PREPARED STATEMENT OF

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BEFORE THE
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Mr. Chairman and Committee members, I welcome the opportunity to testify before you today. I am J. Craig Venter, Ph.D., Founder, Chairman, and Chief Executive Officer of the J. Craig Venter Institute (JCVI). The JCVI is a not-for-profit research institute in La Jolla, CA and Rockville, MD dedicated to the advancement of the science of genomics; the understanding of its implications for society; and communication of those results to the scientific community, the public, and policymakers. The JCVI is home to approximately 250 scientists and staff with expertise spanning microbiology to human biology, genomics, bioinformatics/informatics, information technology, high-throughput DNA sequencing, policy research, and public education in science. The JCVI is a 501 (c) (3) organization.

I am a Co-Founder and Chief Executive Officer of Synthetic Genomics Incorporated (SGI), a privately held company located in La Jolla, California dedicated to commercializing genomic-driven solutions to address global needs such as new sources of energy, new food and nutritional products, and next generation vaccines.

Finally, I recently co-founded and am Chief Executive Officer of Human Longevity, Inc. (HLI), a genomics and cell therapy-based company focused on extending the healthy, high performance human lifespan. HLI's mission is to identify the therapeutically targetable mechanisms responsible for age-related human biological decline and to develop and apply innovative solutions to interrupt or block those processes, thereby meaningfully extending human lifespan.

In your letter of invitation to testify today, you asked me to address three questions:

1) What are the promises and limitations of synthetic biology, especially in advancing progress and understanding of biomedical problems?
2) How should federal science agencies approach funding of important biomedical science research?

3) How important are non-government research efforts in developing innovative treatments and how do these efforts complement or compete with government investment?

What are the promises and limitations of synthetic biology, especially in advancing progress and understanding of biomedical problems? What legal and ethical issues in synthetic biology must be addressed at this time?

Genetic engineering which has been the engineering of one or a few genes in organisms to create a new trait or effect from that organism has been transformed in recent years into the field of "synthetic biology" with the ability to rewrite multiple genes and pathways or even to create entire chromosomes and genomes from scratch.

These breakthroughs have significantly expanded the tool kit available to scientists and engineers, providing them with far greater capabilities to engineer organisms than previous techniques allowed. The field of synthetic biology includes the relatively new ability to rapidly and inexpensively synthesize long pieces of DNA from chemicals, combined with improved methods for genetic manipulation and design of genetic pathways to achieve more precise control of biological systems. These advances will help usher in a new generation of vaccines and other innovative medical treatments, and equally important, improved understanding of basic biology that will help us to continue solve biomedical problems.

Synthetic biology is changing the nature of *basic molecular biological research* and our understanding of basic biology. As DNA synthesis becomes ever less expensive, researchers will be able to use synthetic biology to rapidly change the DNA sequence of various genes or whole genomes, allowing them to understand basic cellular functions in a rigorous way. Prior to synthetic biology, investigators could only manipulate one or at most a few genes in any given experiment, resulting in a relatively slow discovery process. My laboratories, along with others globally, are using the tools and approaches of synthetic biology to understand the mechanisms of evolution at the molecular level, to define regulators of specific genes or gene pathways and to establish, at the molecular level, the minimal requirements for life.

On this latter topic, for over 15 years researchers at JCVI have been working to construct a "minimal cell", a living cell with the minimal set of genes that can still sustain cellular life. In 2010, we announced a seminal milestone: the creation of a bacterial cell controlled by a chemically synthesized genome. Several of the basic tools of synthetic biology were developed as part of this long-term project. It is our hope and belief that the chemically synthesized minimal genome, once complete, will be used by scientists worldwide as an experimental platform to understand how cells function. Such basic understanding of the rules of biology is vital for continued biomedical progress.

As I mentioned I also head two for profit biotechnology companies. Let me outline a few of the important programs underway there in which we are applying the basic science research of synthetic biology.

In 2013, a team of international researchers from JCVI, SGI, Novartis Vaccines and Diagnostics, and the Biomedical Advanced Research and Development Authority (BARDA, US Department of Health and Human Services) developed new methods to rapidly generate influenza vaccine seeds by using synthetic biology tools and technologies. This method will enable a more rapid pandemic response and yield a more reliable supply of better matched seasonal and pandemic vaccines than are currently available.

That same year, CDC and BARDA requested that the team use this method to develop a vaccine against a new strain of bird flu (H7N9) that appeared in China. BARDA is currently stockpiling that vaccine.

SGI scientists, in collaboration with Lung Biotechnology, Inc., a subsidiary of a local biotechnology company, United Therapeutics, are applying synthetic biology techniques to solve a very different problem: the chronic shortage of lung transplants available to the 400,000 people who die annually from various forms of lung disease. The hope is to develop methods to overcome the genomic incompatibilities that prevent animal lungs from being used in people. Employing the new tools of synthetic biology—DNA design, DNA synthesis, genome editing, and genome modification tools—our two companies hope to create animal organs that are safe and effective for use in humans.

SGI is also developing new nutritional products using algae. The company has partnered programs to develop omega 3 supplements such as DHA, EPA and astaxanthin through genetic engineering and strain selection of algae. SGI continues to explore the possibility of using algae to develop cost effective algae-based biofuels.

I along with all my teams consider the ethical and societal implications of the work to be as important as the scientific research. We examined ethical concerns before beginning any actual experiments or research into constructing a minimal cell or the work to construct the first synthetic cell.

In 1999, we convened the first ethical review of synthetic biology by a panel of experts at the University of Pennsylvania. The panel's independent deliberations, published in the journal Science along with the scientific minimal genome research, concluded that there were no strong ethical reasons that should prevent the team from continuing research in this field as long as they continued to engage in public discussions, which we have continued to do so today.

In 2007, JCVI, along with researchers at MIT and the Center for Strategic and International Studies in Washington, DC, completed a two-year study of biosecurity and biosafety concerns associated with synthetic biology and presented and evaluated a series of policy options for consideration by policymakers. One of those options was issued as guidance by HHS in 2010 for firms that sell synthetic DNA. All major providers, including SGI DNA, follow this screening guidance.

JCVI recently completed a study funded by the Department of Energy, examining how well the current U.S. regulatory system for genetically engineered products will be able to handle anticipated products engineered using synthetic biology. Our conclusion is that U.S. regulatory agencies (FDA, USDA, and EPA) have adequate legal authority to address most, but not all, potential environmental, health, and safety concerns posed by the new technology.

Finally, I should add that ethical issues related to synthetic biology were reviewed by the Presidential Commission for the Study of Bioethical Issues. The 2010 study, "New Directions: The Ethics of Synthetic Biology and Emerging Technologies", recommended that the government "remain forward-looking about the potential benefits and risks to the public", but did "not recommend that additional agencies or oversight bodies need to be created to oversee synthetic biology."

What are your views on how federal science agencies should approach funding on important biomedical science research? What specific recommendations do you have?

The United States is fortunate to have a robust federally funded science program in the form of the National Institutes of Health and the various federal agencies such as the Centers for Disease Control. While there are classic examples of how our government has been key to moving new fields forward such as space exploration and NASA, my experience is centered on the NIH and the human genome project. I was a researcher with NIH in the late 1980s and early 1990s and was privileged to be involved in some of the earliest discussions about a large scale project to tackle sequencing of the human genome.

Fourteen years ago on June 26, 2000, President Clinton, Francis Collins of the NIH, and I, representing Celera Genomics, announced the first sequence of the human genome. My team at Celera spent $100 million over 9 months to obtain our sequence using a then novel approach called whole genome shotgun sequencing , which is now an industry standard. It's just recently become possible to sequence a human genome for around $1,500 in just a few days. This represents is a phenomenal rate of cost and capability improvement even exceeding improvement in computer chips known as Moore's Law.

Recent progress with the use of genomics to improve the treatment of some cancers is likely just the beginning of a genomics-based revolution in human health and the practice of medicine. The ALK gene is a good example. ALK, or "anaplastic lymphoma receptor tyrosine kinase", is responsible for signal transduction and can be switched on or off. Altered forms of this gene, those that do not regulate normally and are permanently switched on, are present in a variety of cancers and occur in about 4% of non-small cell lung cancers. Pfizer developed a drug called Crizotinib (aka Xalkori) that was FDA licensed in 2011 that blocks the carcinogenic kinase activity of the ALK gene and significantly increases progression-free survival of non-small cell lung cancer patients with the ALK mutation. This is just one example of how utilizing information from the human genome can aid in development of better and more targeted therapies, can identify patients that will likely benefit most from certain therapies, and ultimately, lead to improved clinical outcomes.

The advances in genome sequencing and availability of large-scale cloud-based computing platforms are opening an important new opportunity in biomedical science research but substantial challenges remain. To date most human genomics research has focused on: 1) a small part of the genome mostly on exoms, the parts coding for proteins and often looking only at single nucleotide polymorphisms or SNPs even though we know that the whole genome is vitally important to human health; 2) haploid or non-diploid genomes which do not give researchers the complete parental lineage of the individual thereby being unable to resolve compound heterozygote alleles that are likely quite important in human health; 3) variations found in germline and somatic human cells, ignoring the human microbiome, the trillions of bacteria living in and our bodies with diverse genomic and metabolic functions and are inextricably linked to human health and; 4) small study populations unable to identify rare genetics events occurring on the level of 1 in 50,000 people that again are likely to be critically important in human health.

Federal science agencies could dramatically accelerate progress in genomics by recommending a new set of guidelines for funding federal research involving human subjects. Such guidance should include a presumption that human clinical trials require whole human genome sequencing by a qualified laboratory using the latest technologies and bioinformatics methods. These recommendations should include a requirement for full characterization genomic and functional characterization of the human microbiome. Such a requirement would spur private and public sector efforts to address the next frontier of challenges in genomics at relatively low cost to the government.

Setting this guideline will require bold leadership because of the multitude of sensitive and critically important national and international ethical, social, and legal issues. The time to act is now. I expect that pharmaceutical companies will rapidly adopt a whole human genome sequencing standard because their economic incentives are highly aligned with the use of these

data to identify new drug targets, and the potential to increase the therapeutic efficacy of candidate drugs through targeted genomics-based enrollment.

A federal standard requiring whole human genome sequencing for appropriate government-funded human trials should be accompanied by a federal research commitment to also accelerate progress in identifying opportunities to improve human phenotype technologies and methods used in medicine. Phenotype is the general term used to describe the physical, biochemical, and physiologic characterization of humans and other living things; this information is essential to understanding genomics. Despite the progress made in electronic medical record adoption, the medical enterprise remains a largely narrative enterprise. As an example, the current standard for reporting the results of magnetic resonance imaging or MRI is a one- to two-paragraph description of the radiologist's interpretation in the form of a report back to the ordering physician. This is generally inadequate for the quantitative analytics needed to find genomic associations.

At Human Longevity, we've partnered with CorTechs Labs, a company formed to commercialize technologies and research done at the University of California San Diego that has an FDA approved method and software to translate MRI into quantitative neuroanatomical volumetric data. For example, using the NeuroQuant product from CorTechs Labs we can capture the exact volume of the hippocampus, a part of the brain that's important for memory and shows remarkable changes in Alzheimer's disease. We need similar technologies and methods yielding high quality quantitative data across all domains of the human phenotype. This extends even beyond the current medical domain and includes the need for much better characterization of family history, environmental exposures, and social and behavioral determinants of health. The availability of and interest in mobile smartphones and other new sensors to passively characterize human various activities related to health may provide valuable new data in some of these domains.

I think setting a new standard requiring whole human genome sequencing for appropriate government-funded human trials would also accelerate critically important progress in genomic-related regulatory policy in the US and globally, spur an increased commitment by medical schools and allied health professional schools to training in medical genomics, and provide a basis for renewed efforts in public dialogue about the role of genomics in human health and the practice of medicine.

How important are non-government research efforts in advancing drug discovery and developing innovative treatments? How do these efforts complement or compete against government investment on these problems? Are government policy incentives properly structured to encourage private sector investment to make medical breakthroughs?

Government-funded research alone is clearly insufficient to solve the biomedical challenges facing society today. This is now especially true given the recent decline in NIH funding. Research at not-for-profit independent research institutes such as JCVI and at universities across the country is suffering.

The private sector must not only do their share, but also pick up the slack. This is one reason I recently launched my new company, HLI. HLI has raised $80 million dollars to build the largest human sequencing operation in the world. We plan to build the most comprehensive and complete human genome, microbiome, and phenotype database available to tackle the diseases associated with aging-related human biological decline.

HLI's goal is to change the way medicine is practiced by helping to shift to a more preventive, genomic-based medicine model, which we believe will lower healthcare costs. The goal is not necessarily lengthening life, but extending a healthier, high performing, more productive life span.

In brief we are attempting to build the world's most advanced proprietary human health data base including whole human genome sequences, microbiome data, proteomics, and metablomics along with extensive human phenotype data. We are going to try to overcome the major challenges I highlighted earlier including: using the whole sequence instead of just part of the sequence, trying to get to diploid genomes to resolve compound heterozygocity, correlating the human genome with the microbiome, and finally, and maybe most importantly, doing this at a much different scale than has ever been attempted.

We plan to complete our first 1000 human genomes next month. By the end of calendar year we will be at an installed capacity of 40,000 genomes per year and plan to increase capacity steadily. We plan to sequence 50,000 genomes in 2015, and to have the capability to run 100,000 human genomes per year by the end of 2015. By 2020, we anticipate we will have more than one million human genomes in our database. Our bet, and the risk our investors are taking with us, is that if we can do this, solving the numerous genomic, bioinformatics, and phenotype challenges, we may reveal many new clinically actionable associations and by doing this we hope to revolutionize the practice of medicine. I think that at some point in the near future everyone will have their whole genome sequenced, and this sequence will be an essential foundation for our health and the practice of medicine. I may be wrong though. We are going to try the experiment to find out.

HLI's and similar privately funded research complements and builds upon government investments in these areas. Both research funding streams must remain strong if we are to make rapid progress applying genomics and synthetic biology to produce medical breakthroughs. One

of the best ways to encourage private sector investment is to continue to fund research in the basic biology that underpins future biomedical advances.

Government and non-government research efforts are essential for progress in biomedical research science. The Human Genome Project and my efforts with Celera Genomics provide a good example. The scientific leaders who requested $3B of funding from Congress in 1989 to pursue the Human Genome Project and the Executive and Legislative leaders who that approved of this project represent America at its best. The progress made in government and non-government genomics research would not have occurred without this leadership. My decision to leave the my not for profit research institute in 1998 and purse an independent private sector effort for human genome sequencing using a "whole genome shotgun sequencing" approach is a good example of the value of the private sector accepting a risk the government-sponsored Human Genome Project would not. Taking this risk led to innovation that today is standard and responsible for much of the progress that's been made in genomic sequencing. However, there are many examples where taking this risk does not pay off and companies fail, but this why it's such an important complement to governmental research efforts. Government research should establish useful directions and create platforms for the private sector to build on and use to take risk and fail or succeed, whether it's computation and the digital computer, the space program, the Internet, the Human Genome Project, or the Brain Initiative.

I've advocated for you to consider establishing a new federal standard requiring whole human genome sequencing for appropriate government-funded human trials. My company HLI would benefit from establishing such a standard, but so would many other for-profit, non-profit, and governmental research organizations. We all benefit from the competition this would generate and all of our families and communities will win through better health and better medical care at affordable costs. I appreciate the opportunity to share some of my thoughts with you today, and I look forward to further discussion and progress.