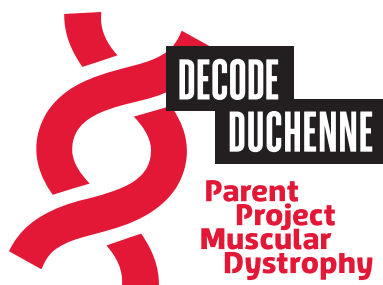


Duchenne Muscular Dystrophy Carriers:
Your Questions Answered



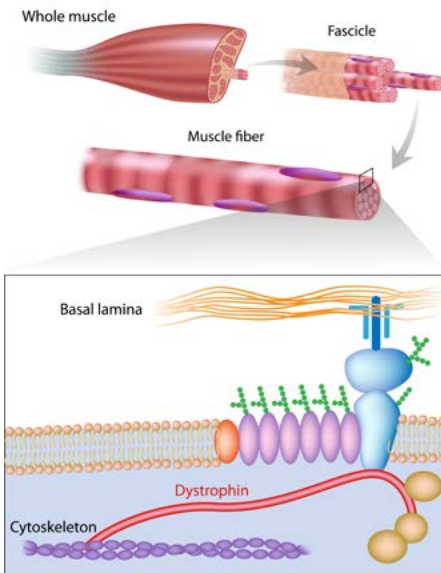


What does it mean to be a female Duchenne carrier?

This brochure is for women who know they are carriers for Duchenne or Becker muscular dystrophy, either because of their family history or because they have had genetic testing that confirms they are carriers. Duchenne muscular dystrophy is a muscle disease known as a **dystrophinopathy**.

Dystrophinopathies can range from mild to severe. A dystrophinopathy occurs when the dystrophin protein (found in the body's muscle cells) has an altered structure or function, or is entirely absent from the body's muscle cells. Becker muscular dystrophy is also a dystrophinopathy with many similarities to Duchenne, but typically the symptoms are milder in progression.

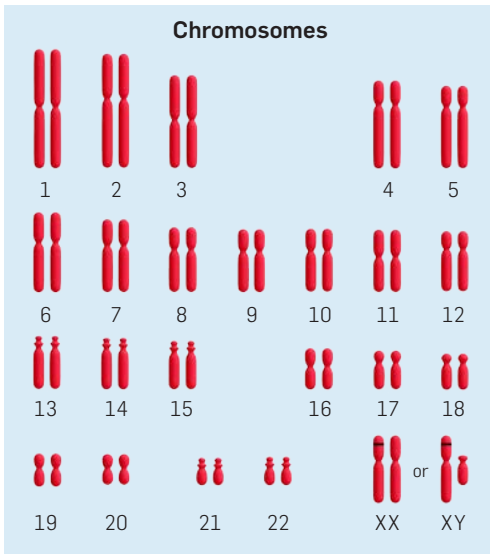
Both Duchenne and Becker muscular dystrophies are genetic conditions that cause progressive loss of muscle function and strength over time. While this brochure is for carriers of both Duchenne and Becker, for simplicity we will use the term Duchenne.



Genetics 101

To understand what it means to be a carrier, it is helpful to review some basic genetics. Genes are the instructions that our bodies use to make all of the substances (usually proteins) that our bodies need to function. Genes are made of the chemicals that we call DNA, which we often abbreviate as the letters, A, C, T, and G. The gene involved in Duchenne is called the **DMD gene**.

The *DMD* gene is a very large gene that provides the instructions to produce the **dystrophin protein**. Dystrophin plays an important role in muscle tissue, acting as a “shock absorber” that allows muscles to contract and relax without being damaged. When a person does not make enough dystrophin, muscles are not able to function or repair themselves properly. The lack of dystrophin in Duchenne is caused by a change or error in the chemicals that make up the *DMD* gene, which is called a mutation or a **pathogenic variant**.



Genes are packaged in chromosomes, which are inherited from our parents. Typically, humans have 23 pairs of chromosomes, with one of each chromosome pair coming from the egg from the mother and the other chromosome of that pair coming from the sperm from the father. The first 22 pairs of chromosomes are exactly the same in men and women, with the 23rd pair determining sex.

Most females have two X chromosomes, while most males have one X and one Y chromosome. Females get an X from their mother and an X from their father. Males get an X from their mother and a Y from their father. The X chromosome is much bigger than the Y chromosome and contains many genes not found on the Y chromosome.

The *DMD* gene is located on the X chromosome, which makes Duchenne an X-linked condition. Consequently, females have two copies of the *DMD* gene while males only have one. Women who have one working copy of the *DMD* gene and one copy of the *DMD* gene with a pathogenic variant are called **carriers**.

Where did this come from?

As a genetic disorder, Duchenne can be passed down from parent to child. Many women who carry a pathogenic variant in *DMD* do not know that they are carriers until after they have a child with Duchenne. Approximately 70% of boys with Duchenne inherited the pathogenic variant from their mother who is a carrier of Duchenne. Some carriers have a family history of Duchenne and know that there are other family members who are also carriers. Even if you have no family history of Duchenne, it is still possible for other family members to also be carriers—just by chance, there might not have been any boys born with Duchenne.

It is also possible that you are the first person in your family to be a carrier for Duchenne. The Duchenne gene is very large, which increases the incidence of a new pathogenic variant occurring during the formation of eggs or sperm. This is why approximately 30% of boys with Duchenne have a **new (de novo) pathogenic variant** that occurred in the egg that made them, and was not inherited from the mother. If you are the first person in your family to be a carrier, this means you have a de novo pathogenic variant—that the sperm or the egg that made you had a pathogenic variant in the *DMD* gene that neither of your parents carried.

It is also possible that a pathogenic variant in the *DMD* gene can occur during early fetal development of the woman. In this case, the woman may have some cells in her body with the *DMD* pathogenic variant and some cells that have no pathogenic variant, which is called **somatic mosaicism** (somatic means “body,” mosaic means “more than one cell type”).

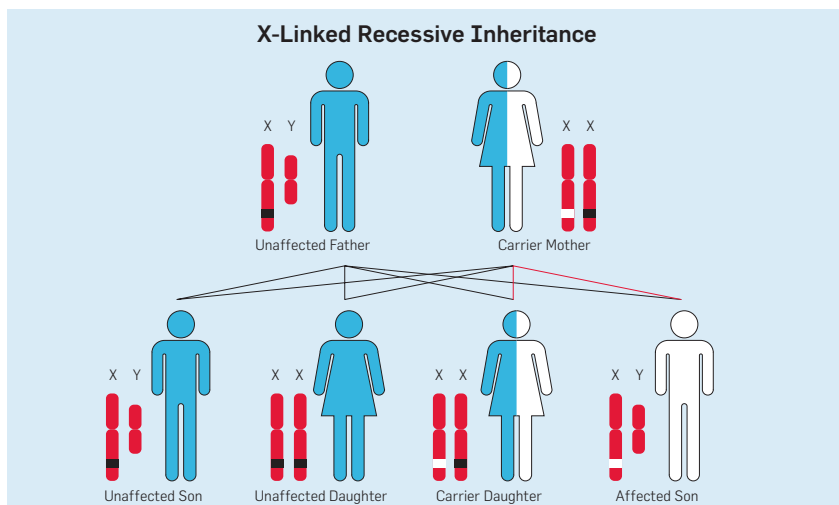
De novo pathogenic variants happen in nature during the process of copying our genes, and are not caused by anything a woman did or did not do during pregnancy. There is also no way to prevent these de novo pathogenic variants.

How does this impact the rest of my family?

What is the risk for my children or future children?

Being a carrier means that all of your biological children have a 50% chance to inherit the *DMD* pathogenic variant. When a woman has children, she passes on half of her chromosomes, or one member of every pair of chromosomes, through her egg. For a woman who is a Duchenne carrier, she will either pass on the X with the functional *DMD* gene OR the X with the *DMD* gene with the pathogenic variant.

- Any boy who inherits the *DMD* gene with the pathogenic variant will have Duchenne, as his one and only copy of the *DMD* gene has the pathogenic variant. How the boy is affected can vary. If you have no family history of Duchenne or Becker, it is important to talk to a genetic counselor with expertise in Duchenne about what is predicted with the pathogenic variant found in you.
- Any girl who inherits the *DMD* gene with the pathogenic variant will be a carrier, as she will inherit a functioning copy of the *DMD* gene from her father.



Whether a baby is male or female is dependent on the sex chromosome (X or Y) that the baby gets from the father through his sperm.

I am worried about having a child with Duchenne. What can I do?

The decision to have children is personal and complicated. For many women, knowing you are a carrier can make this decision even more complicated. If you are concerned about your risk to have a child with Duchenne or a daughter who is a carrier, you and your partner should meet with a genetic counselor or a doctor experienced in Duchenne to discuss your options and your personal beliefs in more detail.

Some women become pregnant and will decide against having any testing during the pregnancy. Babies can be tested after birth or as any concerns arise.

Prenatal Testing

Some women become pregnant and choose to have prenatal testing. This may start with **cell free fetal DNA (cffDNA) screening**, which is a non-invasive technique that determines the sex (and other chromosome information) of an unborn baby by detecting small pieces of the baby's DNA in the mother's blood. If the baby is

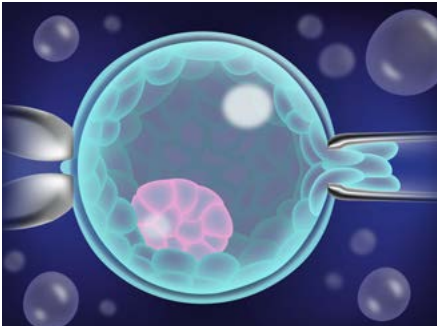


found to be a boy, diagnostic testing of the pregnancy through either **chorionic villus sampling (CVS)** or **amniocentesis (amnio)** can be performed.

- **CVS** is typically performed during week 10–12 of pregnancy and involves removing a small piece of the placenta. Because the baby and the placenta develop from the same embryo, the placenta has the same genetic makeup as the baby.

- **Amniocentesis** is typically performed after week 15 of pregnancy and involves collecting a small amount of amniotic fluid that surrounds the baby. The fluid contains cells that the baby has shed, which can then be tested.
- Both amniocentesis and CVS are considered invasive procedures and have a small risk for complications that could lead to miscarriage. The exact risk is dependent upon the experience of the doctor. Results from this testing typically take around four weeks.

At this time, there is no prenatal treatment for Duchenne. Prenatal testing is often used to prepare for an affected child, or to make pregnancy termination decisions. Women should consider what they might do with the information, before having prenatal testing.



Preimplantation Genetic Testing

Some couples feel that it is important to have a biological child who does not have the condition, but do not want to consider terminating a pregnancy. These couples often choose **Preimplantation Genetic Testing (PGT-M)**. With this technique,

the couple undergoes **in vitro fertilization (IVF)**. Eggs are harvested from the woman, while sperm is collected from the man, and fertilization occurs in the laboratory. The embryo is grown to a certain number of cells, and then a small number of cells are removed for genetic testing for the pathogenic variant in the family. Only embryos that do not have the disease are implanted in the woman, reducing the likelihood that the baby will have the condition. Because of the process of IVF, this technique is more expensive. In addition, not all couples will have a pregnancy as a result of the technique.

Some couples will choose to use IVF but will use an **egg donor** that they know is not a carrier (egg donors can be screened) or will choose embryo adoption

(embryos from an unrelated couple that were not used during that couple's fertility treatments). Some couples will choose adoption. There is no right or wrong decision, and every family may make a different choice that they feel is right for them.

Testing After Birth

If testing was not done during pregnancy, **genetic testing** or **creatine kinase (CK) screening** can be performed after birth. Baby boys can be tested after delivery or as any concerns arise. Some states are considering adding (or may already have) optional newborn screening for Duchenne.

What about the risks to my other family members? My mother? My sister? My daughter?

When a person in a family is identified as having Duchenne or being a carrier of Duchenne, we then know that other family members are potentially at risk. The exact risk depends upon your family history; a genetic counselor can help you determine specific risks for your family members. In some families, you can trace the condition for many generations. Other families may be tricky, especially families with Becker who may have a broad range of severity, including males with very mild symptoms.

Daughters

As we discussed earlier, since you are a carrier, your daughter has a 50% chance to be a carrier. The age at which to do carrier testing in a family is a very personal choice. Some families will wait until adulthood so that the daughter can legally consent and make the choice for carrier testing herself. Other families will choose to have their daughter tested at a younger age.

Genetic testing for carrier status in a young girl with no symptoms may not change how their doctors take care of them, so some doctors prefer to wait until a girl is older. This could change in the future if more information about health risks to carriers becomes available. If a girl has symptoms of Duchenne, such as muscle weakness, difficulties with coordination, or learning disabilities, genetic testing is recommended so that an accurate diagnosis can be made.

Mothers, Sisters, and Extended Family Members

Since you are a carrier, your mother may also be a carrier. If your mother is a confirmed carrier of Duchenne, then your sisters also have a 50% chance of being a carrier. If your mother's carrier status is unknown, or if she had genetic testing showing that she does not carry the pathogenic variant, the risk to your sisters might be lower.

Depending on your family history, extended family members like maternal aunts and female cousins may also be at risk. We encourage you to make sure family members are aware of the family history and the availability of genetic testing. Genetic testing for other family members is typically specific to the variant found in you, so it is important to share the specific variant. There are many different kinds of variants in the *DMD* gene, and it is important that family members are tested for the correct variant. If you are unsure who to inform or how to start the conversation, a genetic counselor can help by reviewing your specific family history, discussing exact risks to family members, and providing resources to share with family members.

Male Relatives

If you are a carrier of Becker or a rare or unclear variant, it is possible that you may have male relatives with Becker who are mildly affected and have not yet been diagnosed. Any family members who have symptoms of a muscular dystrophy should be evaluated by a neuromuscular specialist. With rare or unclear variants, it may be helpful to test other male relatives, even if they don't have symptoms. A genetic counselor can help with this.

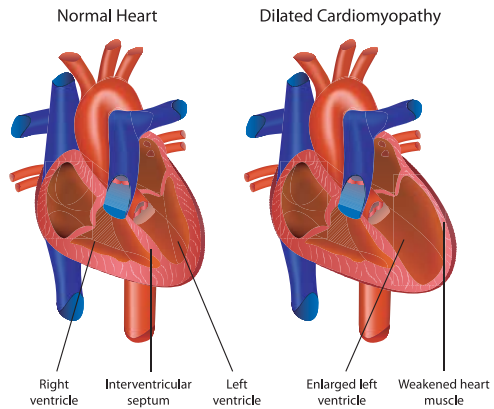
How can being a carrier affect my health?

Most women who are carriers for Duchenne do not have outward symptoms, but there are some increased health risks to be aware of.

How do I monitor and take care of my heart?

Women who are carriers have an increased risk to develop changes in heart function called **cardiomyopathy**. Reports on the frequency of these heart

changes vary depending on the age at which testing is performed, what method is used, and what findings are considered abnormal. Some studies estimate 10–50% of carrier females have findings of cardiomyopathy, most often a dilated cardiomyopathy. These changes are often mild or asymptomatic and may never require treatment. Less often, the heart disease is more severe with more significant heart muscle dysfunction. Because there are interventions that can prevent heart disease from worsening if it is caught early, cardiac screening is recommended for all female carriers.



At a minimum, you should have an evaluation with a cardiologist that includes a heart ultrasound (**echocardiogram**) and a heart rhythm analysis (**ECG**), beginning in your late teens to early adult years. Because heart disease can progress over time, it is important to discuss with your doctor how often you should have your heart monitored. For women with normal heart imaging, every 3–5 years is appropriate. Heart monitoring is especially important during pregnancy, and cardiac screening prior to planning a pregnancy is recommended.

How do I get a cardiac MRI?

Some data suggests that the best screening for the heart for female carriers is an **MRI with LGE** (Magnetic Resonance Imaging with Late Gadolinium Enhancement) done through a clinic familiar with dystrophin cardiomyopathy. This technique allows for the doctor to better identify scarring or fibrosis in the heart. Experts suggest this screening should start around age 30.

To get a cardiac MRI, you should first see a cardiologist. If at all possible, a cardiologist who has experience with dystrophin cardiomyopathy is recommended. Cardiac MRI is more expensive than an echocardiogram and may require additional insurance authorization or predetermination.

What about cardiac medications?

If you are diagnosed with a cardiomyopathy, you may be prescribed medications. Some examples of potential medications:

- ***Blood-Pressure Lowering Medications***
These are medications that end in “-pril” (lisinopril, captopril, enalapril, etc.) or “-tan” (losartan, valsartan), and are used primarily to lower blood pressure. These agents work to make arteries (blood vessels leaving the heart and supplying the rest of your body) from the heart open wider. This allows the heart to pump blood throughout the body using less pressure. There are additional studies in boys with Duchenne that also suggest a direct effect on the heart muscle that may help when fibrosis is seen.
- ***Beta Blockers***
These help the heart muscle relax and beat more slowly, so it has more time to fill and pump more completely and efficiently.
- ***Antimineralcorticoids (Spironolactone, Aldactone, Eplerenone)***
These are medications that help lower blood pressure by blocking the action of aldosterone. Aldosterone increases reabsorption of sodium and water, which increases the volume of blood the heart has to pump. The more blood the heart has to pump, the more pressure it needs to pump blood from the heart to the body.
- ***Diuretics***
These help the body remove extra water in patients with symptomatic heart dysfunction, so that there is less blood volume for the heart to pump.

Are my muscle symptoms such as weakness, imbalance and fatigue related to being a carrier?

Possibly. Muscle weakness and fatigue are common symptoms that can be caused by many different conditions.

Studies suggest that 10–20% of women who have a *DMD* pathogenic variant will have skeletal muscle symptoms. In the past, these girls and women were called manifesting carriers. Now some experts suggest that a better term is ***female with dystrophinopathy***. The symptoms can be variable, ranging from very mild symptoms, to symptoms as severe as a male with muscular dystrophy.

A common symptom is muscle weakness, which can be asymmetric, meaning that one side of the body may be more affected than the other. Other common symptoms include fatigue, problems with balance, falls, muscle pain, and cramping. Most women who report these symptoms note that the symptoms are mild.



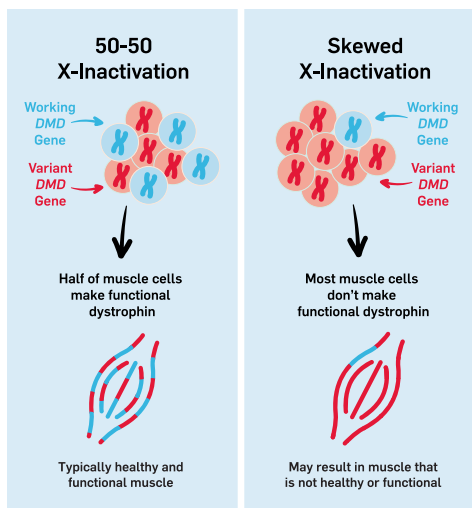
However, a small percentage of girls and women have much more severe symptoms. Some women experience a progression or worsening of symptoms as they get older or after times of illness.

A small portion of females with dystrophinopathy have all of the classic symptoms of Duchenne, including enlarged calf muscles, lack of coordination, significant muscle weakness, difficulty rising from the floor or going up stairs, and learning disabilities.

Because symptoms of fatigue, muscle pain, and muscle weakness are common and may be seen in many different conditions including aging, women who have these symptoms are sometimes misdiagnosed. A small number of females with dystrophinopathy are the first person in their family to have a dystrophinopathy. When there are no relatives with Duchenne or Becker, doctors may be even less likely to think of the condition in women. Some women with dystrophinopathy report having been misdiagnosed with fibromyalgia or Limb-Girdle muscular dystrophy.

Why is there so much variability?

Some of the variability comes from **X-inactivation**. During fetal development,



a woman's cells go through a process called X-inactivation. In that process, most of one copy of the X chromosome is turned off in every cell. This is usually a random process. However, in some women, one X can be turned off more often than the other, which is called **skewed X-inactivation**. If the skewed X-inactivation results in the X with the working copy of the *DMD* gene being turned off, that woman will make less dystrophin than is typical.

We know that in some cases, females with dystrophinopathy have skewed X-inactivation such that their X with the working copy of the *DMD* gene is turned off in more cells. This may be from unknown reasons or it may be because one of their X chromosomes has a structural chromosome difference that results in skewing. X-inactivation studies can be done on blood to see whether skewing is present, but because the X-inactivation can vary in different places in the body and from muscle to muscle, the blood X-inactivation testing is often not very helpful.

In a number of other women and girls, skewed X-inactivation does not explain their symptoms. In these cases, **modifier genes** in combination with the *DMD* pathogenic variant are thought to be responsible for the symptoms. Modifier genes are genes that produce other proteins that work with dystrophin, for example other muscle proteins or proteins involved in inflammation. All of us have variations within genes that have minor effects on the proteins made. Some of these variations in combination with a *DMD* pathogenic variant may cause more severe symptoms in some girls and women.

In addition, there are a small number of females with dystrophinopathy who have a second *DMD* pathogenic variant or a pathogenic variant in another muscular dystrophy gene as well.

What should I do?

If you have physical symptoms discussed above, the first step is to talk to your primary care provider. A referral to a neuromuscular specialist familiar with Duchenne is recommended. Based on these findings, your neurologist may recommend physical therapy.

All people should do their best to live a healthy and balanced lifestyle, which includes a diet high in fruits and vegetables, regular exercise, a healthy body weight, not smoking, and alcohol in moderation. Most women who are carriers do not have symptoms, but it remains important to maintain your general health. If you are a female with dystrophinopathy, you should talk to your doctor about what forms of exercise are beneficial and whether there are any recommended limitations. It is important to understand that not all doctors agree about what exercise is beneficial. If you have heart disease, it is especially important to avoid other risk factors such as smoking. A healthy body weight may also be beneficial for reducing fatigue and enabling more activity.

For some girls and women, their doctor may recommend additional testing beyond the standard *DMD* genetic testing. This is more commonly done in young girls with more severe or unusual symptoms. **CK (creatinine kinase)** levels can be used to look for muscle damage. In some instances of unusual or unclear symptoms, a doctor may recommend genetic testing for other muscular dystrophy genes. Occasionally, a **muscle biopsy** is recommended to better evaluate the muscle fibers and how much dystrophin is present.

Before doing any additional testing, it is important to discuss with your doctor the benefits, limitations, risks, possible results, and how the results could impact your health care.

Knowing I am a carrier is causing so many emotions. Is that normal?

Yes. Learning that you are a carrier can cause many strong emotions. It is common for women to feel sad, angry, worried, or guilty after learning that they are carriers. These feelings are very normal and may change from day to day and year to year.

Guilt is one of the most common emotions mothers report after finding they are a carrier. ***It is important to remember that no one can control which genes they inherit and which genes they pass on to their children.*** Although no one is in charge of which genes they pass on to their children, many women wish that they could control their genes or take back the illness.

Carriers considering having children (or more children) may be afraid of the possibility of having an affected child (or another affected child). Sometimes these fears change their plans about having children. Some women choose to have prenatal genetic testing during pregnancy. Other women choose to have children no matter what. These decisions are very complicated and personal, and there is no "right" answer.

Finding out you are a carrier can affect relationships in your family, both in your immediate family and in your extended family. Because Duchenne is a genetic condition, learning you are a carrier may mean that others in your family are also carriers. In some cases, this can strain relationships or cause other difficulties as family members may make different choices or approach situations and risks differently. While it is important to inform your family members of their potential chances, it is also important to remember that they may make different choices than you. In your immediate family, it is common for couples to each cope with the information differently.

Females with dystrophinopathy may have additional feelings related to the uncertainty around their own health. It is difficult to predict if the symptoms may get worse, and if so, at what rate. It can be especially challenging for

females with dystrophinopathy who are trying to take care of an affected child while dealing with their own symptoms.

How do I deal with knowing that I am a carrier?

Connect with Professionals

The first step in coping with being a carrier is being fully informed. After meeting with your health care provider, you may want to consider receiving other forms of support, such as speaking with a genetic counselor or therapist. A genetic counselor can provide additional information about genetic risk, assist in ensuring you are making informed decisions about family planning and your own health, as well as offer emotional support for you and your family. A therapist can also be a great resource in offering tools to help cope with the stress that can come with learning about being a carrier. Talk to your primary care provider or insurance to help you identify a counselor or therapist in your area. Some women will consider individual therapy, while for others, couples or family therapy may be most helpful.

Prioritize your mental health

While experiencing a range of negative emotions when learning about being a carrier is normal, sometimes these negative emotions can seem to take on a life of their own, lasting weeks at a time and getting in the way of living your daily life. If you notice this for yourself, consider talking with your primary care doctor and/or a mental health professional, including a psychologist or licensed clinical social worker, to discuss treatment options that are right for you.



Engage with the Duchenne community

Parent Project Muscular Dystrophy (PPMD) can help by putting you in contact with other women who are carriers and have experienced similar situations. Talking to another woman who has gone through the same thing can be an excellent source of support. Getting involved in the Duchenne community via volunteering, advocacy, fundraising, or education can help. For some women, being able to “do” something, to help others, makes them feel empowered. For other women, the idea of joining community organizations may feel overwhelming. This is normal and everyone moves at their own pace. Engage in the Duchenne community in the way that feels most comfortable and beneficial to you, and acknowledge that your needs may change over time. For these and other resources, visit ParentProjectMD.org.

Participate in research

The effects of being a carrier on a woman’s health are still not completely understood. Participating in research can be another way to both help other carriers and potentially yourself. Enrolling in The Duchenne Registry is an easy way to provide important information to the Duchenne research community as we try to better understand the cardiac and muscle risks. Enrolling in a clinical trial or natural history study is another way to participate in research. Of course, prior to participating, you should always carefully consider the potential benefits and risks of the study and discuss the options with your medical providers. To join The Duchenne Registry, visit DuchenneRegistry.org.



Resources

Parent Project Muscular Dystrophy ([ParentProjectMD.org](https://parentprojectmd.org))

An excellent resource and comprehensive guide for all aspects of Duchenne care and research

Decode Duchenne Free Genetic Testing Program ([ParentProjectMD.org/Decode](https://parentprojectmd.org/decode))

For family members who may need genetic testing

The Duchenne Registry ([DuchenneRegistry.org](https://duchenneregistry.org))

Register yourself (and affected family members) and share your data to advance research in Duchenne and Becker muscular dystrophy

Psychology Today ([PsychologyToday.com/us](https://psychologytoday.com/us))

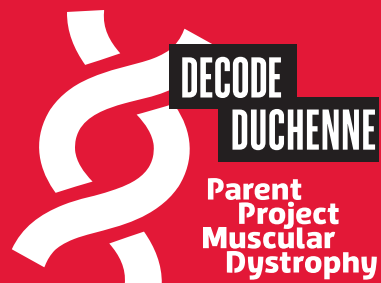
Find a therapist or counselor in your area

National Society of Genetic Counselors ([NSGC.org](https://nsgc.org))

Find a genetic counselor in your area

ClinicalTrials.gov ([ClinicalTrials.gov](https://clinicaltrials.gov))

Look for potential research studies and trials



Parent Project Muscular Dystrophy

JOIN THE FIGHT.
END DUCHENNE.

Parent Project Muscular Dystrophy fights to end Duchenne for every single family.

[ENDDUCHENNE.ORG](https://endduchenne.org)

