Public Comments to the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children

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REGARDING NEWBORN SCREENING FOR PRIMARY IMMUNE DEFICIENCY DISEASES SUBMITTED TO THE ADVISORY COMMITTEE ON HERITABLE DISORDERS AND GENETIC DISEASES IN NEWBORNS AND CHILDREN

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Mr. Chairman, thank you for the opportunity to present testimony on behalf of the Immune Deficiency Foundation (IDF).

IDF is the national non-profit, voluntary health organization dedicated to improving the treatment and diagnosis of primary immunodeficiency diseases through research and education. Head-quartered in Towson, Maryland, IDF was founded in 1980 by a group of parents of primary immunodeficient children and their physicians who wanted to focus attention on the needs of the primary immunodeficiency community.

Genetically determined primary immunodeficiency diseases (PIDD) are disorders in which part of the body's immune system is missing or does not function properly. In contrast to secondary immune deficiency disease in which the immune system is compromised by factors outside the immune system, such as viruses or chemotherapy, primary immunodeficiency diseases are caused by inherited defects in the immune system. More than 140 different primary immunodeficiency diseases are now recognized. These disorders affect people of all ages and races and both sexes. They are generally thought to be rare; however, neither the incidence nor prevalence of these disorders is known. This is due to the fact that there is no screening for any primary immunodeficiency disease at birth or during childhood or adulthood anywhere in the world. Thus, most patients are not diagnosed until they develop a serious infection, which certainly adversely affects the outcome of therapy. I suspect that these conditions are at least as common as the conditions currently screened for in newborn testing.

Based on IDF's 2002 National Patient Survey, the average length of time between the onset of symptoms in a patient and a definitive diagnosis of PIDD is 9.2 years. Some patients had been hospitalized up to 20 times before the diagnosis was made. In the interim, those afflicted may suffer repeated and serious infections and possibly irreversible damage to internal organs. Additionally, the number of permanent functional impairments increases dramatically the longer it takes to diagnose a patient with a primary immune deficiency. Many primary immunodeficient patients are able to maintain their health through regular infusions of intravenous immunoglobulin (IGIV). IGIV is a pooled plasma derivative that bolsters the patient's immune system. IGIV is administered intravenously, on average, every three to five weeks for the lifetime of the patient. However, if primary immune deficiency diseases are not properly diagnosed and treated, they can lead to serious illness and early death.

In November 2001, a workshop was convened by the CDC to discuss ways to improve health outcomes among persons with primary immune deficiency diseases. A multidisciplinary panel of persons knowledgeable in PIDD and public health met to identify and discuss public health strategies that can be applied to primary immune deficiency diseases and possibly for other genetic disorders. IDF actively participated in the process. As a result of that meeting, the CDC developed a strategic plan to address the problem of PIDD. The plan included the following four components:

- Public health assessment --- application of traditional public health methods to assess the impact of PIDD on community health;
- Population-based interventions --- development, implementation, and evaluation of screening tests administered to newborns and clinical algorithms for early recognition of symptomatic persons to facilitate the earliest possible diagnosis and treatment;
- Evaluation of screening and diagnostic tools --- evaluation of screening and diagnostic tools to ensure their quality and appropriateness for identification of patients with PIDD;
- Communication --- communication with health-care providers and the public to facilitate prompt and appropriate diagnosis and intervention.

In July 2002, NICHD, CDC, and HRSA held a workshop to explore the feasibility of developing newborn screening technology for Severe Combined Immunodeficiency Disease (SCID), also know as "bubble boy disease." The goal of the workshop was to generate prioritized recommendations, approaches, and strategies for developing advanced, cutting-edge technologies for effective newborn screening of SCID with blood spots. Another goal was to enhance collaboration and communication among basic scientists, biotechnologists, clinicians, epidemiologists, and policymakers so newly developed technology can be translated rapidly into effective newborn screening programs for SCID. IDF again participated actively in this meeting.

Infants with SCID have the most serious of the primary immunodeficiency diseases, with little or no immune system. They die from infection before their first or second birthday if not given immune reconstitution by bone marrow transplantation. SCID is a pediatric emergency.

If a SCID baby receives a bone marrow transplant in the first 3.5 months of life, the survival rate can be as high as 97 percent. However, the survival rate drops to 69 percent for infants who are transplanted after that age. The main causes for the drop in survival rate are serious infections SCID babies develop in the first few months of life. The condition can be detected at birth; however, it is currently not among the genetic diseases routinely tested for in newborn screening. For most SCID infants, the diagnosis is not made until 6.5 months of age on average, and most patients are critically ill by then. Nine forms of SCID have been identified in the past 11 years, caused by mutations of single genes. The most common form of SCID is X-linked recessive, a mutation inherited on the X chromosome. This form of SCID affects only boys, but accounts for 46 percent of U.S. cases.

My colleagues at Duke University Medical Center and I treat SCID patients via stem cell transplants derived from donor bone marrow, typically from a parent or matched sibling. Infants with SCID have a complete absence of T cell function. T cells are white blood cells that are essential for normal function of the immune system. Because they lack T cells, SCID infants do not need pretransplant chemotherapy, as they cannot reject the transplants. The donor bone marrow is processed to remove donor T cells, preventing the graft from attacking the recipient by a process known as graft-versus-host disease or GVHD. By taking out the T cells from the donor marrow, prophylactic treatments with immunosuppressive drugs to prevent GVHD are not necessary. Mature, donor-derived, T cells typically appear in SCID patients within 90 to 120 days after transplant. Of the 137 SCID patients I have treated at Duke, 106 (77 percent) are alive. Most are in good general health. The oldest is 22 years of age. All 16 recipients of marrow from perfectly matched donors and 90 of the 121 recipients of T cell-depleted marrow from parental donors are among the survivors. Twenty-four of the 31 deaths occurred from viral infections present at the time of diagnosis; there were no deaths from GVHD.

Of the 38 infants I have transplanted during the first 3.5 months of life, all but one (97 percent) survive, compared to 68 survivors among the 98 transplanted after that age (69 percent success). SCID patients who received stem cell transplants within the first 28 days of life developed earlier and more robust immune function than did those who received transplants later, with higher levels of T cell reconstitution and output from the thymus gland.

At a recent Newborn Screening and Genetic Testing Symposium sponsored by CDC, Dr. Jennifer Puck at the National Human Genome Research Institute announced that she had developed a technology that could be used to test newborns for SCID. Now that the technology has been developed, a pilot study should be done to begin screening all newborns for SCID at birth. Early treatment not only saves lives

but also reduces costs. For example, a bone marrow transplant performed in a SCID infant in the first three months of life can cost less than $50,000, but the cost of care skyrockets up to millions of dollars in older SCID patients, primarily for treatment of their life-threatening infections, with less assurance of success.

Mr. Chairman, I cannot begin to stress enough the importance of early diagnosis and newborn screening for immunodeficiency diseases. While technology has not been developed to screen newborns for all primary immunodeficiencies, it has been developed for the most severe form, SCID. Dr. Harry Hannon and Dr. Robert Vogt of the Newborn Screening Branch at the National Center for Environmental Health at CDC have indicated their commitment to newborn screening for SCID. Dr. Vogt will be looking to the Immune Deficiency Foundation to develop a protocol for any newborns that test positive for SCID to receive the correct treatment in an expedited manner.

The Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children will be making recommendations to Secretary Thompson on grants and projects to help states and local public health agencies improve screening, counseling and health care services to newborns and children who have or are at risk for heritable disorders. Additionally, the Committee will be recommending the screening tests to be included in the Heritable Disorders Program.

Mr. Chairman, on behalf of the primary immunodeficiency community, I respectfully request that you and your fellow committee members include screening all newborns for SCID in your recommendations of the screening tests to be included in any and all programs this Advisory Committee has influence over, as well as any early diagnosis programs for the other primary immune deficiency diseases. Without an effective early intervention, the majority of SCID babies die during the first years of life. The majority of patients with other forms of primary immunodeficiency diseases have guarded prognoses, being chronically ill and requiring intensive treatment. Screening methods have to be developed to detect these as well.

We look forward to working closely with you. Thank you.