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Pediatric Rare Disease Research at the National Institutes of Health

Statement of

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Good morning, Mr. Chairman and Members of the Committee, my name is Alan E. Guttmacher, and I am representing the National Institutes of Health (NIH), an agency of the Department of Health and Human Services (HHS), at today's hearing on pediatric rare diseases. By background, I am a pediatrician and medical geneticist and currently serve as Acting Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) at the NIH. We appreciate the Committee's interest in this topic, which is so important to the individual children who are affected by rare diseases and to their families. A rare (or orphan) disease is generally considered to have a prevalence of fewer than 200,000 affected individuals in the U.S.

Let me begin by offering a specific example: one of my former patients, Kevin Hartmann, has Marfan syndrome. This is a genetically inherited disorder which affects the body's connective tissue. Individuals with this condition tend to grow extremely tall and thin, have unusually lax joints and share certain other physical features. One of the most serious issues associated with this condition is that the aorta can become stretched so thin that it tears, requiring emergency replacement of the aortic root or sometimes resulting in sudden death, as was the case with the U.S. Olympic volleyball star, Flo Hyman. Individuals with Marfan syndrome are usually counseled to avoid physical stress to their hearts or other tissues caused by many sports, and must be monitored closely all their lives. Kevin has made a terrific video about his life with Marfan syndrome, http://vimeo.com/12005105.

Clearly, the availability of a medication that could slow aortic growth and prevent tearing would make an enormous, literally potentially lifesaving difference to Kevin, his family, and others with Marfan. In 2007, a clinical trial began, funded by the National Heart, Lung, and Blood Institute (NHLBI) at the NIH and conducted through its Pediatric Research Network, comparing two drugs – Atenolol and Losartan, which are already on the market -- to see if one is better than the other at slowing the speed of aortic enlargement. Both of these drugs are commonly used to lower high blood pressure, but groundbreaking research using a mouse model and published in 2006, supported by several NIH Institutes and Centers (ICs), showed that losartan prevented aortic enlargement and other features seen in individuals with Marfan syndrome.

Many such examples exist across the NIH. Although the NICHD supports the bulk of research on normal and abnormal child health and development, most of the NIH's 27 ICs include pediatric research in their portfolios. In Fiscal Year 2009, the last year for which we have complete data, the NIH funded nearly $3 billion in pediatric research, with another $505 million for pediatric research from funding under the American Recovery and Reinvestment Act. Although the NIH does not report specific funding information on rare diseases, it does collect and report on the category of orphan drugs; in FY 2009, the portion of grants funded by the NIH in the Orphan Drug category that was also reported in the Pediatric category was just over $86 million.

Developing and testing drugs in children has long posed a particular challenge, even for drugs used to treat more common conditions, because of the vulnerable nature of this population and because children change substantially as they grow. The Best Pharmaceuticals for Children Act (BPCA), most recently reauthorized in 2007, sought to redress the lack of information on medication safety, effectiveness, and dosing in children through several means. Under the Act,

the NIH is authorized to identify therapeutic gaps in pediatrics and support the research necessary to fill those gaps. Led by the NICHD, all of the NIH ICs that have a significant pediatric portfolio contribute funds and expertise to implement the BPCA. Current co-funded projects include many studies on understanding and treating rare diseases: the National Cancer Institute's (NCI) Children's Oncology Group is performing five BPCA pediatric cancer drug studies, the NHLBI is supporting the "Baby HUG" trial, aimed at demonstrating whether the drug hydroxyurea is effective at decreasing painful crises and preventing chronic organ damage in young children with sickle cell disease, and the Foundation for the NIH has contributed to NICHD's pharmacokinetic and safety study of Baclofen to treat spasticity in children with cerebral palsy.

Some rare conditions affect individuals systemically, thus requiring the expertise of several of the NIH ICs. One mechanism used at the NIH to deal effectively with such conditions, is the establishment of a trans-NIH working group. The NICHD leads one such group, the NIH Fragile X Research Coordinating Group. Fragile X syndrome (FXS) is the most common inherited cause of intellectual and developmental disabilities. Nine participating NIH ICs meet regularly to discuss implementation of the Research Plan on Fragile X and Associated Disorders, which the group developed with the input of outside experts and published in FY 2008. Each goal area of the plan is being addressed by grants funded across the member institutes. One excellent example is a Phase I trial of a novel drug that may effectively compensate for the missing protein in individuals with Fragile X; through support from several NIH ICs [the NICHD, the National Institute of Mental Health (NIMH), the National Institute of Neurological Disorders and Stroke (NINDS)] and the private foundations Autism Speaks and FRAXA, scientists at Seaside Therapeutics are testing a leading compound in healthy adults as a potential treatment for FXS. Results suggest that the medication is safe and tolerable; a Phase II clinical trial study of dosage and efficacy in adults with FXS is planned. Should the results from these adult trials prove promising, the compound will be assessed for pediatric safety and clinical trials in children. Such public-private partnerships can help leverage investment and other resources for rare disorders for which no treatment is currently on the market.

Individually, the NIH ICs are engaging in a wide variety of research projects on pediatric rare diseases. Established in 1993, the NIH Office of Rare Diseases Research (ORDR) helps to coordinate and support these activities across the NIH and to provide information to the research and patient communities about these conditions, potential treatments, and ongoing research opportunities. Among other activities, the ORDR, in collaboration with six other NIH ICs, oversees the Rare Diseases Clinical Research Network, which comprises ten consortia with more than 70 sites across the U.S. The goals of these sites are to make investigational studies and treatments more accessible to patients with rare diseases, and to facilitate the recruitment of patients for clinical trials. Researchers affiliated with the Network study more than 40 rare diseases, many of them pediatric, such as intellectual and developmental disorders, rare bone marrow failure conditions, and rare pediatric liver disease. Many Network members are testing the safety and efficacy of new therapeutic agents, including pediatric therapeutics. For example, the NINDS supports several of the research consortia within the Network, including the Inherited Neuropathies Consortium and the Lysosomal Disease Network, both of which include research on disorders affecting children. The Network also is targeting early stage investigators to encourage them to center their careers in rare diseases; in September 2010, the Network and the

NIH Clinical and Translational Science Awards (CTSAs) are cosponsoring a conference to teach new researchers and junior faculty about rare disease research methodology.

Another new NIH program is aimed specifically at the issue of development of therapeutics for rare and neglected diseases, including pediatric conditions. Announced in May 2009, the Therapeutics for Rare and Neglected Diseases (TRND) initiative is a trans-NIH, collaborative program overseen by ORDR and administered by the National Human Genome Research Institute (NHGRI). TRND investigators will begin with a chemical compound that is known to have some biological effect in the laboratory on a given disease, and progress to a candidate compound for a new drug application to the Food and Drug Administration. Often, the candidate compounds will be licensed to pharmaceutical companies for clinical testing, permitting the TRND program to remain focused on the most scientifically challenging stages of preclinical development. The goal is to "de-risk" development of new drugs for less common diseases to make them more attractive to private companies. At the same time, this innovative program will advance the entire research enterprise by allowing open dissemination of the information learned during the initial testing phases, expanding the overall research base and potentially shortening the time period for the development of new drugs. Among the new projects initiated in 2010 is a mid-stage "re-purposing" (testing a drug developed for another purpose) project for the rare pediatric condition, Niemann-Pick Type C (NPC), a neurodegenerative disease. As will be true of many of TRND's efforts, this project is a collaboration of government, academic scientists, and patient advocacy groups.

In addition to the research activities already mentioned, a sampling of the types of research across the NIH illustrates the range of basic to clinical research activities underway and also provides a sense of why therapeutics for some pediatric rare conditions remains so elusive.

- The NCI's Childhood Cancer TARGET Initiative is a public-private partnership developed to harness the power of cutting-edge genomics technologies to identify valid therapies for childhood cancers rapidly. The program's initial focus was on neuroblastoma and acute lymphoblastic leukemia (ALL) but was expanded with ARRA funds to include several other conditions. As a result of TARGET, there will be a virtually complete catalogue of gene mutations and other gene alterations that occur in these childhood cancers.
- The Children's Oncology Group (COG) develops and coordinates cancer clinical trials at over 200 member institutions throughout the U.S. and around the world. Through the COG network, children with cancer can access state-of-the-art therapies regardless of where they live. One of the many consortia of investigators within COG, the Pediatric Brain Tumor Consortium, aims to rapidly conduct phase I and II clinical evaluations of new therapeutic drugs, biological therapies, and radiation treatment strategies for children.
- The National Eye Institute has sponsored research that provides health care professionals with improved prognostic indicators and treatments options for retinopathy of prematurity, a blinding disease that affects premature infants. The Early Treatment for Retinopathy of Prematurity study demonstrated that therapy administered in the early stages produced far better outcomes than traditional timing of treatment. The study also

resulted in an improved risk assessment model to identify those infants at highest risk for developing severe vision loss.

- In addition to its research on rare pediatric genetic diseases, such as cystic fibrosis, sickle cell disease, thalassemia and hemophilia, which has resulted in many individuals with these conditions living into adulthood, the NHLBI also supports research on rare acquired pediatric diseases. For instance, the NHLBI funded the development of recombinant surfactant to improve the lung function of the children with bronchopulmonary dysplasia, a serious lung condition that primarily affects children who received oxygen therapy when they were premature neonates.
- Medulloblastoma, the most common form of pediatric brain tumor, is relatively responsive to traditional cancer treatments (surgery, chemotherapy, and radiation), but long-term survivors often suffer from life-long developmental, behavioral and cognitive disturbances. Investigators supported by the National Institute on Aging are working to understand the basic mechanisms underlying medulloblastoma, so novel treatments can be developed to target tumor cells specifically, without damaging the developing brain.
- The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports a broad portfolio of basic, translational, and clinical research on primary immune deficiency (PID) diseases. PID diseases, such as DiGeorge syndrome, Hyper-Immunoglobulin E syndrome, and Severe Combined Immmunodeficiency (SCID), are rare genetic diseases that lead to recurring, often life-threatening infections in affected individuals. Among other research-related activities, the NIAID-supported Primary Immune Deficiency Treatment Consortium is a multi-center collaborative network focused on studying children with PID diseases and the treatment, with hematopoietic stem cell transplantation, of these diseases.
- Epidermolysis bullosa (EB) is a group of rare, inherited blistering conditions. Recessive dystrophic EB (RDEB) is a particularly severe form of the disease, with debilitating, chronic wounds of the skin, mouth, and esophagus. Researchers supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) have succeeded in healing wounds in a mouse model of this disease by injecting the mice with RDEB patient cells in which the gene defect has been corrected. This approach may be useful in developing therapies for RDEB. On another front, the NIAMS helped to establish the Childhood Arthritis and Rheumatology Research Alliance, a nationwide network of pediatric rheumatologists. The group is completing a clinical study of the effects of statins (drugs used to lower "bad" cholesterol) against fat buildup in the blood vessels of children with lupus, which could lead to preventive treatments for these pediatric patients.
- Recurrent respiratory papillomatosis (RRP) is a disease in which non-cancerous tumors grow in the air passages leading from the mouth and throat into the lungs. The tumors may grow quickly, requiring surgical removal to prevent blockage of the respiratory tract and suffocation. Caused by a virus possibly contracted during childbirth, the tumors often recur, requiring additional surgeries. Researchers funded by the National Institute on Deafness and Other Communication Disorders are exploring whether the use of a common anti-inflammatory drug may delay or prevent the recurrence of these tumors, as well as examining the genetic makeup of individuals of those who are exposed to the virus but do or do not develop RRP.

- In the early 1960s, the life expectancy of a child born with cystic fibrosis (CF) was just 10 years; current life expectancy for individuals with CF has almost quadrupled to 37 years. The 1989 discovery of the CF gene by now-NIH Director Francis Collins opened important windows into understanding the CF disease process, and suggested potential therapeutic approaches. While there is, as yet, no cure for CF, ongoing research provides hope for continued improvement of medical care for CF. Scientists supported by the National Institute for Diabetes and Digestive and Kidney Diseases recently developed a pig model of the disease, which provides an important tool for testing therapeutic strategies. New medications are currently in development, including one which may provide a protein for patients with some versions of the gene, and others to improve the salt-water balance in people with CF to enable them to clear mucus from their lungs.
- Understanding environmental exposures that can lead to clinical disease is critical to the prevention of those diseases or development of therapies to treat them. For example, investigators funded by the National Institute of Environmental Health Sciences are studying cognitive and motor development related to prenatal exposure to organophosphate pesticides in three- to nine-year olds. The study is evaluating the effects of these exposures on brain structure, metabolism, and connectivity among regions of the brain, and assessing attention deficit hyperactivity disorder, pervasive developmental problems and sleep disorders in these children.
- To build on new opportunities made possible through gene discoveries and other basic science advances, the NINDS supports translational research programs to develop therapies for spinal muscular atrophy, muscular dystrophies, and other rare pediatric neurological diseases. Some of these therapies are now entering early clinical trials, and a new clinical trials network that will help expedite such research for these disorders is underway. In May 2010, the NINDS and the NIAMS launched a five-year natural history study of Duchenne muscular dystrophy, which aims to validate non-invasive approaches to monitor the progression and treatment of this disease, with the potential to facilitate the development of promising new therapies.

For many parents whose children have just been diagnosed with a rare condition, it is difficult to find reliable information about that condition. The Genetic and Rare Diseases Information Center (GARD) was created in 2002 by the NHGRI and the ORDR to help people find useful information about these diseases by providing timely access to experienced information specialists who can offer information on what research is being conducted, what genetic testing services are available, and which patient advocacy groups to contact for a specific rare or genetic disease (see http://rarediseases.info.nih.gov/GARD). Genetics Home Reference is a free online health resource from the National Library of Medicine (NLM). It is designed to give patients, families, and caregivers basic information about genetic conditions and the genes or chromosomes related to these conditions. This web site includes summaries of more than 500 rare genetic disorders, many of which directly affect the health of infants and children. The site also provides background materials to help the public understand the significance of genetic disorders and newborn screening. Genetics Home Reference is available at http://ghr.nlm.nih.gov.

For many families whose children have a rare disorder, even obtaining a diagnosis can be a devastating process taking years of frustrated effort. For many conditions, a diagnosis can be

essential in allowing the patient to receive appropriate treatment, even if there is no cure. Early treatment or other intervention can often ameliorate the full impact of the disease. The NIH is taking steps to expand scientific knowledge around rare diseases and diagnoses.

Together, the ORDR, the NHGRI, and the NIH Clinical Center recently organized the NIH Undiagnosed Diseases Program. Using a combination of the extensive scientific and medical expertise available at the NIH, the twin goals of this new program are to provide answers to patients with mysterious conditions that have long eluded diagnosis, and to advance medical knowledge about rare diseases. Any patient, whether a child or adult, with an undiagnosed medical condition can be referred by his or her physician for possible evaluation in the program.

Genetic screening shortly after birth permits referral to medical specialists and treatment for pediatric rare diseases to occur as soon as possible. Starting in the 1960s, with a screening test for a rare disorder (phenylketonuria, or PKU), a majority of states now screen for 29 conditions. The NICHD is leading research efforts to increase the number of genetic tests for a wide range of rare and common conditions through the Hunter Kelly Newborn Screening Program, formally established in 2009 to honor the son of National Football League Hall of Fame quarterback Jim Kelly, who died in 2005 of Krabbe disease, a rare, fatal genetic disorder affecting the nervous system. The NICHD program is aimed at identifying new screening technologies and research on managing and treating conditions that newborn screening can detect.

Because most conditions targeted by newborn screening are rare, large sample sizes are needed for research, and standard coding and terminology are required so data can be compared and pooled across state jurisdictions. In collaboration with other HHS agencies, the NLM created a Newborn Screening Coding and Terminology Guide, a free online resource that provides guidance to promote efficient electronic exchange of standardized newborn screening data. The goal is to encourage widespread use of these national data guidelines for transmitting newborn screening results to support the creation of regional and national data registries that will be used for detection, prevention, and treatment of rare conditions that affect the pediatric population, and facilitate more timely diagnosis and follow-up in the medical home.

Research on pediatric rare diseases, and future breakthroughs, are dependent on the interest and expertise of well-qualified scientists. In addition to the NIH's ongoing research training and career development programs, the NIH's Office of Science Education, in collaboration with ORDR, has developed a science education module for middle schools focused on medical genetics and rare diseases such as Marfan syndrome, childhood leukemia, and flesh-eating bacteria. After taking the lessons, students will have investigated what constitutes scientific evidence, will understand the fundamentals of inheritance and learn that this explains why some rare diseases are more prevalent in some groups than others, and will understand that many people with rare diseases can lead meaningful lives and should not be stigmatized. This curriculum will be available in September and free to teachers, in the hopes that it will engage young people on these topics and catalyze their thinking about choosing scientific careers.

With this breadth of NIH-funded research, and armed with such new resources as the human genome sequence and approaches such as the TRND program, we are poised for an era of greater understanding of the biology of many rare diseases and thus, more effective therapies. Thank you

for the opportunity to present today, and I would be pleased to answer any questions you may have.