Newborn Screening for Duchenne Muscular Dystrophy Workgroup: Lay Report

On March 12, 2004, the Centers for Disease Control and Prevention (CDC) sponsored a one-day meeting to explore issues related to newborn screening for Duchenne muscular dystrophy (DMD). The meeting took place in Atlanta, Georgia, and was attended by experts from around the world. The meeting consisted of presentations and discussions of past and present DMD newborn screening programs and of known and potential risks and benefits of newborn screening for DMD. This report will highlight the issues that were discussed.

The attendees included parents, scientists, clinicians, public health officials, newborn screening coordinators, ethicists, and representatives from several DMD newborn screening programs (Belgium, Canada, Germany, and Wales). Patricia Furlong attended as a representative of Parent Project Muscular Dystrophy (PPMD), and Valerie Cwik represented the Muscular Dystrophy Association (MDA). Government agencies that are involved in newborn screening or muscular dystrophy research, or both, were also represented, specifically CDC, the Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). A full list of attendees is included at the end of this report.

Background:

Newborn screening is a public health program aimed at early identification of babies with conditions that will benefit from early diagnosis and treatment. Historically, these are conditions that cause disability or death if they are not treated within days of birth. Newborn screening has been performed in the United States since the early 1960s. Newborn screening tests are performed on blood from a small prick in the baby's heel. A few drops of blood are collected on a special kind of paper, and then the "blood spot" is dried and sent to a laboratory for analysis. In the United States, several factors are taken into account when deciding if a particular screening test should be routinely performed on all newborn babies, and each state determines which disorders are included in its newborn screening program.

It is important to understand the difference between a *screening* test and a *diagnostic* test. Screening tests will identify people who are more likely to have a certain condition than are other people, but screening tests are not definitive. That is, not all people who have a positive result on a screening test will actually have the condition. People who screen positive are referred for a follow-up diagnostic test. A diagnostic test will tell with greater certainty whether these people have the condition. If a person is positive on the screening test, but is negative on the diagnostic test, the person does not have the condition and the screening result is said to be a "false positive". Likewise, there could be some people with the condition who are not detected by the screening test. The screening test results on these people are "false negatives".

So if screening tests aren't perfect, why aren't the diagnostic tests used on everyone? Generally, diagnostic tests are too expensive to offer to everyone. Screening tests are much less expensive, and public health officials consider how good the screening test is when deciding whether or not to offer the screening test. Ideally, a test will have no false negatives, and few or no false positives. False-negative results could cause a delay in diagnosis and treatment and can, therefore, lead to harm. False-

positive results increase the number of diagnostic tests that are performed and, therefore, increase the cost of the screening program. In addition, false-positive results could cause undue anxiety in parents who might continue to worry that the diagnostic test was wrong and worry that their child really does have the condition. Some studies have found that the stress and anxiety from a false-positive screening result can last for years.

In addition to cost and the number of false-positive and false-negative screening results, there are several other factors that are considered before making a screening test available to the general population. Different countries and even different states within the United States use different criteria for deciding which screening tests to perform on newborn babies. Other important factors include the severity of the condition if the baby is not treated right away, the availability of diagnostic tests, and the availability of treatments.

In the United States, newborn screening for a particular condition is generally performed only if there is evidence that early diagnosis and early treatment will result in an improved medical outcome for the child. There are several arguments for this criterion. One argument is that newborn screening is potentially harmful (for example, it might cause increased stress and anxiety for parents if the screening test result is a false positive) and that a proven medical benefit for the children who are diagnosed with the condition is necessary to outweigh potential harms.

Another argument is that decisions regarding a baby's medical testing and care are the right and responsibility of the parents, and that routine newborn screening takes this decision out of the hands of the parents. Therefore, universal newborn screening is justified only if harm to the child will occur if the condition is not diagnosed and treated in a timely manner. To address this issue, some states have two different sets of newborn screening tests that are offered to new parents: mandatory and optional. In most states, mandatory tests are routinely performed on all newborn babies unless the parents refuse the tests in writing. In a few states, parents are not allowed to "opt out" of the test (that is, decline to have the test done) and all babies are screened. Some states offer newborn screening as an option for an additional set of conditions. Generally, tests are offered on an optional basis if there is reason to believe that early diagnosis and treatment will result in a better medical outcome, but more studies are needed to confirm the medical benefits. Optional newborn screening tests generally require signed, informed consent by a parent. Informed consent means that the parents gave their permission, or consent, for their baby to be screened after they were informed of the risks, benefits, and limitations of the screening test.

Review of Past and Present DMD Newborn Screening Programs:

In the mid-1970s, researchers demonstrated that a screening test for DMD could be performed on the newborn screening dried blood spots. Since that time, there have been several trials of newborn screening for DMD, and newborn screening for DMD continues to be offered in some parts of the world. Newborn screening for DMD is currently offered in at least parts of Belgium, Canada, Germany, and Wales. In the past, newborn screening for DMD was offered in at least parts of Brazil, Cyprus, France, New Zealand, Puerto Rico, and the United States (specifically, parts of Iowa, New York, Oregon, Pennsylvania, and Texas). In the majority of past and present DMD newborn screening programs, screening has been or is voluntary and offered only to male

newborns. The test used is a measurement of creatine kinase (CK) activity in a blood sample from the newborn. The blood sample is generally collected as a blood spot at the same time that blood spots for other newborn screening tests are collected. Most newborn screening programs for DMD require the parents to give signed, informed consent before proceeding with the screening test.

CK activity is elevated in newborns who have DMD. It is also elevated in some babies with other forms of muscular dystrophy. However, while the CK test appears to identify all male newborns with DMD, it picks up only some of the males with the other forms of muscular dystrophy. In addition, CK levels can be elevated for reasons that have nothing to do with muscular dystrophy, such as muscle stress experienced by the baby during delivery. In these cases, the CK levels return to normal within a week or two. Therefore, if a baby is found to have elevated CK at birth, it is necessary to test the baby's blood again a few weeks later to see whether the CK is still elevated. In fact, most of the babies who have a high CK level at birth do not have a high CK level at the second screening. If the CK is still elevated at the second screen, additional tests are used to confirm whether the baby has muscular dystrophy. Babies who have a high CK only on a screening test but who do not have muscular dystrophy are called "transient positives" or "false positives".

Most newborn screening programs for DMD have found the CK test to have very few, if any, false-negative results. On the other hand, there can be many false or transient-positive results. Of the babies who have a positive test at birth, only about 1 in 10 will continue to have an elevated CK level when the screening test is repeated a few weeks later. Of the babies who are also positive on the repeat screening test, most but not all will have DMD or another muscular dystrophy. So for every baby boy identified with DMD, there are 10 or more baby boys with a false-positive screening test result. The exact percentages of false-positive and false-negative results vary between programs because different programs may use different laboratory techniques, and because different laboratories have different definitions of "elevated" results.

The CK screening test results are difficult to interpret in females. Some female carriers of DMD are detected by the screening test, but not all. In addition, it is not possible to predict from the screening test whether a female carrier will have symptoms or not. Because of these complications, and because full expression of DMD in carrier females is not common, most newborn screening programs for DMD offer screening only for male babies.

The number of false-positive newborn screening results for DMD decreases if the test is performed on babies who are a few months old. Thus, at least one program offers CK screening to infants through pediatricians' offices rather than at birth hospitals. There are pros and cons to this approach. Not all families bring their children in for routine pediatric visits, and not all pediatricians are comfortable explaining and offering the screening test. Moreover, while newborn screening programs reach virtually all births, informed consent is problematic. Not all pregnant women obtain routine prenatal care, so consent must be sought in the birth hospital. Clearly, the time around labor and delivery is not the ideal time for parents to become truly informed about the screening test before they decide whether to consent. Some parents of boys diagnosed with DMD through newborn screening programs were frustrated because they had not realized that they were consenting for screening for a condition that has no cure.

Newborn screening programs for DMD have faced several challenges in their development. As mentioned previously, false-positive screening results can cause lasting stress and anxiety in parents. Some programs wait days or even months before offering the test in order to decrease the number of babies who have a false-positive screening result. Informed consent before screening and the counseling of families with false-positive screening results are two other strategies that have been used to help reduce stress and anxiety.

While a diagnosis of DMD is devastating at any time, some families and newborn screening program officials have indicated that receiving this diagnosis very shortly after birth can be particularly problematic and might interfere with bonding between the parents and their newborn. Delayed screening or reporting of results, along with psychosocial support, appear to reduce some of these negative consequences of diagnosis through newborn screening.

The most common reason given for discontinuing DMD newborn screening programs is that early diagnosis of DMD has not been shown to improve the medical outcome of boys with DMD. One program discontinued because laboratory reagents that they had been using became unavailable. This program might reimplement its newborn screening for DMD once assays are developed in its laboratory using alternative reagents. The programs that continue to offer newborn screening despite this limitation do so because of nonmedical benefits to the boys diagnosed with DMD and their families. These nonmedical benefits are discussed in more detail in the next section.

The public health officials and researchers associated with these programs are continuing to study the potential benefits and the potential harms of newborn or infant screening for DMD.

Review of the Benefits and Risks of DMD Newborn Screening:

As previously mentioned, newborn screening programs within the United States traditionally include only those conditions for which there is an effective early treatment. Currently, there is no evidence that diagnosis at birth will improve the medical outcome of boys with DMD. However, early identification of DMD has other nonmedical benefits for diagnosed babies and their families. For example, some families take a diagnosis of DMD in a family member into account when considering school districts, the purchase of a particular home, or an employment opportunity. Other major life planning could also be changed by the diagnosis, such as the timing and location of major vacations.

Without newborn screening, a child with DMD might not be diagnosed until he is 3 to 5 years of age. By the time of the diagnosis, parents have often been expressing concerns about their son's development to health care professionals for months or even years. Parents are often told that their son will "grow out of it" or to "wait and see", and numerous physicians are often consulted before a diagnosis is finally made. This process, referred to as the "diagnostic odyssey", is costly to families in terms of time, stress, frustration, and health care provider visits. Thus, a potential benefit of newborn screening for DMD is the avoidance of this diagnostic odyssey.

A diagnosis of DMD can change the way that parents plan for future pregnancies. A delayed diagnosis also means that a family could have additional children with DMD

before the first child with DMD is diagnosed. An earlier diagnosis of DMD would allow families to plan future pregnancies with the knowledge that there is a chance that future children could also have DMD, and that prenatal diagnosis might be available if desired. Also, some parents choose to wait a longer interval before having their next child after a diagnosis of DMD in an older child.

While there are clearly nonmedical advantages to an earlier age at diagnosis, it is also clear that reasonable parents could decline to have their child screened for DMD. For this reason, if DMD is added to existing newborn screening programs, it would need to be added as an optional test and the informed consent process would need to be changed. Although this might seem relatively straightforward, adding DMD screening to state newborn screening programs would be challenging for many reasons. First, there are a growing number of conditions, such as fragile X syndrome, for which families advocate newborn screening because of the nonmedical benefits of early diagnosis. The large number of conditions that are in this category could overwhelm the public health system that is responsible for screening and follow up of all positive screening test results, especially if informed consent is necessary for screening. Second, if information for reproductive planning is a valid reason for newborn screening, then identification of a carrier daughter is just as informative to parents as identification of a son with DMD and, consequently, screening of females would be warranted under this argument. However, carrier detection in female infants is problematic for the technical reasons discussed in the previous section, and because most genetics professionals question the ethics of carrier detection in minors.

Newborn screening of females using the CK test is further complicated by the fact that a few female carriers might develop DMD ("manifesting carriers"). If females are not screened, or if females are screened but the test is more likely to miss a female than a male with DMD, then a manifesting female carrier might be less likely to be identified in a newborn screen, and she and her family would not receive the same benefits of early diagnosis as do males with DMD and their families.

If newborn screening for DMD is implemented, it could be as either a mandatory or voluntary test. If it is a mandatory test, then there is little or no chance for informed consent to be provided. Most states do not require informed consent for mandatory newborn screening tests, and in those states that do require informed consent, it is usually obtained by having a parent sign a form that they are asked to read. Consequently, there is little or no chance for new parents to be truly informed of risks and benefits in the birth hospital setting. On the other hand, if the newborn screening test for DMD is voluntary, it is possible that parents could confuse the distinction between voluntary and mandatory tests and could consequently (1) opt out of all tests if they mistakenly believe that the lack of a cure also applies to the mandatory conditions or (2) decide to participate in the voluntary screening tests because they mistakenly believe that there is an effective treatment for DMD as there is for each of the mandatory conditions. Thus, if newborn screening for DMD is offered on a voluntary basis, it is optimal to keep the mandatory testing and voluntary testing separate in both time and space.

Summary of Conclusions of the Workgroup:

Consideration of newborn screening for DMD is a complex issue. The experiences of past and present newborn screening programs for DMD and the possible

risks and benefits were discussed in depth by the workgroup members. The discussion was very well-rounded and propelled by the diversity of experiences and expertise brought by the various participants. There was an appreciation of complexity of the issues related to newborn screening for DMD, and an appreciation that the risks and benefits are weighed differently by different people and in different regions. However, most members of the group agreed on the following key points:

- An earlier age at diagnosis of DMD might improve the quality of lives of families.
- There are no universal early signs or symptoms by which all children with DMD can be recognized by pediatricians at an early age.
- The current newborn screening standards do not justify *mandatory* newborn screening for DMD given the lack of evidence of medical benefit to the child.
- *Voluntary* newborn screening for DMD, as a supplement to mandatory newborn screening programs, might be problematic because (1) the period immediately before or after birth is a difficult time to obtain true informed consent, and (2) parents might have trouble distinguishing voluntary testing for DMD from other mandatory newborn screening tests.
- Mandatory and voluntary newborn screening tests ideally should be separated in time and space.
- False or transient-positive screening results might have a negative impact on families.
- Screening later in infancy will reduce the number of false or transient-positive screening results.
- Screening later in infancy might introduce inequities into the system because not all families have equal access to routine pediatric services.
- Identification of appropriate personnel and protocols for informing parents of test results is critical.

Future Directions:

To further research the issues identified by the group, the National Center on Birth Defects and Developmental Disabilities at CDC recently announced that funds are available under a cooperative agreement for research in both infant and newborn screening for DMD. CDC plans to fund two programs: one to conduct a trial of newborn screening of DMD and evaluate the feasibility of true informed consent in the birth hospital, and one to conduct a trial of screening during infancy through pediatricians' offices and evaluate the feasibility of eliminating inequities in access to the screening test. Both programs will evaluate the effectiveness of the informed consent process, the impact of false-positive screening results, the experiences of families with the screening process, and the attitudes of pediatricians and other clinicians to the screening program. Depending on the applications that are received in response to this announcement, one state could be selected to conduct both newborn and infant screening for DMD, or two separate states could be selected to conduct either newborn or infant screening. In addition, CDC will continue to explore other ways to decrease the age at diagnosis of DMD and improve the quality of lives of families touched by DMD.

We at CDC are very grateful to all of the participants who attended the meeting, many of whom came from quite a distance, for sharing their experiences and expertise. In addition, we have received a great deal of input from individuals who were not able to attend, and we are also grateful for this. Unfortunately, we were not able to invite all of

the many people who are interested in this topic. We look forward to continuing to work with our partners and other collaborators on newborn screening and other public health aspects of Duchenne muscular dystrophy.

Contact Information:

Website: www.cdc.gov/ncbddd/duchenne/default.htm

E-mail: dmd@cdc.gov

Address: Duchenne/Becker Muscular Dystrophy Program
Division of Human Development and Disability
National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention
Mailstop E-88
1600 Clifton Road NE
Atlanta, Georgia 30333

Workgroup Participants:

Denise Avard, PhD
Public Law Research Center, University of Montréal

Coleen Boyle, PhD, MPH
National Center on Birth Defects and Developmental Disabilities, CDC

Don Bradley, PhD
Newborn Screening Wales, University Hospital of Wales

Linda Bradley, PhD
Office of Genomics and Disease Prevention, CDC

Edward Brann, MD, MPH
Division of Human Development and Disability
National Center on Birth Defects and Developmental Disabilities, CDC

Emma Ciafaloni, MD
Neuromuscular Disease Center, University of Rochester

Anne Comeau, PhD
New England Newborn Screening Program, University of Massachusetts Medical School

Chris Cunniff, MD
Section of Medical and Molecular Genetics, University of Arizona

Valerie Cwik, MD
Muscular Dystrophy Association

Marie Earley, PhD
Newborn Screening Branch, Division of Laboratory Sciences
National Center for Environmental Health/Agency for Toxic Substances and Disease Registry, CDC

Diana Escolar, MD
Research Center for Genetic Medicine, Children's National Medical Center

François Eyskens, MD, PhD
Provincial Center for Metabolic Disorders, University Hospital at Antwerp

Paul Fernhoff, MD
Division of Medical Genetics, Department of Human Genetics, Emory University

Kevin Flanigan, MD
Department of Neurology, University of Utah

Pat Furlong, RN, FSN, MS
Parent Project Muscular Dystrophy

Cheryl Greenberg, MD (by teleconference)
Metabolic Service Section of Genetics and Metabolism, Winnipeg

Lisa Groeger
Division of Human Development and Disability
National Center on Birth Defects and Developmental Disabilities, CDC

Scott Grosse, PhD
National Center on Birth Defects and Developmental Disabilities, CDC

Jim Hanson, MD
Center for Developmental Biology and Perinatal Medicine
National Institute of Child Health and Human Development

Eric Hoffman, PhD
Research Center for Genetic Medicine, Children’s National Medical Center

Aileen Kenneson, PhD, MS
Division of Human Development and Disability
National Center on Birth Defects and Developmental Disabilities, CDC

Katie Kolor, PhD, MS
Division of Human Development and Disability
National Center on Birth Defects and Developmental Disabilities, CDC

Jerry Mendell, MD
Department of Neurology, Ohio State University

Cindy Moore, MD, PhD
Division of Birth Defects and Developmental Disabilities
National Center on Birth Defects and Developmental Disabilities, CDC

Evelyn Parsons, PhD
University of Wales College of Medicine

Rodney J. Pollitt, PhD, FRCPath (UK)
UK Cystic Fibrosis Screening Programme, Sheffield Children's Hospital

Michele A. Lloyd Puryear, MD, PhD
Genetic Services Branch
Health Resources and Services Administration

Lainie Friedman Ross, MD, PhD
Department of Pediatrics
MacLean Center for Clinical Medical Ethics, University of Chicago

Reinhardt Rüdel, PhD
Department of General Physiology, University of Ulm

Günter Scheuerbrandt, PhD
Testlaboratorium Breitnau, Germany

J. Robert Thompson
Newborn Screening and Public Health Chemistry Section
Cadham Provincial Laboratory, Winnipeg