



Newborn Screening and Genetic Testing for Duchenne Muscular Dystrophy: Introduction for Families

With early diagnosis, important interventions could be pursued that may help preserve muscle strength and lead to slower progression of weakness and loss of function. This pamphlet, vetted by geneticists and pediatric neurologists, is an informational guide for parents of a newborn with a positive screen for Duchenne Muscular Dystrophy (DMD).

1 **Newborn Screening:**

Newborn screening (NBS) is the practice of testing babies in the first days of life for certain disorders that may hinder normal development and for which there are available treatments. Most states test for conditions specified by the Health Resources and Services Administration (HRSA) in their Recommended Uniform Screening Panel (RUSP), however DMD is not yet included in the RUSP. While DMD may soon be considered for the RUSP, several programs have started offering supplemental DMD screening for all expecting families. The DMD NBS opportunity may have been presented to you by your physician or the NBS program coordinator at the hospital. A genetic counselor may have explained what NBS is and why it is being offered for DMD. If so, there should be a process specific to the hospital to manage screening and result follow-up.

- **A positive newborn screen:**
Newborn screening for DMD looks for high levels of the muscle enzyme, creatine kinase (CK), in the blood. When this occurs during NBS, the test is often automatically re-run by the laboratory in order to confirm the result. Your provider can request a follow-up CK test to validate the newborn screening result if this was not conducted.
- **NBS Result Management Team:**
Depending on the hospital, the process after a positive screen can be handled by the NICU, nursery medical staff at the hospital or by the family's pediatrician, to ensure adequate follow-up diagnostic testing and care, including a referral to a pediatric neurology clinic or neuromuscular specialist for evaluation. Visit our list of specialists in Step 5 on our [Newly Diagnosed website](#).

Diagnosis:

The newborn screening CK test detects early disease risk but is not diagnostic for a particular disease. Therefore, further diagnostic tests are necessary to indicate presence (or absence) of disease in screen-positive individuals.

● Genetic Testing:

After the positive screen, your provider will consider genetic testing for DMD, or possibly other muscle diseases that can cause elevated CK levels. Genetic counselors can assist you in understanding the need for genetic testing and help determine which testing is appropriate. To find a genetic counselor near you, visit step 6 on our [Newly Diagnosed website](#).

- According to the published Duchenne Care Guidelines (1), genetic testing for common large deletions or duplications in the DMD gene (the gene associated with DMD) is recommended. If a mutation is found, then a genetic diagnosis is confirmed.
- If no large deletion or duplication is found, genetic sequencing for the remaining point mutations causing DMD (approximately 25–30%) is recommended. These mutations include point mutations, non-sense mutations, intronic splice site mutations, small deletions, and small duplications or insertions. If such a mutation is found, then a genetic diagnosis is confirmed.
- If genetic testing does not confirm a diagnosis of DMD, then your neuromuscular specialist will determine if they would proceed to genetic testing for the panel of genes associated with muscular dystrophies and myopathies or a muscle biopsy to ascertain the histology and protein defects (some mitochondrial myopathies present with high CKs and would not be picked up by the LGMD panel).

● Muscle Biopsy:

Despite the great strides that are being made in elucidating the molecular biology of DMD and many myopathies, the performance of genetic testing does not always eliminate the need for a muscle biopsy. For example, if genetic testing reveals a Variant of Unknown Significance (VUS) in the gene for dystrophin, a muscle biopsy can be performed to look for myopathic features in the muscle and to establish whether there is normal or abnormal expression of the dystrophin protein in the muscle by Western blot, thereby providing assistance in determining whether the VUS might be the underlying cause of a myopathy.

- If dystrophin is absent, then a pathological diagnosis of DMD is confirmed.
- If dystrophin is present, then alternative diagnoses should be considered with your physician, including Becker Muscular Dystrophy and Limb Girdle Muscular Dystrophy.

Post-Diagnosis:

A rapid and early diagnosis can lead to a prompt specialist referral and quicker access to a specialty care team familiar with DMD.

- If there is a positive diagnosis of DMD, family members (mothers and male siblings) should be screened. Your physician and genetic counselor will work with you on the testing needed. The mother is typically tested first to find out if she is a carrier of the disease.
- **Carriers:** DMD is an X-linked disease, meaning that the gene responsible for the disease is carried on the X chromosome. Boys who receive the X chromosome with the mutation manifest the disease, while girls, who have two X chromosomes, often do not manifest the disease (because they carry one X chromosome with the mutation, but still have dystrophin protein produced from the other X chromosome without the mutation). Female carriers have a 50% chance of having a son with DMD and a 50% chance of her daughter being a DMD carrier (2). About 2.5-20% of female carriers are manifesting carriers, i.e., they display symptoms (usually between 16-48 years old) that can vary from mild generalized skeletal weakness to difficulties in walking and heart problems (cardiomyopathy) (3).
- In 30% of cases, DMD results from de novo (new or spontaneous) mutations and germline mosaicism is seen but not frequent (4). De novo mutations are mutations that appear in an individual despite not being seen in their parents (5). There is a high chance of accidents/ie mutations in the large dystrophin gene of 79 exons. In a few instances, we see two brothers with DMD and a Mom who tested negative for carrying the dystrophin gene mutation. This Mom would be called a germline mosaic carrier. This means the Mom has the mutation in her egg cells and not the rest of her somatic cells (any other cell besides the reproductive cells); hence the negative carrier test. Moms with negative carrier test result have an estimated 7-10% higher risk for a second son with DMD as opposed to a 50% risk for another son with DMD when the Mom has a positive carrier test result (6).

RESOURCES:

1. To learn more about Duchenne care, advocacy and research, visit: CureDuchenne.org
2. To find the conditions screened by state, visit Baby's First test at: babysfirsttest.org/newborn-screening/states
3. To learn about Supplemental NBS programs for DMD, visit: baebies.com/newborn-screening-hospitals

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