

PROMISE OF THE GENOMIC REVOLUTION

HEARING BEFORE A SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS UNITED STATES SENATE ONE HUNDRED SEVENTH CONGRESS

FIRST SESSION

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WEDNESDAY, JULY 11, 2001

U.S. SENATE,
SUBCOMMITTEE ON LABOR, HEALTH AND HUMAN
SERVICES, AND EDUCATION, AND RELATED AGENCIES,
COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 9:42 a.m., in room SD-192, Dirksen Senate Office Building, Hon. Tom Harkin (chairman) presiding.
Present: Senators Harkin, Landrieu, Specter, Stevens, and Craig.

OPENING STATEMENT OF SENATOR TOM HARKIN

Senator HARKIN. Good morning, and welcome to today's hearing of the Labor, Health and Human Services, and Education Appropriations Subcommittee on the promise of the genomic revolution.

Back in the 1980's when people first started talking about sequencing the human gene, no one expected that we would be finished by now. Scientists thought it would take decades to work through all 3 billion letters of our DNA code. But thanks to people like Dr. Francis Collins, who will be our lead-off witness here today, and thousands of researchers all over the world, that goal was completed, as we know, last year.

Today, in fact, we can access our entire genetic instruction manual from a single CD-ROM. So, here is my entire lifetime right here on a CD-ROM. We can put the whole DNA sequence right now on one CD-ROM. That accomplishment ranks as one of the greatest intellectual achievements in our history. And I am proud to say that this subcommittee, working in a bipartisan effort, provided the funds to help make it possible.

But sequencing the genome is only the beginning of the medical advances that lie ahead. Researchers are now turning to the even more important task of reading the human genome to see what clues it can offer for cures and treating of diseases. For the first time, scientists have learned how to turn off the mechanisms in a cell that cause cancer. They are producing drugs like Gleevec, which is showing promising results in fighting leukemia.

They are also figuring out why a drug might work wonders on one person but have no effect on someone else with the same disease. Just imagine: One day soon, with the help of a simple genetic test, doctors will be able to prescribe exactly the right drugs for a person's particular genetic profile.

Genomics will also revolutionize the way we prevent diseases. We will be able to find out in advance which conditions we are susceptible to so we can take steps to reduce the risks.

But there is a darker side to this. What happens when someone gets fired or loses their health insurance because of a genetic predisposition to a certain disease? What is the value of knowing that you have a predisposition to a certain genetic disease if you are denied health insurance because of that very information?

That is why we need to get legislation through that would make it illegal for employers or health insurance companies to discriminate against people because of their genetic makeup. All of us should enjoy the benefits of 21st century technologies without suffering from the hardship of 21st century discrimination.

We have an outstanding panel of witnesses to discuss these issues this morning. We have a very special guest here this morning, who I am sure needs no introduction. Ben Affleck is a tremendous actor who, as many of you know, won an Academy Award for his first script, "Good Will Hunting". He has also starred in other terrific films like "Armageddon" and "Balance", and "Forces of Nature". Of course, as I told him earlier, he is now my envy as a fighter pilot. I always wanted to fly the kind of fighters he flew in "Pearl Harbor".

But Ben is here this morning for a different kind of war, the war against disease. He will testify this morning on the promise of the genomic revolution. He will talk about a terrible genetic disease called A-T that has stricken a young friend of his, Joe Kindregan. As a celebrity, Ben could use his fame for all kinds of purposes, but there are few causes more noble than fighting on behalf of those who need medical help. I want to thank him personally for being here with us this morning and taking up this cause.

Before we turn to Dr. Collins, let me yield to my good friend and person that I have worked together with on a bipartisan basis to make sure we got the funding for the Human Genome Institute from the very beginning, Senator Specter.

OPENING STATEMENT OF SENATOR ARLEN SPECTER

Senator SPECTER. Well, thank you very much, Mr. Chairman. I commend you for the outstanding work you have done on the genome project and for your leadership in this very important area.

It is truly amazing that the 3 billion units are now within range of understanding the DNA makeup of the human body, and the potential is limitless. So, it is really an extraordinary accomplishment, and we have to utilize these opportunities to the maximum extent possible.

This subcommittee has taken the lead over the past 6 years in advancing the funding for research at the National Institutes of Health. Senator Harkin and I introduced the first amendment to the budget to add \$1 billion for NIH, which was defeated 63 to 37. We sharpened our pencils and found a way to prioritize funding and provide \$1 billion to increase the NIH budget in the appropriations bill.

Having failed in our efforts to get an additional billion dollars in the budget resolution, the next year we sought an additional \$2 billion for the NIH. And again, we were unsuccessful, this time by a vote of 58 to 42. But again, with sharpened pencils, we found the dollars in the appropriation bill. That has progressed so that the funding for NIH has been increased from \$12 billion to now in ex-

cess of \$20 billion. Whereas the President has put in a hefty sum this year of an additional \$2.8 billion, it will require \$3.4 billion to stay on track to double the NIH funding over 5 years, which is our goal and which we are determined to undertake.

But we are concerned as to limitations which exist in law prohibiting the use of Federal funding to extract stem cells from embryos. Senator Harkin and I introduced legislation on that 2½ years ago when it became apparent that stem cells have tremendous opportunities. In November of 1998, this subcommittee held seven hearings, and now I believe we have more than 70 votes, perhaps 75, maybe even more, to reverse that prohibition.

In this morning's New York Times, there is a disquieting story about scientists creating scores of embryos to harvest cells, and where there is no legislation by the Federal Government in the field to regulate what is being done to liberate Federal funding for research at the NIH to be conducted with ethical standards, then the marketplace free enterprise proceeds and you have had these human embryos created expressly for medical experiments, which raises very, very profound ethical questions of propriety.

So, it is my hope that these issues can be addressed, if not by the White House to liberate the prohibition against Federal funding, then perhaps by the Congress if that is necessary, because I do think we have the votes in the Senate, and some 40 Republicans signed on to stem cell research in the House. This is a matter which must be addressed very, very promptly in my judgment.

Today's hearing is a very important one, along the lines of what science can do, and those of us in the Congress, the House and the Senate, ought to be doing our utmost to provide the support and the funding to see that this will become a reality.

Permit me to extend my regrets that I cannot stay for the entire hearing. I am due on the Senate floor at 10 o'clock for a special order, and we have a very important hearing in the Foreign Operations Subcommittee of Appropriations. So, I will be here for a time and will be following the proceeds through staff and through the transcript.

Thank you very much, Mr. Chairman.

Senator HARKIN. Thank you very much, Senator Specter.

OPENING STATEMENT OF SENATOR LARRY CRAIG

Senator CRAIG. Mr. Chairman, thank you for putting together today's hearing on the Promise of the Genomic Revolution.

Last year, a rough draft of the human genome was announced and ignited a worldwide fervor of the possibilities of this achievement. This advance can help people live longer and healthier lives. Diseases once thought incurable may soon be detectable and curable early in life. The Human Genome Project, by producing detailed maps of the 23 pairs of human chromosomes, has already identified the genes responsible for such diseases as glaucoma and cystic fibrosis.

However, this enormous accomplishment has raised ethical and social questions related to genetic information. The potential for misuse of genetic information has extremely serious implications, especially in relation to privacy concerns. Access to employment

and health insurance are just two of the areas that could be affected.

As advances in medical technologies are developed using the mapping of the human genome, it will become increasingly important to protect patient privacy rights. The challenge will be to balance privacy concerns with the medical benefits of this new technology.

Again, Mr. Chairman, thank you for looking at this important and exciting issue. I look forward to hearing from today's witnesses.

[The statement follows:]

PREPARED STATEMENT OF SENATOR LARRY CRAIG

Mr. Chairman, thank you for putting together today's hearing on the Promise of the Genomic Revolution.

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STATEMENT OF FRANCIS COLLINS, M.D., Ph.D., DIRECTOR, NATIONAL HUMANE GENOME RESEARCH INSTITUTE, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Senator HARKIN. Our first witness, Dr. Francis Collins, is the Director of the National Human Genome Research Institute and the leader of the International Consortium of Scientists for Sequencing the Human Genome. He has a Ph.D. in physical chemistry from Yale University, an M.D. from the University of North Carolina. Among many other accomplishments, he helped identify the genes for cystic fibrosis and Huntington's disease. He remains actively involved in research, and he has directed the National Human Genome Research Institute since 1993.

Dr. Collins, welcome back to the subcommittee.

Dr. COLLINS. Well, thank you, Mr. Chairman and Senator Specter. Thank you also for the kind remarks about genomics. I want to say to both of you how much we at NIH appreciate your very strong leadership in the support of medical research that has brought us to this point and which, as we will be talking about this morning, holds the promise of carrying us to truly dramatic developments in the field of medicine. But none of this would be possible without the strong support of the Congress, and the two of you have taken a particularly bold stand in that regard. And it is deeply appreciated, and it makes a difference. In fact, I would say the investment that you boldly made about 10 years ago in the human genome project, even before many in the scientific community were

completely convinced, is paying off in a spectacular way that we will talk about this morning.

I am honored to be here at this hearing with a number of other distinguished witnesses who will outline some of the consequences. Let me say that I am particularly pleased to be here with Joe and his family. Joe who has ataxia-telangiectasia, is a representative of the hundreds of thousands, millions of individuals who have health consequences of glitches in the DNA that we hope to learn more about an ultimately to be able to cure.

Senator Harkin, you showed this CD-ROM containing the 3 billion letters of the human DNA code. It is remarkable that it all fits. It took a special compression program that our colleagues in Santa Cruz designed to be able to make that information fit on a single CD-ROM.

It is amazing that this was possible in the time table that it was. When I was a post-doctoral fellow 20 years ago, you could get a Ph.D. for sequencing 1,000 letters of the code. In order to do this, we had to sequence 1,000 letters a second, 7 days a week, 24 hours a day for a sustained period of about a year and a half. What an amazing quantum leap forward in the speed.

And that we did and it is all in the public domain. It is free on the Internet. Most people do not use that CD-ROM. They go to their computer and tens of thousands of them each day are logged on to the databases using this information to advance their understanding of disease. I keep an informal tally of disease genes that are identified using this information. Just in the last 2 years, it is over 50, and those are all diseases that otherwise would still be trapped in a bottleneck of ignorance but now are on the pathway towards understanding and ultimate prevention and cure.

As another example of the speed with which things are advancing, I spent most of my scientific effort in the 1980's trying to identify the gene for cystic fibrosis. That effort took a number of groups, including my own, about 9 years to come up with the right gene.

About 4 years ago, we talked with considerable excitement about finding a gene for Parkinson's disease. That took about 9 days' worth of effort with the tools that were there.

Just a few weeks ago, there was a publication in the journal called Nature about finding a gene for a very important problem involving the gastrointestinal tract, called Crohn's disease. In that instance, the investigator simply had to go to the Internet and look up the answer. So, less than 9 seconds involved in finding the responsible gene.

So, 9 years to 9 days to 9 seconds. This is the kind of advance in speed that we hope to see happen as a consequence of the genome project.

As you will hear from Dr. Needleman, that has also resulted in the fact that we now have not 480 drug targets, we have 30,000 drug targets. And the advances in that field are truly dramatic.

But I think it is fair to say if you drew the time line of genomics and you tried to say where are we, we are still at the beginning. We have a fantastic foundation here with that sequence of the human genome. We have the code but we need to understand it. I like to say we are now in the decryption business. We need to un-

derstand the cryptography of the genome to be able to understand its role in health and disease and then bring that to the clinic as quickly as possible. As a physician, that of course is my major personal goal.

We are, in fact, at the National Human Genome Research Institute, in the midst of a vigorous and intense effort to engage hundreds of the brightest minds in the scientific community, both public and private sectors, in planning a visionary next phase of the genome project, building on this current foundation. That will include a number of exciting, new projects, such as building a comprehensive picture of how human variation is organized in the genome, which is the way that we are going to uncover the hereditary contributions to diabetes and heart disease and the common cancers and mental illness and multiple sclerosis and virtually every disease that has a hereditary contribution.

We will also—and we had a very interesting workshop the last 2 days about this—need to sequence the genomes of a number of other organisms because they will inform the ability to decrypt the human genome by the comparisons. We need to be sure we are using our sequencing capabilities in the most scientifically robust way.

We will be investigating the way in which proteins do the work of the genes. The genes are the instruction book. The proteins carry out the instructions. The field of proteomics is now the effort to understand that in a global fashion.

Go with me, if you will, though, on the basis of these research developments to what might happen in interaction between a physician and a patient in the year 2015. Linda, age 34, mother of two, comes in to see her physician because maybe for the first time she is beginning to think about the need for good prevention in her own medical care. Her physician mentions that now in 2015 there are a number of tests that are available to predict her future risk of illness or to make an early detection of a current illness. Fortunately, through the good efforts of people like yourselves, in 2015 she need not fear genetic discrimination because that was taken care of by the Congress of the United States way back early in the current century. So, she decides, yes, she would like to go through this battery of tests.

The results indicate that she has an increased risk for heart disease, which surprises her, because her cholesterol is normal, but cholesterol is not everything. The good news is we have in 2015 dietary measures to reduce that risk and noninvasive methods to detect the first sign of actual disease at which point drug therapy is available that is precisely suited for her genetic situation.

Another thing on her report card. It turns out that she is at increased risk for Alzheimer's disease. She is not as surprised there. Her grandmother had recently died of the disorder. In 2015—and Professor Needleman may very well say more about this—we will have interventions available, preventive strategies for Alzheimer's disease that I believe will be amazingly successful, both drug therapies and even a vaccine. So Linda, now at age 34 with no symptoms probably for a couple of decades to come, now has an intervention to keep that terrible outcome from occurring.

Finally and perhaps initially most alarmingly to her, one of the tests done looked at actually the peripheral white cells in her blood stream which are, in 2015, effectively the canaries in the coal mine to tell you that something may be awry, using those white cells as a signal of what is going on within. They indicate that there is a high likelihood that she has the earliest stages of ovarian cancer. A subsequent laparoscopy does, in fact, reveal a very small nucleus of cancer cells, only a few hundred in number, which are easily removed. While she would not have developed symptoms for another 2 years, had this test not been obtained, it is likely at that point it would have been too late.

This kind of molecular surveillance, using genetic tools, is not science fiction in the next decade or two. So, this scenario, which I would argue is not at all outside the realm of reality based on the trajectory we are now on, is a very exciting one, focusing our medical efforts on preventions, keeping people healthy.

I would like to conclude this with a quote from Sir William Osler. He said this exactly 100 years ago: "Osler is the father of medicine in most people's view because he brought the power of rational thinking to the field." When asked to describe what is medical research, Osler said, "To wrest from nature the secrets which have perplexed philosophers in all ages, to track to their sources the causes of disease, to correlate the vast stores of knowledge that they may be quickly available for the prevention and cure of disease, these are our ambitions." Bold words a century ago. But we now have the tools to make this happen. With your strong support and the brightest minds of the scientific community, we can make Osler's vision come true.

Thank you, Mr. Chairman. I would be happy to answer questions.

[The statement follows:]

PREPARED STATEMENT OF FRANCIS S. COLLINS

Mr. Chairman, and Members of the Subcommittee, it is a pleasure to be here today to discuss the recent scientific advances in genetics that will lead to improved health, and the development of therapies to treat various illnesses. First I would like to thank the Subcommittee, and especially you Mr. Chairman and Ranking Member Specter, for your commitment and determination to invest in the Human Genome Project and other areas of basic biomedical research at the National Institutes of Health. Today I would like to focus my remarks on the recent developments in genetics in order to give you a sense of the great promise this field of research holds for all of us. Today you will also hear from patients and advocates who are fighting to find a cure for genetic diseases. All of us have gained a powerful new set of tools from the recent advances in human genetic research. As a physician who has taken care of patients, and as a medical geneticist who has devoted the last decade to the Human Genome Project, I know it is critical that we move the great promise of basic research into the clinic as quickly as possible, in order to make significant progress towards treating or preventing these devastating illnesses.

HUMAN GENOME SEQUENCE

Last year, Human Genome Project scientists capped their achievements of the last decade with a historic milestone—the complete initial reading of the text of our genetic instruction book. This book is written in an elegant digital language, using a simple four-letter alphabet where each letter is a chemical base, abbreviated A, C, G, or T. At present, more than 95 percent of the 3.1 billion bases of the human genome are freely available in public databases. This is an awesome step toward a comprehensive view of the essential elements of human life, a perspective that inaugurates a new era in medicine where we will have a more profound understanding

of the biological basis of disease and develop more effective ways to diagnose, treat, and prevent illness.

Between March 1999 and June 2000 the international collaborators in the Human Genome Project sequenced DNA at a rate of 1000 bases per second, 7 days a week, 24 hours a day. After completing the working draft of the human genome sequence in June of 2000, Human Genome Project scientists and computational experts scoured the sequence for insights. They reported the first key discoveries in the February 15, 2001 issue of the journal *Nature*. Among the findings were the following:

- Humans are likely to have only 30,000 to 40,000 genes, just twice as many as a fruit fly, and far fewer than the 80,000 to 150,000 that had been widely predicted.
- Genes are unevenly distributed across the genomic landscape; they are crowded in some regions and spread out widely in others.
- Individual human genes are commonly able to produce several different proteins.
- The repetitive DNA sequences that make up much of our genome, and commonly regarded as “junk,” have been important for evolutionary flexibility, allowing genes to be shuffled and new ones to be created. The repetitive DNA may also perform other important functions, and provides fascinating insights into history.

FINISHING THE HUMAN GENOME SEQUENCE

Because of the enormous value of DNA sequence information to researchers around the world, in academia and industry, the public Human Genome Project (HGP) has always been committed to the principle of free, rapid access to genomic information through well-organized, annotated databases. Databases housing the human genome sequence are being visited by tens of thousands of users a day. Over the coming two years, the HGP will increase the usefulness of the human genome sequence to the world’s researchers by finishing the sequencing to match the project’s long-standing goals for completeness and stringent accuracy. More than 40 percent of the draft sequence, including two of our 24 chromosomes, have already been finished into a highly accurate form—containing no more than 1 error per 10,000 bases. Finished sequence for the entire genome is expected by 2003.

HUMAN GENETIC VARIATION

While the DNA sequence between any two individuals is 99.9 percent identical, that still leaves millions of differences. For understanding the basis of common diseases with complex origins, like heart disease, Alzheimer disease, and diabetes, it is important to catalog genetic variations and how they correlate with disease risk. Most of these are single letter differences referred to as Single Nucleotide Polymorphisms (SNPs). With a draft of the human genome sequence in hand, the pace of SNP discovery has increased dramatically. In fiscal year 1999, NHGRI organized the DNA Polymorphism Discovery Resource consisting of 450 DNA samples collected from anonymous American donors with diverse ethnic backgrounds. NHGRI has funded studies looking for SNPs in these samples. The non-profit SNP Consortium came into being in April 1999, with the goal of developing a high-quality SNP map of the human genome and of releasing the information freely. Consortium members now include the Wellcome Trust, a dozen companies (mostly pharmaceutical companies), three academic centers, and NIH. This has been remarkably successful, with 5 times more SNPs being contributed to the public domain than the consortium originally planned. As of June 22, the public database that serves as a central repository for SNPs has received 2,972,764 SNP submissions.

With the increased knowledge about human variation, the genetic underpinnings of various diseases, including diabetes, are being discovered. The recent discovery of a gene, *calpain-10*, whose disruption contributes to diabetes, resulted from studies linking diabetes with genetic variations across the whole genome and then in a specific part of chromosome 2. The newly-discovered gene variant suggests that a previously unknown biochemical process is involved in the regulation of blood sugar levels.

GENE EXPRESSION

The new-found abundance of genomic information and technology is propelling scientists out of the pattern of studying individual genes and into studying thousands at a time. Large-scale analyses of when genes are on or off (gene expression) can be used, for example, to study the molecular changes in tumor cells. This exciting new approach combines recombinant DNA and computer chip technologies to produce microarrays or DNA chips. Classifying cancer on a molecular level offers

the possibility of more accurate and precise diagnosis and treatment. Intramural researchers at NHGRI have used large-scale expression studies to discover genetic signatures that can distinguish the dangers from different skin cancers, and that can distinguish between hereditary and sporadic forms of breast cancer.

PROTEIN STRUCTURE, FUNCTION, AND INTERACTION

We must remember that we are at the beginning of genomics era, not the end. With a global view of human genes now possible, scientists are eager to obtain a similarly comprehensive view of human proteins, a field called “proteomics.” Researchers want to know the functions of proteins and how the proteins work together in cells. Only a subset of all possible proteins are present in any given cells at any given time. To study protein function on a wide scale, various groups of researchers plan to identify the locations of proteins, their levels in different cells, their structures, the interactions among different proteins, and how they are modified. NHGRI is contributing to this field by developing technologies for efficient, large-scale analyses, particularly for determining protein interactions and measuring protein abundance in different cells.

PROMISE FOR NEW TREATMENTS AND PREVENTION

With the availability of a comprehensive view of our genes, genetic testing will become increasingly important for assessing individual risk of disease and prompting programs of prevention. An example of how this may work involves the disease hereditary hemochromatosis (HH), a disorder of iron metabolism affecting about one in 200 to 400 Americans. Those with the condition accumulate too much iron in their bodies, leading to problems like heart and liver disease and diabetes. The gene causing the condition has been identified, allowing early identification of those in whom HH may develop. Once people at risk are identified by genetic testing they can easily be treated by periodically removing some blood. The NHGRI and NHLBI are engaged in a large-scale project to determine the feasibility of screening the adult population for this very preventable disorder.

Genetic testing is also being used to tailor medicines to fit individual genetic profiles, since drugs that are effective in some people are less effective in others and, in some, cause severe side effects. These differences in drug response are genetically determined. Customizing medicine to a patient’s likely response is a promising new field known as pharmacogenomics. For example, a recent publication in the journal *Hypertension* showed how pharmacogenomics applies to high blood pressure. Researchers found a variation in a particular gene that affects how patients respond to a commonly used high blood pressure drug, hydrochlorothiazide. Other recent studies reveal that doctors should avoid using high doses of a common chemotherapy treatment (6-mercaptopurine) in a small proportion of children with leukemia. Children with a particular form of a gene (TPMT) suffer serious, sometimes fatal, side effects from the drug.

Genomics is also fueling the development of new medicines. Several drugs now showing promising results in clinical trials are “gene-based” therapies, where an exact appreciation of the molecular foundations of disease guides treatment design. One of the first examples is Gleevec (previously called STI571), produced by Novartis for treating chronic myelogenous leukemia (CML), a form of leukemia that mostly affects adults. CML is caused by a specific genetic flaw—an unusual joining of chromosomes 9 and 22 producing an abnormal fusion gene that codes for an abnormal protein. The abnormal fusion protein spurs uncontrolled growth of white blood cells. Novartis designed a small molecule that specifically inactivates that protein. In phase I clinical trials, this drug caused dramatically favorable responses in patients, while side effects were minimal. By targeting the fundamental biochemical abnormality associated with this form of cancer, rather than killing dividing cells indiscriminately as most chemotherapy does, the drug offers better treatment results and fewer toxic effects on normal cells. In May 2001, FDA approved Gleevec (imatinibmesylate, also known as STI-571) for the treatment of Chronic Myeloid Leukemia after a review time of less than three months. Meanwhile, Bayer and Millennium announced the development of another cancer drug born of genomics in January 2001. GlaxoSmithKline is testing a new genomics-derived heart disease drug that targets a protein involved in fat metabolism. Johnson&Johnson is testing a drug targeting a brain receptor identified through genomics, and involved with memory and attention. Human Genome Sciences has four clinical trials in progress to test gene-based drug candidates.

ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS

From its inception, NHGRI recognized its responsibility to address the broader implications of having access to genetic information and technology. Since the inception of the Human Genome Project Congress has provided funds for research to study the ethical, legal, and social implications (ELSI) of genome research. To that end one of the greatest areas of concern has been in the area of genetic discrimination. Recently President Bush addressed this issue in his Saturday radio address of June 23. In that address the President said, "Just a few months ago, scientists completed the mapping of the human genome. With this information comes enormous possibilities for doing good. As with any other power, however, this knowledge of the code of life has the potential to be abused. Genetic discrimination is unfair to workers and their families. It is unjustified—among other reasons, because it involves little more than medical speculation To deny employment or insurance to a healthy person based only on a predisposition violates our country's belief in equal treatment and individual merit Just as we have addressed discrimination based on race, gender and age, we must now prevent discrimination based on genetic information. My administration is working now to shape the legislation that will make genetic discrimination illegal. I look forward to working with members of Congress to pass a law that is fair, reasonable, and consistent with existing discrimination statutes."

PREDICTIONS FOR THE FUTURE

We must not ignore the ethical, legal, social, and the commercial issues that genetic research raises, but the promise of this research is great for alleviating human suffering. If research continues to proceed vigorously, we can expect medicine to be transformed dramatically in the coming decades.

We can predict that by the year 2010, predictive genetic tests will exist for many common conditions where interventions can alleviate inherited risk; successful gene therapy will be available for a small set of conditions; and primary care providers will be practicing genetic medicine on a daily basis. By the year 2020, gene-based designer drugs are likely to be available for conditions like diabetes, Alzheimer's disease, hypertension, and many other disorders; cancer treatment will precisely target the molecular fingerprints of particular tumors; genetic information will be used routinely to give patients appropriate drug therapy; and the diagnosis and treatment of mental illness will be transformed. By the year 2030, we predict that comprehensive, genomics-based health care will become the norm, with individualized preventive medicine and early detection of illnesses by molecular surveillance; gene therapy and gene-based therapy will be available for many diseases; and a full computer model of human cells will replace many laboratory experiments.

Thank you Mr. Chairman. I would be happy to answer any questions.

Senator HARKIN. Dr. Collins, thank you very much for an outstanding statement and again for all of the wonderful work you have done in leading this project from its very beginning. We owe you a great debt.

I would now like to recognize our former chairman of the full committee and our ranking member of the full committee now who has graced us with his presence for any opening statement that he might have. Senator Stevens.

Senator STEVENS. Well, thank you very much, Mr. Chairman. I am just surveying some of the hearings this morning. So, I stopped for a little while. I appreciate listening to Dr. Collins. Thank you very much, doctor.

Dr. COLLINS. Thank you, Senator, and we appreciate your strong support for NIH.

Senator HARKIN. Senator Stevens has been a very strong supporter of NIH for a long, long time.

I just have a couple of questions and I would like to ask you if you might just stay while I bring the other panel up.

Dr. COLLINS. I would be delighted.

Senator HARKIN. I may have some follow-ups after the panel comes up.

You sort of hinted at this but some people are under the impression that the human genome project is over now that we have completed a draft sequence. First, is that the case, and if not, what is left to be done?

In your written testimony, you predicted that comprehensive genomics-based health care will become the norm by 2030. Is there any way that we can speed this up?

So, that is sort of two parts. What is left to be done and can we speed it up?

Dr. COLLINS. Well, the sequencing of the genome, getting those 3 billion letters all determined, was the most obvious and visible goal of the genome project. But from the outset, this has been a multi-component effort. While it is true that most of the original goals defined in 1990 have now been achieved or will be in the next couple of years, all the way along, the ability to decode, to decrypt the information has emerged as a new and important phase of the effort.

So, you might say we are experiencing an analogy to the field of chemistry. We are now at the point of having defined the periodic table of the elements. The periodic table for human biology has elements that are the normal human genes. It has isotopes which are the variants in those genes. But just as one would have said the field of chemistry began with the periodic table, I think it is fair to say the field of genomics now begins with our own human periodic table of the genes.

Now, the important issues of how do they work and how do they interact together and how are they affecting health and disease can get underway in earnest. I view all of that as the natural continuation of the genome project. In fact, genomics now spills out into virtually every area of research. Some now argue genomics has become the central science of medical research that every institute at NIH is investing in in a big way and, as you will hear later, in the private sector as well.

Senator STEVENS. Mr. Chairman, may I ask just two questions?

Senator HARKIN. Sure.

Senator STEVENS. Dr. Collins, when will your project be completed?

Second, how soon will it be before the information that you have developed in the project will trickle down and be available to the family physician?

Dr. COLLINS. Actually deciding when the human genome project is completed is a bit of a semantic question. You could say that the original goals set in 1990 are close to being completed, but at the same time the project has evolved. Certainly genomics as a research enterprise has probably more promise and more applicability now than it did 5 years ago and certainly more than 10 years ago. So, it is a little hard for me to know exactly what to call the human genome project anymore. Maybe you will argue that we should be more precise about that, and that is something that we are discussing a bit with our advisors in terms of the definitions here.

Senator STEVENS. Well, should we evolve it? Should we say that it is more than the original project now?

Dr. COLLINS. Well, it has become so, as we have in the process of deciding what our goals are, and we do that very regularly, every 3 to 5 years, with input from hundreds of scientists. If you look at the 5-year plan for 1990 and 1993 and 1998 and the one we are building now, we have added new and exciting components along the way because of their scientific opportunity. The genome project is not what it was at the beginning. I think the way to do that is to ask the scientific community, what are the opportunities here, and then let us go after them. That is pretty much the strategy we followed.

As far as the availability to the primary care physicians, this is a major area of concern because most physicians have not had much exposure to the field of genetics. The implications of this are very quickly going to come to pass. Every physician in primary care is going to need to practice genetic medicine in the relatively near future. Working with the American Medical Association and the American Nurses Association, we have a rather ambitious agenda for trying to provide that kind of educational information so that doctors and nurses will be in a position of being able to implement these exciting new opportunities and not just confuse themselves and patients by an unfamiliarity with the new area called genetics. We have a lot of work to do in that regard, but I think the medical community is enormously interested in this. The American Medical Association identifies this as the biggest advance since antibiotics, and they are clearly motivated to get their members up to speed and ready to practice this kind of medicine in the most effective way.

Senator STEVENS. Well, I am afraid it is so esoteric that rural America may be left behind in this first decade of this new century.

Dr. COLLINS. Well, I worry about that, Senator. Yet, at the same time, the esoteric aspects of genetics are partly the scientists' fault, that we tend to enshroud these developments in complex language and using large terms with too many syllables. In my view, genetics is actually the simplest of the biological sciences. It makes enormous sense. If you understand a few principles, the rest of it kind of makes sense by immediate deduction. But we have not done, necessarily, a very good job of explaining that.

We have recently put out—and every high school biology teacher in this country has now access to—and we have sent out 60,000 of these—an educational kit about genetics and the genome project to get the next generation of consumers who are currently juniors or seniors in high school ready to incorporate this kind of information into their thinking about their own health.

Senator STEVENS. Sorry to belabor this, Mr. Chairman.

Will we be able to link the family physician, the primary care provider, by telemedicine to centers where he or she could get instant consultation.

Dr. COLLINS. Senator, I think that is a great idea and I think that is in fact quite potentially viable because many of the questions that need to be answered probably could be done electronically. I envision a circumstance where primary care providers are provided with the kind of information that enables them to handle the basic level of interactions about genetic questions, but when something more complicated arises, they are going to have to have

some connection, some way to get advice, and I think the electronic telemedicine approach is going to be the way to go. We have a limited number, but a very well-trained group, of medical geneticists and genetic counselors who I believe could provide that next level of expertise, and we have to figure out how to organize the system and make sure the services are reimbursed for so that it actually happens.

Senator STEVENS. Thank you very much.

Thank you, Mr. Chairman.

Senator HARKIN. Thank you, Senator Stevens.

Dr. COLLINS, one last thing before I bring the panel up. We read yesterday that the National Cancer Institute is going to allow its researchers to pay for access to Celera Genomics database. I would like to have your thoughts on that since NIH already has access to its own database for free. So, I am wondering why would NIH be willing to pay Celera for that information. I do not understand that.

Dr. COLLINS. Well, I am glad for the question because I think it has been a little confusing what really happened here. Basically the NCI worked out with Celera what the terms would be if one of their intramural investigators working on cancer decided they wanted to subscribe to the Celera database. The cost of that runs in the neighborhood of \$16,000 per year. The researcher would have to decide whether it was worth \$16,000 to them to gain access to this private database. The Celera database, of course, has a lot of human sequence, but 95 percent of the human sequence is available in the public domain. And I think relatively few investigators would find it worth the cost to go to this alternative database because the information is in fact very similar. The Celera database also contains information about the laboratory mouse, but in the public sequence databases, there is about 95 percent of the mouse sequence.

I think therefore it is unlikely that any but a handful of investigators will probably choose to sign up for this. But I think the NCI was anxious not to put up some artificial barrier for the small number of investigators who for some reason could not find what they were looking for in the freely available databases and felt it was worth their while to make this investment. Time will tell how many of them actually decide to take that step.

Senator HARKIN. I see. So, it is not something that is going to take place. It is just sort of if somebody wanted to access it, what would the arrangement be.

Dr. COLLINS. Exactly.

Senator HARKIN. Well, I guess I would have to follow up on this. If researchers wanted to, I would want to know why, and if they are using Government money to do that, if the data is already available, I would like to know more about why that would be the case.

Dr. COLLINS. I can understand your wanting to know those answers, and perhaps with a little time going by, we will see whether people actually do sign up and if so why, and if so, did they get what they were looking for.

Senator HARKIN. Right, exactly.

Dr. Collins, thank you very much. Now I am going to bring the panel up. I wonder if you could just wait, maybe we might have some additional questions later on.

Dr. COLLINS. I would be delighted.

Senator HARKIN. Our panel includes Dr. Needleman, Senior executive vice president and chief scientific officer for research and development for Pharmacia Corporation. He will discuss how pharmaceutical companies are translating basic research into actual drugs.

Dr. Steven Rich, a professor of public health sciences and a genetic epidemiologist at the Wake Forest University School of Medicine. He specializes in type 1 juvenile diabetes.

Dr. Jeffrey Murray, Professor of Pediatrics, Biology, and Preventive Medicine at the University of Iowa. He was the principal investigator of the first human genome center at the University of Iowa. He has served as a member of the NIH review panel on ethical, legal, and social implications of the human genome project.

And Mr. Ben Affleck, a movie star and a screen writer, currently appearing in the film "Pearl Harbor".

Mr. AFFLECK. It sounds so pathetic after the rest of those.

Senator HARKIN. Did I really have to introduce him as being the star of—

Mr. AFFLECK. Ph.D., genetics expert, CEO, schmuck actor.

Senator HARKIN. Now that I will take issue with.

As I said earlier, a few years ago, Mr. Affleck befriended a boy with a fatal genetic disease called A-T, ataxia-telangiectasia.

Mr. AFFLECK. I cannot even pronounce it. I call it A-T.

Senator HARKIN. And he has taken up the cause of raising awareness about it. This young man, Joe Kindregan, is here. Mr. Affleck will be joined by Brad Margus, the President and Co-founder of the A-T Children's Project. He is available to answer questions also.

But what the heck. Can we bring Joe up too? Come on, Joe. Why do you not join us? Maybe you sit between Mr. Margus and Mr. Affleck. Bring Joe up here. We are proud to have you here, Joe.

I would like to ask if you could keep your comments down to, let us say, in the realm of about 5 to 7 minutes. Then we can get through this. We can open it up for a general discussion. Dr. Needleman, we will start off with you and welcome to the committee.

STATEMENT OF PHILIP NEEDLEMAN, Ph.D., SENIOR EXECUTIVE VICE PRESIDENT, PHARMACIA CORPORATION

Dr. NEEDLEMAN. Thank you, Mr. Chairman. I think my role here is to bring the industrial perspective of the implications and the use of human genome data.

For a perspective, I have actually lived in both worlds. I spent 25 years in academia at the Washington University Medical School. I was the chairman of the Department of Pharmacology. I had wonderful support from the NIH and have actively participated in NIH study sections. I was on the Varmus Advisory Committee and have a great affection and appreciation for what has been done about the NIH. I am a member of the National Academy of Sciences and the Institute of Medicine, and I have spent the last 12 years in

Pharmacia as the head of R&D really in the translational research to bring these discoveries into important drugs.

We prepared a document which I hope we could enter in the record which describes at least four uses of the human genome in the practical development of drugs, and I will just highlight two of those issues.

To give you perspective, I have been doing biomedical research in the drug hunt for 40 years. The first 20 years could really be characterized in fact by the imprinting of the NIH. So, in the 1960's and 1970's, the supported research into the biochemical basis of diseases really led to the selection of some protein targets, either enzymes or receptors, that drugs were designed around. The fruit of the labors of those decades were drugs in hypertension, in atherosclerosis, in ulcers, in arthritis, and some drugs in the central nervous system.

The next 20 years have been spectacular. There have been profound advances in chemistry, in analytical chemistry, in computational sciences, in cell and molecular biology, and most recently and perhaps with the most attention, the availability of genomic data in bacteria, in fruit fly, in roundworm, in mouse, and in man now creates a tool kit to attack problems and disease and drugs which were inconceivable to me and my colleagues through much of our career.

Now, I would turn to a consideration of maybe two examples to show you how the use of the human genome's implication is not something far off in the future, but it happens now. I am going to pick two, work in Alzheimer's and work in cancer.

In this devastating disease Alzheimer's, if you have an unfortunate patient who died and analyzed the brain, what you will see is that the nerves are surrounded by tangles of proteins known as amyloid plaque which virtually crush and destroy the nerves. Based on genetic mapping of mutations, two mutations were found, the so-called Swedish mutation and the London mutation, where that protein which was wrapped around was characterized to be over-produced. It is a small 42 amino acid protein and it is massively over-produced in these small families that have genetic predisposition to early Alzheimer's, and it is insoluble, that protein derived from a large protein, which was floating around and innocuous. So, clearly the disease process was hypothesized to be due to something that was a scissor that cut the big protein into a small piece that then gloms onto the nerve and then destroys it.

The nature of the protein told us at Pharmacia what kind of enzyme could be the scissor. We then turned to the genome database. Understand what Francis Collins says, having other species gives you insight. So, we were able to turn to the worm, *C. elegans*, and we found a family of enzymes that had that property. Then when we hit those genes, we went to the human genome and fished out a human gene for a similar enzyme.

We then took that gene and put it into mice and removed that gene from mice. It was a 90 percent reduction in the mice's ability to make this protein that would crush the nerves. We then published that in *Nature* and put it immediately into the public database.

I can tell you this is one of the hottest targets in the entire pharmaceutical industry. We have dozens and hundreds of scientists, molecular biologists, chemists, and others, and we will be advancing a drug that will start and test the hypothesis in Alzheimer's in a reasonable period of time. This is a high urgency.

Second problem. Let us talk about colon cancer. The history of that actually began in my NIH days when we were studying what was the body chemistry of arthritis, and we discovered an enzyme called cox-2, or cyclooxygenase, which is not present in normal cells but is turned on by disease. It is a silent gene and it has to be turned on. We went on and discovered the drug Celebrex, now used in millions of people, which treats the signs and symptoms of arthritis, but it is free of many of the side effects.

Put that aside. We then had the genetic tools and the proteins and antibodies which we used and we supplied to academia. We quickly learned that every stage of colon cancer has over-expression of the cox-2 gene and protein, and that is not normally present in the colon.

Some very elegant work in other places, especially Johns Hopkins, showed that many colon cancer patients have a mutation of a gene called APC. In fact, there are only a couple of thousand of patients in the world where they have inherited mutation, and those poor children by 10 years old have thousands of polyps in their colon. By 30, they have cancer, and the median death age is in the 40's. Those polyps are loaded with cox-2.

You could take that mutation now and genetically modify a mouse and reconstitute that disease called familial adenomatous polyposis, FAP. When you get the polyposis, you get the cox-2, and Celebrex suppresses those tumors in mice.

Based on that, we did a large clinical trial for 6 months, and the FDA has now awarded us approval for the first drug Celebrex which is a nonsurgical treatment which reduces the volume and the number of tumors in the FAP patient. But that is just a couple of thousand.

The much bigger disease is colon cancer called SAP. In the United States, there may be 90,000 to 100,000 new patients a year; 50,000 deaths. It works out that almost half of those patients acquire the APC mutation. They express cox-2, and now we are doing trials in thousands of patients with Celebrex based on the genomic information, based on the mouse data and the FAP, and we will see if we can really do something with the third most prevalent of the cancers.

So, the other examples in the text show how genetic information has pulled out a schizophrenia marker, and then you have talked about Gleevec. We used genetic information. There are 500 kinases of the nature that Gleevec hits, of which we now could reduce to a half a dozen which are possibly involved in cancer.

So, in summary, I would say the availability of the human genome, the wealth of information in science from the NIH and now other foundations has really created a fairly awesome circumstance. It is not hard to predict that:

No. 1, you will have new disease targets. Francis Collins realizes we move by 10- to 100-fold the number of disease targets.

No. 2, we can have genetically modified animals that really recapitulate human disease.

No. 3, as you said in your opening statement, pharmacogenomics, understanding the genetic information that tells us why patients are variable in their response and what are the subtypes of patients will now be possible, and we can target individual therapy for those patients.

So, I would just close by saying that it is not hard for us in Pharmacia to see real hope in Alzheimer's, for significant advances in cancer and arthritis. With these spectacular advances, we will change the nature of the disease and the quality of life with these remarkable tools that we have.

Thank you, Mr. Chairman, for letting me share this with you, and I would be glad to answer any questions.

[The statement follows:]

PREPARED STATEMENT OF PHILIP NEEDLEMAN

My role in today's proceedings is to provide an industry perspective on the promise and utility of human genomic data. For your information I am Chief Scientist of Pharmacia and Chairman of Research & Development. Prior to joining the pharmaceutical industry (in 1989) I spent 25 years in academia serving as Chairman of the Department of Pharmacology at Washington University Medical School. My laboratory was actively supported by funds from the National Institutes of Health. I am a member of the National Academy of Science and the Institute of Medicine.

I have been engaged in the drug hunt for novel approaches to treat unmet medical needs for more than 40 years. When I started in the 60's, the identification and development of a new drug was a hit and miss affair. Often the target for the drug was unknown or its mechanism enigmatic. Many drugs entered development wholly because they showed activity in animal models. In this way advances in drug therapy were incremental. Furthermore, the clinical assessment of new drug candidates in man relied on "traditional" physician assessment, which in many cases had no relationship to the mechanism of action of the drug or the pathology of the disease (if either were known). With time studies of the biochemical and cellular basis of disease led to the discovery of putative target proteins (enzymes and receptors) that served as the basis for drug development. During that period (roughly 70's and 80's) important progress had been made in the treatment of the signs and symptoms of a number of critical diseases including: hypertension, atherosclerosis, ulcers, AIDS, arthritis and some nervous systems disorders.

Modern therapeutic strategies emerged from NIH supported research discoveries in academia and new drugs arose from the translational research in industry that is required to advance a promising hypothesis or lead to a safe, effective drug. The exciting scientific progress of the last couple of decades has been remarkable and is highlighted by: profound advances in chemistry; information technology and computational power; the evolution and application of cell and molecular biology, and most recently the solution of the genome structures of bacteria, fruit fly, worm, human and mouse. This means we can now focus our efforts on specific genes that might be suitable drug targets. When we understand the disease mechanism we want to impact we have much greater control of the whole drug development process. Furthermore, because we can now easily compare the genomes of different species we can be much more astute decisions about the relevance of animal models in drug development. Genomics science has given us a toolset of sufficient sensitivity to analyze tiny samples of human tissue, looking for biological changes associated with drug response.

Without a doubt we are in the greatest period in the history of biomedical research and these advances will enable us to attack the most serious debilitating diseases, including: the central nervous system diseases (Alzheimer's; schizophrenia, and depression); the many types of cancer; the deforming effects of severe arthritis; and diabetes. These approaches were inconceivable during much of my scientific career.

THE HUMAN GENOME AND INNOVATIVE APPROACHES TO THERAPY

Diseases are caused by multiple genes and have both a genetic and an environmental contribution. Hence it is important to know the genes that constitute hu-

mans and also to know the exact DNA sequence (or code of each gene) so that we can identify the changes that are responsible for causation or modification of human disease. Clearly once we know the genes that cause human disease, we can then devise therapies for such diseases. Already, however, we at Pharmacia (and others) are making significant in-roads in this regard. Pharmacia was one of the early access partners that subscribed both to Celera and the public database of the human genome. Some specific examples of how we are using genomic information to discover and validate new targets (ie; the smoking guns of the disease process) and how we are carrying out the hunt for targeted mechanism based drugs will be briefly discussed.

ALZHEIMERS DISEASE

The study of Alzheimers Disease is one area where we at Pharmacia have been applying Genomics. This devastating disease is characterized by the deposition of insoluble protein known as amyloid plaques that coil into tangles around nerves ultimately destroying the brain cells. These plaques are small fragments that are cut by functional scissors from a larger inactive protein called Amyloid Precursor Protein (APP) that in itself is biologically inactive. The cuts of APP are made by enzymes called beta-secretase (1st cut) and gamma-secretase (2nd cut) led to the neurotoxic fragment A-beta 42.

We have focused our study on this gene pathway. Families that have mutation of genes in this pathway develop early onset Alzheimers Disease. Examples of such mutations are the so-called APP Swedish gene mutation and the APP London mutation which are found on human chromosome 21, the chromosome that is extra in Down Syndrome who develop Alzheimers-like plaques in their brains. These mutations increase the production of the APP fragment (A-beta 42).

We wanted to identify the gene that served as the scissors, the so called beta-secretase with a view that decreasing its activity would reduce the production of the A-beta that forms plaques in Alzheimers Disease. We searched the genomic database of worms (*C.elegans*) and found a number of possible candidate genes that may function as the beta-secretase (we had an idea that such a gene belonged to a specific gene family). We then searched the human genome database and found the corresponding human genes and these were tested for their function as beta-secretase. (The gene was found and we published this information in the prestigious journal "Nature" Vol 402: 533, 1999).

To prove that beta-secretase was important in the genesis of the Abeta fragment we generated mice that have all of their genes intact with the exception of the beta-secretase gene. The engineered mice that lack secretase make less than 10 percent of the A-beta fragment that accumulates in Alzheimers plaques. Hence providing powerful evidence that turning down beta-secretase will reduce the production of the noxious material that deposits in Alzheimers plaques. Importantly also, we were able to show that the mice appeared normal thus suggesting that we would not expect major toxicities from drugs that reduce beta-secretase activity. We, like many companies, plan major clinical trials in Alzheimer's patients with selective secretase inhibitors.

SCHIZOPHRENIA

Similarly we have found a number of new genes that may be important in Schizophrenia. We have identified the location of novel genes from the human genome sequence database that belong to a specific family of genes. These genes are found in regions on human chromosomes that are thought to harbor schizophrenia genes (these regions are identified by studying families that individuals with the disease and others that are disease free and identifying regions that track with the disease). Thus these genes are candidates for targeting schizophrenia therapy.

We have further studied one of these genes (on material purchased from the National Institute of Mental Health) and found a change (SNP = Single Nucleotide Polymorphism) that occurs more frequently in schizophrenic patients as compared with non-affected family members, adding further evidence that this gene may be a target for schizophrenia therapy.

In addition, it is clear to many of us in the industry that patients vary in their response to drugs. A significant component of this variation is likely to lie in the subtle changes we see between different genomes. Through the discovery and utilization of single nucleotide polymorphisms (as described by Francis Collins) we hope to be able to identify patients best suited for certain therapies as well as those who might be a risk when exposed to certain drugs.

We are on the first step of the way to personalized medicine, where patients can be given the best therapy based on their condition and gene background. Pharmacia

was a member of the consortium that invested in a Public effort which detailed approx. 800,000 SNP throughout the genome and that this facility assists in enabling this type of research both in academic and industrial settings.

If Genomics is the study of how genetic differences contribute to disease, Pharmacogenomics is the science of how genetic variation influences the efficacy and safety of medicines. Doctors have always known that many medicines work differently in different patients. Pharmacogenomics will tell us how and why.

At Pharmacia we have begun a pioneering program to find out how genetic type influences outcome among people who take part in our clinical trials. This is a long term and costly exercise but we believe it will result in better, safer clinical trials and, in turn, better targeted drug treatments for people with different genetic types. Our aim is to improve human health and to produce new medicines that are safer, have more predictable side effects and are more efficacious.

KINASE GENES AS TARGETS FOR CANCER TREATMENT

Kinase genes are a class of genes that have important function in signaling cellular responses such as cell growth and multiplication. Changes or mutations in these genes that make them more active and which signal an enhanced rate of cell multiplication have been found in several human cancers and in several cancer-causing viruses.

We at Pharmacia have searched the human gene database for novel members of the kinase class with a view of investigating which of these may be drugable targets for cancer treatment. Upon the completion of the sequencing of the entire human genome and its assembly (sticking together of the different pieces of the genome) we have now determined that there are about 500 of kinase genes.

We have initiated the important task of evaluating which of these kinase genes play a role in cancer formation as well as working out what they normally do for a living. We have focused our search on kinase genes that are too active in cancers with the idea that we may develop drugs that could reduce their activity. An example of such a kinase is the Vascular Endothelial Growth Factor Receptor (VEGFR). This gene is involved in the formation of blood vessels (angiogenesis) which the tumors need for a blood supply to keep them nourished. A drug that inhibits blood vessel formation may therefore have therapeutic utility in the treatment of cancers. One such drug that is in clinical trials at Pharmacia targets the VEGFR. We also have several other drugs that target different kinase genes in various tumor types at various stages of our drug discovery program.

In addition, we have studied a family of kinases that appear to be actively involved in the symptoms and progression of rheumatoid arthritis and we have started initial clinical trials to establish the safety and efficacious of these novel drugs.

THERAPEUTIC APPROACH TO COLON CANCER

Our studies into the underlying processes that cause the swelling, pain and stiffness of osteo- and rheumatoid- arthritis led to the discovery of a protein/gene called cox-2 (cyclooxygenase) that is not present in normal stomach or colon tissue but is turned on by tissue injury, inflammation, and various body chemicals released by disease processes. We ultimately developed a mechanism-based drug, Celebrex, that specifically inhibits the abnormal cox2, and which relieves the signs and symptoms of arthritis with a much lower level of side effects than pre-existing therapy.

These discoveries led to the availability of new analytical tools which allowed us and several academic laboratories to identify the presence of cox2 in precancerous, cancerous and malignant colon cancer. Additional experiments demonstrated that colon cancer produced in rats with chemical treatment was associated with the appearance of cox2 and we found that Celebrex treatment suppressed the animal tumors.

Many human colon cancers are known to involve a change (mutation) in the human tumor suppressor gene adenomatous polyposis coli or the APC gene. This gene is known to be "switched off" in these patients and hence these colon polyps grow unchecked. A mouse model where this gene has been "knocked out" or switched off also develop colon polyps analogous to that in humans providing compelling evidence that the loss of this gene is causative for colon cancers. These transgenic mice with mutated APC recapitulate the genetic and the intestinal polyps of a human precancerous colon cancer known as Familial Adenomatous Polyposis (FAP). The polyps from the APC mutated mice indeed exhibited cox2 expression and, again, inhibition of cox2, either with Celebrex or by the genetic elimination of cox2, reduced the number and volume of the precancerous polyps. Based on the demonstrated presence of cox2 in human colon cancer; and in chemically and genetically induced colon cancer, we conducted a 6 month clinical trial in FAP pa-

tients and Celebrex treatment reduced the tumor volume and size of the precancerous polyps which resulted in FDA approval of the first non-surgical treatment of this condition. These trials provide the essential proof of concept for a major contributory role of this protein in the initiation and progress of tumors. However, FAP is a rare inherited disease which occurs in just a few thousand patients. The much larger colon cancer population, the so called Sporadic Adenomatosis Polyposis (SAP) results in about 50,000 deaths per year in the United States alone. Many of these patients acquire an APC mutation and exhibit elevated cox2 levels. Based on the successful FAP data and the compelling data strongly suggest the involvement of cox2. We are now in the midst of large, international, clinical trials in SAP patients being treated with Celebrex.

CONCLUSION

In summary, the availability of the human genome database, in the context of the years of productive discovery that have arisen from the funding of basic research by the NIH and other foundations provides industry with a unique toolbox for novel drug development. The implications are awesome. You can anticipate the identification and validation of the targets that are the engines of disease. The candidate genes will be useable both to make reliable animal models of human disease and will provide the reagents to start the hunt for drugs that will alter the targets and suppress or ameliorate the disease process. Furthermore, genomic information provides the potential markers that will allow the identification of disease subtypes and that hopefully would allow rapid, small trials and which might predict responders from non-responders. We therefore can look forward to targeted, optimal, individualized therapy. Finally, I expect that our efforts will be providing important new treatments that will change patient anguish, suffering and especially their quality of life. I foresee in our own Pharmacia efforts the prospects for: disease modification in rheumatoid and osteoarthritis; in the progression of Alzheimers; and leading to significant advances in the treatment of cancer.

Senator HARKIN. Thank you very much, Dr. Needleman, for a very provocative statement. I mean provocative in terms of making people think. I really appreciate it. A very good statement.

Dr. Rich, we will turn to you now.

STATEMENT OF STEPHEN S. RICH, Ph.D., PROFESSOR, WAKE FOREST UNIVERSITY SCHOOL OF MEDICINE

Dr. RICH. Thank you, Chairman Harkin. Again, I am Stephen Rich and I am a professor of public health sciences at Wake Forest University School of Medicine. I would like to mention that I will come back to the issue of public health at the end of my short presentation here. But I would also like to mention I serve as the chairman of the International Type 1 Diabetes Genetics Consortium, which I will also come back to, which was mentioned by Dr. Spiegel some time ago.

What has actually been accomplished in the genetic basis of type 1 diabetes? I will just give some perspective on that. When I first took my faculty position at the University of Minnesota, just north of Iowa I think, some time ago, in 1980, very little was known about the genetic basis of type 1 diabetes. We and others spent about the next 7 years understanding that there was probably a major gene that contributes to the genetic basis of type 1 juvenile onset diabetes in the region that contains the major histocompatibility complex, or the HLA region, which is involved in transplantation and autoimmunity. So, it made sense.

Unfortunately, at that time in the mid to late 1980's there really was not very much known about the genetics of that region, and we did not have the genomics resources to really go after the genes in those very complex regions. So, we turned our attention to did this region really contribute to everything that contributed to genetic risk of type 1 diabetes, and it turned out it did not. We found

out that there are multiple genes that probably contribute in addition to how it interacts with environmental triggers. So, we know that there are things in the environment which trigger this auto-immune cascade that causes type 1 diabetes. So, it is the interaction of genes and environment that really is the fundamental basis of how this disease gets started in kids and why this is the third most common chronic disease in children.

So, we then decided to try to find those additional genes. In the early 1990's, it was very difficult because there still was not the genomics material available to allow us to do that. They were being developed, but it was only with the advent of the human genome project that we were able to scan the entire genome to try to find out where in the genome were potential genes that could cause increased risk for type 1 diabetes.

This was actually a major breakthrough from the standpoint of science of genetic basis of chronic disease or other diseases. In the early 1990's, we began making progress. At the same time, we were not able to find those specific genes. The reasons were really two-fold. First, we became convinced that individual scientists working as individuals could not have sufficient resources to track down these genes. Second, it became apparent that the genomics material were at not the stage to allow us to identify specific genes.

So, it has only been in the last few years that we have been able to, No. 1, decide that united we stand and can succeed, divided we fail. So, we formed the Type 1 Diabetes Genetics Consortium of investigators across the world who are interested in finding genes that cause risk for type 1 diabetes. This will allow us to collect approximately 2,500 families with two children with type 1 diabetes, two parents, an additional child unaffected with diabetes to reform the genome screen, to look through the entire genome to find these genes, at least the regions, and then use the material that the human genome project has provided us in the sequencing of the DNA to start looking more closely at what is actually there. This will allow us to continue to search and to characterize these genes to help decide who is at increased risk.

Now, remember that I mentioned earlier that type 1 diabetes is probably an interaction. It is not just genetic risk. There are environmental triggers that cause this cascade of problems in the pancreas that in susceptible people lead on to diabetes. So, with the genes in hand, we can then decide what are those environmental risk factors and then decide on a public health basis individual screening.

Now, this gets at two issues. As Dr. Collins mentioned, you need to take the findings from the bench to the clinic. From a public health standpoint, we want to take the findings from the bench to the clinic and to the community. That is where we can actually then process our knowledge of genomics and our knowledge of the environment and determine who really is at risk genetically and define the interventions, as well as defining the drug targets and the new therapies.

So, I know that the support of this committee has been crucial in development of the genomics initiatives and the initiatives for the Diabetes Institute to continue with the research and the genetic basis and finding cures for diabetes and complications. I

would just like to end by saying that timing is everything. I think we are at the stage now where the timing for continued support in the genomics initiatives and timing for support in the diabetes initiatives will certainly lead us in the next, I would say, 10 years to understanding better this terrible disease in children and hopefully come up with a means for identifying those at risk and hopefully curing this disease.

Thank you, and I would be happy to answer any questions.
[The statement follows:]

PREPARED STATEMENT OF STEPHEN S. RICH

Mr. Chairman, and Members of the Subcommittee, it is an honor to be asked to discuss with you the prospects of using the tools of the Human Genome Project to gain an understanding of the genetic basis of type 1 diabetes and its complications. My name is Stephen Rich and I am a Professor of Public Health Sciences and a genetic epidemiologist at the Wake Forest University School of Medicine. I am also the Chair of the Type 1 Diabetes Genetics Consortium and a member of the Juvenile Diabetes Research Foundation Medical Science Review Committee.

Today I would like to focus my comments on genetic complexity of type 1 diabetes and the accelerating progress made in understanding genetic predictors of disease risk. I also want to describe to you the role that the Human Genome Project has played in serving as a catalyst for genome research in type 1 diabetes, and how we are now at a critical phase in this research. Finally, I will present to you the problems that need to be resolved to identify genes for type 1 diabetes and how continued support of the National Institutes of Health, particularly the National Human Genome Research Institute (NHGRI) and the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK), can address these problems.

INTRODUCTION TO THE PROBLEM

Type 1 diabetes is the third most common chronic disease in children, estimated to affect over 120,000 in childhood and about 300,000 to 500,000 Americans of all ages. There are about 30,000 new cases of type 1 diabetes each year. In addition, there is growing evidence that the number of new cases of type 1 diabetes is increasing, perhaps by as much as 5 percent per year. All children are at risk of type 1 diabetes (although the highest incidence is among Caucasians, followed by Mexican-Americans and African-Americans) and the complications of type 1 diabetes. Although the economic impact of type 1 diabetes is large (over \$40,000 per case), the medical and social impact on the person with type 1 diabetes and their families is enormous.

In contrast, type 2 diabetes is a highly prevalent disease of adults, with over 8 million individuals diagnosed with disease, a prevalence rate of 3 percent of the population of the United States. The incidence of type 2 diabetes appears to be increasing, with the concomitant increase in obesity and physical inactivity in adults and children. As is the case of type 1 diabetes, the risk of type 2 diabetes is present for all ethnic groups, although the non-Caucasian populations appear to be at higher risk of disease. Mortality in people with type 1 and type 2 diabetes is usually from the complications of disease. Diabetes, and particularly diabetic retinopathy, is the leading cause of new cases of blindness in the United States. It is estimated that 12 percent of new cases of blindness are attributable to diabetes. Neuropathy, the inflammation and degeneration of peripheral nerves, occurs in nearly one-third of type 1 diabetic subjects. Diabetes now accounts for almost 40 percent of all new cases of end-stage renal disease in the United States, and persons with diabetes make up the fastest growing group of renal dialysis and transplant recipients. Diabetes is also a leading risk factor for atherosclerosis, myocardial infarction and stroke. Elimination of type 1 and type 2 diabetes will necessarily eliminate diabetic complications.

ETIOLOGY OF TYPE 1 DIABETES

Type 1 diabetes was described more than 2,000 years ago by Aretaeus of Cappadocia (150 A.D.) who described the disorder as “. . . a moist and cold wasting of the flesh and limbs into urine . . . ; the secretion passes in the usual way, by the kidneys and the bladder.” The role of the pancreas in diabetes was defined in 1889 by von Mering and Minkowski, which led to the discovery of therapeutically active insulin for the treatment of human diabetes. Epidemiological studies, beginning

with those by Elliott Joslin in the 1920's, but clarified by others in the 1980's, demonstrated that type 1 diabetes clustered in families. At the same time, immunological studies found that the autoimmune destruction of pancreatic islets in type 1 diabetes was a chronic process that could be slowly active for years prior to development of clinical disease. Evidence of the importance of genetic factors in the etiology of type 1 diabetes came from twin and family studies, in which it was estimated that nearly one-half of the risk for type 1 diabetes was due to genetic factors. Finally, an association was established between risk of type 1 diabetes and variants of genes in the human major histocompatibility complex (MHC), confirming the importance of genetic factors on risk.

The etiology of type 1 diabetes remains unresolved. The environmental factors that are required to "trigger" the autoimmune destruction of pancreatic islets have yet to be identified. The genetic factors that determine an individual's level of susceptibility to environmental triggers are known to exist, yet most have not been isolated. It is also likely that the interaction between an individual's genotype with environmental exposure is important in determining ultimate risk. Thus, type 1 diabetes is an example of a complex genetic disease. However, given the progress made to date in genetics of type 1 diabetes and the tools now available from the Human Genome Project, there are data suggesting that these genes can be identified. Type 1 diabetes may serve as a model for use of genomic tools to understanding disease etiology, prevention, treatment and cure.

GENETIC BASIS OF TYPE 1 DIABETES

Type 1 diabetes clusters in families. The risk of diabetes in a sibling of a person with type 1 diabetes is about 8 percent, compared to a risk of 0.5 percent in the general population. This 16-fold increase in risk is attributable to multiple genes, including those in the human major histocompatibility complex (MHC) that account for nearly one-half of the genetic susceptibility. The complexity of the genes in the human MHC (on chromosome 6) is only now being understood, due to the available DNA sequence data obtained through the Human Genome Project.

Genes that confer risk for (or protection against) type 1 diabetes also exist outside the human MHC. The availability of highly polymorphic genetic markers (that is, a gene with alternate forms) have made genome-wide searches possible for a number of complex human diseases. Type 1 diabetes was one of the first diseases to be explored in this fashion. To date, three groups have used large numbers of polymorphic genetic markers to scan the genome at regular intervals (roughly every 10 million base pairs of DNA sequence) in families with type 1 diabetes. These "genome-wide searches" for type 1 diabetes susceptibility genes have been performed with varying number of families and with different level of success. The results confirm the presence of at least one type 1 diabetes genes in the human MHC on chromosome 6. Another gene may likely be near the insulin gene on chromosome 11. Based upon the individual data, the number and location of additional risk genes has been difficult to determine. In order to maximize the available genetic data, the individual researchers have agreed to collaborate on an international scale to help find the genes responsible for genetic risk of type 1 diabetes. This collaborative effort is being supported by the NIDDK and the JDRF, and has resulted in the establishment of the Type 1 Diabetes Genetics Consortium. The Consortium currently is combining all available genome screen data for type 1 diabetes in order to identify potential regions of importance, but recognizes that a much larger set of human and genomic resources are needed to identify genes. A similar consortium, supported by the NIDDK, is underway for type 2 diabetes.

SEARCH FOR TYPE 1 DIABETES GENES

While specific regions of potential interest have been identified, it has become apparent that the number of families to be collected to provide adequate statistical power to detect type 1 diabetes genes is much larger than originally anticipated. Recent evaluation of research needs have estimated that 2,400 families will be needed to successfully scan the human genome for type 1 diabetes genes. To collect the required 2,400 families (with two parents, two children with type 1 diabetes, and one child without diabetes), to obtain important clinical and immunological data and to perform the genome-wide search, a major collaborative research effort will be required. This first phase of the genome search will be followed by a collection of 5,000 families (with two parents, one child with type 1 diabetes and one child without diabetes), in which the resources of the Human Genome Project will be used to narrow our region of search. Finally, the DNA and clinical resources collected through the Consortium will be made available to scientists to identify the genes responsible for type 1 diabetes genetic risk. The Consortium represents an outstanding example of

public-private partnership in scientific discovery for the improvement of public health.

PATHS TO GENE DISCOVERY

The purpose of the Type 1 Diabetes Genetics Consortium is multi-fold. The first purpose is to collect human materials in a consistent, ethical, and standardized manner that will expedite the identification of disease susceptibility genes. Collection by individuals using different protocols fail in the size of the sample collected and in the ability to provide a common framework for sample distribution and data collection. Having a large resource of materials that provide adequate statistical power to discover genes has yet to be accomplished for type 1 diabetes, or other common diseases. The collection of human resources is expensive but represents a necessary first step.

The application of existing genomic technologies is the second step in discovery. The Human Genome Project has made available the reagents available for the genome-wide search. Through the remarkable public-private partnership called The SNP Consortium, there are now genetic maps of densely spaced SNP markers that make the search for genes more efficient. Importantly, these resources are freely available and in the public domain. The technology for using the SNP maps is still evolving, however, and continued support for automation and development of high through-put technologies is needed to enable a rapid evaluation of specific intervals in the human genome.

Development of future genomic technologies is a critical third step. The search for genes currently requires scanning hundreds, if not thousands, of SNP variants within a given genetic region to determine which of many small genetic segments require further exploration. The continued efforts of the Human Genome Project to formulate a genetic map of conserved chromosomal segments (a "haplotype" map) would facilitate an efficient screening of these candidate regions that contain type 1 diabetes susceptibility genes. Ultimately, the "currency" of the Human Genome Project, the DNA sequence, will be critical to identify those genes that affect risk of type 1 diabetes. In that regard, it is critical that NIH efforts to sequence the genomes of other organisms such as the mouse and the rat go forward with all due haste. The comparison of human sequence to mouse and rat sequence will help us pinpoint the critical regions of our own genome. In addition, support of the animal research will accelerate the development and exploration of better animal models of diabetes for testing of interventions and new therapeutics.

PROMISE OF GENOMICS

The outcome of the Type 1 Diabetes Genetics Consortium, using resources and reagents from the Human Genome Project, will lead to the discovery of potential type 1 diabetes susceptibility genes. This outcome will represent the "end of the beginning" in genetics of type 1 diabetes. The next phase of research will focus on the function of the candidate genes, the way they act (both in isolation and in concert with other susceptibility genes) to increase genetic risk of type 1 diabetes, and how they are affected by environmental exposure to cause the autoimmune cascade. The manner in which the genes interact and the way in which the proteins are modified to increase or decrease disease risk will require new and emerging technologies that are the future of genomics and proteomics. These investigations will likely continue the productive partnerships already established between the public (NIH) and non-profit foundations.

The understanding of the genes and the gene products and their interactions will lead to improved risk prediction based upon genotype, not just family history and presence of immune markers. This knowledge will permit more efficient clinical trials of compounds developed using genomic information that holds the promise of prevention of type 1 diabetes. An example of the infrastructure for development of these clinical trials is TrialNet, supported by the NIDDK. TrialNet establishes a consortium of clinical centers and core support facilities that would perform intervention studies to preserve pancreatic beta cell function for the purpose of preventing type 1 diabetes. In early stages of molecular medicine, knowledge of genetic risk and the identification of the environmental triggers could establish vaccination against (for example) a virus that acts as the autoimmune "trigger". Thus, the knowledge of genetic risk would first establish a pathway to prevention against exposure. As scientific knowledge expands, a "genetic vaccine" could be made available which, in combination with the protection from environmental exposure, could eliminate an individual's risk of type 1 diabetes.

There are enormous potential benefits of genomic research to individuals who may carry a "genetic load" for type 1 diabetes, and it is important for this research to

go forward quickly. However, a major impediment to participation in genomic investigations is the participant's concern about potential discrimination based upon genetic information and violations of genetic privacy. Assurance of legal and social protection of an individual's rights from genetic discrimination will increase participation in genetic studies, facilitate gene discovery and enhance evaluation of novel therapeutics in clinical trials. The use of molecular medicine and genomic public health approaches will facilitate individual genetic risk assessment and pre-symptomatic treatment of complex human disease. The potential to bring an end to type 1 diabetes and its complications is real and possible, with your continued support.

Thank you Mr. Chairman. I would be happy to discuss any questions that you or others may have.

Senator HARKIN. Dr. Rich, thank you very much for all your work on type 1 diabetes.

Now we turn to Dr. Murray, Professor of Pediatrics at the University of Iowa. Dr. Murray.

STATEMENT OF JEFFREY C. MURRAY, M.D., PROFESSOR OF PEDIATRICS, BIOLOGY, AND PREVENTIVE MEDICINE, UNIVERSITY OF IOWA

Dr. MURRAY. Well, Senator Harkin, I would also have to lead out by thanking you and the committee for the wonderful support that you have given to NIH and the other health related Federal agencies over the years. With the self-effacing Mr. Affleck on my left, I would also have to say that I guess I am the simple country doctor representative that is here.

I have had the opportunity to work as a pediatrician in both our nurseries and our genetics clinics at the university for about 15 years now. I would like to tell you two quick stories about patients that I saw just last week whose lives have been very much impacted by the genome project.

The first is Rebecca and she is a 2-year-old now, who I first saw when she was 1 day of age, who was admitted to my nursery for a combination of birth defects that included heart problems and inability to move her legs. Rebecca's dad is a minister and her mom is a teacher, and she has four older brothers and sisters. Over the last couple of years, through the combined efforts of a number of different physicians and nurses, we have been able to improve her life.

When I saw her a week ago, her older brother asked me, as he had once before, if I knew what the cause of Rebecca's problems were, and I can genuinely and honestly say that 5 years ago I would not have been able to give him an answer. But just in the last several months, in fact particularly through the efforts of Dr. Collins' colleague, Eric Green, at the Genome Institute in Bethesda, we have been able to show that a very small region on the end of chromosome 7 is missing in Rebecca and is responsible for this collection of birth defects that she has.

Now, while this finding by itself is not going to directly lead to improvements or a cure for what she has, it does provide answers for her family that they are very genuinely seeking, and in fact, it will enable her brothers and sisters to understand what their own reproductive risks might be when they become older. This kind of advance is entirely due to the very powerful resources that are available through the computer databases and the CD that you hold up there that enable us to look at this genetic material in a very, very fine way.

To Senator Stevens, who asked earlier about the impact on family physicians, we have also been able to share this information with Rebecca's family doctor in Cedar Rapids, and he has been very appreciative of the larger body of knowledge that he now has as well.

A second patient that I have spent a lot of time with is Sam. Sam was born with a kind of a neural tube defect. The most common description is something called spina bifida or an open spine. Sam is also from Iowa, from Solon, and has had very, very terrible mental retardation and movement problems as a result of this.

Now, as we have just heard from Dr. Rich, the genome project not only teaches us about genetics, but it also helps us to understand how genes and environment interact with one another. In the last 2 years, there has been an amazing success story that is built off of the genetic findings of the genome project and coupled with the work that epidemiologists and private volunteer organizations such as the March of Dimes have done.

We have known for several years now that folic acid, a common B vitamin, can be used to prevent spina bifida and related birth defects if the mother takes it beginning before pregnancy occurs. Starting 2 years ago, the FDA mandated that all enriched cereals and breads in the United States be supplemented with folic acid, much in the way that vitamin D is put in milk.

In these last 2 years, there have now been, as shown in a report that came out a month ago from the CDC, 1,000 fewer babies born with spina bifida in the United States. This is an amazing achievement and the fact that there are now 1,000 healthier, happier, wonderful children running around who do not have to suffer the pain and expense of this terrible disability is an amazing preventive success story.

Just as Dr. Collins and Dr. Rich have told us, we now have the opportunity to use these genomic advances to understand not only things that we will be converting into treatments and preventions 15 years from now, but ones that we can do today and tomorrow and the next day. This is really a marvelous benefit for someone like myself and I think for all of us who have family members who might be affected with these kinds of disorders.

I do want to also sound a couple of cautionary notes. You brought several of these up in your introductory statements.

First of all, we need to, as you have said, temper our enthusiasm for the excitement of these findings with concerns about how the information might be used. When I was a member of the Ethical, Legal, and Social Panel, we frequently had families ask us about whether this information was going to be used in a way that could discriminate against them in either employment or for insurance purposes. You and others have already made efforts in trying to minimize and limit the kind of discrimination that can take place. But I think that this is still a concern, and again, as Dr. Collins told us, we need to be very vigilant that this kind of information is not used against the very families that it is designed and meant to try and help.

A related area to this is in the area of research that many of us here on this panel are directly involved in and patients who will benefit from that research. Scientists and physicians, such as my-

self and others up here today, need to have access to the families, to have families voluntarily participate in these kinds of studies in a way that that information can be used to be converted into the kinds of treatments and preventions and cures that they would like to have.

At the same time, the families need to be reassured that that information is not going to be used against them in some way. So, scientists and physicians need to have access to databases, the information and the DNA samples that are contained in those, in an easy way that allow them to pursue their scientific investigations. Families need to go through an important process of informed consent where they give their full and open permission to participate in these studies. And then those same families need to be protected so that the information contained in these research databases is not misused in any way.

Then finally, also as we hear alluded to today as well, for some of the findings that are taking place today, it may not be a year or two, but it may be 5 or 10 or 15 years before the findings are converted directly into those treatments and preventions. We as scientists and physicians need to be careful that we do not over-promise to families, that the fruits of the genome project will all immediately be converted into cures and treatments.

All of us recognize here in this room that the genome project is also an international effort, and that involves not only the people in the United States but many other countries as well. It also involves many other kinds of organisms, and we have heard that from Dr. Needleman.

The health problems of the world today include not only things that the genome project will directly solve, but are still built around things such as unsafe drinking water, poor nutrition and treatable or preventable infections like HIV or measles. So, at the same time that we are taking advantage of these very powerful immediate advances, we need to also ensure that the genome project is applied in a beneficial way across all strata of society and everywhere.

Again, I want to thank you and the committee for the wonderful support and job that you have done over the years for NIH and the CDC and the other Federal organizations. As a genuine practicing physician and one who really on a daily basis gets to see these applications put into direct practice for families, as Dr. Collins has told us, we are really at the beginning of the genome project, not the end of the genome project. Now we have the opportunity to convert these very, very wonderful findings into things that are going to benefit all of us and even more importantly I think our children.

Thank you.

[The statement follows:]

PREPARED STATEMENT OF JEFFREY C. MURRAY

First, I would like to thank you, Senator Harkin, and the other members of the panel for the opportunity to speak with you today. I am a pediatrician and a molecular biologist who has spent the last 20 years of my career caring for children with prematurity and birth defects and working in the laboratory to better understand the genetic and environmental causes of these terrible disorders. For the last two days, I have been attending a meeting in Bethesda, sponsored by the Child Health Institute. This meeting brought together investigators to see how advances in the genome project can be put to use to decrease the terrible impact of birth defects.

Birth defects afflict one in thirty newborns and can lead to a lifetime of disability. Just last week, before leaving for this meeting, I was seeing patients in our genetics clinic. One is Rebecca, a now two-year-old girl I first took care of in the intensive care nursery at our university and who is the youngest of four siblings born to a minister father and teacher mother in Marion, Iowa. At birth, Rebecca had several different birth defects that prevented her from moving her lower legs and also affected her bowels and her heart. Through the combined efforts of many physicians and nurses caring for her, she now has a life that is far better than could have been anticipated even a decade ago. Her parents and oldest brother asked me what caused Rebecca to be born like this. Five years ago, I would not have had an answer, but now I can say that through the advances in the Human Genome Project, we have been able to identify a very specific region on chromosome number seven that seems to be missing in Rebecca. While this information by itself will not change the care that we provide for her, it does provide answers for her family and relatives and holds out the promise for us being able to better prevent or treat children with disorders similar to Rebecca's in the future. Up until a few years ago, it might have taken our laboratory ten or even twenty years of work to identify this cause while now it was completed through the work of a single graduate student in a few months, making use of the very powerful computer databases that contain the DNA sequence information and using genetic maps constructed in part in the Iowa Genome Center.

Another patient I have cared for now for three years is Sam, who comes from Solon, Iowa, and who I also first took care of in our intensive care nursery. Sam has a very severe brain malformation of a type called neural tube defects, which are most commonly represented by spina bifida, or an open spine. We have known for some time that folic acid taken as a prenatal vitamin can prevent spina bifida. Just one month ago, in work that was sponsored by the CDC, the NIH, and the March of Dimes, the first report appeared demonstrating that since the FDA requirement for the fortification of folic acid in cereal grains was instituted in 1998, the prevalence of spina bifida and related neural tube defects has dropped by 20 percent in the United States. It was possible to document this change by using the information provided by birth defects registries which have received critical support from the CDC and March of Dimes at a time when our concerns about the genetic and environmental causes of birth defects has never been greater or more available to change. This is an amazing success story and a strong testament to how federally sponsored research and law can work together to improve the lives of children and adults. This 20 percent reduction means that there are 300 fewer babies born per year with spina bifida in the United States, sparing their families and themselves years of pain, suffering, and expense. In this case, a simple and safe environmental change—food fortification—has had a dramatic impact and will now stop many other Sam's from a future of surgery and mental retardation. This illustrates the close connection between genes and environment and how knowledge of one can interact with outcomes of the other. The partnerships that have led to these remarkable findings and advances are a wonderful testament to the support that the Senate, the House, and the President have provided with their generous increase in funding to the NIH and in particular to the Human Genome Project over the last several years. By continuing to provide this kind of support, we will be able to build upon the developments that have already taken place to provide an even more promising future for our children filled with possibilities rather than disabilities.

At the same time that these remarkable advances are taking place, we need to temper our enthusiasm with a few concerns. First, the power of DNA and gene sequencing has also raised concerns about the use of this information in both the public and private sector. Our families frequently ask us whether this diagnosis will have an impact on their children's ability to obtain health insurance. The treatments for these disorders are incredibly expensive and far beyond the means of all but a few very wealthy families, so families need resources and assurances. Similarly, these children, when they grow up, and their siblings are concerned about opportunities in employment and education and whether their genetic background will in some way influence decisions that may affect their life choices. The Congress and the President have already begun to address these concerns through legislation protecting individuals from discrimination in employment or insurability, but these regulations as well as a system of comprehensive health coverage needs further strengthening.

In parallel with this have been similar concerns raised by participants in research projects who provide the necessary information to use the genome project to investigate inherited disorders. The genome project has provided powerful tools for genetic study, but still only tools that must now be used with real people and real diseases like you see here today to realize the promise of the technology. The suc-

cesses that we have and will hear about in diabetes, ataxia telangiectasia, spina bifida, and others have all been built on the cooperation of patients and families who have these conditions and who willingly provide information as well as blood and tissue samples for scientific research. This information and samples reside in databases—an essential tool for the physician-scientist in determining causes. Yet, these individuals must be protected in their participation in research and not have this information used in any way to discriminate against them. While serving as a member of the Genome Project, ELSI (Ethical, Legal, and Social Issues) Review panel, we were confronted time and again with this seeming disparity. The potential conflict arises in the desire for families to participate in research that will benefit them and others balanced against their need for privacy. We must be able to strike a balance of proper informed consent from individuals enrolled in studies, safeguards to ensure that no outsider can intrude on the data stored and smooth access by scientists and physicians to the critical data and samples needed to convert genome information into genome based treatment and prevention.

A second reality test of our enthusiasm must be that even the identification of DNA sequence information does not itself immediately lead to preventions and cures. One oft-cited example is that we have known since 1949 and the work of Linus Pauling what the cause of Sickle Cell Anemia is, a common genetic disorder frequently found in African Americans. Although the care for individuals with Sickle Cell Anemia has improved dramatically over the last 50 years through the efforts of many kinds of caretakers, the promise of the genome has not yet allowed us to cure or prevent this disorder in a primary way. We hope that many of the findings being discovered today will lead more quickly to these cures and prevention, but we also need to be careful not to over-promise to the public that the fruits of our research will be immediate in their application to their own specific disorders.

A final tempering comes from the realization that the genome is international. In my own work in the Philippines and Brazil I have come to know that the major problems of world health are not those of genetics, but are simple problems best addressed through basic sanitation and clean drinking water, with immunization against tetanus or measles, by providing basic nutrition or population control methods and through programs to prevent HIV, malaria, or TB. At the same time that we are excited and enthusiastic about the work of the Genome Project, we need to continue to be aware of the need for these approaches to preventive medicine so often taken for granted in the developed world.

It has been a great honor and privilege for me to have participated in some small way in the mapping of the human genome and to have lived at a time when I can see the successful realization of so many scientific projects now becoming a reality in their direct application to patient care and treatment. I can only hope that you and others like you will continue to provide the necessary support for these projects in creating a truly brighter future for our children and their children to follow.

Senator HARKIN. Thank you very much, Dr. Murray.

Dr. Murray gave a couple of examples. Now we turn to really what this is all about, about a human being, about a person, about someone for whom this promise of genomic research and the applications that your scientists, all of you have been talking about, is meaningful and is real.

I have the highest respect, as you know, for each one of you, and for all of the wonderful work that you have done in the scientific realm to bring us to this point and which you will be continuing to do in the future. I also have the highest respect for those who have attained a position of celebrity status in our society because of their abilities in other areas and who take the time and the effort to get involved in bringing to the public conscience what we are doing here.

It is in that vein that I welcome Ben Affleck to this table, Joe Kindregan's friend. Maybe I should introduce you that way. Right? Joe Kindregan's friend.

Mr. AFFLECK. Most appropriate probably, yes.

Senator HARKIN. And also Joe and Mr. Margus.

We thank you very much, Mr. Affleck, for being here and again, as I said, for being willing to step out in front and to publicize in a very meaningful way what it is we are all about here.

STATEMENT OF BEN AFFLECK, ACTOR

ACCOMPANIED BY:

BRAD MARGUS, PRESIDENT AND CO-FOUNDER, A-T CHILDREN'S PROJECT

JOE KINDREGAN, A-T PATIENT

Mr. AFFLECK. Thank you, Senator, and I thank you and Senator Specter for your brave leadership in this regard, your pursuit of funding for stem cell research, the genome project, and the model of bipartisanship and leadership that you and this committee represent. Frankly, I am impressed and I feel very honored to be asked to be here and I thank you very much.

Second, I am really inspired by all you gentlemen. It is really a pleasure to sit next to you. It is truly impressive, and what is really marvelous, beyond even all of your day-to-day work in the business of helping of people, is your capacity, I think equally important in many ways, to make that process, which, as Senator Stevens mentioned, can sometimes seem a little obtuse and complex and nebulous, tangible and accessible to folks and to our leadership. I think that is equally important. You have done a fine job and I am honored and a little humbled to sit in your company.

I will try to stick to the 5-minute rule, although, you know, in Hollywood we get 15 minutes.

To the horror of the folks I came with, I am going to speak extemporaneously for a few moments before I go into the prepared text and just say that ultimately why I am here is I am obviously neither a politician nor a doctor nor even whatever this woman does who appears to be sucking on ether over there.

Is that not what that looks like?

That is why you look like you are falling asleep, ma'am.

It is impressive really. Able to maintain consciousness throughout the proceedings.

I am here because of my friendship with a guy who has really moved me and am here to talk about the human toll in this. Sometimes we get into debates and we talk about policy and appropriations and funding and pharmaceuticals and genome, and it is all really tremendous and important work. But what is also important is to remember the human costs in these things, to remember that there is a time pressure, to remember that they are real people doing real suffering who otherwise could be living wonderful, normal lives.

This is why I would urge you and the committee to go to a vote on the stem cell question, which I think has support not only of Congress, of the Senate, but of the vast majority of the American people who understand that this research, particularly recently we have come to understand, can be enormously helpful in neurological disorders and spinal cord disorders. I am sure you would do a lot better job of explaining why exactly, but it is.

You were asking what is A-T. It is actually pronounced ataxia-telangiectasia.

I met Joe a few years ago. I was working at Dulles Airport. We were filming a movie and he wanted to get a better view of what we were doing. We just kind of hit it off. At the time I met Joe, he was in a wheelchair but he was using a power wheelchair, but I also learned that he loved karate and he had a yellow belt. Since then Joe has stopped his lessons because it has become too difficult for him to stand and balance at attention as a result of the neurological deterioration from A-T.

A-T affects the body's coordination. It predisposes children to lethal cancers. It severely compromises their immune systems. Most children with A-T are sentenced to a life in a wheelchair. If you can imagine a disease that combines the worst aspects of muscular dystrophy, cancer, and AIDS, you would have a pretty good idea of what a kid with A-T and their families endure on a daily basis. A-T is a progressive disease. It gradually robs children of their muscle control. They lose ability to walk, to talk, to read, and to play games. A-T is exceptionally cruel because children with A-T lose their physical capabilities inch by inch, but they never lose their intellect or mental faculties. And I can assure you that Joe is every bit as sharp and mentally alert as I am. Although there are people who will tell you that is not saying much, he is young.

I promise you he is a very bright, spirited young guy.

Since we first met, I have had the pleasure of seeing Joe on a number of occasions. In fact, this past spring Joe and his family joined me in Hawaii for the premier of "Pearl Harbor". I have seen firsthand the progression of Joe's A-T. Where Joe and I used to carry on a conversation, his mom now often has to translate more and more of what Joe says because his speech has been affected by A-T, although sometimes his mom jumps in a little too much and henpecks him, and I have to tell her just give him a minute or he tells her.

Joe and I used to be e-mail pals, and he has written me some very funny and interesting and wonderful e-mails. It used to be something that I really looked forward to on a daily basis. But Joe can no longer type his part of the conversation, so his mom does that for him now.

As Joe is entering his adolescence, he is becoming more and more dependent upon those around him to assist him with daily tasks. As I recall, adolescence was a time for increasing independence. Some of us too much independence, but for Joe, A-T has made this normal right of passage for a teenager go backwards.

The great thing about him, however, is that he is full of hope and optimism, just like every other kid in America. But in his case, his hopes are somewhat different than most 12- or 13-year-olds. He hopes the benefit of medical research on diseases like A-T will help him to walk again, speak easily, play with friends, and I look forward one day to playing sports with him. These dreams will only be possible if the vision of the A-T Children's Project is realized, which is a cure for A-T.

The A-T Children's Project is a nonprofit organization established by Brad and Vicki Margus. Since its inception 8 years ago, the Children's Project has raised over \$10 million. They have done what many small disease organizations do, raising money through numerous grassroots events, such as walk-a-thons, dinners, and

auctions. They have successfully garnered the guidance from a respected board of objective scientists to award these funds to researchers around the world studying A-T. The A-T Children's Project has established tissue and cell banks so that researchers interested in studying A-T can easily obtain patient tissue or DNA. They have successfully encouraged international collaborations among scientists from the United States, the United Kingdom, Australia, Israel, Turkey, Italy, France, and Germany. In addition, these collaborative efforts have generated numerous research strategies as a result of their two scientific conferences that they host annually.

Research funded by the A-T Children's Project has led to the identification of a defective gene that causes A-T in children. In addition, the A-T Children's Project has funded the work of several labs to use genetic engineering to develop mice with A-T. These mice have many of the same symptoms seen in A-T kids. Now that an animal model exists, it is possible to explore potential therapies to treat the effects of A-T and hopefully one day find a cure.

Mr. Chairman, members of the committee, this is a remarkable track record of progress for a small foundation in a short time. Now it is vitally important that your leadership ensure that kids like Joe get to the finish line.

When you have a disease that affects such a small number of Americans like A-T, it is imperative that the resources of the NIH be devoted to it. One of the things I am asking you here to do is to support not only A-T but other what they call orphan diseases, just because there are very few people who have the disease relative to, say, Dr. Needleman's favorite disease, which was colon cancer. There are many similar small clusters of diseases that fall under a larger umbrella. There are various variations of neurological disorders, and I am here to urge you to increase funding for these diseases which oftentimes get lost even in places like NIH because, obviously, you are focused on diseases that afflict more people.

My message is simply this. A-T needs a bigger piece of the NIH pie. I was just speaking extemporaneously again. The support of the Congress and the investment of the NIH in A-T research is vitally important if kids like Joe are to have their hopes and dreams fulfilled.

Another important aspect of research for children with A-T that needs to be considered is the training of clinical researchers. As a result of the competitive health care marketplace, it is extraordinarily difficult for clinical researchers to devote time and academic resources to translational and clinical research initiatives. While strides have recently been made through the passage of the clinical research legislation in the last Congress, it is imperative this aspect of our biomedical research infrastructure be monitored carefully.

Increased funding for NIH will give children and adults with neurological disorders, such as A-T, an increased chance of reaching their full potential. With an increase in funding at this time, along with monumental advances in genomics, researchers will learn not only how to prevent diseases like A-T, but how to reverse the neurological damage that has already been done. The research

is not only critical for A-T but also for many other neurodegenerative diseases, including Parkinson's and Alzheimer's. This Congress has the ability to make a tremendous impact on the future of modern medicine and the suffering of individuals and their families.

My friend Joe often refers to the time when he gets well. He knows that the reality of his recovery is just around the corner. Right now funding means hope for all of these families, hope that medical research will produce a miracle in Joe's lifetime. For Joe, it will mean a second chance at being a kid. For me, I intend to work with him on his next karate belt as soon as research advances get him out of his wheelchair. With your help, these dreams will become a reality.

This concludes my formal statement. Brad and I will be happy to answer any questions that you may have for us. Thank you.

[The statements follow:]

PREPARED STATEMENT OF BEN AFFLECK

Mr. Chairman, Members of the Committee, thank you for the opportunity to appear before you today on behalf of the A-T Children's Project. Brad Margus, President and Co-Founder of the A-T Children's Project joins me at the witness table. Eight years ago two of Brad's four sons, Jarrett and Quinn were diagnosed with a disease called ataxia-telangiectasia or A-T for short. I am also honored to be accompanied to today's hearing with a friend of mine, Joe Kindregan. Joe is 13 years old and has A-T.

You may be asking, as I did a few years ago, "what is A-T?" A-T is a genetic disease that attacks its victims in early childhood. It is very rare, only about 600 children in the United States have the disease, and this fact makes it all the more difficult to get doctors, researchers, the government and pharmaceutical companies interested in investing the millions of dollars necessary to develop innovative ways to diagnose and treat A-T.

A-T affects the body's coordination; it predisposes children to lethal cancers, and severely compromises their immune systems. Most children with A-T are sentenced to a life in a wheelchair and rarely live beyond their teens. If you could imagine a disease that combines the worst aspects of muscular dystrophy, cancer and AIDS you would have a pretty good picture of what a child with A-T and their families endure daily. A-T is a progressive disease that gradually robs children of their muscle control; they lose their ability to walk, to talk, to read and to play games. A-T is exceptionally cruel because while children with A-T lose their physical capabilities inch-by-inch, children with A-T never lose their intellect or mental faculties. Regrettably, they are trapped in a body that progressively fails them. In addition to the neurological deterioration, their chance of getting leukemia and lymphoma and succumbing to cancer is 1,000 times higher than normal. In short, the outlook for these kids is horribly grim.

So, it is for Joe, Jarrett and Quinn and the hundreds of other children with A-T across America, that I bring their plight to Congress today. I would like to help the Committee, and your colleagues in the Senate, understand the human aspects of this horrendous disease and suggest some ways that Congress can assist these children and their families.

I first met my friend Joe 3 years ago at Dulles Airport while filming "Forces of Nature." He had come to Dulles with his mom and sister to see what it was like on a movie set. He was in a wheelchair and couldn't see through the crowds of people so he was allowed down on the set to get a better view.

Joe was 10 years old at the time and had just started using his power wheelchair. During the course of the afternoon I learned that Joe loved karate and even had attained a yellow belt. Unfortunately, Joe had to stop his lessons when it became too difficult for him to stand and balance at attention as a result of his neurological deterioration from A-T.

Since we first met, I have had the pleasure of seeing Joe on a number of occasions. In fact, this past spring Joe and his family joined me in Hawaii for the premiere of Pearl Harbor. I have seen firsthand the progression of Joe's A-T. Where Joe and I used to carry on a conversation, his mom now has to translate more and more of what Joe says because his speech has been affected by A-T. Joe and I used

to be e-mail pals, but Joe can no longer type his part of the conversation so his Mom does that for him now. As Joe enters adolescence he is becoming more and more dependent upon those around him to assist him with daily tasks. As I recall, adolescence is a time for increasing independence, but for Joe, A-T has made this normal right of passage for a teenager go backwards.

One thing that I have learned about Joe is that he is full of hope and optimism, just like every other kid in America. But in Joe's case, his hopes are somewhat different than most 12 or 13 year olds. Joe hopes that the benefit of medical research on diseases like A-T will help him to walk again, speak easily, play with his friends, and maybe even someday play sports again. These dreams will only be possible if the vision of the A-T Children's Project is realized: a cure for A-T.

The A-T Children's Project is a non-profit organization established by Brad and Vicki Margus. Since its inception eight years ago, the Children's Project has raised over \$10 million. They have done what many small disease organizations do, raising money through numerous grass-roots events such as walkathons, dinners and auctions. They have successfully garnered the guidance from a respected board of objective scientists to award these funds to researchers around the world studying A-T. The A-T Children's Project has established tissue and cell banks so that researchers interested in studying A-T can easily obtain patient tissue or DNA. They have successfully encouraged international collaborations among scientists from the United States, the U.K., Australia, Israel, Turkey, Italy, France and Germany. In addition, these collaborative efforts have generated numerous research strategies as a result of their two scientific conferences that they host annually.

Research funded by the A-T Children's Project has led to the identification of the defective gene that causes A-T in children. In addition, the A-T Children's Project has funded the work of several labs to use genetic engineering to develop mice with A-T. These mice have many of the same symptoms seen in A-T kids. Now that an animal model exists it is possible to explore potential therapies to treat the effects of A-T and hopefully, one day, find a cure. Mr. Chairman, Members of the Committee, this is a remarkable track record of progress for a small foundation in a short period of time. Now, it is vitally important that your leadership ensure that kids like Joe get to the finish line.

On behalf of the A-T Children's Project, we urge your continued support of the doubling of the budget of the National Institutes of Health (NIH). The Congress has been an incredible ally in pushing the frontiers of research through the investment you have made in medical research. It is vitally important that the fourth installment in meeting this important objective be made this year.

When you have a disease that afflicts such a small number of Americans, like A-T, it is imperative that the resources of the NIH be devoted to it. I am confident that you have hundreds of requests annually for funding specific initiatives at the NIH. With that said, my message is simply this—A-T needs a bigger piece of the NIH pie if we are to fully exploit the scientific possibilities that exist. The support of the Congress and the investment of the NIH in A-T research is vitally important if kids like Joe, Jarrett, and Quinn are to have their hopes and dreams fulfilled.

The A-T Children's Project has directed resources to support basic research looking at the biological defect and the role of the A-T gene/protein in cells in academic laboratories. They have demonstrated the capacity to bring together scientists on a global basis, not allowing geographic boundaries to inhibit fully exploiting the best and brightest scientific minds to tackle this disease. What the A-T Children's Project does NOT have the capacity to support is the translational research that seeks to apply the findings from basic research to the kids with A-T. We need the government to intercede here and encourage the NIH intramural program to work in partnership with industry on translating the basic science advances. The new Clinical Center at the NIH has the capacity to enhance translational research in this crucial area.

Another important aspect of research for children with A-T that needs to be considered is the training of clinical researchers. As a result of the competitive healthcare marketplace, it is extraordinarily difficult for clinical researchers to devote time and academic resources to translational and clinical research initiatives. While strides have recently been made through the passage of the Clinical Research legislation in the last Congress, it is imperative that this aspect of our biomedical research infrastructure be monitored carefully.

In spite of the boom in biotechnology venture funding, progress in developing new tools to accelerate research is not fast enough for kids with A-T. While the gene was identified six years ago, faster methods and tools for figuring out exactly what the gene and its proteins do in healthy people and how we can compensate for its absence in A-T kids have not been forthcoming. These types of assays and tools are vitally important and NIH should be encouraged to pursue them.

Increased funding for NIH will give children and adults with neurological disorders such as A-T an increased chance of reaching their full potential. With an increase in funding at this time along with the monumental advances in genomics, researchers will learn not only how to prevent diseases like A-T, but also how to reverse the neurological damage that has already been done. This research is not only critical for A-T, but also for many other neurodegenerative diseases including Parkinson's and Alzheimer's. This Congress has the ability to make a tremendous impact on the future of modern medicine and suffering of individuals and their families.

My friend Joe often refers to the time when he gets well. He knows that the reality of his recovery is just around the corner. Right now, funding means hope for all of these families. Hope that medical research will produce a miracle in Joe's lifetime. For Joe, it will mean a second chance at being a kid. For me, I intend to work with him on his next karate belt as soon as research advances get him out of his wheelchair. With your help, dreams will become reality.

PREPARED STATEMENT OF BRAD MARGUS

Mr. Chairman and Members of the Committee, thank you for giving me the chance to tell you how a terrible disease has affected two of my sons and how families like mine have tried to accelerate research toward a cure. After describing my background to you, I would then like to explain four specific actions your committee could consider taking to increase the effectiveness of research—not only on my sons' brutal disorder but on many other diseases as well.

MY STORY

Not too long ago, in the early nineties, I knew nothing about the Human Genome Project, nothing about serious health problems, and nothing about how researchers in pharmaceutical companies, academic institutions and government laboratories were trying to exploit molecular biology to discover drugs and treatments for diseases. I knew only about running a small, entrepreneurial business.

After graduating from business school in 1986, instead of going to Wall Street or into venture capital or consulting, I went somewhere few Harvard MBAs go—into the shrimp industry! There, I grew a successful, but admittedly low-tech, seafood company. I also married a beautiful, intelligent woman, and together we had three sons within less than four years. Vicki and I purchased our dream house on a tree-filled lot in sunny Florida and imagined growing old watching our sons turn into strong, healthy men someday. Life seemed perfect.

Then one day, everything changed. We suddenly lost control of our perfect lives. In the spring of 1993, two of my young sons were diagnosed with a terrible genetic disease known as ataxia-telangiectasia (pronounced "ayTACK-see-uh teh-LAN-jick-TAY-sha"), or "A-T" for short.

Our boys with A-T had seemed normal until about the age of two when their walk had become a little "wobbly" and their speech had become slurred. Doctors took nearly two more years, and we spent over \$70,000 in tests to figure out what was wrong, and the final diagnosis was a brutal one. We were told that by the age of nine or ten, our boys with A-T would lose so much control of their muscles that they would need to rely on wheelchairs. And, by their early teens, controlling eye movement and throat muscles would make reading and swallowing extremely difficult for them.

On top of hearing about the neurological progression, we were also told that the boys each had a 40 percent chance of developing leukemia or lymphoma and a 70 percent chance of having a weakened immune system that would make common infections much more serious. Most children with A-T, we were told, died in their late teens or early twenties. And, as the diagnosis kept sinking in, we realized that the quality of their lives would deteriorate long before then.

Devastated by the news about our boys, my wife and I did what many parents do in similar situations. We started learning everything we could about the disease. As I plunged into reading papers about A-T published in scientific journals, I grew to realize that A-T—affecting only about 600 children in the United States—was truly an "orphan" disease. No one with fame or money had ever had a child with this disease and funds to support medical research were extremely limited. Therefore, in the fall of 1993, we started a non-profit organization called the A-T Children's Project.

I also realized that to have any effectiveness at all, I needed to learn enough molecular biology so that I could comprehend the research strategies being taken and

could appreciate which scientists were competent and which were not. I enlisted the help of several Ph.D. scientists who tutored me every night by phone and fax.

At the same time, I made an effort to ask many scientists and grant-giving organizations for their impressions about other non-profits whom they believed were especially effective. I wanted to learn from other model organizations so that I would avoid common pitfalls. I could not afford to learn by trial and error. As a result of this process, I immediately recruited a team of objective, first-rate scientists and physicians to serve on my Scientific Advisory Board. I didn't want to take any chance that a particular scientist or physician might sway me too much (as often happens to parents desperately seeking a cure for their kids' disease). I also began to visit the National Institutes of Health regularly to learn how our government funded research and to try to encourage increased interest in my kids' obscure disease.

While continuing to manage my shrimp company, I learned how to raise money by leading a grass-roots effort that organized walkathons, dinners and diverse other events around the nation to support research. We started by writing letters and gradually developed a base of wonderful volunteers who helped us raise money. Events included walkathons, celebrity golf tournaments, horse shows, races, dinner dances, auctions, retail-level point-of-purchase "heart" sales, and hundreds of other ideas . . . The funds we raised grew from a few hundred thousand to over two million dollars per year.

Raising money for a rare disease with a name that is nearly impossible to pronounce is not easy. And, because this disease is so rare, we could never depend solely on the help of volunteers who have a personal connection with an affected child in the way that organizations for more common diseases can. Instead, we had to persuade total strangers to reach out and help us.

Of course, besides raising money, it was critical to recruit first-rate scientists and to persuade them to work on A-T. At least twice a year, we orchestrated and sponsored scientific workshops that brought together researchers from different disciplines to compare results, generate new research approaches and form collaborations. At each of these meetings, I worked hard to concoct the right mix of scientists and to provide the perfect atmosphere so that they would candidly share their latest, unpublished data and work cooperatively with each other even after the meeting ended.

Our organization also played an important role in making sure researchers had easy access to patient tissue samples. We set up an international cell bank for blood and skin samples and a brain tissue bank as well.

In the summer of 1995, the laboratory of a researcher at Tel Aviv University in Israel, Dr. Yosef Shiloh, succeeded in finding the gene that, when mutated, causes this disease. The NIH laboratory of Dr. Francis Collins—who is also testifying at today's hearing—had collaborated with the Israeli team, and we will always be thankful to Dr. Collins for the contribution his group made to our gene hunt.

Having found our gene, we could not celebrate for long. Instead, we quickly recruited geneticists who were experts in frogs, zebra-fish, fruit flies, worms, yeast and fungus so that we could utilize their experiences with similarly spelled genes in these lower organisms. We also assisted several laboratories in developing strains of "knock-out" mice that had the A-T gene disrupted so that we would have a model of the disease in a mammal. We helped several scientists raise antibodies against the A-T protein—an important tool for studying the activity of the protein in various tissues. And then, we helped to make sure these antibodies were freely shared with any new researcher who became interested in our kids' rare disease.

Still other labs were encouraged to use bacteria to make "recombinant" A-T protein with which experiments could be performed, and two groups succeeded at tagging the A-T protein so that its movement could be followed in the cell. We also used various methods such as yeast-two-hybrid screens and mass spectrometry to identify other proteins and protein complexes that interacted with the A-T protein.

Besides finding the A-T gene in 1995, we realized that year that we needed one place in the world where a multidisciplinary team of physicians were accumulating data on this disease (until then, most physicians overseeing a child with A-T had never seen another case). Therefore, after seeking proposals from many leading medical centers, we established an A-T Clinical Center at Johns Hopkins Hospital in Baltimore, Maryland. It included physicians covering every field relevant to A-T (such as neurology, immunology, oncology, ophthalmology, and pulmonary) as well as experts in brain imaging, brain pathology, swallowing problems, physical therapy, occupational therapy, speech therapy, and assistive technology.

About the same time, we set up an internet web site plus a list server that provided a forum by which A-T families and caregivers around the world could share

ideas about managing the disease day-to-day and give each other emotional encouragement.

The scientific research continued to move swiftly as our sons' rare disease became quite well known in biological research and especially among cancer researchers. Because the A-T protein missing in my sons was found to interact with a famous tumor suppressor gene called "p53" as well as a gene called BRCA-1 that is associated with breast cancer, oncologists around the world became increasingly interested in A-T. The A-T protein, known as "ATM," was found to play an important cellular role in sensing DNA damage and regulating the copy-and-divide cycle of cells that when corrupted, leads to cancer or brain cell death.

Other researchers published new findings that the A-T gene was misspelled in the tumors of most patients with a particular form of leukemia. And, the chromosomes inside the cells of A-T children were also found to have shortened ends (or "telomeres"), that are known to shorten with age, making A-T an intriguing model of premature aging.

After studying how major medical progress had been made through history, I realized that significant medical discoveries often have roots in unrelated basic breakthroughs. Therefore, I concentrated on surveying every area of science in hopes of finding new approaches and brilliant investigators. I worked late into the night, struggling to keep up with the science while sending faxes and e-mails in hopes of engaging world-class scientists to study my sons' disease. I often fantasized about a day when every scientist on the planet would be aware of this disease. And gradually, researchers working on cancer, neurodegeneration, immune deficiency and aging became involved.

In 1997, we thought for a moment that we had found a treatment! A research team had discovered that in mice engineered to lack the A-T protein, a certain type of brain cell was dying that was also known to die in people who have Parkinson's disease. When the scientists injected a common drug for Parkinson's Disease called "L-dopa" into the mice, the animals seemed to improve a little. As a result, we immediately organized a blinded clinical trial of L-Dopa in A-T kids, but the results were disappointing (no significant improvement compared with children receiving the placebo). Nevertheless, running our first clinical trial helped us realize the important issues in designing drug trials for children with A-T (such as establishing reliable, quantitative, clinical end-points with which to measure and observe any changes in the kids resulting from the drug).

Children with A-T have an extreme risk of developing cancer, and because radiation is lethal to them, treating A-T children for cancer is especially challenging. Therefore, in 1999, we established a cancer clinic for A-T kids at St. Jude Children's Research Hospital in Memphis, Tennessee where pediatric oncologists are now striving to develop unique protocols that should improve the management of cancer in children with A-T.

Besides running several scientific meetings each year that were attended by M.D.s and Ph.D.s, we also organized and sponsored other types of meetings that brought families of A-T children together with doctors to learn about managing the symptoms of A-T and coping with the exhausting lives they endured. We also published a manual that provided a lot of practical information to physicians, parents and therapists who took care of children with A-T.

Recently, much of the research we supported held promise for other diseases besides A-T. For example, by this past year, we were funding work on cultured neural stem cells that not only held the potential of helping to "reseed" the brains of A-T kids, but might also help patients with Alzheimer's, Parkinson's, ALS, spinal cord injury and stroke. We were also funding work aimed at transferring and expressing a healthy copy of the A-T gene into the brain cells of A-T children. If this virus-based system of gene therapy worked, it could also be applied to numerous other neurological disorders.

We were also supporting trials of new "super antioxidant" compounds on A-T mice that had been shown to extend the lives of worms by 40 percent, and we were working with still other researchers to combine gene targeting and nuclear transfer (cloning) techniques to make animal models of A-T in monkeys, cows and pigs. We were even checking to see if neural auto-antibodies, ion channel defects, mitochondrial dysfunction, nuclear inclusions or cytokines were playing roles in the disease, and whether growth factors might have therapeutic potential.

In short, we had done our best to "catch up" with the efforts of the big, well-known disease organizations. And many people therefore said that we had made much progress. But we had not succeeded. We had still not found a single way to slow the progression of this relentless disease for even one day.

I received various accolades for our work, including invitations to serve on advisory councils that directed the National Institutes of Health and chances to tell Sen-

ate committees how I would improve the government's funding of medical research. I was also given the opportunity to serve as a board member of the Genetic Alliance—an umbrella organization that represents over 300 genetic disease organizations. Barbara Walters hosted an hour-long ABC News television show in 1996 about our efforts. And this past year, I was given the opportunity to become Chief Executive Officer of a new Silicon Valley-based biotech company called Perlegen Sciences that recently raised \$100 million in first-round financing from private investors (this career move has allowed me to leave the food industry and to focus all facets of my life on scientific research aimed at understanding and treating diseases).

Yet, in spite of these votes of confidence, I am compelled every day to realize that until now, I have still failed in finding a treatment or cure for children with A-T.

Time has passed quickly, and A-T children like my boys have continued deteriorating and dying. My son Jarrett is now twelve years old, and Quinn is ten. Time is running out. Both boys now use power wheelchairs and rely on full-time aides in school. Their minds are unaffected by the disease, but they are trapped inside bodies that are letting them down. As they become less able to share activities with healthy friends, my wife and I struggle to figure out how we're going to help them deal with their social isolation and physical limitations.

Of course, my fight to cure or treat A-T has now reached far beyond merely fighting to save my own two sons. I have visited families of hundreds of children who have A-T, some of whom have subsequently lost their lives to this disease. My wife and I are no longer alone in this fight but now share our mission with other families of A-T children around the world who are doing whatever they can to raise money and increase awareness. Several of those families are here in this room today.

And, I cannot tell you how thrilled I am today that such a talented and admired motion picture actor and Academy Award-winning screenwriter has stepped forward to help us in our fight. Today, families like mine across America are overwhelmed with joy, realizing that Ben Affleck is not merely testifying before you today about A-T but—through his friendship with thirteen year-old Joey Kindregan—truly knows what our kids face.

STEPS YOU COULD TAKE TO ACCELERATE RESEARCH

The question I am most often asked is, "What do you still need to accomplish in order to find a cure or treatment for A-T?" My answer always includes the same four themes: "translational research," "physicians willing and able to do clinical research," "new tools and technology," and "a more involved NIH." Please allow me now to explain four steps that you could take to help us in these areas:

Encourage the NIH to support translational research on diseases like A-T

Even though my small organization, the A-T Children's Project, has been able to support basic research conducted by academic laboratories looking at the biological defect and the role of the A-T gene/protein in cells, it has been exceedingly difficult for us to persuade clinical researchers to conduct what is referred to as "translational research."

Translational research seeks to apply the findings from basic research in a clinical setting. This type of research is typically done by pharmaceutical companies rather than by academics, and I am sure you can imagine how difficult it is for us to persuade drug companies to devote resources to a rare disease that represents a miniscule market potential. Therefore, we really need the help of the National Institutes of Health (NIH) in encouraging this kind of applied research on A-T, even though it is a rare disease.

I know that from time to time, I have heard discussion in your hearings about why there is a need for an intramural program at the NIH. The best reason I have heard is so that research can be done there that cannot be done anywhere else. It would be great if you could encourage the NIH's intramural clinical researchers to focus more attention on diseases like A-T. We cannot help hoping that the new clinical center being built on the NIH campus might undertake some clinical research projects involving A-T.

Provide for physicians to do more clinical research

Everyone who wants to find a treatment for a disease, and especially families affected by pediatric neurological diseases, want to see more physicians who are able to do clinical research. But over the last few years, we have found that the time clinicians have for doing clinical research on diseases like A-T at leading medical centers—even at teaching hospitals—is quickly shrinking.

We need your committee to allocate more funds so that excellent physicians with the talent to contribute as researchers can do so. Some tactics tested by the NIH have already helped, such as repaying medical school loans for physicians who agree to go into research, but we need you to encourage the development of more solutions to this problem. Important strides were recently made on this front through the passage of the Clinical Research legislation in the last Congress, but it is important that this aspect of our biomedical research infrastructure be monitored carefully.

Encourage the development of new tools for "downstream" biological research

The progress in creating new tools to accelerate research has not been fast enough for families like mine who watch our kids slip a little further from us each day. Keep in mind that researchers found the gene that causes A-T over six years ago but there is still not a single treatment available. Since then, the progress in understanding the function and role of that gene in the human body has been substantial but still not adequate. Just as breakthrough technologies such as automated DNA sequencers and polymerase chain-reaction (PCR) have super-charged the hunts for disease genes, we need new high-throughput methods and tools for elucidating the protein pathways directed by those genes in order to know what to do about the genetic defect.

With your direction, the NIH and other government agencies could scale-up their efforts and be more innovative in encouraging scientists and engineers with inventive skills to create these technologies, even when they have risky ideas for which venture capital funding may not be possible or when they have approaches that would benefit only rare diseases with limited markets.

Support greater interaction between NIH program directors and the research and disease community

At each NIH institute, a different program director typically oversees each specific area of research. This individual plays a critical role in implementing the research priorities and strategic plans that are conceived by NIH leaders and Congress. Program directors must therefore represent first-rate talent and must be given ample support.

My organization has found that when program directors are more aware of the research activities on any particular disease, announced requests for proposals are more appropriate, redundant research projects are minimized, and fewer scientific opportunities are missed. In other words: the NIH's funds are stretched much farther. These individuals tend to be extremely dedicated to keeping up on developments in their scientific areas, comparing notes with disease advocate groups, and providing guidance to investigators preparing grant proposals. But they are also spread very thin, and their travel budgets to meet with researchers and patients are often restricted.

More program directors are needed, and their proactive involvement in the research community needs to be encouraged. While allocating funds to this "administrative expense" instead of toward direct research grants may at first glance seem wasteful to you, in our experience, having highly-qualified program directors with more time and resources to keep on top of their areas would be tremendously worthwhile. In addition, in order to encourage more translational research, we feel it would be valuable for the NIH to take steps to recruit more program directors who have clinical experience.

Mr. Chairman and Members of the Committee, as you can see, none of the steps I have suggested requires you to set aside funds specifically for my sons' disease. And yet, I am confident that these steps would ultimately accelerate research progress on A-T as well as many other diseases.

I would be happy to answer any questions you may have, and I would also be eager to work with your staff to develop legislative language for insertion in the appropriations bill to cover these areas of concern.

Thank you.

Senator HARKIN. Thank you very much, Mr. Affleck.

Joe, you have got a good friend there. He says he is going to help you get your next belt.

Mr. Margus, welcome also. I understand you also have a couple of children with A-T. Is that right?

Mr. MARGUS. Yes. Joe knows them. They are Jarrett and Quinn. Quinn is 10 and Jarrett is 12. They also have A-T.

Senator HARKIN. Is Joe's mother here? Do I understand that? Hi, mom.

Ms. KINDREGAN. I am not allowed to speak.

Senator HARKIN. You are not allowed to speak? You are allowed to speak if you would like to speak.

Mr. AFFLECK. It was Joe that told her she was not allowed to speak.

Senator HARKIN. Well, Joe, where are you from?

Mr. KINDREGAN. Springfield, Virginia.

Senator HARKIN. Oh, Springfield, Virginia. Oh, not too far from here.

How did you two meet? At Dulles?

Mr. KINDREGAN. Yes.

Mr. AFFLECK. Yes. I was shooting "Forces of Nature" and we were at Dulles and Joe was heckling me.

Mr. AFFLECK. I told him to clam up and we almost got in a fist fight. It was an awkward thing, but then we made up.

Remember that?

Mr. KINDREGAN. Yes.

Senator HARKIN. So, Joe, you went to the premiere of the movie, "Pearl Harbor"?

Mr. KINDREGAN. Yes.

Senator HARKIN. That is pretty exciting. Did you see him in "Good Will Hunting" also?

Mr. KINDREGAN. Yes.

Mr. AFFLECK. Did your mom let you see that movie? The 143 swear words in that movie.

Some of the benefits of being in a wheelchair is mom lets you watch the R-rated movies.

Mr. KINDREGAN. Some of them.

Senator HARKIN. Well, Joe, we are really proud that you are here and proud you brought your friend Ben here. If you had anything that you wanted us to know or if you want to say anything, by gosh, the floor is yours.

Mr. KINDREGAN. No.

Senator HARKIN. Well, okay. Did Ben say it all for you? Pretty much.

Mr. KINDREGAN. Yes.

Senator HARKIN. Good. Well, we thank you for being here, Joe, and I can assure you that these people who are sitting down the table from you here, all these scientists and Dr. Collins and Dr. Rich and Dr. Needleman and Dr. Murray, I know that every day they go to work they think about you and they think about the people out there that are going to be helped by the research and the investment of time and their lives that they have done. This is who they think about. I do not know them all. Some of them I know better than others, but I know that this is what they are about. I have a great deal of faith in their abilities to get the research done and the interventions and cures that we need for a lot of these illnesses and especially for the one that is affecting you, A-T.

I was not aware of it either until you came here today. Believe me, I am now aware, and I am going to be asking more and more questions of NIH of what they are doing to make sure that we get more research into this area.

But I just turn to all of you, all the scientists who are here. When I think of Joe and A-T—I do not know if any of you are fa-

miliar with A-T. I sure was not, but Dr. Collins is. Tell me what we are here for this morning in terms of the human genome project and finishing it and moving ahead with it. Tie that in with Joe Kindregan. How does that work for Joe?

Dr. COLLINS. Well, I will take a try at that. I think Joe's situation is emblematic of hundreds of thousands of other folks who have disorders that may not make the headlines but which are very real every day for them and their families.

The genome project has, I think, a view that every gene matters and therefore every disorder matters. In fact, the ability to look at the whole thing is one of the best antidotes against that tendency to only focus on common illnesses. When I mentioned 50 disease genes had been found in the last couple of years, most of those are for relatively rare conditions like A-T. Wearing my research hat, I was honored to be part of the team that found the A-T gene about 5 years ago, and part of the team that helped develop this mouse model that Brad Margus referred to.

Yet, now with those powerful tools we are poised to unravel at the biochemical level why the single gene that is not working in that condition causes the havoc that it does. We still have several steps to traverse. That means understanding this particular protein. It is a very large, complicated protein. What is it normally there for and why, when it is not doing its job, does this wide array of problems occur, the immune system, the neurologic system, the risk of cancer?

I would give Mr. Margus a huge amount of credit for the way in which his A-T Children's Project has worked very effectively with NIH—and over the years Brad and I have grown to be good friends—in a very productive, effective partnership to try to get the best science applied to this problem. Most of the scientists working on A-T today had not heard of it until somebody like Brad came along and invited them to a conference.

So, I think it is fair to say this relatively rare condition has now become the focus of a lot of scientific interest, and it turns out that while inherited alterations in this gene are relatively uncommon and afflict people like Joe, that you can acquire a misspelling in this gene during your lifetime. That plays a significant role in the risk of things like lymphoma and leukemia. Once again, the study of a rare condition sheds light on a much broader array of issues, in this case cancer, and that in turn draws more people into the area of interest.

But what we really need to understand now is what does this protein do, what other proteins does it interact with, and how can you compensate for it not working in a certain circumstance, like what Joe lives with every day. I think the tools to do that that are now marshaled, that attack the problem, are profoundly more powerful than they were even 5 years ago. But complexity is still the norm in human biology, and to unravel all that in the direction of an actual cure takes a lot of steps, a lot of support, a lot of good science.

Senator HARKIN. But can I tell Joe, sitting here today, that there are more people working on unraveling this mystery than there was a year ago or 2 years ago?

Dr. COLLINS. Absolutely, and I think Brad would agree with that. We are getting to the point now where there may be more people working on A-T than have the disease, and I think that is great.

Senator HARKIN. That is good.

Mr. AFFLECK. Correct me if I am wrong. My understanding this is a disease which falls under a much, much larger umbrella, the set of diseases which all could benefit from stem cell research. These cells have been demonstrated, as I am sure you know, Senator, when extracted and then reinserted into brains and spinal cords of mice, to go to the place in the brain that is deteriorating and regrow in the brain and to regrow some spinal tissue. So, I think that is very important. I think A-T would benefit enormously at least from that research.

And the Federal Government plays an important role in that. Being a Democrat, of course, I am a great fan of regulation. So, I think it is research that needs to be regulated, and I think it is one that needs to be supported by the Federal Government. And I admire and appreciate your bipartisan support of that.

Senator HARKIN. Thank you very much, Mr. Affleck.

I am going to turn to Senator Landrieu. When Senator Landrieu gets finished, I am going to come back to a question I want you to ponder. I want you to tie together stem cell research and genomic research for me.

Senator Landrieu, welcome. Again, Senator Landrieu represents a number of highly respected national research institutions in her State of Louisiana.

Senator LANDRIEU. Thank you, Mr. Chairman. Let me begin by thanking you for your focus on this important work. I can see from the numbers of people here and from the numbers of people who are tuned into this hearing that it is a vitally important issue for our Nation. There are many parents and doctors and communities and children who are looking very carefully at the policies that are laid out here to provide the kind of hope and excitement that has been talked about this morning. So, I want to thank all of you and thank you, Mr. Chairman, for keeping us focused so that we can take the steps every week and every year here in Congress whether through policies or appropriations to further this important work.

Joe, I want to thank you so much for being so brave and so wonderful to be such a good example to all of us to come here to Washington, not the easiest place to get to and not the most comfortable place sometimes to testify, but for your braveness, being an example to children everywhere and to adults about the ways that you can become a great advocate so we can continue to do the kind of work that we do. To you, Ben, and to you, Mr. Margus, for your stepping out.

Brad, I was not here for your opening statement. But what could we do immediately to help you as you have done so successfully to bring this particular disease to the forefront? What could we do in Congress to help sort of multiply your efforts in a faster, more direct way so that we can really build on the great work that Joe has done and that Ben has done?

There are many larger policy issues that this Congress is going to grapple with and there will be some controversies about these issues of morality and responsibility and liability, et cetera. But

there are some things that should not at all be controversial about the Federal Government stepping up to help you and these other “orphan” diseases to try to expedite the good results. Could you just comment maybe briefly? I think the chairman and I would both be interested.

Mr. MARGUS. I would love to give you a nice example of something that is on our wish list that would not just benefit A-T but would benefit a lot of diseases.

When we first started the A-T Children’s Project, my kids were diagnosed and there was really nothing going on, to speak of, in A-T research. We reached out to do everything that had been done for more common diseases. So, we said, why can we not get our gene if cystic fibrosis has theirs? Why can we not do mouse models or other animal models and other organisms like *Drosophila* and fruit flies? But there were things that were already being done for the more common diseases, and we said, we deserve to have that for ours. That was kind of my spiel with NIH and if I could run into any of you.

Today a lot of what needed to be done has been done, and a lot of the obstacles we run into are the same ones that are for more common diseases. I will not dig into all the more controversial ones, but the one that is really clear Dr. Collins mentioned. We have been really fortunate in that our disease gene—the protein that is missing in Joe because the gene is misspelled is a protein that plays a real critical role in cell biology. It is involved in cancer. The protein actually interacts with another protein called P53 that has been found to be mutated or misspelled in the majority of all tumors. It also interacts with another gene or protein called BRCA-1 that is involved with breast cancer. So, it is really this hot, popular protein in cell biology, even though most of you have never heard of A-T. Because of that, there are a lot of great, first-class scientists, basic biologists working on the mechanism of the A-T protein and what it is doing.

The frustrating thing for parents like me and for kids like Joe is that even though all this great science is being done downstream from finding the gene—we found the gene 6 years ago—it is not a treatment. If you look at how long it might take to figure out the complete biological pathway of how that one gene causes all these symptoms, it could be 20 or 30 years, maybe longer.

If you look at the history of medical discovery and most of the drugs that the drug companies are selling, I hate to say it, but they do not develop them by this rational approach of figuring it all out. Most of them have been chance discoveries or discoveries that came about from looking for one thing and something else became useful.

That may all change now because the tools have really improved. The human genome project will change that tremendously and there are a lot of other technologies coming out that should accelerate molecular biology.

But what we really need is ways to apply it. So, how can we get, even before we have all the answers, to something that we can treat our kids with? I think one of the real obstacles that maybe you can help us with is to get more clinicians, doctors involved in research. We have some great scientists working on the basic cell biology, but we do not have many doctors who are trained neurolo-

gists and trained immunologists who are able or willing to go into research.

Part of the reason is what Ben mentioned in his testimony; that is, there are a lot of pressures on doctors today with managed care and so on. Doctors have less and less time to spend doing research. But we really need to find a way to find really good physicians who can translate or take the basic research and apply it in the clinic.

If A-T were a disease like it is but kids die a month after they were diagnosed, then you would be going nuts doing everything you could just applying things just the way they treat really aggressive cancers, but because it is kind of over time most of the time, scientists tell us, wait till we have the answers completely figured out on the biology. And we really cannot wait for that. What we need is more physicians who are also able to go into research.

I know that the NIH has done some things recently, repaying student loans for med school and things like that, to encourage physicians, doctors to go into research.

Senator LANDRIEU. Mr. Chairman, could I follow up with one question on this? Because I think you and I would be particularly interested. Because children cannot wait and neither can parents, I would like Dr. Collins or Dr. Murray to follow up, adding to that some specific things that we could take action on now that has limited or no controversy associated with it, that we could expedite the treatment and hope for Joe and for his family and for Mr. Margus and his family. Is there something that you could add to the testimony that could help us to really focus in this budget cycle on what could be done along those lines?

Mr. MARGUS. You have a really great, huge clinical center being built on the NIH campus I noticed. Obviously, there is a big push now to do more clinical research. We just hope some of that will be done on A-T.

Senator LANDRIEU. Anybody for the record?

Dr. COLLINS. Well, I think your question is very appropriate. Certainly for myself as a physician, I have been deeply concerned to watch, over the last 20 years, the number of physicians doing clinical research gradually decline. That decline got quite precipitous a few years ago, particularly because with the advent of managed care, a physician who wanted to do clinical research in a medical center out in one of our great universities increasingly was under pressure not to do the research but to be out there in the clinic or on the ward seeing patients and getting reimbursements because all the academic centers were struggling so much. This is a big part of the dynamic, the way in which our change in reimbursement has placed academic centers in a position of basically providing disincentives for physicians to do research. And that issue is far from resolved.

NIH has made a number of bold steps I think to try to provide some backstopping of those who would like to do this. And I think it has, to some degree, turned the tide so that that steady decline has begun to reverse, but we are still way behind where we need to be.

Certainly I am the first to agree, genomics is a wonderful basic science, but it does not matter a whole lot if it does not end up benefiting individuals, people with diseases. That translational process

requires people who understand the practice of medicine, those clinical researchers, and we do not have enough of them.

The loan repayment program may be a way to get rid of one of the financial disincentives to people who come out of medical school already owing \$100,000 or more. Being a clinical researcher will not make you rich. You will be driving a 10-year-old car when your friends out there are getting their second Mercedes of the year. It is not the sort of thing that somebody without a great deal of personal commitment is going to be able to do. Yet, there are ways I think that we could make that financial situation a little less onerous and provide some encouragement to those who do want to do this, that they do not have to be forced into just delivering patient care for reimbursement all the time the way their medical centers often ask.

I would be glad to provide some more information for the record about the programs that NIH has already put in place and some ideas about other things that we could do that are even more ambitious.

Senator LANDRIEU. That was very helpful and I appreciate it.
[The information follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES,
NATIONAL INSTITUTES OF HEALTH,
NATIONAL HUMAN GENOME RESEARCH INSTITUTE,
Bethesda, MD, August 7, 2001.

Hon. TOM HARKIN,
Chairman, Subcommittee on Labor, Health and Human Services, Education, and Related Agencies, Washington, DC.

DEAR SENATOR HARKIN: It was a pleasure to testify before your committee on July 11, 2001. During that hearing Senator Landrieu asked about efforts by the National Institutes of Health to promote clinical research. Below is a description of some of the activities currently underway at the NIH to promote clinical research.

In 1999, following a detailed analysis by a subcommittee of the Advisory Committee to the NIH Director, the NIH launched three clinical research programs: the Clinical Research Curriculum Award (K30), the Mentored Patient-Oriented Career Development Award (K23) and the Mid-Career Investigator in Patient-Oriented Research Award (K24). The K30 program provides support to institutions for the development and conduct of didactic courses for clinical investigators to enhance their fundamental knowledge in study design, biostatistic, ethical and regulatory issues with clinical trials. The NIH has awarded a total of 55 K30 awards. The K23 program provides didactic training and mentored research experience for investigators who are interested in doing patient-oriented research. Since their inception, the NIH has funded 279 K23 awards. The K24 program provides protected research time and mentoring opportunities to mid-career investigators by relieving them of patient care and administrative responsibilities. The NIH has awarded 158 K24 awards since 1999. These programs have been successful and continue to attract enthusiastic response from the clinical research community.

The NIH also sponsors a loan repayment plan (LRP) which assist in increased participation in clinical research by young scientists. The LRPs pay a maximum of \$35,000 a year toward participants' outstanding eligible educational debts. In return, participants must sign a contract agreeing to conduct qualified research activities as NIH employees. Participants in the LRP may apply for additional, 1-year renewal contracts and continue to receive loan repayment benefits. There are four different types of LRPs:

- The NIH AIDS Research Loan Repayment Program (AIDS-LRP) is designed to attract highly qualified physicians, nurses, and scientists to HIV/AIDS research and research training.
- The NIH Clinical Research Loan Repayment Program (CR-LRP) is designed to recruit highly qualified physicians, nurses, and scientists from disadvantaged backgrounds to serve as clinical researchers.
- The NIH General Research Loan Repayment Program (General-LRP) is designed to attract highly qualified physicians, nurses, and scientists to conduct research at the NIH.

—The NIH General Research Loan Repayment Program for ACGME Fellows (ACGME-LRP) is a pilot initiative of \$5,000 per year in loan repayment currently available to fellows employed by the NIH in subspecialty and residency training programs accredited by the Accreditation Council for Graduate Medical Education (ACGME). Qualifying fellows must hold a three year appointment at the NIH beginning July 2000, 2001, or 2002.

In 2000 Congress passed the Clinical Research Enhancement Act as part of the Public Health Improvement Act (H.R. 2498). The legislation instructs the director of NIH to expand the agency's role in clinical research by awarding grants for the establishment of new General Clinical Research Centers (GCRCs), creating new enhancement awards, and expanding the NIH loan repayment program for clinical researchers to include extramural investigators.

In addition to these programs, the NIH is currently developing a program announcement to provide support to institutions to develop degree-granting programs in clinical research. It is anticipated that the National Center for Research Resources will take the lead in this initiative and launch it in fiscal year 2002. We believe that these new programs, along with the existing clinical career development awards, e.g., K08, K12, etc, have gone a long way in addressing the need for training more qualified physician scientists.

I hope this gives you an idea of the programs the NIH is working on with regard to clinical research. Please let me know if you have any further questions.

Sincerely,

FRANCIS S. COLLINS, M.D., PH.D.,
Director.

Senator LANDRIEU. Dr. Needleman.

Dr. NEEDLEMAN. Senator, it occurs to me—what is the distance between getting a drug to a patient and the discoveries and what are some of the limitations? So, it is really extremely important on the genomic end to understand all the multiple implications of the expressed genes. The human genome is like the Lewis and Clark trip. It did not tell us what the country was. It was the map. We have to figure it out.

I will go to the back end. Maybe the NIH ought to think about the development of genetic or biological markers that enable assessment of clinical trials so clinical trials could be done in patient populations that are diagnostic and help invest the science because the regulatory environment is not yet built for genetic markers and biomarkers. You might have to do trials now till mortality. So, if you want to change a chronic disease that slowly evolves, then I think a wise investment, both in industry and in fundamental science, in how to use genetic markers to see the progression of the disease and the maintenance of its factors and the proofs that are necessary to change the regulatory environment, then you could truncate years off the process between a great idea, a lead molecule, and when it is approved for use. No sacrifice of safety. But we need a revolution in genetic and biological markers.

Senator LANDRIEU. Thank you.

Dr. MURRAY. I would like to also follow up on Dr. Collins' comments. I do think this question about the clinical research is one that you do need to address right now. We are going to lose a whole generation of physician scientists soon if we are not careful. When I see young faculty coming into our own university, it is impossible for them to be both researchers and clinicians, the way Dr. Collins and myself and others were when we started out 15 or 20 years ago. The financial demands now on the clinicians force them to spend 100 percent of their time seeing patients, with no opportunity for them to begin these kinds of research projects, often that come directly from the clinic. Just as Mr. Affleck met Joe here and

became interested and a friend of his, that is how clinicians get interested in problems and then take them into the laboratory. If the clinicians, especially beginning ones, do not have the time and the resources, the protected time, to do that, they will not be able to begin and start these projects that can lead to the kinds of successes that we are hearing today. So, I think you need to support through things like loan repayment, through medical scientist training programs, through the full reimbursement of the clinical people working in academic centers to allow them opportunities to do this.

Senator HARKIN. I look forward to working with you on this, Senator Landrieu, to make sure that we can get those various things implemented. This has bedeviled us for a few years now and we have not worked our way out of it yet. But we really do. The academic health centers have—well, I would not say they have been forgotten, but they have been kind of pushed aside in a number of ways, and we need to focus more on them and to provide the kind of financial support to the academic health centers whereby people do not have to see patients day after day after day, where they can go back in the lab. But I tell you, it is a real problem and we need your best thoughts on how to solve it.

The tax thing, the forgiveness of the loans is one thing. The other thing is also to make sure the academic health centers get the kind of financial support they need to continue this research. That comes right from here, and it has to do with priorities and what we are spending our money on in this country and things like that. With the budget constraints we have right now, it is going to be tough to get that done. But it has to be done and we are going to do everything we can on this subcommittee to provide those funds.

I just had one last question. Then we need to wrap it up. But I asked, before Senator Landrieu asked her questions, you to tie together for me stem cell research and genomic research. We have the human genome project. We have done the research. You, Francis, talked about how we have got to keep going forward on it. Now we have got the whole area of stem cell research that hopefully we are going to get a favorable decision on here soon. Tie the two together. Where do they meet? How do they support one another?

Dr. MURRAY. One example that I think of that will really bring this together really well. Unfortunately for the rest of you, it comes from again Iowa. But 10 days ago, I went to a party that was a celebration for a friend of my daughter who is a 15-year-old girl who a year ago exactly on Sunday had received a kidney transplant. Her family has a very unusual and as-yet undefined genetic immunologic disorder. She has an older brother with diabetes who would love to have a cure for that. She received a kidney transplant a year ago from her father.

Her father turns out actually to be a pediatric surgeon and loves his daughter just as much as mom loves her son and all of us love our own children. And he made a tremendous sacrifice for her to give her this kidney.

The genome project holds out the prospect for their particular disorder to be identified and studied in the same way that A-T is in many of the other disorders that we have heard about today.

But even once that has happened, we need to convert that information into something that is useful for that particular family. Certainly stem cell research and related projects hold out the prospect of fathers in the future not having to give up their own kidneys or organs to their children or someone else doing that, but to be able to use those stem cells to generate a kidney, an artificial organ on the outside, which will now be compatible with that child that she could receive herself. And it will be through those kinds of findings we can do it.

Senator HARKIN. Very good. Anything else? Does anyone want to add anything?

Mr. MARGUS. I have a good example you might be interested in. We have 18 mice that do not have the gene and therefore have the same disease the kids have. We have, obviously, been excited that stem cells could reseed the brains of these mice. So, if you inject in those stem cells that have not decided what kind of cells they are going to become yet and migrate to different areas, hopefully they will have an affinity for the areas that are damaged and that is where they will go and produce growth factors and become wired.

The problem is it is a very exciting field that everyone has hopped on, but it is really an early stage of the field. There is not a lot known about what those stem cells really do. So, one thing that a lot of stem cell researchers are doing right now is they are looking at the genes that are turned on or off in the environment inside the brain at different stages of life. So, when you stick stem cells in an elderly person who has a stroke, they may not do very much, and if you stick those stem cells into a baby mouse, these stem cells seem to go to the right place. Well, there must be other things turned on in there at that stage of life that direct those stem cells.

So, one of the things a lot of researchers are doing is using different technologies to find out which genes are turned on and which ones are off so that they can really guide and control those stem cells.

Now, once you have used those technologies to pull out genes that are involved at different stages, you have to know what those genes are. At that point, you can get on the Internet today and probably find that gene in the human genome project's data.

The reason I know this is because I explain it to families, not just mine, but my wife, a lot of other families. We are all hoping that stem cells may have great promise. But the thing I warn them of is that what if it kind of works but not great. If it worked perfectly, then, hurray, we have got a home run, and we do not care if we know how those stem cells work. But chances are it will almost work but not quite, and if you do not know exactly what is going on, you cannot tweak it. You cannot really perfect it. And the way to know what is going on is by knowing those genes that are turned on and off. So, the genome project and genetics really does enlighten and elucidate what is going on when stem cells are doing their thing.

Senator HARKIN. Thank you very much, Mr. Margus.
Does anyone else have anything to add?

Dr. NEEDLEMAN. You do not know the traffic cops for stem cells, so you really have to use genomics and proteins to say when am I going to differentiate into a heart cell or a brain cell. So, you really need a lot of fundamental discoveries yet. It is not just taking a cell and growing it for an organ, but we can take control some day of the direction of the cells even in the body. So, you really need genomics and fundamental studies to understand the traffic cops and when it is on and when it off. It is like your red light.

Dr. RICH. Just one thing, reflecting on what Dr. Collins said earlier, is that even though we are probably 99 percent similar at our DNA level to other organisms, you can tell that that little 1 percent or less than 1 percent is highly variable. I am not much like Francis. He has a lot more hair than I do for one thing.

But that means that there is a lot of variation in stem cells potentially, and we need to have lots of stem cells to track that variation. So, in a sense we need to have the variation in the stem cell resource that we do in people to help provide this information and decide what is the traffic cop and how it works.

Dr. COLLINS. Senator, I think this group has described it extremely well.

It always comes as a surprise to those who hear it for the first time that we have the same instruction book, the same set of DNA in a liver cell or a brain cell or a cell in the islet of the pancreas or a cell in the muscle. They all have that same instruction book, and one of the most amazing developments of the last 3 or 4 years is the recognition of the plasticity that seems to exist of how cells can reprogram themselves from being a bone marrow cell to a heart muscle cell, as has recently been demonstrated, or a variety of other such examples.

That all has to come about because the genome, that set of instructions, has the ability to be modulated down different pathways, and the understanding of that is critical to our medical applications of this really surprising set of new biological insights.

Senator HARKIN. Well, thank you all very much. This has been terribly enlightening, and it has been great. I compliment you all for moving these frontiers of knowledge. This committee will do what it can to continue to provide the funding, and hopefully we can get the money to do that.

Mr. Margus, thank you for being here. Mr. Affleck. Joe, do you have any last thing you want to say to all these scientists?

Mr. KINDREGAN. No.

Senator HARKIN. How about I say for it for you? Hurry up.

CONCLUSION OF HEARING

Thank you all very much for being here, that concludes our hearing.

[Whereupon, at 11:15 a.m., Wednesday, July 11, the hearing was concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]