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FOR IMMEDIATE RELEASE

LANDMARK 30-YEAR STUDY ON CRIGLER-NAJJAR SYNDROME DESCRIBES BEST CLINICAL PRACTICE AND UNDERSCORES THE NEED FOR NEW THERAPIES

STRASBURG, PA- A new study summarizes more than 30 years of clinical experience and describes the clinical course of 28 individuals homozygous for damaging mutations in the *UGT1A1* gene who were born between 1984 and 2015 with Crigler-Najjar syndrome. This morbid and life-threatening disorder is characterized by high levels of toxic bilirubin in the blood which can lead to irreversible brain damage or death. The study yields novel insights about the pathophysiology of bilirubin encephalopathy, demonstrates principles of effective phototherapy, and provides a framework to judge emerging molecular therapies. The project was a broad collaborative effort led by clinicians and researchers at the Clinic for Special Children (CSC) and appears in the journal *Hepatology*.

The study cohort was followed for 520 aggregate patient-years and provided critical data regarding the effectiveness of phototherapy and liver transplantation therapies. Researchers used an index of neurological risk by measuring unbound (“free”) bilirubin in patient blood sera to determine the binding of unconjugated bilirubin to albumin. Four infants (14%) developed brain damage between 14 and 45 days of life, demonstrating the need for early intervention for Crigler-Najjar syndrome.

Two different systems of blue light therapy (i.e. phototherapy) were used to control bilirubin levels in the blood. Researchers found that starting phototherapy as early as possible is crucial; treatment delayed for more than 13 days after birth increased the risk of brain damage 3.5-fold. Consistent phototherapy kept bilirubin levels within safe limits throughout childhood, but average blood bilirubin increased with advancing age to reach dangerous concentrations by age 18 years.

Liver transplantation restored nearly 100% functional UGT1A1 enzyme activity and provided protection from brain damage. Seventeen (60%) of 28 patients received a liver transplant at a median age of 16.2 years. Bilirubin levels decreased dramatically within days after transplant and remained stable thereafter, eliminating the need for daily phototherapy. Post-transplant graft and patient survival were 100%. The researchers noted while liver transplantation provides an effective therapy, it entails well established short- and long-term risks.

Based on these observations, the authors conclude that despite advances in clinical care, Crigler-Najjar Syndrome remains a morbid and potentially fatal disorder, and there remains a critical unmet need for safer and more effective disease-modifying interventions that leverage emerging gene replacement and editing technologies.

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The research was conducted by a team including the study's first author Kevin A. Strauss from the Clinic for Special Children, Strasburg, PA, Penn-Lancaster General Hospital, Lancaster, PA, and Departments of Pediatrics and Molecular, Cell, & Cancer Biology, University of Massachusetts School of Medicine, Worcester, MA; senior author Hendrik J. Vreman from the Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA; Millie Young, Lauren E. Bowser, Karlla W. Brigatti, Erik G. Puffenberger, and Vincent J. Carson from the Clinic for Special Children, Strasburg, PA, Charles E. Ahlfors from the Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, Kyle Soltys and George V. Mazareigos from the Department of Surgery, Division of Pediatric Transplantation, Hillman Center for Pediatric Transplantation, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, Michael D. Fox from the Clinic for Special Children, Strasburg, PA, Department of Pediatrics, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, Diagnostic Referral Division, Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE, James E. Squires, Division of Gastroenterology and Hepatology, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, and Patrick McKiernan, Division of Pediatric Gastroenterology, Hepatology and Nutrition, UPMC Children's Hospital of Pittsburgh and Pittsburgh Liver Research Center, Pittsburgh, PA.

The Clinic for Special Children received grants from Audentes. The authors have no other potential conflicts to disclose.

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About the Clinic for Special Children

The Clinic for Special Children (CSC) is a non-profit organization located in Strasburg, PA, which provides primary pediatric care and advanced laboratory services to those who suffer from genetic or other complex medical disorders. Founded in 1989, the organization provides services to over 1,050 active patients and is recognized as a world-leader in translational and precision medicine. The organization is primarily supported through community fundraising events and donations. For more information, please visit www.ClinicforSpecialChildren.org