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Session 1GS
General Session

KEYNOTE SPEAKER: DR. J. CRAIG VENTER†

Summary: Imagine a world where a person's entire genetic code can be downloaded onto a CD-ROM inexpensively and in a matter of seconds. What promise does such knowledge give to each individual and to society at large? The general session keynote speaker, Dr. J. Craig Venter, won international fame in 2001 when he announced that his company, Celera, had completed the sequencing and first analysis of the human genome, the complete complement of genes in a human being. Dr. Venter has since launched several nonprofit research institutes devoted to new genetic sequencing projects and the study of the resulting policy and ethical implications of this research. His landmark work is destined to reshape many facets of life including the assumptions that govern life and health insurance as well as retirement systems.

MR. HARRY PANJER: Good morning. This meeting is called to order. I'd like to welcome all of you to Orlando and the 54th Annual Meeting of the Society of Actuaries. We'll begin by acknowledging and welcoming the special guests we have with us today. It is with pleasure that I welcome 11 past presidents of the Society of Actuaries: Bob Myers, Bill Halvorson, Barbara Lautzenheiser, Walt Rugland, Steve Radcliffe, Sam Gutterman, Dave Holland, Anna Rappaport, Norm Crowder, Rob Brown and Jim MacGinnitie.

†Dr. J. Craig Venter, not a member of the sponsoring organizations, is president and chairman of the Center for the Advancement of Genomics, the Institute for Biological Energy Alternatives and the J. Craig Venter Science Foundation.

Please join me in welcoming our current president-elect, Neil Parmenter and our incoming president-elect, Steve Kellison. I'd also like to take this opportunity to again introduce Sarah Sanford, the executive director of the Society of Actuaries. We will now recognize members newly elected to serve on our Board of Governors. Elected as vice-presidents are Chris DesRochers, Larry Gorski and Dale Yamamoto. Elected as board members are Chris Bone, Tim Harris, Shu-Yen Liu, Barry Shemin, Dick Wendt and Teresa Winer. Please join me in welcoming the new members of the Board of Governors.

It's also my pleasure to welcome several dignitaries from other actuarial organizations. From the American Academy of Actuaries, we have President Bob Anker and President-Elect Barbara Lautzenheiser. From the Canadian Institute of Actuaries, we have President Mike Lombardi. From the Institute of Actuaries of the U.K., we have President Jeremy Goford. And from Japan, we have the deputy secretary of the Institute of Actuaries of Japan, Jun Miyamoto.

From the International Actuarial Association (IAA), we have with us President Jim MacGinnitie and President-Elect Luis Huerta. Please welcome Jim MacGinnitie, who's going to say a few words about that association.

MR. JAMES MACGINNITIE: It's an honor to be here today representing the IAA at the annual meeting of one of its largest and most active members. The IAA was formed in 1895 to organize international congresses of actuaries every three or four years. In 1998 it was reorganized to become an association of associations and to enable those associations to work together on international issues. That work was led by two members of the Society of Actuaries, Paul McCrossan and Walt Rugland. Today we have 50 full members, of which the Society is one, 24 associate members and three observer members. The associate members are primarily younger associations that are working toward full membership. Our members encompass about 35,000 actuaries working in 70 countries around the world.

The IAA has four sections and an embryonic fifth one. The oldest is the actuarial studies in non-life insurance sector (ASTIN), which conducts studies in property and casualty. It will celebrate its 50th anniversary in 2007. More recently actuaries interested in financial risks formed the Approach for Financial Risks (AFIR) section. And in 2002, with the encouragement and leadership of our past-president, Howard Bolnick, a new health section was formed, The International Association of Consulting Actuaries (IACA), and the pension actuaries are in the process of forming a new section. All these sections have individual actuaries as members, and they conduct regular meetings with very strong scientific programs. ASTIN publishes the *ASTIN Bulletin*, in conjunction with AFIR.

Meetings in 2004 include health in Germany in April and ASTIN in Norway in June. In November, the AFIR meeting will be in the United States, in conjunction with our investment symposium. The consultants and pension sections will be meeting in Australia. If you are interested in any of these, I encourage you to join and to

participate. You will find that there are many similarities to the problems and challenges that actuaries face around the world and many insights to be gained from the experience of others.

The IAA itself is organized into a council with representatives from all full members and some 20-plus committees. Some of these committees are administrative but most deal with major issues of a global nature, such as the international accounting standards (IAS). By representing the entire global profession we've been able to help the accounting standard setters move toward a sounder approach to insurance and pensions. Much of that work has been carried by two members of the Society of Actuaries, Paul McCrossan and Sam Gutterman. Not all standards have been written in an actuarially perfect manner, but the emerging results are considerably better than if our profession had not been effectively represented.

Another committee maintains relationships with the International Association of Insurance Supervisors, and the supranational relations committee deals with bodies such as the World Bank, the World Health Organization and the Asia Development Bank. We have an advice and assistance committee that works to help actuaries in developing and emerging economies organize professional bodies that can aspire to full membership in the IAA. And, as a result of the luncheon speech to our Society on our 50th anniversary in 1999 by Steven Lewis, who was then executive director of UNICEF, we are working on the development of an actuaries-without-borders group.

The work of our committees depends on volunteers and especially volunteer leaders. Several of the key committees are headed by members of the Society of Actuaries, and most of them have received many important contributions from our members. But there's always more to be done, and I would urge those of you who are interested to contact Stuart Wason, who's the member of the Board of Governors with international responsibilities, or Martha Sikaras, who's the manager of global initiatives in the Society office.

Finally, the original purpose of the IAA was to organize congresses. Last year the Mexicans and Luis Huerta hosted a very successful congress in Cancun. In 2006 the French will host us in Paris. In 2010 it will be the South Africans. And in 2014 the congress will be in Washington, in conjunction with the centennial of the Casualty Actuarial Society. I hope to see many of you there.

MR. PANJER: Thank you very much, Jim, for informing all of us about the IAA, a very important international association of which the Society is a key member. Congratulations are in order for a group of members celebrating their anniversary as Fellows or associates. Celebrating his 45th year as a Fellow is Peter Plumley. Peter also served as executive director of the Society from 1975 to 1979. Celebrating his 45th year as an associate is John Beekman. Celebrating their 40th year as Fellows are Jack Cooper, Norm Crowder, Anthony Houghton, Jerry Johnson and Anna Rappaport. Celebrating their 35th year as Fellows are Robert Brown, Garry

Eckard, James Gordon, Curtis Huntington, Joseph Kandrac, Franklin Pendleton, Frederick Rickers and John Tulloch. Please join me in congratulating these members.

Now it's my great honor to announce the recipient of the John E. O'Connor, Jr., Distinguished Service Award. It was created in 1999 for distinguished service by a volunteer member of the Society of Actuaries. It was presented at the Board of Governors' dinner on Saturday night. For this award I have selected a very prominent and successful actuary, a leader in many areas of Society activity, and a former president of the Society, but this award is for none of these. It's for public service, and I stress the word public. This award is presented to Anna Rappaport for her work in drawing attention to the needs of older women in American society. In particular, she has been a tireless advocate of retirement security for all Americans, but especially for women. She has devoted considerable personal time to the education of women on financial issues. Anna, we're very proud of your contributions to the public. Please join me in honoring the recipient of the John E. O'Connor, Jr., Distinguished Service Award: Anna Rappaport.

Now it's also my privilege to continue the tradition of honoring outstanding individuals with the President's Awards. These awards were also presented at the Board of Governors' dinner on Saturday. This year I've decided to present the President's Awards to a small number of actuaries who have contributed to the Society through lifelong careers in actuarial teaching and whom I consider my own role models. They are my personal heroes. Not only does the Society owe them big time, but so do their thousands of students. The award winners are: John Beekman, Geoff Crofts, Jim Hickman, Don Jones, John Mereu and Gaston Paradis. I'd like to tell you a bit about each one.

First, I will tell you a little about John Beekman. Following his Ph.D. from the University of Minnesota, John began teaching full time in 1963 at Ball State University. He retired in 1996 but continued teaching for another year on a part-time basis. That's over 34 years of teaching at Ball State. John, thank you for your contribution to the Society.

Next I will give you some background on Geoff Crofts. Following graduation from the University of Manitoba and three years at Great West Life, Geoff joined the faculty of the University of Manitoba. After six years he moved on to Occidental Life and Occidental College in Los Angeles for nine years. In 1964 he went on to Northeastern University in Boston where he developed and headed the legendary Northeastern program in actuarial science. From 1982, for the final 10 years of his teaching career, he was with the University of Hartford. I count 43 years of teaching in Geoff's career. Geoff, thank you.

Now I want to tell you a little about Don Jones. Don began teaching in 1955 while a Ph.D. student at the University of Iowa. Following his Ph.D., he taught at Michigan

from 1959 to 1990 and then at Oregon State for eight more years until retirement in 1998. This totals about 43 years of contribution to the Society through teaching.

And now I'm going to discuss John Mereu. John is a really very special person to me. He's remarkable. He has never been a full-time academic. John joined the University of Western Ontario's actuarial program as a part-time lecturer in 1957, a position he still holds. He has taught continuously at Western Ontario since that time and is still teaching. He is now in his 47th year of continuous teaching of actuarial students. Every student in the actuarial program there since 1957 has taken a class with John. I was one of those 35 years ago. Although he has not made a full-time career of actuarial teaching, his career is certainly equivalent to a full-time career.

And finally I am going to tell you about Gaston Paradis. Gaston is a legend in Canada and an even greater legend in Quebec. Prior to Gaston's arrival at Laval University in Quebec in 1958 as a lecturer, there was virtually no actuarial science taught in French Canada. Gaston was personally responsible for the development of the now-legendary and probably world's largest actuarial program at Laval University in Quebec City. Gaston retired in 1992 as a founder and director of the School of Actuarial Science at Laval. Thank you, Gaston.

I want to point out that one recipient who is not here is Jim Hickman. He's very well known to you all. His full-time teaching career spans the period 1961 to 1993 at the Universities of Iowa and Wisconsin. At Wisconsin he served, among other things, as a dean of the Business School.

I give my thanks go to each one of you for your major contributions to the profession through teaching actuarial science. Please join me in honoring the President's Award recipients for 2003. I know that there are many former students of these fine gentlemen out there.

Next it is my honor to welcome the newest members of the actuarial profession. We have 28 new associates attending their first meeting.

Over this past year Stuart Klugman, Rob Brown and I have had the pleasure of meeting many of our new Fellows at the Fellowship Admissions Courses in Atlanta, Montreal, Houston and McLean, Va. Please join me in congratulating the 54 individuals who are here attending their first meeting as Fellows of the Society of Actuaries. Welcome to the club.

Many Society members serve the profession by volunteering their time, and we would like to recognize their contributions. If you're a member of the board, a committee or a task force, please stand and be recognized. I'm really very proud of the spirit of volunteerism in our organization. Thank you for all that you do for our profession.

One of our major volunteer roles is that of the chairperson of the annual program committee. As you can imagine, the annual meeting program is quite an undertaking. So, we owe a debt of gratitude to this year's chairperson, Carl Meier. I also want to thank the all-volunteer annual program committee, which worked hard last year to make this meeting happen. The committee consists of representatives from all Society of Actuaries sections and other actuarial organizations as well. Thank you all for your hard work and dedication in putting together what promises to be a first-class annual meeting.

And now for our feature event: Our keynote speaker this morning is Dr. J. Craig Venter who is the president and chairman of the Center for the Advancement of Genomics, the Institute for Biological Energy Alternatives and the J. Craig Venter Science Foundation. He is also the former president and founder of Celera Genomics. His life story is thus far simply extraordinary. After barely graduating from high school, he headed for the surfing beaches of southern California. Well, that made him a prime target for the draft, and the Navy sent him to Vietnam as a medical corpsman. When he came back his self-described surfer boy mentality was gone. Only six years later he had earned his Ph.D. in physiology and pharmacology from the University of California at San Diego and became a researcher at the National Institutes of Health (NIH) where he began to sequence the genes that make up DNA.

In 1994 he and his wife, Claire Fraser, founded a private research firm, the Institute for Genomic Research. Within a year the firm published the bacterial genome, the first free-living organism to be fully sequenced. In 1998 he founded Celera Genomics and announced that Celera would decode the human genome faster and more economically than the publicly funded consortium of scientists. That challenge is now credited with creating the climate of urgency that spurred competition and substantially accelerated the project's successful conclusion. *Time Magazine* has said that Dr. Venter has started nothing short of a biological revolution. Thanks to him the world can now read the score of the human symphony.

At the White House press conference announcing the sequence of the human genome, President Bill Clinton called it the most important, most wondrous map ever produced by mankind. Dr. Venter's landmark work is destined to reshape many facets of life, including the assumptions that govern life and health insurance, as well as retirement systems. And now please join me in extending a warm welcome to Dr. J. Craig Venter.

DR. J. CRAIG VENTER: Thank you very much for the extremely kind introduction. It's a pleasure to be with you in Orlando, Fla. Genomics is a topic and a field that's even relatively new to science, not just to society in general. So I thought I would try to give you a little walk-through of what's been happening in this young field and how things have advanced.

Prior to 1991 when we published a new method for rapidly discovering human genes, every scientist that wanted to study a protein or a gene had to spend in some cases decades to try to isolate that protein or gene. In my own case I spent roughly a decade trying to find the receptor protein for adrenaline to work out how it acted on the heart and the brain. Now, only about 12 years later, any student anywhere in the world that wants to find a human gene to begin to study its function can do that in roughly a five-second computer search. Had science proceeded without genomics, it would have taken most of this current century and part of the next one to find all the human genes.

This field took a real leap forward in 1995 when we sequenced the genome of haemophilus influenzae. Many of you will appreciate this. The biggest advance in this field was a mathematical breakthrough, not a biological technique. We hired a young computer scientist TIGR, Granger Sutton, who built a new algorithm to assemble sequences. Prior to that, the largest number of sequences that anybody could deal with was roughly 1,000, somewhere between 500 and 800 letters long. With this new tool we could deal first with hundreds of thousands and then later millions of sequences. We were sitting around looking and thinking about genomics, and we decided maybe we could solve complete genomes by using these new algorithms to basically solve a jigsaw puzzle.

We started this project in 1994 and submitted a grant to NIH saying that we had a new tool for analyzing genomes, but the wisdom of the field said this tool would not work at all, and they refused to fund the study. Roughly a month after getting our pink sheet, we published this paper in *Science*. That's the history of genomics. It's not intuitive unless you have some type of mathematical background of how these techniques could work.

Since that first genome in 1995 there's just been an explosion in genomics. As of right now there have been roughly 150 different species, including our own, that have had their genetic code determined. That number will probably double in 2004. And by the end of 2005, when the human genome was supposed to be completed along with four other species, we will have well over 1,000 different species to have their genomes determined simply from applying high-performance computing and new mathematical approaches. The first genomes were roughly two million letters of genetic code. In the last year alone my team sequenced over a hundred billion letters of genetic code.

We scaled up things again in 1999 and 2000 at Celera, first sequencing the Drosophila (fruit fly) genome—180 million letters of genetic code—in less than a year. As soon as we finished that we started the human genome. We had five individuals who contributed to the sequence. Three of them were women and two were men. The self-described ethnicity of these individuals is African-American, Hispanic, Chinese and Caucasian. And I think one of the most important findings from sequencing the genome from these individuals was we found additional supporting evidence that race is a social, not a scientific, concept. We had the

privilege of announcing the first-ever actual scientific announcement from the White House with President Clinton and the following year published our analysis in *Internal Science*, the public consortium publishing simultaneously in the journal *Nature*.

This is when things started to get interesting. We found, contrary to popular belief, that we only had on the order of 26,000 genes in our genetic code. The number that had been going around for decades was 50,000 to 100,000, but over the preceding years that number increased to over 350,000. If you think in a genetically deterministic fashion, as most people in our society unfortunately do, you would think that we had to have a large number of genes if there's a different gene for each trait, each function, each structure and, as some have proposed, each memory. If you were in the biotech field and viewed these genes as commodities, you wanted to have large numbers of them, and two companies claim they patented over 350,000 genes, even though there are only now 26,000.

Some in the biotech industry, as I said, viewed these as commodities. The initial CEO of Human Genome Sciences, the late Wally Steinberg, called me up screaming obscenities at me in the telephone after I published a paper saying there were only 50,000-80,000 human genes. After he finally calmed down I said what possibly could be wrong with saying there are only 80,000 human genes? He said he just sold 100,000 of them to SmithKline-Beecham.

The reasons for the inaccurate estimations of the density of genes came from not understanding how much our gene density varies from chromosome to chromosome. I think it's a great irony that the largest calculation ever done in biology and medicine can only have its results shown on a large sheet of paper. If we tried to show it on a computer screen in its entirety, the genes would be smaller than single pixels. The gene density was so high we had to annotate the genes on both sides of the chromosome.

The first two regions we did our test sequencing on at NIH had that type of density, so scientists extrapolated from that assuming homogeneity around our chromosomes. But, we found an area we call the desert where we no longer find millions of letters of genetic code. The extent of the desert regions in our genetic code was one of the major discoveries.

As soon as we finished sequencing the human genome, we sequenced the mouse genome and things got even more interesting. We found 116 genes on a mouse chromosome that don't occur in our genetic code, and we found a few hundred in our genetic code that don't occur in mice. But if you were expecting, as some were, that our genetic code was totally unique because we're defining the terms, you're obviously very disappointed, and it's very clear that we're part of a continuum.

In September we published the dog genome, the genetic variation in dogs, all deriving from the same starting point. The roof is even greater than in humans.

There is over six-fold difference in height and 30-fold in weight. But one of the advantages with the dog species is that there are unique behavioral traits that segregate with some of the different breeds.

It's possible to find the genetic links to diseases in dogs and then extrapolate back to the human genome. Since we published this data in September, a major cause of blindness in dogs and humans was discovered using this data.

Huge segments of the dog chromosome align with our chromosomes, and essentially all the same genes working down the chromosomes are in the same order. In fact, over twice as much of the dog genome aligns uniquely with our genetic code than from the mouse, and this was a major surprise to scientists because people thought that the mouse was closer evolutionary-wise than canines were.

A little under 400 million letters of the mouse genome can be laid almost right on top of our genetic code, but with the dog it approaches 650 million base pairs. That's roughly half of the eu-chromatic regions of the genome. This shows that, in fact, we're much closer evolutionary-wise to the dog. In fact, one of the things it showed is that the mouse is evolving at a much faster rate than humans and dogs. It becomes even more stunning when we look at the chimpanzee genetic code. It differs from our genetic code only by 1.27 percent. That varies a little bit from chromosome to chromosome, but the human x chromosome differs from the chimpanzee x chromosome only by 0.9 percent. That 0.9 percent difference is across the 75 percent of the chromosome that are just the spacers between genes—intergenic regions. It's across the 24 percent of the chromosome that are the spacers within genes, the introns, and it's across the 1.1 percent of the chromosome that actually codes for genes.

It's very likely that within the next one or two decades, from all these different mammals and other species having their genomes decoded, we will likely know the precise evolutionary events that took place in our speciation. That's pretty stunning. We have the tools to understand our genetic and evolutionary history. We're now taking the tools that we developed for sequencing the human genome to other arenas, including the environment. I'm sure many of you know that we're putting a net of three billion tons of new carbon dioxide molecules into the atmosphere each year. We take the result of biological processes that took billions of years to develop—coal and oil—burn those over decades and put those in our atmosphere. This has been increasing for quite a while. We can't do that indefinitely or you will have a tremendous problem in terms of covering the future of humanity with insurance. We're trying to see if biology can contribute to reversing some of this damage.

Hydrogen is a very clean-burning fuel that can be developed biologically. The first hydrogen fuel station has just opened in Iceland. Iceland has a way to make hydrogen now that the rest of the world doesn't. They can use their hydrothermal

energy to split water, producing hydrogen and oxygen. They've made it a goal to be the first nation to have a hydrogen-based economy. We're exploring new biological resources to see if we can contribute to the situation using biology.

Some of you may know that only roughly 1 percent of all species on this planet have been characterized, particularly microbial species. Therefore, there's a tremendous amount to discover. If a microbial species won't grow in the laboratory, it doesn't get studied. We decided just to go take the DNA out of the environment and do shotgun sequencing. We started with the Sargasso Sea off of Bermuda, which is the only sea that's actually bounded by ocean currents. There are several stations that have been characterized for over 50 years that made them useful for comparison.

We chose the Sargasso Sea because it has the lowest nutrient environment of any known ocean. We simply pumped 200 liters of sea water through a series of smaller and smaller filters, collecting all the viruses and microorganisms. We then took them back to our research institute in Rockville, Md., where it's set up to sequence 100 million letters of genetic code every 24 hours. This is a completely automated $50 million facility that runs seven days a week, 24 hours a day, with a small handful of people.

We were stunned by what we found. We found new members of every branch of microbial life. We've discovered over 1,800 new species and over one million new genes. Over 400,000 of those are completely new to biology. They don't look like anything we've seen before in over a dozen complete to nearly complete genomes. That's between a 20 and 30 percent increase in the number of genes known already, and we think that it indicates the pool on this planet is in the tens of billions of genes, which means we really don't understand biology.

We have put together an evolutionary tree and we have made significant discoveries, such as molecules that interact and capture photons from the sun and help produce chemical energy in certain cells. This is a tremendous increase just in this one protein molecule of understanding how life transforms solar energy into metabolic energy. We found the genes varied from site to site, and we think that as we measure different ocean sites around the world we will discover over the next year on the order of a billion new genes.

We have a project funded by the Department of Energy (DOE) on synthetic genomes. We're trying to take new metabolic pathways we discover in the ocean and put them in an artificial chromosome to have artificial cells produce unique chemical compounds. We're building these in a cassette base fashion that mimics how we think cellular evolution expanded. The basis for this was the third genome we sequenced. This came from a high temperature vent a mile and a half deep in the Pacific Ocean. At our body temperatures this organism is frozen solid. It comes to life about 60 degrees centigrade. Its temperature optimum for growth is 85 degrees centigrade, and it can easily tolerate boiling water temperatures.

We're all trained that if you want to kill microbes, you boil them. That's true for a handful of human pathogens, but there's more biomass on this planet in this branch of life than all the plants and animals we can see with the visible eye. We have barely yet begun to tap this resource. This organism captures carbon dioxide from the environment as its carbon source. It uses hydrogen as its energy source, and it makes everything it needs from inorganic constituents. That gave us the idea to try to change and capture some of these metabolic processes.

We're in the process of trying to modify photosynthesis with some of these new molecules we found to take the energy directly from the sunlight and convert it into hydrogen production.

If you think back a few years ago, a decade or so ago when taxol was discovered in the bark of the yew tree, it was found that it would take a couple of trees to treat each woman with breast cancer, and this was a very rare tree. Another tree was found that had an intermediate, and that's what's used now to produce taxol. Today we would start with sequencing the genome of the yew tree, find the taxol metabolic pathways and try to put them in a synthetic cell.

We found organisms that can take carbon monoxide out of the atmosphere, use the reducing power of that to split water, producing hydrogen and oxygen. So we're looking for new ways to produce metabolic energy. I think engineered species will be a key part of our economy going forward and might replace the existing petrochemical industry where the carbon comes back from the atmosphere, not from the ground. It might be the source of most future food, a major source of energy, sources of pharmaceutics and bioremediation.

Now let me switch back to your field. The emerging field of genomic medicine is going to transform the practice of medicine. We're going from gene-based studies where one gene at a time is measured possibly in amniocentesis procedures to where we will measure all the genes in each of us. There are several advances that need to take place to make this viable. We need new genome technology to be able to sequence a genome in the course of this lecture for less than $1000. My foundation just announced a $500,000 prize to the scientists who make that key technological breakthrough.

We need the challenge of getting clinical records digitized, and there are many efforts around the world in that regard. We need to understand the knowledge of interpreting the genetic code in a clinical paradigm, and we need a dramatic new computer infrastructure. I predicted that the doctor-patient relationship in the future will be largely unchanged, except it will be consumer driven. Most of you do that now. If you or a member of your family gets a disease, most of you go right to the Internet, and you probably found that you educate your physicians about the details of those diseases, not the other way around. That's going to change even more when you have your own genetic code.

Let me give you an example. Early on we discovered three new mismatched DNA repair enzymes. Bert Vogelstein at Johns Hopkins University showed these were linked to colon cancer, and there's now a commercial test available for getting your sequence of these key enzymes. I've argued that knowing this information about whether you have an increased risk of getting colon cancer gives power to individuals over their own life outcomes. For example, if you know you have a 30 percent increased risk, instead of waiting for age 50 to get a colonoscopy, you can take measures in advance. As many of you know, many people die before the age of 50 from colon cancer.

I think this is the group that can help show that a preventative medicine paradigm not only will transform medicine, it will transform the cost of medicine. The statistics on colon cancer are pretty stunning. If it's detected very early before symptoms appear, there's greater than a 95 percent chance of a 10-year survival. If it's detected after symptoms appear, that goes down to less than a 65 percent chance of five-year survival. If you know you have an increased genetic risk, it makes sense to early on change your diet perhaps but certainly to get increased numbers of exams to detect that cancer early.

Let me give you another example with HIV. A recent U.N. report showed that over 6,000 young people are infected every day with HIV. The U.N. has actually now modified its population statistic planning for the world. Instead of being close to nine billion people by 2050, the estimations are now falling to only seven billion people because of one disease. That's a pretty stunning change if that, in fact, takes place.

It turns out there's genetic susceptibility and resistance to HIV infection in our genetic code. Some of these lead to very rapid progression of HIV and early death, and some are associated with almost complete resistance. Steve O'Brien at the National Cancer Institute characterized the CCR5 gene, saying a major change in that gene leads to very significant resistance to HIV infections. But, interestingly, it occurs in about 9 percent of Caucasians but only 0.1 percent of blacks. What does that tell us? It tells us it was a very recent evolutionary event because we all evolve out of the same African populations. Steve O'Brien has traced that event back to about 700 years ago. The same allele that protects against AIDS seems to protect against Yersinia pestus, one of the causes of the plague. The plague killed tens of millions of people in Europe but had almost no impact on Africa. So there's no natural resistance at all in Africa to HIV while there are in European populations.

Medigenetics is already beginning to affect our understanding of the course of cancer. Medigenomics in the case of work out of Duke University is measuring the expression of a large number of genes in breast cancer tumors and showing they can predict with high and low probabilities which of these individuals will develop metastases. Looking at 100 patients, they were initially divided just on that gene expression pattern into 60 with low risk and 40 with high risk. Using additional

clinical markers and genetic markers, the high-risk group was divided into 25 with almost 100 percent probability of developing metastatic breast cancer, and 15 had a very low risk of developing the tumor metastases. With the low-risk group, 10 of those in fact are of extremely high risk. This would totally change the course of treatment. We're now seeing similar studies like this with almost every major tumor. Using genomics and genomic tools we can predict what's going to happen with increasing accuracy.

I've predicted that within 10 years, before a baby that's born in a hospital leaves, their parents will have the option of having their child's genetic code on a CD-ROM or its equivalent. Obviously the impact of that will change much of our society. The movie Gattaca is based on the premise of genetic determinism. Your genetic code tells you everything about your life outcomes. I don't know any scientists in this field that actually believe that. We share a tremendous degree of physical similarity and metabolic identity that can lead to predictions about disease and possibly disease outcomes as I showed you, but that's very different from life outcomes. If we're genetically programmed at all, we're genetically programmed to probably be the most adaptive species on this planet, and those adaptations cannot be measured in measuring the genetic code.

Congress just passed legislation—or at least the Senate did, it's pending in the House—on the genetic nondiscrimination bill that certainly affects your industry. I've argued that this legislation is essential right now because of the degree of ignorance in this field and in our society about genetic determination. Genes are part of our language. Start paying attention to how often you see that word in everything from Super Bowl ads to headlines. We reduce very complex biological and social concepts down to a single gene. That's not the way our biology works. And eventually, as we understand the genetic code and what it can tell us, those types of laws won't be necessary because the science will prevail. In your field I think you have a wonderful chance to use this information to lower health care costs by proving the preventative medicine paradigm as a viable economic paradigm.

I mentioned computer infrastructure. You think predicting ahead 10 years is pretty wild. Let's look back 10 years. The palm pilot that many of us use has more storage than the average desktop computer of 10 years ago. A Nintendo Game Boy has more computer power than all the computers used to send Apollo 11 to the moon. In 1992 the largest computer was only 59 gigaflops. In 1999 the computer that we built to assemble the human genome at 1.5 teraflops was the largest civilian and third largest overall computer in the world. Today it doesn't even rate in the top 100. The largest today is 45,000 gigaflops, and computing is changing substantially.

Our computer occupied over 6,000 square feet of floor space. Within 20 or 25 years we will have computers that perform hundreds of petaflops in the size of this podium. In the future with computers that powerful, with large databases of genomic and clinical information, we will be able to make the associations between

multiple genetic alleles and disease prediction and disease outcome, at least the genetic components of those. It will change the practice of medicine from where half of medical practice in this country doesn't even conform to the basic standards of medical care to where every physician will have a tremendous set of tools available to them.

This is an exciting field in its earliest stages with tremendous social, legal, ethical and economic importance. I hope to work with you and your colleagues going forward to do this in an intelligent fashion.

MR. PANJER: Dr. Venter will field questions from participants and provide insights into the implications that human genome sequencing holds for mortality- and morbidity-based insurance products. Incidentally, Dr. Venter is no stranger to actuaries. His brother is a good friend of mine and a collaborator on actuarial matters. He's a Fellow of the Casualty Actuarial Society (FCAS) working with Guy Carpenter in New York.

FROM THE FLOOR: Currently the insurance industry is at a standoff with our elected representatives about what insurance people can do about using risk selection and genomic determination. Right now there is a moratorium on any kind of legislative tax against the insurance industry, and we as insurers have decided that we're having a moratorium on any kind of use of the new genetic risk selection tools. We're basically waiting for something to break. We're waiting for some sort of sign from the scientific community that we can proceed one way or the other in deciding what genomics can offer us in the way of risk selection. Do you have any idea what this kind of sign would look like?

DR. VENTER: It's not clear, but there are many different sites around the world setting up to measure genes for everything from predicting your metabolism to your sexual orientation. I think most of us that work at the forefront of this field feel there's a small handful of gene and gene associations that are truly reliable as predictive factors. I think that has to go a very long way before you would want to use this in terms of actually trying to predict outcomes. Even for the genes associated with breast cancer, the bracket 1 and bracket 2 genes, the information and the interpretation of that change quite dramatically. These were very rare alleles in families with tremendous genetic history of breast cancer. You could determine that same history, and many of you do, with a simple questionnaire. You don't need a genetic test for understanding that level of risk. What the field did, which I think was inappropriate, was take a genetic test that had meaning in a very small population, fewer than 10 percent, of women that get breast cancer and extrapolate it to the whole population.

We're still trying to understand that risk. So I think we need a partnership in terms of trying to make sense out of which tests are actually meaningful and give any kind of predictive value. I think the colon cancer ones for the families that have that type of genetic history are probably extremely beneficial. It might be great for test

cases to go forward and try the preventative medicine paradigm on some economic model that should work. This is a very young field. It's limited by our entire human history of how we think of genetics. Some of us think in a deterministic fashion, and I don't think we're ready to go forward and use it in making determinations, other than what you already do in life insurance. You do physicals and family histories. Those are genetic histories. So you're already extensively using genetic information, but there's a long history of how to interpret that information wisely. We're not there yet with the new genomic data.

FROM THE FLOOR: The DOE is the government sponsor of a lot of this work. Why the DOE? I did see some hints of energy implications, but it seems like a lot more on the biology side. Why not the Food and Drug Administration (FDA)? Why not Health and Human Services? Why did DOE take over sponsorship of this?

DR. VENTER: Well, the genome project actually originated in the DOE because one of the things they're charged with is studying radiation damage and its effect on biology, particularly after Hiroshima. NIH took over the majority of the human genome project and funded the majority of the public effort to sequence, which cost the public about $5 billion. Just as a side note, we sequenced the human genome in nine months for under $100 million, but it was not taxpayer money.

The DOE is the key funder of some of our work on the environmental genomics and these efforts to try to develop ways to capture carbon dioxide back from the environment and develop biological energy in terms of hydrogen. The DOE is also charged with a lot of bioremediation because some of the sites they have to clean up are the worst ones in our nation's history. So, Health and Human Services does fund a majority of the human health related applications of this, but I think some of the other societal implications of which the DOE is the sole funder are really critical going forward.

FROM THE FLOOR: Is there reason to expect that the work of the human genome and the changes in medicine that are likely to happen will lead us to longer maximum life spans, longer average life expectancy or changes in mortality at certain ages?

DR. VENTER: It's certainly been the case throughout the history of human health and medicine. As we improve nutrition, as we improve sanitation, as we improve diet, as we improve healthcare, our longevity does keep changing. We can now understand the apoptosis programs, the programmed cell death that takes place in our cells. Some people are working to try to change that. I personally don't think that should be a goal of science or this field, particularly if we can't feed or deal with the pollution from the six to seven billion people we're going to have, but we'll likely see extended lifetimes.

FROM THE FLOOR: Please forgive me if this is a Biology 101 question, but how do you determine if a genetic sequence actually comprises a gene?

DR. VENTER: It's actually simple questions like that that are the most difficult to answer. It's still an art form. It's not complete science. We don't have computer algorithms yet that are totally successful just taking the genetic code and seeing where the genes are. We can do that in microorganisms where over 90 percent of the genetic code codes for genes. In our case imagine the statistical problem: 1.1 percent of three billion letters, the same letters, A, C, G and T, code for proteins. We know some of the punctuation and some of the alphabet. For example, it takes three letters of the genetic code to code for each amino acid. We have other three-letter sets that are the punctuation. They are the initiation of sentences and also the periods of that block of the end of a gene. So, trying to look at these stretches with proper punctuation, called open reading frames, is one of the ways we do that. However, right now there are so many components and randomly variant pieces of genetic code to this that statistically we can end up things that look like genes that do not have those biological properties. So, it's not a trivial question at all, and it's why the number of human genes keeps changing as we better understand those statistics.

FROM THE FLOOR: Throughout human history advances in knowledge have often been met by irrational and hysterical responses that have set back the progress for centuries in the past. Is anything being done or can anything be done to mute that kind of irrational response?

DR. VENTER: I hope so. We're getting some of that response today. The Brownback bill almost passed Congress. This was anti-cloning legislation that would make scientists that grew stem cells in a Petri dish criminals and subject to prison sentences longer than anybody who committed second-degree murder. In addition, it would have made criminals out of any individual who sought stem cell therapy. For example, if Christopher Reeve went to England to try to get therapy to reattach his spinal cord, he would be a criminal upon returning to the United States.

It went further. It made parents subject to criminal acts and imprisonment if they sought stem cell therapy for their children. This almost passed Congress. It's pretty stunning that something that Draconian didn't even achieve broad public attention, and it almost passed. So, I think what you mention is of great concern to everybody in this field, and hopefully through public education and open discussion we can get past small groups that try to enforce their religious doctrine on the rest of our society.

FROM THE FLOOR: In Europe and Africa there's a lot of resistance to genetically engineered foods, maybe due to political reasons as well, but it would seem that a lot of the world's starvation problems could be addressed through genetically modified foods, and I am interested in your thoughts on that issue.

DR. VENTER: It's a good question and it's something that truly puzzles me. Some argue that the hysteria in Europe was largely driven by economic forces, starting

with French farmers that were worried about the economic competition. But this has sort of developed into hysteria Europe-wide. It's difficult to understand. The same people that say they want to eat natural fruits and vegetables and don't want anything that's genetically modified, don't understand that, for instance, natural tomatoes are small green things about the size of my thumb that are very bitter tasting. That's a natural tomato. And through genetic selection and randomly mixing entire genomes, we've come up with a different set of species that most of us consume today.

Imagine if a scientist said, "I'm going to take this genetic code and totally mix it with this one today." There would be panic. But even if we only change one gene in a knowledge-based fashion, that's somehow dangerous. There are dangers in putting genetically modified organisms into the environment without adequately testing them, and that hasn't been thoroughly vetted properly, but this is a wonderful chance to change how we feed the world. It was quite stunning.

The golden rice that actually helps prevent blindness was rejected by several African nations because of the hysteria in Europe over it being genetically modified. We cannot afford any longer to have science be an option for our society. There's so much that we have to do going forward that is based on understanding these basic principles. We have to change our fundamental basis of education. I was very turned off to science early on, and that's why I became a surfer, because it was taught very badly. It was taught as rote memorization of some pretty dull facts that all turned out to be wrong anyway. If science were taught on the excitement of these concepts versus rote memorization, I think it would change our societal view of this information and allow us to proceed in a much more intelligent fashion. We obviously have a very long way to go there.

FROM THE FLOOR: In an earlier question-and-answer exchange dealing with the use of genetic information for insurance risk selection, you pointed out in effect that the knowledge base isn't there yet, that all the things aren't understood, and presumably over time those knowledge barriers will gradually recede. However, some commentators have actually said that it's not a knowledge-based question, or at least not entirely that, that it's more of a societal question. When is it appropriate to use these kinds of information and when is it not? And, are you in effect making people the victim of their own genetic code? I wonder if you have a view beyond the current state of knowledge as to where, with broader knowledge, it is and is not appropriate to go with these kinds of things.

DR. VENTER: It's easy to see in the future when we have, if you can imagine, a database with 10 to 100 million genomes with clinical outcomes associated with those. It'll be a massive compute, but we will be able to actually deconvolute in a very accurate statistical fashion the links between variations in the genetic code across the genome and those outcomes when they are clearly linked. Half the equation is knowing the environment. With colon cancer, one of the questions you should have asked is: If those DNA repair enzymes are deficient in every one of our

hundred trillion cells, why do you get colon cancer? Why not brain cancer or liver cancer? And the answer lies in that it's actually toxins in our colon from bacteria metabolites and from what we eat that damage the DNA and the colon epithelial cells. If you accumulate sufficient damage, it can lead to unregulated cell growth, cancer. So, if you can't repair that damage, then your odds of getting cancer go up. So is that environmental disease or is that a genetic disorder? It's clearly both. Right now, because we can for the first time measure the genetic code, tremendous emphasis is being given to that, whereas I think most diseases will be similar to colon cancer. They'll have an environmental and a genetic component. So, until we can do these large accurate calculations and get really meaningful data, we will continue to have some absurd steps in medicine.

For example, there were recent suggestions that hypertension treatment should be done on the basis of skin color because there were minor statistical differences with some drugs. That's absolutely absurd to me and other scientists in this field because there's more genetic variation in individuals with black or dark skin than there is between people with dark skin and Caucasians. So, using these statistical paradigms, we will have a number of new categories that have nothing to do with skin color or even necessarily socioeconomic status but maybe will show commonalities between different populations that do get hypertension or do get different types of cancer. I think until we can do this on a meaningful scientific basis we need to be extremely cautious.

FROM THE FLOOR: Going back to another earlier question you were asked about, the possible implications of genetic research for longevity, one thing you said was you had a preference that people not look into some of these things that might extend life because of the situation in the world and the ability to take care of the people who are here. However, from our point of view we have a responsibility to take care of, in a very long-term sense, the financial implications of things like this. For example, we have to be sure that pension plans and social security systems are funded properly. On the other side, if we're building up large books of life insurance, they may have a lot more value than expected if longevity is increased. So, apart from preferences and things, what do you think is the actual outlook for some of this life extending, and would this type of therapy have an impact on existing populations or would it only have an impact on people who are to be born in the future?

DR. VENTER: I think as our fundamental knowledge changes about our own biology, and it's an important caveat there because of those 26,000 genes, we don't even know what half of them do at all. They're totally new to science. Of the half that look like something we know something about—I'd say about 10 percent—do we truly understand those functions?

The reason these things are hard to predict is if you look back at the linear bases of science over the last 50 years in this field, you can't use that as a prediction for going forward because at one bright line in history all of a sudden we have all this

information. It's changing the experimental paradigms on an exponential basis now. So, it could be next year where somebody comes up with a breakthrough that allows us to totally understand apoptosis on a grander scale, and there could be a point change in longevity. That's not super likely, but you can't rule that out. I think the average length of human life will continue to extend. For the "Next Thousand-Year Conference" I use the number of 250 years, roughly, in a couple of centuries for what an average lifetime will be. Changes will come. It's almost entirely impossible for me to imagine the pace at which they'll come, but it will be much sooner than anybody predicted from the last 10 or 20 years of science.

FROM THE FLOOR: I'd like to go back to the question of predicting the medical and insurance implications of genomic research. I think one of the difficulties may be that as an insurer, if you can give me a $1000 test that gives me a 2 to 3 percent increase in accuracy, I'm going to want to jump on that. I'm not going to be concerned with the fact that it's wrong a lot of the time. If it increases my ability to predict, then it's of economic value. I'd like to hear you talk a little bit more about how society might deal with the implications of imperfect knowledge as we go along the road to sort of more perfect knowledge.

DR. VENTER: I think all of our knowledge is imperfect, and I think one of the problems in this field is probability. The same couple that will take a 50/50 probability risk of having a severely deformed child will go out and buy a lottery ticket where they have a one-in-a-hundred-million chance of winning, and they really don't understand the differences in those probabilities. So I think a challenge we have is understanding that all this knowledge is imperfect. Genetics and genomics will rarely give a yes/no answer. It's all going to be in probabilistic statistics, and you're going to be the number-one messenger of how to interpret that. What you say about the 1 to 2 percent difference also gives me encouragement because the biggest impediment right now in terms of developing a preventative medicine paradigm is the lack of perceived incentive on third-party payers to actually go that route. It's certainly clear that, if it were left up to the U.S. government, we would probably never go that route. So perhaps this industry is going to be the one that leads us down that road into preventing disease and proving that it has a solid economic basis of doing that.

FROM THE FLOOR: How feasible do you see this genetic knowledge, this database you're building, to allow people to start designing dream babies in the future—the baby that doesn't have the marker for colon cancer and the markers for breast cancer, the baby that's blond-haired, blue-eyed, extremely intelligent and athletic?

DR. VENTER: Will it be feasible? Yes. And you can even make a very good case that it's desirable with meaningful diseases, diseases like ataxia-telangiectasia or other neuronal developmental diseases that will probably be impossible to cure or treat after the fact. If we're laying down the wrong pathways, you can't go back and tear up those roads and lay down new ones. So medically you'd like to be able to prevent the disease and eliminate those contributing genetic factors.

The problem is how do you do that without jumping to the second half of your question of people using that for trivial human traits of hair color or eye color or perceived perfection? My wife was initially insulted, but she's gotten over the fact that I said I've never met somebody that I thought should be cloned. I think we would all define perfection differently, and that underlies the problem of how we would deal with such technology. It's going to be a challenge. I think it will happen. I think it's inevitable. I hope not this century. Our knowledge is way too limited to do it even remotely intelligently. But probably within 200 to 300 years that will be a necessary part of human life perhaps to survive if we don't do something more dramatic about the environment.