Statement by Lynn Jorde, Ph.D., Chair of the Department of Human Genetics University of Utah Health Sciences Center on FY 2016 Appropriations for the Department of Health and Human Services submitted to the Subcommittee on Labor, Health and Human Services, Education and Related Agencies Committee on Appropriations – United States House of Representatives April 29, 2015

Good morning, Chairman Cole, Ranking Member DeLauro, and distinguished members of the Subcommittee. Thank you for allowing me to testify. Today, I would like to talk with you about genetic discovery, precision medicine, and the telescope.

A New View

Though many contributed to the technology, a Dutch eyeglass maker named Hans Leppershey is credited as the first to file a patent on the telescope. In 1608, when astronomers first began to use this groundbreaking invention, human understanding of our place in the universe was forever changed.

Today, we genetic scientists find ourselves at a similar threshold as we begin to map the genetic universe in a search for the seeds of inherited disease. Thanks to modern DNA sequencing technology, what once took 10 years and 1 billion dollars can now be achieved with a few days' time and a few thousand dollars. For about the cost of an MRI, we can now sequence an entire human genome, enabling a view into the 3-billion base pairs of DNA that makes each of us unique. Our genomes dictate the color of our eyes, the curl of our hair and, in many cases, the diseases that we will confront in our lifetimes.

These diseases, both rare and common, are the very reason we are on this journey of genetic discovery—because when we know the genetic causes of disease, we can develop precision medications and diagnostics to treat and, in some cases, prevent them from ever occurring.

The Promise of Precision Medicine

From this genomic observatory we see gains in both the short and long terms. In the short term, we can describe illnesses more accurately; and we can better utilize existing therapies and basic tools like family history and diagnostics to identify at-risk patients. In the long term, when we identify disease-causing genes we can tailor our treatments to the unique genetic constitution of each patient—improving outcomes and avoiding the enormous financial costs of trial-and-error drug administration.

Take, for example, the recently discovered *PCSK9* gene. *PCSK9* is expressed in the liver, where it is involved in the processing of cholesterol. In a small number of families, a variant of the *PCSK9* gene causes abnormally high cholesterol levels that are inherited from generation to generation and often lead to fatal heart disease. Genetic studies of these families revealed the cause of their high cholesterol levels. This discovery in turn gave scientists the clue they needed to develop a new class of drugs that lower cholesterol levels by more than 50%. Importantly, these drugs, called PCSK9 inhibitors, lower cholesterol not just in these rare families, but also in the great majority of people who have high cholesterol levels—including those who are already taking statin drugs. The PCSK9 story illustrates how collaborative genetic studies can benefit millions of people worldwide.

Another story is that of the *APC* gene, which was discovered at the University of Utah more than 20 years ago. Those who have disease-causing variants in *APC* are virtually certain to develop colorectal cancer by age 50 or so. Once identified, at-risk family members can be genetically tested to determine whether or not they have inherited a disease-causing *APC* variant. Those who inherit the variant can be closely monitored by colonoscopy and treated when necessary, a life-saving procedure that can prevent

colon cancer in these patients. Those who do not inherit the variant do not need costly annual colonoscopies, avoiding anxiety and needless medical expense.

Genetic research at our institution also contributed to the discovery of the major genes that cause familial breast and ovarian cancer (*BRCA1* and *BRCA2*) and dozens of others. Genetic tests for disease-causing versions of these genes have helped to save thousands of lives and millions of dollars.

The Value of Genetic Science

With the costs of health care continuing to skyrocket, we are driven to improve the outcomes we deliver for every precious dollar spent. As we increase our ability to identify the genetic and environmental origins of disease, we advance our capacity to practice precision medicine by delivering the right intervention to the right patient at the right time and at the right cost.

At the University of Utah, we have a long history of genetic discovery and translational science. In our health care system—an ecosystem dedicated to operationalizing medicine in a high-quality, patient-centered and value-based manner—we view advances in genetic science and precision medicine to be in direct alignment with our ability to improve patient care.

So how do we find these genetic culprits?

Genetic Science, Powered by Families

Finding an unknown disease-causing gene in an individual's 3 billion base pairs of DNA is like scouring all the books in the Library of Congress for one misspelled word. Despite the needle-in-a-haystack challenge, scientists at the University of Utah have identified dozens of genes responsible for diseases—in addition to the aforementioned

breast cancer, ovarian cancer and colon cancer genes—including cardiac arrhythmia and high blood pressure. Much of this success is due to Utah's large and well-documented families, who serve as a singular resource for genetic discovery. Indeed, some Utah founders have more than 10,000 living descendants. These families are part of the 7.3-million-member Utah Population Database (UPDB), the world's largest repository of family histories linked with more than 22 million public health and clinical records. The second largest, by comparison, is the deCode database that contains records from about 500,000 persons from Iceland, which is genetically distinct from the Utah population and therefore is likely to contain a distinct set of disease-causing genetic variants.

The families recorded in UPDB allow us to trace a gene as it is passed from generation to generation. These families are thus a genetic "magnifying glass," which enables us to identify the causes of disease with a precision and efficiency that has never before been achievable. The Utah Genome Project (UGP), which was launched in 2012 at the University of Utah, capitalizes on this unique resource and harnesses the power of Utah's large families to discover new disease-causing genes that underlie conditions such as diabetes, psoriasis, Crohn disease, obesity, and heart disease. UGP discoveries are enabling the development of genetic diagnostics and precision therapies that can transform health care.

Most of the large-scale genetic discovery projects currently under way involve large cohorts of unrelated patients and controls. These resources are extremely valuable, but the UGP is unique in that it provides large-volume family data, where genetic signals are most easily discovered because they occur in multiple family members. Imagine a faint star in a distant galaxy. With only one fleeting view in a telescope, we can't be sure

of its existence. But with multiple, repeated views, our confidence grows. In the same way, families offer repeated signals of the same genetic variant, greatly increasing our ability to discover and validate a disease-causing gene. Because of the added power of family analysis, fewer individuals need be analyzed in order to make genetic discoveries. The UGP thus complements existing cohorts and provides a wealth of added potential for discovery.

Another major challenge in modern genome analysis is the sheer volume of data (3 billion DNA bases) generated for each of thousands of patients. To meet this challenge, Utah Genome Project investigators have built a software platform for efficient, accurate analysis of family genetic data. In just hours, each person's disease-predisposing genetic variants can be identified. This genetic search engine, now used globally in more than 300 research institutions, will lead to genetic discoveries, new genetic tests and precision treatments to end diagnostic odysseys and advance precision medicine.

The Utah Genome Project is already enabling gene and drug discovery, identification of at-risk families, and development of some of the best genomic analysis platforms in the field. With continued support for UGP, and synergistic programs like it, the analytic tools and informative data generated by the UGP will become international resources for genetic research. In fact, the UGP has already catalyzed active collaborations with scientists and physicians at Washington University in St. Louis, Vanderbilt University, and Phoenix Children's Hospital.

It is estimated that the $3 billion spent on the Human Genome Project has yielded nearly $800 billion in economic return. Likewise, our ongoing research on genetics and

precision medicine is a sound investment in the future. By using genetics to target the right treatment for each individual patient, continued investment will save billions of health-care dollars and millions of patient lives.

Outlive Your Family History

Each of us has a history of diseases that run in our families. As a nation, we have the opportunity to unlock the genome and apply these discoveries to precision diagnostics, treatments, and drug developments. With this knowledge, we have the opportunity to outlive our own family histories.