Newborn screening for DMD shows promise as an international model

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Investigators at Nationwide Children's Hospital, working with the DNA Sequencing Core Facility at the University of Utah, have developed an approach to newborn screening (NBS) for the life-threatening genetic disorder, Duchenne muscular dystrophy (DMD) and potentially other muscular dystrophies. As a model for NBS, the approach published online in January in the *Annals of Neurology* provides evidence that this approach could be implemented if approved by regulatory bodies at a state level or alternatively through the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children.

DMD is the most common, severe childhood form of muscular dystrophy, inherited as an X-linked recessive disorder. Progressive muscle weakness with loss of ambulation by 12-to-13 years of age is the expected outcome. Heart involvement is significant and may require treatment to avert premature death. On average, patients are diagnosed with DMD at 5 years of age, although parents often notice impaired motor skills at an earlier age.

Over the last three decades, creatine kinase (CK) testing on dried blood spots has been attempted as a method for newborn screening for DMD. CK is an enzyme that leaks into the blood from damaged muscle cells; it is markedly elevated in DMD and some other muscular dystrophies. Using CK testing on dried blood spots derived from heel-sticks to identify DMD cases during the newborn period was validated in 1979 and launched a pathway for this method of testing at birth. If CK was elevated, it was repeated at four to six weeks of age on venous blood

obtained in the doctor's office. If elevation persisted, blood was again taken and DNA was isolated from white blood cells and tested for DMD mutations to establish a definitive diagnosis. This three-step screening process took shape in New Zealand and spread to programs in Edinburgh, Germany, Canada, France, Wales, Cyprus and Belgium and Western Pennsylvania. The longest running DMD newborn screening program in history, in Wales, recently closed. To this day, Antwerp, Belgium is home to the only program that maintains newborn screening for DMD.

"The three-step model is poorly adapted to newborn screening in the USA," said Jerry R. Mendell, MD, principal investigator of the study and current director of the Center for Gene Therapy at The Research Institute at Nationwide Children's Hospital. "It can work efficiently in a publically-funded health care system where newborn care is designated at specific times post-delivery making follow-up blood draws a realistic part of the total program for child welfare." In the USA, mother and child are discharged within 24 to 48 hours following uncomplicated deliveries and post-natal care cannot be enforced. Thus, many newborns with elevated CKs at birth would be lost to follow up.

The two-tier system developed by Dr. Mendell permits heel blood taken at birth to be tested initially for CK with follow up DNA testing for DMD. A CK is obtained on the dried blood spot and if the level exceeds a predetermined threshold, DNA testing is automatically done from the same sample. No follow up blood samples are required. "This two-tier system (CK and DNA testing on same sample) is practical, comprehensive, and cost effective," said Dr. Mendell, who is also a faculty member in The Ohio State University College of Medicine.

Promising new DMD therapies have rekindled interest in establishing a pathway for newborn screening in the DMD patient population. In 2004, Center for Disease Control workshop participants concluded that early

diagnosis of DMD could have potential advantages for families, considering multiple treatment strategies were on the horizon. Funds were made available to Dr. Mendell and his team at Nationwide Children's Hospital to explore the feasibility for establishing a model for DMD newborn screening in the United States.

The study appearing in Annals of Neurology documents a nearly-four-year pilot study of a voluntary DMD newborn screening program in Ohio. Over the course of the study, 37,749 newborn boys were screened and six were discovered to have DMD gene mutations. In cases where CK was elevated and DMD mutations were not found, the investigators extended the study to identify limb-girdle muscular dystrophy (LGMD) gene mutations as part of the screening process. The published study results confirmed that this was possible and reported that three of the cases had gene mutations found in LGMD.

"The program we have introduced differs from past programs and the current Antwerp approach to newborn screening for DMD that require a three-step process," said Dr. Mendell. "This new process fits current U.S. obstetrics practices and allows us to readily distinguish false and true positive test results."

Whether DMD treatment has advanced to the point of justifying newborn screening is a judgment yet to be made by state and federal agencies. "If and when an early therapy that improves the health outcome for individuals with DMD becomes available, our study serves as a model for implementation of newborn screening for DMD," said Dr. Mendell.

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