"Planning for Prostate Cancer Research: Expanding the Framework and Professional Judgment Estimates"

Statement of
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Good morning, Senator Specter and Members of the Subcommittee. I am Richard Klausner, M.D., Director of the National Cancer Institute (NCI). I am accompanied today by Harold Varmus, M.D., Director of the National Institutes of Health (NIH).

We are pleased to appear before you today to describe our response to the Congressional request to submit 1) a report outlining activities NIH is undertaking to enhance prostate cancer research programs and 2) a report outlining NIH's professional judgment for prostate cancer research for the next five years. The Congress has also asked NIH to make prostate cancer a top priority in allocating funding increases; to accelerate spending on prostate cancer; and to consult closely with the research community.

The nature and magnitude of the burden of prostate cancer has been tracked by NCI's surveillance program, and we estimate that about 180,000 men will be newly diagnosed with prostate cancer this year and about 37,000 will die. Prostate cancer exacts a particularly devastating toll on African American men; incidence rates are substantially higher among African Americans, and mortality rates in African American men remain more than twice as high as rates in white men.

This catalogue of statistics, while accurate, does little to convey the very real pain, fear, and uncertainty experienced by every man who is diagnosed with prostate cancer. Despite advances over the past decade, our treatments for prostate cancer are inadequate, the side effects of treatment are unacceptable, and troubling questions remain about the efficacy of early detection for the disease. Every day, too many men in the United States hear the life-changing words "You have prostate cancer." Every day, too many men are faced with the agonizing decision of how to treat their prostate cancer. And every day, too many men are dying too young of this disease. The limited knowledge about the

causes of prostate cancer, how to prevent it and how to successfully treat it demand a clearly articulated and adequate approach to research.

Overview

The NIH, with leadership from NCI, has aggressively sought participation from researchers, advocates, and patients in reviewing the prostate cancer research portfolio and charting a plan for a vigorous expansion of the prostate cancer research program. The initial evaluation of the research program and a broad outline of future directions were completed in August 1998 and are described in part I of the report being presented today, "Planning for Prostate Cancer Research: Expanding the Scientific Framework." The NIH efforts in coordinating a research plan for prostate cancer have focused on continuing development of a widely disseminated research program coordinated and supported by the NIH and accompanied by continuing involvement of researchers, professional societies, advocacy groups and patients. The report of the NCI-convened Prostate Cancer Progress Review Group described a nationwide program involving a significant investment in infrastructure across the nation. It is recognized that each of the 35 NCI Comprehensive Cancer Centers, geographically dispersed throughout the nation, devote significant effort to education, training, treatment and research on prostate cancer and cover the full spectrum of prevention, early diagnosis and treatment.

Part II of the report, "Planning for Prostate Cancer Research: Five Year Professional Judgment Estimates," describes prostate cancer research opportunities from 1999 through 2003. NIH has increased prostate cancer research funding significantly from a 1998 level of $114 million to a current projection of $180 million in 1999. This plan estimates that $420 million of potential research opportunities could be supported in 2003. It must be noted that this estimate is based on our assessment of scientific opportunities over the next five years, without consideration of economic constraints or other competing priorities of the NIH or the Federal government. This plan includes many efforts already initiated in 1999. Two institutes, the National Institute of Mental Health and the National Institute of Deafness and Other Communication Disorders were not previously focused on prostate research, but are now newly included in the NIH prostate efforts. Furthermore, this level of support must be integrated with other research efforts of the NIH. A total of nine institutes have important intersecting interests that contribute to the NIH prostate cancer research effort and have been consulted in the development of this plan.

NCI Highlights

The NCI is the lead NIH institute for prostate cancer research. The report describes a number of new NCI initiatives, projects, and mechanisms that have the potential to directly improve the quality of life of prostate cancer patients and survivors, as well as those at risk for the disease. Indeed, fully 70 percent of the research opportunities presented here are targeted at clinical or translational research that would have a direct impact on patients, survivors, and at-risk men.

The request in last year's appropriation bill for such a report came at a propitious time in NCI's internal planning and implementation processes. Before describing this plan, following are several relevant features of the NCI planning processes

For the past 3-1/2 years, the NCI has taken an intense three-part approach to planning. First, we established a series of blue-ribbon committees to review and propose reforms to our major venues for cancer research including clinical trials, cancer prevention, cancer control and the drug discovery and development processes. Scores of recommendations to create more effective and efficient means of making progress have or are being implemented.

Second, we established a process to evaluate areas of extraordinary opportunity with new investments and new programs that promised to capitalize on untapped, near term opportunities to make progress against cancer. These opportunities and the plans and progress made are outlined in the NCI By-Pass Budget.

Neither of these first two planning approaches are specific to cancer sites. Rather, the planning and implementation processes are specifically charged with establishing the commonality of needs across all cancer sites and to assure that the opportunities for progress are likewise implemented for all cancer sites.

Third, over two years ago, we initiated a disease-specific planning process called a progress review group or PRG. The Prostate Cancer PRG involved scores of individuals--scientists, clinicians, and advocates--and challenged the prostate cancer research community and the NCI to review our current prostate cancer research portfolio, to develop a prioritized set of questions that needed to be answered and resources that needed to be developed or applied, and provide a vision to chart a course for research and progress in prostate cancer. The PRG report was presented to the NCI last September and since then we have acted to implement a plan that we believe will fulfill the vision of progress articulated by the PRG. The PRG report, which I am pleased to provide to this committee, represents an important component of the scientific opportunities and professional judgment report which we are presenting today.

The PRG not only gave us a consensus vision of what the needs are but, importantly, greatly reinforced the premise of our other planning processes in that the vast majority of identified research needs in prostate cancer (and for breast cancer from the parallel breast cancer PRG) could be directly accommodated and accomplished through the several dozen programs already initiated as a result of our more global planning.

In all three of our planning phases we have involved a variety of members of the prostate cancer communities including researchers, clinicians and advocates. To ensure that the professional and advocacy groups were fully represented, the PRG invited the input of 32 "stakeholder" groups that represented both professional societies and advocacy groups.

The report being presented today highlights that NCI plans to spend $141.5 million on prostate cancer research in FY 1999, a 63% increase over FY 1998. NIH in total expects

to spend $180 million on prostate cancer research in FY 1999. At the Congress' request, we have also developed a five-year professional judgment estimate in collaboration with eight other Institutes and Centers that includes what we foresee as prostate cancer research opportunities over the following four fiscal years. If we could not be concerned with any economic constraints or other competing priorities of the NIH or the Federal government, we estimate NCI could support $340 million, and NIH in total could support $420 million worth of targeted prostate cancer research by FY 2003.

We have begun, in an aggressive way, to accelerate funding for prostate cancer as reflected in the report being presented here today.

- A special section of the NCI Web site calls attention to more than 20 initiatives through which high priority areas can be addressed.
- I have met with the representatives of the prostate cancer research community, the PRG, and the leadership of professional societies, such as the American Urological Association, in order to communicate these initiatives and to enlist the research community's support in responding to these opportunities.
- Extensive outreach and advertising will alert the larger research community to these opportunities to energize their participation in this prostate cancer research program.

The scientific opportunities we project are presented in four major areas:

1. Clinical Science-- the near term direct testing of new interventions in patients or in those at risk for prostate cancer.
2. Translational Science -- moving ideas from the laboratory to the point of clinical testing.
3. Risk, Burdens & Outcomes Science -- attempting to ask critical questions about cause, the unequal levels of cancer in different populations, outcomes and survivorship.
4. Basic research and discovery -- longer term investments in gaining insight into the development and biology of prostate cancer and the development of models for study.

Priorities are identified in the report. Seventy percent of the targeted research opportunities are directed to clinical and translational research. Let me illustrate with a few examples. In the area of clinical trials for patients with prostate cancer, we need to test new approaches and new agents aimed at a variety of clinical situations. We have established "Quick Trials," a new program to provide a rapid and efficient way to move new ideas for therapeutic interventions into Phase I and II clinical trials for prostate cancer. This program has been set up in recognition of the urgent need for new types of interventions that are effective at different stages of prostate cancer, as well as the growing number of therapeutic ideas that are ready to be tested in patients.

In this type of project, where it is necessary to evaluate untested leads in the absence of preliminary data, conventional application and review procedures are not well suited.

Quick Trials utilizes a process for rapid approval of early clinical trials. The NCI's goals are to increase the number of patients participating in early clinical trials by two to three-fold and to initiate 10-15 new trials through this accelerated mechanism. In addition, this year through NCI's Cancer Therapy Evaluation Program, we will initiate approximately 35 new Phase I/II trials in Prostate Cancer with agents directed against a number of particularly promising molecular targets and mechanisms. The targets include:

- angiogenesis and metastasis, the processes by which cancers induce new blood-vessel formation, invade these blood vessels, and spread throughout the body;
- growth factors and their receptors, which mediate growth signals to cancer cells; and
- tissue-specific genes expressed selectively in prostate or prostate cancer cells, thus allowing for the targeting of tumor-killing modalities to these cells.

We will test:

- Novel small molecule drugs
- Specific antibodies
- Vaccines
- Virus-based gene therapy
- Targeted radiation sensitizers

Compared to the current level of effort, this plan could more than double the number of early clinical trials in prostate cancer in the first year, with another doubling projected at the full professional judgment in the next four years.

This year, we will activate 5 new multi-center phase III clinical trials in prostate cancer that will attempt to optimize and test new hormonal and chemotherapeutic approaches for the most common clinical presentations of the disease, including:

- adjuvant therapy in the setting of primary surgical or radiation treatment;
- neo-adjuvant therapy, which has shown promising results in reducing the mortality from locally advanced prostate cancer;
- treatment after hormone therapy;
- treatment in the setting of rising PSA levels after definitive local therapy; and
- advanced disease, particularly directed at bony metastases.

With this initial ramp up in clinical trials, we project the ability to double the number again over the following four years.

We have initiated a new program creating a drug development process that enables investigators to begin clinical trials with novel molecules discovered in academic laboratories. We do this by giving academic investigators access, on a competitive basis, to NCI's preclinical drug development resources and expertise. Investigators who have molecules that hold promise for cancer treatment but without access to the development resources required for initiation of clinical studies are invited to submit applications twice

a year. Those selected for support are assisted with necessary development steps to enable IND filing with the Food and Drug Administration and to begin initiation of proof-of-principle clinical trials. For FY 1999, our goal is the development of three to five new therapeutic agents, each relevant to prostate cancer. Projects already approved include development of a bioreductive compound with potential as a radio and chemosensitizer, and a gene-therapy approach that will convert inactive pro-drugs into toxic agents within prostate cancer cells. Over five years, 15 new therapeutic agents for prostate cancer could potentially be developed.

The plan covers a number of additional central questions about prostate cancer and describes potential strategies to address them. These include:

1. Testing promising preventive agents, particularly in high risk individuals;
2. Developing new, predictive molecular diagnostics;
3. Validating current and new early detection markers;
4. The linkage of imaging to therapy;
5. Epidemiologic studies to attempt to systematically identify correlates of the profound geographic and population differences in prostate cancer rates; and
6. Developing new animal models that faithfully reproduce human prostate cancer in order to better understand tumor development and spread, and to better test preventive and therapeutic interventions.

This plan also envisions opportunities for a four-year increment of 215 investigator-initiated research grants that target 18 areas of clinical, translational, epidemiologic and fundamental research.

The five year professional judgment report I am presenting today builds on a strong base of existing prostate cancer research including:

1. The Cancer Genome Anatomy Project (CGAP), the goals of which are to build an index of all genes that are expressed in tumors and support development of new technologies that will allow high throughput analysis of gene and protein expression as well as mutation detection. The tumor type with the highest representation in the early stages of the CGAP effort is prostate cancer. NCI has facilitated investigator collaborations of interdisciplinary studies following the recent discovery of a susceptibility gene on chromosome 1. Leads from this effort may help to clarify genetic and gene-environment interactions responsible for black-white differences in risk.

2. NCI funded (in total or in part) 246 clinical trials in prostate cancer, including 80 Phase III studies and 37 Phase II studies. NCI clinical studies in prostate cancer have significant African-American participation. One NCI study shows that 14.7 percent of men enrolled onto NCI sponsored prostate cancer treatment trials are

African American while 10.3 percent of Americans diagnosed with prostate cancer are African American.

3. NCI's ongoing Prostate Cancer Prevention Trial (PCPT) involves 18,000 healthy men over the age of 55 to determine if the drug finasteride can prevent prostate cancer.

4. NCI's ongoing Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) is assessing the efficacy of prostate cancer screening. New PLCO sites are being added to enhance minority patient accrual. NCI is sponsoring two trials in which "watchful waiting" is being compared in terms of outcome with surgical removal of the prostate and with radiation therapy. These trials are intended to determine if treatment of localized disease is effective.

5. NCI staff and the Department of Defense have collaborated in a study of treatment data and shown that equal treatment yields equal outcome within stage. This finding suggests that all NCI efforts to improve prevention, diagnosis and treatment of this disease benefit all patients equally. However, NCI staff analyzing SEER Program data have shown that there are tremendously differing patterns of care among black and white men with prostate cancer.

6. NCI, along with the American Cancer Society and the Centers for Disease Control and Prevention sponsored a Leadership Conference on Prostate Cancer in the African-American Community in November of 1997. Developed in cooperation with the 100 Black Men of America, the Intercultural Cancer Council, the National Black Leadership on Cancer, and the National Prostate Cancer Coalition, the conference represented a significant step toward developing a strategy for the full participation of African Americans in prostate cancer research and control.

7. In addition, NCI recently conducted a large interview-based study of prostate cancer in African Americans and whites. Analysis of the results have not thus far revealed any specific factor that could explain the racial differences in risk. However, further studies are underway, including an extensive evaluation of the role of different components of the diet.

Other Institutes

Several NIH Institutes conduct and support research on prostate cancer and related diseases that will advance our knowledge of prostate cancer [National Institute of Diabetes and Digestive & Kidney Diseases (NIDDK); National Human Genome Research Institute (NHGRI); National Center for Research Resources; National Institute of Environmental Health Sciences (NIEHS); National Institute on Aging; National Institute of Nursing Research; National Institute of Mental Health; National Institute of Deafness and Other Communication Disorders]. These research activities are coordinated through formal and informal collaborations, interest groups, and other interactions. Following are highlights from some of these Institutes' professional judgment of potential research opportunities. A complete description of the research activities of other NIH Institutes may be found in the report, "Planning for Prostate Cancer Research."

NIDDK

The discoveries that will lead to improved therapy and ultimately prevention and cure need to be sought through a number of avenues:

- The outcome of cancer depends not just on the behavior of the tumor cell - but also on the normal surrounding cells that are not themselves cancerous. We need to know more about the normal prostate cells -B and the genes they express - in order to identify new targets for disease intervention. We also need to know more about the interactions between prostate cancer cells and bone, to understand the determinants of metastasis.
- Developmental biology is proving to be an important source of clues about disease. We need to understand the developmental program for formation of the prostate and the lineage of the cells that make up the gland.
- What is the action of androgen, the genes it controls and the mechanisms by which the hormone turns genes on and off? These are critical basic questions broadly anticipated to yield the basis for new therapeutic approaches.
- We know too little about the variation in susceptibility of different populations to the disease of the prostate. Careful monitoring of epidemiological trends in the burden of benign and malignant prostate disease is an important priority. Particularly, the enhanced susceptibility of certain racial groups to prostate cancer - and the relative protection of other groups - are phenomena that we need to understand.
- Better strategies to prevent the two feared complications of surgery on the prostate - urinary incontinence and impotence - are needed urgently. Although new surgical approaches for both benign prostatic hypertrophy and prostate cancer have reduced the rate of these complications, further progress is needed.
- Prostate cancer is a hormone responsive tumor and the major forms of treatment of advanced prostate cancer involve pharmacologic blockade of the gonadatrophin release or antagonism of the androgen receptor. There are new and emerging opportunities to improve these approaches.

NHGRI

Over the next five years, NHGRI investigators aim to identify all of the common contributing genes to hereditary susceptibility - besides HPC1 and HPCX, there is strong evidence pointing to another region of another chromosome, and other regions also contain hints of hereditary factors. As the precise genes are identified, clinical studies would be undertaken to offer genetic testing to men from high risk families, to identify those at greatest risk for life-threatening disease and design a program of surveillance to identify their cancers early enough to achieve cure. In addition, using the chip technology, the common changes in gene expression that contribute to various steps in malignant transformation would be cataloged, and used to derive new hypotheses about the molecular steps involved in prostate cancer. These would in turn suggest new and more powerful ways to treat or prevent the disease.

NIEHS

Human diseases, such as prostate cancer, are generally the consequence of both genetic susceptibility and environmental exposure. The tools of molecular genetics provide new opportunities to understand the genetic basis for individual differences in susceptibility to environmental exposure. The NIEHS is expanding its research program on genetic susceptibility to environmentally-associated diseases through a new Environmental Genome Project. Over the next five years, the Environmental Genome Project would systematically identify the allelic variants of disease susceptibility genes in the U.S. population, develop a central database of known polymorphisms for these genes, and foster population-based studies of gene-environment interaction in disease etiology. By identifying those genes and allelic variants that affect individual response to environmental toxins, we can better predict health risks and develop environmental policies to protect the most vulnerable subgroups of the population from such diseases such as prostate cancer.

The NIEHS Environmental Genome Project would be a broad, multi-center effort to identify systematically in the U.S. population the alleles of environmental disease susceptibility genes. Susceptibility genes will be chosen through a peer-reviewed process and are expected to include five broad gene classes: genes controlling the distribution and metabolism of toxicants; genes for the DNA repair pathways; genes for the cell cycle control system; cell death/differentiation genes; and, genes for signal transduction systems controlling expression of the genes in the other classes. This effort would result in the systematic identification of the polymorphisms of these genes found in the U.S. population. A central database of the polymorphisms would be made available. This database will support both functional studies of alleles and population-based studies of disease risk.

Public Understanding

Communicating with cancer patients, individuals at high risk for cancer, the general public, and the health care community is a central component of NCI's mission and

mandate. For prostate cancer, the institute communicates information to all of those groups, as well as to the cancer research community.

Materials available from NCI, including print, video, and web products, range from basic information about the disease, information about research now ongoing to improve understanding and management of the disease, and information for men about early detection and treatment options.

One of the most recent communications initiatives is a partnership with the prostate cancer advocacy organization, US TOO, to develop a national communications initiative, called *Know Your Options*, to better inform men and their families about the disease. The initiative is based on an information package or kit that provides a solid base of information about prostate cancer to help US TOO chapters work with their hometown media. The media, in turn, use the information provided by US TOO with the NCI imprimatur, to keep their readers, listeners, and viewers informed about the disease. The kit includes the latest medical and scientific information available, as well as information about where US TOO chapter leaders can go for more information, advice, and help.

In addition, information specialists from the NCI-sponsored Cancer Information Service provide more than 60,000 people annually with information about prostate cancer, information about research on the disease, information about screening and treatment options, and information about coping with physical and psychological side effects of the disease and its treatment. The NCI web site provides information about prostate cancer clinical trials as well as information about treatment options for every stage of the disease.

During this summer and next fall, NCI is working with the Centers for Disease Control and Prevention and with the Health Care Financing Administration to develop an educational video for men on issues they could face about prostate cancer screening, diagnosis, and treatment. The video, intended to be relevant to a general male audience, will be developed to have special relevance to African-American men. The video will provide educational material on what men need to know about prostate cancer screening options, what they need to know about diagnostic followup if a screening test is positive, and what they need to know about treatment options if the diagnosis is positive.

NCI's basic print product about the disease, "What You Need to Know about Prostate Cancer," is now available on the web as well. It provides information about prostate cancer; its symptoms, diagnosis, staging and treatment; clinical trials; side effects of treatment; nutrition and other support for prostate cancer patients; and what prostate cancer research holds for the future.

A new publication from NCI, "Understanding Prostate Changes: A Health Guide for All Men," will soon be available on the web too. It covers all aspects of prostate cancer in more depth than the basic booklet, but also describes non-cancerous prostate conditions. Another product in development, called "Prostate Cancer Treatment: Know Your

Options," will be published in print format soon and will also be available on the NCI web site.

NCI is communicating vigorously with the cancer research community. Earlier this year, NCI staff described all of the prostate cancer research initiatives that exist at the institute, and placed that information on its web site. The institute then promoted the availability of that information and issued an invitation for grant applications from the scientific community. The promotion of the information on the web site including the placement of advertisements in major scientific journals, the distribution of packets of information to the nation's cancer centers, and the distribution of information through direct mail to cancer investigators. Since the promotion began in late February, the web page listing prostate cancer grant opportunities has had thousands of hits from those seeking information about the grant opportunities.

Mr. Chairman, I appreciate the level of interest this Committee has shown in prostate cancer. I hope this plan demonstrates NIH and NCI's commitment to advancing our knowledge about prostate cancer as rapidly as possible. Our activities over the past year have invigorated the prostate cancer research community. It is this essential partnership between NIH, other funders and that research community that will successfully accomplish the ambitious goals of this plan. Dr. Varmus and I would be pleased to answer any questions you may have.