PRESIDENT'S CANCER PANEL

2004-2005
Annual Report

Translating Research Into Cancer Care: Delivering on the Promise

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

National Cancer Institute

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Translating Research Into Cancer Care: Delivering on the Promise

Prepared by

Suzanne H. Reuben
for
The President's Cancer Panel

June 2005

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

The President's Cancer Panel

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The President
The White House
Washington, DC 20500

Dear Mr. President:

The National Cancer Program has matured considerably since enactment of the National Cancer Act in 1971, when cancer was believed to be a single disease that, with sufficient effort and resources, could rapidly be eradicated. We now understand how diverse and complex cancers are, and each day brings important new knowledge about this deadly family of diseases. The national investment in cancer-related research has yielded extraordinary advances in our understanding of genetic and molecular mechanisms that permit tumors to grow and spread. Some of these discoveries have been developed successfully into new treatments for people with cancer and new ways of identifying cancer risk. Still, many basic science discoveries with apparent promise for improving the outcomes of people with cancer and those at risk have yet to be developed into preventive, early detection, diagnostic, therapeutic, or supportive interventions. Why?

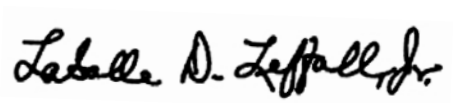
Some of the technologies needed to translate these advances into interventions have only recently become available, and others have yet to be devised. But progress also is being slowed by a constellation of multifaceted and interdependent barriers related to regulatory constraints, education and communication issues, and access to care limitations. Of critical importance, testimony presented to the Panel this year made it clear that the culture, focus, and infrastructure of the research and health care delivery enterprises are the root of many existing barriers to translation. These obstacles, described in this report, can and must be surmounted to deliver on the promise made to the American people in 1971 – to prevent, control, and cure cancers. Doing so, however, will require support at the highest levels of government, academia, and industry.

Mr. President, as you know, cancer recently eclipsed heart disease as the leading cause of death in America for people under age 85. With our demographics shifting toward an older population at greater risk for cancer, we must act boldly to stem the rising annual numbers of cancer cases that are anticipated and improve care for those who develop cancer. To do this, we must do a better job of turning research advances into effective cancer prevention and cancer care for all segments of the population. We also must preserve the current statutory authorities of the National Cancer Institute to ensure that this goal will be achieved most expeditiously.

This report offers recommendations for overcoming barriers that are limiting progress in translating research to reduce the growing burden of cancer, and suggests stakeholders with major responsibility for action. In addition, the Panel recommends an evaluation in five years of progress in accelerating research translation.

To varying degrees, these recommendations will be difficult to achieve, as they will challenge convention, commitment, and culture in the research, health care delivery, and legislative communities. Yet unless the Nation confronts these barriers to delivering research advances to the American people, the national investment in cancer research will be tragically squandered, for discoveries that do not lead to improved patient outcomes are tantamount to no discovery at all.

Sincerely,



LaSalle D. Leffall, Jr., M.D., F.A.C.S.
Chair

Lance Armstrong

Margaret L. Kripke, Ph.D.

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2004 – 2005 Meeting Minutes available online at:

http://pcp.cancer.gov

Executive Summary

With passage of the National Cancer Act of 1971 (P.L. 92-218), a promise was made to the American people – to conduct the full spectrum of research and related activities necessary to prevent, control, and cure cancers. The President's Cancer Panel, established by the National Cancer Act, is charged to monitor and evaluate the National Cancer Program (NCP) and to report at least annually to the President of the United States on impediments to the fullest execution of the program.

The tragic toll of cancer – in lives and productivity lost, diminished quality of life, family distress, and health care costs – is incontrovertible. Through national investments in cancer research and the efforts of dedicated scientists, health care providers, educators, and others, progress against some forms of cancer is being achieved. But other cancers remain intractable and new cancer cases are expected to increase markedly as the population ages and greater numbers of people reach the ages at which cancer risk rises significantly.

Testimony presented to the Panel in recent years touched upon myriad diverse yet interconnected problems affecting the speed at which the extraordinary discoveries in basic cancer research – particularly on the genetic and molecular underpinnings of cancer – are being developed into new interventions for cancer prevention, early detection, diagnosis, treatment, and supportive care. To explore these issues and barriers in greater depth, the Panel conducted four regional meetings between August 2004 and January 2005. Testimony was received from 84 academic, industry, and public sector basic, translational, clinical, and applied science researchers and administrators; community-based cancer care providers; specialists in drug and medical device development and commercialization; regulatory experts; public and private health care payors; statisticians; sociologists, professional and industry association representatives; media representatives, and patient advocates. Based on this testimony, this report describes and offers recommendations for overcoming major barriers that are limiting progress in translating research to reduce the growing burden of cancer, and suggests stakeholders with major responsibility for action.

To conquer cancer, many important tasks need to be accomplished, and these range from achieving critical insights in the laboratory all the way to delivering the right care in the community.

– Regulatory official

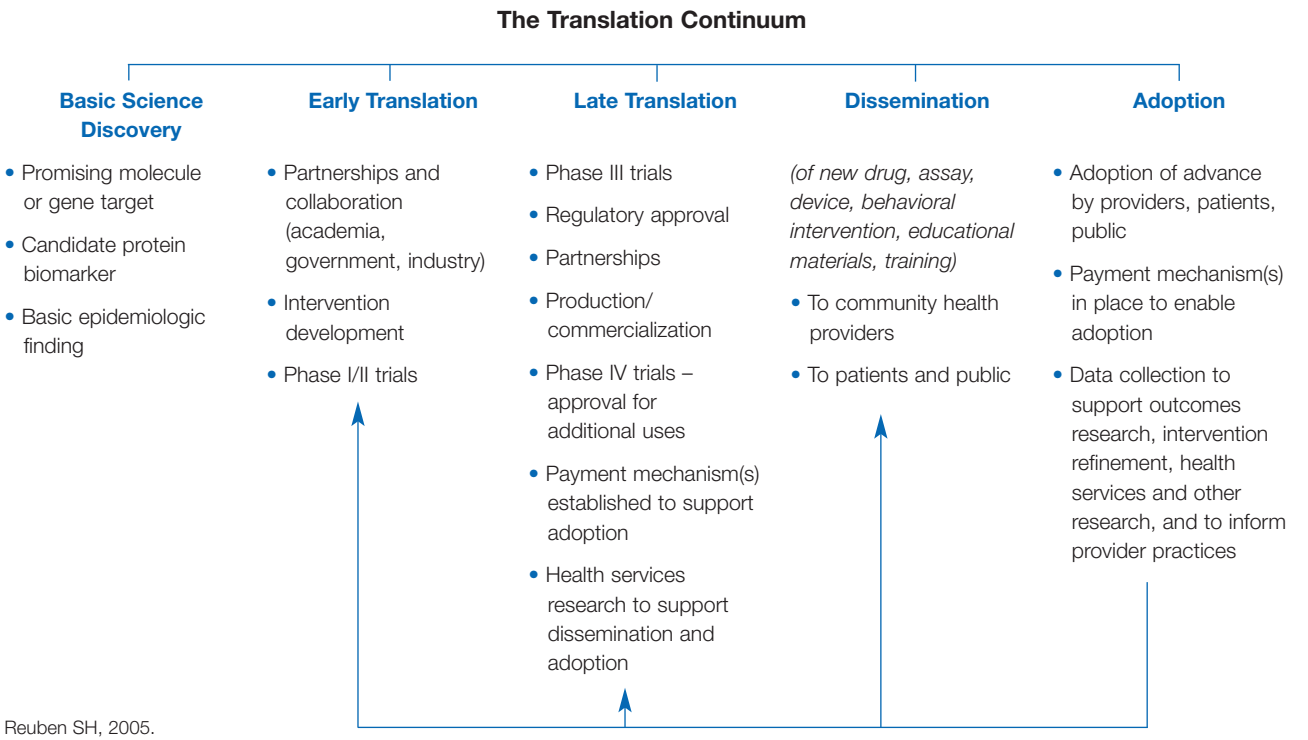
The Research Translation Continuum – Turning Discoveries into Cancer Care

Research **translation** encompasses all of the processes involved in developing promising basic laboratory and epidemiologic discoveries into cancer-related drugs and biologics, medical devices, behavioral interventions, methodologies, and instruments, and making these readily available to all segments of the public with cancer and those at risk for cancer (Figure 1). Along this broad continuum, ***early translation*** generally refers to development activities that begin following a promising discovery in the laboratory or in basic epidemiology and continues to the point at which an intervention undergoes initial (Phase I/II) testing in the clinic or community. ***Late translation*** begins when an intervention demonstrates efficacy in a larger population, receives regulatory approval, if required, and is commercialized or produced so that it can be made available to the public. Late-stage translation also may include testing of approved agents or devices for new uses.

Late translation must be followed by ***dissemination*** of the intervention (including information, training, and resources) to providers and/or the public, and by ***adoption*** (sometimes called diffusion) – the uptake of new interventions into standard practice by providers or the acceptance of behavioral interventions by patients and the public. The adoption phase also should include post-marketing data collection to support intervention refinement; outcomes, health services, and other research; and provider practice pattern analysis. Without dissemination and adoption, the fruits of new knowledge never become a part of the health care available to the American people.

Across the translation continuum, the Panel identified complex barriers related to the current culture of research; regulatory issues; dissemination, education, and communication needs, public trust and community participation issues, and access to cancer information and cancer care.

Figure 1: Translating Research to Reduce the Burden of Cancer



Reuben SH, 2005.

Team Science and the Culture of Research

The current culture and structure of the cancer research enterprise – both public and private – are the root of many of the impediments to translating basic science discoveries into improved cancer prevention and treatment interventions. These factors significantly affect cancer research priorities, the perceived desirability among institutions and individual investigators of conducting collaborative research, and resource allocations.

The growing complexity of cancer-related research, requiring collaboration among professionals with highly diverse skills and training, is sharply at odds with traditional, single investigator-oriented research approaches. Yet team science approaches clearly are proving to be the paradigm for achieving progress in translating basic science discoveries into useful interventions. Many of these efforts are large-scale collaborative projects to develop essential core resources needed to answer the most challenging scientific questions.

The [Human] Genome Project has spawned a new discipline in bioinformatics. What we need to now understand is the clinical significance of the information that we obtain. Population biologists would clearly play a key role, and medical economists….This is an example of an interdisciplinary or team approach that is quite different from the way science was conducted just in the recent past.

– Academic medical center researcher

Peer Review

Established peer review systems, particularly of the National Institutes of Health (NIH) and others modeled on the NIH system, tend to be biased toward proposals with a high probability of success and historically have been oriented strongly toward single investigator grants for basic and preclinical studies. In addition, the system favors established investigators over younger, less experienced scientists. As a result, novel, higher-risk proposals, those led by young investigators, and projects in translational and clinical science have been at a disadvantage in a system with limited funds and far more high quality proposals than can be funded. Recent reorganization of the NIH peer review system (including the focus and boundaries of study sections and efforts to include more clinical scientists as reviewers) as well as a growing recognition of the importance of research translation may improve the future success rate of collaborative, translational, and clinical cancer research proposals.

Other Disincentives to Collaboration

The academic research environment itself is a barrier to team science, since it rewards individual achievement rather than collaborative effort. Investigators are rewarded with promotions, compensation, tenure, laboratory or clinic space, staffing, and prestige depending on their success in bringing grant and contract revenue into their institutions. Success also is measured by the number of papers published in scientific journals on which an investigator is the lead author. These incentives also discourage collaboration, since collaborative efforts may decrease the amount of funds coming into the institution and until very recently, only one individual could be designated the principal investigator on a grant. Moreover, translation-oriented research is not the principal focus of the most prestigious journals, and papers reporting translational studies may be difficult to get

published. Even within individual academic institutions, collaboration is impeded by rigid departmental boundaries that limit communication among scientists in different disciplines, even though all may be engaged in cancer-related research.

The academic research culture, and its structures, practices, and reward systems must be changed to remove these major obstacles to collaborative, multi- and transdisciplinary research.

Infrastructure Required for Research Translation

The existing translational research infrastructure is inadequate to support the work that must be done to develop new knowledge into beneficial interventions and deliver them in the community. Major barriers to progress involve the current organization of the clinical trials system, workforce issues, and a lack of key research resources.

The Clinical Trials System

Despite increasing research and development investments, the annual number of new drug approvals is declining, a major source of frustration among public and private sector researchers and policymakers. It often does not become clear that a new compound is of little or no benefit – or is no better than existing therapies – until large Phase III trials are well underway. By this time, most development costs already have been incurred. Moreover, cancer drugs tend to have a higher late trial failure rate than new drugs for other diseases – more than 50 percent. Ways must be found to identify earlier the chemical and biological compounds with clear anti-tumor activity or impact on critical genetic and molecular pathways associated with carcinogenesis, tumor progression, or metastasis.

The clinical trials system in the United States must be simplified and made more cohesive, efficient, and effective without compromising the safety of study participants. It was suggested that for any clinical trials system to be successful, it must: (1) have a mandate and a philosophy that embraces clinical trial enrollment as a central precept, (2) offer provider incentives and recognition associated with doing the extra work involved in trial participation, (3) have stable resources, (4) have a structure that provides a broad base of opportunity for participation by community providers and patients, and perhaps, (5) employ navigators to help patients through the system.

A number of efforts are underway to overhaul the national clinical trials system. Both NIH and the National Cancer Institute (NCI) are exploring strategies to streamline and improve their extramural and intramural clinical trials systems. A joint initiative of cancer center and oncology professional associations is working to devise a system for smaller, “smarter” trials that will take advantage of emerging technologies and use human resources more productively to expedite research translation. A more sweeping proposal would join public, private, and nonprofit stakeholders – including researchers, research sponsors, regulators, health care consumers, health care purchasers, physicians, and non-physician health professionals – to establish a single, integrated national clinical trials enterprise that could overcome obstacles now slowing translation.

…the administrators in research institutions squeeze the time allocations for research and force investigators to identify sources of income to help pay their salaries…there are fewer young researchers being funded through the [NIH] R01 mechanism, and this is likely to reach crisis proportions unless there is some redirection of the funding to allow [them] to gain research support and not leave the field.

– Nonprofit cancer organization executive

The Research Translation Workforce

Compared with the basic science workforce, there is a dearth of translational and clinical researchers. This workforce imbalance is a major factor contributing to the infrastructural bottleneck that now limits the translation of cancer-related discoveries. Translational researchers must be trained in both basic and clinical science, and therefore, often require a longer training period than does an individual pursuing either basic or clinical science alone. These physician-scientists are in short supply and are dwindling in number – now only two percent of the physician workforce nationwide. Few training programs exist that are designed specifically to develop this special mix of skills and knowledge.

In addition, translational and clinical researchers have relatively few opportunities to secure "protected time" (i.e., salary support that relieves them of revenue-generating activities so that they can pursue research projects). Appropriate mentors within the academic setting also are scarce. With grant funding for translational and clinical research more limited than for basic research, some talented young investigators are choosing careers in other scientific areas. Expanded educational loan repayment programs may be a tool to help young physicians to pursue translational and clinical cancer research careers. Support also is inadequate for other essential components of the translation workforce, including health services researchers, research and oncology nurses, radiologists, statisticians, data managers, sociologists, behavioral medicine specialists, oncology social workers, community primary and ancillary care providers, health communication specialists, and others whose contributions across the translation continuum are critical if research advances are to reach the public. Many of these personnel are too few in number to meet the need for their skills, and in some cases, their services may not be reimbursable, creating a barrier to their participation in research-related activities.

Research Resources

Numerous public initiatives have been implemented to expand and refine research resources that support basic science discovery. Funding for shared resources supporting translational activities, however, has been far less robust, with relatively little support coming from the private and nonprofit sectors. Some publicly funded translation-oriented programs exist, but are too few in number and too small to support the research needed to turn promising discoveries into better cancer prevention and cancer care. Other research resources needed to speed translation include:

- Interoperable bioinformatics systems with standardized formats and datasets.
- More robust cancer surveillance data.
- Coordinated, linked biorespositories with standardized information on specimens.
- Validated biomarkers of carcinogenesis and treatment response, and biomarkers to identify disease subgroups and predict prognosis.
- Enhanced applied and health services research capacity.
- Interoperable electronic health record systems.

Although initiatives are underway, principally in the public sector, to enhance capacity in each of these areas, substantially increased funding and effort will be required to develop the resources needed to fully support research translation.

Regulatory Issues Affecting Translation

Nearly every aspect of cancer-related research and drug development is controlled by myriad Federal and state regulations. These regulations have been developed over the past few decades principally to protect the public from harm due to financial conflicts of interest in the research and pharmaceutical communities, inadequate patient protection in research studies, unsafe drugs and devices, and invasions of privacy. But many of the current regulations, though well-intentioned, are having unintended consequences that are impeding the pace at which new discoveries in basic science can be developed into interventions and delivered to the public.

…the lack of sound policy is presenting real barriers in the fight against cancer – in particular, innovation policy, including research funding and procurement; regulatory and reimbursements challenges; intellectual property as it results particularly in gene patents; the setting of standards, particularly in information technology and health care; and proactive policy in areas of genetic privacy and nondiscrimination.

– Biotechnology company executive

Further, the regulatory structure related to clinical trials in many ways thwarts efforts to create the most efficient, effective, and least costly cancer clinical trials system. In particular, regulations related to multi-institutional trials have become so complex that they are a significant obstruction to progress. Coordinating multiple grant participants, Institutional Review Boards (IRBs), and Federal and state regulations is a costly undertaking that often delays trials and in some cases, prevents important trials from being conducted at all.

Institutional Review Boards and Human Research Subject Protections

Ideally, the IRB process should be streamlined such that a single scientific review and single IRB review meet the needs of all stakeholders. Using a central IRB for multisite trials, or alternatively, using nationally agreed-upon IRB standards, are possible options for solving some of the current problems. Standardized reporting requirements and formats for adverse events occurring during clinical trials also are needed.

Intellectual Property, Patents, and Conflict of Interest

Several issues in this area are impeding translation and have become more complex as greater numbers of patents are granted for biomedical discoveries that previously would have resided in the public domain, as large-scale projects require the use of many patented products, and as industry-academic partnerships have increased. Perhaps most importantly, strident protection of intellectual property rights, patents, and licensing arrangements make it exceedingly difficult to test combination therapies of drugs not yet approved by the Food and Drug Administration (FDA), despite wide recognition that combination therapies targeting multiple cancer pathways have the best chance of success. In addition, as subtypes of common cancers are identified, each requiring different treatment, the market for individual cancer drugs is shrinking, along with private industry's interest in developing them. Options identified to address these issues include a standard patent exclusion for research purposes, standard contract clauses governing collaborative drug and device development efforts, modifications to the periods of exclusivity now provided by current patent law, greater government involvement in early drug development, and designating all cancers as "orphan" (low incidence) diseases eligible for special drug development assistance under the Orphan Drug Act of 1983.

Conflict of interest, intellectual property, and patent issues can be managed successfully with strict disclosure rules and firm enforcement, but cannot be eliminated. Some drugs, biologics, and devices for which early translation tasks were supported by public funds may require "gap funding" from nonprofit or other sources to continue their development to the point that the private sector will risk the significant funding needed to commercialize them.

Food and Drug Administration

Suggested changes in the FDA process and interface of medical product reviewers and academic and private cancer drug and device developers were to: (1) enable developers to meet earlier in the translation process with FDA officials to discuss the types of trials and data that will be required for approval, (2) accelerate FDA efforts to develop product review tools that keep pace with scientific advances, (3) develop an improved mechanism to enable FDA to share clinical trials information with the academic community that both accommodates the proprietary environment and does not compromise the approval process, (4) encourage the rapid development of regulations to guide the development and approval of chemopreventive agents and combination drug trials, and (5) support the FDA-NCI partnership to streamline the clinical evaluation process and identify biomarkers and other surrogate endpoints for use in assessing the efficacy of new agents in clinical trials.

Centers for Medicare and Medicaid Services (CMS)

The potentially chilling impact on drug development and community oncology services availability due to Medicare reimbursement changes under the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) was discussed at length at the Panel's meetings, and such changes should be monitored closely as various provisions of the MMA are implemented.

CMS will become more involved in collecting data on "off-label" uses (i.e., uses other than those approved by the FDA) of cancer drugs and cancer care technologies, as well as new agents and devices, to support more expeditious coverage decisions. These activities reflect a growing recognition that cancer treatment is becoming more individualized, and that treatment planning and reimbursement should become more decentralized. CMS is teaming with NCI to, among other objectives, develop data collection and data sharing strategies to expedite coverage decisions and improve patient and provider information access, and create a process for post-approval studies on priority questions.

Health Insurance Portability and Accountability Act (HIPAA)

Obstacles to research erected by the HIPAA privacy provisions that took effect in 2003 include redundancy with existing privacy-related components of informed consent documentation that creates unnecessary burdens on clinical researchers and trial participants without improving patient protection. Further, HIPAA prohibits access to medical records that would enable researchers to: (1) identify patients who may benefit from participating in a specific clinical trial, (2) use tissue specimens remaining from a previous clinical trial for additional studies, including outcomes research, (3) examine linkages between disease trends and environmental factors, (4) obtain long-term follow-up data on patients, and (5) more easily use existing databases and tissue banks.

Dissemination, Education, and Communication Issues Affecting Translation

Since 80 percent of cancer patients and survivors receive their care in the community, disseminating prompt, accurate information in usable formats to physician and non-physician health care providers and the public about cancer prevention and treatment advances is a critical step in the translation process – the link between an intervention's development and its adoption into clinical practice. Yet research to identify the most effective strategies for disseminating advances to multiple audiences is in its infancy. Moreover, dissemination suffers from a lack of leadership and chronic underfunding, as no agency has been given the authority and budget to coordinate dissemination research and activities. To achieve the ultimate goal of dissemination – enabling individuals and organizations to adopt evidence-based approaches that will help reduce the risk and burden of cancer – specific education and communication needs of the public, health care professionals, and research community must be met.

Public education is needed in three important, though not mutually exclusive areas: (1) education about basic scientific and research concepts, (2) general education about cancer as a disease process and about available cancer prevention and care interventions, and (3) clinical trials education and awareness. Provider education is needed to increase the adoption of cancer screening, preventive interventions, and other care shown to be of benefit; to facilitate adoption of new treatments and technologies; and to improve provider openness to and awareness of clinical trials, as well as their ability to communicate with patients about trials. In the research community, targeted education is needed to improve the ability of scientists to communicate with potential clinical trial participants about the risks, processes, and potential benefits of trials. Researchers also need training to better understand regulatory requirements related to drug and device development, and the tasks and resources needed to successfully commercialize new products.

…some of the expertise needed for dissemination may exist outside our academic medical centers and cancer centers. For example, it may reside within business schools. Partnerships may be needed to stimulate discussions between people with effective interventions and those who know something about marketing and dissemination.

– Dissemination researcher and cancer center administrator

The Impact of Public Trust and Community Participation

Public trust and community participation are essential if research advances are to make the transition from the clinic to community cancer patients/survivors and those at risk for cancer. Issues of public trust permeated the testimony presented to the Panel. Trust is an expectation of certain behaviors, reliability, competence, and power sharing. The research community has fallen short in meeting the public's expectations in this area such that a longstanding distrust of medical research is firmly entrenched and is a significant obstacle to clinical trials participation and the acceptance of new treatments and other interventions. Establishing trust between researchers and minority communities is of special importance.

Involving the community (the public, physician and non-physician care providers, regulators, advocates, and local government) in assessing the need for specific studies, and in planning and conducting the research itself have proven effective in overcoming distrust and expanding the reach of prevention and treatment advances into communities. Specifically, communities must be involved early in research protocol development, and researchers must ensure that the community benefits from participation and receives research results. Further, the expertise of cancer advocates and survivors, who can help maintain a patient-centered focus on research projects, could be utilized more fully. Community involvement and support is particularly crucial to ensure the sustainability of interventions shown to be of benefit.

The Importance of Access to Successful Translation

Even if research advances are translated into cancer prevention and care improvements, the burden of cancer will not be reduced unless all segments of the population have geographic and financial access to appropriate clinical trials, approved therapies and technologies, and the information that will enable individuals and their health care providers to identify and evaluate cancer-related prevention and care options. The Panel has reported extensively on issues of access to cancer care and many of these complex and pervasive issues were reiterated in the testimony received. Encouragingly, several potential models for extending the availability of clinical trials and state-of-the-art cancer care and overcoming provider and patient information access barriers were described.

We will get there with a commitment on the part of this Nation to do what is necessary...to fulfill the dream that we began in 1971 to conquer cancer...given the opportunity that's before us – if we seize it and if we accomplish it, we will end the suffering and death due to cancer and bring that about in this country by 2015.

– NCI director

Conclusions

The translation continuum described in this report – spanning the multitude of processes needed to turn a laboratory discovery into improved cancer care that is available to all who need it – is unbalanced and obstructed by bottlenecks that are keeping cancer research advances from reaching the public. The Panel's recommendations for action to remedy major barriers now limiting translation progress are enumerated in the attached matrix, along with suggested responsible stakeholders or other entities. Importantly, those suggested do not necessarily comprise the universe of stakeholders or others with an interest in these issues.

The critically needed changes described in this report cannot be achieved without cost. Specifically:

- Increased funding for translation-oriented research – particularly collaborative, team efforts – is urgently needed across the translation continuum. Targeted Federal funding for translation-oriented research is drastically out of balance relative to financial commitments to basic science. Ways must be found to increase human tissue and clinical research resources without slowing the discovery engine. Supplemental funding may offer a temporary solution but will be inadequate in the long term.

- A funding gap exists for agents or other interventions that require further development before they are ready for commercialization, but which have exhausted available public funding.

- The translational research infrastructure is inadequate to enable the work that needs to be done; resources must be committed to develop the tools and workforce required.

- Research on cancer prevention must receive higher priority and funding to expand the body of knowledge that can be translated into new interventions to reduce cancer incidence and mortality and reduce the overall cancer burden. Additional research also must be funded to improve cancer early detection interventions.

- Dissemination research must be expanded and accelerated to improve understanding and develop strategies that will increase the adoption rate of new cancer care interventions.

- Cancer centers and academic centers must be adequately funded to conduct outreach and dissemination activities. Institutional commitment is essential to sustain outreach to improve clinical trials accrual, disseminate research findings, and help ensure that advances are adopted into standard practice. Network models may offer efficiencies of scale and opportunities to extend the reach of cancer centers and academic institutions, but funding will be needed to foster and maintain regional linkages.

- Training funds are needed to strengthen and expand the translation research workforce and improve public understanding of cancer and cancer research. Specifically, funds are needed to support: (1) training and mentoring to attract investigators to translational research careers, (2) continuing training of translation-oriented investigators, (3) community provider training on clinical trials and new therapies, (4) investigator and community provider training on regulatory requirements related to drug and device approval, and (5) public education.

- Outcomes and cost-effectiveness research are needed to better understand the benefits and actual total costs of care for various types of cancer at different stages of disease; for outreach, prevention, and early detection activities; and the components of total cost. Without this information, it is difficult to assess the long-term efficacy of new interventions or align reimbursement strategies to cost.

- The funding necessary to support these essential activities across the translation continuum must be garnered, either through carefully considered reallocations of currently available funds, or by identifying and committing new resources.

In addition, the Panel believes it is imperative that the success of the numerous initiatives launched or planned to address diverse aspects of the research translation problem is assessed so that programs can be refined as needed. Therefore, the Panel further recommends:

In five years, a thorough evaluation should be conducted to assess the effectiveness of the many public and private initiatives now underway or planned to accelerate the translation of basic science discoveries into improved cancer prevention and cancer care.

Moreover, the Panel believes that:

To ensure continued progress in translating cancer research advances into new cancer care interventions, the current statutory authorities of the National Cancer Institute should be preserved in any reauthorization of the National Cancer Act.

All stakeholders in the cancer research, medical, public health, advocacy, legislative, and regulatory communities must make it their priority to ensure that biomedical advances are developed more rapidly into cancer care interventions and that this care is provided affordably and equitably to all – to prevent, control, and cure cancers to the maximum extent of our knowledge and skill. This is the commitment that was made to the American people, who finance with their tax dollars and their health insurance premiums the cancer research and health care delivery systems that together comprise the translation continuum. It is the promise on which we must deliver, and we must do no less.

Recommendations and Suggested Responsible Stakeholders or Other Entities

Recommendations	Responsible Stakeholder(s) or Other Entities*
Overarching Recommendations	
In five years, a thorough evaluation should be conducted to assess the effectiveness of the many public and private initiatives now underway or planned to accelerate the translation of basic science discoveries into improved cancer prevention and cancer care.	• Institute of Medicine (IOM)
To ensure continued progress in translating cancer research advances into new cancer care interventions, the current statutory authorities of the National Cancer Institute should be preserved in any reauthorization of the National Cancer Act.	• Congress
Team Science and the Culture of Research	
1. The existing culture of cancer research must be influenced to place more value on translational and clinical research. To effect this culture change, a task force representing key stakeholders in academic research should be convened to examine and modify existing reward systems (e.g., compensation, promotion/tenure, space and resource allocation, prestige) to encourage collaborative research and ensure that all contributors (including but not limited to pathologists, radiologists, and research nurses) benefit from participating in these research activities.	• Association of American Medical Colleges (AAMC), Council of Deans • Association of Academic Health Centers (AAHC) • American Association for Cancer Research (AACR) • American Society of Clinical Oncology (ASCO) • Association of American Cancer Institutes (AACI) • Association of Community Cancer Centers (ACCC) • Association of Oncology Social Workers (AOSW) • National Comprehensive Cancer Network (NCCN) • Oncology Nursing Society (ONS) • American Society of Clinical Pathology (ASCP) • American Society for Therapeutic Radiology and Oncology (ASTRO) • International Biometric Society (IBS) • National Coalition for Cancer Survivorship (NCCS) • Biomedical Engineering Society (BES) • International Committee of Medical Journal Editors (ICJE)
2. Governmental and private research sponsors must place greater emphasis on and substantially increase funding for clinical research and human tissue research. Funding mechanisms should promote collaborative science and include greater support through the R01 mechanism.	• National Cancer Institute (NCI)/National Institutes of Health (NIH) • National Science Foundation (NSF) • Centers for Disease Control and Prevention (CDC) • Department of Defense (DoD) • Department of Veterans Affairs (VA) • Pharmaceutical Research and Manufacturers Association (PhARMA) • Biotechnology Industry Organization (BIO) • Lance Armstrong Foundation (LAF) • American Cancer Society (ACS) • Howard Hughes Medical Institute (HHMI) • Agency for Healthcare Research and Quality (AHRQ)

*Please note that this list is not exhaustive and does not preclude participation by other interested parties.

Recommendations	Responsible Stakeholder(s) or Other Entities
3. The National Institutes of Health and other research sponsors should facilitate collaboration in large research projects by requiring team approaches to the extent appropriate to the science and designating a percentage of project funding for such efforts.	• NIH • DoD • CDC • VA • AHRQ • HHMI • LAF • ACS
4. To stimulate team science, the National Institutes of Health and other research sponsors should rapidly devise implementation plans for permitting co-principal investigators who share grant funding and attribution for these efforts, consistent with the January 2005 directive from the Director of the Office of Science and Technology Policy.	• NIH • VA • DoD • CDC • NSF • AHRQ
Infrastructure Required for Research Translation	
5. To attract and retain young investigators to careers in translational and clinical research: (a) Protected research time and mentoring must be provided earlier and potentially for a longer period of time than is now the norm. Government training funds may be needed to enable academic institutions to provide this supportive environment. (b) New or expanded student loan buy-back programs should be established to enable young investigators to pursue the additional training necessary for a career in translation-oriented research. (c) Academic institutions should make special efforts to recruit and retain young scientists from underrepresented population groups.	• NIH • DoD • NSF • VA • National Postdoctoral Association (NPA) • AAMC
6. The Rapid Access to Intervention Development program should be expanded and revitalized to accelerate the development of innovative interventions and technologies for cancer.	• NCI
7. Specialized Programs of Research Excellence (SPOREs) have proven effective in stimulating collaborative and translational research. The program should be expanded, with the focus of selected SPOREs shifted to emphasize clinical over basic research.	• NCI
8. The Centers for Medicare and Medicaid Services should explore the possibility of collecting cancer stage data, at least at the time of diagnosis, to better inform treatment decisionmaking, ensure appropriate payments, enrich the body of information about provider practice patterns, and support treatment research.	• Centers for Medicare and Medicaid Services (CMS)

Recommendations	Responsible Stakeholder(s) or Other Entities
9. The proposed Human Cancer Genome Project should be supported to accelerate progress in genetic knowledge that will enable the development of new cancer prevention and treatment advances. Funding for this large effort should come from a special supplement rather than from participating agencies' budgets.	• Congress • NIH • NCI • National Human Genome Research Institute (NHGRI) • DoD
Regulatory Issues Affecting Translation	
10. The current partnerships between the National Cancer Institute (NCI) and the Food and Drug Administration to expedite cancer drug reviews and between NCI and the Centers for Medicare and Medicaid Services to generate clinical data on new interventions to support Medicare coverage decisions should be continued and strengthened.	• NCI • FDA • CMS
11. To encourage private sector investment in cancer therapies, all new cancer chemoprevention and chemotherapy drugs and biologics should be designated orphan drugs under the Orphan Drug Act of 1983.	• Congress
12. A task force of private, nonprofit, academic, and government stakeholders affected by current barriers to research translation due to intellectual property and patent issues should be convened to develop and reach consensus on: (1) standard language for patent exemptions for research purposes, (2) standard clauses for contracts governing collaborative research, and (3) other agreements as needed to resolve intellectual property and data-sharing issues.	• NIH • DoD • VA • FDA • CMS • AACI • AACR • PhARMA • BIO • AAMC • HHMI • ACCC • ASCP • ASTRO
13. The Institute of Medicine should be commissioned to evaluate the impact of the Health Insurance Portability and Accountability Act provisions and provide guidance to legislators on amendments needed to remove unnecessary obstacles to cancer research and make this law better serve the interests of cancer patients and survivors. *(This is a restatement of prior Panel recommendations.)*	• Congress • IOM
Dissemination, Education, and Communication Issues Affecting Translation	
14. A lead agency for cancer-related dissemination research and activities should be designated and provided with the budget and authority to carry out this crucial function.	• Office of Science and Technology Policy, White House

Recommendations	Responsible Stakeholder(s) or Other Entities
15. The National Cancer Institute should increase significantly funding for research and implementation activities to improve dissemination and adoption of cancer research advances. As part of this effort, Comprehensive Cancer Centers should be required and funded to take an active role in disseminating new cancer-related interventions into their communities/ regions and facilitating their adoption by community cancer care providers, including non-physician personnel.	• NCI/NIH • Congress • NCI-designated Comprehensive Cancer Centers • Coalition of National Cancer Cooperative Groups (CNCCG) • NCCN
16. The translation process should be expedited through bi-directional education between regulators and cancer researchers to ensure that regulators better understand rapid advances in biomedical science and technologies, and that researchers better understand and are able to navigate and meet regulatory requirements.	• NCI • FDA • NSF • Private sector pharmaceutical and biotechnology companies
The Impact of Public Trust and Community Participation	
17. Clinical and prevention research funders should require community participation early in protocol design and in research implementation.	• NCI/NIH • CDC • CNCCG • AHRQ
18. Research results must be shared with the individuals and communities that participate in clinical trials and other studies.	• NIH • CDC • DoD • VA • CNCCG
19. Clinical and prevention research grantees should be required to include as part of the grant application a plan for disseminating and sustaining new interventions into the community.	• NCI/NIH • CDC
20. Existing community-based participatory research models should be evaluated to determine the potential for adopting them in other geographic areas and populations.	• IOM • AHRQ
The Importance of Access to Successful Translation	
The President's Cancer Panel has made recommendations to improve access to cancer care. These recommendations may be found in the following reports: • *Living Beyond Cancer: Finding a New Balance*, May 2004 • *Facing Cancer in Indian Country: The Yakama Nation and Pacific Northwest Tribes*, December 2003 • *Voices of a Broken System: Real People, Real Problems*, March 2002	(See recommendations in these documents)

Preface

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

Over the past few years, the Panel has examined health care system and other problems that keep populations across the Nation from receiving the most appropriate cancer-related care. Most recently, the Panel reported on special problems facing cancer survivors and their loved ones due to the health care system, the disease itself, or its aftermath. Testimony provided during the series of meetings addressing these issues led to the report, *Living Beyond Cancer: Finding a New Balance*,[1] submitted to the President in May 2004.

The testimony given at those meetings also touched upon numerous issues concerning the pace at which cancer research advances are reaching the public. To more fully explore the effectiveness of this component of the NCP, the Panel conducted a series of meetings entitled *Translating Research to Reduce the Burden of Cancer*. Testimony was received from 84 academic, industry, and public sector basic, translational, clinical, and applied science researchers and administrators; community-based cancer care providers; specialists in drug and medical device development and commercialization; regulatory experts; public and private health care payors; statisticians; sociologists; professional and industry association representatives; media representatives; and patient advocates. A roster of participants is included in Appendix A.

Four meetings were conducted between August 2004 and January 2005 at the following locations:

August 30, 2004	University of California at San Francisco Comprehensive Cancer Center San Francisco, California
September 27, 2004	The Ohio State University Comprehensive Cancer Center Arthur G. James Cancer Hospital Richard J. Solove Research Institute Columbus, Ohio
November 1, 2004	The University of Texas M. D. Anderson Cancer Center Houston, Texas
January 24, 2005	Memorial Sloan-Kettering Cancer Center New York, New York

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

With passage of the National Cancer Act of 1971, a promise was made to the American people – to conduct the full spectrum of research and related activities necessary to prevent, control, and cure cancers. At that time, the complexity of cancer was little understood, and science has made enormous strides toward understanding the fundamental molecular and genetic nature of this diverse and dreaded family of diseases. These research discoveries need to be translated into new prevention, early detection, diagnosis, treatment, and supportive care interventions, and advances must become part of standard medical practice for the translation process to be complete.

Part I Translating Research – Introduction

Cancer in America

Without question, cancer continues to exact a terrible toll on the Nation. In 2005, an estimated 1,373,000 new cases of cancer will be diagnosed, and more than 570,000 people will die of cancer.[2] For the first time, cancer has surpassed heart disease as the leading cause of death among Americans under age 85.[3] Due to prevention efforts (primarily reduced smoking rates among men), earlier detection, and better treatments, the total number of deaths from cancer per 100,000 population has begun to decline slowly, approximately one percent per year since 1999, with more rapid mortality declines for some cancers. But lower smoking rates,[4] together with improved surgical techniques and devices, better medications for cardiovascular conditions, and improved control of major risk factors such as hypertension and high cholesterol have reduced heart disease mortality substantially faster.

Risk for most cancers rises with age. The U.S. population over age 65 is growing rapidly,[5] and life expectancy continues to rise.[6] The annual number of new cancer cases is likewise expected to grow, potentially doubling by 2050.[7] This trend is projected even though the incidence rates of some cancers (e.g., stomach, colorectal, male lung cancer) per 100,000 population[8] continue to decline slowly and others (e.g., female lung cancer) are stabilizing. Incidence rates of some cancers (e.g., kidney cancers,[9] adenocarcinoma of the esophagus,[10] multiple myeloma[11]), however, are rising for reasons not well understood.

At the same time, people with most types of cancer are surviving longer following their diagnosis than at any time in the past. The overall five-year relative survival rate for all cancers combined is now 64 percent, and an estimated 9.8 million Americans are living with a cancer history.[12] Much of this progress is due to prevention efforts (e.g., tobacco use prevention and cessation programs), earlier detection, and improved treatments. Survival rates vary considerably by cancer site and stage at diagnosis – combined five-year relative survival for children with cancer is now more than 70 percent, and more than 80 percent of adults with testicular, uterine, bladder, breast, prostate, thyroid, and melanoma skin cancers can expect to live at least five years beyond their diagnosis (all stages combined).[13] Some of these child and adult survivors, however, may still have active disease, recurrences, or second cancers. A small number of cancers (e.g., liver, pancreas) remain almost universally fatal regardless of stage at diagnosis. Further, significant disparities in mortality and survival persist in some population groups (e.g., minorities, adolescents, recent immigrants) compared with the adult Caucasian majority, due principally to differences in access to early detection interventions and prompt, appropriate care.

The National Institutes of Health (NIH) estimate the overall costs of cancer in 2004 at $189.8 billion, of which $69.4 billion was for direct medical costs, $16.9 billion was indirect morbidity cost (i.e., lost productivity due to illness), and $103.5 billion was for indirect mortality costs (i.e., lost productivity due to premature death).[14] With rising numbers of cancer cases, longer survival, and escalating health care costs, these cancer-related costs also will grow. In addition, individual costs (e.g., direct non-health care costs such as paid child care, patient time costs such as the value of time to attend treatment or screening, employment costs including days lost from work[15]) have been difficult to measure but comprise a major component of the total economic cost of cancer. Intangible costs, such as pain and emotional distress suffered by people with cancer and by their families, are impossible to quantify.

To address and reverse these trends, the extraordinary advances in knowledge and technology achieved over the past three decades – in cancer biology and immunology, genomic information, imaging and bioinformatics technologies, screening, treatment and supportive care interventions; cancer communication techniques; and nascent nanotechnology, proteomics, and metabolomics applications – must be brought to bear on all aspects of the cancer problem. Numerous leaders in cancer research and care[16,17,18,19] believe that these discoveries and related improvements in cancer control are, with exceptions such as those noted above, having their intended impact: increasing survival and decreasing the number of deaths from specific cancers. Further, they maintain, these predominantly basic science advances have brought us to the threshold of the next levels of achievement in more sensitive early detection and diagnostic tools, targeted therapeutics, bioinformatics, and biomarkers of treatment response and disease prognosis.

However, despite the multitude of advances in understanding the fundamental nature of cancer and substantial outcome improvements for people with some cancers, critics of the National Cancer Program (NCP)[20,21,22] question its research focus, the speed at which research advances reach the public as widely available advances in care, and most of all, the return on the national research investment in terms of cancer patients' duration of survival and quality of life, the number of lives saved, and our ability to prevent cancer.

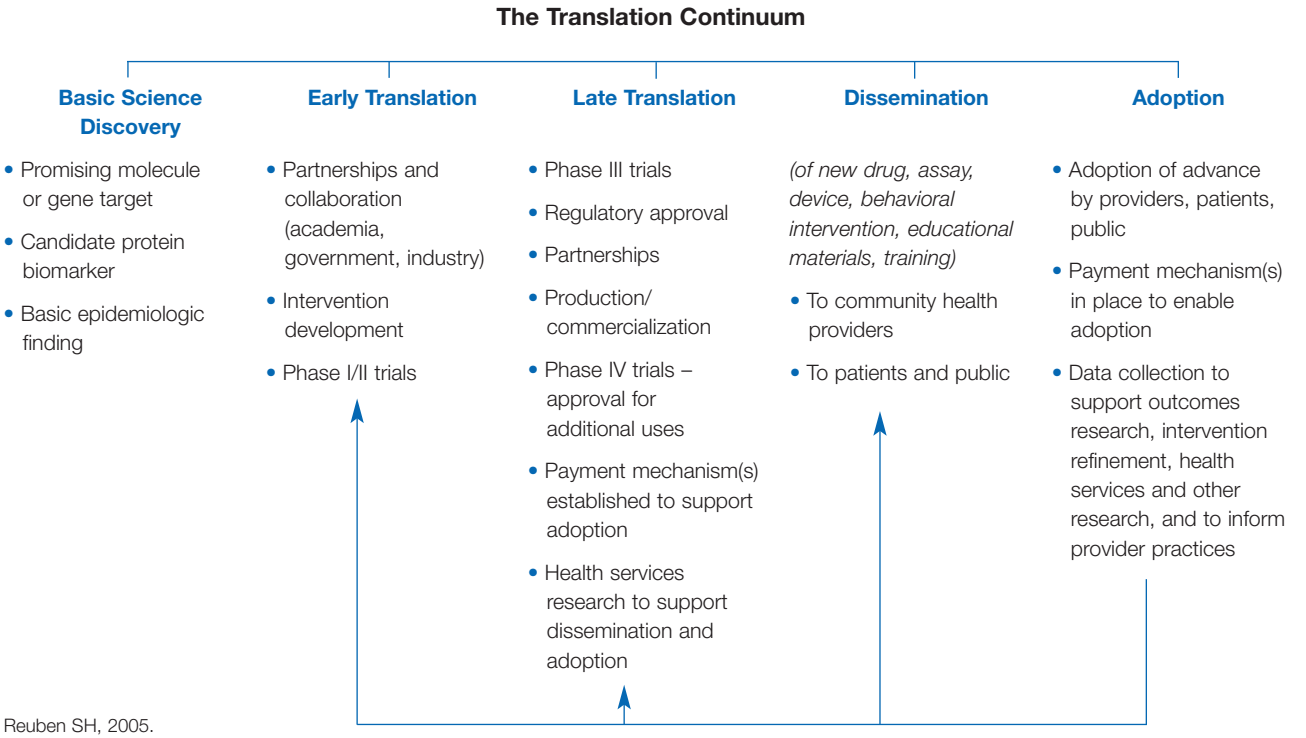
Translation – Bringing Cancer Research Advances to the Public

In its 1999 assessment of the NCP,[23] the Panel expanded on an earlier depiction of the research and development enterprise[24] to describe four domains spanning the cancer research and care continuum that must function and interact effectively if research advances are to reach the public (Appendix B). The Panel also suggested the essential activities and stakeholders related to each domain. Since that time, this schema has been, and continues to be modified; for example, the National Cancer Institute's (NCI) activities now are organized around three "Ds" – Discovery, Development, and Delivery, and the NCI has committed to providing resources for this continuum as part of a challenge goal to eliminate the suffering and death due to cancer by 2015.

Viewpoints concerning the nature and bounds of translational research and developmental activities have been diverse and evolving. The demarcation between activities considered applied research and those that are health care delivery concerns is sometimes blurred and continues to be an area of considerable discussion.

In this report, **translation** is defined as being broader than translational research alone, encompassing all of the processes involved in developing promising basic laboratory and epidemiologic discoveries into cancer-related drugs, medical devices, behavioral interventions, methodologies, and instruments, and making these readily available to all segments of the public with cancer and those at risk for cancer (Figure 1). Within this conceptualization, ***early translation*** generally refers to development activities that begin following a promising discovery in the laboratory or in basic epidemiology and continues

Figure 1: Translating Research to Reduce the Burden of Cancer



Reuben SH, 2005.

to the point at which an intervention undergoes initial (Phase I/II) testing in the clinic or community. ***Late translation*** begins when an intervention demonstrates efficacy in a larger population, receives regulatory approval, if required, and is commercialized or produced so that it can be made available to the public. Late-stage translation also can include testing of approved agents or devices for new uses.

Late translation typically is followed by ***dissemination*** of the intervention (including information, training, and resources) to providers and/or the public, and ideally, by ***adoption*** (sometimes called diffusion) – the uptake of new interventions into standard practice by providers or the acceptance of behavioral interventions by patients and the public. The adoption phase also should include post-marketing data collection to support intervention refinement; outcomes, health services, and other research; and provider practice pattern analysis. Dissemination and adoption must be considered part of the translation process, since without them, the fruits of new knowledge never become a part of the health care available to the American people.

Clinical trials sit squarely in the middle of the journey from laboratory to patient, but the continuum of drug discovery, development, marketing, and real-world experience functions optimally as a closed loop rather than a linear process.

– Pharmaceutical company executive

Each of these stages of translation is highly complex and fraught with distinct infrastructure, cultural, workforce, regulatory, fiscal, education/communication, and other challenges that affect the speed at which discoveries move through the developmental process. These factors frequently are interdependent, and issues of public trust span the translation continuum.

This report does not attempt to provide an exhaustive analysis of all of the issues that impact the translation process. Instead, the Panel's objective is to illuminate key rate-limiting steps on the path from discovery to adoption with a focus on recommendations that, with the commitment of public and private sector decisionmakers and other stakeholders, can be implemented in a relatively short timeframe to more rapidly translate research into prevention and care that will reduce the burden of cancer in the United States.

Organization of the Report

The remainder of this report describes in greater detail many of the issues that affect the translation process and highlights the testimony presented in several areas:

- Team Science and the Culture of Research
- Infrastructure Required for Research Translation
- Regulatory Issues Affecting Translation
- Dissemination, Education, and Communication Issues Affecting Translation
- The Impact of Public Trust and Community Participation
- The Importance of Access to Successful Translation
- Conclusions

In addition, a roster of participants at each of the four Panel meetings, a matrix of recommendations and suggested stakeholder responsibility, and a list of organizations and acronyms are provided as appendices.

The existing culture and structure of the cancer research enterprise – both public and private – are the root of many of the impediments to translating basic science discoveries into improved cancer prevention and treatment interventions. These factors significantly affect cancer research priorities, the perceived desirability among institutions and individual investigators of conducting collaborative research, and resource allocations for training and technology.

Part II Team Science and the Culture of Research

Cancer Research Priorities

Although opinions differed as to how cancer research priorities should be reordered, speakers agreed that a major shift toward a more balanced approach across the translation continuum is needed. For decades, cancer research has been focused heavily on basic science discovery. Translation efforts have been concentrated primarily on early translation activities, e.g., developing promising agents or technologies into testable drugs or devices, respectively.

Speaker suggestions for refocusing cancer research included the following:

- Focus on understanding and treating metastases, since metastases are the ultimate cause of mortality from cancer.
- Emphasize molecular targets rather than specific cancer types.
- Shift research focus to a greater emphasis on prevention and avoidable causes of cancer. This should extend beyond encouraging lifestyle changes to acknowledging and addressing environmental influences that contribute to carcinogenesis.
- Increase emphasis on early detection, particularly biomarkers of carcinogenesis and the presence of cancer; also seek and validate biomarkers of tumor aggressiveness and treatment response.
- Expand dissemination research to support more rapid adoption of prevention, early detection, diagnostic, treatment, and supportive care advances.

Speakers underscored, however, that even in an era of constrained budgets, alternate priorities such as these must be pursued in addition to, and not at the expense of basic science.

Team Science – A New Research Paradigm

The growing complexity of cancer-related research, requiring collaboration among professionals with highly diverse skills and training, is sharply at odds with traditional, single investigator-oriented research approaches. Yet team approaches clearly are the paradigm for achieving progress in translating basic science discoveries into useful interventions that are adopted into medical practice. Many of these collaborations require the participation of disciplines not typically involved in biomedical research – engineering, mathematics, sociology, computer science, and others. Multidisciplinary, interdisciplinary, and transdisciplinary approaches (see definitions, Exhibit 1) to research increasingly are referred to as *team science*. Very large projects of this type, usually to develop a resource to be shared by the research community, often are termed *large-scale science*, or *big science*.

Exhibit 1: Definitions of Team Science Approaches

Multidisciplinary	Coordination of research among different disciplines, e.g., a project involving multiple disciplines that may be a coordinated effort to study a particular cancer issue although individual projects may be discipline-specific. Different disciplines are represented within a research environment or team.
Interdisciplinary	Cooperation of different disciplines on issues that fall between disciplines.
Transdisciplinary	Collaborations in which exchanging information, altering discipline-specific approaches, sharing resources, and integrating different disciplines achieves a common scientific goal. Transdisciplinary refers to integrated (not specific to a discipline) research methods, conceptual development, multiple levels of analysis and science that produces new models and understanding exceeding the sum of the parts.

Source: Cancer Centers Branch, National Cancer Institute. Policies and Guidelines Relating to the Cancer Center Support Grant — Interim, September 2004, p.2. At: http://www3.cancer.gov/cancercenters/guide9_04.pdf (accessed 1/19/05)

Figure 2 outlines some of the key differences between smaller, single investigator-oriented research and large-scale scientific projects. Success in team science depends greatly upon effective and flexible partnerships among governmental organizations, academic medical institutions, community health care providers, pharmaceutical and biotechnology companies, and the public.

In September 2003, recognizing the need to define and embrace this new research paradigm in the context of its own mission and activities, NIH launched its Roadmap for Medical Research.[25] The Roadmap encompasses a series of complex initiatives that are designed to speed the pace of basic life sciences discovery and its translation into practice for the benefit of the public. In developing the Roadmap, NIH focused on goals that no one Institute could or should undertake alone and on areas that would facilitate the work of all Institutes. The initiatives center on three major themes: (1) fostering team science and partnerships and removing barriers to interdisciplinary research; (2) re-engineering the clinical research enterprise, including network integration, harmonization of regulatory requirements, and workforce training; and (3) developing tools and technologies to support basic science discovery, including nanoscience, bioinformatics, standards and reagents for proteomics and metabolomics, genotyping, imaging, and other shared resources.

Figure 2: Selected Characteristics of Small- Versus Large-Scale Science

Conventional Small-Scale Research	Large-Scale	Very Large-Scale Collaborative Research
Smaller, more specific goals	→	Broad goals (encompassing an entire field of inquiry)
Short-term objectives	→	Requires long-range strategic planning
Relatively shorter time frame	→	Often a longer time frame
Lower total cost, higher unit cost	→	Higher total cost, lower unit cost
Hypothesis driven, undefined deliverables	→	Problem directed with well-defined deliverables and endpoints
Small peer review group approval sufficient	→	Acceptance by the field as a whole important
Minimal management structure	→	Larger, more complex management structure
Minimal oversight by funders	→	More oversight by funders
Single principal investigator	→	Multi-investigator and multi-institutional
More dependent on scientists in training	→	More dependent on technical staff
Generally funded by unsolicited investigator-initiated (R01) grants	→	Often funded through solicited cooperative agreements
More discipline-oriented	→	Often interdisciplinary
Takes advantage of infrastructure and technologies generated by large-scale projects	→	Develops scientific research capacity, infrastructure, and technologies
May or may not involve bioinformatics	→	Data and outcome analysis highly dependent on bioinformatics

Note: There is much overlap between the characteristics of small- and large-scale research. These characteristics vary along a continuum that extends from traditional independent small-scale projects through very large, collaborative projects. Any single project may share some characteristics with either of these extremes.
Source: Adapted from Nass SJ and Stillman BW (eds.). *Large-Scale Biomedical Science: Exploring Strategies for Future Research*, Institute of Medicine, The National Academies Press, Washington, DC, 2003.

The complexity, the expense, the technological demands, and the critical role of basic research throughout the biomedical research effort demand a new paradigm for biomedical research, a paradigm of partnerships….Fortunately, this paradigm has begun to take shape.

– Pharmaceutical company executive

Large-scale science initiatives already are proving their worth. Perhaps best known is the Human Genome Project, the results of which are now informing hypothesis-driven research in cancer and myriad other biomedical fields. NCI's Specialized Programs of Research Excellence (SPOREs), which are cancer site-specific, demonstrate the value of bringing together physicians and scientists from diverse disciplines to move basic science discoveries into development.[26,27] Other more recent initiatives hold great promise for advancing translation. For example, the NCI/NIH nanotechnology initiatives, including Nanotechnology Centers of Excellence, will bring the potential of these technologies to bear to address human cancer and other disease conditions. In conjunction with the Foundation for the National Institutes of Health and the Electrical Manufacturers Association, NCI recently launched a Web-accessible Imaging Database Resource Initiative. Joined by eight imaging companies, the goal is to create an accessible and valid computed tomography (CT) database to improve the clinical management of lung cancer. Large-scale bioinformatics and biocomputing initiatives, patient databases, and specimen banks are other examples of team science endeavors that will shape scientific pursuit in the coming years (see also Research Resources, pp. 29-40).

The Structure and Culture of the Research Enterprise

Collaboration between research and medicine is essential for understanding clinical problems. Despite the potential of collaborative research, investigators interested in pursuing it face significant barriers and powerful disincentives. These obstacles, and possible options for overcoming them, have been the subject of considerable discussion and analysis.[28,29,30]

Numerous speakers testifying before the Panel likewise highlighted aspects of the current structure and culture of the cancer research enterprise that impede research translation and team science. Major barriers were identified in the peer review system, institutional reward systems, and fiscal pressures on academic medical centers that discourage collaboration.

A collaboration among medical centers is important for fostering the delivery of important translational research to the community, but also overlooked is the ability within medical centers to have clinical and basic scientists work together.

– Young physician-scientist

Peer Review

NIH provides more money for university research than any other single source[31] and has a well-established system for peer review of grant applications. Other cancer research sponsors have similar, though less complex, systems tailored to their specific research interests and constituencies.

National Institutes of Health

The existing NIH peer review system for extramural investigator-initiated research has been successful for decades as a mechanism for ensuring that proposed studies are scientifically sound and make responsible use of public tax dollars. Approximately 70,000 grant applications are submitted to NIH annually. But as speakers noted, and an Institute of Medicine report[32] points out, this commitment to accountability and to funding proposals that have a high probability of success may create a strong bias toward conservatism. Novel, higher-risk proposals that lack robust preliminary data, have uncertain outcomes, and/or will be led by young investigators without extensive track records of success are likely to be at a disadvantage in a system with limited funds and far more high-quality, competing proposals than can be supported. This tendency may be exacerbated by the tighter budget conditions envisioned for at least the next several years, and the result may be that important research advances will be missed. Similarly, in the private sector, pressure exists to develop agents or devices with the best chance of Food and Drug Administration (FDA) approval and a substantial market.

The conservatism prevalent in peer review suggests that mechanisms are needed through which to fund highly innovative, higher-risk research. For example, the Small Grants for Exploratory Research program at the National Science Foundation (NSF) focuses on preliminary work on untested and novel ideas; the application of new expertise or new approaches to research topics; work related to urgently needed data access, facilities, or resources; and quick-response research related to unanticipated events (e.g., natural disasters).[33] The Department of Defense (DoD) has a long-established Defense Advanced Research Projects Agency, which specifically seeks out high-risk research with the full

expectation both that many of the projects will fail and that enough breakthroughs will be achieved to justify the total investment. NIH is piloting a similar program (Pioneer Awards) as part of the Roadmap initiative.

NCI currently sponsors QuickTrials for Novel Cancer Therapies: Exploratory Grants (early translation Phase I/II trials of novel agents or approaches for inhibiting tumor growth directly or impacting the tumor microenvironment). Some early pilot studies are supported through the SPOREs, and a number of cancer center consortia have been developed to study new agents. Other NIH Institutes may have similar small programs. All of the Institutes fund some innovative proposals through their Small Business Innovation Research and Small Business Technology Transfer Research programs. Even in the aggregate, however, these initiatives do not provide adequate opportunity for investigators wishing to pursue higher-risk, innovative studies. A speaker from industry suggested that a portion of funding currently set aside for Research Project Grants (R01s) should be redirected to a quick-response review process with resources managed by each NIH Institute Director to "invest" as a venture capital fund for promising research that otherwise would be ignored in the R01 process. The Directors would be accountable annually to Congress for the funding choices in that portfolio.

We must have more open peer review of grant applications because now, the system seems to insist that people who study mice act as judges of scientists who study people.

– Physician-scientist

In response to recommendations contained in a 1997 review of its clinical research program,[34] NIH restructured its peer review groups so that patient-oriented grant applications would be evaluated by study sections in which at least half of the grant applications involve human research and revised the number, organization, and scientific boundaries of the study sections.[35] But an initial analysis of application scoring under the new study sections, as well as another recently published analysis[36] indicates that research involving human subjects still is less likely to receive funding through the NIH peer review system compared with laboratory research, particularly if the research is categorized as addressing mechanisms of disease, interventions, or clinical trials. This information is consistent with speaker testimony that translational research applications, particularly large-scale, multi-institutional projects, prevention research, and applied research still do not fit well into the existing study section structure and therefore are likely to be disadvantaged in the review process. Some speakers suggested that translational and clinical research grant applications may be further disadvantaged in the current system because they often still are reviewed by basic scientists and others who do not fully understand translational science. Consistent with this pattern, clinical research grant applications submitted to NCI during fiscal years (FY) 2003 and 2004 were funded at substantially lower rates than applications for basic science grants.[37] However, with leadership from a Special Advisor on Clinical Research Review and input from consultants and advisory groups, NIH is further analyzing and modifying the membership of study sections to include more experienced clinical researchers. A larger

pool of clinically-oriented researchers is needed to effect these changes, and nominees are being actively solicited from clinical professional societies. One of the two new study sections that will review clinical applications almost exclusively focuses on clinical oncology. Future analyses will assess the impact of these changes.

…the value systems in academia – which are teaching, community service, and unfettered individual research – really do not reward the detailed, time-consuming, process-oriented research that's required for translation.

– Translational researcher

In October 2004, NIH updated its peer review criteria to better accommodate interdisciplinary, translational, and clinical projects. Previously, the section of the criteria that instructs reviewers to assess the potential significance of the project made no mention of clinical research or clinical benefit. The updated version now asks reviewers to consider whether "scientific knowledge or clinical practice" will be advanced by the proposed project and whether the research environment employs "useful collaborative arrangements."[38]

The newly formed NIH Peer Review Advisory Committee[39] (PRAC, which replaces the Center for Scientific Review Advisory Council and the Peer Review Oversight Group) will be considering several key issues in the coming months. For example, the length of the review cycle for extramural grants (currently nine months), has been identified as a funding barrier, particularly for young investigators, whose first applications have approximately a one in four chance of being funded. Resubmission and re-review can bring the total elapsed time from initial submission to two years or more, and the grant still may not be funded. In 2001, the most recent year for which data are available, only four percent of R01s were awarded to applicants younger than age 35.[40] The concern is that these early experiences may be sufficiently discouraging that these talented researchers will move to industry, turn to other research areas, or leave science altogether.

PRAC also may examine how best to secure and retain high quality reviewers on peer review committees. Difficulties stem from the long term of service required (usually four years), the low overall success rate of meritorious applications due to limited funding, the daily pressures on reviewers to conduct their own research, and in the case of clinical researchers, to fulfill their patient care responsibilities.[41] In addition, PRAC will consider options for incorporating new information technologies into the peer review system. NIH has decided to allow electronic grant submissions beginning in 2005.

Department of Defense

Since 1992, the Congressionally Directed Medical Research Programs (CDMRP) within the U.S. Army Medical Research and Materiel Command, has administered DoD's targeted research programs in breast, ovarian, and prostate cancers, and chronic myelogenous leukemia. Based on recommendations contained in an Institute of Medicine report[42] commissioned in FY1993, CDMRP devised a two-tiered review strategy consisting of scientific peer review and programmatic review. The first tier review is conducted by

external scientific, clinical, and advocate/consumer reviewers, and the second tier is conducted by an advisory committee composed of leading scientists, practicing clinicians, and consumers.

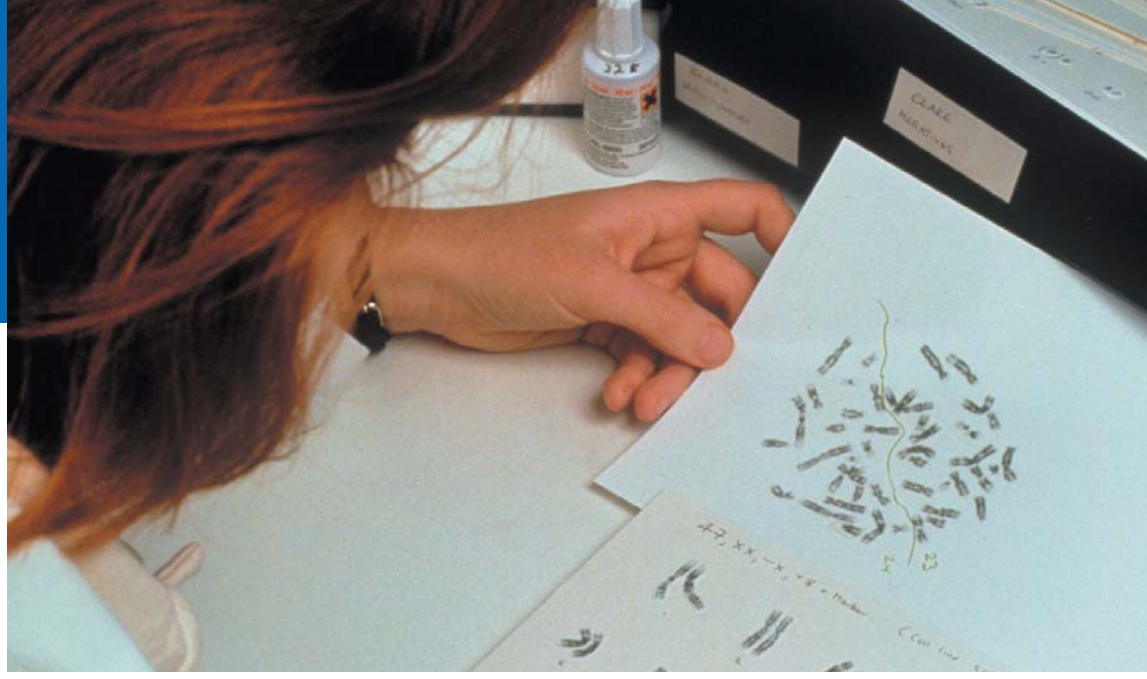
The system was designed to ensure that the research portfolio reflects not only the best science but the most programmatically relevant studies (i.e., those most relevant to the disease and consistent with the goals of that year's program). Funding opportunities offered often change over the course of a CDMRP program's lifetime. The earmarked, Congressionally funded programs (which are not part of the DoD's regular programmatic budget) are targeted, annual, and limited in nature, concentrating on high-risk/high-gain areas, underfunded research areas, or where gaps in funding exist. There is particular emphasis on facilitating biotechnology/academic partnerships to accelerate research translation into new therapeutics and chemopreventives. A DoD representative credits the success of the review process to, among other factors: (1) the program's willingness to broaden the expertise on peer review panels, including scientists from other disciplines (to evaluate multidisciplinary studies), consumers, and clinicians, and (2) maintaining a clear focus on research that meets the needs of people affected by the disease.[43]

Peer Review by Nonprofit Cancer Research Sponsors

Numerous nonprofit cancer advocacy organizations, health service organizations, and foundations fund cancer research. Each has devised a peer review system suited to its research objectives, the volume of applications received, and other factors. All call on experts in the field of inquiry to review proposals, but the range of expertise solicited may vary considerably, as may the inclusion of cancer survivors, who may provide comment on the relevance of proposals to patient needs only, or may be full participants in the peer review process. Some systems have already moved to electronic application submissions and use electronic systems to send applications to reviewers and to receive and compile application scores.

Institutional Reward Systems and Fiscal Pressures

In academic research settings, including cancer centers, investigators are rewarded for individual achievements, not for team efforts. In NIH-funded cancer research, the primary mechanism of support is the R01. R01s, and similarly structured grants in the public and nonprofit sectors, are awarded to an institution via the principal investigator of a study. Typically, young scientists work in the laboratories or clinics of senior researchers (the principal investigators) until they prove themselves able to win grants of their own. Once they are able to do so, young investigators then can set up their own laboratories or clinics and begin establishing independent careers. Demonstrated ability to bring grant revenue into an institution is a major factor in promotion, compensation, and tenure decisions; in allocation of laboratory or clinic space and staffing; and in an individual's prestige within an institution and the larger scientific community. Similarly, investigators who are able to attract lucrative pharmaceutical/biotechnology company contracts to conduct clinical trials for agents being developed by industry are well rewarded under the current system.[44]



…we over-reward individual achievement and under-reward group achievement. While academic centers certainly are guilty of this, I'd argue that this is just a pale reflection of our society, which does the same thing.

– Cancer center director

This reward system strongly discourages the collaborative, multidisciplinary efforts required in translation-oriented and other team research because the principal investigator designation and grant revenue typically go only to a single individual and institution. Activities are underway to address this issue. The Research Business Models (RBM) Subcommittee of the Committee on Science is part of the Cabinet-level National Science and Technology Council.[45] The RBM subcommittee is charged with facilitating a coordinated effort across Federal agencies to address policy implications arising from the changing nature of research, and examining the effects of these changes on business models for the conduct of federally sponsored research. The Committee on Science recently concluded that team research would be enhanced if all Federal agencies allowed more than one principal investigator to be designated on individual research awards. This finding led to a January 2005 directive from the Director of the Office of Science and Technology Policy in the Executive Office of the President approving the practice.[46] Each agency is responsible for developing its own plan for implementing the policy, and input from all Federal research funding agencies has been requested to identify potential problems related to the policy. This is an important step, but it still will be up to academic research centers to decide how attribution for work will be assigned and how team-oriented work will be credited to individual investigators relative to promotion and tenure determinations.

Although mechanisms exist to fund team research (e.g., NIH P01 Program Project, P30 Center, and P50 SPORE grants; U54 Cooperative Agreements), the resources allocated to these projects are a small fraction of the funding for individual project grants. Speakers repeatedly emphasized the need for additional mechanisms to facilitate partnerships between basic and clinical scientists. Some evidence suggests that a shift toward greater emphasis on collaboration may be occurring, albeit slowly. Examples include requirements in specific grant applications to demonstrate collaborative effort in order to receive continued funding, and substantial awards for new collaborations such as the Broad Institute in Boston.[47]

The culture that currently exists in many academic medical centers hinders collaboration between the clinic and the laboratory. The structure often favors departmental versus interdisciplinary programs.

– Cancer center director

Speakers testified that the "silo" orientation prevalent in many academic departments poses a further barrier to collaboration, limiting multidisciplinary collaboration even within a single institution. Currently, little communication exists among researchers in different disciplines, who have their own lexicon and methods, and tend to read narrowly within their own fields. As a result, though all may be involved in cancer research, epidemiologists, for example, are likely to know relatively little about tumor biology; head and neck cancer specialists little about prostate cancer; or surgical oncologists little about psychosocial issues in cancer. These patterns impede efforts to establish transdisciplinary linkages and develop collaborative studies. Speakers suggested that departmental leadership at academic medical centers, cancer centers, and other biomedical research institutes must become actively involved in fostering cross-communication among scientists at their institutions to counter these aspects of the research culture.

Unfortunately, this disease- and department-oriented organization of academic institutions is mirrored in the organization of scientific journals, funding agencies, and professional societies. Having studies published in highly respected medical journals is another key determinant of an individual scientist's prestige and professional success. The principal investigator typically is listed first if there is more than one contributor to a published paper, and the study is forever attributed in the literature (and by the media) principally to the first author. In some instances, the first author listed is the one who did most of the empirical work (e.g., data analysis, conceptual contributions, writing the first draft), and the author listed last is the intellectual force behind the project, the laboratory or project director, or primary recipient of the project's funding.[48] These conventions, therefore, create another powerful disincentive to participate in team science. Moreover, translation-oriented research is not the principal focus of the most highly respected journals publishing cancer-related research, and papers reporting translational studies may be difficult to get published.

At the institutional financial level, academic medical and cancer centers may discourage collaborative translational and clinical research that will reduce the grant revenue component of the center's bottom line. In addition, institutions participating in multisite studies may be unable to recover appropriate indirect costs. The negative bias this situation engenders is compounded by the fact that translational and clinical physician-scientists tend to see fewer patients than other physicians, and therefore generate less patient care revenue – a significant consideration in the current fiscal climate in which medical institutions must survive. These researchers also are less likely than basic scientists to have "protected time" for research, wherein some or all of their salary is compensated by a grant or another outside source. Further, few academic medical centers and cancer centers view translational research as an added value their institutions can offer or promote to attract more patients.

Several speakers stated emphatically that these basic structures, practices, and reward systems of academic medicine that are central to the current research culture must be changed to remove obstacles to collaborative, multi- and transdisciplinary research. Making these changes will require the cooperation and consensus of university and cancer center leadership, including university Presidents, Deans, Department Chairs, and cancer center Chief Executive Officers and Directors. These considerations notwithstanding, however, speakers also remarked that both institutions and individual investigators will become more open to collaboration if team participation is required to receive funding. They suggested that public, nonprofit, and industry research sponsors should establish collaboration as a funding criterion when it is likely to increase the ultimate benefit of the proposed project.

RECOMMENDATIONS

Team Science and the Culture of Research

1. The existing culture of cancer research must be influenced to place more value on translational and clinical research. To effect this culture change, a task force representing key stakeholders in academic research should be convened to examine and modify existing reward systems (e.g., compensation, promotion/tenure, space and resource allocation, prestige) to encourage collaborative research and ensure that all contributors (including but not limited to pathologists, radiologists, and research nurses) benefit from participating in these research activities.

2. Governmental and private research sponsors must place greater emphasis on and substantially increase funding for clinical research and human tissue research. Funding mechanisms should promote collaborative science and include greater support through the R01 mechanism.

3. The National Institutes of Health and other research sponsors should facilitate collaboration in large research projects by requiring team approaches to the extent appropriate to the science and designating a percentage of project funding for such efforts.

4. To stimulate team science, the National Institutes of Health and other research sponsors should rapidly devise implementation plans for permitting co-principal investigators who share grant funding and attribution for these efforts, consistent with the January 2005 directive from the Director of the Office of Science and Technology Policy.

The existing translational research infrastructure is inadequate to support the work that must be done to develop new knowledge into beneficial interventions and deliver them in the community. Speakers identified major barriers to progress related to the current organization of the clinical trials system, workforce issues, and a lack of key research resources.

Part III Infrastructure Required for Research Translation

The Clinical Trials System

The national cancer clinical trials system for new drugs and devices has vital public, private, and nonprofit components (Table 1). Many meeting participants discussed the current clinical trials system in the United States and suggested changes to simplify the system and make it more cohesive, efficient, and effective without compromising the safety of study participants. According to one speaker, for any clinical trials system to be successful, it must: (1) have a mandate and a philosophy that embraces clinical trial enrollment as a central precept, (2) offer provider incentives and recognition associated with doing the extra work involved in trial participation, (3) have stable resources, (4) have a structure that provides a broad base of opportunity for participation by community providers and patients, and perhaps, (5) employ navigators to help patients through the system.

Clinical Research Trends

Of every 5,000 potential medicines screened, only five on average are tested in clinical trials for any medical indication, and only one of the five is eventually approved for use by patients.[49] In 2003, an estimated 350 new agents were in development for cancer or cancer-related indications.[50] Yet despite increasing research and development investments, the annual number of new drug approvals is declining, a major source of frustration among public and private sector researchers and policymakers. Between 2000 and 2003, only five new anticancer agents were approved by the FDA for the treatment of 21 oncologic indications. Projected through 2004, this represents a 68 percent reduction in new drug approvals and a 37 percent reduction in approved claims for new cancer indications compared with the preceding five years (1995 to 1999).[51]

Developers use a variety of tools to characterize and assess the performance of a candidate product… animal toxicology, animal efficacy models, various biomarkers, computer modeling, and human safety and efficacy testing….Some of these tools…have changed little over the past 50 years – and this at a time when knowledge is exploding in other fields. Others, such as clinical trial design and analysis or the development of surrogate endpoints, are pursued in an *ad hoc* manner and suffer from the lack of an academic base. Given its importance to people's health and its economic impact, the lack of technological focus on product development is actually astounding.

– Regulatory official

Table 1: Major Components of the U.S. Cancer Clinical Trials System

Sponsorship	Implementation	Regulation
Public Sector	Academic Medical Centers	Food and Drug Administration (new drug/device approval; private sector IRB regulations)
National Cancer Institute	Cancer Centers	
Other NIH Institutes	NIH Intramural Program	Office of Human Research Protections, DHHS
Centers for Disease Control and Prevention	Military and Veterans Hospital Systems	
Department of Defense	Managed Care Organizations	Centers for Medicare and Medicaid Services (reimbursement)
Department of Veterans Affairs	Other Medical Centers and Hospitals (for-profit, nonprofit)	
Private Sector	Physician Group Practices	
Pharmaceutical Companies	Solo Practitioners	
Biotechnology Companies	Contract Research Organizations	
Private Research Institutes		
Nonprofit Sector		
Nonprofit Health Plans		
Advocacy Organizations		
Foundations		

Legend: IRB – Institutional Review Boards, DHHS – Department of Health and Human Services

As speakers noted, it often does not become clear that a new compound is of little or no benefit – or is no better than existing therapies – until large Phase III trials are well underway. By this time, the majority of development costs have been incurred. Moreover, cancer drugs tend to have a higher late trial failure rate than new drugs for other diseases – more than 50 percent.[52] Speakers from the public, private, and nonprofit research sectors agreed that ways must be found to make the clinical trials system more agile and better able to identify early the chemical and biological compounds with clear activity against tumors or critical genetic and molecular pathways associated with carcinogenesis, tumor progression, or metastasis.

In private industry, "experimental medicine" is a relatively recent development that is being used to help companies select agents to move forward into large clinical trials.[53] With a goal of reducing the massive costs of drug development and speeding new treatments to the marketplace, drug researchers are conducting limited, quick tests on small groups of people to gauge an agent's potential before committing to the larger, far more expensive trials. At such early stages of development, this testing traditionally has been done in animals. These small trials, which must be FDA- and Institutional Review Boards-approved, are Phase I trials in that they are assessing a drug's safety and appropriate dosage, but they also typically include more testing and imaging than usually is included in traditional Phase I trials. For example, researchers are taking advantage of functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) to ensure that drugs are reaching their targets in the body and to detect treatment response weeks before other indicators, such as tumor shrinkage, might be evident. In this respect, these Phase I trials, which are not intended to supplant all preclinical animal studies, are gauging efficacy rather than just safety and dosage. Because of the additional imaging and other costs, these trials can be as much as 10 times more expensive than a traditional Phase I trial, but

researchers are optimistic that these investments will more than pay for themselves if they enable the company to avoid a failed Phase III trial. Thus far, no risks exceeding those in other Phase I trials have been reported.

A speaker noted that private industry now sponsors more biomedical research than the Federal Government,[54] and others expressed concern about the influence of industry's profit orientation on decisions about which agents to develop and test. Moreover, recent moves to compel publication of inconclusive and negative clinical trial results may cause companies to hesitate to test a promising agent for all of its possible indications, and new cancer prevention and treatment advances could be missed (see also discussion, pp. 93-95). Reduced clinical testing for this reason also poses a potential financial concern for many academic centers that depend heavily on industry contracts to support their clinical research programs, particularly since industry payments per patient enrolled far exceed payments by government research sponsors.

In addition, as patient care reimbursements shrink, revenue that had been used to subsidize research costs has been lost. To help replace these funds, a speaker suggested that academic institutions negotiate a special overhead rate with public and private research sponsors to cover the additional costs of conducting clinical trials.

A speaker emphasized the importance of persistence in drug development, noting that the trends described above may cause investigators to abandon a potentially valuable compound that does not initially show antitumor activity. The discovery and development of paclitaxel, for example, took approximately 30 years.[55] Had researchers given up trying to find an effective drug formulation and methods of harvesting and processing the relatively rare tree bark from which it is derived, patients now would not have the benefit of taxanes, the related class of anticancer agents that has since been developed. The speaker also asserted that the future of new therapies for cancer is unlikely to be found in single agents, but from combination chemotherapies, and chemotherapy/biologics combinations, with or without radiation therapy. In the drug discovery process, patent and intellectual property issues remain formidable barriers to sharing unapproved agents for testing in combination trials (see additional discussion, pp. 46-54). Further, speakers testified that as the private sector becomes increasingly risk-averse, leadership and support necessary to facilitate development must come from the public sector, either through public-private Cooperative Research and Development Agreements (CRADAs), as was the case in developing paclitaxel, Clinical Trial Agreements, or other mechanisms.

Clinical Trials System Reorganization and Integration

In 1997, a panel commissioned by the NIH Director reported its findings and recommendations for remedying problems in the clinical trials system that had been recognized for years, but which had become particularly severe due to managed care and new restrictions on the Federal budget at that time.[56] At the same time, concerns about fragmentation, duplication, and other problems in NCI clinical trials prompted a similar review (the Armitage Report)[57] of the Institute's clinical trials system. The two reports reached many similar conclusions and highlighted system complexities contributing to inefficiencies, an eroded ability to generate new ideas to reduce the cancer burden, and financial strains, but also noted the

opportunities in clinical research offered by progress in cancer biology, informatics, and other areas. Among the recommendations were calls for standardized trial data collection that gathers only the minimum necessary information; interoperable informatics systems to facilitate investigators' ability to prioritize trials; increased funding for NCI's clinical research Cooperative Groups; and greater collaboration at all levels – between investigators and physicians, industry and academia, academia and NCI, and NCI and industry. Other recommendations addressed the need for increased training opportunities for new and mid-career clinical investigators, the need for public education about the value of clinical trials, and the importance of involving advocates and the communities in which research is conducted in the clinical trial decisionmaking process (see also Community Involvement, pp. 79-82).

The challenge over these next decades is to make our progress in the clinic look more like our progress in the laboratory by building a stronger, wider bridge between the laboratory and the clinic.

– Academic medical center translational researcher

Steps have been taken toward implementing a number of the reports' recommendations. Major new collaborations and partnerships have been established, informatics platforms are under development, and initiatives have been launched to address identified issues concerning barriers faced by young clinical investigators (see also sections below, Bioinformatics, the Translation Workforce). In addition, NCI established a Clinical Trials Support Unit (CTSU), a central, Web-based service that lists approximately 60 Cooperative Group trials and makes it possible for any credentialed investigator to enter patients on those trials. To date, however, the CTSU has not been utilized as fully as anticipated for reasons not yet identified.[58]

In 2004, the National Cancer Advisory Board (NCAB) convened a Clinical Trials Working Group (CTWG) to review all of NCI's trials, including those conducted through the Community Clinical Oncology Programs (CCOPs), Cooperative Groups, cancer centers, SPOREs, single investigator grants (R01), program project grants (P01), and Phase I and II clinical trials contractors.[59] Continued fragmentation and duplication of effort, limited communication between investigators working in different clinical trials programs, and continuing advances in information and research technologies persuaded NCI that new efforts are needed to better integrate the program across six key issues: coordination across different funding mechanisms, regulatory issues, core research services, patient accrual, standardization and infrastructure, and prioritization. In early 2005, the CTWG posted more than two dozen questions pertaining to these areas on its Web site[60] to gather input from the public and private cancer research, care, and advocacy communities. Final recommendations informed by the more than 2,220 responses received are scheduled to be presented to the NCAB in June 2005.[61]

As part of the NIH Roadmap for Medical Research, a National Electronic Clinical Trials and Research Network (NECTAR)[62] will be established with the goal of linking up to 100,000 physicians by FY2009. The database, which will be integrated with the caBIG bioinformatics platform (see below, p. 32), is intended to recapture the clinical research skills possessed by many physicians who have left academia for community practices, and to maximize connectivity among existing and newly created clinical research networks. NECTAR also will aid in standardizing patient data collection and storage procedures to facilitate data sharing.

NIH also is examining ways to restructure and streamline its Intramural Clinical Research Program (ICRP). A Director's Blue Ribbon Panel on the Future of Intramural Clinical Research recently made recommendations including several aimed at removing regulatory and other barriers to conducting patient-oriented research at all NIH Institutes and Centers and creating translational, multidisciplinary intramural and extramural partnerships among General Clinical Research Centers, the Children's Clinical Research Centers, NIH-funded extramural networks, the NIH Clinical Research Center, and the ICRP. In addition, the recommendations urge NIH to continue to emphasize the study of rare diseases at the Clinical Research Center and to promote a strong emphasis on pathophysiology and novel therapeutics, combining the expertise of several Institutes and Centers.[63]

In addition to Federal efforts to redesign the clinical trials system, a joint initiative to augment the existing trials system has been launched by the American Association of Cancer Institutes, the American Association for Cancer Research, and the American Society of Clinical Oncology.[64] The goal is to develop a new approach to conceiving, developing, and implementing smaller, "smarter" trials that will take advantage of emerging technologies and use existing human resources more productively to expedite research translation.

Another clinical research reorganization proposal of a more sweeping nature has been put forward in the literature, suggesting that the three-year-old Institute of Medicine Clinical Research Roundtable could serve in part as a model for a new National Clinical Research Enterprise (NCRE) that includes all public, private, and nonprofit stakeholders and has the capacity to break current bottlenecks that slow translation.[65] As envisioned, stakeholders include researchers, research sponsors, regulators, health care consumers, health care purchasers, physicians, and non-physician health care professionals. The goal of the NCRE would be to overcome a major rate-limiting step to research translation by transforming what its proponents see as a fragmented cottage industry into a cohesive and coherent national clinical trials system. Funding for the NCRE (including infrastructure improvements, clinical research training programs, research funding, and other functions) would come from a new, direct and/or in-kind contribution by all stakeholders totaling 0.25 percent of the total current U.S. health care budget, similar to Canada's seemingly successful one percent commitment to reinvigorate its biomedical research efforts.[66] While numerous issues would remain to be resolved, proponents of the NCRE believe that stakeholder participation would be easier to achieve than might be anticipated because of the widespread dissatisfaction with the current clinical research system.

The Research Translation Workforce

Compared with the basic science workforce, there is a dearth of translational and clinical researchers. This workforce imbalance is a major factor contributing to the infrastructural bottleneck that now limits the translation of cancer-related discoveries. Translational researchers must be trained in both basic and clinical science, and therefore often require a longer training period than does an individual pursuing either basic or clinical science alone. These physician-scientists (often M.D./Ph.D.s) are in short supply and are dwindling in number (down 22 percent between 1983 and 1998[67] and totaling only two percent of the physician workforce nationwide[68]). Few training programs exist that are designed specifically to develop this special mix of skills and knowledge.

One speaker observed that basic scientists in academia have limited understanding of clinical medicine; physicians have limited understanding of basic science; and both groups have a limited understanding of the translation process as it occurs in industry.[69] Testimony was presented on the Health Sciences and Technology (HST) program, an innovative academic collaboration between Harvard University and the Massachusetts Institute of Technology established in the 1970s. Its objective is to train and nurture postdoctoral individuals who learn to work effectively in multidisciplinary environments through hands-on experiences that integrate science and technology across each step of the translation process. The speaker testified to the transformative nature of this learning experience, noting that program participants tend to retain this integrative approach to scientific problem-solving throughout their careers. A recent Institute of Medicine report[70] describes a number of other training programs that likewise are aimed at increasing the cadre of researchers with the skills and perspective to conduct interdisciplinary research. Speakers also underscored the importance of beginning translational and team science training earlier than the postdoctoral level and cited the need for curriculum development in these areas.

The numbers of people moving into the M.D./Ph.D. program – it's a long, burdensome program – are few enough….I had the tragedy of seeing M.D./Ph.D. students leave academic medical centers to do other things, not because they were passionate about other things, but because of the fear that without grants – and quickly – given all the preparation they had had, they actually might be without a job.

– Cancer center director

To develop the expertise to become productive independent investigators, both young scientists and more senior basic science researchers who would like to do translation-related research need appropriate mentors within the academic medical setting and "protected time" (i.e., financial support for a portion of their salaries that relieves them of revenue-generating activities so that they can conduct research projects). A considerable number of career development programs, many funded through NCI/NIH, are designed to provide protected time for basic scientists, and some academic institutions may provide protected time to basic researchers. Far fewer such opportunities exist for translational and clinical researchers (see Table 2), and resources are limited. NCI's SPOREs are required to have career development programs designed to increase the cadre of basic and clinical researchers who conduct translational research. Though not cancer-specific, NIH plans to address this issue through one of its Roadmap initiatives, Exploratory Centers for Interdisciplinary Research and Training for a New Interdisciplinary Research Workforce.[71] In addition, NIH plans an inventory and evaluation of clinical research training programs in the United States to determine their extent and scope and whether data are available on trainee outcomes. The study will help identify best practices for clinical research training programs to provide models for the future and identify gaps and opportunities for new programs.[72]

...the administrators in research institutions squeeze the time allocations for research and force investigators to identify sources of income to help pay their salaries...

– Nonprofit cancer organization executive

Some academic institutions offer prizes designed to recognize and encourage young investigators. For example, the Paul Marks Prize for Cancer Research, established by the Memorial Sloan-Kettering Cancer Center in 2001, recognizes young investigators who have contributed to basic or clinical cancer research. The prize is awarded to up to three investigators every other year. Nominees must be age 45 or younger at the time of the submission deadline, and winners share a cash award of $150,000. Though important, awards such as these do not solve the larger problems of the need for protected research time and greater funding for investigators involved in translation activities.

Table 2: Examples of Training Opportunities for Translational and Clinical Cancer Researchers

NIH	• Exploratory Centers for Interdisciplinary Research and Training for a New Interdisciplinary Research Workforce (planned) • Multidisciplinary Clinical Research Career Development Program • National Clinical Research Associates • Predoctoral Clinical Research Training Programs
NCI	• Clinical Scientists Patient-Oriented Research (K12, K23, K22, K24) for scientists at various stages of their careers • Prevention, Control, Behavioral, and Population Scientists (R25T, K07, K22, K05) • Transdisciplinary Sciences – Cancer Education and Career Development Program (R25T); Mentored Quantitative Research Career Development Award (K25) • Continuing Umbrella of Research Experiences – a program of research training opportunities ranging from high school through junior investigator. Focuses on increasing the pool of underrepresented minorities in research. Not limited to translational or clinical research. • Clinical Research Curriculum Award • Paul Calabresi Award for Clinical Oncology (K12) • Cancer Prevention Fellowships
FDA/NCI	• Cancer Fellowship Training Program – to develop a cadre of physicians and scientists expert in clinical research, the translation of research advances into clinical practice, and the regulatory process. Will enable NCI researchers to train at the FDA, including training as product reviewers.
DoD	*(associated with disease-specific research programs)* • Career Development and New Investigator Awards • Pre-and Postdoctoral Training Awards • Partnerships for faculty and staff training at Historically Black Colleges and Universities • Multidisciplinary Postdoctoral Training Award • Protected time funding to develop physician-scientists • Undergraduate Summer Training Program Award • National Health Research Service Awards (requires service time payback)
VA	• Medical Research Service Awards – Merit Review, Career Development, and Merit Review Entry Grants (basic and clinical science) • Health Services Research and Development Awards – Career Development, Investigator-initiated Research, Merit Review Entry, and Nursing Research Initiative Program • Research Enhancement Award Program grants (similar to NIH P01)
Academic Medical Centers/Cancer Centers	• Morehouse School of Medicine Clinical Research Career Development Program (Master of Science in Clinical Research) • M. D. Anderson Cancer Center Clinical Cancer Research Doctoral program • Harvard-MIT Health Sciences and Technology program
Nonprofit, Foundation and Professional Association Awards	• Breast Cancer Research Foundation/American Society of Clinical Oncology Advanced Clinical Research Award • ASCO Career Development and Young Investigator Awards • International Union Against Cancer Translational Research and Technology Transfer Fellowships – various, in partnership with NCI, American Cancer Society, and industry sponsors • Lance Armstrong Foundation – awards for young investigators in behavioral sciences

…academic medical centers are in a unique position to be at the forefront of translating research into the community, but we can't do that unless we have the physician-scientists as well as the basic scientists involved, and that means training them – not [only]…as a resident, but also from the levels of college and medical school – and setting up programs so that young, talented students have an idea of what it's like to go into academic medical [centers] and how clinical trials are conducted, and that becomes part of the culture of and incorporated into the curriculum of medical schools.

– Young physician-scientist

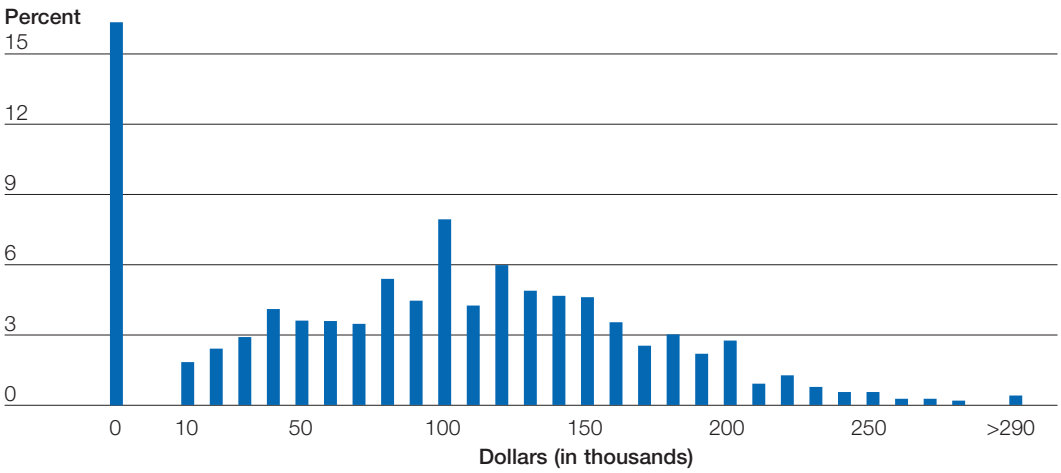
As indicated above, funding for translational and clinical cancer research is limited compared with support for basic research. Without a reasonably robust funding stream to support a career in translational research, many talented young investigators are choosing careers in other scientific areas. Most have large educational debts to repay and many have families to support. Figure 3 illustrates typical levels of debt for new medical school graduates; average debt level is $99,000, but close to five percent graduate more than $200,000 in debt, and only 17 percent graduate debt-free.[73] Some student loan repayment programs exist, but are not cancer-specific. For example, NIH offers five loan repayment programs (LRPs): the Clinical Research LRP, Clinical Research for Individuals from Disadvantaged Backgrounds LRP, Contraception and Infertility Research LRP, Health Disparities LRP, and a Pediatric Research LRP. Each can repay up to $35,000 of qualified educational debt for health professionals with doctoral-level degrees who are pursuing research careers in any of these areas (www.lrp.nih.gov). Other LRPs may exist at the state level or through philanthropic sponsors. For example, the Damon Runyon Cancer Research Foundation offers clinical investigator awards to five young physicians each year to encourage them to select careers in clinical research. The $1 million awards include up to $100,000 in medical school debt repayment, as well as an annual salary, research funding, and a stipend for the recipient's mentor.[74]

In 2004, the NIH Director's Blue Ribbon Panel on the Future of the Intramural Clinical Research Program recommended establishing new training and career pathways in patient-oriented research with necessary infrastructure and mentoring. Further, the panel called for the development of a premier postdoctoral fellowship program in translational research, an advanced clinical research training program for extramural academic researchers, and initiatives to recruit and retain innovative patient-oriented investigators with benefits and salaries that are competitive with those in academic health centers.[75]

If we [want to] have translational cancer research, which is so important in addressing the reduction of [the cancer] burden, and it's economically impossible, we have a real problem on our hands. As a career, it cannot now compete with income in private practice with respect to paying back the bank and supporting a young family. Many have written on this topic, but the NCI Cancer Centers are seeing a national depletion now of those willing and wanting to dedicate their lives to translational research [because they] simply cannot afford it.

– Cancer center director

Figure 3: Educational Debt of Medical School Graduates in 2003



Source: Association of American Medical Colleges (AAMC) Graduation Questionnaire, 2003.

Speakers suggested, however, that both young and more seasoned investigators are leaving the extramural academic setting for private sector biotechnology and pharmaceutical firms to seek a more promising career track and better compensation. Speakers also emphasized the need for greater efforts to attract and retain young scientists from populations currently underrepresented in translation-oriented cancer research and all of the biomedical sciences.

Several presenters noted the limited funding available for health services research. Some in the scientific community view health services research as "soft science," which historically has conferred less prestige and received less support. Major sponsors of health services research include the Agency for Healthcare Research and Quality (AHRQ), the Centers for Disease Control and Prevention (CDC), the Veterans Administration (VA), Centers for Medicare and Medicaid Services (CMS), foundations, and nonprofit advocacy and support organizations. Health services research is a critical but underappreciated aspect of translation that studies how best to disseminate and encourage the adoption of research advances and new interventions by health professionals and the public. Unless these investigators have a reasonable expectation of a stable career in cancer-related health services research, they too will pursue other areas of study. Increased support for health services researchers may depend on their greater inclusion in multi-and transdisciplinary projects.

Other personnel also are essential to translation success. They include research nurses, oncology nurses, pathologists, radiologists, statisticians, data managers, sociologists, oncology social workers and other patient support personnel, health communication specialists, community primary and ancillary care providers, and others whose contributions across the translation continuum are critical if cancer research advances are to reach and benefit the public. Many of these personnel are too few in number to meet the need for their skills, and in some cases, their services may not be reimbursable, creating a barrier to their participation in research-related activities.

To develop a cadre of cross-trained scientists in research and research-related regulatory review, policies, and regulations, the NCI-FDA Interagency Oncology Task Force recently established a joint fellowship program.[76] It is anticipated that these Fellows, trained in preclinical oncology research, cancer prevention, clinical trials methodology, medical product, and other regulatory research-related review also will learn to build awareness of regulatory requirements into the early stages of medical product development and provide a bridge across the development and review processes. Individuals trained through the program will bring valuable skills to academia, the pharmaceutical and biotechnology industries, and government research sponsors.

Research Resources

Numerous public initiatives have been implemented to expand and refine the research resources that support basic science discovery. For example, the International HapMap Consortium is generating a human haplotype map based on the genomes of four ethnic populations to better enable researchers to determine the relationship of genes to common diseases or drug reactions.[77] NCI and other components of NIH support diverse basic science initiatives, such as the Cancer Genome Anatomy Project, the Mouse Models of Human Cancer Consortium, a genotyping center for single nucleotide polymorphisms (SNPs), a chemical genomics initiative, oncologic imaging resource development, and natural products collection programs, to name but a few. In this series of meetings, the Panel heard testimony concerning a proposed Human Cancer Genome Project, designed to identify all of the genes that are important in human cancers. It is crucial that the basic science infrastructure is maintained and strengthened, since without continued basic science advances, there will be little to translate into improved cancer prevention and care interventions.

Funding for shared resources supporting translational activities, however, has been far less robust. Unfortunately, speakers noted, support for these infrastructure needs (e.g., databases, repositories) is difficult to obtain from private and nonprofit donors because the “reward” (e.g., discovering new knowledge, a new drug, or other invention) may not be evident for some time, or easily attributable to a specific donor. Simply put, donations to enhance research infrastructure, though essential, are not attractive to many donors. Public funds, therefore, have been the mainstay of support for translational research infrastructure.

...we need manufacturing facilities to produce the newly conceived and some of the existing clinical-grade reagents, because now the demands and the associated delays to obtain these reagents are formidable – at least one to three years.

– Physician-scientist

Existing Translation-Oriented Programs

The NCI program, Rapid Access to Intervention Development (RAID), was cited by speakers as a valuable platform for advancing translation-oriented research, but they indicated that the program is underfunded and its facilities are now obsolete, particularly for testing and evaluating new biologics. Retooled and more strongly supported, they stated, RAID could be a more important resource for early translational efforts. A number of academic medical centers are in the process of developing RAID-like programs. NCI also funds a RAID-like program for imaging technology development.

As part of the NIH Roadmap initiatives, a RAID-like program will be developed to foster translation across all NIH Institutes and Centers. In addition, planning grants have been made available for the development of Regional Translational Research Centers.[78] Once operational, these centers will provide a broad menu of clinical research expertise, services, and core technologies to multiple institutions in a region to facilitate translational research activities.

NCI's Unconventional Innovations Program (UIP) actively seeks partnerships with industry scientists outside the cancer research community to spur the development of radically new technologies in cancer detection, diagnosis, and treatment, rather than pursuing incremental improvements to the state of the art. Initiated in 1999, UIP will invest $50 million over the 10-year period ending in 2008.

In response to recommendations from several of its Progress Review Groups to accelerate the advancement of new interventions into clinical trials, NCI is establishing four to six Academic Public-Private Partnership Program (AP4)[79] sites. The AP4 program goal is to generate, through multidisciplinary partnerships with nonprofit organizations, academia, and industry, novel molecularly targeted cancer drugs and diagnostics. These potential interventions will be tested in clinical trials for orphan cancers or defined subsets of more common tumor types. AP4 is modeled on the NSF's Industrial/University Cooperative Research Centers program. Key features of AP4 will include a flexible management structure, autonomy to decide what projects to pursue, and access to NCI-funded developmental resources and research talent that will reduce industry partners' risk in developing new agents.

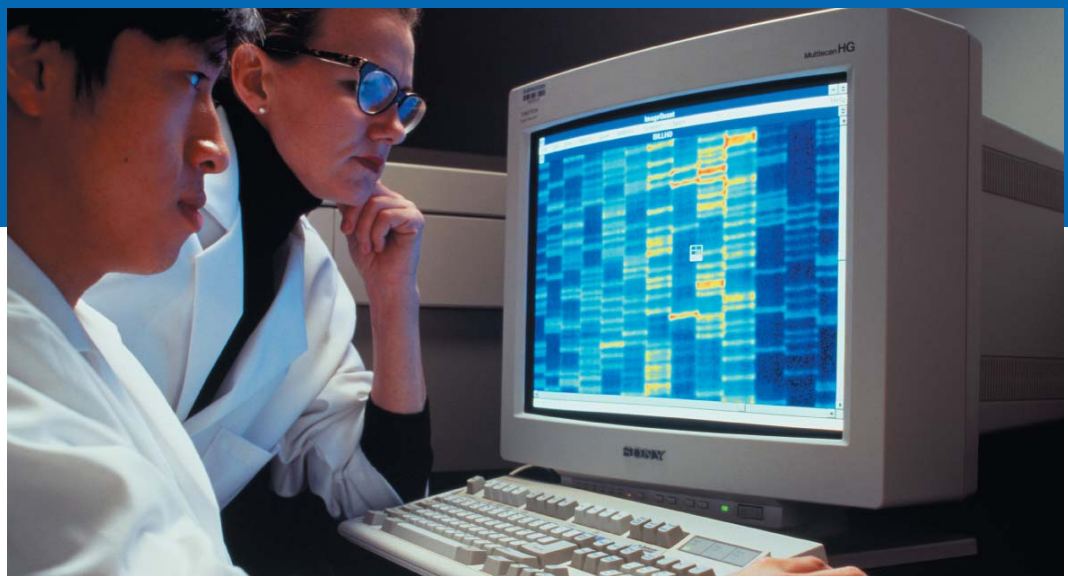
Other translation-oriented programs are sponsored at NIH. For example, the National Institute of General Medical Sciences funds so-called "Glue Grants"[80] designed to provide the funding needed to establish multidisciplinary consortia to address large-scale biomedical challenges. One such consortium focuses on understanding the mechanisms of cell migration; the findings will be used to inform the development of new therapeutics.

According to speakers, many of the larger pharmaceutical and diagnostics companies have extensive developmental laboratories and cancer databases that could support academic research on mechanisms of resistance, predictive markers, and multidrug treatment strategies – which are not the primary interest of private sector researchers – if incentives could be structured to facilitate sharing of these resources. Meeting participants also discussed the potential for large, publicly funded national laboratories (such as the Lawrence Berkeley, Los Alamos, and Lawrence Livermore National Laboratories) to participate in multidisciplinary, team-oriented cancer research. Because the laboratories have exceptional computational capacities and expertise in managing large projects, they could provide a highly valuable addition to the translational research infrastructure. It was suggested that barriers currently inhibiting collaborations between the laboratories and NIH- or NSF-sponsored researchers should be removed.

Data collection and analysis issues were raised by numerous speakers. Among the data needs cited were expanded and integrated data on cancer incidence, prevalence, morbidity, mortality, disease stage, and treatment; physician and hospital practice patterns; clinical annotation of human blood and tissue samples; database linkages; and electronic health records.

...NCI could help by matrixing the existing [Specialized Programs of Research Excellence]...cataloging the interests of SPORE investigators and then bringing them together with selected investigators who are working on particular molecular targets.

– Academic medical center translational researcher



Bioinformatics Platforms

Incompatible formats, data sets, and standards, and privacy concerns have stymied efforts to improve research data analysis and sharing needed to accelerate the translation process. Repeatedly, speakers addressed the lack of coordinated, standardized, and interoperable bioinformatics systems in the research and medical communities and urged that all possible steps be taken to remove this major roadblock to research collaboration. A number of efforts to do so already are underway. NCI has established the foundation for the cancer Biomedical Informatics Grid (caBIG),[81] a voluntary network of nearly 500 individuals from approximately 50 NCI-designated Cancer Centers. Its goal is to speed the delivery of innovative approaches for preventing and treating cancer through data sharing and the development of data analysis tools, uniform data elements, and guidelines. All tools and applications are available free to the caBIG community and other interested parties. caBIG provides information for cancer center directors, vendors, patient advocates, the general public, and the media. Among the new tools now available and compatible with caBIG is caArray, a software tool to help medical researchers share and analyze microarray data to identify new genes associated with specific cancer types, classify tumors, and predict patient outcomes.[82]

NCI's intent is that all existing and planned databases will be made compatible with and accessible through caBIG. One such informatics platform, the Shared Pathology Informatics Network (SPIN),[83] is being feasibility tested by two academic consortia, each of which was awarded a five-year (2001-2006) grant. SPIN's objective is to use state-of-the-art informatics techniques to establish an Internet-based virtual database that will enable investigators to locate appropriate archived human tissue specimens for their research. The SPIN software also will enable approved users to access de-identified clinical data associated with the specimens. Thus, researchers at participating network institutions will have access to many more samples than would otherwise be the case. The project responds to the need for more effective ways of sharing biospecimens and related data in modern biomedical research (see also below, Biorepositories, pp. 33-35).

We need to develop better databases that link clinical outcomes to clinical research….and I think it's important for us to come up with additional funding mechanisms to link all of our component community sites with our academic medical centers....we need to be able to link those together nationally as well as locally.

– Cancer center director

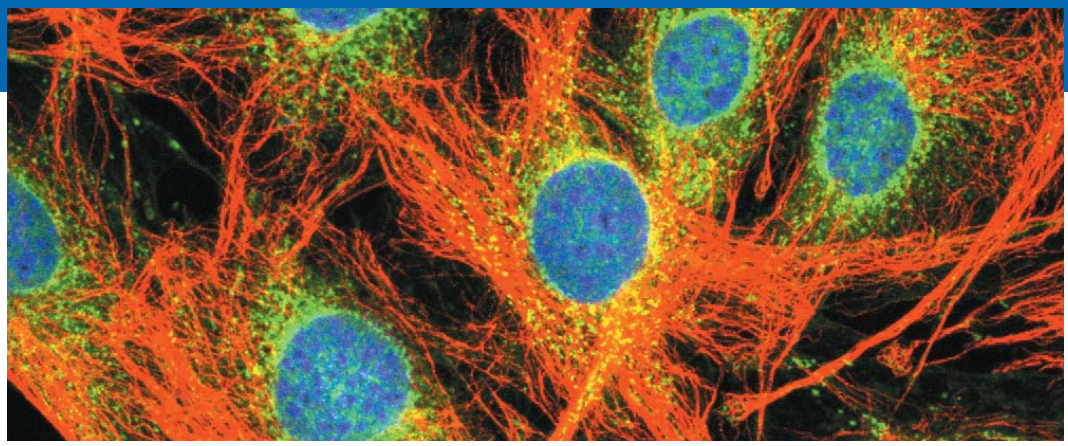
Cancer Surveillance and Treatment Data

The cancer registry system in the United States – comprised of NCI's Surveillance, Epidemiology, and End Results (SEER) program and the CDC National Program of Cancer Registries (NPCR) – continues to be strengthened and expanded. SEER now covers 24 percent of the population, with oversampling of certain minority populations, and every non-SEER state now has an NPCR registry. However, speakers called for even more robust registry data; for example, with limited exceptions, only data on first course of cancer treatment currently are collected by SEER; consistent information on subsequent treatment courses and treatment of recurrences and second cancers would be of enormous value in evaluating the longer-term benefits and risks of specific treatment regimens.

The Medicare database, frequently linked with SEER data to identify disease and cancer treatment patterns among Medicare beneficiaries, does not collect data on stage of disease at diagnosis. It was suggested that CMS require stage data on claim forms as a condition of payment to augment cancer registry data and support studies of cancer treatment and physician practice patterns. While such a requirement would be a significant step forward in cancer surveillance, it would be costly (both in terms of additional documentation costs and record review expenses). Moreover, potential problems could include Medicare claims stage data that conflict with SEER data, instances in which stage is not clearly known but treatment must be initiated, and the possibility of inappropriate claims rejection.

Biorepositories

Stored tissues play an extremely important role in research to understand cancer and other serious medical conditions. Based on conservative estimates,[84] more than 300 million specimens currently are stored in the United States; a substantial percentage of these are tumor and normal tissues obtained from cancer patients and individuals at high risk of cancer (e.g., participants in familial cancer registries). These samples, most of which are paraffin-embedded, are housed in myriad facilities across the country – large, federally-supported repositories, pathology departments at academic institutions, forensic DNA banks, the laboratories of individual investigators, and other sites. NIH is believed to be the largest funder of extramural tissue repositories.[85]



However, no central database captures information about all stored tissue samples. Further, attempts to aggregate data on tissues from various sources for research purposes have been limited by a lack of standards for tissue collection and preservation, and the lack of a uniform data set for collecting clinical information related to individual samples. Researchers' efforts to obtain samples, once identified, may be hampered by community pathologists' reluctance to cooperate, since they often have neither the time nor incentive to participate in research activities. In addition, pathology departments may be loath to relinquish their stored tissue resources. Privacy and informed consent issues associated with obtaining and using tissue samples have become more complex since it has become possible to analyze DNA from minute specimens and legislative/regulatory provisions (e.g., HIPAA) have tightly limited specimen use. Consensus, therefore, is needed on approaches to consent, data de-identification, and access (see also Part IV, Regulatory Issues Affecting Translation).

At cancer centers, a speaker noted, stored patient tissue samples may not reflect the characteristics of either the center's local population or the national population. This limitation has the potential to distort study findings. Some centers are attempting to address these problems. For example, NCI's Prostate SPOREs are planning the pilot of a biorepository coordination system and an interoperable informatics infrastructure for prostate cancer research. Initial steps will be to assess the feasibility of biorepositories for post-genomic cancer research and to evaluate standardized approaches for biospecimen collection, storage, and distribution.

…we've got to start using humans as a model organism…to start analyzing human tumors….I'm not advocating that we ignore all the animal models and the extraordinary power that one can use in animals and cell culture studies, but I think human biology is going to be the wave of the future.

– Research laboratory president/chief executive officer

In the past year, a conference attended by representatives from the nonprofit, private, and government sectors, as well as international representatives, was held to discuss the future of biorepositories, including networking options.[86] Finding solutions to biospecimen and characterization data-sharing issues is crucial – recent studies have demonstrated that analysis techniques, such as x-ray fluorescence spectroscopy[87] and readily available reverse-transcriptase polymerase chain reaction (RT-PCR),[88] can derive important data from paraffin-embedded samples that are decades old, underscoring the value of biospecimens in longitudinal studies of disease and risk. However, many new genomic and proteomic applications require fresh "snap-frozen" tissue, and RNA and protein quality can begin to erode in minutes. Standard annotation for these tissues also must be agreed upon so that researchers can have confidence in the information characterizing each sample.

Since 2002, NCI has been working to unify existing biobanks through a planned National Biospecimen Network.[89] A three-year pilot phase has been delayed, however, to resolve the many issues concerning standardization of specimen collection and annotation, and even to gain consensus on what constitutes a biospecimen. NCI plans to manage the data associated with the network through caBIG.

Biomarkers

Biomarkers are physiological characteristics that indicate specific normal and disease processes or responses to pharmacologic or biologic agents. Numerous speakers described the urgent need to accelerate biomarker development. Biomarkers, along with necessary evaluative technologies, performance standards, and predictive tools based on animal and computer models, were seen as an invaluable means of better forecasting medical product failure either before human testing begins or earlier in the clinical trials process. Having biomarkers for this purpose, speakers claimed, would save time and money and enable resources to be focused on products with the best chance of success.

The last decade of biomarker research is beginning to bear fruit; examples include the identification of protein biomarkers for ovarian cancer[90] and a promising noninvasive test for an enzyme in urine that may detect early breast cancer and accurately track tumor growth.[91] Researchers are working to identify similar markers in urine for prostate and other cancers, as well as cancer biomarkers in serum and tissue. A speaker also described the potential of biomarkers to identify genetic or protein changes that occur during the earliest stages of carcinogenesis, allowing intervention well before the development of clinically evident cancer. Researchers have identified a small panel of genes that accurately predict recurrence risk in women previously treated with hormonal therapy for breast cancer.[92] Further, the common assay method used to profile the genes of interest suggests that the technology could be widely and rapidly adopted in community hospital practice.

…we need to, and can, learn from our cardiovascular colleagues. They took a disease that resulted in strokes and myocardial infarctions and dramatically reduced the incidence of these terrible problems. As oncologists, we're 30 years behind. We're still dealing primarily with metastatic disease. We need [to pinpoint] the [equivalent of] high blood pressure and cholesterol for oncology.

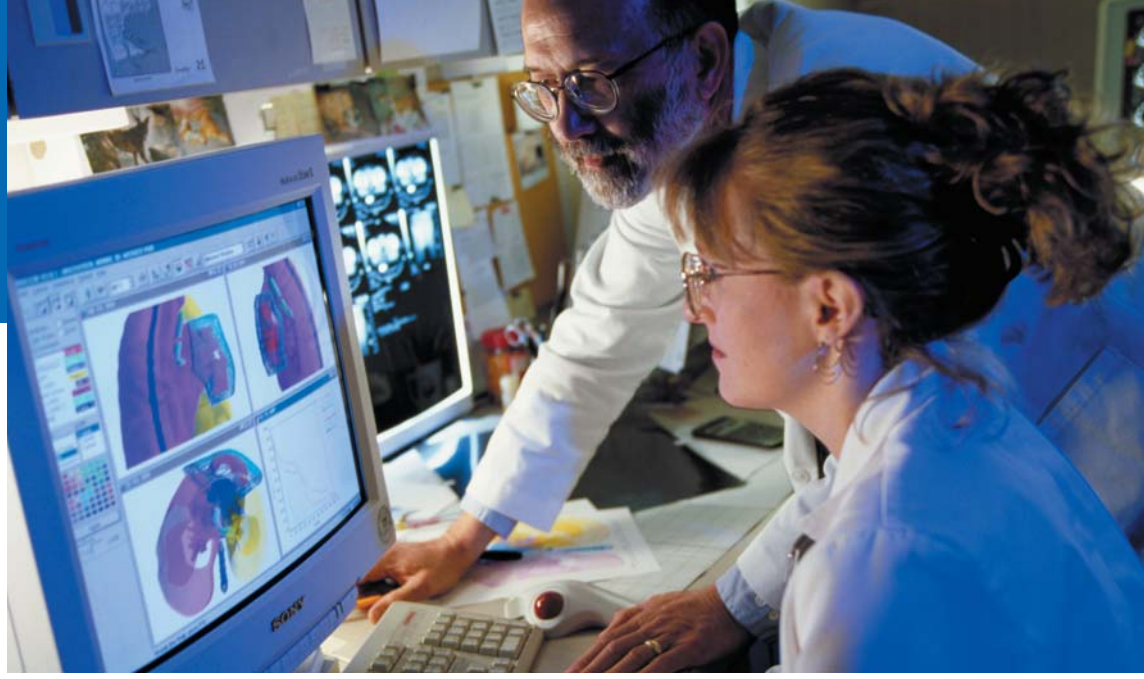
– Pharmaceutical company executive

Other potential uses of biomarkers include defining homogeneous disease subgroups at the molecular level, improving understanding of disease pathways, and selecting patients most likely to respond to specific treatments. With validated biomarker surrogate endpoints, it will be possible to conduct clinical trials more efficiently, thereby safely accelerating new drug approvals.

The NCI Early Detection Research Network (EDRN)[93] was launched in 1999 to facilitate academic, government, and industry multidisciplinary collaborations to identify, characterize, refine, and validate genetic, protein, and other biomarkers related to specific types of cancer that could be used to identify early cancer and cancer risk. Its principal components include biomarker development and validation laboratories, clinical and epidemiologic centers, and a data management and coordinating center. A second round of five-year grants was awarded in October 2004. Investigators outside of the network can collaborate as Associate Members in biomarker development, testing, and validation; these investigators can apply for supplemental funding or for the use of shared network resources. EDRN recently launched a three-year study to validate a test for biomarkers in urine that indicate bladder cancer recurrence.

In late 2004, NCI awarded grants to two teams from ten cancer research institutions to collaboratively develop, using mouse models of human cancer, standard tools and resources needed to accelerate protein biomarker discovery and new approaches to cancer early detection and diagnosis. Information on the products and technologies developed through this two-year effort will be integrated and distributed through caBIG.[94]

NCI and FDA collaborate on a proteomics research program that is exploring and validating methods for identifying cancer-related proteins in blood serum that eventually could be developed into biomarker tests. Since 1997, the two agencies also have collaborated on a clinical proteomics program that is analyzing proteins from blood or tissues with mass spectrometry and protein microarrays; the ultimate goal is to use this information for earlier detection of cancer, patient-tailored therapies, and more effective therapeutic monitoring.[95]



To make optimal use of all of the current and proposed resources devoted to biomarker development, validation, and use, it will be crucial that diverse supporting informatics, reagent, and technology assessment activities are fully integrated. International organizations of scientists working to identify and share gene and protein information and resources include the Human Genome Organisation and its protein-oriented counterpart, the Human Proteome Organisation.

Health Services Research and Other Applied Research

In a recent report, the Institute of Medicine[96] noted the importance of health services research and the wide array of concerns it encompasses (e.g., monitoring and improving quality of care; the organization of health services and health information dissemination strategies; understanding community health behaviors in support of intervention adoption). The report recommends greater coordination between principal Federal sponsors of health services research – NIH, AHRQ, VA, and CMS – to advance this developing field. Several speakers maintained that health services research, particularly dissemination research, is a seriously underdeveloped component of the translation continuum. Limited understanding of effective dissemination practices, they asserted, is a major factor slowing the adoption of established and new preventive and treatment interventions by the general public; specific socioeconomic, cultural, and racial/ethnic populations; and the health care provider community. Other speakers, however, maintained that sufficient, if not perfect, evidence on dissemination methodologies exists to guide more aggressive outreach efforts that are needed now (see also Research Dissemination Issues, pp. 65-67).

In 2002, the Cancer Prevention and Control Research Network, a partnership of academic, public health, and community partners across the Nation, funded by CDC and NCI, was launched to conduct community-based cancer prevention and control intervention and dissemination research, translate effective interventions into practice, and evaluate community-based cancer control programs.[97] CDC also supports Health Promotion and Disease Prevention Research Centers[98] and participatory research on community interventions to increase utilization of cancer preventive and treatment services. AHRQ supports Practice-Based Research Networks[99] that focus on translating research into primary care practice. In the nonprofit sector, a number of foundations (e.g., the Commonwealth Fund, Project Hope, Henry J. Kaiser Family Foundation, American Cancer Society, Lance Armstrong Foundation, Robert Wood Johnson Foundation, Howard Hughes Medical Institute) are significant sponsors of health services and other applied research, or related health policy research, both generally and specific to cancer prevention and care services. A number of the major insurance/managed care companies conduct health services research they need to support their own operations.

Electronic Health Record Systems (EHRs)

Testimony provided to the Panel concerning the processes involved in research translation also emphasized the potential importance of health information technology to improve utilization of proven cancer-related interventions (e.g., cancer screening) and new research advances in community clinical practice (e.g., identifying relevant clinical trials and new treatment options). Since the Panel's last report,[100] EHRs (also called electronic medical records, or EMRs), have received considerable attention, principally for their perceived potential to improve information access, cut overall health care costs, reduce medical errors, and improve quality of care. Legislation has been introduced in both the House of Representatives and the Senate to support health information technology adoption.[101] The Department of Health and Human Services (DHHS) has developed a 10-year plan to create continuously updated and accessible electronic health records.[102] The plan also reports health information initiatives by the Office of Personnel Management related to the Federal Employee Health Benefits Plan, Department of Defense initiatives targeting rural and medically underserved areas, and initiatives at the Department of Veterans Affairs. Medicare is creating an Internet portal to allow beneficiaries to access their personal records and will accelerate development of regulations for electronic medication prescription to quickly disseminate common standards.[103] Grants have been made available for pilot and demonstration projects aimed at developing information infrastructure, standards, and exchange systems. These actions also may respond to administrative simplification provisions (Title II) of HIPAA that require DHHS to establish national standards for electronic health care transactions and national identifiers for providers, health plans, and employers. The goal of these provisions is to encourage widespread use of electronic data interchange in health care and improve the efficiency and effectiveness of the health care system overall.[104]

Potential models for national EHR systems exist. For example, the Veterans Health Administration (VHA) has established an integrated electronic medical record (VistA), performance measurements, and other measures in a coordinated effort to improve the quality of health care for veterans. A recent quality of care comparison for a national sample of patients in the VHA system and non-VHA patients[105] found that patients from the VHA scored significantly higher for adjusted overall quality, chronic disease care, and preventive care, though not for acute care. The best VHA system performance was aligned with processes targeted by system performance measures. KP HealthConnect, a robust electronic medical record system now being deployed across all eight Kaiser Permanente regions, eventually will include the nonprofit health maintenance organization's (HMO) eight million members and will augment existing data collection and quality measurement systems.

Important issues remain to be resolved in moving toward a seamless, paperless national electronic medical records system that instantly provides a longitudinal patient history to all medical personnel when needed, appropriately protects patient data to avoid abuse, and is always accessible to the patient. Interoperability may be the most pivotal of these issues. Expert opinion is divided, however, as to the necessity of building interoperability standards into the national EHR system at the outset to avoid a proliferation of stand-alone systems that could not communicate and that could come to be treated as a proprietary asset of delivery systems. Those who do not favor first developing interoperability standards believe they will follow naturally from widespread EHR adoption.[106,107]

The most important findings must be impossible to avoid, but this will require a fairly substantial shift from simply posting new information on Web sites to customizing delivery of information of the latest evidence to the point of care….information could be delivered to a clinician seeing a patient right then, during an encounter, that says, "Your patient is eligible for the following trials."

– Health services research director

Other issues include the need for incentives to encourage and enable community providers to obtain necessary hardware and software. Adoption of information technology among providers has been slow due to concerns about declines in physicians' productivity while they learn new systems, as well as high costs, low initial savings, and the possibility that insurers may use electronic data to reduce physician compensation. Not surprisingly, adoption has been greater in larger physician practices compared with smaller groups and solo practitioners.[108] Providers in solo or small practices, particularly those in rural areas, are most likely to require financial assistance to acquire health information technology. Some large health systems already are giving equipment, bonus payments, and higher reimbursements to providers who adopt electronic ordering (e.g., for medications, diagnostic tests, ancillary services).[109] Some providers are concerned, however, that they may face prosecution under anti-kickback or anti-fraud statutes and regulations if they accept certain kinds of information technology from health systems. In response to provider concerns, DHHS is crafting exceptions and advisory opinions to address this issue.[110]

…the biggest barrier to consistently performing preventive services in primary care practices is simply forgetting it – not thinking about a patient's screening history and not knowing when they're due for their next mammogram. We are not going to make a lot of progress on that problem until doctors have electronic medical records that simply do the job of remembering for them.

– Journal editor

Infrastructure Required for Research Translation

5. To attract and retain young investigators to careers in translational and clinical research:

   (a) Protected research time and mentoring must be provided earlier and potentially for a longer period of time than is now the norm. Government training funds may be needed to enable academic institutions to provide this supportive environment.

   (b) New or expanded student loan buy-back programs should be established to enable young investigators to pursue the additional training necessary for a career in translation-oriented research.

   (c) Academic institutions should make special efforts to recruit and retain young scientists from underrepresented population groups.

6. The Rapid Access to Intervention Development program should be expanded and revitalized to accelerate the development of innovative interventions and technologies for cancer.

7. Specialized Programs of Research Excellence (SPOREs) have proven effective in stimulating collaborative and translational research. The program should be expanded, with the focus of selected SPOREs shifted to emphasize clinical over basic research.

8. The Centers for Medicare and Medicaid Services should explore the possibility of collecting cancer stage data, at least at the time of diagnosis, to better inform treatment decisionmaking, ensure appropriate payments, enrich the body of information about provider practice patterns, and support treatment research.

9. The proposed Human Cancer Genome Project should be supported to accelerate progress in genetic knowledge that will enable the development of new cancer prevention and treatment advances. Funding for this large effort should come from a special supplement rather than from participating agencies' budgets.

Nearly every aspect of cancer-related research and drug development is controlled by myriad Federal and state regulations. These regulations have been developed over the past few decades principally to protect the public from harm due to financial conflicts of interest in the research and pharmaceutical communities, inadequate patient protection in research studies, unsafe drugs and devices, and invasions of privacy. Indeed, many of the regulations have been developed in response to tragedies that exposed system failures, rather than through a proactive planning process. Other regulations addressing drug pricing and reimbursement for health care services and medications also affect research translation and patient access to cancer prevention and care advances.

Part IV Regulatory Issues Affecting Translation

…a fundamental and pervasive barrier is what I will label a "culture of protectionism" in government, academia, and the private sector that leads to undesirable and often unnecessary regulations and practices that stifle collaboration and slow the pace of progress.

– Clinical cancer researcher

Speakers agreed that many of the current regulations, though well-intentioned, are having unintended consequences that are impeding the pace at which new discoveries in basic science can be developed into interventions and delivered to the public. Those cited included Health Insurance Portability and Accountability Act (HIPAA) privacy regulations, informed consent requirements, and other human subject protections rules. The research community itself was faulted by some speakers for failing to help legislators understand the potential unintended consequences of their actions.

Further, the regulatory structure related to clinical trials in many ways thwarts efforts to create the most efficient, effective, and least costly cancer clinical trials system. Particularly for multi-institutional or other collaborative efforts, speakers stated that regulations related to trials – for example, HIPAA, Food and Drug Administration (FDA), and human subject protections rules – have become so complex that they are a significant obstruction to carrying out trials. Coordinating grant participants, multiple Institutional Review Boards (IRBs), and numerous Federal and state regulations is a major undertaking that often delays trials and in some cases, prevents important trials from being conducted at all. It was suggested that participant organizations and individuals need to reach consensus at the outset on how to manage each group's regulatory requirements, which IRB to use, and the like. Speakers also commented that regulators could facilitate this process by providing assurances that trialists will not be penalized for trying to resolve these issues in a creative manner.

Academic and community medical centers, industry partners, and other participants all are affected by the difficulty of coordinating numerous and sometimes conflicting regulatory requirements, but speakers noted that community medical centers and provider groups often are least familiar with regulatory requirements associated with clinical research. This problem also complicates the development of clinical trial and outreach networks that could bring cancer prevention and treatment trials more quickly to a larger segment of the population.

Institutional Review Boards and Human Subject Protections Regulations

IRBs, the organizational structures for evaluating research protocols to ensure the safety of human research participants, were established beginning in the 1960s. Most sizable academic medical centers, cancer centers, and public and private hospitals have an IRB if they participate in federally funded research involving human subjects. IRBs at these institutions must be registered with the DHHS Office of Human Research Protections (OHRP).[111] The regulations governing IRBs (45 CFR Part 46), define a human subject as a living individual about whom an investigator (including students) conducting research obtains data through intervention or interaction with the individual or obtains identifiable private information.

FDA regulations govern "independent" IRBs that review privately funded research;[112] the majority of IRBs operate under one or both sets of Federal regulations. In addition, some nongovernmental organizations have established groups to review research not subject to OHRP or FDA regulations.[113]

The current IRB system was designed to accommodate the protocol review requirements associated with single-site studies, not the multisite, multi-institutional clinical trials that increasingly are needed to answer important scientific questions. A recent study[114] of IRB processes at 68 U.S. hospitals (mean bed size 465) found that the time from submission of a protocol to the IRB to approval averaged 45.4 days; "expedited" reviews actually required more time (mean, 54.8 days). Further, the study found current IRB processes

cumbersome and nonstandard. The authors concluded that these processes may unnecessarily impede national clinical research without improving patient safety.

One solution suggested by speakers and others[115] is to have all institutions use a central IRB for multisite trials, a solution that also was viewed positively due to its potential cost savings. Some centralized IRBs already exist. In consultation with OHRP, NCI established an adult Central Institutional Review Board (CIRB) in 2001 that meets monthly, reviewing Phase III trials from nine of the Cooperative Groups, as well as other protocols opened in the Cancer Trials Support Unit. A pediatric CIRB was formed in June 2004 and began meeting in November 2004; it reviews all NCI-approved Children's Oncology Group Phase II, III, and pilot protocols. Both of the CIRBs include individuals from a broad range of disciplines, such as oncologists, nurses, patient advocates, pharmacists, ethicists, and attorneys. No NCI employees participate on the CIRBs.[116]

A 2004 Association of American Medical Colleges survey[117] of 125 medical schools found that of those that had used a centralized IRB (slightly less than a quarter of surveyed institutions) most were satisfied with the review quality and shorter review time. However, there appears to be confusion at many institutions about how to interact with a centralized IRB versus an individual IRB.[118] Activities are underway to explore central IRB options further. The DHHS Secretary's Advisory Committee on Human Research Protections has initiated an evaluation of the relative advantages of a centralized IRB system compared with academic and independent local or regionalized IRB models. The advisory committee will consider the reasons for current variations in operations, the costs of various approaches, and the impact of various approaches on recruiting reviewers to serve in the IRB process, among other issues.[119]

Even with the existence of a central IRB, a speaker pointed out that a Phase III NCI Cooperative Group trial conducted under an Investigational New Drug application still must be reviewed by the NCI Cancer Therapy Evaluation Program, Cancer Trials Support Unit, central IRB, company sponsor, FDA, and hundreds of local IRBs. A mechanism is needed to further streamline the process, preferably such that a single scientific review and single IRB review meet the needs of all stakeholders.

A suggested alternative to the central IRB approach is to develop nationally agreed-upon IRB standards so that IRBs at individual institutions could be assured of the quality of a proposed protocol that met those standards. At the request of DHHS, the Institute of Medicine conducted a study of how to update the IRB system to meet the evolving needs of research. The resulting 2001 report[120] recommends developing standards for accrediting and evaluating IRBs (the concept of which was expanded and renamed Human Research Participant Protection Programs) with four principal functions: (1) ensuring that research design is sound and that a study's promise for augmenting knowledge justifies the involvement of human participants, (2) assessing the risks and benefits independently of the investigators who carry out the research, (3) ensuring that participation is voluntary and informed, and (4) ensuring that participants are recruited equitably and that risks and benefits are fairly distributed.

IRBs are responsible not only for granting approval of proposed human research, but for monitoring and evaluating adverse events that occur during clinical trials. This function also has become more complicated with the growing number of multi-institutional trials. A trans-agency task force with representatives from FDA, NIH, CDC, DoD, VA, OHRP, and AHRQ is developing guidance aimed at standardizing terms and definitions used to describe adverse events in clinical trials. These guidelines are intended primarily to assist IRBs and to facilitate research collaborations.[121]

Intellectual Property, Patents, and Conflict of Interest

Considerable testimony was presented on barriers to research translation that stem from intellectual property considerations, product patents and licensing, conflicts of interest, and commercialization issues. These issues have both multiplied and become more complex as greater numbers of patents are granted for biomedical discoveries that previously would have resided in the public domain, as large-scale scientific projects require the use of many patented products, and as industry-academic partnerships have increased.

Intellectual Property, Patents, and Licensing

In 1980, a Supreme Court decision held that a recombinant bacterium produced by an individual was patentable subject matter under the patent statute,[122] a decision that led to vastly increased private investment in biotechnology research, the growth of the biotechnology industry, and many key discoveries in molecular medicine.[123] The same year, Congress enacted the Bayh-Dole Act (P.L. 96-517, as amended), which provided that nonprofit organizations (including universities) and small businesses could elect title in (i.e., establish an ownership interest in, or patent) and grant patent licenses (i.e., permission to use patented materials) for the commercial development of inventions originating in the course of federally funded research. This legislation and its amendments were intended to facilitate efficient licensing of government funded inventions, promote growth of the domestic economy, encourage the participation of small business firms in federally supported research and development, promote collaboration between commercial concerns and nonprofit organizations, and ensure that inventions made by nonprofit and commercial concerns would be used to "promote free competition and enterprise without unduly encumbering future research and discovery."

As many speakers attested, some of these aims – the last in particular – have not been realized. As patents have proliferated for the composition and use of genetic sequences, cell lines, transgenic animals, antibodies, and other material used as research tools or reagents, research has been encumbered by real and potential patent infringement issues. Infringement of a patent is defined as the making, using, and/or selling of a patented invention without the patent owner's authorization. Two patent infringement exceptions have been recognized: a "safe harbor" exemption solely for uses related to developing and submitting data for regulatory approval to market a drug, biologic, or medical device, and a narrowly-defined experimental research exception for research for "amusement, to satisfy idle curiosity, or for strictly philosophical inquiry" – i.e., having no potentially commercial purposes. Other uses of patented biotechnology research tools or reagents do not fall within either of these exceptions and would constitute patent infringements.[124]

A patent license is a contract between the owner of a patent and an independent party that wishes to make, use, or sell the invention claimed in the patent. The patent owner agrees not to sue the licensee for patent infringement if the licensee abides by the terms of the contract. A patented invention may be licensed to a single entity (an exclusive license) or to as many entities as are interested in negotiating an agreement (non-exclusive licensing).[125] In reach-through licensing, patent holders retain rights to future discoveries enabled by the use of their inventions. They are most common where the patented product is an "upstream" product or research tool. Rights may take the form of royalties on sales that result from use of the upstream research tool, an exclusive or non-exclusive license on future discoveries, or an option to acquire such a license. Because the potential products or discoveries arising from the use of patented material may be hard to anticipate at the time of licensing, reach-through licenses of patented research tools have been a contentious issue.[126]

Scientists trying to organize research activities to develop new diagnostics, therapeutics, or core research tools and technologies now find that they must negotiate licensing arrangements and patent exemptions with patent holders that may number in the dozens. For example, an industry speaker noted the frustration of researchers with an interest in studies requiring access to the whole human genome, who must negotiate multiple agreements to use patented gene sequences and other naturally-occurring genomic elements. It was his recommendation that government and the private sector act aggressively together to guarantee the greatest possible access to genomic information for basic researchers and to stimulate competition and innovation in new therapeutics and diagnostics development. Establishing a life sciences "patent pool," possibly starting with one area of cancer wherein intellectual property interests could be made available collectively to publicly funded and private sector basic researchers, may be one avenue for overcoming patent-related obstacles to translation. Existing strategies for dealing with intellectual property concerns and data release include those developed by the Single Nucleotide Polymorphism Consortium and the National Human Genome Research Institute, which are aimed at keeping genomic information in the public domain to maximize its availability for research and development.[127]

Because biotechnology, diagnostic, and pharmaceutical companies so fiercely protect their intellectual property, results generated in this sector usually are not available to academic researchers. This proprietary environment discourages information sharing that could prevent some trial failures and accelerate translation. Moreover, because of intellectual property issues, companies tend to test combinations of their own drugs, not necessarily the most promising combinations of drugs. Even this is difficult, according to a speaker, because Federal regulations on approval of drug combinations are not clear.

...the industrial community must overcome barriers to combining agents from different companies early in [drug] development.

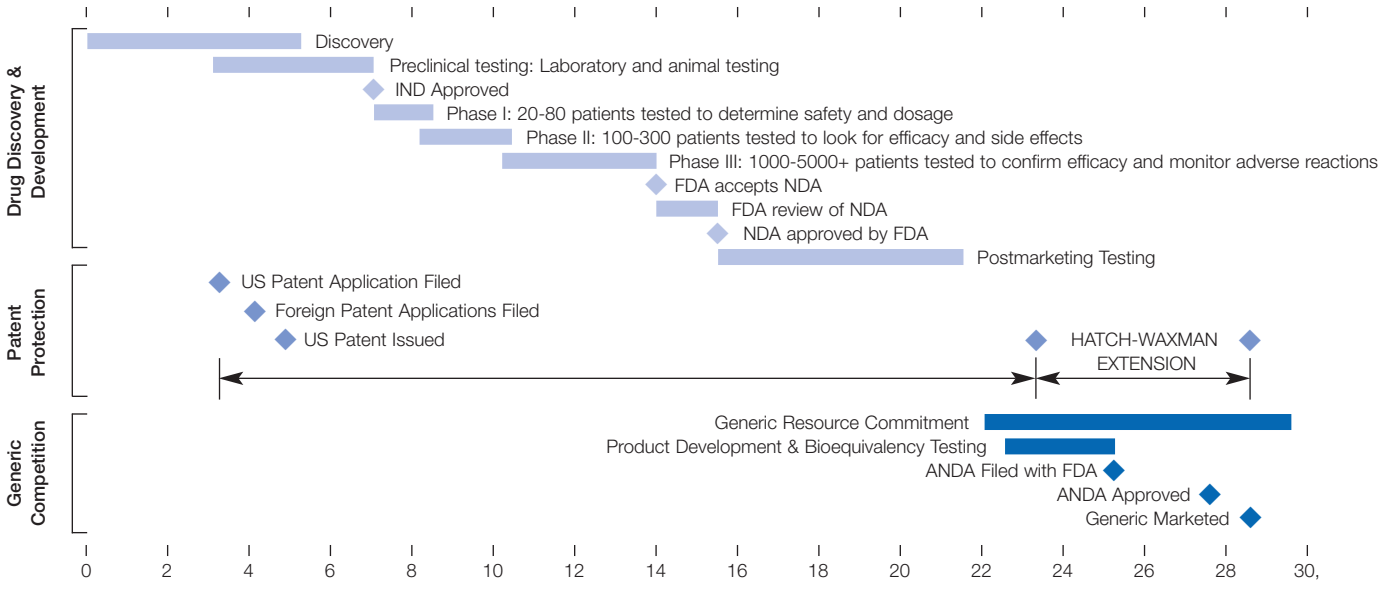
– Practicing oncologist and physician-scientist

The Patent and Drug Development Processes

Pharmaceutical companies seek patents to protect their return on investments in high-risk and high-cost product development. Biotechnology companies are able to attract investment capital, to a great extent, based on their patent portfolios.[128] Figure 4 maps the patent process to an average new drug development and FDA approval timeline, illustrating how these two schedules converge to fuel some of the patent protection issues that may slow translation and contribute to high drug prices that affect access to state-of-the-art cancer diagnostics and therapeutics.

Typically, academic or industrial inventors seek a patent as soon as it is reasonably clear that a drug or biologic may have clinical potential. This may roughly coincide with the start of preclinical testing, as indicated in Figure 4, or may occur even earlier. When the patent application is filed, a 20-year period of market exclusivity begins, during which no competitor can make, use, sell, or offer to sell the product or invention.

Figure 4: Approximate Timeline for New Drug Development (Years)



Adapted from: Mossinghoff GJ. Overview of the Hatch-Waxman Act, *Food and Drug Law Journal,* 1999; 54:187-194.
Legend: FDA – Food and Drug Administration, IND – Investigational New Drug, NDA – New Drug Application, ANDA – Abbreviated New Drug Application

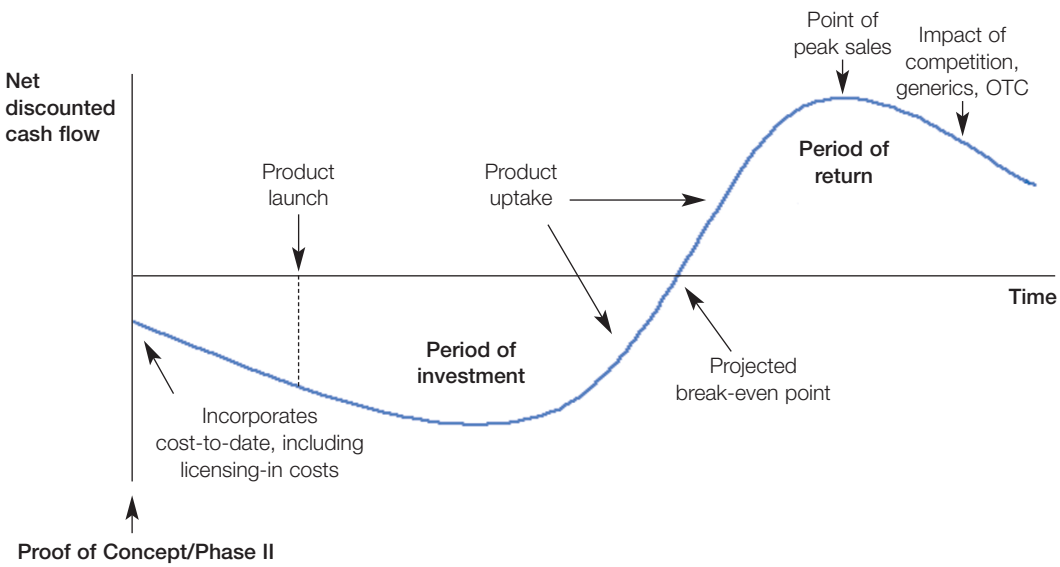
Much longer and larger clinical trials are required to show that a cancer can be prevented….Even with these huge commitments, the true risk/benefit ratio of the chemoprevention drug can be very challenging to demonstrate….the time required to develop a chemoprevention drug quickly erodes available patent life that enables the private sector to fund these huge, high-risk research and development investments….this 20-year [market exclusivity] clock starts ticking when the patent application is filed, but drug patents must be applied for very early in the drug's discovery and development process because this is such a competitive business. That's years before the first patient ever receives a dose of the drug in a clinical trial.

– Pharmaceutical company researcher

Speakers and others have estimated that it now takes from 10 to 15 years and about $800 million[129] to as much as $1.7 billion[130,131] to bring a promising compound or biologic from discovery to market launch. At that point, five to eight years generally remain for pharmaceutical and biotechnology companies (and their investors) to recoup development costs and generate a profit before the expiration of patent exclusivity. Figure 5 illustrates this product lifecycle for a hypothetical pharmaceutical.

An analysis of the 22 drugs approved by FDA for cancer therapy between December 1992 and June 2003 showed that the average time from patent to approval was 93 months, average wholesale price (AWP) per dose was $4,699, and AWP per treatment cycle was $17,488.[132] Critics of drug industry pricing maintain that high prices are not the result of the lengthy development and approval processes, but are due to a lack of pricing controls.

Figure 5: A Hypothetical Cash-flow Curve for a Pharmaceutical Product



Source: Gregson N, Sparrowhawk K, Mauskopt J, Paul J. Pricing Medicines: Theory and Practice, Challenges and Opportunities, *Nature Reviews – Drug Discovery*, 2005;4:121–130, Figure 4.
Legend: OTC – over-the-counter

Upon expiration of a patent, under the provisions of the so-called Hatch-Waxman Act,[133] generic versions of the product can be produced and sold. The Act also allows patent holders to apply for a patent extension of up to five years to "restore" at least part of the period of exclusivity that may have been lost during the approval process (Figure 4). In addition, some drug makers have been criticized for making minor modifications (e.g., extended-release versions of a medication) to secure a new patent on a product whose original patent is about to expire or a patent extension of up to three years, and thereby stave off generic competition.[134]

Generic versions of a drug invariably are available at a lower cost than the original brand name product, since generics producers do not have the development costs to recoup and must file only an abbreviated new drug application (ANDA) demonstrating equivalent bioavailability (i.e., that the same amount of the active agent is in the bloodstream at the same dosage over a specified period of time). In an environment in which health care cost containment pressures continue to intensify, generics quickly erode the market for the original product.

It should be noted that provisions of the Hatch-Waxman Act apply to small-molecule chemical entities, but not to biologics, which are genetically engineered proteins or peptides produced not by chemistry, but by living cells in highly complex manufacturing processes. Generic drug makers are now pressing for legislation to create a parallel process permitting the production and market entry of generic biologics, which they believe will offer considerable savings to public and private health care purchasers. Biologics makers warn, however, that "reverse engineering" of a biologic is far more complex than for a pill and that even small differences in the manufacturing process can cause dramatically different and variable effects in the body, including serious and long-lasting immune reactions.[135]

Suggested Strategies to Address Drug Development/Approval, Patent, and Licensing Issues

Development Costs and Drug Approval. Speakers maintained that the patent system and the average duration and cost of product development, described above, are major contributors to the extremely high prices of many cancer therapeutics. The magnitude of this front-end investment puts enormous pressure on companies to advance through their development pipelines only agents that are likely to have significant profit potential, because the drug or device may be used by many people and/or because patients will take the medication or use the device for a long period of time. From this perspective, cancer drug development is a risky proposition for most companies, since the number of potential patients for even the most common cancers (e.g., lung, prostate, breast) is dwarfed by, for example, the potential market for drugs to treat hypertension or high cholesterol. According to a speaker, pharmaceutical companies generally are not interested in developing a drug that is expected to have a market of less than $500 million per year in sales.

Moreover, as subtypes of common cancers (e.g., lymphomas, breast) are identified, each requiring different treatment, the potential markets for specific cancer drugs are shrinking. Speakers emphasized that this trend is essentially making all cancer drugs "orphan" drugs (i.e., drugs for low-incidence diseases) – as drugs to treat pediatric cancers always have been – and suggested that they should be designated as such. Under the 1983 Orphan Drug Act, FDA is authorized to promote the development of drugs for diseases having fewer than 200,000 cases in the U.S. by designating them "orphan," which confers an additional seven years of exclusive marketing rights and tax credits for research conducted to generate data required for market approval. Unless the drug includes an indication for other than a rare disease, it also is exempt from FDA user fees.[136] In addition, developers can receive grants (up to $300,000/year for three years) to defray clinical trial costs.[137] As of 2003, more than 1,000 orphan products had been designated; of these, more than 200 were approved for marketing. Of those, 31 were approved for cancer indications.[138]

Other speakers called for the Federal Government to take a larger role in, and absorb more of the costs of early development of promising agents to limit financial risk to private companies and thereby increase interest in developing cancer prevention and treatment drugs/devices. One possibility proposed is for NIH to take on responsibility for developing small-market drugs, providing a small but sufficient return to the industrial donor of the patented product. A related suggestion was to make the NIH Clinical Center available to investigators nationwide as a site at which to conduct novel translational studies that require intensive and sophisticated patient monitoring. The speaker suggested that funding for studies of proprietary agents could come from user fees charged to the sponsor.

NCI's Developmental Therapeutics Program (DTP) has been a successful mechanism for partnering with industry to support drug development. Currently, DTP works more with small biotechnology companies that require this assistance compared with the larger pharmaceutical companies, which now have substantial drug development resources and infrastructure. Through a contract mechanism, DTP also funds a number of drug development consortia that conduct Phase I and II trials. These consortia also work together in that researchers in one consortium can enroll patients in trials being conducted by the other consortia if that is the best option for the patient.

As much as we know that the answer for cancer lies in prevention, therapy will always be a component of what we do. No matter how well we try to prevent cancer, there will be those stricken with cancer who do need therapy. Our patients, our colleagues, our children will continue to be diagnosed with cancer, and we need options. We need to create a better incentive for [the pharmaceutical industry] to engage academic medical centers in partnering on drug development, and that might mean…structuring patents differently for prevention and for therapy.

– Cancer center director

Patent Exemptions and Standard Contract Language. NCI was urged to convene a small working panel representing the research, commercial, and patent law communities to craft language for a standard experimental-use research exemption from licensing of patented products that will promote cancer research while continuing to permit patent owners the ability to protect their commercial interests. Speakers noted that enabling patent exemptions for research would bring U.S. research practices and regulations more in line with those in the European Union; currently, some American investigators are conducting drug studies in Europe because of the more conducive patent rules in those countries. Similarly, standard contract language for licensing agreements and collaborative and private/public partnerships is urgently needed.

In 2004, Congress enacted the Cooperative Research and Technology Enhancement Act of 2004 (CREATE, P.L. 108-453), which is intended to correct a provision in the Bayh-Dole Act. While the Bayh-Dole Act encourages private entities and nonprofits such as universities to form collaborative partnerships that promote innovation, the current law states that a previously claimed invention by one of the collaborating parties can in certain circumstances be considered "prior art," thereby making the subject matter of the collaboration not patentable. CREATE ensures that non-public information cannot be deemed "prior art" when the information is used in a collaborative partnership under the Bayh-Dole Act.

According to speakers, financial incentives are needed to help break the intellectual property logjam deterring companies from collaborating in developing target therapies, biomarkers, and reagents; one option may be extending patent life for new chemical entities that are registered based on a successful collaboration. Another speaker suggested that the period of patent exclusivity for new entities, whether collaboratively developed or not, should begin at the point at which the new drug, biologic, or device is licensed rather than when the patent application is filed.

Using Patents as an Incentive for Private Sector Outcomes Research

At the other end of the translation spectrum, the need for outcomes research is thwarted by the lack of a mechanism in the private sector (e.g., insurers, managed care organizations) to recoup the high costs of randomized controlled outcomes research and cost-effectiveness comparisons of approved interventions. If an organization conducts such outcomes research and develops improved treatment guidelines, its competitors can take advantage of the findings without having to invest in the research. Increased public sector funding of outcomes research in the near term is unlikely. "Use patents" (providing a clear period of marketing exclusivity protection for specific proven health care interventions, procedures, or uses of medications, devices, and other products) have been proposed[139] as a way of stimulating private sector outcomes research. Such patents could be granted even to individuals or institutions not holding the original product patent on underlying medications or devices, or drug combinations. They also could be granted for outcomes research related to generic and over-the-counter products that have been on the market for many years. Use patent enforcement would be complicated and difficult, but could result in significant societal benefit resulting from greater outcomes knowledge demonstrating the benefits of specific interventions in lives saved and illnesses avoided.

Conflict of Interest

Conflicts of interest (sometimes referred to as competing loyalties, competing interests, or dual commitments) in the development and marketing of cancer-related drugs or devices most often arise when an inventor, study author, peer reviewer, or journal editor has financial or other relationships that are thought to inappropriately influence his or her actions (Exhibit 2). As the International Committee of Medical Journal Editors notes, the most easily identified financial relationships potentially resulting in conflict of interest include employment arrangements, consultancies, stock ownership, honoraria, and paid expert testimony. Conflicts also can arise as a result of personal relationships, academic competition, and even out of intellectual passion.[140]

Exhibit 2: Types of Academic/Industry and Government/Industry Relationships

Relationships with industry are defined here as arrangements in which academic or government scientists or administrators carry out research or provide intellectual property in return for considerations of various types (research support, honoraria, consulting fees, royalties, equity, etc.). The following are among the most common types of relationships:

Research Relationships	Support by industry, usually through a grant or contract.
Consulting Relationships	The compensated provision of advice or information, usually from an individual academic or government scientist or administrator, to a commercial organization.
Licensing Relationships	The licensing of government- or university-owned technologies to industry, often negotiated and managed by an office of technology transfer located within the government, university, medical school, or independent hospital.
Equity Relationships	The participation by academic or government scientists in the founding and/or ownership of new companies commercializing university- or government-based research.
Training Relationships	In these cases, industry provides support for the research or educational expenses of graduate students or postdoctoral fellows, or contracts with academic institutions to provide various educational experiences (such as seminars or fellowships) to industrial employees.
Gift Relationships	Gift relationships are based on the transfer of scientific and nonscientific resources, independent of an institutionally negotiated research grant or contract, from industry to academic or governmental scientists.

Source: Campbell EG, Koski G, Zinner DE, Blumenthal D. Managing the triple helix in the life sciences, *Issues in Science and Technology,* 2005;XXI(2):48-54.

Acknowledging the profound changes in the academic biomedical research environment and eroding public confidence in research that is threatening academic medicine and public health, the Association of American Medical Colleges (AAMC) convened a task force to develop guidance regarding academic medicine's management of financial conflicts of interest in human research. The task force issued two reports, the first offering policy and guidelines for the oversight of individual financial interests in research involving human subjects,[141] and the second providing principles and recommendations for demarcating appropriate conduct when an institution hosts research involving human subjects and the institution or its administrators have direct financial interests in the research.[142] Among its many other findings, for example, the task force maintained that institutions should "limit the conduct of human subjects research by financially interested individuals to those situations in which the circumstances are compelling" and that such situations should be analyzed on a case-by-case basis.[143] At the Panel's meetings, there was general

consensus among speakers that while it is inappropriate for an inventor with financial interest in a product to be involved in late-stage testing of the product, ways should be found to enable the inventor to participate in early testing, particularly as he or she may be the person who best understands the product at that point. Speakers asserted that conflicts of interest cannot be entirely eliminated, but they can be managed through strict disclosure requirements. National conflict of interest guidelines were suggested, to be applied by independent national review panels that include individuals from academia, the private sector, and patient advocate groups.

Inventions by NIH intramural researchers are viewed as an output of an individual's government service, and the government therefore owns the rights to the invention. These investigators are required to disclose to potential study subjects that they are the inventors of agents being tested in a clinical trial. However, some intramural inventors have held stock in or had other equity relationships with companies or others that have been licensed by the government to develop the product; some of the companies have been founded specifically for that purpose. In this situation, the inventor may have the opportunity for substantial financial gain (via stock appreciation, royalties, or other compensation) should the product achieve FDA marketing approval. Under a February 2005 supplement to existing ethics regulations,[144] certain NIH intramural investigators and other staff are required to disclose and divest themselves of stock holdings in and terminate consulting, advisory, and equity relationships with any company or other NIH grantee with the potential to develop or commercialize their inventions. The rules also stipulate limitations on outside income, acceptance of prizes, and other possible financial relationships that could cause or appear to cause conflicts of interest. Some, both within and outside the scientific community, view the new rules as a positive step toward greater disclosure to and protection of research participants, and it has been suggested that the new rules should be extended to extramural researchers receiving Federal grants.[145] Others believe the rules will result in an exodus of scientific talent from the NIH intramural research program and further, will discourage the best scientific minds from coming to NIH to pursue their research. NIH will evaluate the impact of this interim regulation over the course of a year and modify it as warranted by experience with its implementation.

Commercialization Issues

Commercialization of promising products developed in academic centers, according to a venture capital company representative, often is complicated because most academic intellectual property and technology transfer departments lack the benefit of input from scientists with business experience. In addition, most investigators have limited business skills, which may result in unrealistic perceptions of the activities and funding needed for production and commercialization of their discoveries. Some biomedical products in early development may need funding beyond what is typically available through government or institutional sources to develop them to a point at which they are ready for commercialization. Because the return on investment in products at this stage of development is highly uncertain, the venture capital market has little interest in them. As a result, funding (usually $500,000 to $2 million) from some other source is needed to cover this developmental gap; a speaker suggested that this high-risk capital most often comes from "angels" — private donors or investors with an interest in the product. Nonprofit organizations also might be a source of gap funding for products in which they have an interest.

Food and Drug Administration

As the regulatory agency responsible for ensuring that medical innovations made available to the public are safe and effective, FDA uses available scientific knowledge to set product standards. An FDA representative acknowledged that the process for obtaining approval for a promising medical product (drug, biologic, or device) is a long and arduous one. By some estimates, the cost of bringing a new medicine to market now ranges from $800 million to $1.7 billion.[146,147] Yet despite rapidly escalating increases in research and development spending and burgeoning basic science innovation, applications for FDA approval of new drugs, biologics, and medical devices have declined over the past several years.[148] Unless this trend toward increasing cost and difficulty of medical product development is reversed, the flow of new therapies and other products to patients may stagnate and decline further.

We need to improve the technology that we use in cancer research in order to perform less costly trials on fewer numbers of people and still provide scientific evidence that our interventions are specific, safe, and effective.

– NCI administrator

FDA is perhaps unique in its opportunity to observe the full range of successes, best practices, barriers, and failures that occur during the clinical trials process. The agency conducted an analysis of the pipeline problem and described the "critical path" to new product development.[149] This path has three major dimensions: (1) assessing safety, (2) demonstrating medical utility, and (3) industrialization. Examples of activities in each of these stages are shown on Table 3.

Though citing the need for improved tools consistent with advances in scientific techniques to help identify early those products most likely to fail, FDA believes that its reviewers possess the cross-cutting expertise to help physicians and scientists avoid common problems and weaknesses in each dimension of development. For this reason, FDA reviewers believe it would benefit product developers – saving both time and money – to have very early discussions about products for which they contemplate seeking approval. Figure 6 indicates the usual intervals of consultation with FDA along the development path. Medical product developers, however, often fear that doing so will only increase the difficulty of clearing regulatory hurdles.

Table 3: Three Dimensions of the Critical Path

Dimension	Definition	Examples of Activities
Assessing Safety	Show that the product is adequately safe for each stage of development	**Preclinical:** Show that the product is safe enough for early human testing; eliminate products with safety problems early **Clinical:** Show that the product is safe enough for commercial distribution
Demonstrating Medical Utility	Show that the product benefits people	**Preclinical:** Select appropriate design (devices) or candidate (drugs) with high probability of effectiveness **Clinical:** Show effectiveness in people
Industrialization	Go from a lab concept or prototype to a manufacturable product	Design a high-quality product • Physical design • Characterization • Specifications Develop mass production capacity • Manufacturing scale-up • Quality control

Source: Food and Drug Administration. *Challenge and Opportunity on the Critical Path to New Medical Products*, March 2004, Table 1.

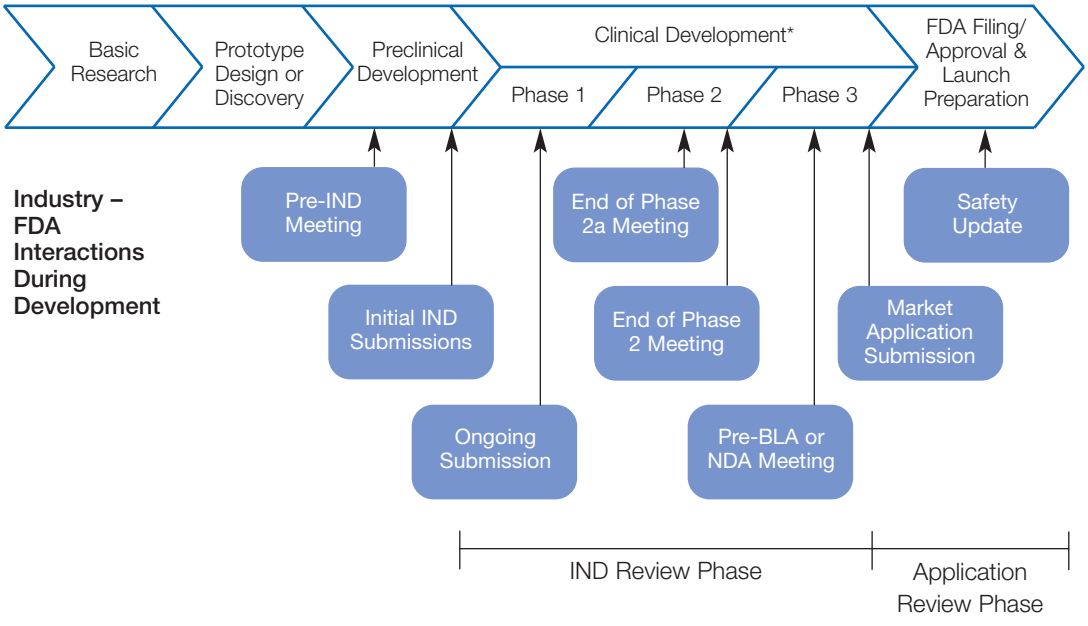
Discussions [with FDA] regarding preclinical testing models, the extent of data collection and verification, and better definitions of endpoints could result in less expensive, streamlined, rational drug development.

– Pharmaceutical company executive

Speakers remarked that FDA needs a mechanism for sharing clinical trials information with the academic community that accommodates the proprietary environment and does not compromise the approval process. One way FDA seeks to make information available without jeopardizing these constraints is through guidance documents, workshops, or peer-reviewed publications.

FDA is developing guidelines for early investigational studies, but speakers emphasized that regulations to guide the development of chemopreventive agents and combination drug trials also are greatly needed.

Figure 6: Industry-FDA Interactions During Drug Development



*Note: Clinical drug development is conventionally divided into 3 phases. This is not the case for medical device development.
Souce: Food and Drug Administration. *Challenge and Opportunity on the Critical Path to New Medical Products*, March 2004, Figure 7.
Legend: IND – Investigational New Drug, NDA – New Drug Application, BLA – Biologic License Application

FDA and NCI have worked since 2003 to develop a system for electronic submission of investigational new drug applications under the caBIG project. Since formation of FDA's Office of Oncology Drug Products, NCI and FDA have collaborated on enhancing the drug and therapeutic biologics review processes. As a part of that effort, FDA and NCI established an Interagency Oncology Task Force (IOTF), a joint agreement to enhance the efficiency of clinical research and scientific evaluation of new cancer medications. Among its other objectives, the IOTF will facilitate knowledge and resource sharing among researchers and will work to identify potential clinical endpoints (such as functional imaging indicators and biomarkers) for use in assessing the effectiveness of new agents in clinical trials.[150]

Additional partnerships with other organizations are being established to develop the tools FDA cites in the Critical Path report, such as animal- or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques to improve predictability and efficiency along the path from laboratory concept to commercial product.[151]

…no fatal disease that we've been able to successfully deal with has ever been changed unless we dealt with a combination of strategies to circumvent diverse mechanisms of resistance.

– Academic drug development researcher

Accelerated Approval (AA)

Some observers have expressed strong concern as to whether FDA's Accelerated Approval (AA) program,[152] implemented in 1992 to help make new drugs available to people with life-threatening conditions, adequately safeguards the public.[153] This program has been used to accelerate reviews of certain new cancer drugs. Under the program, marketing approval can be granted for an agent shown to have strong effects on measures of biological activity correlated with a disease, but these markers need not be proven to be markers of efficacy (i.e., improved patient outcome). For example, a drug that causes temporary tumor shrinkage may not cause a decrease in symptoms or significantly increase survival but could receive marketing approval under the AA program.

Drugs approved under AA must be further tested in at least two additional clinical trials to validate the marker as a true surrogate for clinical efficacy endpoints that would have to be demonstrated under the regular approval process. History to date has shown, however, that once AA marketing approval has been granted, drug companies tend to lose their sense of urgency to continue clinical testing. Of more than 1,300 post-marketing studies to which drug companies have committed, 65 percent have not been started, but FDA has not responded to these lapses by withdrawing a drug from the market.[154]

Moreover, a review of oncology drugs approved under the program in its first five years projected that it could take up to 10 years to complete the additional trials required for each drug. Meanwhile, the drugs are available outside of a research setting, where experience in using them is less stringently monitored. Furthermore, patients are far less motivated to enroll in a trial if the drug is already available and reimbursable in the community. The initial validation study of one of the oncology drugs approved through the AA program did not confirm efficacy, yet marketing of the intervention continued.[155]

Centers for Medicare and Medicaid Services (CMS)

Adequate reimbursement for cancer care services and medications is critical to translation; without insurance coverage, new treatments and preventive strategies will be unavailable to many who need them. The Medicare program, administered by CMS, is the primary payor for health care services for the elderly, who comprise the majority of cancer patients.

The Panel heard extensive testimony on recent changes in CMS's reimbursement rates, coverage decisions, and program direction following passage of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA). Several providers from the oncology community expressed concern about the change in physician reimbursements for most infusion and injectable chemotherapy drugs and biologics. In 2004, Medicare Part B reimbursed physicians at 85 percent (down from 95 percent in 2003) of the average wholesale price of these drugs, and did not reimburse for the cost of drug administration, such as nursing care, disposable supplies, equipment, and facility costs. For years, the drug reimbursement substantially exceeded the cost paid by physicians, who used the margin to cover the administration costs. Under MMA amendments to the Social Security Act of 1965 (Medicare law is contained in Title XVIII of the Social Security Act of 1965), data were collected from pharmaceutical manufacturers to determine average selling prices of their Part B drugs (not paid on a cost or prospective payment basis). Beginning in 2005, oncologists and other physicians who administer injectable/infusible drugs in their offices will be paid 106 percent of the average selling price. MMA also now provides for a separate payment to cover administration costs. It will remain to be seen if this level of reimbursement (based on projected drug cost inflation rates) actually covers physician costs. The oncology and cancer advocacy communities are concerned that if (contrary to CMS estimates) reimbursements fall substantially short of actual cost, access to oncology care will be reduced for Medicare beneficiaries. Providers may cease offering office-based chemotherapy services, including participation in clinical research in community settings because they cannot afford to provide these services at an ongoing financial loss. Speakers recommended that this situation be monitored closely.

Recent coverage decisions reflect CMS's greater emphasis on evidence-based cancer care, as well as a growing recognition that innovation in cancer treatment often has come from "off-label" uses of approved drugs. Physicians have long used drugs off-label to tailor treatments to individual patients' cases. CMS is mandated to cover off-label uses that are listed in one of a number of drug compendia, which indicates that evidence exists that the drug provides more benefit than risk. Medicare's regional contractors, however, have some flexibility to authorize payment for uses not included in a compendium. CMS has launched a demonstration project in which it will pay for the off-label use of four colorectal cancer treatment drugs as long as the patient enrolls in one of nine clinical trials sponsored in part by NCI. In this way, CMS will collect treatment data to increase the evidence base to support coverage decisions. Similarly, CMS will pay for positron emission tomography (PET) for certain cancers if patients agree to enroll in a registry that will collect data on the utility of the scans for diagnosing, staging, and monitoring treatment response in these diseases. In a second year-long demonstration project, CMS will for the first time pay physicians for monitoring cancer patients' levels of pain, nausea, vomiting, and fatigue. CMS will use data generated from patients' responses and subsequent responses during treatment for these symptoms to analyze outcomes of this care.

MMA also now provides reimbursement for orally-administered replacements for injectable or infusible cancer treatment drugs. This provision had been sought for some time by the cancer advocacy community and community oncology providers, particularly those serving rural Medicare patients. These elderly and often very sick patients previously had to travel long distances for infusion chemotherapy because equivalent oral drugs were not reimbursed.

Further, CMS has an expressed interest in helping to gather information on investigational agents so that when efficacy is shown sufficient for FDA approval, reimbursement decisions can be expedited and the drugs can reach the market more quickly. A Council on Technology and Innovation has been established to provide guidance in this regard to product developers. Drug developers, however, are concerned about being perceived as "rushing the process" to gain an early reimbursement decision and thereby jeopardizing the chance of the drug's approval. Some concern also exists that clinical trials and/or data collection conducted as part of the approval process might be modified to better accommodate a coverage decision.

Building on the FDA-NCI Interagency Oncology Task Force, NCI and CMS have entered into a collaboration to identify and initiate high-priority clinical trials in areas in which clinicians and patients have said they need better clinical information to guide their decisions about new or competing treatment regimens. Other objectives of the collaboration will be to: (1) create a process for conducting post-approval studies to address priority questions, (2) design a

We need to develop a paradigm where we can change the locus of decision making and not make reimbursement decisions as sort of "one size fits all" in Washington, trying to fit square pegs into round holes, but allow the communities to make decisions that are appropriate for each patient and help them get the tools and the information they need to do that.

– CMS administrator

systematic process for consultations between CMS and NCI experts in evaluating new diagnostic and therapeutic cancer technologies for the purposes of payment and coverage decisions, (3) develop more efficient methods of collecting clinical evidence on new cancer technologies as well as strategies for making the information more widely available to patients, clinicians, and researchers – possibly including making CMS claims data available on caBIG to facilitate outcomes and other analyses, (4) develop a joint process for prospectively identifying and evaluating emerging technologies so that reimbursement policies will anticipate and expedite their adoption in the community, and (5) identify data-sharing opportunities and resources to improve quality of care, including palliative and end of life care, and address cancer health disparities and excessive treatment pattern variations.[156]

The Health Insurance Portability and Accountability Act (HIPAA)

The obstacles to research erected by the HIPAA privacy provisions (Privacy Rule) enacted in 2003 were a topic of considerable discussion at each of the Panel's meetings. Likewise, HIPAA was a frequently raised issue during the Panel's previous meeting series, with respect to the effect of the Privacy Rule on cancer survivor-related research and surveillance of long-term treatment effects, among other issues.

With respect to the HIPAA regulations, something must be done. The problem varies all the way from simple, mundane things — like who pays for the shredders that every small hospital and every small clinic or office needs — to more serious questions about how to get research material released from dead people who, at the time that they gave it earnestly hoped that it would be used for some legitimate research purpose. Yet, if the wording of the initial consent isn't correct and you can't find the nearest living relative, the material goes to waste.

– Cancer center director

The Privacy Rule, administered and enforced by the DHHS Office of Civil Rights, is intended to safeguard individually identifiable health information on persons both living and deceased and to regulate known and unanticipated risks to privacy that may result from the use and disclosure of personal health information. The Privacy Rule applies to health care clearinghouses, health plans, and health care providers that transmit health information electronically in connection with a transaction (e.g., NIH funded research) for which DHHS has established HIPAA-related standards. In addition, the Privacy Rule may affect researchers who obtain individually identifiable health information from such "covered entities" through collaborative or contractual arrangements.[157]

One speaker maintained that the research and medical communities are now struggling with problems created by HIPAA because they did not participate adequately in the dialogue when the regulations were proposed. For example, the lengthy HIPAA consent forms that must be signed by clinical trial participants are in addition to privacy-related components of informed consent provisions mandated by the OHRP. Speakers maintained that this additional paperwork does little to add to privacy protection, but it does add to patient confusion at a time of personal stress and to the administrative burden of medical researchers. In addition, a speaker asserted that HIPAA inappropriately elevates the priority of privacy to that of the

critical issues of safety and side effects of experimental treatments; concern was expressed that study participants may actually be distracted from focusing on these crucial issues as they attempt to absorb all of the additional verbiage related to HIPAA provisions. Moreover, the possibility exists that patients who are less educated or have limited literacy or English language skills will be intimidated by the complicated forms and refuse to participate in studies, thereby preventing researchers from studying a true cross-section of the population.

HIPAA bars access to medical records when: (1) an investigator wants to find patients with a specific diagnosis or treatment so they can be contacted and offered inclusion in a new therapeutic trial, (2) an investigator wants to test a hypothesis about cancer causation by applying new measurement technologies (e.g., genomics, proteomics) to tissue specimens left over from previous clinical diagnostic studies and then linking the results to patients' clinical outcomes, (3) an investigator detects a trend in the environment or in dietary patterns and wants to determine whether the pattern is related to disease incidence in a given locality, or (4) several investigators working for different organizations want to collaborate to develop a new diagnostic test or treatment; HIPAA prohibits the transfer of private medical information between them.

HIPAA also significantly limits researchers' ability to obtain long-term follow-up data on patients participating in national registries and complicates the use of other databases and tissue banks. While some of these problems can be overcome, albeit with considerable difficulty and cost, a danger is that young researchers with fresh ideas, who are so greatly needed for the future of translational and clinical cancer research, will seek less troublesome types of research projects, and community researchers will withdraw from participating in clinical studies. All of these issues, and others, are summarized in feedback from a survey of NCI Comprehensive and Clinical Cancer Centers, Cooperative Groups, and SPOREs[158] and a similar survey of member organizations by the AAMC.[159] Speakers firmly agreed that the HIPAA privacy regulations should be reviewed and amended to remove research barriers while still protecting personal health information.

Especially for those of us who work on the translation of basic discoveries to patients, the HIPAA regulations are burdensome at best and, at times, even crippling.

– Academic clinical researcher

RECOMMENDATIONS

Regulatory Issues Affecting Translation

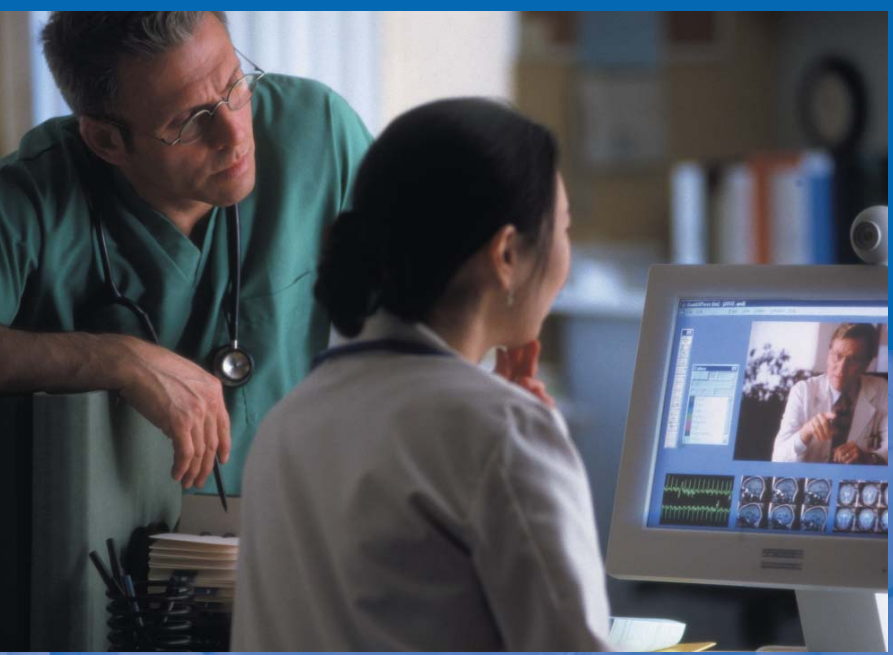
10. The current partnerships between the National Cancer Institute (NCI) and the Food and Drug Administration to expedite cancer drug reviews and between NCI and the Centers for Medicare and Medicaid Services to generate clinical data on new interventions to support Medicare coverage decisions should be continued and strengthened.

11. To encourage private sector investment in cancer therapies, all new cancer chemoprevention and chemotherapy drugs and biologics should be designated orphan drugs under the Orphan Drug Act of 1983.

12. A task force of private, nonprofit, academic, and government stakeholders affected by current barriers to research translation due to intellectual property and patent issues should be convened to develop and reach consensus on: (1) standard language for patent exemptions for research purposes, (2) standard clauses for contracts governing collaborative research, and (3) other agreements as needed to resolve intellectual property and data-sharing issues.

13. The Institute of Medicine should be commissioned to evaluate the impact of the Health Insurance Portability and Accountability Act (HIPAA) provisions and provide guidance to legislators on amendments needed to remove unnecessary obstacles to cancer research and make this law better serve the interests of cancer patients and survivors. *(This is a restatement of prior Panel recommendations.)*

Eighty percent of cancer patients receive their treatment in community settings. Information about cancer research advances must be disseminated effectively through education and targeted communication to the public, physician and non-physician health care personnel, and community-based researchers.



Part V Dissemination, Education, and Communication Issues Affecting Translation

Research Dissemination Issues

Disseminating prompt, accurate information in usable formats to community health care providers and the public about cancer prevention and treatment advances is a critical step in the translation process – the link between an intervention's development and its adoption in clinical practice. As a speaker explained, dissemination research is in its infancy; it has become clear that passive information dissemination (e.g., distribution of print materials) is largely ineffective in influencing clinical practice, but little is known about the most effective active interventions for encouraging adoption of research advances by specific target groups. The evidence to date in cancer control suggests that multi-component interventions are more effective than single interventions in promoting adoption of medical procedures, technologies, clinical behaviors, and lifestyle modifications.[160] Importantly, dissemination interventions that are not developed to reach all segments of the population affected by cancer may have the unintended effect of increasing cancer-related health disparities.

We need academic medical centers to do more research on the behavioral factors that motivate physicians and patients to "do the right thing."

– Journal editor

Developing and testing new dissemination and adoption-oriented strategies and interventions is the purview primarily of health services, communications, educational, social work, nursing, behavioral, and social science research. These strategies and interventions may include outreach and navigation programs, education and training initiatives, public information campaigns, publication and communication technology development and distribution, evaluative tools and methods, and other products. Implementing these interventions generally is the responsibility of health and social service components of Federal, state, and local governments; academic medical centers and cancer centers; other public and private health care providers; community- and faith-based programs; educators at the elementary, secondary, collegiate, and professional (including continuing education) levels; and the media.

…some of the expertise needed for dissemination may exist outside our academic medical centers and cancer centers. For example, it may reside within business schools. Partnerships may be needed to stimulate discussions between people with effective interventions and those who know something about marketing and dissemination.

– Dissemination researcher and cancer center administrator

Among other considerations, effective dissemination requires an understanding of the "wholesale" and "retail" consumers of specific cancer information. Wholesale consumers usually are systems that provide health services and information to the public, to whom evidence for the benefit of new prevention, early detection, treatment, and survivorship interventions must be presented and reinforced. Wholesale dissemination offers the best chance for widespread practice and policy changes, compared with dissemination to individual retail consumers. However, effective retail information dissemination also is important to generate demand for evidence-based services.

The NCI houses an Office of Communications that provides information on research advances intended for both wholesale and retail information consumers. The Web sites of advocacy groups primarily target the individual retail consumer of cancer information. The Cancer Control PLANET Web site, a collaboration among NCI, AHRQ, CDC, the American Cancer Society, and the DHHS Substance Abuse and Mental Health Services Administration, is one example of a wholesale dissemination strategy.[161] PLANET is an Internet-based resource for research-tested cancer control intervention programs and related materials. Its audience includes state- and local-level cancer control planners, program staff, researchers, and others involved in planning, implementing, and evaluating cancer control programs to bridge the gap between discovery and program delivery. In addition, NCI and the National Cancer Institute of Canada are developing a joint venture to involve key stakeholders (primary care researchers/practitioners, oncology specialty researchers/practitioners, and population-public health researchers/practitioners) in strategies to improve knowledge transfer and research translation across the cancer control continuum from primary prevention to survivorship and end of life care.

Effective dissemination of cancer research advances currently suffers from a lack of leadership. Scientists, practitioners, and policymakers view their own and others' roles in dissemination quite differently. While all may be committed to dissemination research and to working in partnership to implement evidence-based dissemination strategies, none of the groups sees itself in a leadership role,[162] and no single agency has been given the authority and budget to coordinate dissemination research and activities.

Further, as vital as dissemination- and adoption-oriented research and implementation activities are in bringing cancer research advances to the public, they have been chronically underfunded. Of the combined NCI extramural and intramural research budget for FY2005, a small fraction (less than 15 percent) is allocated for cancer prevention and control research.[163] Moreover, some of these funds may be for studies of potential chemoprevention agents and other cancer prevention and control research, leaving even less for dissemination- and adoption-oriented intervention development and testing. CDC, through its Comprehensive Cancer Control program, conducts cancer control research and funds cancer control capacity-building programs, local screening, outreach, and information programs for the public and the health care community, but it too is underfunded to fulfill the potential of these programs or support a robust program in dissemination research. As noted earlier, AHRQ funds a substantial amount of the current cancer-related health services research portfolio. Similarly, a variety of patient advocacy and support organizations and foundations disseminate information about cancer research advances to their constituencies. Even in the aggregate, however, these resources fall far short of the commitment needed to bridge the gap between the development of new cancer-related interventions and their availability to all parts of the population.

A recent Donahue Institute report[164] notes that factors contributing to a gap between research and practice may differ considerably from one geographic region to another, and that while solutions may originate nationally, action generally is taken locally. NCI-designated Comprehensive Cancer Centers are required to conduct outreach to the communities (health care providers and the public) in which they are located to disseminate research findings. Historically, however, funding for these activities has been minimal, and most center efforts have been commensurate with these resource levels. It was suggested that comprehensive cancer centers should take a much more active role in ensuring adoption of research advances not just in their immediate communities, but in their geographic regions, and that appropriate funding should be made available to enable them to fulfill this role.

The ultimate goal of dissemination is to enable individuals and organizations to adopt evidence-based approaches that will help reduce the risk and burden of cancer. The sections below describe specific public, health professional, and research community education and communication needs cited by speakers as necessary to speed the translation process.

Public Education Needed to Facilitate Translation

Public education is needed in three important, though not mutually exclusive areas: (1) education about basic scientific and research concepts, (2) general education about cancer as a disease and available cancer prevention and care interventions, and (3) clinical trials education and awareness.

Education about Basic Scientific and Research Concepts

Speakers observed that much of the public has little understanding of basic scientific concepts or the purpose and process of research. A 2001 National Science Foundation study confirms this assessment.[165] The study found that two-thirds of Americans do not have a firm grasp of what it means to study something scientifically (i.e., the scientific process), though the same study found widespread support of government funding for basic research. Only 15 percent described themselves as well informed about new scientific discoveries and the use of new inventions and technologies, while a third characterized themselves as poorly informed. Lacking this fundamental knowledge, it is little wonder that many people are skeptical and/or fearful of new medical treatments and technologies and wary of medical researchers. Speakers asserted that the health and education components of the Federal Government have primary responsibility for raising the level of general knowledge in these areas.

General Education about Cancer and Cancer Care

As a result of intensive and long-term public education efforts, much of the American public now understands that heart attacks and other cardiovascular conditions are the result of a disease process that usually progresses over many years and is strongly influenced by diet, exercise, smoking, inherited predisposition, and other risk factors. According to testimony presented to the Panel, the public does not have a similar understanding of cancer as a process that typically is ongoing for years before symptoms appear. A common (though certainly not universal) public perception is that a person only has cancer upon diagnosis, or at the point that symptoms manifest. Speakers maintained that the public must be taught, beginning in the elementary school years when lifestyle

habits are forming as well as throughout the lifespan, that modifiable lifestyle behaviors and environmental exposures affect the cancer process. It is now estimated that as many as half of all cancer deaths could be avoided by the population-wide application of existing knowledge about cancer screening, weight control, physical activity, nutrition, tobacco use, and other lifestyle factors.[166] This education, they stated, should be provided by primary care physicians, other health care providers, and educators, with reinforcement through strategic use of mainstream and population-targeted media.

…when we understand cancer as a disease process rather than as a diagnosis at a point in time, participation in prevention efforts — even lifestyle modifications, which would be hugely important — would be much more likely.

– Pharmaceutical industry researcher

Marketing concepts and techniques should be applied to public health education about cancer. Message development and delivery must take into account diverse cultures and varying levels of literacy and health literacy (see also pp. 89-95, Access to Information). A speaker observed that the public is so bombarded with conflicting information about the benefits of various dietary and exercise regimens, the significance of newly discovered genetic variations, and seemingly daily medical "breakthroughs" that most can no longer distinguish what information is important from what is not.

In an increasingly media-driven society, the media have an important role in providing accurate information and encouraging participation in the health care system, as well as a responsibility (as have researchers and pharmaceutical developers) not to overstate research findings or progress. Recognizing the power of entertainment-based education, CDC, NCI, and the Hollywood, Health & Society program at the University of Southern California established a partnership through which medical and public health experts provide consultation, education, and resources for writers and producers who develop scripts with health storylines and information.[167]

A model for media-based cancer education was presented by the founder of a prevention-oriented primary care health clinic in Washington, DC, who coupled the clinical services with daily radio and television broadcasts on cancer-related and other health topics. He based the program on his perception that the target population (the area's Latino community) was eager for understandable information about cancer prevention and wellness in general and that health information could be "sold" with the same communication techniques used to promote other products and services. The highly successful and popular programs are now nationally syndicated on Spanish-language radio and television. The speaker recommended that DHHS launch a similar sustained, nationwide, multichannel, multi-audience public cancer education program. CDC has an established television outlet, CDC-TV, which could serve as a wholesale provider of cancer education content to retail media distributors and outlets.

If average, intelligent people had a sense of context about the scale and scope of research and its directions and its possibilities, they would be far more inclined to embrace information about their own treatment and about clinical trials….Many companies are secretive about early-phase trials and about the entire process in general…[but] you can't be secretive about the process and then successfully convince people to join in on something they know nothing about. Also, if something is secret, some people think it is dangerous. That is not a positive mindset in which to cultivate volunteers.

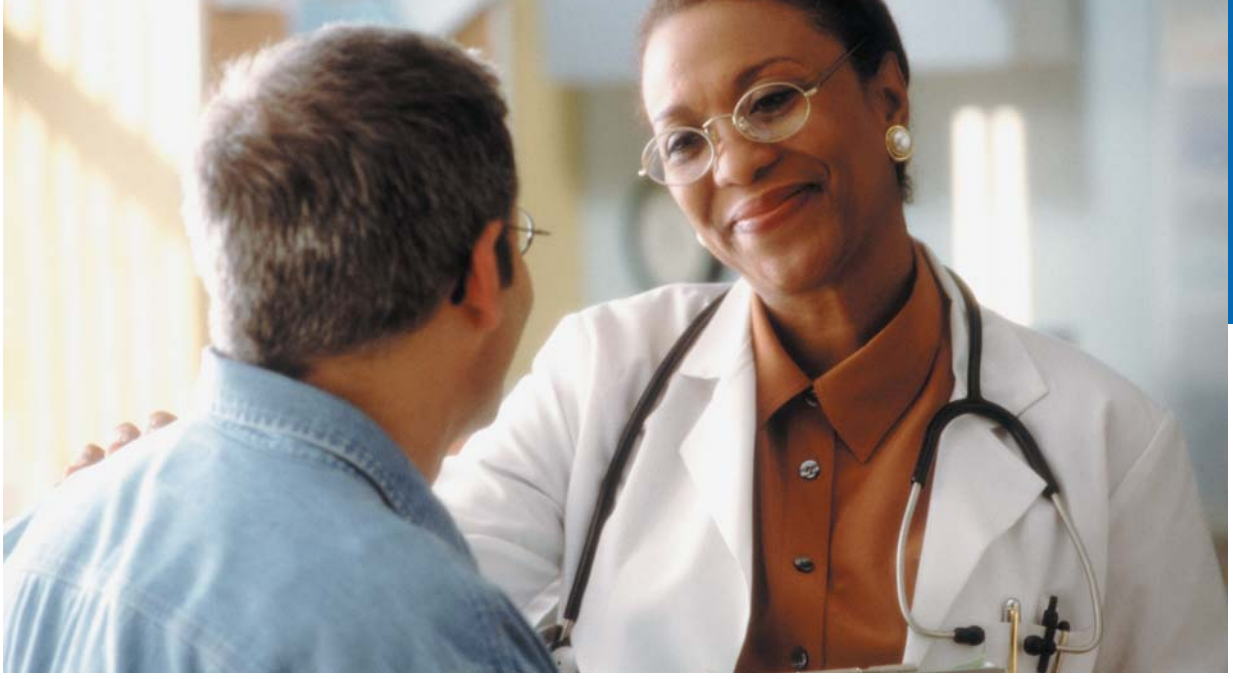
– Journalist

Clinical Trials Education and Awareness

Many people are unfamiliar with the purpose, process, or value of clinical trials, or they are fearful of them. Cancer patients often do not know that trial participation is available to them, or they may hesitate to participate because of uncertainty about insurance coverage. Moreover, adult patients and their families commonly believe that clinical trials are a last resort, to be considered only when other treatment of aggressive or recurrent cancer has failed. Yet despite these fears and misconceptions, families are much more likely to see clinical trials as the best treatment option when a child has cancer. A majority of children with cancer are treated in clinical trials, compared with only three to five percent of adult patients. A speaker urged that the public be helped to understand that trials should be among the first treatment choices considered for both adults and children when an appropriate trial is available.

Highly visible public education campaigns and events (e.g., sponsored races and walks, cycling tours) in recent years appear to be having a positive effect on public awareness and understanding of the value of clinical trials. In fact, such efforts, together with activities aimed at increasing physician participation, appear to be boosting overall clinical trial enrollments. After many years during which annual accrual totaled about 20,000 patients, NCI Cooperative Group trials accrual rose from just over 20,000 in 1998 to an estimated 27,000 in 2004. Moreover, a number of key NCI-sponsored trials have accrued patients much faster than expected.[168] Unfortunately, however, some patients become aware of clinical trials and ask to participate, only to find that no appropriate trial is available because of geographic inaccessibility, lack of insurance coverage, or other health problems that cause them to be ineligible.

Along with these apparent improvements in trial participation, concerns have been raised by some medical ethicists as to whether some clinical trials promotion (e.g., paid advertising by certain groups) inappropriately blurs the distinction between research and treatment, since some evidence indicates that patients on trials have no better outcomes than those treated outside of trials.[169] They suggest that patients may not understand at the time they enroll that the primary purpose of clinical trials is data collection to support the development of future treatments (particularly in early-phase trials), rather than treatment of the trial participants. The National Bioethics Advisory Commission has called this the "therapeutic misconception,"[170] since most patients do have an expectation of personal benefit.[171] This issue underscores the importance of effective informed consent procedures.



It may take that next generation of cancer survivors to really walk in the door and say, "I don't want to be treated here unless you can show me that your treatment is as good as a clinical trial or you can offer me a clinical trial if there is not an appropriate therapy."

– Cancer survivor advocate

Health Professional Education

According to speakers, targeted health professional education is needed to: (1) increase adoption of recommended cancer screening, preventive interventions, and other evidence-based cancer care, (2) encourage adoption of new treatments and technologies, and (3) enhance provider understanding of and participation in clinical trials.

Provider Education to Increase Adoption of Cancer Screening, Preventive Interventions, and Other Evidence-based Care

Speakers underscored the crucial, but often underappreciated, role of the primary care provider in translation. These providers, who may be the only doctor many patients see, have an important role in primary and secondary cancer prevention, particularly in the elderly.[172] Many of these physicians require education and encouragement to more actively counsel patients about cancer risks and preventive measures. Screening and prevention tend not to be discussed during illness-oriented visits due to focus on the presenting problem, lack of time, and lack of nursing or other staff to provide patient education in these areas. A recent study[173] indicates that primary care physicians are most likely to discuss colorectal cancer (CRC) screening during preventive care visits, suggesting that provider education to encourage such discussions with older patients during illness-oriented visits could markedly improve CRC screening rates in this population, which is at highest risk for this disease.

We now recognize that publishing an article or a systematic review alone will not transform practice.

– Health services research director

Primary care physicians and oncologists also should provide support and direct patients to available and accessible specialty resources, such as dieticians, exercise therapists, and smoking cessation programs. But these recommendations must be made with an understanding of the patient's insurance status and income, which may limit access to such services. Of note, Medicare now provides coverage of smoking cessation counseling for beneficiaries with smoking-related diseases. In addition, providers must be cognizant that lower-income individuals (including the elderly) often are unable to afford healthy foods such as fruits and vegetables, and many of all ages who work have little time for food preparation, physical activity, or support groups (e.g., for smoking cessation, weight control). In this respect, cancer risk-promoting behaviors may be driven more by economics than by choice,[174,175] and the provider therefore must tailor his or her recommendations to these realities. Providers also must tailor their recommendations to patients' cultural values, belief systems, and behavioral differences.

Provider Education to Facilitate Adoption of New Treatments and Technologies

The constantly increasing volume of information a health care provider must absorb to remain current in the knowledge base needed for clinical decisionmaking, coupled with intensifying time constraints, is a significant barrier to achieving dissemination and adoption of research advances into community clinical practice. According to one estimate, the knowledge base of physicians is more than two million pieces of information, with a doubling time of 15 to 20 years; this means that to deliver a current standard of care, a physician must relearn everything he or she knows twice in the course of a career. Estimates are similar for other cancer care professionals.[176]

This information overload is exacerbated by the proliferation of dissemination channels. Speakers noted that it is no longer uncommon for providers to learn about clinical trials or new drugs from patients who bring information gathered from Internet searches to their appointments. In addition, like members of the public, health care professionals may not always know whether media reports of research findings or individual reports in medical journals are sufficient evidence to prompt a change in practice. Many community physicians are skeptical about the generalizability of research findings to their own patient populations.[177] A related barrier is the limited informatics skills of many providers, which prevents them from efficiently seeking information they require to verify the relevance and reliability of new evidence. Electronic health information systems with "just in time" links to screening, diagnosis, and treatment guidelines, including appropriate clinical trials, are envisioned as an important tool to help overcome these dissemination and adoption barriers.

Speakers also remarked that some physicians view treatment guidelines as an encroachment on their professional judgment, but fear that failure to follow guidelines is a possible invitation to malpractice litigation. Many managed care plans profile physician practice patterns and compare them with expected use of evidence-based interventions. This activity often is aimed at cost containment, but also can be used to demonstrate differences in patient outcomes. The overwhelming majority of physicians want to provide the best possible care to their patients, speakers noted, and showing providers data demonstrating that their practice patterns are outside the acceptable range of variation in terms of patient outcomes is effective in fostering acceptance of change.

Provider Education about Clinical Trials

As indicated above, the vast majority of cancer patients are treated in the community. It is imperative that the family physicians and internists who refer patients with suspected cancer to community oncologists, and the oncologists themselves, understand and are open to the possibility of clinical trial participation for their patients. Many community general medicine and cancer care providers have had little or no clinical research training and therefore need targeted education to enable them to explain clearly the process and potential value of clinical trial participation, correct misconceptions about trials, and ensure that patients' consent to participate is fully informed. Training should extend to non-physician personnel including nurses, physician assistants, nurse practitioners, social workers, and others who provide care. Speakers maintained that academic medical centers and cancer centers should assume responsibility for this training as part of their community outreach efforts, but emphasized that leadership and support will be necessary for them to carry out this activity.

Participants also raised the possibility of adapting the pharmaceutical marketing model that relies on "detail" personnel (company representatives who regularly visit physician offices to provide information and product samples) to the dissemination of information about clinical trials, as well as new research evidence, practice guidelines, and state-of-the-art prevention and treatment interventions. Such an approach can be labor-intensive, however, depending on the size of the community provider population, but speakers agreed that ways must be found to provide this education to community physicians who are the gatekeepers to clinical trial accrual.

A speaker observed that lack of education is not necessarily the barrier to greater community physician participation in clinical trials. For example, concern persists among primary care and oncology providers that they will lose patients if they refer them to a clinical trial at a cancer center or out of the geographic area. In addition, community oncologists may not want to enroll their patients in trials addressing marginal differences in survival or offer trials to patients with advanced disease when the likelihood of benefit is small. According to one speaker, refocusing trials to patients with earlier-stage and more curable disease is more likely to increase accrual and help answer questions that will save more lives. Another speaker commented that community physicians would be more willing to enroll patients in promising Phase III trials for the major cancers, but that the ancillary studies attached to many trials are a barrier to oncologists in office practices who lack the facilities, equipment, and staff to conduct the additional testing and to draw and store all of the additional samples required. It should be made possible for these physicians to enroll patients in the treatment part of the study without participating in the ancillary study.

Research Community Education

Speakers described three distinct areas in which education is needed in the research community to accelerate the translation process. First, limited understanding among researchers and particularly among community cancer care providers about regulations related to clinical trials was cited as a frequent problem that slows the organization and conduct of multisite trials and compliance with approval process requirements. As indicated earlier (pp. 24-29, The Translation Workforce), NCI and FDA have established a joint fellowship program to train a cadre of scientists knowledgeable about regulatory requirements so that these individuals can return to their institutions and apply their expertise to improve protocol development and avoid unnecessary problems during the application and approval processes. In addition, regulators need ongoing training to stay abreast of developing knowledge and technologies in cancer research to enable them to perform appropriate reviews of medical products submitted for approval.

Second, a speaker observed that most scientists understand little about the tasks or resources required to commercialize an invention, which can lead to unrealistic expectations and an inability to secure development funding beyond what is available through government grants. It was suggested that improving researchers' understanding of the business side of research translation would be of benefit.

Lastly, speakers emphasized that good communication skills (e.g., active listening, checking for comprehension) are essential to ensure that potential clinical trial participants understand the possible risks and benefits of the study, but that many investigators have had no training and little experience in this type of communication. Training in this area for both young and more experienced investigators was recommended.

Dissemination, Education, and Communication Issues Affecting Translation

14. A lead agency for cancer-related dissemination research and activities should be designated and provided with the budget and authority to carry out this crucial function.

15. The National Cancer Institute should increase significantly funding for research and implementation activities to improve dissemination and adoption of cancer research advances. As part of this effort, Comprehensive Cancer Centers should be required and funded to take an active role in disseminating new cancer-related interventions into their communities/regions and facilitating their adoption by community cancer care providers, including non-physician personnel.

16. The translation process should be expedited through bi-directional education between regulators and cancer researchers to ensure that regulators better understand rapid advances in biomedical science and technologies, and that researchers better understand and are able to navigate and meet regulatory requirements.

Public trust and community participation (including community providers, payors, advocates, and the public) are essential if research advances are to make the transition from the clinic to community cancer patients/survivors and those at risk for cancer.

Part VI

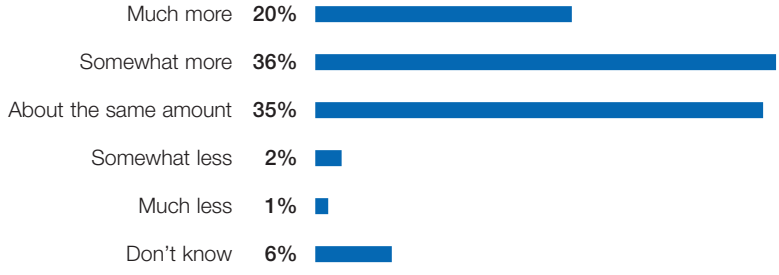
The Impact of Public Trust and Community Participation

Public Trust

Issues of public trust permeated the testimony presented to the Panel. As a speaker pointed out, trust is an expectation of certain behaviors, reliability, competence, and power sharing. The research community has fallen short in meeting the public's expectations in this area such that a longstanding distrust of medical research is firmly entrenched. Paradoxically, however, surveys suggest that most of the population believes medical research should be more strongly supported and is necessary to improve health care[178,179] (Figures 7 and 8). Nonetheless, at the individual level, distrust has been an ongoing and significant barrier to clinical trials participation, based in part on misunderstandings – that research participants are "guinea pigs" or that they may be given a placebo and left untreated. Some patients fear that they will be given standard treatment that is known to be minimally effective rather than the investigational agent. For understandable reasons (e.g., the infamous Tuskegee syphilis experiment) distrust of the medical and research communities is particularly strong and durable among some minority and disadvantaged groups. More generally, the public tends to hear most about failures of human subject protection in clinical research, such as those recently uncovered at a number of VA research facilities.[180] Patients also may fear, sometimes with cause, that clinical trial or treatment recommendations are driven by physician compensation (e.g., royalties from inventions, higher reimbursement for recommended treatment compared with other options, potential for personal financial gain should an experimental agent gain FDA approval).

Figure 7: Americans Want More Spent on Health Services Research

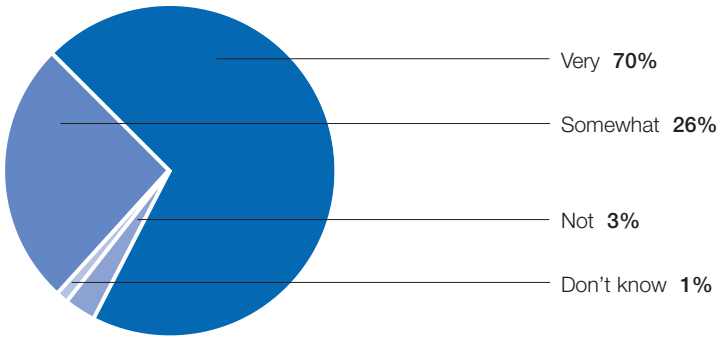
Currently, much less than one cent of each health dollar spent in the U.S. is spent on research that helps translate discoveries into medical practice. How much of each health dollar do you think we SHOULD spend?



Source: Research!America National Poll on Americans' Attitudes Toward U.S. Health Care, 2005.

Figure 8: Americans Think Investment in Research Important for Health Care

How important do you think it is that we invest in more research to assure that there is a solid scientific base for healthcare?



Source: Research!America National Poll on Americans' Attitudes Toward U.S. Health Care, 2005.

Recent findings that drug companies withheld information about possible increased cardiac risks associated with COX-2 inhibitor pain medications used by many arthritis patients and information about increased suicide risk among teenaged and other users of certain antidepressant medications continue to fuel public distrust. The cardiac risks associated with the COX-2 inhibitor celecoxib prompted NCI to halt a clinical trial (the Adenoma Prevention with Celecoxib trial) testing the drug as a cancer chemopreventive agent.[181] Distrust about the safety of pharmaceuticals also was inflamed by a recent survey by the DHHS Inspector General and Congressional testimony indicating that numerous scientists involved in FDA drug reviews felt pressured to approve drugs despite doubts about their safety and about FDA's ability to monitor the safety of drugs on the market.[182] Some have speculated on the objectivity of FDA reviews, particularly since enactment of the Prescription Drug User Fee Act of 1992. Developers submitting a drug for approval pay considerable fees to the FDA; these fees have enabled FDA to add many more review staff and thereby shorten the length of the review process.[183]

The revelations about medications already on the market have led to public and Congressional demands for better FDA oversight of post-market adverse effects and fuller and more rapid access to information about potential problems with specific medications. In response, FDA has established an advisory board to monitor drug complications and inform the public about potentially unsafe drugs.[184] In addition, FDA will soon tap into large databases such as those at CMS, to look for dangerous side effects of approved drugs. FDA also has stated that it could better safeguard the public if the agency had authority to rewrite product warning labels when a post-market problem is discovered rather than having to negotiate label language with the manufacturers, as most often is the case.[185]

Mistrust of the health care system is [an] important issue. We have to really focus on trying to garner trust that's real…there's fear and fatalism about cancer treatment; we have to overcome those.

– Cancer center director

Speakers also emphasized that some minority and underserved populations still do not receive equal care for the same stage and grade of disease as the majority population and that distrust is fed by the view that the scientific and medical communities still have not adequately acknowledged or addressed disparities in cancer care and disease outcome. Other speakers emphasized that trust must be established if cancer survivors and at-risk family members are to consent to long-term follow-up and the future use of tissue samples taken during the course of their care. To help facilitate public trust, speakers emphasized that both government and private organizations have an obligation to explain scientific and research concepts in understandable terms (see also Part V, Dissemination, Education, and Communication Issues Affecting Translation).

Community Involvement

Involving the community (the public, the health provider community, regulators, advocates, and local government) in assessing the need for specific studies, and in planning and conducting the research itself has proven effective in defusing distrust and expanding the reach of prevention and treatment advances into the community. Specifically, according to speakers, communities must be involved early in research protocol development, and researchers must ensure that the community benefits from participation and receives research results. Community involvement and support is particularly crucial to ensure the sustainability of interventions shown to be of benefit.

We need to accelerate the dissemination of effective community-based interventions and develop long-term partnerships between the cancer centers [and] underserved communities that are mutually beneficial and culturally relevant.

– Community cancer researcher

Several speakers emphasized the particular importance of building trust between researchers and minority communities. More important than outreach, they indicated, is "in-reach" – understanding the needs and barriers within communities, establishing relationships, and entering the community through and with the support of respected leaders and organizations, such as the local church. Such approaches, explained one speaker, were a crucial factor in the success of an oncology clinical trials program in Tennessee that achieved a 15 percent accrual rate among newly diagnosed cancer patients screened for trial eligibility over a four-year period – far exceeding the national norm. Ethnicity among these patients was 58 percent African American and 42 percent Caucasian, consistent with their representation in the local population.

In October 2004, the NIH Council of Public Representatives presented draft recommendations to the NIH Director on ways to ensure that researchers dedicate more attention to interaction with their communities.[186] These short- and mid-term recommendations focus on training researchers to communicate with geographic, social, racial, and ethnic communities, forming partnerships with health care providers and the public, educating the public about the need for and benefits of clinical research, using best practices in public communication, acknowledging the contributions of study participants, and disclosing the results of clinical trials to them and to the public.

Testimony presented to the Panel highlighted a number of ongoing efforts consistent with these recommendations. Since 2000, NCI has funded the Special Populations Networks, which recently were reconfigured as the Community Networks Program (CNP).[187] As of February 2005, 25 CNP sites were funded; their goal is to reduce cancer health disparities by conducting community-based participatory education, training, and research among racial/ethnic minorities and underserved populations and to improve cancer interventions in these communities. The CNPs actively involve their communities in planning and conducting cancer prevention and early detection research.

CDC and NCI have established a Cancer Prevention and Control Research Network and are co-funding eight CDC Prevention Research Centers. Their purpose is to build a community-based participatory research infrastructure to expand the comprehensive cancer control evidence base, replicate and disseminate proven cancer control interventions, and create evaluation tools for use by states in developing their cancer control plans.

Social networking, [the] use of social institutions as an entry point into the community, and understanding the cultural belief system and literacy levels to inform the development of cancer prevention materials and strategies are necessary.

We have to work on promoting and sustaining a long-term relationship with the community, because it's not for [a grant period of] five years that we want to intervene. We want to effect the change permanently…and the only way to do that is through a successful community-based partnership.

– Cancer center director

Similarly, AHRQ promotes community-based participatory research and has convened foundation and other government partners, researchers, funders, and leaders of community organizations to discuss how to dispel community distrust and increase participation in research.[188] Though not cancer-specific, the recommendations developed apply fully to cancer-oriented community-based research; these include actively combating the existing legacy of distrust, attracting more people from underrepresented and low-income groups into health professions and research, increasing resource sharing between universities and the communities, and ensuring that the entire community is represented in project planning and execution. Optimally, these NCI, CDC/NCI, and AHRQ networks will coordinate their efforts, along with those of other community-based research efforts and the NCI cancer centers to make the best use of available resources and maximize the involvement of communities in cancer-related research from which they may benefit.

Involving Advocates in Translation

Speakers asserted that the research community could make fuller use of the expertise of cancer advocates and survivors, who can help maintain a patient-centered focus on research projects. Advocates now participate in most peer review processes, though generally not as scientific reviewers. A speaker described an integrated community model for advocate involvement that involves the advocates from the beginning of the research planning process, rather than at the end, as is often the case. In this model, informed advocates work with scientists on research focus, educate policymakers about the importance of the research, and disseminate information about the research to patients, survivors, their families, and the community at large.

NCI has expanded its mechanisms for obtaining input from the advocacy community over the past several years. In addition to the Director's Consumer Liaison Group (DCLG)[189] and the Consumer Advocates in Research and Related Activities,[190] approximately 30 of the 58 SPOREs have established Patient Advocate Research Teams (PART),[191] which are funded jointly by NCI and the AVON Foundation. Though the program is unique to each site, the overall focus of the PART program is to provide input that will help improve research results, in part by identifying common SPORE issues and helping to resolve them, and by building resource banks for SPORE clinical trial development.

To further improve communication with the cancer advocacy community and enhance its participation in research-related program planning, NCI recently launched the "NCI Listens and Learns" Web site (http://ncilistens.cancer.gov/). The site is a pilot forum for NCI to ask members of the community for input and for members of the community to offer NCI feedback on key issues. It aims to facilitate dialogue between NCI and two distinct segments of the community: registered cancer advocacy organizations and members of the general public. The pilot forum was designed, and is being overseen, by the DCLG.

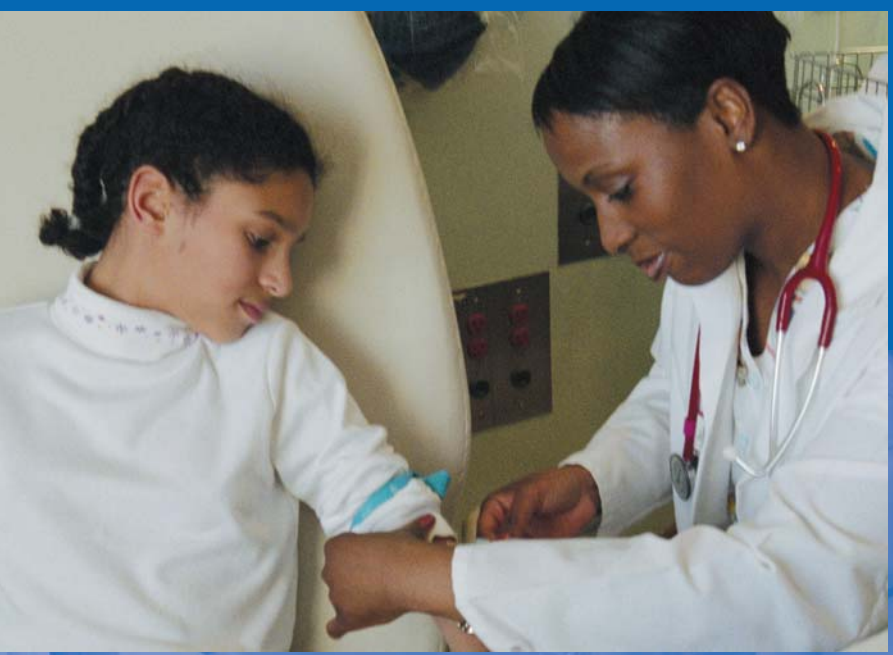
The Impact of Public Trust and Community Participation

17. Clinical and prevention research funders should require community participation early in protocol design and in research implementation.

18. Research results must be shared with the individuals and communities that participate in clinical trials and other studies.

19. Clinical and prevention research grantees should be required to include as part of the grant application a plan for disseminating and sustaining new interventions into the community.

20. Existing community-based participatory research models should be evaluated to determine the potential for adopting them in other geographic areas and populations.



Even if research advances are translated into cancer prevention and care improvements, the burden of cancer will not be reduced unless all segments of the population have geographic and financial access to appropriate clinical trials, approved therapies and technologies, and the information that will enable individuals and their health care providers to identify and evaluate cancer-related prevention and care options.

Part VII The Importance of Access to Successful Translation

…the single most effective way to reduce disparities in cancer would be to ensure that everything we know should be delivered *is* delivered to all American people.

– Cancer Center director

The Panel has reported extensively on issues of access to cancer care,[192,193,194] as have others.[195,196,197] In this inquiry, many of these pervasive issues were reiterated. Encouragingly, however, several potential models for resolving some of the problems were described. This significant testimony underscores the importance of access to successful translation.

Access to Clinical Trials

Although about 20 percent of patients are medically eligible for clinical trials[198] (assuming availability of an appropriate trial), trial participation among adult cancer patients remains at about three percent, and minority and other underserved populations continue to be underrepresented in clinical research. A recent study found that elderly patients (those aged 65 and older) comprise 60 percent of Americans with cancer, but only 36 percent of the patients enrolled in clinical trials; only elderly women with breast cancer in trials of hormonal therapy for both early and advanced disease had clinical trial participation consistent with the age distribution of their disease in the general population.[199]

Speakers remarked that limited access to cancer prevention and treatment trials outside of cancer centers and other academic medical centers remains a serious barrier to greater trial participation. In 1983, NCI established the Community Clinical Oncology Programs (CCOPs) to extend the reach of NCI-supported clinical cancer research into the community by enabling physician practices, community hospitals, and medical centers to affiliate with the program. In 1989, Minority-based CCOPs were added to increase the participation of facilities serving largely minority populations. Approximately one-third of all patients in NCI-sponsored treatment and prevention trials are recruited through CCOP facilities.[200] Yet, as industry-sponsored clinical trials have become more prevalent, CCOP participation rates have been challenged by the higher per-patient fees industry sponsors pay providers for enrolling and monitoring patients on trial, compared with fees paid by NCI (or other Federal research sponsors). Overall national trial participation rates, however, have not changed with the changing balance in clinical research sponsorship.

…you also have to have clinical studies that are appropriate for your patient population and not appropriate only for the select, elite patients who may not represent all the issues that the average patient presents in oncology. This means that patients who are not in the best health should have available clinical studies.

– Community clinical oncology program director

Some cancer centers are devising clinical trials networks in their geographic regions to expand access. The Panel heard testimony describing a "hub-and-spoke" network model that ties together area cancer centers and more than 40 community providers, including hospitals, freestanding medical and radiation oncology outpatient centers, and medical offices in the region. In addition to improving clinical trials availability and accrual, the network has been successful in bringing state-of-the-art cancer care (such as intensity-modulated radiation therapy) to communities in the region. The network leadership has active, ongoing communication and education programs with all network participants to ensure that concerns are addressed, and information technology is a central tool in maintaining communication among network participants.

It takes me about three times as much time to put a patient on a clinical trial as it does to give standard therapy….It is much, much harder, it takes much more work….

– Community oncology researcher

…in our own medical center…we have eight different sites, all of which have faculty, and some of those faculty are full-time at the community site…they go from home to their community site and [back] home every day and maybe, videoconference with us once a week so that they are engaged and involved. And we put the stuff on their computers so they can see it and know what trials are open to them.

– Academic medical center and cancer center director

In another area of the country, a small, regional disease-oriented consortium of providers at academic medical centers and a local cancer center has enhanced institutional resource and information sharing and improved continuity of care for melanoma patients. At several sites in the western and southern United States, NCI-supported navigator programs are reducing barriers to trial participation among Native American and other underserved populations and bringing state-of-the-art radiation oncology clinical trials to areas with limited health infrastructure.

Cost is another key barrier to trial participation. A representative from a large not-for-profit managed care organization estimated that the mean cost of care for members participating in clinical trials exceeds the cost of usual care by approximately 10 percent. These added costs are passed on to the plan membership as a whole as dues increases. He acknowledged that patients participating in trials may incur greater out-of-pocket costs compared with patients receiving standard care. In addition to medical care costs, trial participants may have to take extra time off from work, pay for additional childcare, and incur greater travel-related costs that may include lodging, meals, fuel, tolls, and parking.

Paperwork associated with enrolling and monitoring patients on trials was cited as a significant disincentive deterring community physicians from participating in clinical research. Most community physicians lack the time and support staff needed to enroll and follow patients on trials. A speaker suggested that in geographic areas with cancer centers, the center should be provided funding to employ a research nurse who would travel among community hospitals and physician practices to assist with documentation. Speakers also stated that adequate reimbursement for the added time and cost of research activities would enable more community providers to participate in clinical studies.

Access to Approved Therapies and Technologies

Relatively few people are able to pay the full cost of cancer care out-of-pocket, therefore, for most Americans, access to state-of-the-art care, or even to minimum standard care, is determined by the coverage and reimbursement decisions of public and private payors. In some cases, individuals find that needed preventive, early detection, treatment, and supportive services are covered by their insurance plans, but that the level of reimbursement leaves a co-payment that is unaffordable. A speaker suggested that a new class of underinsured people – particularly Medicare beneficiaries and retirees whose health benefits are shrinking[201] – is developing in the United States: those with health insurance, but without supplemental insurance to cover co-payments.

Concerns about future benefits for Medicare beneficiaries as provisions of the MMA are implemented are discussed above. Medicare beneficiaries' access to cancer prevention and treatment clinical trials must be monitored carefully to ensure that neither legislative changes nor policy decisions of the variously autonomous regional Medicare carriers limit access to appropriate trials or the best available care. Vigilance in this regard is particularly important, since private payors historically have taken their lead on coverage decisions from Medicare.

The Medicaid program, funded by Federal payments to states and state funds, provides health care for the poor who meet state-defined eligibility standards. DHHS, through CMS, is offering states somewhat greater flexibility in designing their programs, and encouraging expanded coverage for children. However, anticipated Medicaid cuts[202] in the form of benefit limitations for other optional populations, or other benefit reductions, and reduced Federal payments to states already struggling under the burden of their burgeoning Medicaid programs will almost certainly put new preventive, early detection, state-of-the-art treatment interventions, and improved palliative care further out of the reach of the poor. For example, the newest targeted and "designer" therapies based on individual genetic profiles are unlikely to be made available to these populations.

Speakers noted other factors with the potential to limit patient access to approved therapies and technologies. Some community providers may resist changing their established practice patterns; it was suggested that these physicians must be provided data demonstrating clearly that specific aspects of the care they provide are inconsistent with the best available medical evidence on alternative practice patterns that improve patient outcomes and/or cost effectiveness. Individual and institutional providers also may resist change if they have vested interests in older technologies (e.g., imaging), particularly if they are unable to acquire newer technologies with reduced practice income due to lower reimbursements.

Patient access to the most appropriate therapies may be limited if physicians fear losing patients whom they refer to cancer centers or other ancillary care providers. Lack of time and support staff needed to explain and administer newer treatments also may limit patient access. Further, speakers noted that older patients may not be offered newer or more expensive therapies because of Medicare or other payor reimbursement limits, because physicians believe elderly patients cannot withstand aggressive treatments, or due to other provider bias.

Several speakers maintained that the structure and emphasis of the health care system (e.g., acute rather than preventive care, fragmentation of care, concentration of ancillary services in highly populated areas) prevent millions from receiving preventive services, screening, treatment, and supportive care known to be of benefit. NCI has produced data demonstrating that higher cancer incidence and mortality occurs in geographic areas with lower socioeconomic status (measured in part by family income, the percent of the population living in poverty, and educational attainment levels).[203] As the President's Cancer Panel has reported previously,[204,205] these geographic areas typically have fewer available, accessible, and culturally acceptable cancer screening, diagnosis, treatment, and supportive services, and higher numbers of uninsured people. It is important to note that not all of these underserved areas are rural; many are poor urban neighborhoods across the country. A speaker suggested that absent any additional research discoveries or new interventions, the burden of cancer in these geographic regions – and nationally – would be substantially reduced if existing evidence-based prevention, early detection, and treatment interventions were made consistently and promptly available to the populations now suffering the highest cancer incidence and mortality rates.

Access to Information

Individuals who have the opportunity to learn about advances in cancer prevention and treatment create demand for quality care. Newly diagnosed patients need access to information to explore treatment options and make informed decisions; family members need up-to-date information to provide the best care for loved ones with cancer. Survivors need access to the most current information about interventions for late effects of treatment, second cancers, and other medical issues related to their disease. In all cases, information must be presented in understandable language, in usable formats, and in culturally appropriate ways in order to be of value.

Literacy and Language Issues

The Panel has reported previously on the effect of limited literacy and health literacy (see definitions, Exhibit 3) on an individual's ability to make informed health decisions for him or herself, or for family members, and these issues have been well documented by others.[206,207] The volume and complexity of information an individual must absorb upon receiving a cancer diagnosis is overwhelming even to people who are accustomed to reading, processing, and discussing large amounts of text and quantitative information. Importantly, the prevalence of inadequate or marginal health literacy is higher among older people – the population most at risk for cancer – compared with younger population groups, as well as among the poor and some minority groups.[208]

As the U.S. population continues to grow more diverse, health care providers, researchers, and health communicators increasingly are challenged to provide cancer prevention and cancer care information in culturally appropriate ways in the wide array of reading levels and languages required. Many medical centers struggle to locate translators with sufficient medical knowledge to assist health care providers in communicating with patients who speak little or no English. A speaker stated that it can cost up to $1,500 to have one page of an informed consent document translated from English into another language.

Exhibit 3: Literacy and Health Literacy – Definitions

Literacy	The ability to read, write, and speak in English and compute and solve problems at levels of proficiency necessary to function on the job and in society, to achieve one's goals, and to develop one's knowledge and potential. (National Literacy Act of 1991)
Health Literacy	The degree to which people have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions (Parker, et al. Health literacy: a policy challenge for advancing high quality care. (*Health Affairs,* 2003;22[4])

The reading level and complexity of informed consent documents has been a concern for many years. As a speaker emphasized, if a person does not understand the document's text and terminology, consent cannot be considered informed. In 1998, an Informed Consent Working Group comprised of physicians, nurses, patient advocates, IRB members, ethicists, legal experts, communication experts, and pharmaceutical industry representatives was convened by NCI, the Office for Protection from Research Risks (now the Office of Human Research Protections, OHRP), and FDA, and issued recommendations for developing informed consent documents for cancer clinical trials.[209] The recommendations are used by investigators and IRBs when writing and reviewing consent forms. The working group also developed, among other components of its report, a template that includes all of the federally required elements, a checklist to assist in standardizing format and reading level, and sample questions to help the researcher assess potential participant understanding. Speakers suggested, however, that despite

…cultural and language barriers play into the acceptance of research. It is very difficult to go through a 20-page consent form with a well-educated, English-speaking patient. It is much more difficult using the AT&T language translation line [to explain] it in Tagalog or Farsi.

– Managed care organization medical director

the availability and use of these tools, ensuring informed consent remains a significant problem, especially among prospective research participants with low literacy and health literacy skills, and those whose first language is not English.

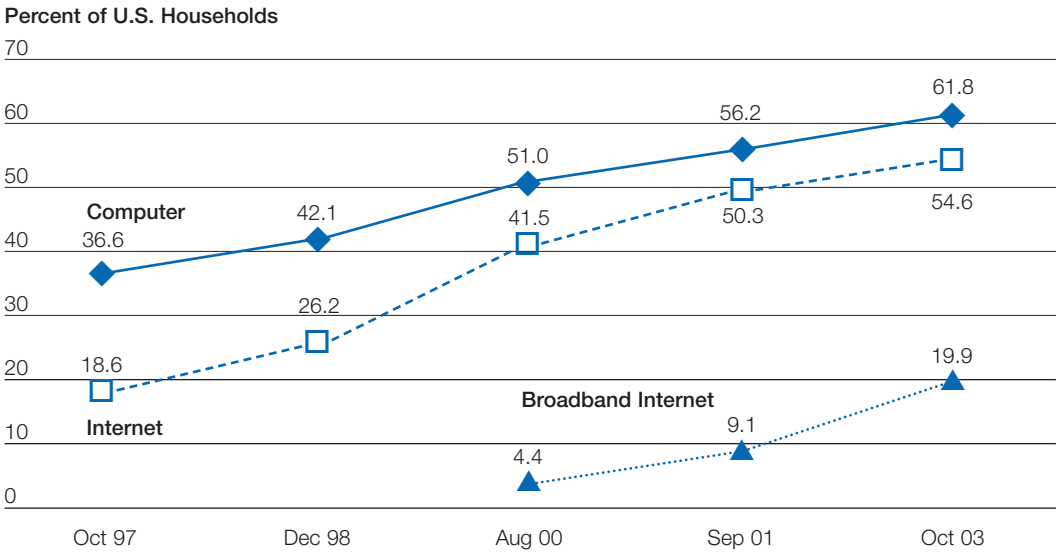
Internet Health Information

The number of U.S. households with a computer and Internet access continues to climb (Figure 9), and an increasing number of the general U.S. population now use a computer to access health-related information – an estimated 93 million adults in 2002.[210]

Many of the newer health information sources are being developed only in online formats, yet the largest population of people with cancer – those 65 years of age and older – are the least likely to go online for cancer information. A recent Kaiser Family Foundation survey of older Americans[211] found that only 31 percent have ever gone online, and only 21 percent have used the Internet to find health information. Survey respondents listed the Internet fifth on a list of media sources of health information (following television, books, newspapers, and magazines). Older seniors (those 75 and older), women, and those with lower incomes and less education were the subgroups of seniors least likely to have gone online. Notably, more than two-thirds (70 percent) of the next generation of seniors surveyed (aged 50 to 64 years) have used the Internet for any reason, and 53 percent have sought health information online. This group rated the Internet as their number one source of health information. These findings indicate that while the Internet will become an increasingly important source of health information for future generations of seniors, a significant digital divide exists for the current population of seniors that may well impact the health-related decisionmaking of many of these individuals.

Due to lack of communications infrastructure, populations in rural and remote areas also have limited Internet access and therefore less access to information about cancer or other health issues. These groups include Native Americans,[212] Alaska Natives, and the rural poor. Lower-income populations, regardless of location, tend to have less online access at home; though access at libraries and other locations is increasing somewhat, it is access at home that is associated with meaningful participation in the resources of Internet commerce and information sources. It is estimated that less than one-quarter of those with annual incomes below $25,000 have Internet access at home, compared with over three-quarters of those with incomes above $50,000.[213] The disabled have reduced access because of the limited investments to date in assistive technologies development.[214]

Figure 9: Percent of Households with Computers and Internet Connections, Selected Years, 1997-2003*



*Note: 2001 and 2003 reflect 2000 Census-based weights and earlier years are 1990 Census-based weights.
Source: *A Nation Online: Entering the Broadband Age*, U.S. Department of Commerce, September 2004.

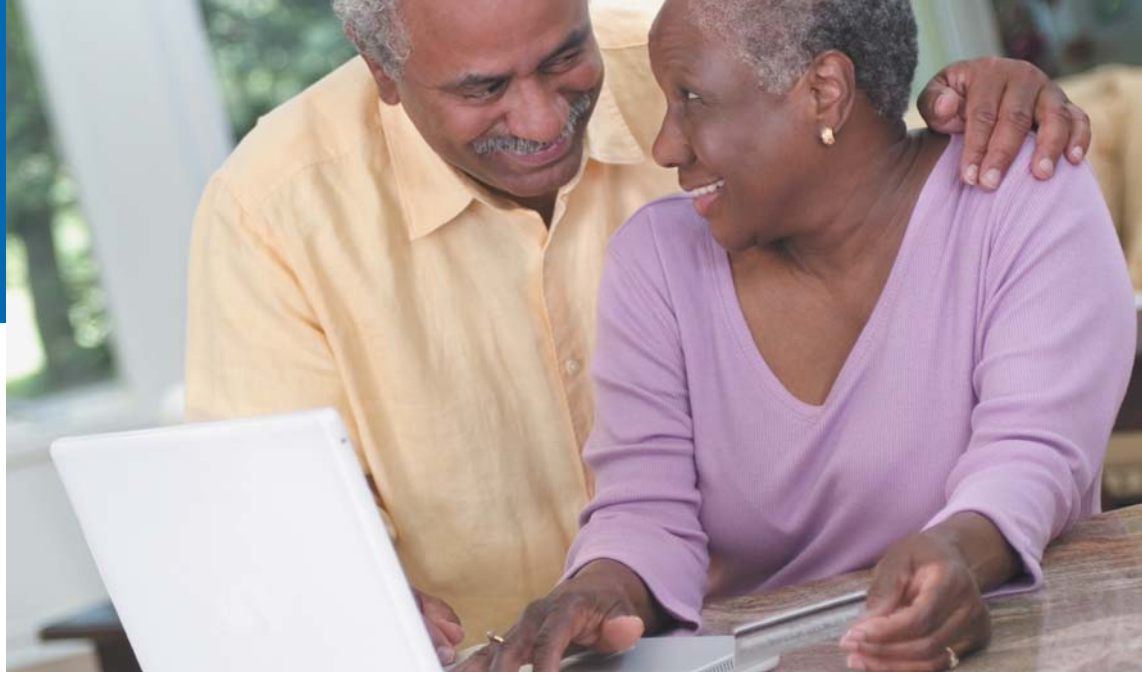
…different people or different groups have differential capacity for accessing information, using that information, and putting that information into practice.

– Professor, community-based research

Adults with low literacy also may encounter obstacles when searching the Internet for health information; most health Web sites require at least high school reading proficiency to make optimal use of the available information. In addition, a small study of Internet use by low-literacy adults[215] noted that subjects had difficulty generating search terms and were reluctant to use links to obtain more information.

Patient advocates collaborated with NCI to simplify the language contained in cancer information statements and clinical trials descriptions available through the Physician Data Query (PDQ®) database,[216] and the information now is being refashioned to provide more Web-friendly presentations. Users are offered a variety of view and print options, and the patient-oriented summaries also include illustrations of key medical concepts. Medical and scientific terms are linked to an online dictionary.[217] Physician-oriented information summaries include reference lists and links to literature citations in the National Library of Medicine's PubMed® database.

Cancer patient/survivor advocates also have urged clinical trial sponsors to make it easier for people with cancer to find clinical trials for which they may be eligible and to streamline the enrollment process. NCI currently is evaluating technical and privacy safeguard issues associated with data tools that would enable patients to create a personal online information profile that they could use to help expedite trial matching.[218]



In 2001, a colorectal cancer advocacy group teamed with university researchers and an online cancer resource center to establish a database through which to facilitate patient enrollment in clinical trials.[219] Patients could enroll either on the Internet or through a telephone call center. The investigators found that more patients enrolled via the Internet, but that they tended to be younger than those using the call center; this finding is consistent with other research concerning Internet use by age group. Overall, those who registered were predominantly female and Caucasian.

Public Access to Research Results

Cancer patients/survivors, the general public, and health professionals (particularly those in small group or individual practices and/or not affiliated with large medical centers) increasingly have demanded timely access to the results of research funded with public dollars. Most of these studies are published in one of many dozens of medical journals for which each annual subscription may cost several hundred to several thousand dollars. Not surprisingly, subscribers are mostly large medical and academic institutions and to a lesser extent, public libraries. In response to this situation, so-called "open publishing" or "open access" policies are being established.

Beginning in May 2005, NIH's Enhanced Public Access Policy requests authors whom it funds to submit electronic versions of their manuscripts (once they have been accepted for publication) to the National Library of Medicine (NLM), at which point their research results would become available to the public at no cost through the PubMed Central digital archive.[220] However, authors have the flexibility to wait up to 12 months after journal publication to submit their manuscripts to NLM.[221] This optional delay responds to objections primarily from nonprofit publishers who maintain that the anticipated loss of subscriber revenue would cripple their fiscal viability and compromise the peer review process, although NIH-funded research only makes up approximately 10 percent of all research published in medical journals.[222] Some patient advocates and others maintain that the voluntary nature and 12-month delay allowance undermines the intent of open access rules and will prevent patients from having access to the most current information when they are faced with making difficult treatment choices.

Other organizations are taking steps to increase timely public access to research results. A consortium of technical publishers, patientINFORM, proposes to allow the American Cancer Society, American Diabetes Association, and American Heart Association to select hundreds of medical journal articles to make available at no cost through the organizations' Web sites.[223] The three groups would add new articles over time, with explanatory text from experts in the relevant field. The arrangement, developed as an alternative to the NIH plan, is scheduled to begin in Spring 2005 and may be expanded to other organizations.

The nonprofit Public Library of Science (PLoS)[224] was initiated in 2000 and launched in 2003 to make scholarly science publications freely available to the public and to scientists. It currently offers two peer-reviewed online journals, *PLoS Biology* and *PLoS Medicine*. The journals, which currently are supported in part by donations, charge a $1,500 fee to authors to have their papers published in the journals and to cover the costs of peer review, editorial oversight, and production. The expectation, however, is that the research sponsors, rather than the authors, will pay these fees.[225]

In addition, the Internet search engine Google™ recently launched a beta (test) version of Google Scholar,[226] which restricts search results to material appearing in academic texts, journal articles, theses, preprints, and technical reports in any research area. Google also plans a six-year project to digitize and archive approximately 15 million books from the major research libraries of the world. Intellectual property and copyright issues remain to be resolved.

Public access to clinical trials results – both positive and negative – has been an issue of increasing prominence in the wake of allegations of suppressed information about the safety of COX-2 inhibitors, antidepressants, and other medications. Pharmaceutical companies currently are required under the 1997 FDA Modernization Act (P.L. 105-115) to post data on clinicaltrials.gov (authorized by FDA but operated by the National Library of Medicine), but only for open trials that involve treatments for life-threatening diseases or conditions. All government-sponsored trials are posted on the site. Drug companies must inform FDA of all clinical trials performed in the United States; however, data must be publicly disclosed only if the trial is part of an application for FDA approval. FDA posts selected New Drug Application (NDA) reviews on Drugs@FDA.[227,228]

Pharmaceutical companies have resisted posting data on early-stage trials and those with inconclusive or negative outcomes. A number of pharmaceutical companies have recently agreed to post the results of trials, including some early-stage trials, on one of a number of Internet registries or their own Web sites. It has been suggested that to decrease confusion and maximize public access, all trials should be listed on a single government-managed site;[229] legislation is being developed in Congress that would compel such a registry.[230] An expanded clinicaltrials.gov Web site has been proposed as the registry site, but FDA has indicated that it has insufficient enforcement authority under current law to compel industry compliance.[231] Other suggestions include expanding Drugs@FDA and linking it to clinicaltrials.gov.[232]

The move toward greater public access to all clinical trial results has been strengthened by the September 2004 decision of the International Committee of Medical Journal Editors to publish papers on completed studies only if they have been listed on a free public, searchable registry at or before the start of patient enrollment.[233] However, the possibility exists that to avoid publication of numerous negative trial results (with potentially negative impact on a firm's competitiveness or stock price), companies may hesitate to test an agent under development for all of its possible indications.[234] Should this occur, effective new interventions for cancer prevention or treatment may be missed.

Other Sources of Cancer-Related Information

NCI's Cancer Information Service (CIS), established nearly 30 years ago, continues to be a valuable source of cancer information, including information about clinical trials, particularly for individuals who do not use computers or prefer to obtain information in print format or by telephone (the service, at 1-800-4-CANCER, receives approximately 250,000 calls per year). Through 15 regional centers, CIS works with a network of local partners, distributing multimedia materials designed for diverse audiences, including those with limited literacy. A growing selection of materials is available in languages other than English. In addition, CIS has added an instant messaging service, LiveHelp, accessible though the NCI Web site.

Telephone, print, and online cancer information also is available through the many large (e.g., CancerCare, American Cancer Society, Lance Armstrong Foundation, National Coalition for Cancer Survivorship) and smaller, often cancer-site focused, advocacy and support organizations throughout the country. Some of these organizations provide materials developed for limited literacy and specific racial, ethnic, or cultural population groups. Additionally, many cancer centers and other medical centers have established patient information and support programs; some of these include resource centers with print and audiovisual material libraries.

RECOMMENDATIONS

The Importance of Access to Successful Translation

The President's Cancer Panel has made recommendations to improve access to cancer care. These recommendations may be found in the following reports:

- *Living Beyond Cancer: Finding a New Balance*, May 2004
- *Facing Cancer in Indian Country: The Yakama Nation and Pacific Northwest Tribes*, December 2003
- *Voices of a Broken System: Real People, Real Problems*, March 2002

The translation continuum described in this report – spanning the multitude of processes needed to turn a laboratory discovery into improved cancer care that is available to all who need it – is unbalanced and obstructed by bottlenecks that are keeping cancer research advances from reaching the public. The Panel's recommendations for action to remedy major barriers now limiting research translation, included in each of the preceding chapters, also are summarized in Appendix C, together with suggested responsible stakeholders or other entities. Importantly, those suggested do not necessarily comprise the universe of stakeholders or others with an interest in these issues.

Conclusions

The critically needed changes described in this report cannot be achieved without cost. Specifically:

- Increased funding for translation-oriented research – particularly collaborative, team efforts – is urgently needed across the translation continuum. Targeted Federal funding for translation-oriented research is drastically out of balance relative to financial commitments to basic science. Ways must be found to increase human tissue and clinical research resources without slowing the discovery engine. Supplemental funding may offer a temporary solution, but will be inadequate in the long term.

- A funding gap exists for agents or other interventions that require further development before they are ready for commercialization, but which have exhausted available public funding.

- The translational research infrastructure is inadequate to enable the work that needs to be done; resources must be committed to develop the tools and workforce required.

- Research on cancer prevention must receive greater priority and funding to expand the body of knowledge that can be translated into new interventions to reduce cancer incidence and mortality and reduce the overall cancer burden. Additional research also must be funded to improve cancer early detection interventions.

- Dissemination research must be expanded and accelerated to improve understanding and develop strategies that will increase the adoption rate of new cancer care interventions.

- Cancer centers and academic centers must be adequately funded to conduct outreach and dissemination activities. Institutional commitment is essential to sustain outreach to improve clinical trials accrual, disseminate research findings, and help ensure that advances are adopted into standard practice. Network models may offer efficiencies of scale and opportunities to extend the reach of cancer centers and academic institutions, but funding will be needed to foster and maintain regional linkages.

- Training funds are needed to strengthen and expand the translation research workforce and improve public understanding of cancer and cancer research. Specifically, funds are needed to support: (1) training and mentoring to attract investigators to translational research careers, (2) continuing training of translation-oriented investigators, (3) community provider training on clinical trials and new therapies, (4) investigator and community provider training on regulatory requirements related to drug and device approval, and (5) public education.

- Outcomes and cost-effectiveness research is needed to better understand the benefits and actual total costs of care for various types of cancer at different stages of disease; for outreach, prevention, and early detection activities; and the components of total cost. Without this information, it is difficult to assess the long-term efficacy of new interventions or align reimbursement strategies to cost.

The funding necessary to support these essential activities across the translation continuum must be garnered, either through carefully considered reallocations of currently available funds or by identifying and committing new resources.

In addition, as this report has described, numerous initiatives have been launched or are planned to address diverse aspects of the research translation problem. The Panel believes it is imperative that the success of these efforts is assessed so that programs can be refined as needed. Therefore, the Panel further recommends:

In five years, a thorough evaluation should be conducted to assess the effectiveness of the many public and private initiatives now underway or planned to accelerate the translation of basic science discoveries into improved cancer prevention and cancer care.

Moreover, the Panel believes that:

To ensure continued progress in translating cancer research advances into new cancer care interventions, the current statutory authorities of the National Cancer Institute should be preserved in any reauthorization of the National Cancer Act.

All stakeholders in the cancer research, medical, public health, advocacy, legislative, and regulatory communities must make it their priority to ensure that biomedical advances are developed more rapidly into cancer care interventions and that this care is provided affordably and equitably to all – to prevent, control, and cure cancers to the maximum extent of our knowledge and skill. This is the commitment that was made to the American people, who finance with their tax dollars and their health insurance premiums the cancer research and health care delivery systems that together comprise the translation continuum. It is the promise on which we must deliver, and we must do no less.

References

1 Reuben SH. *Living Beyond Cancer: Finding a New Balance*, 2003-2004 Annual Report, The President's Cancer Panel, National Institutes of Health, National Cancer Institute, May 2004.

2 American Cancer Society. *Cancer Facts & Figures 2005*, American Cancer Society, Atlanta, 2005, pp.1-2. Estimated incidence figure excludes *in situ* cancers except of the urinary bladder, and basal and squamous cell skin cancers.

3 Ibid., p.2.

4 Between 1965 and 2000, smoking prevalence among adults fell by nearly half. National Center for Health Statistics. *Health, United States, 2003 with Chartbook on Trends in the Health of Americans*, Public Health Service, Hyattsville, MD, 2003, and National Center for Health Statistics, Centers for Disease Control and Prevention. Cigarette smoking among adults – United States, 2002, *Morbidity and Mortality Weekly Report* 2004;53(20):427-431.

5 U.S. Census Bureau. Current Population Reports, P25-1104, 1993.

6 Hoyert DL, Kung H-C, Smith BL. Deaths: preliminary data for 2003, *National Vital Statistics Reports*, Centers for Disease Control and Prevention, National Center for Health Statistics 2005;53(15):1-48.

7 Edwards BK, Howe HL, Ries LA, Thun MH, Rosenberg HM, Yancik R, Wingo PA, Jemal A, Feigal EG. Annual report to the nation on the status of cancer, 1973-1999, featuring implications of age and aging on U.S. cancer burden, *Cancer* 2002;94(10):2766-2792.

8 Adjusted to 2000 population standard.

9 Hock LM, Lynch J, Balaji KC. Increasing incidence of all stages of kidney cancer in the last two decades in the United States: an analysis of Surveillance, Epidemiology, and End Results program data, *Journal of Urology* 2002;167(1):57-60.

10 Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinomas incidence, *Journal of the National Cancer Institute* 2005;97(2):142-146.

11 National Cancer Institute. *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2003*, National Cancer Institute, National Institutes of Health, NIH Publication No. 02-4373, p.94.

12 American Cancer Society. op.cit., pp.1-2.

13 American Cancer Society. op.cit., p.17.

14 American Cancer Society. op.cit., p.3.

15 Brown ML. "The Economic Cost of Cancer," Presentation, The Economic Cost of Cancer Health Disparities CRCHD Think Tank, Bethesda, MD, December 6, 2004.

16 von Eschenbach AC. A vision for the National Cancer Program, *Nature Reviews: Cancer* 2004;4:820-828.

17 DeVita VT Jr. The 'War on Cancer' and its impact, *Nature Clinical Practice: Oncology* 2004;1(2):55.

18 Young RC. Cancer statistics, 2002: progress or cause for concern? *CA: A Cancer Journal for Clinicians* 2002;52(1):6-7.

19 Hartwell L. "Basic Science Leads the Charge in the War on Cancer," *NCI Cancer Bulletin* 2004;1(14):8.

20 Epstein SS. Why we are still losing the winnable cancer war, *The Humanist*, January/February 2005, pp.34-47.

21 Bailar JC III, Gornick HL. Cancer undefeated, *New England Journal of Medicine* 1997;336(22):1569-1574.

22 Leaf C, Burke D. "Why We're Losing the War on Cancer (And How to Win It)," *FORTUNE*, Time, Inc., 2004;149(6):76-82, 84-86, 88, 90, 92.

23 Freeman HP (Chair), Reuben SH (ed.). *The National Cancer Program: Assessing the Past, Charting the Future*, 1999 Report of the Chairman, President's Cancer Panel, National Institutes of Health, National Cancer Institute, May 2000.

24 Subcommittee to Evaluate the National Cancer Program. *Cancer at a Crossroads: A Report to Congress for the Nation*, National Cancer Advisory Board, National Cancer Institute, September 1994.

25 Zerhouni E. The NIH Roadmap, *Science* 2003;302:63-64, 72. See also additional material at: www.sciencemag.org/cgi/content/full/302/5642/63/DC1

26 http://spores.nci.nih.gov

27 National Cancer Advisory Board. *Advancing Translational Cancer Research: A Vision of the Cancer Center and SPORE Programs of the Future*, Report of the P30/P50 Ad Hoc Working Group, February 2003.

28 Committee on Facilitating Interdisciplinary Research. *Facilitating Interdisciplinary Research*, Institute of Medicine, The National Academies Press, Washington, DC, 2005.

29 National Institutes of Health. "Catalyzing Team Science: Report from The 2003 BECON Symposium," Bioengineering Consortium, June 23-24, 2003, Bethesda, MD. At: http://www.becon.nih.gov/symposium2003.htm (accessed 1/20/05)

30 Nass SJ, Stillman BW (eds.). *Large-Scale Biomedical Research: Exploring Strategies for Future Research*, National Cancer Policy Board, Institute of Medicine, The National Academies Press, Washington, DC, 2003.

31 Brainard J. "A Makeover for the NIH's Peer-Review Process," *The Chronicle of Higher Education*, March 18, 2005.

32 Committee on the Organizational Structure of the National Institutes of Health. *Enhancing the Vitality of the National Institutes of Health: Organizational Change to Meet New Challenges*, Institute of Medicine, The National Academies Press, Washington, DC, 2003, pp.93-96.

33 National Science Foundation. *FY 2004 Guide to Programs*, Document Number: nsf04009. At: http://www.nsf.gov/publications/pub_summ.jsp?ods_key=gp (accessed 3/14/05)

34 National Institutes of Health. *The NIH Director's Panel on Clinical Research Report to the Advisory Committee to the NIH Director*, December 1997. At: http://www.nih.gov/news/crp/97report/index.htm (accessed 3/9/05)

35 Brainard J. op.cit.

36 Kotchen TA, Lindquist T, Malik K, Ehrenfeld E. NIH peer review of grant applications for clinical research, *Journal of the American Medical Association* 2004;291(7):836-843.

37 NCI data, received 3/22/05.

38 National Institutes of Health. NIH Announces Updated Criteria for Evaluating Research Grant Applications, Notice Number NOT-OD-05-002, October 12, 2004. At: http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-05-002.html (accessed 2/27/05)

39 Coleman J. "NIH Extramural Grant Review: 'Is Nine Months Too Long?' Zerhouni Asks," *Washington Fax*, January 28, 2005.

40 Brainard J. op.cit.

41 Coleman J. "NIH Peer Review Policy Changes Need Evidence-based Testing, Zerhouni Says," *Washington Fax*, January 31, 2005.

42 Institute of Medicine. *Strategies for Managing the Breast Cancer Research Program: A Report to the U.S. Army Medical Research and Development Command*, Institute of Medicine, The National Academies Press, Washington, DC, 1993, pp.1-58.

43 Bertram K. "Barriers to Translating Research into Reductions in the Burden of Cancer," White Paper and Presentation, President's Cancer Panel meeting, San Francisco, CA, August 30, 2004.

44 Meier B. "Contracts Keep Drug Research Out of Reach," *The New York Times*, The New York Times Company, November 29, 2004.

45 The National Science and Technology Council (NSTC) was established by Executive Order 12881 on November 23, 1993. This Cabinet-level Council is the principal means for the President to coordinate science, space, and technology to coordinate the diverse parts of the Federal research and development enterprise. The President chairs the NSTC. Membership consists of the Vice President, Assistant to the President for Science and Technology, Cabinet Secretaries and agency heads with significant science and technology responsibilities, and other White House officials.

46 Marburger JH III. Policy concerning the treatment of Principal Investigators, Memorandum, Office of Science and Technology, Executive Office of the President, January 4, 2005.

47 Softcheck JT. " 'Big Science' Necessitates Communal Reward Structure to Facilitate Collaboration, Says Harvard's Altshuler," *Washington Fax*, November 12, 2003.

48 Murray B. The authorship dilemma: who gets credit for what? *APA Monitor* 1998;29(12). At: http://www.apa.org/monitor/dec98/credit.html (accessed 4/6/05)

49 Tufts Center for the Study of Drug Development. "Backgrounder: How New Drugs Move Through the Development and Approval Process," Tufts Center for the Study of Drug Development, November 1, 2001. At: http://csdd.tufts.edu.NewsEvents/RecentNews.asp?newsid=4 (accessed 11/12/2004)

50 Rothenberg ML, Carbone DP, Johnson DH. Improving the evaluation of new cancer treatments: challenges and opportunities, *Nature Reviews: Cancer* 2003;3:303-309.

51 Ibid.

52 Zimmerman LJ. "Barriers to Translating Research into Reduction in the Burden of Cancer," White Paper and Presentation, President's Cancer Panel meeting, September 27, 2004.

53 Pollack P. "In Drug Research, the Guinea Pigs of Choice Are, Well, Human," *The New York Times*, The New York Times Company, August 4, 2004.

54 University of California at San Francisco. *Trends in U.S. Funding for Biomedical Research*, Chapter 1, Center for the Health Professions, 1997. At: http://www.futurehealth.ucsf.edu/pdf_files/usfunding.pdf. (accessed 6/4/05)

55 Cragg GM. Paclitaxel (Taxol®): a success story with valuable lessons for natural product drug discovery and development, *Medicinal Research Reviews* 1999;18(5):315-331.

56 National Institutes of Health, 1997. op.cit.

57 National Cancer Institute. *Report of the National Cancer Institute Clinical Trials Program Review Group*, National Cancer Institute, August 1997. At: http://deainfo.nci.nih.gov/advisory/bsa/bsa_program/bsactprgmin.htm (accessed 3/7/05)

58 McNeil C. "Redesigning NCI's Clinical Trials System: Integration is the Goal," News, *Journal of the National Cancer Institute* 2005;97(2):92-93.

59 Doroshow JH. "CTWG to Unveil Draft Proposal and Invite Continuing Input at NCAB," *NCI Cancer Bulletin*, 2005;2(7):1-2. At: http://cancer.gov/NCICancerBulletin/NCI_Cancer_Bulletin_021505 (accessed 2/15/05)

60 http://integratedtrials.nci.nih.gov

61 Doroshow JH, Fine HA. "Clinical Trials Working Group Draft Recommendations to the National Cancer Advisory Board, Presentation," February 17, 2005, Bethesda, MD.

62 National Institutes of Health. NIH Roadmap Initiatives. At: http://nihroadmap.nih.gov/initiatives.asp (accessed 2/25/05)

63 Hooper C. "Blue Ribbon Panel Points Intramural Program Toward Clinical Research Uniqueness," *The NIH Catalyst*, January-February 2004. At: http://search2.google.cit.nih.gov/search?q=cache:DN3SHAlzhwAJ:www.nih.gov/catalyst/2004/04.01.01/page1.html+Blue+Ribbon+Panel+on+the+Future+of+Intramural+Clinical+Research&access=p&output=xml_no_dtd&ie=UTF-8&client=NIH_frontend&site=NIH_Master&oe=UTF-8&proxystylesheet=NIH_frontend (accessed 3/7/05)

64 Johnson D. "Translating Research to Reduce the Burden of Cancer," White Paper and Presentation, President's Cancer Panel meeting, January 24, 2005.

65 Crowley WF Jr, Sherwood L, Salber P, Scheinberg D, Slavkin H, et al. Clinical research in the United States at a crossroads: proposal for a novel public-private partnership to establish a national clinical research enterprise, *Journal of the American Medical Association* 2004;291(9):1120-1126.

66 Friesen HG. Reshaping health research in Canada: an initiative whose time has come, *Clinical and Investigative Medicine* 1999;22:119-120.

67 Ley TJ, Rosenberg LE. Removing career obstacles for young physician-scientists—loan-repayment programs, *New England Journal of Medicine* 2002;346:368-373.

68 Zemlo TR, Garrison HH, Partridge NC, Ley TJ. The physician-scientists: career issues and challenges at the year 2000, *FASEB Journal* 2000;14:221-230.

69 Gray M. "Barriers to Translating Research into Reductions in the Burden of Cancer," White Paper, President's Cancer Panel meeting, November 1, 2004.

70 Committee on Facilitating Interdisciplinary Research. op.cit.

71 Zerhouni E. op.cit.

72 National Institutes of Health. "Re-engineering the Clinical Research Enterprise: Clinical Research Workforce Training," Backgrounder, (undated).

73 Ley TJ, Rosenberg LE. op.cit.

74 Coleman C. "Industry Funding of External Cancer Research Increasingly Vital – Lilly VP," *Washington Fax*, April 14, 2005.

75 Hooper C. op.cit.

76 http://iotftraining.nci.nih.gov

77 Laas M. "HapMap Consortium Receives $3.3 mil. to Expand Human Genome Mapping Project," *Washington Fax*, February 8, 2005.

78 National Institutes of Health. Regional Translational Research Planning Grants, RFA-RM-05-008. At: http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-05-008.html (accessed 3/8/05)

79 National Cancer Institute. "Program Promotes Collaboration, Rapid Generation of New Interventions," Director's Update, *NCI Cancer Bulletin*, 2005;2(4):1. Additional information at: http://deainfo.nci.nih.gov/concepts/AP4conceptU54.htm (accessed 2/28/05)

80 http://www.nigms.nih.gov/funding/gluegrants.html

81 http://cabig.nci.nih.gov

82 http://ncicb.nci.nih.gov

83 National Cancer Institute. Shared Pathology Informatics Network, Cancer Diagnosis Program, National Cancer Institute. At: http://cancerdiagnosis.nci.nih.gov/spin/index.html (accessed 2/28/05) See also: http://grants.nih.gov/grants/guide/rfa-files?RFA-CA-01-006.html

84 Eiseman E, Haga SB. *Handbook of Human Tissue Sources: A National Resource of Human Tissue Samples*, Rand Corporation, 1999, MR-954-OSTP, ISBN: 0-8330-2766-2, p.xvii.

85 Ibid, p.xviii.

86 National Cancer Institute. "The Promise of Molecular Medicine Pushes U.S. Biorepositories to Network," Special Report, *NCI Cancer Bulletin* 2004;1(48):3.

87 Abnet CC, Lai B, Qiao Y-L, Vogt S, et al. Zinc concentration in esophageal biopsy specimens measured by x-ray fluorescence and esophageal cancer risk, *Journal of the National Cancer Institute* 2005;97(4):301-306.

88 Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer, *New England Journal of Medicine* 2004;351:2817-2826.

89 Hede K. "NCI's National Biospecimen Network: Too Early or Too Late?" News, *Journal of the National Cancer Institute* 2005;97(4):247-248.

90 Petricoin EF III, Ardekani AM, Hitt BA, Levine PJ, Fusaro VA, et al. Use of proteomic patterns in serum to identify ovarian cancer, *Lancet* 2002; 359(9306):572-577.

91 Roy R, Wewer UM, Zurankowski D, Pories SE, Moses MA. ADAM-12 cleaves extracellular matrix proteins and correlates with cancer status and stage, *Journal of Biological Chemistry* 2004;279(49):51323-51330.

92 Paik S, Shak S, Tang G, et al. op.cit.

93 http://www3.cancer.gov/prevention/cbrg/edrn/organization.html

94 U.S. Department of Health and Human Services. "National Cancer Institute Announces Awards to Accelerate Cancer Biomarker Discovery," Press Release, *NIH News*, December 8, 2004.

95 National Cancer Institute. "Questions and Answers: Distinction Between the NCI/FDA Ovarian Cancer Proteomics Research Program and Diagnostic Tests by Private Industry (e.g., OvaCheck™)," NewsCenter, National Cancer Institute, August 26, 2004. At: http://www.cancer.gov/newscenter/pressreleases/ProteomicsOvarian/ (accessed 2/23/05)

96 Committee on the Organizational Structure of the National Institutes of Health. op.cit., pp.55-56.

97 Harris JR, Brown PK, Coughlin S, Fernandez ME, Hebert JR, Kerner J, et al. The Cancer Prevention and Control Research Network, Preventing Chronic Disease [serial online] 2005;2(1).
At: http://www.cdc.gov/pcd/issues/2005/jan/04_0059.htm (accessed 2/26/05)

98 http://www.cdc.gov/prc/news/announcement.htm

99 Agency for Healthcare Research and Quality. Primary Care Practice-based Research Networks: Fact Sheet.
At: http://www.ahrq.gov/research/pbrnfact.htm (accessed 2/26/05)

100 Reuben SH, 2004. op.cit.

101 H.R. 4880 and S. 2710.

102 Department of Health and Human Services. *The Decade of Health Information Technology: Delivering Consumer-centric and Information-rich Health Care*, DHHS, July 21, 2004. At:
http://www.hhs.gov/onchit/framework/hitframwwork.pdf (accessed 3/10/05)

103 Department of Health and Human Services. "Thompson Launches 'Decade of Health Information Technology,'" July 21, 2004.

104 Centers for Medicare and Medicaid Services. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) – Administrative Simplification. At: http://www.cms.hhs.gov/hipaa/hipaa2/default.asp (accessed 3/15/05)

105 Asch AM, McGlynn EA, Hogan MM, Hayward RA, et al. Comparison of quality of care for patients in the Veterans Health Administration and patients in a national sample, *Annals of Internal Medicine* 2004;141(12):938-945.

106 Brailer DJ. Interoperability: the key to the future health care system, *Health Affairs – Web Exclusive*, January 19, 2005, W5-19 – W5-21. At: http://content.healthaffairs.org/cgi/content/abstract/hlthaff.w5.19 (accessed 1/19/05)

107 The Commonwealth Fund. "Frist Says Feds Should Focus on Health Care IT Interoperability," *Health Policy Week in Review*, March 14, 2005.
At: http://www.cmwf.org/healthpolicyweek/healthpolicyweek_show.htm?doc_id=266654&#doc266661 (accessed 3/15/05)

108 Audet A-M, Doty MM, Peugh J, et al. Information technologies: when will they make it into physicians' black bags? *Medscape General Medicine* 2004;6(4), posted December 7, 2004. At:
http://www.medscape.com/viewarticle/493210_print (accessed 3/14/05)

109 The Henry J. Kaiser Family Foundation. "Group of Large Companies Expanding Program That Gives Bonuses to Providers That Implement IT Improvements," *Kaiser Daily Health Policy Report*, May 26, 2004.

110 The Commonwealth Fund. "Fear of Infotech – What HHS is Doing About It," *Washington Health Policy Week in Review*, August 23, 2004. At: http://www.cmwf.org/healthpolicyweek/healthpolicyweek_show.htm?doc_id=236147 (accessed 8/23/04)

111 http://www.hhs.gov/ohrp

112 Institutional Review Boards, 21 CFR § 56 (2004).

113 Committee on Assessing the System for Protecting Human Research Subjects. *Preserving Public Trust: Accreditation and Human Research Participant Protection Programs*, Institute of Medicine, The National Academy Press, Washington, DC, 2001, pp.2-5.

114 Larson D, Bratts T, Zwanziger J, Stone P. A survey of IRB process in 68 U.S. hospitals, *Journal of Nursing Scholarship* 2004;36(3):260.

115 American Society of Clinical Oncology. American Society of Clinical Oncology policy statement: oversight of clinical research, *Journal of Clinical Oncology* 2003;21(12). Published ahead of print on April 29, 2003 as 10.1200/JCO.2003.04.026.

116 National Cancer Institute. The Central Institutional Review Board Initiative. At: http://www.ncicirb.org/CIRB_Project.asp (accessed 3/8/05)

117 American Association of Medical Colleges, July 2004.

118 Hawkins AJ. "HHS Human Subjects Advisory Panel Will Weigh Merits of Central Institutional Review Board System," *Washington Fax*, October 12, 2004.

119 Ibid.

120 Committee on Assessing the System for Protecting Human Research Subjects. op.cit.

121 Hawkins AJ. "Adverse Event Reporting is Goal of Federal Task Force," *Washington Fax*, February 2, 2005.

122 *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980) (interpreting 35 USC § 101).

123 Mays T. "Barriers to Translating Research into Reductions in the Burden of Cancer," White Paper and Presentation, President's Cancer Panel meeting, Houston, TX, November 1, 2004.

124 Ibid.

125 Nass SJ, Stillman BW (eds.). op.cit.

126 Ibid.

127 Nass SJ, Stillman BW (eds.). op.cit., p.178.

128 Federal Trade Commission. *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy*, Federal Trade Commission, October 2003.

129 Tufts University Center for the Study of Drug Development, 2001. op.cit.

130 "R&D Execs Paint Bleak Picture of Industry Productivity: $1.4 bil. Per NME," *The Pink Sheet*, August 18, 2003.

131 Gilbert J, Henske P, Singh A. "Rebuilding Big Pharma's Business Model," *In Vivo, The Business & Medicine Report*, Windhover Information 2003;21(10).

132 Cox MC., Figg WD, Thurman PW. Correspondence: no rational theory for drug pricing, *Journal of Clinical Oncology* 2004;22(5):962-963.

133 Drug Price Competition and Patent Term Restoration Act of 1984, P.L. 98-417.

134 Pollock RW, Johnston GR. Pharmaceutical Patent and Exclusivity Complexity: Implications for Generic Product Introductions, Temple University and the Council for Pharmacy Education. At: https://secure.pharmacytimes.com/lessons/200208-01.asp (accessed 3/28/05)

135 Kaufman M. "Biotech Drugs' Generic Future Debated," *The Washington Post*, The Washington Post Company, February 10, 2005. At: http://www.msnbc.msn.com/id/6942872/ (accessed 2/10/05)

136 The Orphan Drug Act (as amended). At: www.fda.gov/orphan/oda.htm (accessed 2/2/05)

137 Food and Drug Administration. *Challenge and Opportunity on the Critical Path to New Medical Products*, U.S. Department of Health and Human Services, March 2004.

138 Conti R. Balancing safety, effectiveness, and public desire: the FDA and cancer, Issue Brief #615, The Commonwealth Fund, April 2003.

139 Hay JW, Yu WM. Commentary: pharmacoeconomics and outcomes research: expanding the healthcare "outcomes" market, *Value in Health* 2000;3(3):181-185.

140 International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, Updated October 2004, p.4. At: http://www.icmje.org/icmje.pdf (accessed 2/20/05)

141 Task Force on Financial Conflicts of Interest in Clinical Research. *Protecting Subjects, Preserving Trust, Promoting Progress: Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research*, American Association of Medical Colleges, December 2001.

142 Task Force on Financial Conflicts of Interest in Clinical Research. *Protecting Subjects, Preserving Trust, Promoting Progress II: Principles and Recommendations for Oversight of an Institution's Financial Interests in Human Subjects Research*, American Association of Medical Colleges, October 2002.

143 Ehringhaus S, Korn D. Conflicts of interest in human subjects research, *Issues in Science and Technology* (online), Winter 2002. At: http://www.issues.org/issues/19.2/ehringhaus.htm (accessed 1/28/05)

144 5 CFR Parts 5501 and 5502, Supplemental Standards of Ethical Conduct and Financial Disclosure Requirements for Employees of the Department of Health and Human Services, interim final rule with request for comments, *Federal Register*, 70(22), February 3, 2005.

145 "Sunshine on Research," Editorial, *Los Angeles Times*, February 7, 2005, p.B.10.

146 Tufts Center for the Study of Drug Development, 2001. op.cit.

147 Gilbert J, Henske P, Singh A. op.cit.

148 Food and Drug Administration. op.cit.

149 Ibid.

150 National Cancer Institute. *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2006*, National Cancer Institute, National Institutes of Health, NIH Publication No. 05-5612, December 2004, p.24.

151 Woosley RL, Rice G. A new system for moving drugs to market, *Issues in Science and Technology* 2005;XXI(2):63-68.

152 21 CFR 314.500-314.560

153 Fleming TR. Surrogate endpoints and FDA's accelerated approval process, *Health Affairs* 2005;24(1):67-78.

154 Okie S. What ails the FDA? *New England Journal of Medicine* 2005;352(11):1063-1066.

155 Meeting Transcript of the FDA Oncology Drugs Advisory Committee (March 12-13, 2003); and Dagher R, et al. Accelerated approval of oncology products: a decade of experience, *Journal of the National Cancer Institute* 2004;20(96):1500-1509.

156 Center for Medicare and Medicaid Services. "CMS and NCI Collaborating to Bring New Drugs and More Effective Treatment to Cancer Patients," Press Release, June 7, 2004.

157 National Institutes of Health. NIH Guide: Impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts, February 5, 2003.

158 National Cancer Institute. *The HIPAA Privacy Rule: Feedback from NCI Cancer Centers, Cooperative Groups, and Specialized Programs of Research Excellence*, Executive Summary, August 20, 2003.

159 Levy R. "The Unintended Negative Consequences of HIPAA on Our Quest to Solve the Cancer Problem," White Paper and Presentation, President's Cancer Panel meeting, San Francisco, August 30, 2004.

160 Agency for Healthcare Research and Quality. *Dissemination and Diffusion of Evidence-based Cancer Control Interventions*, Evidence Report/Technology Assessment No. 79, Publication No. 03-E032, May 2003.

161 http://cancercontrolplanet.cancer.gov

162 National Cancer Institute, Center for the Advancement of Health, Robert Wood Johnson Foundation. *Designing for Dissemination – Conference Report*, December 2002.
At: http://cancercontrol.cancer.gov/d4d/d4d_conf_sum_report.pdf (accessed 3/18/05)

163 NCI data.

164 University of Massachusetts. *Dissemination and Implementation of Evidence-based Medicine: Barriers, Complexities and Strategies, Preliminary Results*: *A Review of the Literature 1980 to Present*, Donahue Institute, May 2004.

165 National Science Foundation. *Science and Engineering Indicators 2002*, Chapter 7, National Science Foundation, 2002. At: http://www.nsf.gov/sbe/srs/seind02/c7/c7h.htm (accessed 4/3/05)

166 American Cancer Society. *Cancer Prevention & Early Detection Facts & Figures 2005*, American Cancer Society, Atlanta, GA, 2005, p.1.

167 Norman Lear Center. "Hollywood, Health & Society, Overview," USC Annenberg Norman Lear Center.
At: http://www.learcenter.org/html/projects/overview1.php?cm=hhs (accessed 4/2/05)

168 McNeil C. "Clinical Trial Accrual Efforts: Some Progress Amid Ongoing Debate," News, *Journal of the National Cancer Institute* 2004;96(19):1417-1418.

169 Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review, *Lancet* 2004;363(9405):263-270.

170 McNeil C. op.cit.

171 Nurgat ZA, Craig W, Campbell NC, Bissett JD, Cassidy J, Nicolson MC. Patient motivations surrounding participation in phase I and phase II clinical trials of cancer chemotherapy, *British Journal of Cancer* 2005;92:1001-1005.

172 Hajjar RR, et al. Cancer in the elderly: is it preventable? *Clinical Geriatric Medicine* 2004;20(2):293-316.

173 Patel P, Forjuoh SN, Avots-Avotins A, Patel T. Identifying opportunities for improved colorectal cancer screening in primary care, *Preventive Medicine* 2004;39(2):239-246.

174 McCarthy M. The economics of obesity, *Lancet* 2004;364(9452).

175 Hill JO, Sallis JF, Peters JC. Economic analysis of eating and physical activity: a next step for research and policy change, *American Journal of Preventive Medicine* 2004;27:3S:111-116.

176 University of Massachusetts, 2004. op.cit.

177 Strand M, Phelan KJ, Donovan EF. Promoting the uptake and use of evidence: an overview of the problem, *Clinics in Perinatology* 2003;30(2):389-402.

178 Blendon RJ, Scoles D, DesRoches C, Young JT, et al. Americans' health priorities: curing cancer and controlling costs, *Health Affairs* 2001;20(6):222-231.

179 Research!America. Research!America National Poll on Americans' Attitudes Toward U.S. Health Care, Research!America, 2005. At: http://www.researchamerica.org/polldata/index.html (accessed 3/10/05)

180 Sontag D. "Abuses Endangered Veterans in Cancer Drug Experiments," *The New York Times*, The New York Times Company, February 6, 2005, p.1.

181 National Cancer Institute. "NCI-Sponsored Trials of Cyclooxygenase (COX) Inhibitors for Cancer Prevention and Treatment – Cardiovascular Toxicity in the Adenoma Prevention with Celecoxib Trial: Questions and Answers," Press Release, February 15, 2005.

182 Kaufman M. "Many FDA Scientists Had Drug Concerns, 2002 Survey Shows," *The Washington Post*, The Washington Post Company, December 16, 2004, p.A01.

183 Slater EE. Today's FDA, *New England Journal of Medicine* 2005;352(3):293-297.

184 Harris G. "FDA to Create Advisory Board on Drug Safety," *The New York Times*, The New York Times Company, February 16, 2005.

185 Kellman L. "FDA Wants Power to Write Warning Labels on Drugs," Associated Press, March 1, 2005.

186 Director's Council of Public Representatives. *Report and Recommendations on Public Trust in Clinical Research*, National Institutes of Health, Department of Health and Human Services, January 14, 2005.

187 http://crchd.nci.nih.gov/spn/current_network/current_initiatives.html

188 Agency for Healthcare Research and Quality. *The Role of Community-based Participatory Research: Creating Partnerships, Improving Health*, AHRQ Publication No. 03-0037, June 2003.
At: http://www.ahrq.gov/research/cbprrole.htm (accessed 8/8/2003)

189 http://deainfo.nci.nih.gov/ADVISORY/dclg/dclg.htm

190 http://la.cancer.gov/CARRA/

191 http://spores.nci.nih.gov/part/index_part.html

192 Freeman HP (Chair), Reuben SH (ed.), 2000. op.cit.

193 Freeman HP (Chair), Reuben SH (ed.). *Voices of a Broken System: Real People, Real Problems*, President's Cancer Panel Report of the Chairman 2000-2001, National Cancer Institute, National Institutes of Health, NIH Publication No. 03-5301, March 2002.

194 Reuben SH. *Facing Cancer in Indian Country: The Yakama Nation and Pacific Northwest Tribes*, President's Cancer Panel 2002 Annual Report, National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services, December 2003.

195 Smedley BD, Stith AY, Nelson AR (eds.). *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care*, Institute of Medicine, The National Academies Press, Washington, DC, 2003.

196 Anderson RM, Rice TH, Kominski GF. *Changing the U.S. Health Care System: Key Issues in Health Services, Policy, and Management*, Second Edition, Jossey-Bass, San Francisco, 2001.

197 Trans-HHS Cancer Health Disparities Progress Review Group. *Making Health Disparities History*, Department of Health and Human Services, March 2004. At: http://www.hhs.gov/chdprg/pdf/chdrpg/pdf (accessed 2/15/05)

198 U.S. House of Representatives Committee on Government Reform. Full committee hearing on Cancer Clinical Trials Participation, May 13, 2004.

199 Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trails for cancer drug registration: a 7-year experience by the U.S. Food and Drug Administration, *Journal of Clinical Oncology* 2004;22(22):4626-4631.

200 National Cancer Institute. "Community Clinical Oncology Program: Questions and Answers," Cancer Facts, December 2003. At: http://cis.nci.nih.gov/fact/1_3.htm (accessed 2/22/05)

201 The Henry J. Kaiser Family Foundation, Hewitt Associates. *Current Trends and Future Outlook for Retiree Health Benefits: Findings from the Kaiser/Hewitt 2004 Survey on Retiree Health Benefits*, December 2004.

202 The Commonwealth Fund. "Can the Senate Finance Committee Come Up with $10 Billion in Medicaid Cuts?" *Washington Health Policy Week in Review*, May 2, 2005.
At: http://www.cmwf.org/cnlib/pub/enews_clickthrough.htm?enews_item_id=16486&return_url=http%3A%2F%2Fwww%2Ecmwf%2Eorg%2Fhealthpolicyweek%2Fhealthpolicyweek%5Fshow%2Ehtm%3Fdoc%5Fid%3D275130%26%23doc275131 (accessed 5/2/05)

203 Singh GK, Miller BA, Hankey BF, Edwards BK. *Area Socioeconomic Variation in U.S. Cancer Incidence, Mortality, Stage, Treatment, and Survival, 1975-1999*, NCI Cancer Surveillance Monograph Series, Number 4, National Cancer Institute, NIH Publication No. 03-5417, 2003.

204 Freeman HP (Chair), Reuben SH (ed.), 2002. op.cit.

205 Reuben SH, 2003. op.cit.

206 Dubow J. "Adequate Literacy and Health Literacy: Prerequisites for Informed Health Care Decision Making," Issue Brief, Public Policy Institute, American Association of Retired Persons, June 2004.

207 Nielsen-Bohlman L, Panzer AM, Kindig DA (eds.). *Health Literacy: A Prescription to End Confusion, Committee on Health Literacy*, Institute of Medicine, The National Academies Press, 2004.

208 Dubow J. op.cit.

209 Informed Consent Working Group. *Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials*, National Cancer Institute, updated 12/6/04.
At: http://www.cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs (accessed 3/8/05)

210 Fox S, Fallows D. *Internet Health Resources: Health searches and email have become more commonplace, but there is room for improvement in searches and overall Internet access*, Pew Internet & American Life Project, July 2003.

211 Rideout V, Neuman T, Kitchman M, Brodie M. *eHealth and the Elderly: How Seniors Use the Internet for Health Information*, The Henry J. Kaiser Family Foundation, Publication No. 7223, January 2005.

212 Twist K. "A Nation Online, But Where Are the Indians?" Digital Divide Network.
At: http://web.archive.org/web/20021024001606/www.digitaldividenetwork.org/content/stories/index.cfm?key=215 (accessed 2/25/05)

213 Cooper MN. *Does the Digital Divide Still Exist? Bush Administration Shrugs, But Evidence Says "Yes,"* Consumer Federation of America, May 30, 2002, p.4.

214 Digital Divide Network. "Access," Digital Divide Network.
At: http://web.archive.org/web/20020811022458/www.digitaldividenetwork.org/content/sections/index.cfm?key=3 (accessed 2/25/05)

215 Birru MS, Monaco VM, Charles L, et al. Internet usage by low-literacy adults seeking health information: an observational analysis, *Journal of Medical Internet Research* 2004;6(3), article e25.
At: http://www.jmir.org/2004/3/e25/ (accessed 2/17/05)

216 http://cancer.gov/cancertopics/pdq

217 http://cancer.gov/dictionary/

218 http://ncilistens.cancer.gov/moderator.asp?action=discussion&discussion=46 (accessed 2/22/05)

219 Wei SJ, Metz JM, Coyle C, Hampshire M, et al. Recruitment of patients into an Internet-based clinical trials database: the experience of OncoLink and the National Colorectal Cancer Research Alliance, *Journal of Clinical Oncology* 2004;22(23):4730-4736.

220 http://www.pubmedcentral.nih.gov

221 National Cancer Institute. "NIH Public Access Policy to be Activated in May," *NCI Cancer Bulletin* 2005;2(6):7.

222 The Henry J. Kaiser Family Foundation. "NIH Guidelines on Voluntary Public Access to Research Released," *Kaiser Daily Health Policy Report*, February 4, 2005.
At: http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=27986&dr_cat=3 (accessed 2/04/05)

223 The Henry J. Kaiser Family Foundation. "Consortium of Publishers to Provide Access to Research at No Cost," *Kaiser Daily Health Policy Report*, December 8, 2004.
At: http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=27134 (accessed 12/08/04)

224 http://www.plos.org

225 Washington Fax. "PLoS Medicine Launches, Touts Open Access 'Author Pays' Model," *Washington Fax*, October 20, 2004.

226 http://scholar.google.com

227 Turner EH. A taxpayer-funded clinical trials and results database, *PLoS Medicine* 2004;1(3):179-181.
At: http://www.plosmedicine.org (accessed 1/30/05)

228 http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

229 Agovino T. "More Transparency Offered in Drug Trials," Associated Press, January 7, 2005.

230 *The Henry J. Kaiser Family Foundation*. "Bill Would Require Disclosure of Clinical Trial Results in Electronic Database," *Kaiser Daily Health Policy Report*, March 1, 2005.
At: http://www.kaisernetwork.org/daily_reports/print_report.cfm?DR_ID=28395&dr_cat=3 (accessed 3/1/05)

231 Washington Fax. "Unilateral FDA Action to Force Drug Industry Postings on Trials Database Unlikely," *Washington Fax*, July 3, 2004.

232 Turner EH. op.cit.

233 International Committee of Medical Journal Editors. op.cit., p.10. Note: This policy, limited to ICMJE member journals, applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment prior to this date, registration is required by September 13, 2005. Studies of pharmacokinetics or major toxicity (e.g., Phase I trials) are excluded. At: http://www.icmje.org/#peer (accessed 2/20/05)

234 Washington Fax. "Clinical Trials Rethink: New Medical Journal Paradigm Should Factor Into Study Plans," *Washington Fax*, October 27, 2004.

Appendix A. Participant Roster, President's Cancer Panel Meetings: Translating Research to Reduce the Burden of Cancer, August 2004-January 2005

NOTE: White papers were not requested of the Chair of the President's Cancer Panel, Cancer Center Directors, Discussion Panel Chairs, or the Director, NCI. Written testimony only was provided as indicated below.

Meeting: San Francisco, California, August 30, 2004

Name	Affiliation	Speaker Type/Testimony
Anna D. Barker, Ph.D.	National Cancer Institute	Discussion Panel Chair
Kenneth Bertram, M.D., Ph.D.	Congressionally Directed Medical Research Programs Department of Defense	
Moon S. Chen, Ph.D., M.P.H.	UC-Davis Cancer Center	
Peter B. Corr, Ph.D.	Pfizer Inc	
James H. Feusner, M.D.	Children's Hospital and Research Center at Oakland	
Joe W. Gray, Ph.D.	Lawrence Berkeley National Laboratory	
Robert Hiatt, M.D., Ph.D.	UCSF Comprehensive Cancer Center	
Jon F. Kerner, Ph.D.	National Cancer Institute	
LaSalle D. Leffall, Jr., M.D., F.A.C.S.	Howard University College of Medicine	President's Cancer Panel Chair
Ronald Levy, M.D.	Stanford University Medical Center	
Robert Lipshutz, Ph.D.	Affymetrix, Inc.	
Frank McCormick, Ph.D., F.R.S.	UCSF Comprehensive Cancer Center	Cancer Center Representative Discussion Panel Chair
Heather Hay Murren, C.F.A.	Nevada Cancer Institute	
Craig R. Nichols, M.D.	OHSU Cancer Institute	
Joanne Schottinger, M.D.	Kaiser Permanente Southern California	
Margaret Tempero, M.D.	UCSF Comprehensive Cancer Center	Discussion Panel Chair
William Lynn Weaver, M.D., F.A.C.S.	Morehouse School of Medicine	
Janet Woodcock, M.D.	U.S. Food and Drug Administration	
Brad Zebrack, Ph.D., M.S.W., M.P.H.	USC School of Social Work Association of Oncology Social Work	

Meeting: Columbus, Ohio, September 27, 2004

Name	Affiliation	Speaker Type/Testimony
Lucile Adams-Campbell, Ph.D.	Howard University Cancer Center	
Bill Bro	Kidney Cancer Association	
Michael A. Caligiuri, M.D.	The Ohio State University Comprehensive Cancer Center James Cancer Hospital and Solove Research Institute	Cancer Center Representative Discussion Panel Chair
Mark Clanton, M.D., M.P.H.	National Cancer Institute	Discussion Panel Chair
Robert L. Comis, M.D.	Coalition of National Cancer Cooperative Groups, Inc. Group Chair, Eastern Cooperative Oncology Group	Discussion Panel Chair

Stanton Gerson, M.D.	Case Comprehensive Cancer Center and Ireland Cancer Center of University Hospitals of Cleveland Case Western Reserve University	
Gary Gordon, M.D., Ph.D.	Abbott Laboratories	
Scott Gottlieb, M.D.	Centers for Medicare and Medicaid Services	
Michael Rhodes Grever, M.D.	The Ohio State University Medical Center	
Catherine D. Harvey, R.N., Dr.P.H., AOCN	National Coalition for Cancer Survivorship	
Ronald B. Herberman, M.D.	University of Pittsburgh Cancer Institute	
Clifton Leaf	FORTUNE Magazine	
LaSalle D. Leffall, Jr., M.D., F.A.C.S.	Howard University College of Medicine	President's Cancer Panel Chair
Homer L. Pearce, Ph.D.	Eli Lilly and Company	
Stephen M. Prescott, M.D.	Huntsman Cancer Institute	
Eddie Reed, M.D.	Mary Babb Randolph Cancer Center	
Paul L. Schaefer, M.D.	Toledo Community Oncology Program	
Harold C. Sox, Jr., M.D.	Annals of Internal Medicine	
K. "Vish" Viswanath, Ph.D.	Center for Community-Based Research Dana-Farber Cancer Institute	
Steven N. Wolff, M.D.	Meharry Medical College	
Lisa J. Zimmerman, M.S.	Duke Clinical Research Institute	

Meeting: Houston, Texas, November 1, 2004

Name	Affiliation	Speaker Type/Testimony
J. Carl Barrett, Ph.D.	National Cancer Institute	Discussion Panel Chair
Robert C. Bast, Jr., M.D.	The University of Texas M. D. Anderson Cancer Center	
Eric Berger, M.P.A.	US Oncology	
Kevin T. Brady, M.P.H.	Centers for Disease Control and Prevention	
Otis W. Brawley, M.D.	Emory University	
Deborah Collyar, B.S.	PAIR: Patient Advocates In Research	
William S. Dalton, M.D., Ph.D.	H. Lee Moffitt Cancer Center and Research Institute	
Harry R. Gibbs, M.D.	The University of Texas M. D. Anderson Cancer Center	
Jack Gill, Ph.D.	Vanguard Ventures	
Martha Gray, Ph.D.	Massachusetts Institute of Technology	
Elmer Emilio Huerta, M.D., M.P.H.	Washington Cancer Institute Washington Hospital Center	
Anthony J. Infante, M.D., Ph.D.	University of Texas Health Sciences Center–San Antonio	
William M. Jordan, D.O.	Texas Cancer Care–The Center for Cancer Care and Blood Disorders	
Paula Kim	Pancreatic Cancer Action Network	
LaSalle D. Leffall, Jr., M.D., F.A.C.S.	Howard University College of Medicine	President's Cancer Panel Chair
Lynn M. Matrisian, Ph.D.	Vanderbilt University School of Medicine	
Thomas Mays, Ph.D., J.D.	Federal Trade Commission	
John Mendelsohn, M.D.	The University of Texas M. D. Anderson Cancer Center	Cancer Center Representative Discussion Panel Chair
Paul Papagni, J.D.	UMDNJ–Robert Wood Johnson Medical School	
Amelie G. Ramirez, Dr.P.H., M.P.H.	Baylor College of Medicine	Discussion Panel Chair

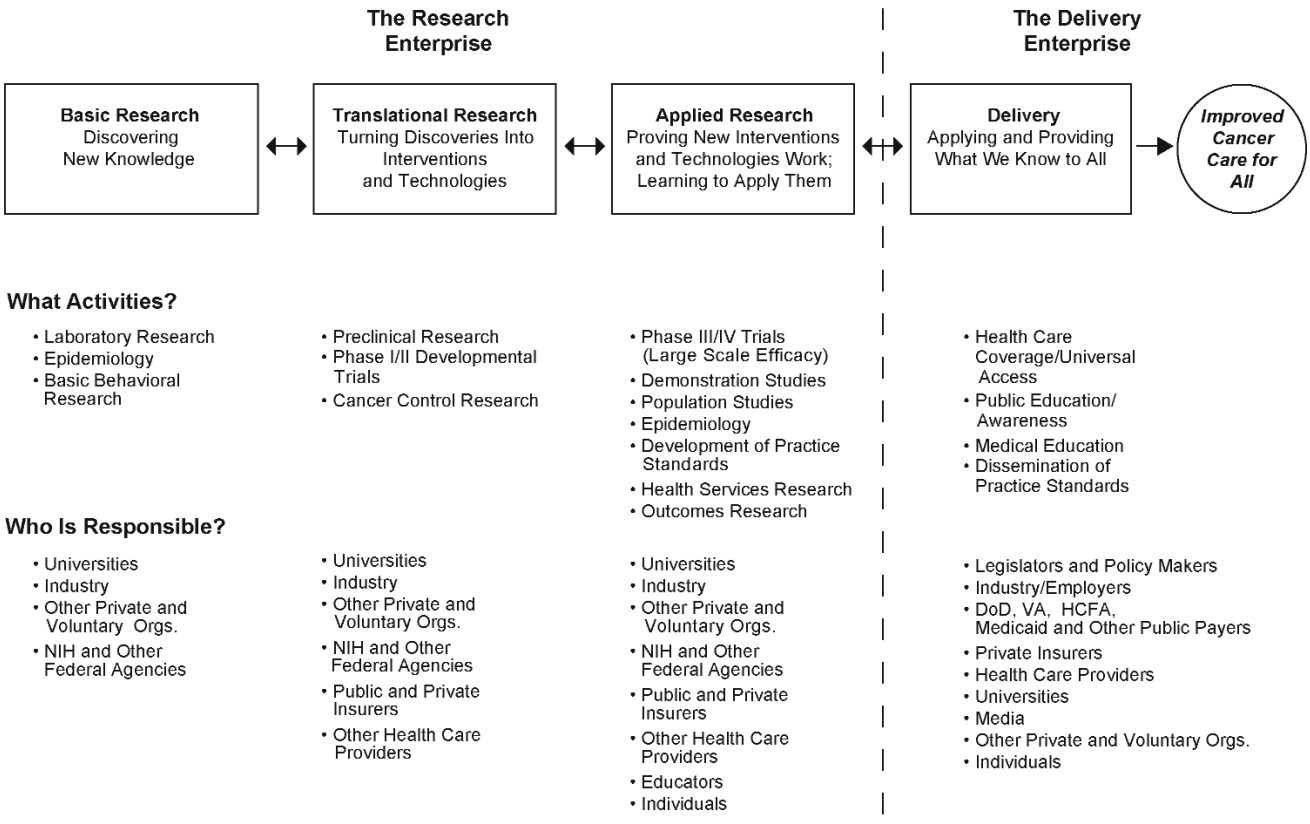
Lynn Schuchter, M.D.	Abramson Cancer Center University of Pennsylvania	
Jonathan W. Simons, M.D.	Emory University	
Andrew C. von Eschenbach, M.D.	National Cancer Institute	National Cancer Institute Director

Meeting: New York, New York, January 24, 2005

Name	Affiliation	Speaker Type/Testimony
Karen Antman, M.D.	National Cancer Institute	Discussion Panel Chair
Wendy Chung, M.D., Ph.D.	Columbia University Medical Center	
Carolyn M. Clancy, M.D.	Agency for Healthcare Research and Quality	
Ethan Dmitrovsky, M.D.	Dartmouth Medical School	
Harold P. Freeman, M.D.	The Ralph Lauren Center for Cancer Care and Prevention	
William N. Hait, M.D., Ph.D.	The Cancer Institute of New Jersey	Written Testimony
Kathie-Ann Joseph, M.D., M.P.H.	Columbia University College of Physicians and Surgeons	
Howard Koh, M.D., M.P.H.	Harvard School of Public Health	Written Testimony
LaSalle D. Leffall, Jr., M.D., F.A.C.S.	Howard University College of Medicine	President's Cancer Panel Chair
Kitta MacPherson	The Star-Ledger	Written Testimony
William G. Nelson, M.D., Ph.D.	The Johns Hopkins University School of Medicine	
Larry Norton, M.D.	Memorial Sloan-Kettering Cancer Center	Discussion Panel Chair
Kenneth Olden, Ph.D., Sc.D., L.H.D.	National Institute of Environmental Health Sciences	Written Testimony
Drew M. Pardoll, M.D., Ph.D.	The Johns Hopkins University School of Medicine	
Gary M. Reedy	Johnson & Johnson	
Barbara K. Rimer, Dr.P.H.	UNC School of Public Health	Written Testimony
Richard L. Schilsky, M.D.	Biological Sciences Division University of Chicago	Written Testimony
Joseph V. Simone, M.D.	Simone Consulting	Discussion Panel Chair
Ralph M. Steinman, M.D.	The Rockefeller University	
Bruce Stillman, Ph.D.	Cold Spring Harbor Laboratory	
Lawrence S. Sturman, M.D., Ph.D.	New York State Department of Health	Written Testimony
Selwyn M. Vickers, M.D.	UAB Cancer Center	Written Testimony
Andrew C. von Eschenbach, M.D.	National Cancer Institute	National Cancer Institute Director
Susan L. Weiner, Ph.D.	The Children's Cause for Cancer Advocacy	
Peter H. Wiernik, M.D.	Comprehensive Cancer Center Our Lady of Mercy Medical Center New York Medical College	
Robert E. Wittes, M.D.	Memorial Sloan-Kettering Cancer Center	Cancer Center Representative
Jerome W. Yates, M.D., M.P.H.	American Cancer Society	

Appendix B.

Figure A: Bringing Cancer Care Advances to the Public: Bridging the Divide Between Research and Delivery



Source: Reuben, S.H., 2000. Adapted from *Cancer at a Crossroads*, Figure 2, 1994.

Appendix C. Recommendations and Suggested Responsible Stakeholders or Other Entities

Recommendations	Responsible Stakeholder(s) or Other Entities*
Overarching Recommendations	
In five years, a thorough evaluation should be conducted to assess the effectiveness of the many public and private initiatives now underway or planned to accelerate the translation of basic science discoveries into improved cancer prevention and cancer care.	• Institute of Medicine (IOM)
To ensure continued progress in translating cancer research advances into new cancer care interventions, the current statutory authorities of the National Cancer Institute should be preserved in any reauthorization of the National Cancer Act.	• Congress
Team Science and the Culture of Research	
1. The existing culture of cancer research must be influenced to place more value on translational and clinical research. To effect this culture change, a task force representing key stakeholders in academic research should be convened to examine and modify existing reward systems (e.g., compensation, promotion/tenure, space and resource allocation, prestige) to encourage collaborative research and ensure that all contributors (including but not limited to pathologists, radiologists, and research nurses) benefit from participating in these research activities.	• Association of American Medical Colleges (AAMC), Council of Deans • Association of Academic Health Centers (AAHC) • American Association for Cancer Research (AACR) • American Society of Clinical Oncology (ASCO) • Association of American Cancer Institutes (AACI) • Association of Community Cancer Centers (ACCC) • Association of Oncology Social Workers (AOSW) • National Comprehensive Cancer Network (NCCN) • Oncology Nursing Society (ONS) • American Society of Clinical Pathology (ASCP) • American Society for Therapeutic Radiology and Oncology (ASTRO) • International Biometric Society (IBS) • National Coalition for Cancer Survivorship (NCCS) • Biomedical Engineering Society (BES) • International Committee of Medical Journal Editors (ICJE)

*Please note that this list is not exhaustive and does not preclude participation by other interested parties.

2. Governmental and private research sponsors must place greater emphasis on and substantially increase funding for clinical research and human tissue research. Funding mechanisms should promote collaborative science and include greater support through the R01 mechanism.	• National Cancer Institute (NCI)/ National Institutes of Health (NIH) • National Science Foundation (NSF) • Centers for Disease Control and Prevention (CDC) • Department of Defense (DoD) • Department of Veterans Affairs (VA) • Pharmaceutical Research and Manufacturers Association (PhARMA) • Biotechnology Industry Organization (BIO) • Lance Armstrong Foundation (LAF) • American Cancer Society (ACS) • Howard Hughes Medical Institute (HHMI) • Agency for Healthcare Research and Quality (AHRQ)
3. The National Institutes of Health and other research sponsors should facilitate collaboration in large research projects by requiring team approaches to the extent appropriate to the science and designating a percentage of project funding for such efforts.	• NIH • DoD • CDC • VA • AHRQ • HHMI • LAF • ACS
4. To stimulate team science, the National Institutes of Health and other research sponsors should rapidly devise implementation plans for permitting co-principal investigators who share grant funding and attribution for these efforts, consistent with the January 2005 directive from the Director of the Office of Science and Technology Policy.	• NIH • VA • DoD • CDC • NSF • AHRQ

Infrastructure Required for Research Translation

5. To attract and retain young investigators to careers in translational and clinical research: (a) Protected research time and mentoring must be provided earlier and potentially for a longer period of time than is now the norm. Government training funds may be needed to enable academic institutions to provide this supportive environment. (b) New or expanded student loan buy-back programs should be established to enable young investigators to pursue the additional training necessary for a career in translation-oriented research. (c) Academic institutions should make special efforts to recruit and retain young scientists from underrepresented population groups.	• NIH • DoD • NSF • VA • National Postdoctoral Association (NPA) • AAMC
6. The Rapid Access to Intervention Development program should be expanded and revitalized to accelerate the development of innovative interventions and technologies for cancer.	• NCI
7. Specialized Programs of Research Excellence (SPOREs) have proven effective in stimulating collaborative and translational research. The program should be expanded, with the focus of selected SPOREs shifted to emphasize clinical over basic research.	• NCI

8. The Centers for Medicare and Medicaid Services should explore the possibility of collecting cancer stage data, at least at the time of diagnosis, to better inform treatment decisionmaking, ensure appropriate payments, enrich the body of information about provider practice patterns, and support treatment research.	• Centers for Medicare and Medicaid Services (CMS)
9. The proposed Human Cancer Genome Project should be supported to accelerate progress in genetic knowledge that will enable the development of new cancer prevention and treatment advances. Funding for this large effort should come from a special supplement rather than from participating agencies' budgets.	• Congress • NIH • NCI • National Human Genome Research Institute (NHGRI) • DoD

Regulatory Issues Affecting Translation

10. The current partnerships between the National Cancer Institute (NCI) and the Food and Drug Administration to expedite cancer drug reviews and between NCI and the Centers for Medicare and Medicare Services to generate clinical data on new interventions to support Medicare coverage decisions should be continued and strengthened.	• NCI/NIH • FDA • CMS
11. To encourage private sector investment in cancer therapies, all new cancer chemoprevention and chemotherapy drugs and biologics should be designated orphan drugs under the Orphan Drug Act of 1983.	• Congress
12. A task force of private, nonprofit, academic, and government stakeholders affected by current barriers to research translation due to intellectual property and patent issues should be convened to develop and reach consensus on: (1) standard language for patent exemptions for research purposes, (2) standard clauses for contracts governing collaborative research, and (3) other agreements as needed to resolve intellectual property and data-sharing issues.	• NIH • DoD • VA • FDA • CMS • AACI • AACR • PhARMA • BIO • AAMC • HHMI • ACCC • ASCP • ASTRO
13. The Institute of Medicine should be commissioned to evaluate the impact of the Health Insurance Portability and Accountability Act provisions and provide guidance to legislators on amendments needed to remove unnecessary obstacles to cancer research and make this law better serve the interests of cancer patients and survivors. *(This is a restatement of prior Panel recommendations.)*	• Congress • IOM

Dissemination, Education, and Communication Issues Affecting Translation

14. A lead agency for cancer-related dissemination research and activities should be designated and provided with the budget and authority to carry out this crucial function.	• Office of Science and Technology Policy, White House
15. The National Cancer Institute should increase significantly funding for research and implementation activities to improve dissemination and adoption of cancer research advances. As part of this effort, Comprehensive Cancer Centers should be required and funded to take an active role in disseminating new cancer-related interventions into their communities/regions and facilitating their adoption by community cancer care providers, including non-physician personnel.	• NCI/NIH • Congress • NCI-designated Comprehensive Cancer Centers • Coalition of National Cancer Cooperative Groups (CNCCG) • NCCN

16. The translation process should be expedited through bi-directional education between regulators and cancer researchers to ensure that regulators better understand rapid advances in biomedical science and technologies, and that researchers better understand and are able to navigate and meet regulatory requirements.	• NCI • FDA • NSF • Private sector pharmaceutical and biotechnology companies

The Impact of Public Trust and Community Participation

17. Clinical and prevention research funders should require community participation early in protocol design and in research implementation.	• NCI/NIH • CDC • AHRQ
18. Research results must be shared with the individuals and communities that participate in clinical trials and other studies.	• NIH • CDC • DoD • VA • CNCCG
19. Clinical and prevention research grantees should be required to include as part of the grant application a plan for disseminating and sustaining new interventions into the community.	• NCI/NIH • CDC
20. Existing community-based participatory research models should be evaluated to determine the potential for adopting them in other geographic areas and populations.	• IOM • AHRQ

The Importance of Access to Successful Translation

The President's Cancer Panel has made recommendations to improve access to cancer care. These recommendations may be found in the following reports:

(See recommendations in these documents)

- *Living Beyond Cancer: Finding a New Balance*, May 2004
- *Facing Cancer in Indian Country: The Yakama Nation and Pacific Northwest Tribes*, December 2003
- *Voices of a Broken System: Real People, Real Problems*, March 2002

Appendix D. Acronyms and Organizations

AA	Accelerated Approval
AACI	Association of American Cancer Institutes
AACR	American Association for Cancer Research
AAHC	Association of Academic Health Centers
AAMC	Association of American Medical Colleges
ACCC	Association of Community Cancer Centers
ACR	American College of Radiology
ACS	American Cancer Society
ADA	American Diabetes Association
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
ANDA	Abbreviated New Drug Application
AOSW	Association of Oncology Social Workers
AP4	Academic Public-Private Partnership Program
ASCO	American Society of Clinical Oncology
ASCP	American Society of Clinical Pathology
ASTRO	American Society for Therapeutic Radiology and Oncology
APC	Adenoma Prevention with Celecoxib Trial
AWP	Average Wholesale Price
BES	Biomedical Engineering Society
BIO	Biotechnology Industry Organization
BLA	Biologic License Application
caBIG	cancer Biomedical Informatics Grid
CARRA	Consumer Advocates in Research and Related Activities
CCOP	Community Clinical Oncology Program
CDC	Centers for Disease Control and Prevention
CDMRP	Congressionally Directed Medical Research Programs
CGAP	Cancer Genome Anatomy Project
CIRB	Central Institutional Review Board
CIS	Cancer Information Service
CMS	Centers for Medicare and Medicaid Services
CNCCG	Coalition of National Cancer Cooperative Groups
CNP	Community Networks Program
CRADA	Cooperative Research and Development Agreement
CRC	Colorectal Cancer
CREATE	Cooperative Research and Technology Enhancement Act
CT	Computed Tomography
CTSU	Clinical Trial Support Unit
CTWG	Clinical Trials Working Group

DCLG	Director's Consumer Liaison Group
DHHS	Department of Health and Human Services
DoD	Department of Defense
EDRN	Early Detection Research Network
EHR	Electronic Health Record
EMR	Electronic Medical Record
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
HHMI	Howard Hughes Medical Institute
HIPAA	Health Insurance Portability and Accountability Act
HMO	Health Maintenance Organization
HST	Health Sciences and Technology (joint Harvard-MIT program)
IBS	International Biometric Society
ICJE	International Committee of Medical Journal Editors
ICRP	Intramural Clinical Research Program
IND	Investigational New Drug
IOM	Institute of Medicine
IOTF	Interagency Oncology Task Force
IRB	Institutional Review Board
KP	Kaiser Permanente
LAF	Lance Armstrong Foundation
LRP	Loan Repayment Program
MMA	Medicare Prescription, Improvement, and Modernization Act
MMHCC	Mouse Models of Human Cancer Consortium
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
NCAB	National Cancer Advisory Board
NCCN	National Comprehensive Cancer Network
NCCS	National Coalition for Cancer Survivorship
NCI	National Cancer Institute
NCP	National Cancer Program
NCRE	National Clinical Research Enterprise
NDA	New Drug Application
NECTAR	National Electronic Clinical Trials and Research Network
NHGRI	National Human Genome Research Institute
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NLM	National Library of Medicine
NPA	National Postdoctoral Association
NPCR	National Program of Cancer Registries
NSF	National Science Foundation
OHRP	Office of Human Research Protections
OHSU	Oregon Health & Sciences University
ONS	Oncology Nursing Society
OSU	The Ohio State University
OTC	Over-the-Counter

PART	Patient Advocate Research Team
PBRN	Practice-based Research Network
PCP	President's Cancer Panel
PDQ®	Physician Data Query
PET	Positron Emission Tomography
PhRMA	Pharmaceutical Research and Manufacturers Association
PLANET	Plan, Link, Act, Network with Evidence-based Tools
PLoS	Public Library of Science
PRAC	Peer Review Advisory Committee
RAID	Rapid Access to Intervention Development
RBM	Research Business Models
RT-PCR	Reverse-Transcriptase Polymerase Chain Reaction
SEER	Surveillance, Epidemiology, and End Results Program
SNP	Single Nucleotide Polymorphism
SPIN	Shared Pathology Informatics Network
SPORE	Specialized Program of Research Excellence
UAB	University of Alabama at Birmingham
UC-Davis	University of California at Davis
UCSF	University of California at San Francisco
UIP	Unconventional Innovations Program
UMDNJ	University of Medicine and Dentistry of New Jersey
USC	University of Southern California
VA	Department of Veterans Affairs (Veterans Administration)
VHA	Veterans Health Administration