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Session 4PD
The Human Genome Project: What Is It and How Can It Benefit Both the Health and the Life Insurance Industries?

Track: Product Development/Futurism

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Panelists: J. ALEXANDER LOWDEN†
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Summary: An expert panel describes the goals and current progress of the Human Genome Project (HGP). The discussion covers the implications of the current research and explores the impact on public health. The presentation addresses how the research affects the life insurance industry.

MR. PAUL A. SCHUSTER: Phil Smalley is an internal medicine specialist with 10 years of insurance medicine experience. He's vice president and medical director of RGA International, Ltd. Phil has also worked as a consultant for a multitude of direct insurance companies. Phil received his medical degree from the University of Toronto in 1986. He went on to complete his specialty training in internal medicine at the Royal College at the University of Toronto in 1990. Phil is a recognized lecturer, with post-graduate training in education and leadership. Following his training, Phil practiced and taught medicine at Wellesley Hospital, which is the University of Toronto teaching hospital.

DR. PHILIP S. SMALLEY: I presented to the Canadian Institute of Actuaries on genetic topics last fall. Genetics is a topic that is really going to impact pricing, the way we underwrite, for the future. The Human Genome Project: I'm going to be talking a little bit more about some of the basics of genetics because you do have to understand some of the principles to understand where we're going from here. I'm going to talk about the genetics of aging, some of the diseases that are associated with certain genetic defects, but also about some of the common diseases that we're faced with in day-to-day underwriting.

Paul mentioned the importance of not just looking at genetic defects but also at some of the proteins that are causing them. I think we will get more benefit in the insurance industry by understanding some of the therapeutics that are being designed because of our understanding of genetics. There has been a lot of press

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recently on genetic screening of asymptomatic persons. So I'm going to stress a lot about the genetic therapeutics and then try to provide a practical perspective on how this might affect some of your pricing. Then I'm going to pass it over to Sandy. Dr. Sandy Lowden, a geneticist, will talk a little bit more about the Human Genome Project: where it started, where it's going, and explain what the research means for underwriting and pricing as well.

Now I wish underwriting and pricing were this easy. I like this Web site (http://www.deathclock.com). All you have to do is put in the applicant's date of birth (this is my information), click here, and you find out that I will die on Saturday, February 19, 2033. But we know it's not really that easy. I'm interested in the statistics behind this because I hope I live longer than that.

There's one study by Christakis that actually showed how bad physicians are at predicting mortality in depth. This is a study in which they asked doctors of people who had very significant diseases how long they thought their patients would live and then studied how long they actually lived.

I'm not sure how many people are in this room whose companies pay out insurance policies like accelerated death benefits or terminal illness benefits, but if there's a very good chance that the person will pass away within a year, the death benefit will be paid in advance. Well, you can see the potential for lawsuits if you decline those claims for the loss of income if you paid them out and they last too long. So I think our role here is to use evidence-based risk assessing, appraise the literature critically, and look at some of these medical studies that we're presenting for you today to get more of our mortality assumptions and more of our pricing on this line to benefit both the applicants and our stockholders.

Looking at differences in longevity around the world is interesting when we start talking about genetics because we know there are a lot of reasons for this variance of mortality that we see from country to country. This is a study that equated or calculated the mortality of the United States at 100% mortality and then compared that to different countries around the world. We can see, and I think everybody in this room is well aware, that the Japanese and people from Iceland live quite long with very good mortality experiences. But other countries around the world actually have higher mortality, and it's interesting to postulate why.

If we understand or try to evaluate the genetic and the environmental factors, and I think if we understand these principles and study them further, we're hoping that we'll improve quality and quantity of life for the future, not just overall mortality. If we look at even some of the diseases that make up the mortality in each of the countries, we can see wide ranges in some of the common causes of death claims, living benefit claims, and health claims that you're seeing from all of these different diseases from country to country. Again, this is a mix of nature and nurture, which I'm going to be speaking more about throughout my presentation.

So is it really all in our environment? Is it healthy lifestyle—out fishing, relaxing, or stressed out in a downtown center? Is it our diet? When you're looking at differences in mortality around the world, I think we need to look at all these

components, but we also need to look at reasons in our genes. Yes, obesity is a problem in North America, but I don't think that's the kind of genes that we're talking about today.

So what happens when one moves? I don't know how many people in this room are doing business offshore or are looking at ex-patriates who have moved from one country to another. You take your genes with you. The Japanese who move to the U.K. have higher blood pressure values and higher cholesterol values compared to the Japanese who live in Japan. The heart disease rate in Chinese who live in New York is higher than the heart disease rate of Chinese who live in China. Looking at hypertension in South Africa, the Zulu people who live in rural areas have a prevalence of hypertension of around 2 to 8%. When these Zulu people move into the downtown core, their prevalence of hypertension goes up to about 25%. So you can see that it's not just the genetics. Environmental influences are extremely important when we look at the whole picture.

Another example of this is nature versus nurture. If we look at the rates of colon cancer of Japanese versus Americans, we can see there's about a tenfold difference—it's much more common in America. But when Japanese move to Hawaii, their rates of colon cancer, once they start adopting the American diet—McDonald's, etcetera—their colon cancer rates are somewhere between the Japanese rate and the American rate. But for the second generation of Japanese living in Hawaii, rates of colon cancer equal the American rate. So again, this underscores the importance of environmental and diet factors, not just genetics.

I've heard a number of geneticists say that most diseases that we look at in medicine do have some genetic basis, so I'm not saying that genes don't play a role. I'm just saying that there are other factors we need to look at when we're looking at this whole problem or this whole area of medicine.

We know that there are 23 different chromosomes inside our cells. They're inside the nuclei, and these chromosomes are made up of 30 billion base pairs. Those base pairs are those Gs, As, Ts and Cs, and they come together to give you a code that translates out towards these proteins. These bases come together to give genes. The genes are the important areas of code inside these chromosomes. They code for the various proteins that make us healthy or make us sick. So it's this whole process of the DNA that's being translated from DNA molecules in the nucleus. It's translated to ribonucleic acid (RNA), similar to DNA.

The important thing here is what Paul Schuster has mentioned, the proteins. It's when this RNA is translated, based on the code here, to make a protein. If one of these letters has a mistake in it, that amino acid is going to have an error in that protein, and then the protein will not function properly. It will cause disease, or it will actually, with its deficiency, end up causing other problems as well.

So, what is a mutation? It's really a change in one of those base pairs. You can have a mutation that you inherited from your parents. Therefore, it came in your gametes, the sperm and egg coming together. Therefore, that genetic mutation is actually in every cell of your body. We receive many mutations from our parents.

This is one of the problems we think about when we look at the possibility of genetic screening in the future because we've all got these in our bodies. We also can acquire genetic mutations. That's when you get sun damage or viral damage or chemical damage that can damage DNA and cause a mutation in a particular cell line. That cell could then possibly become cancerous or cause some other disease.

But not all mutations cause disease. This is extremely important to remember. Actually, evolution is dependent on genetic variation. Some diseases actually protect a population. For example, the mutation that causes sickle cell disease or trait actually protects those who carry it from malaria. Interesting as well, 1% of the population is immune to HIV disease because of a genetic defect in one of the receptors on one of the white cells. Also, just because you are carrying a genetic defect, which Dr. Lowden's going to talk more about, doesn't mean you're going to develop disease. That risk of developing disease is what we call penetrance, and that's a real problem we have in the predictability of these tests in an asymptomatic population.

Looking at the genetics of longevity overall, we've already found some longevity genes in yeast, flies, and worms. They say that about a quarter of the variation in mortality around the world is indeed due to genetic factors. That means that the majority of some of the variations shown earlier are due to other issues, the lifestyle factors. I think that's still another area in which we're going to get a lot more improvement in morbidity and mortality in the future as we continue to work on trying to get people to live healthy lifestyles. There was a study in Japan, in Okinawa, in which they looked at people who had lived more than a hundred years. They looked at their genetic makeup, and they did indeed find that people who had lived more than a hundred years had a certain common type of gene in their HLA parameters. So even in the humans we're looking at, there are some genes that might lead us towards longer life expectancy.

Geneticists have now been able to extend the life expectancy in some worms, an increase of up to five times, by changing some of the genetics in some of these animals. There is an ethical implication to this, but again, it shows that genes do play a role in our life expectancy. There are a number of different genetic defects that are associated with a lot of diseases, and we're not going to go through these in a lot of detail. I just want to touch on some of these diseases for you today because I think they have implications for our mortality pricing for the future.

There's one syndrome called Werner's Syndrome. It's quite rare, but it does underscore the importance that genes play in aging. There's a genetic defect on Chromosome 8 that causes the body to age at an accelerated rate after adolescence. They get the degenerative problems. They get heart disease in an earlier stage. They're more at risk for cancers. So yes, there are some genetic defects that predispose premature aging.

You've all heard about a lot of press around Huntington's Disease. It's a neurological abnormality in the brain, and we found the genetic defect that causes this disease. Little bits of DNA at the end of the chromosome are repeated. If you have a lot of these repeats, it's almost certain that you will develop Huntington's

Disease at some point in your life. But again, this is not black and white. This is one area in which I think medical technology might help us actually place more business on the books than in the past. Why? Looking at the number of these CAG repeats, the more you have, the earlier you start developing this disease. So maybe by knowing the genetics of somebody with Huntington's Disease—it's possible that we might have declined some of these diseases in the past, but now we might actually be able to make a pricing decision—and this is the same theme with other technologies. So I don't think we need to be afraid of this genetic testing in people with documented disease. I think it can help us to underwrite if we have somebody in that type of a situation.

Also there are many genetic defects associated with cancer. A number of genetic defects cause cancer in a number of different ways. Again, these are not black and white. There are actually a hundred different mutations in the breast cancer gene, but they are important. How many companies here are dealing with critical illness, dread disease, where you actually pay on incidence of disease? This is important because there was a claim that I saw in Australia that involved a woman who had a positive family history for breast cancer, was rated for the dread disease, the critical illness, and declared it, and the policy went into force. She then went ahead and saw her oncologist, and indeed, she was found to be carrying the abnormal gene. Now what oncologists in America and Canada are suggesting is that some women who have strong positive family histories for breast cancer and carry the abnormal gene have both breasts and both ovaries removed, drastic surgery for someone who is just carrying a genetic predisposition towards a disease. So this woman in Australia had the surgery done and then claimed for a critical illness for breast cancer just because she had a genetic predisposition to the disease. The courts deemed that the policy had to be paid because of the spirit of the policy. So you can see the potential for how it could impact our industry as we move forward.

Looking at the genetics of heart disease, there are about 50 different genes known to cause different forms of heart disease, and I'm certainly not going to go through these for you. There are a lot of different diseases. I just want to touch on a few of them because again, I think it illustrates the practical implications of this line of research on our pricing and mortality assumptions for the future.

We all know about the most common form of heart disease. I've been looking at the genetics of athrosclerosis. This is actually a disease that's multi-factorial. It's not just genetics. It's the mix of the environment with the genes. So the research here, looking at the various genes towards athrosclerosis, is still at a primitive state. It's the mix of genes with the environment that's so important with these multi-factorial diseases, particularly heart disease, diabetes, most of the cancers, the common diseases that we are faced with and that we have to price for as actuaries.

There are even genes involved with some of the higher risk behaviors, such as alcohol consumption. There's a genetic defect that predisposes people, which is associated with populations drinking a little bit more. They've looked at a number of different diseases and different genetics. I think I saw an article saying that there are about a thousand diseases for which they have found the genes. But there was

another very good statement in the article that talked about cystic fibrosis genes and the timeframe. This gene was found in 1989, and this article asked, where's the cure? Just because you find the gene doesn't mean that we're going to have a cure in the next week or so. It actually is a long research process, and I think that's something we need to be aware of when the Human Genome Project is pending completion in 2003.

Now, I think genetics will help, though, to prognosticate people with documented disease. I'm going to give you two examples of this. So this is somebody—and this is now already being used in clinical practice—who has got the disease. We can look at the genetics of that person, and we can prognosticate somebody, similar to the argument that I talked about with Huntington's Disease. This is a disease called cardiomyopathy. This is a problem with the heart muscle, a genetic problem that causes the heart muscle to become too thick, and it can cause heart rhythm problems, sudden death, etcetera. Well, based on the genetic mutation that the person has with that disease, you see it will help us to prognosticate more accurately in the future, helping us to sell more products to the public and better serve the insurance industry.

Another example of how genetics help us prognosticate involves leukemia. In the future, underwriters are not going to see a doctor's report just saying that this applicant had a simple leukemia as a child. They're going to get a doctor's report that states "inversion 16" or "translocation t (8, 21)," and the underwriters are going to need to understand that because of drastically different prognoses based on the genetics of the cancer cell. They're giving different therapies just based on the genetics of the cancer cell. Even if courts deem that we cannot use this information for underwriting an asymptomatic person, underwriters need to have an understanding of this terminology because I think they will be seeing these kinds of reports on people with documented disease.

Now, you might have seen an article in *Time* magazine that looked at our first success story. I really think this is the area in which we're going to see this in our lifetime, certainly with underwriting and pricing, where genetics research is being translated into a very good form of therapy. This is towards one of the forms of cancer. It's actually not a common form of cancer. It's chronic myelogenous leukemia. It affects about 7,000 people in the United States per year, but we know the genetic defect that causes this cancer. It's actually that a little bit of the chromosome kind of switches spots from one chromosome over to another one. When those two little bits that aren't supposed to be lined up are indeed lined up, the gene actually clones for a protein and makes a mistake. It clones for an abnormal protein. It's an abnormal protein that causes cancer. So, we knew the genetic defect because we could see that down a microscope. We were able to clone the problem. Therefore, we were able to make this abnormal protein and find out how it causes cancer. The *Time* magazine article described how we found a therapy because we knew the abnormal protein that that genetic defect was making.

That abnormal protein makes cancer because it binds perfectly with this effector cell. What, then, we could do was design a perfect bullet that would only affect that

abnormal protein. Initially the drug was called STI 571. We just received Food and Drug Administration (FDA) approval on May 10, 2001. Gleevic is its trade name. What's beautiful about this is it affects only the cancer cell because it's only the cancer cell that makes this abnormal protein. Therefore, this substrate now does not bind with the effector cell, and the cancer can at least be controlled. Then those cancer cells kind of die off on their own. Now, it's expensive. These people might have to be on it longer than we think, but it's one of our first success stories that I see, where knowing the genetics have translated into proteins, like what Paul Schuster was saying. We were able to make a magic bullet because we could analyze that protein.

For a little bit more of other lines of genetic research that I think have other ethical implications, here is another form of gene therapy that involves injecting a gene into the body. There's a study that was done by Lorsodo of five people. That's not a lot of people, of course, but the study provided very interesting preliminary research. These were patients who had inoperable heart disease. They couldn't have surgery done on them. They're having angina just walking from here to the door, so they were people who were very sick. They found the little bit of DNA that clones for the protein that makes new blood vessels grow. They wrapped up this little bit of DNA in a common cold virus. They then inject that virus into the body, into the heart, and it was taken up by the cells around the heart that then started translating and incorporating that DNA. The cells started making the protein that causes new blood vessels to grow, and it cured their angina. They didn't need nitroglycerine. Their heart scans improved. It's very interesting research and could really help some people who have very bad heart disease.

But again, the ethical implications here are that you're altering the human genome. What if this virus gets out, goes into the testes, into the ovaries? And I think you might have seen in the press that there was a problem with one study that was looking at this form of therapy. It actually caused one child to die because of an allergic reaction or some reaction to the actual vector, to the virus itself. Where's this going on genetic therapeutics? I think we're going to have to look at this for the future.

So I've talked about a number of ways that genetics actually will translate into therapeutics that will favorably affect mortality and morbidity for the future, but this research is in its early stage of pharmacogenetics. I think what we will be seeing is that we'll be analyzing people with documented disease and looking at their genetic profile medically to be able to dictate which patients will respond to which form of therapies—which patients should be on cholesterol lowering drugs—just by looking at their genetic profiles. We'll be able to tailor the therapies more accurately. We'll be able to determine genetically if they will respond to a therapy, or if they will develop a side effect of the therapy.

Right now medicine is a probability game, like what we play in insurance, but it's a hit or miss. I think you've seen articles in the newspapers about the amount of mortality that's associated with medical error. Well, by knowing some of the genetic profiles, we can better tailor medical therapies that will allow us to better treat patients for the future. But again, with some of these other forms of therapy, I

think we have to think about the long-term risk and, of course, the ethical implications of what we're doing.

I'm not going to talk about the genetic testing issue. Some of the genetic therapeutics is allowing us to sell more insurance at better rates, but there is some anti-selection potential to this form of research. There was a survey of government employees who were asked, "If insurers could not underwrite based on genetic information, would you go out and buy insurance?" Fifteen percent said they were somewhat likely to buy life insurance in the next 12 months. Five percent said they were very likely to do so. They then said to these same people, "What if you found out you had a genetic predisposition to a lethal or very serious disease, and again, insurers could not use that information? Would you now go out and buy insurance?" And look—61% said they now would be at least likely to go out, and 38% claimed they'd be very likely to. So that shows you the potential of anti-selection, although this has been refuted in the medical literature.

There was a study by Zick that was published in the *American Journal of Medical Genetics* in July 2000 that looked at women who were found to be at a high risk of breast cancer and then asked whether or not they were indeed more likely to go out and buy insurance, and they said no. So I think we need to look at this a little bit carefully, but I think that potential is certainly there. This could have a significant impact on the insurance industry.

For actuarial pricing, I think what you have to look at is the number of the diseases I've talked to you about today. If we see various medical advances, such as genetic research, some of the new therapeutics, we want to translate that into mortality assumptions for the future. So, if we start thinking of curing or treating diseases that are in the early phases of life, such as congenital heart problems or cystic fibrosis, then we can maybe move this curve up a little bit in your pricing modeling. If, because of genetic research we're better able to treat and prognosticate people with heart disease, then I think we might be able to move this middle zone up a little bit in our mortality assumptions. Cancer usually starts at about the age of 50. So, if we start developing those magic bullets like that Gleevic story, genetics will help us to treat some cancers, and then you're talking about impacting that older age group and then into long-term care—with Alzheimer's therapies, etcetera, even older still. How do you translate that practically into your mortality assumptions and pricing? Where will some of the numbers come from?

So, in summary, disease really is a mix. Mortality and morbidity is a mix of nature and nurture. We all know that, and I think I've shown you a number of studies that really illustrate it. It's not just genetics. It's the mix of the genetics with the environmental factors. I think it's unlikely that decoding the human genome that Dr. Lowden's going to talk to you about will immediately revolutionize medicine, but I do think this line of research is very exciting and will have very good implications on morbidity and mortality in the near future.

Francis Collins, director of the Human Genome Project, said that life expectancy by the year 2040, because of all the medical therapeutics and genetics, would be around the age of 90. He said that you'd be able to get your human genome

completely cloned, carry it around with you, for about $1,000. So, it'll be interesting to see whether some of these predictions come true, and I'd be interested in knowing what Sandy has to say as he talks more about the Human Genome Project. I do think that this form of research will continue to cause some increased healthcare costs. That is a problem for all of us in both America and in Canada. But I do think this new technology, like other new technology, will help the insurance industry sell more insurance at lower rates.

MR. SCHUSTER: Next, I'd like to introduce our second speaker. Dr. Lowden is senior vice president and medical director of Lab *One*, Inc., and medical director of Lab*One* Canada, Inc. He graduated in medicine from the University of Toronto and trained in pediatrics at the Hospital for Sick Children. Sandy completed a Ph.D. in biochemistry at McGill and the Montreal Neurological Institute. Following his training he combined a research and clinical career in biochemical genetics at the Hospital for Sick Children and was a professor in the departments of pediatrics and clinical biochemistry at the University of Toronto. From 1976 to 1986, he was associate director of the Research Institute at the Hospital for Sick Children, where he established the HSC Research Development Corporation, an applied research and technology transfer company, and served as president and CEO of that company.

Sandy has been a director of several biotechnology companies, and, in 1990, joined Crown Life as vice president and chief medical director. He was a member of the Executive Canadian Life Insurance Medical Officers Association from 1991 to 1998 and was president of that association from 1994 to 1995. Sandy lectures frequently on the use of genetic tests in insurance risk assessment and consults on genetic issues to insurance companies.

DR. J. ALEXANDER LOWDEN: These are probably the leading and most-read journals in the scientific world—*Science*, published in the U.S., and *Nature*, published in Britain—and they both had articles about the Human Genome Project published simultaneously the 15th of February this year (2001). There are all kinds of politics and commotion and everything else about this. The articles in *Science* were all about the work done by an American company called Solara. The articles in *Nature* were all about the work done by the public process through granting agencies, the largest one of which is the U.S. Institute of Human Genome Research.

They're fascinating articles, and they tell you lots of things about what's likely to happen with genetic knowledge in the future. They talk about the sequence of the 3 billion bases, which has mostly been characterized now, at least 95 percent of it has. They pointed out that the number of genes is a lot smaller than we thought. When they began this process, they thought there were about 100,000 genes in the human genome. It now appears there's somewhere between 30,000 and 40,000. But they have lots of comparisons with other species, and they're going to open the doorway to a lot of new sciences.

S. cerevisiae is a yeast. It has 5,800 genes. C. elegans is a worm, and it has 19,000 genes. Drosophila is that fruit fly that geneticists have used for years. It has 13,000 genes. The Human Genome Project, depending on whether it's the one published in *Science* or the one published in *Nature*, has some number that's in the

30,000s. So, in other words, a worm has two-thirds the number of genes that a human does. But these genes do a lot of different things, and one of the things that is interesting about this is how many genes there are per million bases. The Cs and Gs and As. In the yeast there are 484 genes per every million bases, whereas in humans there's somewhere around 12 or 15 genes per million human bases. There's a lot of genetic material in there that is not genetic. There's a lot of DNA that doesn't have genes in it, which doesn't code for anything, and we don't know what it does. That's really what's going to be interesting from a scientific point of view in the next decade or so as people try to figure out what this project is all about.

So, where's this really taking us, and what's it going to lead to from the insurance point of view? It has a lot of biological information, but there's a big impact associated with using that information on people instead of just using it in the scientific lab. It raises huge consumer concerns about the impact of testing. What's it going to do to me and to the rest of my family? And, as a result, particularly in the U.S., it's generated tons of concerns about controls on this testing. There are many, many states—I think about 40 now—that have legislation that says, "Thou shalt not use genetic tests for looking at health insurance," and two states that have legislation saying that you can't use genetic information to look at life insurance.

In fact, yesterday, apparently, Maureen MacTeer—who the Canadians in the room know is the wife of Joe Clark, the leader of the nondescript Conservative Party who once was the prime minister—stood up at the Canadian Institute of Actuaries and said that insurers should be banned from doing blood tests because they might store the blood and someday go back and test it, do genetic tests on it, and thereby bring some adverse action against their policyholders. They're going to have to break a lot of laws, and a lot of lawyers are going to be kept in business if somebody ever thought of doing something like that. But people have lots of funny, bad ideas about what they're going to do with genetics. What they're not recognizing is that there are some really good things, and Phil talked about this in terms of pharmacogenetics, genomics and proteomics. These are just words that say, "Look at the genes and look at the proteins they produce."

Why do actuaries care? Well, these new sciences are going to change morbidity and mortality calculations, and at some point in time, people are going to have to start thinking about what's likely to happen now, instead of looking back to what happened last week or last year or 20 years ago. These are really going to change the prognoses for people's life expectancies, and we're going to have to make some predictions on future underwriting, if you will, instead of using old, past experience. Underwriting is going to change.

Genetic testing is not the issue. There are all these kinds of concerns. Do you really want to know that you've got a bad gene that says when you get to be age 55, you're likely to have a myocardial infarction and you've got a 10 or 15% chance of dying then and a 40% chance of dying within the next five years? Do you really want to know that today, if you can't do anything about it? That's the real issue—if you can't do anything about it.

Phil talked about Huntington's Disease. It's a devastating neurologic disease that people die from, and you can't do anything about it today. Heart disease is a different thing. We can do lots of things to modify treatment for heart disease. Those things are going to change, though. We're going to have to start looking at different ways of thinking about this. But these are the concerns of people, and they're real concerns.

Discrimination is the word they use. Discrimination's just a dirty word to the average person, but, in fact, it's what underwriters do. They discriminate against risks, and it's a good thing to do because that's how we keep our companies solvent. But we need a better strategy to explain to people what we really do. We're outside of the insurance industry. Nobody knows what the insurance industry does, how it works, or anything about it. You talk to your next-door neighbor who has an insurance policy, but he has no idea really how it was determined, how much he paid for that policy or why. And people really ought to know this. I don't know how we get to tell them that.

Legislators love genetics because it's something everybody can climb aboard. They're going to protect their voters by writing legislation that says you can't do this and you can't do that, even if it makes a lot of sense to do this or that. The target in the U.S. today is medical expense insurance, but the real issue down deep underneath is life insurance, and it's not going to escape for very long. The legislation is full of very difficult definitions. What is genetic information, vis-à-vis what is the sequence of your own DNA, and which of those are important, and what's the difference between any of that and what your family history is? And family history is considered by many geneticists to be the best genetic test available at this point.

Why did all this happen so fast? Well, it happened because of new technology, and it's new technology that's going to change things in the future. You know, Phil talked about this article about how the cystic fibrosis gene was described in 1988, and here we are, a dozen years later, and nobody's cured it. But what they're waiting for is new technology, and what the Human Genome Project did was new technology. When it started, it took perhaps 100,000 bases in a day. If you take 100,000 and divide it into 3 billion, you can see how many days it's going to take to determine what the sequence of the whole genome is—a lot of days and a lot of time. They didn't have time to do that, so they built new technology, really fascinating technology, which allowed them to look at long, long strings of DNA very, very rapidly.

My own experience in that began about 20 years ago because I was then doing research in a lab on a genetic disease. We knew what the disease was. We found the enzyme defect that caused this disease. It's a single-gene disorder. So it had one protein that wasn't working properly. We figured out how to extract that protein. We used human placenta because it was a great source of human tissue. You didn't have to worry about what the ethicists and the lawyers were going to say about taking parts of people's bodies and not burying them with them.
We extracted the enzyme from this tissue. Then we purified the enzyme. We

chopped it up into pieces. We figured out some amino acid sequences, and then we figured out what the possible different DNA codes would be for that amino acid sequence. So we made some bits of DNA. We made a probe, and then we used that probe to look for the gene. It took us about 10 years to do that, to clone a single gene. Today they do that in moments. They don't bother isolating the proteins. They just grab the DNA and look at the sequence.

Technology is what's going to convert something that once took years to accomplish into something that takes hours. The same thing is going to happen with the way we use genetic information to treat disease. Some kind of breakthroughs in the way that technology works are going to be what changes it, not just knowing what the genes are.

What about genetic tests? Genetic tests are a big issue. What do they teach us? They tell us only what we ask. We hardly ever test a whole gene. We test little pieces of it where we know there are mistakes. If we don't look in the right place, we may say there's no mistake in this gene when, in fact, the mistake was over here, and we were looking down there.

There are many different kinds of genetic diseases that are defined by where you find the defect. The single-gene defects like cystic fibrosis are found by a mistake in the sequence. The chromosomal ones are found by looking at the chromosomes that have morphologic changes in them. But most disease is multi-factorial. There are many different kinds of inherited mutations. There are somatic mutations. Phil talked about those.

But if you look at the frequency of diseases as a cause of death, you can see that chromosomal things, like Down's Syndrome, don't kill very many people. Sixty-five percent of people die with a multi-factorial disease. Almost all of us die with some kind of genetic disease, apart from those that get run down by trucks—and most of the people who get run down by trucks probably have a genetic defect that prevents them from looking where they're going. But the thing that's important here is that the smokers can get killed from smoking, or the people who sit in the sun can get melanoma, but this applies to most of us. Most of us are going to die from multi-factorial disease, many genes working together with our environment.

The effect of a mutation is really interesting because a single mutation may or may not show itself. As Phil said, penetrance is the important thing, and we don't know very much about the penetrance of most diseases. In fact, as we look at genetic information, the information that we get changes all the time because our original data was collected on large family groups that contained many affected people. We could say that guy's father and his grandfather and his uncle and his uncle's kid all died with heart disease. It's likely this person is at risk for heart disease. It doesn't tell us much. It's just likely. And you can calculate some numbers on how likely that is if you have enough cases like that, but for the individual, you can't tell them anything.

The idea of a genetic test is that maybe it'll help tell you something about that person, provided you know something about the penetrance. But penetrance, as we

learn more about a genetic disease mutation, changes. BRCA1, that breast cancer gene that everybody reads about in the paper, was first described in about 1991. In 1993, Easton collected all the data he could find on breast cancer, and he said 85% of women who had a mutation in this gene would get breast cancer. Years later, looking at this same kind of data, plus more that had been collected on other people, said that, in fact, the risk was less than 60%. Today it could be less than 40% of people who have this mutation will get breast cancer.

Why is that? It's because, in fact, the disease doesn't come from the single-gene mutation. It comes from the gene mutation, plus probably some environmental factors, plus probably some other genetic mutations that are associated with these people. So if you look at families with a lot of affected people, they probably have a high incidence of having other genetic mutations. But remember, those families probably also live close together and do the same kinds of things, so they're also affected by the same nurture as well as the genes they inherited.

What's the personal value of having a test? Why would anybody go and have a test if it might say that if I have this test, I'm not going to be able to buy life insurance? I'm not going to be able to get a job? I'm going to have whatever? They really should do it because it should help them improve their understanding of their own long-term risks, and begin planning for the future. But more importantly, they can start trying to do something about it to protect themselves. So there is a huge value for us as insurers to encourage people to have most kinds of genetic tests. We can't do anything about Huntington's Disease, but that's a rare disease that occurs in about one in every 10,000 people. BRCA mutations occur in one in every 200 people. And somebody with a BRCA mutation could do something about it, perhaps not as drastic as Phil said, but they could.

What can we do today? We can recognize that there's going to be more and more legislation that's going to make it more difficult to use genetic testing. We can try and get people to think about what genetic testing really means. But the most important part of this is that we have to preserve our right to underwrite. Maureen MacTeer, whom I talked about earlier, doesn't understand that, in fact, we really want to get more policyholders, not get rid of them. Pretty soon we won't be able to underwrite because we won't be able to do any of the things that we currently do, such as ask questions about people's health. We should convince people to determine their own risks so that we can insure those with known mutations. But we can encourage them to be tested to remove the fear factor and to do something to guard against potential health problems.

One of the interesting things about genetics that's going to come in the next few years, rather than waiting for the 10 or 15 years that changes in pharmacogenetics may take, is, I think, that we're going to see changes in the way we describe diseases. For a disease that's caused by a single gene or by two or three genes, that cause heart disease or cancer or whatever, it's probably better to define this as this gene with that group of etiologies that has the same outcome. It's going to be different from the other one. People with BRCA mutations have a kind of breast cancer that is quite different from some other kinds of breast cancer that probably can be treated in different ways and can be understood in different ways. We're

going to have to stop using the old pathological definitions of disease and think about genetic definitions of disease. That's going to happen pretty soon.

What's going to happen in the future? Is this going to affect testing and rating and declining or ignoring people? What are we going to do? I think we're going to have to rethink our rating system. There are going to be lots of new tests, but there are also going to be new treatments and new technologies, ways of managing those diseases that are going to affect ratings. There are many kinds of devices now that use a little chip that can hold 30,000, 40,000, 100,000 bits of DNA and can do a lot of tests on a single drop of blood. You can test for not just cancer, but for cancers and cancers and cancers and heart diseases and heart diseases and heart diseases. You can get a whole lot of information. As these things get refined a little more, people are going to be having more and more tests like this that'll tell them a whole lot about their life risks, what they should be doing, and how to manage it. This technology is in its infancy today, but there are many, many companies now producing things like this, other ways of doing multiple tests, all in the same vehicle.

Phil talked about pharmacogenomics. I don't need to say much more about that, but we're going to develop compounds that learn how to treat disease. These are happening already. There's now a pretty good compound to treat breast cancer, but it works only in certain people with a certain kind of mutation, and you can distinguish on a genetic basis which of those people it is. That's what I'm talking about, redefining what genetic disease is. There's a group of people that will respond to this drug called Herceptin, and other people won't respond to it at all. There's no point in giving it to them. It might make them feel uncomfortable or whatever, and it costs a lot of money. So you give it to the people that it's going to work on, and that's what pharmacogenomics is going to do. It's going to change the way we do simple things like treating hypertension with some pills. We all know people who have mothers or fathers taking these pills for hypertension that never controlled it. The doctor changed them, and it worked like a bomb. Well, he's going to be able to use that test and be able to tell him or her which pills she should take rather than waiting to see what happens.

Improved medical management. Medical management has changed a lot in my medical lifetime. When I started as a pediatric resident 40-odd years ago, cystic fibrosis was a disease that killed kids when they were about 6 or 7. Now the average life expectancy for someone with cystic fibrosis is about 35 years. That's a huge difference, but it has nothing to do with knowing anything about the gene. It has to do only with knowing how to treat the disease. But knowing about the gene is going to help us know how to treat the disease faster.

How about replacing inactive gene products? Phil talked about this. We now replace inactive gene products. We put insulin into people who have diabetes. There's a bunch of enzymes that people have used to treat rare single-gene defects, and some of them work quite well. But they're not the real answer because sticking stuff into people every day or every week or every month is not the greatest fun. It's far better to do something that can change the situation right away.
There are some neat approaches to that right now. You might have read in the

paper just yesterday or today about the people in Calgary who've been looking at something called a reovirus, which is a virus that may cause a little bit of upper respiratory sneezes or a little bit of diarrhea, usually in small children, but it doesn't do anything else to humans. If you take that reovirus and stick it into cancer cells growing in a tissue culture tube, it kills them. It kills them in the presence of normal cells. It doesn't do anything to normal cells.

These guys are now looking at using this as a way to treat brain cancer, and it's really exciting work. They can do it now in mice. They stuck some tumor cells into a mouse's brain. They stick some reovirus into that mouse, and it cures its brain cancer.

There are going to be some neat ways of using genetic materials—the virus is just a piece of gene with a little bit of protein around it—to change what happens to certain kinds of diseases. Most disease is multi-factorial, so you're not going to be able to do a single-gene defect and make a diagnosis on most kinds of disease.

What about single genes? Is there a role for these in underwriting? Well, let's look at three of them, and, yes, I think there really is. There are many cancer genes. Most of them do things like suppressing the growth of tumor cells. Some of them arise because our DNA—while we have it, and it's all there, and it's all sort of constant—in fact breaks down and replaces itself all the time, just like we replace our skin. When you burn your hand, the skin gets all blistery and falls off, but you still have new skin there when your hand is finished healing. Your DNA does the same sort of thing, except sometimes if you burn your hand really badly, it doesn't heal very well. When that happens, we have special genes that go along looking for errors in that gene, and they repair it. They usually work very well. When they don't work, we get cancer.

These are two of the cancer genes that have received a lot of publicity, but they occur pretty rarely, each of them in about one in 200 people. One causes breast cancer. One causes colon cancer. But most forms of breast and colon cancer are not caused by single-gene defects, and genetic tests aren't going to aid in their prediction. In other words, if you said, "I know that that BRCA and HNPCC genes cause cancer, why don't I test every applicant for them?" you'd have to test a lot of people to find the one who's going to get it, for two reasons. First of all, the gene's rare. Second, everybody who has the gene doesn't get the cancer.

What's the risk of dying with breast cancer? The lifetime risk for women to get breast cancer is at least one in 10. Most cases occur in older women. The mortality is about 25%, maybe a little bit higher. In other words, about one in 40 women is going to die with breast cancer. With BRCA testing and the knowledge of it, the mortality should be less than that because of increased awareness, increased surveillance, and perhaps preventative treatment. In other words, a woman who came from a family with a history of breast cancer, not a woman who just had known mutation, probably might consider some of the drastic surgery Phil was talking about or long-term treatment with anti-cancer agents such as Tamoxifin.

Early diagnosis, though, leads to a better outcome, and you can show that people

who are diagnosed at Stage 1 of breast cancer have somewhere between a 5 and 10% mortality, whereas I said the mortality in general for breast cancer is at least 25%. That's because women don't do breast self-examination, and they don't have mammograms often enough. They don't find tumors when they're in their earliest stages.

What's the risk of a breast cancer mutation? If you take the lifetime risk for anybody, there's about a 4% chance that someone will die with breast cancer. The mortality from all forms of breast cancer, though, is about 2.5%. There's not a big difference, and you can change these numbers really fast. This is the lifetime risk of getting the disease because the penetrance is 40% for BRCA. If the mortality is 10%—and I said it could easily be 5% with increased surveillance—that brings the combined risk down to 2%. So, in other words, a woman who has a BRCA mutation is not any more at risk of dying from breast cancer than a woman who doesn't have the mutation because she's more likely to be doing something about it. The same thing can be said for colon cancer. People who know they have colon cancer genes should be more likely to have a colonoscopy a lot more often than people who don't know that. So how do we underwrite them? You underwrite them with care, but by age 50, if a woman is cancer-free, the excess mortality is negligible.

Here's a different one. Interleukin-1 is a gene for a cytokine, which is a funny little bit of protein that tells other proteins and other organs that this person probably needs an inflammatory response. There are four known mutations called single nucleotide polymorphism (SNP) mutations and certain patterns predict the risk of coronary artery disease in 35% of Caucasians. Now, 35% of Caucasians about equals the number of people who die from coronary artery disease. This is a disease for which we can really predict who's going to have a heart attack and who isn't. I think that's one that really has a use. There are at least 1.4 million, and maybe as many as 2 million, SNPs in the human genome. Everybody looks different because we have SNPs that make us all different. A few of these polymorphisms make us sick. Some of them don't do anything at all. Some of them just make us have a big nose or something like that.

So what about Interleukin-1? If a test were available, should it be used? This test isn't available right now. It's going to be in clinical trials for about two years. It's a test that's going to be used by your doctor to tell you whether you should be taking statins now, even though you don't have high cholesterol or apparent risk for heart disease.

If somebody's going to do that, does that impact how you should underwrite their insurance? I think it does. Is it fair to discriminate using that kind of information? Is it fair to let applicants conceal that information? Let's look at the flip side for a minute. What about a protective mutation? Could that be used in preferred underwriting? Here's one that just may do that. This gene, called ADCA 1, is a cholesterol transporter gene, and it has a whole bunch of mutations. When it occurs, it gives people a protective effect against coronary artery disease. In fact, about 30% of people apparently have this mutation, and they end up with low triglycerides and high HDL and a very low coronary artery disease risk. That should be a great gene to have, if you're doing preferred underwriting, to identify people

who are unlikely to have coronary artery disease. So, there are some good kinds of tests that are around.

We're still in a diagnostic area, but diagnostic genes suggest that changes in lifestyle may have value in prolonging life, and these changes are going to affect the things we use to underwrite. Here's another example. At both ends of a chromosome is a telomere. When a chromosome divides, the telomeres aren't replicated as easily by DNA telomerase. When a chromosome divides to make two cells, two chains split in half to form a new copy of each half. Out at the end, where the telomere is, that new copying doesn't take place as easily as it does in the middle of the chromosome, so the telomere is shortened with each cell division. When the telomere shortens to a critical length, the cell dies. So I have shorter telomeres than anybody else in the room because I'm older.

An enzyme called telomerase is activated in fetal life and in early newborn life and keeps those telomeres long. But when we get to some time around the second year of life, the telomerase activity disappears. The gene's still there, but it doesn't work. When cells become cancerous and divide and divide and divide, telomerase is activated again. The telomeres don't shorten when the cell divides. What happens then if you try to get around that sort of immortality for those cancer cells by blocking telomerase activity in cancer cells? Then, when the cells divide very rapidly, which is what cancer cells do, they're going to have shortened half-lives. If you block it, can you really change the life expectancy of a cancer cell? Can you transform it from being an immortalized cell to one that's going to die because its telomeres get too short?

Cancer causes about 25% of all mortality. So, if we block the telomerase, can we prevent half of those deaths, 12.5% of deaths? I just played with numbers the only way I know. If you added 5.6 years' life expectancy to all the people you insure, and that's what this is based on, what's that going to do to pricing? That's the sort of thing that's going to happen if genetic uses of, or genetic approaches to, treatment of disease result in things like this.

There are going to be big-time effects. We're going to save 2% of people who have heart attacks from dying. We're going to save half or more of the people who are dying from cancer by some funny, little, strange gene that we don't even really understand. You can do this in cells right now, you can do it in tissue cultures, and pretty soon somebody's going to show how you can do it in people. That's really going to have an impact. Think of what it'll do to annuities. Are you ready to price for that change? That's the sort of thing that I think you really have to think about.

Genetic technology will affect our business. We'll make better risk assessments. Mortality will improve, but we'll need to be ready to change because, otherwise, we're going to be underwriting against old principles that don't have any validity in today's world.

FROM THE FLOOR: There are a couple of statements that I'm interested in having either Sandy or Phil answer. One is that Francis Collins, in a speech at Hammerford College last June, predicted that by 2030 we would have the genes responsible for

aging in hand and would be in clinical trials with drugs to retard the aging process. The other statement was made by Leonard Haflick, who's one of the early researchers in aging and the aging process. Haflick said that although people die of the diseases of old age, and there's been a lot of time and money spent on cures for those diseases, the real underlying cause is the aging process itself. I'd be interested to hear what you have to say.

DR. LOWDEN: Well, first of all, Francis Collins is the pitchman for genetic research. He has to say things that are really upbeat because that's how he keeps his institute funded. He's always been a huge promoter of what is going to come from genetic research, and most of the time, I think what he's saying is correct. Sometimes his timeframes are a little bit too excitable—2030 is so far away, in genetic terms. I think you can't even begin to dream about what's going to happen then.

I talked about how long it took my group to find that gene and to sequence it. That was 16 years ago, and today, that's just trivial. If somebody did something like that today, he couldn't write a scientific paper about it. Nobody would want to read it. Nobody would publish it because it's so trivial. When we did it, it was a huge deal. And I think in another 15 years there will be similar huge advances in the technology that will allow people to make other kinds of knowledge advances that we can't dream about, even today. That's really what Francis is trying to get at, I think.

Now, I just talked about telomerase. If you could figure out some way to activate telomerase, you could stop those cells from aging. That's the theory. And if you stopped all those cells from aging, we'd either get to be really old, or we'd die from cancer. All these things have fallback positions. I'm very excited about what's going to happen. I have absolutely no idea what it really is, and neither does Francis Collins, but he likes to stand up and talk about it because that's what pays his salary and keeps his institute alive. He's a very smart guy, but why did he pick aging? I don't know.

DR. SMALLEY: The only thing I would add to that is that I do think this research is looking at promoting longevity, but also I think it's very important that we're going to be improving quality of life as well. I think that's what the second half of your question was getting at, and I think if we can start treating some of the morbidity diseases in our older ages, I think we're going to have, again, more success in this live research.

MR. SCHUSTER: I have a few closing remarks. I hope there were some good takeaways, maybe not so much anything on a specific disease but certainly for challenging yourself as you go back and consider what this might do to the reserving on annuities or the pricing on my life insurance or long-term-care incidence rates, things like that. None of us really knows. And, last, I'd really like to extend thanks to both Sandy and Phil for coming and enlightening us with some really great information.