including quality of life assessment • Full access to clinical trials for Medicare and Medicaid recipients 	<ul style="list-style-type: none"> • NCI, other NIH/Federal Agencies • Health Care Providers • Health Industry, other Private Organizations 	Ongoing

1 Intermediate, observable effect

2 As outlined in Figure 1, page E-10

3 Immediate: Substantial progress toward completion in 1 to 2 years; Initiate: Major new effort to be started in 1 to 2 years; Ongoing Continued and increased support of current efforts.

Recommendation	Measurable Outcome ¹	Responsible NCP Component ²	Priority ³
APPLICATION OF RESEARCH (continued)			
I-9. Develop and conduct clinical research to identify differences in culture and biology in minority and underserved populations that may affect success in cancer prevention, detection, treatment, supportive, and terminal care.	<ul style="list-style-type: none"> Increased clinical research to detect key cultural/biological differences among underserved and minority population groups 	<ul style="list-style-type: none"> NCI, other NIH/Federal Agencies Health Care Providers Health Industry, Foundations, other Private Organizations Individuals 	Initiate and Ongoing
I-10. Modify, coordinate, and expand existing data collection systems to improve the conduct of research; collect data on the efficacy of cancer control measures in diverse populations.	<ul style="list-style-type: none"> Completed inventory of data systems available for research Enhanced data systems access and increased utilization Expanded and heightened integration of data systems 	<ul style="list-style-type: none"> NCI, other NIH/Federal Agencies Health Care Providers 	Ongoing
I-11. Increase attention to cancer prevention, detection, diagnosis, treatment, supportive care, and survivorship issues in basic medical and other health professional curricula. Emphasize cancer topics in continuing education for practicing health care providers.	<ul style="list-style-type: none"> Increased emphasis on cancer in basic and continuing medical/health professions education Increased knowledge of cancer among physicians and other health care professionals Increased percentage of physicians and other health professionals utilizing appropriate patterns of cancer care 	<ul style="list-style-type: none"> Universities, other organizations conducting/supporting health professions education Health Care Providers 	Initiate
I-12. Provide educational support or loan forgiveness to develop or support cancer care providers, with emphasis on underrepresented minority health care providers, who will practice in designated underserved areas and areas with disproportionately high cancer incidence, suffering, and mortality.	<ul style="list-style-type: none"> Incentives offered for cancer care professionals to practice in cancer underserved areas Increased number of cancer care providers practicing in cancer underserved areas 	<ul style="list-style-type: none"> NIH, other Government Agencies Health Care Providers 	Initiate
I-13. Continue support and expansion of public cancer information systems (e.g., Cancer Information Service), making special efforts to reach rural, culturally diverse, and other health care providers among whom these systems currently may be underutilized.	<ul style="list-style-type: none"> Increased CIS capacity to respond to queries and conduct targeted outreach Increased utilization of CIS by traditional nonusers and underusers 	<ul style="list-style-type: none"> Private Organizations Government Health Care Providers Individuals 	Ongoing

1 Intermediate, observable effect

2 As outlined in Figure 1, page E-1 0

3 **Immediate:** Substantial progress toward completion in 1 to 2 years; **Initiate:** Major new effort to be started in 1 to 2 years; **Ongoing:** Continued and increased support of current efforts.

Recommendation	Measurable Outcome ¹	Responsible NCP Component ²	Priority ³
TRANSLATION OF RESEARCH			
<p>II.1. Conduct research on internal (endogenous) factors influencing cancer development:</p> <ol style="list-style-type: none"> 1. Conduct studies to identify hereditary and genetic abnormalities associated with cancer development, and investigate the role of carcinogen metabolism in cancer susceptibility. Target screening and prevention programs to individuals with the highest risk of developing cancer. 2. Establish the role of hormones in the etiology and prevention of certain cancers. 	<ul style="list-style-type: none"> • Increased knowledge of individual internal factors influencing cancer induction and progression (grant support and scientific publications as indicator of new knowledge) 	<ul style="list-style-type: none"> • NCI, other NIH/Federal Agencies • Private Organizations 	Ongoing
<p>II.2. Conduct research on external (exogenous) factors related to cancer prevention and causation:</p> <ol style="list-style-type: none"> 1. Develop cancer risk assessments for occupational and environmental carcinogens, based on sound epidemiologic evidence, potency of the carcinogen, and prevalence of human exposure. 2. Establish the role of diet and nutrition in etiology and prevention of cancer, and continue work toward standardized dietary guidelines across Federal agencies. 3. Establish the relationship between infectious agents and cancer development, and investigate immunization and/or antibiotic therapies. 4. Establish the role of external hormones (e.g., from plant or environmental sources) in the etiology and prevention of certain cancers. 	<ul style="list-style-type: none"> • Increased knowledge of exogenous factors influencing cancer induction and progression (grant support and scientific publications as indicator of new knowledge) 	<ul style="list-style-type: none"> • NCI, other NIH/Federal Agencies • Private Organizations 	Ongoing
<p>II.3. Develop effective strategies and methodologies for encouraging individuals to avoid behavior that increases cancer risk and to adopt health-promoting practices.</p>	<ul style="list-style-type: none"> • Increased number of proven strategies to stem individuals' cancer risk behaviors 	<ul style="list-style-type: none"> • Government • Private Organizations 	Ongoing
<p>II.4. Develop technologies to improve cancer detection and treatment:</p> <ol style="list-style-type: none"> 1. Further develop and define the appropriate utilization of less invasive and more precise diagnostic procedures. These range from imaging devices and blood tests for early detection of cancers, to biochemical and molecular characterization of the cancer tissue to predict tumor behavior. 2. Further develop and define the appropriate utilization of new treatment-related tumor imaging, radiation therapy and minimally invasive surgical procedures and technology. Examples include laser therapy, cryotherapy, thermal therapy, computer-assisted radiation therapy, and particle therapy. 3. Analyze cost-effectiveness of new and/or expensive technologies prior to widespread implementation. 	<ul style="list-style-type: none"> • Increased knowledge of cancer detection and treatment technologies (grant support and scientific publications as indicator of new knowledge) • Increased number of detection/treatment technologies undergoing premarket evaluation of efficacy • Increased number of new and/or expensive technologies undergoing cost-effectiveness analysis 	<ul style="list-style-type: none"> • NCI, other NIH/Federal Agencies • Private Organizations 	Ongoing

¹ Intermediate, observable effect

² As outlined in Figure 1, page E-10

³ Immediate: Substantial progress toward completion in 1 to 2 years; Initiate: Major new effort to be started in 1 to 2 years:

Ongoing: Continued and increased support of current efforts.

Recommendation	Measurable Outcome ¹	Responsible NCP Component ²	Priority ³
TRANSLATION OF RESEARCH (continued)			
<p>II.5. Develop agents for cancer prevention and treatment:</p> <ol style="list-style-type: none"> 1. Support chemoprevention studies, including the identification of novel uses of chemopreventive agents, through basic and epidemiologic investigations. 2. Develop novel strategies such as cancer vaccines to prevent the development of cancer and to treat cancer recurrence and metastasis. 3. Conduct preclinical developmental research on novel therapies such as chemotherapeutic agents, radiation modifiers, biotherapy, gene therapy and immunotherapy. 	<ul style="list-style-type: none"> • Increased knowledge of agents for cancer (grant support and scientific publications as indicator of new knowledge) • Increased number of cancer agents undergoing premarket efficacy evaluation 	<ul style="list-style-type: none"> • NCI, other NIH/Federal Agencies • Private Organizations 	Ongoing
<p>II.6. Develop methodologies and technologies to better predict and improve cancer patient outcomes:</p> <ol style="list-style-type: none"> 1. Develop surrogate or intermediate endpoints (i.e., outcomes other than cancer development or mortality) to predict incidence and mortality and speed the development of new preventive and therapeutic approaches by reducing the length of clinical trials. 2. Further develop and define appropriate utilization of predictive and prognostic indicators, e.g., tumor markers and clinical characteristics that might alter therapeutic strategies 3. Pursue research to identify the reasons for different outcomes among patients who receive the same treatment. Such knowledge will lead to more effective prevention and control measures and to novel treatments. 4. Further develop and define the appropriate utilization of measures that eliminate or reduce acute and late treatment toxicity. Developing strategies to reduce acute toxicity (e.g., infection, hair loss), prevent long-term complications (e.g., organ dysfunction, secondary malignancy), and increase treatment efficacy requires the use of appropriate animal models. 	<ul style="list-style-type: none"> • Increased knowledge of determinants of cancer patient outcomes (grant support and scientific publications as indicator of new knowledge) • Increased availability and use of cancer patient outcome analysis methods and technologies • Increased ability to tailor prevention and treatment interventions to individual characteristics • Reduced acute and long-term toxicities and side-effects of cancer treatments 	<ul style="list-style-type: none"> • Government • Private Organizations 	Initiate and Ongoing
<p>II.7. Improve grant administration and peer review processes to strengthen support for translational research:</p> <ol style="list-style-type: none"> 1. Using the peer review process, phase into the Cancer Centers Program an additional \$60 million per year (i.e., an average of approximately \$1 million per NCI-approved Comprehensive and Clinical Cancer Center) to support translational investigation. 2. Modify the peer review system for translational research grants to ensure fair review and provide a reasonable probability of success for an individual who wishes to pursue a translational research career. 3. Establish an NIH Clinical Research Initial Review Group (IRG). Revise the composition of existing IRGs to enable translational research to compete on equal footing with basic science research. 	<ul style="list-style-type: none"> • Increased Cancer Centers Program funding • Changes in NIH peer review including establishment of a Clinical Research IRG • increased number of funded clinical and translational research applications • Increased participation of clinical and translational researchers on IRGs 	<ul style="list-style-type: none"> • Congress • NCI, other NIH/Federal Agencies • Universities and Academic Health Centers 	Immediate

1 intermediate, observable effect

2 As outlined in Figure 1, page E-10

3 Immediate: Substantial progress toward completion in 1 to 2 years; Initiate: Major new effort to be started in 1 to 2 years;
Ongoing: Continued and increased support of current efforts.

Recommendation	Measurable Outcome ¹	Responsible NCP Component ²	Priority ³
TRANSLATION OF RESEARCH (continued)			
II.8. Encourage research and development firms to enter into cooperative agreements with the Federal government to conduct cancer research. Create a mechanism to examine and refine laws and regulations for drug and device approval. Current laws and regulatory practices inhibit adequate return on investment in cancer research for people with cancer, academic centers, industry, and investors.	<ul style="list-style-type: none"> • Reinvented systems of industry-government collaboration • Increased number of Cooperative Research and Development Agreements (CRADAs) leading to licenses and patents • Laws and regulations that foster public/private research and product development collaborations 	<ul style="list-style-type: none"> • NCI, FDA, other NIH/Federal Agencies • Industry, Universities • Congress 	Immediate
II.9. Streamline the FDA approval process for Phase I and early Phase II studies. Alternative review processes should be more efficient, yet remain as safe as they are now.	<ul style="list-style-type: none"> • Shortened interval for FDA review/approval decisions 	<ul style="list-style-type: none"> • FDA, NIH, other Federal Agencies 	Ongoing
II.10. Provide support for clinical trials of new treatments, screening, and diagnostic approaches. This includes support from health care payers for outpatient and inpatient clinical care costs incurred in the context of Phase I and II trials.	<ul style="list-style-type: none"> • Increased percentage of clinical trials participants with full coverage for health care costs associated with treatment • Full access to clinical trials for Medicare and Medicaid recipients 	<ul style="list-style-type: none"> • NCI, other NIH/Federal Agencies • Health Care Providers • Health Industry, other Private Organizations 	Initiate and Ongoing
II.11. Support activities to evaluate scientifically the possible efficacy of complementary (also known as unconventional or alternative) therapies.	<ul style="list-style-type: none"> • Increased knowledge about the efficacy of high-interest complementary therapies (grant support and scientific publications as indicator of new knowledge) 	<ul style="list-style-type: none"> • NCI, FDA, other NIH/Federal Agencies • Universities 	Ongoing

¹ Intermediate, observable effect

² As outlined in Figure 1, page E-1 0

³ Immediate: Substantial progress toward completion in 1 to 2 years; Initiate: Major new effort to be started in 1 to 2 years; Ongoing. Continued and increased support of current efforts.

Recommendation	Measurable Outcome ¹	Responsible NCP Component ²	Priority ³
BASIC RESEARCH			
<p>111.1. Increase the pool of funds for investigator-initiated grants. R01, R29, R37, and POI grants provide the most appropriate and efficient mechanisms for providing support for investigator-initiated research. At least \$890 million should be available in FY 1995 for investigator-initiated grants, with 3 percent real annual growth (e.g., adjusted for inflation using the Biomedical Research and Development Price Index) through FY 2000. Increases in funding are also necessary for all other Federal institutions engaged in cancer-related research.</p>	<ul style="list-style-type: none"> • At least \$890 million in FY 1995 for investigator-initiated NCI cancer research grants with 3 percent real annual increases from FY 1996/2000 • Decreased percentage of earmarked research funds 	<ul style="list-style-type: none"> * Congress and Executive • NCI/NIH, other Federal Agencies • Private Organizations 	Immediate
<p>111.2. Preserve the infrastructure that supports academic research. A stable pool of funds is required to support research and education of basic and clinical researchers. Enable new construction, renovation and conversion of outdated research facilities.</p>	<ul style="list-style-type: none"> • Increased pool of cancer researchers • Improved retention of cancer researchers • Maintained or enhanced academic research infrastructure • Positive change in legislative authority, policy, and financing for infrastructure maintenance and development 	<ul style="list-style-type: none"> • Congress and Executive • NCI/NIH, other Federal Agencies • Private Organizations 	Immediate
<p>11.3. Restructure the grant administration process:</p> <ol style="list-style-type: none"> 1. Revise the application process to reduce time spent in writing and reviewing grant applications. 2. Increase the funding period of individual research grants, 3. Decrease the time between application and funding (currently 9-12 months). 4. Explore mechanisms for quickly identifying the most meritorious grant applications while still providing young scientists sufficient feedback to enable them to improve their unsuccessful grant submissions, 	<ul style="list-style-type: none"> • Decreased percentage of investigator effort spent on grant administration • Decreased percentage of research budget expended on overhead • Increased percentage of five year awards for investigator-initiated projects • Decreased research grant application review process duration (six months) 	<ul style="list-style-type: none"> • NCI/NIH, other Federal Agencies • Universities and Academic Health Centers, other Private Organizations 	Immediate
<p>11.4. Develop a full understanding of the molecular and cellular basis for cancer development and progression:</p> <ol style="list-style-type: none"> 1. Continue development of technologies and tools, such as human genome mapping, x-ray crystallography, nuclear magnetic resonance analysis, and three-dimensional protein modeling using super computers, that support this critically important research. 2. Improve understanding of genetic instability and differences among cancer cells (e.g., variations in drug resistance and tendency to metastasize) and how these factors contribute to disease progression and cancer treatment failure. 	<ul style="list-style-type: none"> • increased knowledge of the molecular/cellular basis of cancer (grant support and scientific publications as indicator of new knowledge) • Increased knowledge of genetic instability/cancer cell variation (grant support and scientific publications as indicator of new knowledge) • Increased number molecular/cellular research technologies 	<ul style="list-style-type: none"> • NCI/NIH, other Federal Agencies • Universities and Academic Health Centers, other Private Organizations 	Ongoing

1 Intermediate, observable effect

2 As outlined in Figure 1, page E-10

3 *Immediate*: Substantial progress toward completion in 1 to 2 years; *Initiate*: Major new effort to be started in 1 to 2 years;

Ongoing: Continued and increased support of current efforts.

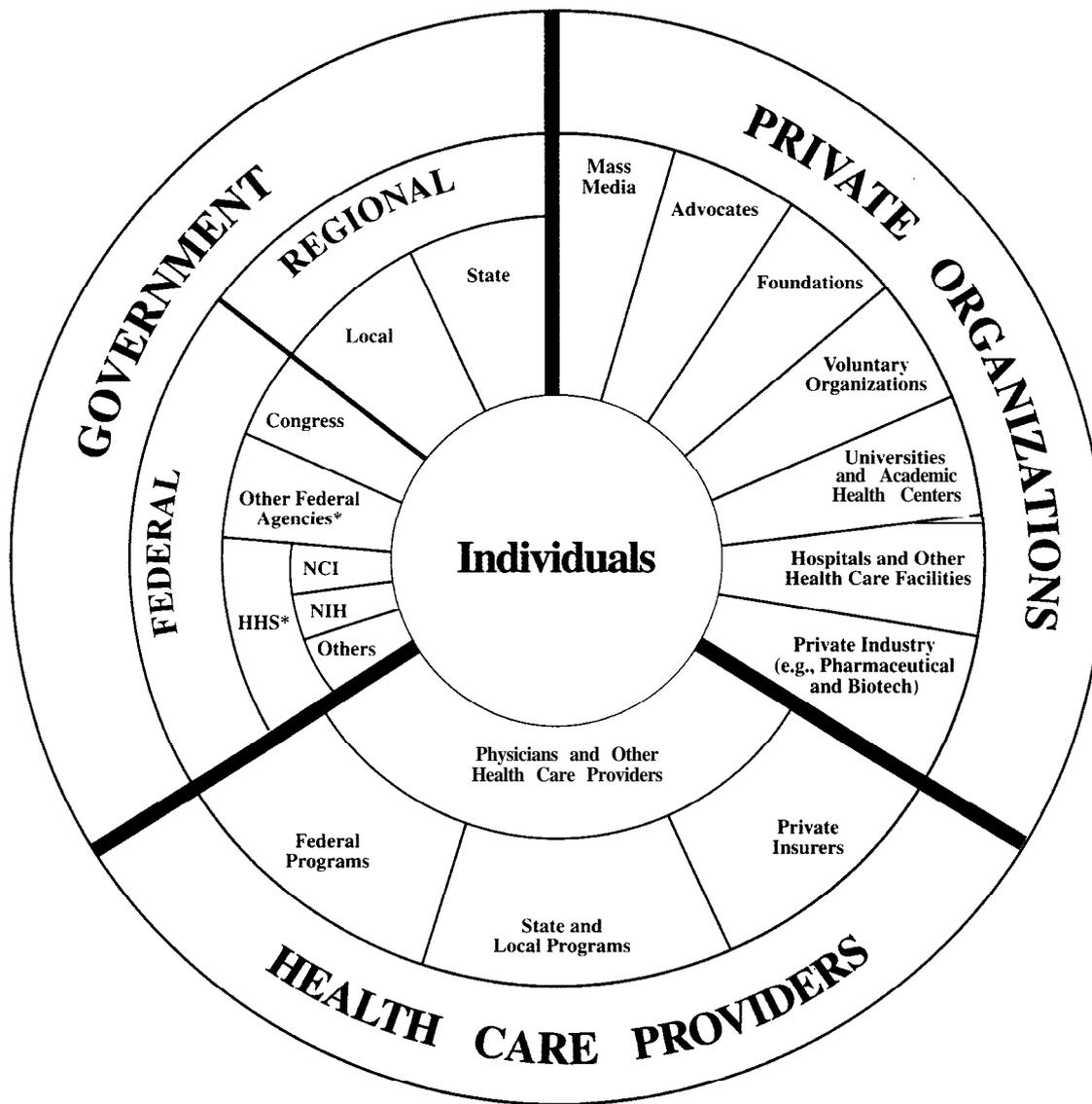
Recommendation	Measurable Outcome ¹	Responsible NCP Component ²	Priority ³
BASIC RESEARCH (continued)			
III.5. Conduct epidemiologic and laboratory investigations to determine the causes of cancer, including the interactions between hereditary, environmental (including lifestyle and occupational), dietary, infectious, and hormonal risk factors.	<ul style="list-style-type: none"> Increased knowledge of interactions among cancer causing factors (grant support and scientific publications as indicator of new knowledge) 	<ul style="list-style-type: none"> NCI/NIH, other Federal Agencies Universities and Academic Health Centers, and other Private Organizations 	Ongoing
III.6. Expand knowledge of cell cycle control, tumor biology, and host-tumor interactions and how they affect responses to treatment.	<ul style="list-style-type: none"> Increased knowledge of cell cycle control/tumor biology/host-tumor interactions (grant support and scientific publications as indicator of new knowledge) Increased knowledge of tumor biology-related effects on treatment response (grant support and scientific publications as indicator of new knowledge) 	<ul style="list-style-type: none"> NCI/NIH, other Federal Agencies Universities and Academic Health Centers, and other Private Organizations 	Ongoing
III.7. Expand basic knowledge of tumor virology/microbiology, including isolation and characterization of existing and/or new microorganisms associated with cancer initiation, and of mechanisms by which these microorganisms contribute to tumor formation	<ul style="list-style-type: none"> Increased knowledge of tumor virology/microbiology (grant support and scientific publications as indicator of new knowledge) 	<ul style="list-style-type: none"> NCI/NIH, other Federal Agencies Universities and Academic Health Centers, and other Private Organizations 	Ongoing
III.8. Encourage collaboration between basic scientists and translational and clinical researchers to accelerate cancer prevention, detection, and treatment technology development.	<ul style="list-style-type: none"> Increased multidisciplinary collaborative research awards for projects involving basic and clinical scientists 	<ul style="list-style-type: none"> NCI/NIH, other Federal Agencies Universities, other Private Organizations 	Initiate
III.9. Speed scientific progress and foster creativity by facilitating scientific interaction and collaboration through novel use of information technology and shared instrumentation and resources.	<ul style="list-style-type: none"> Increased availability of shared-use scientific instrumentation, information technology, and other research resources Increased collaborative research involving late generation information technology Increased application of high performance computing and communications (HPCC) in cancer research 	<ul style="list-style-type: none"> NCI/NIH, other Federal Agencies Universities, other Private Organizations 	Ongoing

¹ intermediate, observable effect

² As outlined in Figure 1, page E-10

³ Immediate: Substantial progress toward completion in 1 to 2 years; Initiate: Major new effort to be started in 1 to 2 years; Ongoing Continued and increased support of current efforts.

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
 - ▶ Centers for Disease Control and Prevention
 - ▶ National Institute for Occupational Safety and Health
 - ▶ Food and Drug Administration
 - ▶ Health Care Financing Administration
 - ▶ Indian Health Service
 - ▶ Health Resources and Services Administration
 - ▶ Agency for Health Care Policy and Research
 - ▶ Agency for Toxic Substances and Disease Registry
- ◆ 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

