Best Practice Guidelines on molecular diagnostics in Duchenne/Becker muscular dystrophies


A summary of this article: A group of experts got together in 2008 to agree on the best way to diagnose Duchenne and Becker muscular dystrophy (D/BMD). Timely diagnosis is becoming even more important as new clinical trials become available. The article explains what the group recommended.

Terminology: “Molecular diagnosis” means the same as “genetic testing” and refers to testing done on DNA. “Dystrophinopathies” means disorders caused by changes to the dystrophin gene, and include D/BMD.

1. The labs that do genetic tests should follow good lab practices and meet standards.

2. Males suspected to have D/BMD because of high CK levels or a muscle biopsy result should be referred to a specialist for genetic testing. Finding a mutation confirms D/BMD. Not finding a mutation makes it much less likely that the boy has D/BMD, but doesn’t reduce the chance to zero. Basically, genetic testing is very good for ruling out (saying no about) the diagnosis, but it is not perfect; it is extremely good at confirming (saying yes about) a diagnosis.

Different types of mutations (changes) in the dystrophin gene can cause D/BMD. Genetic testing should happen in this order: test for duplications and deletions first. If no mutation is found and the patient has not already had a muscle biopsy, the healthcare provider should think more about whether the patient really has the signs of D/BMD. If yes, then consider doing a muscle biopsy and/or move on to testing for the other, less common types of mutations (very small changes to the gene first, then very rare types of mutations second, if necessary). The article includes details of the different lab tests that can be used to find different mutations.

Getting a diagnosis as quickly as possible may be important for some families. If those families do not want to wait for the results of genetic testing, their healthcare provider may consider a muscle biopsy to look at the dystrophin protein, which can also give a diagnosis. The authors also pointed out that a diagnosis helps with genetic counseling about why the disorder happened and the chances that it could happen again. Overall,
the diagnostic approach needs to be flexible to meet the needs of the family and the clinical setting.

3. The recommendations for **carrier testing in women** depend on whether a relative has already had a genetic test where a mutation was found. **If a mutation has already been found**, the health care provider should choose a lab method that can do two things. First, the lab method needs to be able to find the type of mutation that is known to be in the family. Second, the lab method needs to work for carriers, which means that it has to be able to tell between the gene with the mutation and the normal gene (remember that women have two copies of the dystrophin gene, and carriers only have a mutation in one of the copies).

When a woman wants carrier testing **when no mutation has already been found** in the family, it is best to start by testing someone with D/BMD, if possible, to find his mutation first. If that can’t be done, it is best to start carrier testing with the woman who has the highest chance to be a carrier. This is usually the mother of a boy with D/BMD. Carrier testing should start with duplication and deletion testing. If no mutation is found, the authors suggest that the healthcare providers think carefully about whether the family history really looks like D/BMD, rather than some other disorder. If it does match with D/BMD, the healthcare provider should do testing for less common types of mutations (very small changes to the gene). In some families, another method called haplotype analysis (or linkage testing) can be used to give “very likely” or “very unlikely” (but not yes or no) answers about carrier status; this type of testing requires multiple people in the family to have genetic testing, including individuals with D/BMD.

The authors remind us that a negative genetic test (which means that no mutation was found) means that a woman is a lot less likely to be a carrier, but it does not mean that she is definitely not a carrier. We know that some women have no mutations in their blood cells (where genetic testing is usually done) but may still have mutations in their egg cells (where genetic testing can't be done).

4. **Females who have symptoms of D/BMD**, called manifesting carriers, are rare. Genetic testing for females with symptoms is the same as for males suspected to have D/BMD. Females with full symptoms of D/BMD should also have a chromosome analysis (which looks at entire chromosomes rather than specific genes) to make sure they aren’t missing some or all of one of an X chromosome in their cells.

5. **Prenatal testing** to tell during pregnancy if a developing baby will have D/BMD should only be done on boys (because most girls will have no signs of D/BMD, even if they
have a mutation in one of their dystrophin genes). It is best if the mutation in the family is known before having prenatal testing. If it isn’t known, it is best to have DNA from the affected male to compare to the developing baby’s DNA. It is also important that the lab checks to be sure that they are really testing the developing baby’s cells, and not accidently testing the mother’s cells. (All of these recommendations aim at making the answer from prenatal testing as certain as possible. You can imagine how difficult it would be to get a “maybe yes, but maybe no” answer during a pregnancy, or even worse, the wrong answer altogether.) The authors note that many of these guidelines also apply to preimplantation genetic diagnosis (PGD), which is a way of using IVF techniques plus additional genetic testing to tell whether an embryo is likely to have the disorder.

6. The authors then go on to provide lots of detailed information about interpreting and reporting on genetic test results. Of note, they remind us that it is usually, but not always, possible to tell if a boy will have the symptoms of DMD or the symptoms of BMD based on his genetic test result. They also point out that there are instances when it is important to follow up a genetic test result with more testing. They give lots of advice about what information should be included in the lab report so that healthcare providers can understand what the results mean.

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Summary provided by
Holly Peay, MS CGC
PPMD’s Senior Director of Education and Outreach