

PREPARED STATEMENT OF FRANCIS COLLINS, M.D., PH.D. DIRECTOR, NATIONAL CENTER FOR
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Body

INTRODUCTION

Madame Chairman and members of the Committee, we are pleased to appear before you today to discuss our programs at the National Institutes of Health. Revolutionary advances in our understanding of human genetics have opened a window on the chemical quirks in our genes that make us susceptible to many devastating diseases including cancer. Over the past two decades, using the tools of recombinant DNA technology, researchers identified a number of "single gene" diseases, in which an alteration in just one gene may cause disease. Most human disease, however, is thought to arise from the complex interplay between inherited genetic alterations and the environment. Analyzing these complexities and teasing apart the genetic and environmental components involved represents both a daunting challenge and an important scientific opportunity. This challenging research is done using a wide range of approaches, including basic research in the laboratory, clinical applications, translation to community practitioners, and research into behavioral and lifestyle factors, and is supported across the National Institutes of Health (NIH) and the many institutions across the country that receive funding from NIH through a rigorous competitive process. Recently, there have been many spectacular and far-reaching discoveries of genes associated with cancer. After years of intensive research, we have learned that first and foremost cancer is a genetic disease. Mutations in our own genes drive the development of this disease, which strikes more than a million Americans each year. Determining which mutations render us vulnerable to cancer is at the heart of genetic

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research today. Although we still have a long way to go, a cautious optimism is beginning to ripple through the scientific community, as a result of an enormous increase in our understanding of just what happens to transform a normal cell into a cancer cell.

Changes in DNA are responsible for the progression toward and development of cancer, and these changes accumulate over a lifetime of exposures and are the result of multiple events. However, the single most important carcinogen, responsible for over 30 percent of all cancer deaths, is smoking. A vast amount of research conducted on tobacco use over the past 40 years conclusively demonstrates its harmful effects. Children, especially teenagers, are highly vulnerable to the addictive nicotine-delivery systems marketed as cigarettes. Unfortunately, they will carry into their futures the increased risk of disease and premature death caused by tobacco use. Research supported primarily by NIH is attempting to develop effective interventions to reduce tobacco use, particularly among our youth, and investigates other effective methods to reduce the terrible public health burden of tobacco use on our country.

Our new understanding of cancer has evolved in part from the observation that cancer runs in certain families. Through studying these families, researchers have learned that a single genetic event is associated with an increased risk for cancer. The development of a cancer is the result of gradual and sequential changes in perhaps half a dozen genes in a single cell over the lifetime of that cell. While scientists have identified a few genes associated with several cancers in high risk families, genes associated with cancers in the general population are not yet known. Discovering both the candidate genes for sporadic cancers and the mix of non-genetic factors, such as the environment and diet, which may contribute to the disease, is part of the research challenge that lies ahead.

An immediate spin-off of these advances in cancer gene discovery is the potential for genetic testing, which predicts an individual's risk for developing the disease. In the short term, this may transform the practice of preventive medicine by encouraging individuals who carry these genetic errors to alter their life styles or participate in increased screening. This is particularly effective for cancer, where early detection is often the best chance for cure.

Yet not all individuals will want to know their genetic script. The ability to read our genetic blueprints raises troubling societal and personal issues that must be addressed. Of particular concern is the fear that we will lose our jobs or health insurance because we are shown to be at high risk for cancer. And what are the personal ramifications of knowing our own cancer risk? Will available treatments keep pace with new genetic tests? How will physicians and health care workers relay sensitive information and stay on top of rapidly evolving gene discoveries?

The National Cancer Institute, the National Center for Human Genome Research and the National Institute of Environmental Health Sciences are all working to take advantage of the promise that human genetics offers to alleviate human suffering. As leaders in genetics research, each institute has a dual responsibility to advance promising scientific findings and to ensure the appropriate use of this new information.

THE HUMAN GENOME PROJECT

Last Fall we celebrated the fifth anniversary of the Human Genome Project with a record of excellent progress toward our goals. Co-funded with the Department of Energy, the Human Genome Project is an historic 15-year research endeavor with the goal of producing detailed maps of the 23 pairs of human chromosomes and sequencing the 3 billion nucleotide bases that make up the human genome. The primary mission of the project is to develop research tools--genetic and physical maps, DNA sequence information, and new technology--to allow researchers to find and analyze quickly and efficiently the 50-100,000 genes present in our cells. The project thus far has been successful in meeting or exceeding the goals outlined in its original plan. The human genetic map has been completed and is much more detailed than was originally contemplated. Recently, a team of scientists published a physical map of the human genome composed of over 15,000 well-ordered markers, and covering approximately 94% of the genome. This a major milestone on the way to completing a comprehensive physical map of the human genome. Though original projections were that this map would not be completed until the end of 1998, completion is now expected by early 1997.

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The most challenging goal of the Human Genome Project is to sequence the entire 3 billion nucleotides that comprise the human genome. This year we are embarking on this ambitious and exciting phase of the Human Genome Project. Improvements in DNA sequencing technology and strategy have dramatically reduced the cost of sequencing and increased the efficiency. To further stimulate development of high-capacity DNA sequencing capability, pilot projects for large-scale human sequencing and for further improvements in DNA sequencing will get underway, in April. As a result, a number of laboratories are now positioned to sequence over 10 million basepairs a year by 1997.

Though we look forward to the first complete DNA sequence of the human genome with great anticipation, we do not have to wait until the end of the project to reap its benefits. Already this information is changing the way biomedical research and the practice of medicine are being conducted. The information, tools and resources generated by the Human Genome Project are quickly disseminated to and utilized by researchers across the United States and throughout the world. All of the information from the Human Genome Project is placed in public electronic databases which are accessed by researchers over 150,000 times each week.

The tools and technology created by the Human Genome Project are being used by scientists to help in their discovery of the genes associated with disease. Already the maps generated by the Project have greatly facilitated gene discovery. For example, more than 10 years of research were required to isolate the gene for cystic fibrosis in 1989, while the recent isolation of the second breast cancer gene, BRCA2, took about 2 years. When the Human Genome Project is complete, isolating a disease gene of interest will take just a couple of months. In addition to the reductions in time required to find disease genes, there will be significant reductions in cost.

Most of the disease genes isolated so far are so called "single gene" diseases where a misspelling in a single gene is sufficient to cause disease. Many common diseases including diabetes, Alzheimer's, alcoholism and cancer are much more complex and may involve the interactions of many genes as well as environmental factors.

CANCER GENETICS

Years of intensive research have established how tumors develop. First and foremost, mutations in our own genes drive the development of cancer. These mutations alter the normal processes that help a cell regulate its fate. When they go wrong, control is lost and tumor development is promoted. Second, we now understand that a cancer will arise only after several mutations occur in the same cell. One mutation is never sufficient, and in some adult cancers ten or more mutations may be needed to generate the full set of changes that make tumors aggressive. Third, we have learned that the number of different genes that can be mutated and contribute to all types of cancer is large, but the number may be no more than ten altered genes for a specific cancer. Certainly the number of genes involved in cancer overall will be in the hundreds; our current guess would suggest that it will not reach one thousand. These numbers are large, daunting perhaps, but not impossible to handle.

Cancer is a disease caused by mutations in key target genes that give a selective advantage to the growth of the tumor cell. The accumulated mutations allow the cells to grow out of control. They divide, obstruct, invade, and destroy normal tissue architecture. Through the accumulation of genetic changes, these cells acquire properties that allow them to escape the normal biological defenses and controls and, in turn, pose a life-threatening problem to the affected individual.

While cancer is a disease of genetic changes, it is generally not an inherited disease like cystic fibrosis or sickle cell anemia. Rather, most cancers arise within a cell of the body that, through its lifetime, accumulates the genetic changes peculiar to each cancer. For some cancers, we now know that the gradual and sequential change in perhaps half a dozen genes signals the transformation from a normal, well-behaved cell to a growing and spreading cancer. In about ten percent of cancers, an individual has inherited an alteration in one gene which predisposes them to the subsequent genetic changes that will result in cancer. These individuals may have a ninety percent chance of developing cancer over the course of their lifetime.

The identification of these cancer predisposition genes and the determination of how these genes function normally, and of how the loss of function of these genes predisposes to cancer, are vitally important research questions.

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Discoveries in this area are profoundly and fundamentally changing our knowledge, not only of inherited cancers, but of their much more common sporadic counterparts.

The revolution in human molecular genetics is making these gene identifications possible. Over the past two years alone, scientists have identified genes responsible for inherited forms of breast and ovarian cancers, colon cancer, melanoma, and kidney cancer, to name but a few. One of the major goals of cancer research is to predict who will get a particular cancer. With the ability to identify individuals within cancer prone families who do and who do not carry the mutated gene, we can predict who in those families carries the particularly high predisposition to cancer and who does not.

While these inherited cancer syndromes explain a minority of cancers, the number of affected individuals is large--perhaps one million Americans carry a breast cancer predisposition gene mutation and another one to two million Americans carry mutations in colon cancer predisposition genes. In these inherited cancer syndromes, the mutated or defective gene, which results in the cancer predisposition, is present in the DNA carried in each and every of the trillions of cells of the individual. It is present in the DNA of blood cells and it is present from birth, long before cancer develops. It is this fact that allows the possibility of genetic testing to identify those individuals who carry the mutation. We are funding projects at multiple centers aimed at identifying new cancer predisposition genes involved in prostate, gastrointestinal, skin, brain, lung, and other cancers.

This, however, is easier said than done. While the past few years have seen the rapid discovery of some cancer susceptibility genes responsible for inherited cancer syndromes, more await discovery. Each gene is made up of hundreds to many thousands of letters of the genetic code. A defect in spelling anywhere in these enormous genetic words can, theoretically, be the culprit. Even when the cancer gene is discovered, such as the first breast cancer predisposition gene, BRCA-1, which accounts for about 50 percent of inherited breast cancer and greater than 75 percent of inherited breast plus ovarian cancer, nearly every affected family has its own misspelling. The result of this genetic heterogeneity stretches the technical and financial feasibility of screening for mutations outside of families in which the painstaking work of mutation identification has already been done using currently available technology. Because the mutation found in each family is, by and large different, it is not yet feasible to screen the general population.

The remarkable discovery of a single misspelling in the BRCA-1 gene that is found in as many as 1 percent of Ashkenazi Jews, or Jews of Central or Eastern European origin was announced last September. This group represents 90 percent of the 67 million Jews in the United States.

For the first time, the technical ability to actually screen a population for a cancer predisposition gene is feasible. This discovery signals a fundamental change in the many issues we must come to grips with and, because of the pace of scientific discovery, we must be prepared for the challenge of this changing landscape of medicine.

The recent discovery of the gene for ataxia-telangiectasia will also contribute to our understanding of the relationship between genetic alterations and cancer risk. You may have seen Brad Margus and his family recently on the television news program Turning Point. Two of Brad's four sons have ataxia-telangiectasia (A-T). A-T is a rare but fatal childhood neurological disorder. The discovery of this gene paves the way for more accurate diagnosis in the short term and the potential for effective treatments in the long term for children suffering from A-T. One of the interesting aspects of the A-T gene is the indication that it may play a role in predisposition to certain cancers. Although the disease itself is rare, an estimated one percent of the U.S. population are carriers of the altered gene and appear to have an four to five fold increased risk for various cancers, including breast, lung, stomach, and skin cancer.

Significant progress is also being made to identify the genetic contributions to all cancers. Prostate cancer is the most common form of cancer diagnosed in men in the United States, yet little is known about the molecular basis for this disease. Not only does it account for one in every four cancers diagnosed in American men, but it can spread (metastasize) beyond the prostate, killing 40,000 men annually. Although only 25 percent of these cancers are the lethal variety, physicians have no way of determining which prostate cancers can be ignored and which must be surgically removed. This dilemma is further complicated by the fact that prostate cancer surgery is difficult, requiring a lengthy recovery time and frequently rendering a man incontinent or impotent. By characterizing the

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genetic fingerprint of prostate cancer, we will be able to develop screening procedures to identify patients requiring surgery, and we will enhance our ability to develop therapeutic strategies to more effectively treat this devastating disease. Ultimately, studies may lead to the identification of environmental agents involved in the development of prostate cancer.

NEEDS AND CHALLENGES

The recent breakthroughs in cancer genetics have focused on cancer predisposition genes that geneticists refer to as simple traits, in which the inheritance of one specifically altered gene is alone responsible for the increased cancer susceptibility and where the chance of getting cancer, given an alteration in the culprit gene, is very high. Such simple genetic predispositions already provide us with enormous scientific and technical challenges. However, it is fair to say that these simple genetic predispositions are likely to only be the tip of the iceberg of the influence of heredity on cancer predisposition. We will need to develop the ability to identify genetic predisposition in families where it results from inheritance of more than one genetic locus. We need also to be able to identify modifier genes that affect what we call the penetrance of a cancer predisposition gene - in other words, genes that modify the risk of getting cancer in individuals with the inherited predisposition. Finally, we need to establish the non-genetic factors, such as environmental and dietary exposures, behavior and lifestyle, infectious agents, and others that will undoubtedly influence whether the presence of an altered cancer susceptibility gene actually results in cancer and when.

Successfully dealing with these challenges will involve generating and analyzing enormous amounts of data about dozens of genes and hundreds of alterations in each gene plus correlating each of these alterations with clinical outcomes. Therefore, an informatics system is needed to collect, store, analyze and integrate molecular data with epidemiologic and clinical data. For example, as new families that suffer a predisposition to cancer are identified, the properties of their disease need to be passed to the researchers who will map the gene. Basic researchers' discoveries about how a tumor develops must be available to the physicians who treat cancer-prone families. The latest developments in genetic mapping need to be converted into useful genetic tests. These critical information needs demand a new level of exchange that can only be achieved through coordinated efforts. The NIH has recently established a variety of databases, tissue and DNA repositories, tumor registries, and registries of high risk cancer families in order to address all of these issues throughout the country and in multiple populations within our diverse society. One example is the Cooperative Family Registry for Breast Cancer Research, which will provide a registry resource for interdisciplinary studies on the etiology of breast cancer, encourage translational research, and identify a population at high risk that could benefit from new preventive and therapeutic strategies. Another is the NCI/**NIH** Long Island Breast Cancer Study Project which will in part correlate genetic predisposition to breast cancer with environmental exposures, hormone levels, and behavior in this region of the country known to have higher than average rates of breast cancer incidence and mortality.

ENVIRONMENTAL INFLUENCES

Nearly all diseases are thought to arise from the interplay between inherited genetic alterations and the environment. Exciting opportunities now exist to advance our understanding of the environmental and genetic basis of many common illnesses and design effective prevention and intervention strategies to combat their development. Humans are exposed to a multitude of environmental agents from conception to death. These agents include foods and nutrients, synthetic and naturally-occurring chemicals, and physical agents such as heat and ionizing radiation. The extent of exposure to environmental agents with carcinogenic or toxic potential and the possible consequences may be influenced by age, the time of exposure, socioeconomic status, and behavior. Thus, the scope of what comprises the environment has been extended beyond the historical preoccupation with industrial products and byproducts.

Environmental health risk assessment research originated because of the need to determine whether technologic and industrial advances might also impair human health. Environmental health and safety regulations, based on this research, have safeguarded public health and led to dramatic improvements in the environment. Regrettably, however, these regulations may have been more costly and less effective than they might have been because of uncertainties or gaps in the science used in the risk assessment process. Over the past five years, NIEHS has

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involved industry, the public, and academia together have worked to identify gaps in scientific knowledge required for more rational risk assessment decisions. As uncertainties are reduced, the scientific basis for sound risk management decisions is strengthened and better public health prevention practices can be introduced, often at less cost to industry and consumers.

With the advent of sophisticated tools of cell and molecular biology, researchers can now obtain more rigorous data about the environmental effects on human health. This information will be invaluable to physicians and public health officials in preventing, diagnosing and treating disease. It will also assist policy-makers in decisions about risk and regulatory responses, and the research may help clarify the influence that behavior and socioeconomic status have on human susceptibility to environmental agents with carcinogenic or toxic potential. In addition, as many environmental exposure issues are transnational in scope, international research collaboration has an important role in developing the science base relevant to the global environment. Environmental health research is at a critical and exciting juncture. New refinements in molecular biology techniques provide unprecedented opportunities for understanding the molecular and cellular basis of environmentally-associated diseases. These opportunities build upon the foundation of almost 30 years of research.

PRE-CLINICAL MODELS

Technical advances have always played a key role in improving our ability to manage and treat disease. This link between new technical advances and rapid progress is equally true for the discovery process in cancer research. The lack of animal models for human cancer and cancer development has been a major roadblock in cancer research. This roadblock has now been overcome by recent advances in mouse genetics. Recently developed methods in animal genetics allow the study of cancer in ways that were impossible even a few years ago. These new techniques provide the remarkable ability to introduce mutations into the genetic material of mice that can be passed to their offspring. Using techniques developed through NIH support, investigators can now place any mutation they choose into a mouse.

For example, researchers have developed a "knock-out" mouse that lacks the estrogen receptor. The female hormone, estrogen, directs and controls cell growth and differentiation by binding to the estrogen receptor located in tissues throughout the body. Many environmental compounds bind to these same receptors, thus potentially acting as "environmental estrogens." These environmental compounds may play a role in a wide range of diseases. In women, they may be implicated in development of endometriosis, uterine fibroids, and cancers of the breast, uterus, and ovaries. In men, these compounds might explain the increase in testicular cancer, decline in sperm count and other reproductive tract anomalies.

This strategy will ultimately allow us to study in laboratory animals the mutations that are likely to drive the development of human cancer. These mice will provide a natural setting to study carcinogenesis and all stages of tumor development. They will allow us to test in animals early detection, prevention and treatment strategies, and to develop the targeted cancer therapies of the 21st century.

IMPROVED RISK ASSESSMENT THROUGH THE USE OF NEW MODELS AND METHODOLOGIES

The dilemma facing environmental and regulatory scientists is lack of animal models that completely duplicate the toxic or carcinogenic response of humans. Most of the scientific data used in determination of the toxic or carcinogenic properties of environmental agents is derived from experimental animals, typically rodents. Such studies have resulted in a great deal of dissatisfaction, mostly due to unresolved uncertainties and the time and costs required for the conduct of the conventional two-year rodent bioassay. Assessment of dose-response relationships and relevance of the experimental model are often the most difficult and controversial issues in risk assessment. Data in experimental animals is usually obtained with relatively high doses of exposure because of limited resources and the need to minimize the numbers of animals used. This requires use of methods to extrapolate health effects to exposure levels much lower than those for which experimental data are available. Depending on the methods used, risk estimates may vary by several orders of magnitude.

To address this important issue, greater emphasis has been placed on (1) developing a mechanistic understanding of disease etiology for use in extrapolating from rodents to humans, and (2) developing quicker and cheaper

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alternatives to the current two-year rodent bioassay to enable more efficient use of resources. Mechanistic data is now routinely generated during the performance and evaluation of the results of the rodent bioassay. Also, new transgenic mice are being evaluated for their effectiveness in producing reliable, relevant carcinogenic information in a shorter time frame (six months versus two years) using fewer animals. Preliminary results with the transgenic mice have been very promising in that of the approximately 40 chemicals screened to date, test outcomes are comparable to those reported for the rodent bioassay. Partnerships have been developed involving industry, Environmental Protection Agency (EPA), and Food and Drug Administration (FDA) so that the screening required for validation can be completed within two to three years. If validated, the new transgenic models could reduce our dependency on the costly and time-consuming two-year rodent bioassay and would allow for screening of dozens of chemicals annually. Further, the results would be more relevant for the assessment of risk to human health because the tests can be performed with low dose exposures. We estimate that four chemicals can be screened in the new system for the price of a single chemical in the two-year rodent bioassay. Additionally, representatives of the pharmaceutical industry have indicated that shortening the carcinogenicity test from 24 months to six months may result in a net benefit (combination of reduced cost for development and increased sales revenue during patent protection) of up to one half billion dollars per so-called typical drug introduced into the marketplace. Thus, the potential impact of these new models on carcinogenicity testing, human risk assessment, and on the Nation's economy is substantial.

Understanding the environmental components and basic biology of disorders can lead to prevention and intervention strategies that circumvent many adverse health effects. Traditionally, these strategies have focused on eliminating or reducing environmental exposures. These approaches will continue to be important parts of the Nation's environmental health programs. **NIEHS is working to improve risk assessment methodology so that regulation is not needlessly restrictive, but rather protects both public health and economic vitality.** As we gain a better understanding of the molecular and cellular basis of environmentally associated diseases, we may be able to develop prevention and intervention techniques to treat people following an adverse environmental exposure. **These molecular interventions would rely on manipulations of the biological mechanisms underlying environmentally induced diseases, such as activating and inactivating enzymes, receptors, and other molecular components. They would be particularly useful in dealing with environmental exposures that are ubiquitous or difficult to eliminate.** Further, they would have important implications in the pharmaceutical and pesticide industries, which could in the future develop products with maximal effectiveness and minimal adverse effects.

EARLY DETECTION

We are now faced with the new ability to determine the molecular and genetic "fingerprint" of a cancer, whether it results from an inherited predisposition or not. The first identification of a human cancer gene was reported approximately 20 years ago, and progress in this field has been rapidly expanding since then. This explosive increase in our knowledge of the mechanisms that drive tumor development is one of the success stories of modern biology. We now understand the molecular basis for many of the changes that drive tumor development. This explosion in our knowledge needs to be applied to the diagnosis of cancers. Molecular diagnostics provides one of the most obvious, and what promises to be one of the first, links between the molecular characterization of cancer cells and patient care. In its simplest terms, this new phase of cancer diagnostics will provide a snapshot of the properties of a tumor, which will detail the key differences between a normal and cancer cell and will provide a molecular scorecard of the properties of a tumor cell. Molecular diagnostics will transform the practice of clinical oncology. It will allow us to predict the behavior of each cancer - will it grow fast? Will it spread or metastasize? Will it respond to therapy? Ultimately the molecular description of each cancer will guide us to choose new and effective therapies and will be the basis on which we plan patient care.

New opportunities to make major advances in early detection methodology now exist. They include the detection of solid tumors through screening for proteins secreted by them and not by their normal cell counterparts. Tumor cells also harbor certain mutant genes which can be detected in body fluids with which they come into contact, signaling the presence of a nearby cancer. Cancer cells regularly influence the behavior of neighboring and distant tissues, alike. Blood vessels, the kidney, the brain, endocrine glands and other organs are all susceptible to changes in structure and function as tumors grow. The proteins secreted by tumors which account for these changes are being

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rapidly discovered, making sensitive methods for their detection feasible. Detecting such tumor products in a blood sample early in the course of one's disease could signal the presence of small numbers of tumor cells. Diagnostic imaging technology is rapidly becoming more sensitive and specific, enabling the detection of ever smaller numbers of tumor cell collections than ever before. New methods of sensing tumor cell specific signatures should provide opportunities to detect tumors at their earliest stages when even the most potentially aggressive tumors are most likely to be curable. These technology based approaches to early detection are the direct result of our Nation's investment in untargeted basic research. The Radiation Diagnostic Oncology Group provides one national mechanism for multi-institutional clinical trials in imaging. Promising new initiatives in breast, prostate, and aerodigestive imaging, including the coordinated development and application of military and space technology relevant to imaging, has brought together successful consortia that will allow us to learn to detect cancer before it is beyond the possibility of current curative therapy.

PATIENT-ORIENTED RESEARCH

Our knowledge will continue to grow about the function of these genes as researchers analyze at the molecular level the genetic causes of disease, and associate specific gene alterations with an individual's risk for disease. Eventually, researchers will be able to develop new treatments for many of the diseases that result from malfunctions in our genes. Detailed knowledge of the specific genetic alterations underlying disease and an understanding of their role in cellular processes will allow the design and development of rational drug and gene-based therapies. However, there will often be a substantial lag between our ability to offer a genetic test and the ability of researchers to understand the disease sufficiently well to develop new treatments and therapies.

The ability to identify cancer predisposition genes raises a new set of pressing questions that will only be answered by a greatly expanded effort in clinical research. These efforts must be aimed at being able to know what we can do with the information that an individual is at risk of developing cancer. How can we detect such cancers as early as possible? Are there ways to prevent cancer development? What is the optimum treatment if cancer arises? The responsibility of the biomedical community at this point must be aimed at providing information that addresses these issues so that individuals can make informed decisions about whether or not to seek such genetic testing.

It is important to point out that testing negative for a particular cancer susceptibility gene defect tells an individual that they do not carry the risks of a particular cancer or cancers associated with that specific gene defect but does not change the significant risk that this individual, like any individual, has of getting cancer due to causes other than that particular predisposition gene.

On the other hand, what do we have to offer people who do test positive? Here is the central problem. It is attempting to answer this question that takes us to the limits of our current knowledge and tells us what types of information we will need to gather for a particular mutation in a particular cancer susceptibility gene: - What is the risk of developing cancer and when? These are cancer susceptibility genes and even when they confer an 80 to 90 percent lifetime risk of developing cancer, we need to know what other environmental, behavioral, and genetic factors determine when, and if, an individual who carries a particular mutation develops cancer.

- How should "at-risk" individuals be followed to monitor for the development of cancer?
- Finally, how should "at-risk" individuals be counseled in terms of treatment and prevention options?

To answer all these questions requires carefully designed and conducted clinical studies.

Patients and health care providers must have knowledge about and access to studies aimed at answering questions about risks, surveillance, screening, prevention, and treatment.

The identification of genetically high risk individuals provides an extraordinary opportunity to more rapidly and effectively accomplish clinical trials in cancer prevention through dietary, drug, immunologic, or other interventions. It also provides the opportunity to establish trials aimed at developing and evaluating early detection using genetic or other biomarkers as well as imaging technologies.

The extensive clinical research and clinical trials infrastructure of NCI, including 55 cancer centers and cooperative groups involving over 9000 physicians at more than 1500 hospitals, is now being used to incorporate molecular

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diagnostics into clinical research. New funding initiatives have been developed to allow these groups and centers to expand their activities in cancer genetics, informatics, and in clinical trials that correlate molecular properties of tumors with their natural history, prognosis, and predicted response to and selection of therapy. Recently, NCI entered into an agreement with the Department of Defense (CHAMPUS) that may serve as a model for allowing cancer patients access to NCI-sponsored clinical trials as a routine part of their health plan benefits. It has long been observed that cancer runs in families. Today, all of us are participants in a revolution in medicine, in science, and indeed a revolution in our very conceptualization of individual identity and of predicting the type of future an individual may face in terms of his or her health. These discoveries, as with all discoveries, raise opportunities and very serious challenges. We must address ourselves to both the new opportunities raised by these discoveries, opportunities for the early detection, for the possibility of prevention and ultimately for the development of new therapies for cancer. Equally, we must be aware of the challenges. We are ready to address the scientific, technical, and human resource challenges, but the challenges do not end there. The potential power of reading one's own genetic script raises societal and personal issues about insurance, employability, privacy, and personal choice that we cannot ignore.

Genetics is changing the landscape of biomedical research and it will change the landscape of clinical practice. To be prepared for these changes will require attention to human resource development. Foremost is the need for genetic counseling in oncology. There is a real need to train genetic counselors and for physicians, other health care providers, patients and communities to have access to effective educational materials and guidelines for all the issues surrounding the use and interpretation of tests aimed at addressing genetic susceptibility to cancer. We must include training in genetics, risk assessment, and the ethical, legal, social, and behavioral aspects of genetics for health care providers. A recently-initiated comprehensive cancer genetics program will address these issues through the nationwide cancer centers program.

THE ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS PROGRAM

As an integral part of the Human Genome Project, the NCHGR and the Department of Energy (DOE) have each set aside a portion of their funding to anticipate, analyze, and address the ethical, legal, and social implications (ELSI) of the new advances in human genetics that human genome research has made possible. The goals of the ELSI program are to improve the understanding of these issues through research and education, to stimulate informed public discussion, and to develop policy options intended to ensure that genetic information is used for the benefit of individuals and society. The NCHGR ELSI program has focused on several high-priority areas raised by the most immediate potential applications of genome research: 1) privacy and fair use of genetic information; 2) responsible clinical integration of new genetic technologies; 3) ethical issues surrounding the conduct of genetics research; and, 4) professional and public education. The NCHGR has taken two approaches to address the ELSI goals: 1) a research grant program on which NCHGR spends five percent of its annual budget and 2) an interagency working group, the NIH-DOE Joint Working Group on the Ethical, Legal, and Social Implications of Human Genome Research (ELSI Working Group).

Testing and Counseling Initiatives

There are two key initiatives underway at NIH to address some of the crucial questions surrounding genetic testing, especially for cancer susceptibility. To examine issues surrounding the safe integration of genetic testing and counseling for cancer risk into clinical practice, several institutes are supporting clinical research studies on testing and counseling for heritable breast, ovarian, and colon cancer risks. These investigators are studying the psychological and social impact of cancer testing on individuals and their family members and are developing recommendations for approaches to genetic testing and counseling for cancer risk.

The investigators in these projects have formed a consortium to pool resources, reduce duplication of effort, and increase coordination of some aspects of the studies. Some of the key aspects the investigators agreed to coordinate include: the use of a core set of evaluation tools to assist in the comparison of results from the studies; the identification of the key elements to be included in all consent forms used in the consortia studies; and a plan to develop specific recommendations for individuals who test positive for BRCA 1 mutations. The studies are well

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underway, and the investigators have developed draft recommendations for how to counsel patients and families who carry a BRCA 1 mutation.

A second highly relevant initiative funded by the NIH is the Task Force on Genetic Testing (TFGT). The mission of the Task Force is to examine the strengths and weaknesses of current practices and policies relating to the development and delivery of safe and effective genetic tests and the quality of the laboratories providing the tests. The membership of the Task Force includes representatives from the biotechnology industry, the professional medical and genetics societies, the insurance industry, consumers, and the relevant federal agencies involved in the diffusion of new genetic tests. The TFGT was established in April 1995 and is expected to complete its work in early 1997.

The Task Force is concentrating on three areas: 1) scientific validation--developing validation criteria for the sensitivity, specificity, and predictive value of the tests; 2) laboratory quality--addressing the gaps in monitoring the quality of genetic tests; and 3) education, counseling, and delivery-- providing ways to educate practitioners and consumers about the limitations and capabilities of current test technologies, including their predictive and interpretative value. The rapid pace with which genes are being discovered and genetic tests are being developed indicates that the findings of the TFGT are urgently needed and will be crucial to the development of sound policies and practices for the introduction of new genetic tests.

Fair Use of Genetic Information As our knowledge grows about the genetic basis of disease, so too does the potential for discrimination and abuse. One particular concern is that individuals will be denied health insurance or employment based on genetic information. Furthermore, we are all at risk for certain diseases, and as gene discoveries and genetic testing advance, we will have the opportunity to learn more about our individual susceptibilities. A health insurance system that uses this information to deny individuals coverage will be unworkable in the long term. However, there are no Federal laws now in place to prevent health insurance companies from using genetic information to deny coverage. Several states are concerned about the use of genetic information and have passed legislation that protects individuals from being denied health insurance based on their genetic status. These state laws prohibit insurers from denying coverage based on genetic test results, and/or prohibit using this information to establish premiums, charge differential rates, or limit benefits. A few of these states, including California, Florida, and Oregon integrate protection against discrimination in insurance practices with privacy protections that prohibit insurers from requesting genetic information and from disclosing genetic information without authorization. The federal Employee Retirement Security Act (ERISA) exempts self-funded plans from state insurance laws. Thus, state laws do not provide protection for the many Americans who obtain their health insurance coverage through employer based plans. The ELSI Working Group has long been involved in discussions about the fair use of genetic information, particularly as it relates to health insurance. In 1993, the ELSI Working Group's Task Force on Genetic Information and Insurance concluded that, "Information about past, present, or future health status, including genetic information, should not be used to deny health insurance coverage." Another important group recently formed is the National Action Plan on Breast Cancer (NAPBC), a public-private partnership established to address the research, education, and policy issues in breast cancer. The NAPBC has identified the issue of genetic discrimination and health insurance as a high priority.

Building on their shared concerns, the ELSI Working Group and the NAPBC co-sponsored a workshop on July 11, 1995, to address the issue of genetic discrimination and health insurance. Consumers, researchers, federal and state government representatives, and insurance industry representatives came together with the members of these two groups to participate in the one day session. Based on the information presented at the workshop, the ELSI Working Group and the NAPBC developed and published recommendations for state and federal policy makers to protect against genetic discrimination.

The new advances in human genetics offer the promise that we will find new ways to fight some of the most devastating diseases that Americans suffer from today. We must ensure that our health care policies and practices relating to the introduction of new genetic tests and the subsequent use of genetic information keep pace with these significant new advances.

This concludes our remarks. We would be pleased to answer any questions you may have.

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Classification

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