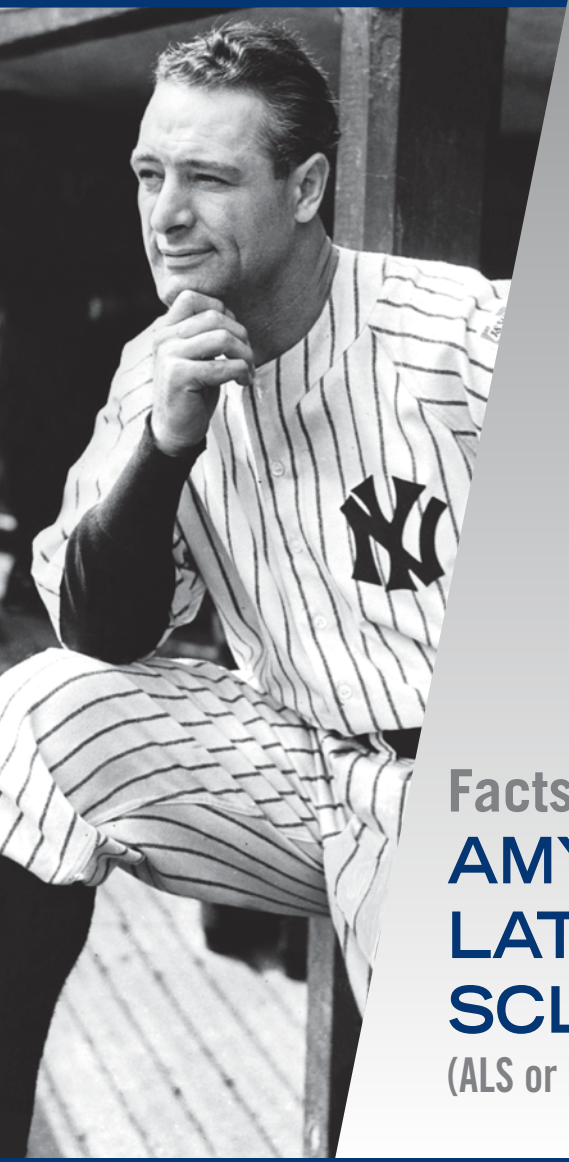
MDA®
Fighting Muscle Disease



Facts About AMYOTROPHIC LATERAL SCLEROSIS

(ALS or Lou Gehrig's Disease)

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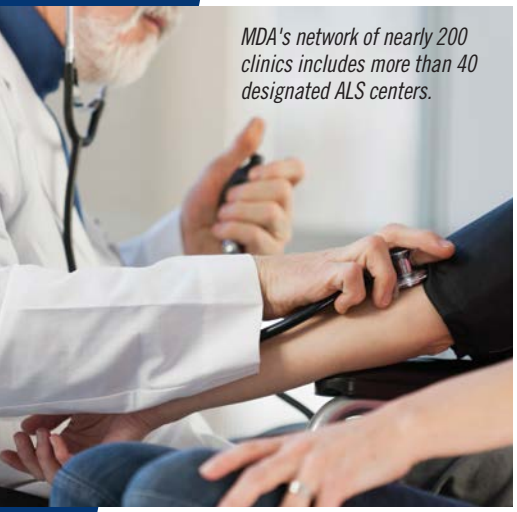
Lou Gehrig

MDA and ALS

MDA is the world leader in fighting ALS (amyotrophic lateral sclerosis). If you've recently received an ALS diagnosis, this booklet will help you understand the disorder, while guiding you to the many services MDA provides.

MDA's involvement with ALS began in the early 1950s, when Eleanor Gehrig, widow of Yankees first baseman Lou Gehrig, was searching for a way to fight the disease that had taken her husband's life. Mrs. Gehrig served more than a decade as MDA National Campaign Chairman.

MDA's nationwide network of nearly 200 specialized neuromuscular disease clinics — including more than 40 designated ALS centers — is the largest in the United States. Nearly 13,500 individuals affected by ALS receive MDA services. They all have access to our specialized clinics, staffed by top health professionals skilled in the diagnosis and medical management of ALS.



MDA's network of nearly 200 clinics includes more than 40 designated ALS centers.

In addition, MDA's Neuromuscular Disease Registry is helping to optimize clinical outcomes and evaluate best practices in ALS care. It complements the National ALS Registry, overseen by the federal Agency for Toxic Substances & Disease Registry (ATSDR), which focuses on the causes of ALS.

In 2013, MDA committed more than $7.8 million to services to help relieve the day-to-day challenges faced by ALS-affected families. Since its inception, MDA has dedicated almost $325 million to ALS research and health care services.

MDA also oversees an ALS Clinical Research Network, housed at five of the largest ALS research centers in the country.

MDA and ALS advocacy

Through MDA's advocacy efforts and community events, we influence public policy and therapy development. Some examples include MDA's recommendations to the FDA following a groundbreaking ALS hearing in 2013; the completion of a 2013 study analyzing all costs, including loss of income, associated with ALS; MDA's 2013 urging of Congress to retain the Orphan Disease Tax Credit, which encourages drug development for rare disorders; and MDA's 2014 support for the FDA Safety Over Sequestration Act, which would allow the FDA to access more of its resources to review candidate therapies. To join in the fight against ALS, become an MDA advocate at mda.org/advocacy.

What is ALS (amyotrophic lateral sclerosis)?

ALS is primarily a disease of the parts of the nervous system that control voluntary muscle movement.

The word "amyotrophic" comes from Greek roots that mean "without nourishment to muscles" and refers to the loss of signals nerve cells normally send to muscle cells. "Lateral" means "to the side" and refers to the location of the damage in the spinal cord. "Sclerosis" means "hardened" and refers to the hardened nature of the spinal cord in advanced ALS.

In the United States, ALS also is called Lou Gehrig's disease, named for the Yankees baseball player who died of it in 1941. In Britain and elsewhere in the world, ALS is often called motor neuron disease in reference to the cells (motor neurons) that degenerate in this disorder.

What happens to someone with ALS?

In ALS, nerve cells that control muscle cells gradually die. In most cases, the cause is unknown. As these motor neurons die, the muscles they control become weak and then nonfunctional. Eventually, the person with ALS may become paralyzed.

Without assistive technologies such as mechanical ventilation and feeding tubes, the average life expectancy is three to five years after an ALS diagnosis.

About 4 to 10 percent of those with the disease live more than 10 years, and some survive for decades, such as British physicist Stephen Hawking, who has had ALS since the 1960s and is still able to practice his profession.

Modern technology has allowed people with ALS to compensate to some degree for almost every loss of function, making it possible even for those with almost no muscle function to continue to breathe, communicate, eat, travel and use a computer.

It's important to note that the involuntary muscles, such as those of the heart, gastrointestinal tract, bowel and bladder, and those that regulate sexual functions are not directly affected in ALS. (However, prolonged inability to move and other effects of ALS can have some indirect impact.) Hearing, vision and touch generally remain normal.

ALS-associated pain can occur as a result of tightness (spasticity) of muscles, decreased range of motion of the joints, and abnormal stresses on the muscles, bones and skin that occur as a result of immobility. Pain and its management should always be discussed with your health care professionals.

Mild cognitive impairment is not uncommon, but severe cognitive impairment, known as "dementia," occurs in only about 3 to 5 percent of cases. Some with ALS may experience involuntary laughing or crying spells that are unrelated to their emotional state. Called involuntary emotional expression disorder, or "pseudobulbar affect," this symptom can be treated with medication. (For more on these cognitive and emotional symptoms, see "Emotions and intellect" on page 13.)

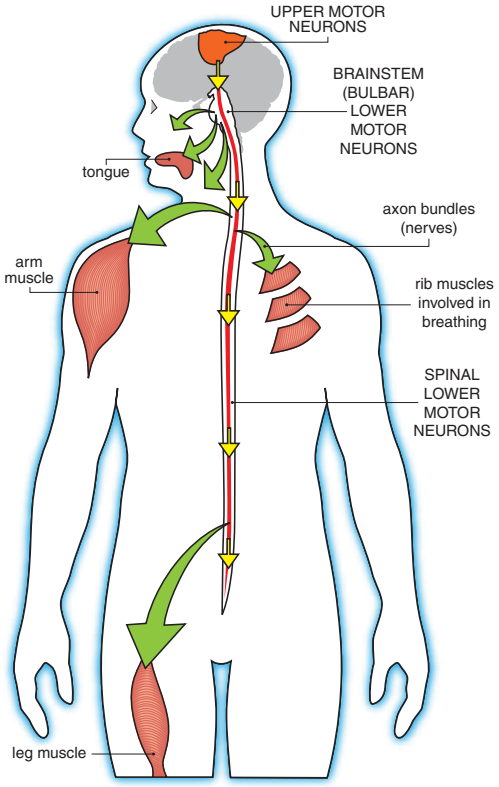
What happens to the nervous system in ALS?

Muscle-controlling nerve cells, or motor neurons, are divided into two types: upper and lower. The upper motor neurons are located on the surface of the brain and exert control over the lower motor neurons, which are in the brainstem and the spinal cord.

The lower motor neurons are directly attached to muscles through "wires" called axons. Bundles of these axons leave the spinal cord and extend out to the muscles. It's these bundles that doctors are referring to when they talk about the "nerves."

The function of lower motor neurons is straightforward. They send "go" signals to muscles. When these cells gradually die in ALS, muscles atrophy (shrink) and become progressively weaker and eventually unable to contract, resulting in paralysis.

The lower motor neurons that control most of the muscles in the body are in the spinal cord. Those that control the muscles of speaking, swallowing and facial expression are in the brainstem. They're sometimes called bulbar motor neurons, because the part of the brainstem that houses them has a bulblike shape. The term bulbar involvement means that the muscles of the face, mouth and throat are affected by the disease.



Upper motor neurons on the surface of the brain control lower motor neurons in the brainstem and spinal cord.

The upper motor neurons have more complex functions. It's harder to study them, and not as much is understood about them, although new techniques are changing that.

These cells seem to exert complex control over the lower motor neurons. This control allows movements to be smooth, directed and varied in intensity. (For instance, they're part of an elaborate system that allows a person to aim a hand at a glass of water, estimate its weight, pick it up, and use the right amount of force to lift it to his or her mouth, all while thinking about something else.) When upper motor neurons are lost and lower motor neurons remain, movements are still possible but can become tight (spastic) and less precise.

In ALS, a combination of these effects is usually seen because both upper and lower motor neurons are dying. People with ALS can have weak and atrophied muscles with tightness (spasticity). Muscle twitches (called "fasciculations") and cramps are common; they occur because degenerating nerves become irritable.

Who gets ALS?

ALS usually strikes in late middle age (the average age of onset in the United States and Europe is between 56 and 63) or later, although ALS also affects younger adults and even children, as well as very elderly people. Some genetic forms of ALS have their onset in youth.

Men are somewhat more likely to develop ALS than are women. Studies suggest an overall ratio of about 1.5 men to every woman who develops the disorder in Western countries. In younger-onset patients, there seems to be a greater male predominance.

ALS usually strikes in late middle age but can occur in young and elderly people.

Genetic factors are involved in the cause of ALS, and the disease can run in families (see "Does It Run in the Family?" on page 18). ALS is "familial" (that is, there is more than one case in a family) about 5 to 10 percent of the time. The other 90 to 95 percent of the time, it is "sporadic" (that is, there is no family history of the disease).

For years, experts have tried to find factors common to people who develop ALS, such as environmental toxins, occupational hazards, places of work or residence, and so forth. So far, the evidence for such risk factors and triggers has been frustratingly unclear, although the finding of an association between developing ALS and having served in the Gulf War in the early 1990s has indicated one of the strongest of these proposed risk factors. (See "What causes ALS?" on page 14.)

How is ALS diagnosed?

ALS usually announces itself with persistent weakness or tightness in an arm or leg, making it difficult to use the affected limb; or in the muscles controlling speech or swallowing, leading to difficulty with these functions. At this stage, it isn't unusual for people to ignore these problems or to consult a physician who likely will find no cause for concern.

However, the disease — if it's truly ALS — continues to progress. It generally spreads from one part of the body to another, almost always in parts adjacent to each other, so that eventually the problem can no longer be ignored or treated with exercise or a cane. It's at this point that the patient is usually referred by a general practitioner to a neurologist, who will then consider ALS among many other possibilities.

A thorough medical and family history and physical examination are the starting points of a neurologic work-up. The person will undergo simple, in-office tests of muscle and nerve function.

If ALS is still being considered at this point, the next step is usually an electromyogram, or EMG. This test measures the signals that run between nerves and muscles and the electrical activity inside muscles to see if there's a pattern consistent with ALS. If there is, more tests likely will be ordered.

Additional tests may include imaging of the spinal cord and brain, usually by MRI (magnetic resonance imaging) scan, and sometimes a test of the fluid surrounding the spinal cord (spinal tap or lumbar puncture), which is performed by putting a needle into the back between two lower vertebrae.

Blood tests to exclude disorders that mimic ALS also are conducted. In some instances, a muscle biopsy, which involves taking a small sample of muscle under local anesthesia, is performed.

MDA clinics and ALS centers are staffed by professionals who are highly skilled diagnosticians.

With the exception of genetic testing that can reveal the source of the disorder in some cases, the diagnosis of ALS is mostly a "rule-out" procedure. This means ALS is diagnosed after all other possibilities have been ruled out by specific tests. Among the conditions that resemble ALS are some forms of muscular dystrophy, the neurologic conditions known as spinal-bulbar muscular atrophy and adult-onset spinal muscular atrophy, the nerve-to-muscle transmission disorder known as myasthenia gravis, Lyme disease, and various causes of compression of the spinal cord or brainstem, such as tumors and malformations.

If your ALS was diagnosed outside a major medical center or without extensive testing, it may be worth getting a second opinion. MDA-supported clinics and MDA/ALS centers are staffed by professionals who are highly skilled at diagnosing ALS and the conditions that resemble it.

What can be done about ALS?

Although ALS research is proceeding at an unprecedented pace, only one medication has been found to be somewhat effective against the disease and is approved by the U.S. Food and Drug Administration (FDA) as an ALS treatment. That medication, riluzole (brand name Rilutek), has a modest effect in prolonging survival. It may work by interfering with the effects of a nervous system chemical called glutamate.

In 2010, the FDA approved the drug Nuedexta for the treatment of uncontrolled expression of emotion related to brain changes in ALS. This condition, also known as pseudobulbar affect, involves laughing and crying spells unrelated to mood.

Several other medications are now in clinical trials (see "MDA's Search for Treatments and Cures" on page 20).

MDA clinics and ALS centers use a team approach to patient care that mobilizes a variety of health care professionals, all of whom aim to alleviate symptoms, maintain function and independence, prolong life and offer guidance for those with ALS and their families.

In-depth information and advice about coping with ALS can be found in MDA's books ***Everyday Life with ALS*** and ***The MDA ALS Caregiver's Guide***. Both are available free online (mda.org) and may be available in print through your local MDA office.

In ALS, when it comes to technology, durable medical equipment and health-enhancing strategies like feeding tubes, the key is to "stay ahead of the game." Investigate and obtain these important aids before you need them, to increase the chances that you will fully benefit from them.

Preserving hand function

Special grips for writing implements and eating utensils, devices that fit over keys to make them easier to turn, zipper pulls and button hooks can help make weakening hands more functional.

Eye-gaze technology provides an alternative to using the hands to access the Internet, write, use a communication device and even drive a power wheelchair.

A professional therapist associated with your MDA clinic or MDA/ALS center can help you with these devices.

Special grips for writing implements can be helpful.

Preserving mobility

Today's technology allows for mobility for almost everyone, no matter how few muscles remain functional. Physical and occupational therapists at your MDA clinic can help you identify the equipment that's best for each stage of the disorder.

In the early stages, a cane or a supportive brace ("orthosis") may be all that's needed. An ankle-foot orthosis, or AFO, can keep the foot from dropping with each step and causing tripping while walking. Later, additional devices may be useful, such as walkers, manual wheelchairs and power wheelchairs.

As mobility becomes more difficult, a power wheelchair is usually highly desirable. A "tilt-in-space" type allows the seat to be positioned at a variety of angles, which relieves pressure and helps prevent skin breakdown. Some models allow the user to be brought into a standing position, which is generally good for circulation, bowel and bladder function, and bone preservation, as well as providing the psychological benefits of standing.

A power chair maximizes mobility for people with ALS.

Careful planning for the type of wheelchair needed and desired, and a thorough knowledge of insurance matters in relation to wheelchairs, is important. Your MDA clinic or ALS center often has a physical therapist and/or wheelchair specialist who can consult with you on these matters.

Custom-fitted power wheelchairs can take many weeks or months to obtain, so plan ahead. Your physician or physical therapist may raise the issue of a power wheelchair before you think you're ready, but this is to avoid long delays between the time the chair is needed and the time it may arrive.

Preserving communication

For many with ALS, speaking ability may be lost as weakness increases in the muscles in the mouth and throat that control speech and in the muscles that help generate the pressure that moves air over the vocal cords. This happens earlier in the bulbar-onset form of the disease (when the disease begins with weakness of the speaking and swallowing muscles) than it does in the limb-onset form (when weakness begins in a limb).

For this reason, speech therapists, or speech-language pathologists, are vital members of the ALS care team.

Speech-language pathologists and the devices they can recommend can help preserve communication.

Early in the disease process, while speech is still normal or nearly so, speech therapists may suggest that a person with ALS record his or her

speech. A number of commonly used phrases can be programmed into a computer, or perhaps the person would like to talk about his or her life for future listening by friends and family.

Later, the therapist can teach the person with ALS special techniques for conserving energy and making speech understood as well as possible. In some cases, a dentist can make a device called a palatal lift that can help compensate for certain types of weakness in the roof of the mouth.

Later still, the therapist can help the person with ALS learn to use a communication device (there are a variety on the market) that can substitute for speech. Some therapists recommend learning the required skills long before they're needed, preferably while good hand function remains and energy levels are fairly high.

Getting enough to eat and drink

As the muscles involved in chewing, moving food toward the back of the mouth and swallowing weaken in ALS, eating and drinking become less pleasurable and more hazardous and time-consuming.

The most serious problems are outright choking — obstruction of the windpipe by a piece of food — and aspiration, which means inhaling food or liquid into the lungs instead of routing it down the esophagus into the stomach. Normally, the throat muscles protect us from aspirating food or drink, but they may lose their ability to do so as ALS advances.

Early solutions to swallowing problems involve changing the consistency of food and liquids.

Speech-language pathologists or therapists are also specialists in swallowing, since these functions involve the same muscles as speech. Some therapists specialize more in speech and others more in swallowing. Your MDA clinic can refer you to a therapist who can help you address swallowing problems as they arise.

Swallowing problems can cause weight loss, and that's not a good thing. In ALS, there is a clear link between weight and survival. Studies show that people who are slightly overweight at the time of diagnosis, and people who maintain their weight through the course of the disease, live longer than those who start out thinner or lose weight as ALS progresses.

Tube feedings can supplement or replace oral nutrition when swallowing becomes hazardous.

Early solutions to swallowing problems involve changing the consistency of food and liquids — usually thickening the liquids and avoiding large pieces of food — as well as changing swallowing techniques.

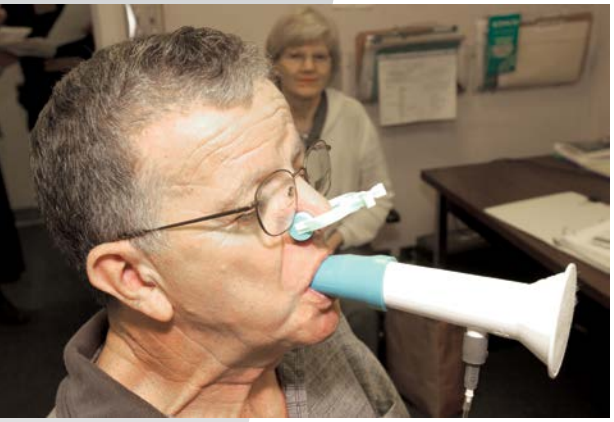
Later, if swallowing becomes hazardous and eating takes a great deal of time and energy, the therapist and physician may recommend inserting a feeding tube (also called a "gastrostomy" tube) that allows food to be delivered directly into the stomach. The term "gastrostomy" refers to making a small incision in the stomach. You may hear a feeding tube referred to as a "PEG," which stands for "percutaneous endoscopic gastrostomy," or a "RIG" tube, which stands for "radiologically inserted gastrostomy." These terms describe the procedures used when the tube is first inserted.

If still able to swallow some foods or liquids safely, people with ALS can continue to eat and drink by mouth after placement of a feeding tube. The tube can be used to supplement calories so that weight is not lost. This can be a relief to those who can't take in enough calories by mouth because they get too tired or are afraid of choking, but who still want to enjoy the taste of food.

Maintaining respiratory function

Perhaps the most serious medical complication in ALS is the gradual deterioration of the muscles involved in breathing. The diaphragm is an arched muscle located just beneath the lungs that moves up and down and allows air to come in and move out. The intercostals are muscles between the ribs that contract and relax and also assist with air movement.

As these muscles weaken, the act of breathing, which is entirely automatic for most people, becomes conscious and energy-consuming.



Regular testing of respiratory function is a crucial part of ALS care.

At or before this stage of ALS, the neurologist will probably bring in a pulmonologist and/or respiratory therapist. These professionals are usually available in or near each MDA clinic or MDA/ALS center.

The physician may recommend that you consider using noninvasive ventilation to compensate for weakening muscles. In noninvasive ventilation, no surgical incisions are made.

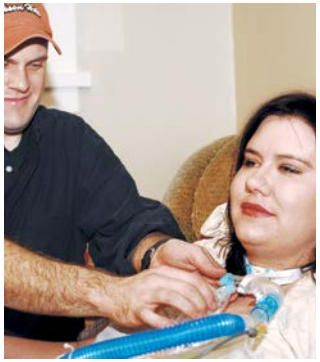
Noninvasive ventilation comes in many forms, but usually consists of two basic elements — an interface (such as a mask or nose inserts), and air delivered under pressure by a small, portable machine. Often, these machines provide a higher pressure for inhalation and a lower pressure for exhalation; this is called a bilevel positive airway pressure device, or BiPAP (BiPAP is a registered brand of Philips Respironics). There are other types of noninvasive ventilators as well, and professionals at the clinic will help you choose the device and interface that best meets your needs.

Pressurized air delivered through a nosepiece or mask is called noninvasive ventilation.

Noninvasive ventilation can be used as needed, and pressures, masks and other aspects of the device can be changed as desired.

Another form of breathing support, known as invasive ventilation, delivers air from a device (ventilator) through a hole in the trachea, or windpipe. The surgical creation of this hole is called a tracheostomy, and the tube through which the air is delivered is called a "tracheostomy" ("trach") tube.

Invasive ventilation is thought by most doctors to be a more reliable means of delivering air to the lungs when ALS is advanced and the respiratory and throat muscles are almost entirely nonfunctional.



Pressurized air delivered through a surgical opening in the trachea is called invasive ventilation.

Decisions about invasive ventilation aren't easy to make. Professionals at the MDA clinic are there to help you.

Another aspect of respiratory care that's important in ALS is assisted coughing. As the coughing muscles weaken, it becomes increasingly difficult to clear mucus from the airways. An assisted coughing device, which pushes air into the airway through a mask and then quickly reverses air flow, can help clear the airways and prevent infection. Your doctor also may recommend other methods to assist with coughing and clearance of secretions from the airways.

Emotions and intellect

Once the shock of the early stages of the disease has passed, many people with ALS report that they have rich emotional lives with family and friends, careers and interests, and a healthy sense of perspective and humor.

However, one "emotional" symptom of ALS that some people experience may be related purely to the physiology of the disease. Known as "pseudobulbar affect," or "involuntary emotional expression disorder," it involves prolonged laughing or crying spells out of proportion or inappropriate to the situation of the moment.

Some experts in neurophysiology believe this symptom arises from the loss of motor neurons in the top part of the brain that normally moderate the activity of the bulbar motor neurons in the brainstem.

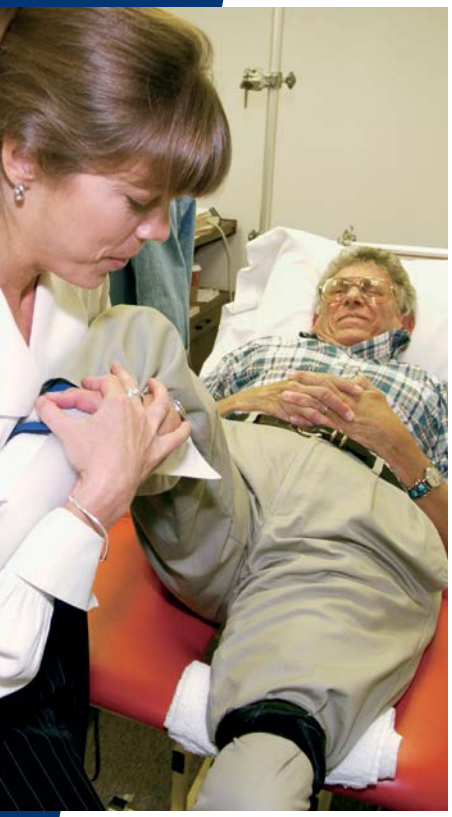
Many people with ALS lead rich, full lives.

These motor neurons activate muscles in the face and throat involved in laughing and crying. Without the influence of the upper brain neurons, more "primitive" parts of the brain may take over, experts believe, leading to physical expressions of emotion that adults normally inhibit. The "pseudo" in the term refers to the fact that the location of the problem isn't in the bulbar neurons themselves but in their loss of connection to neurons elsewhere in the brain.

Antidepressants are sometimes prescribed, and a medication called Nuedexta, developed specifically to combat this problem, was approved in 2010.

Mild cognitive impairment is fairly common in ALS, though not universal. Roughly half of all people with ALS exhibit some symptoms of cognitive impairment at some stage in their disease. Often, these cognitive changes are mild and include experiences like difficulty paying attention in conversations, trouble concentrating or finding words, and difficulty shifting attention from one thing to another. Only a small percentage of ALS patients develop more serious cognitive and behavioral difficulties ("dementia").

ALS is tough to handle alone. Many people with ALS and their families find support groups or Internet chat groups useful. MDA's support groups provide important help for spouses and other caregivers, whose job can be very demanding; ask at your clinic or local MDA office about one in your area.



Health care professionals can help relieve ALS-related symptoms.

Relief of symptoms

While researchers continue efforts to identify compounds that slow or stop motor neuron degeneration in ALS, physicians can prescribe medications to treat troublesome symptoms during the course of the disease. These include drugs to ease cramps and muscle twitches, help in handling saliva, reduce anxiety and depression, treat constipation, help with sleep problems, and alleviate pain associated with prolonged immobility and joint displacements.

What causes ALS?

Years ago, it was widely believed that there might be one cause to explain all cases of ALS. Today, doctors and scientists know that can't be the case. Together, they're working to identify the multiple causes of the disorder.

The findings in the 1990s showing that mutations in the SOD1 gene can cause ALS (see "Does It Run in the Family?" on page 18) opened a window into ALS.

Even though very few ALS patients have flawed SOD1 genes, their disease looks similar to ALS not caused by SOD1 gene mutations, and scientists have concluded that most, if not all, ALS cases, involve common biochemical and physical changes in the motor neurons.

Several additional clues, including several other genetic mutations that can cause ALS, have emerged since the 1990s.

The National Amyotrophic Lateral Sclerosis Disease Registry, created and maintained by the Agency for Toxic Substances & Disease Registry (ATSDR), a sister agency of the U.S. Centers for Disease Control and Prevention (CDC), is collecting information to help experts learn more about who gets ALS and why. To learn more or to join this registry, go to cdc.gov/ALS.

The following possible causes are being studied by ALS specialists, many of whom have received MDA support.

Genetic factors, protein misfolding and several other factors have been implicated in ALS causation.

Genetic factors

Although ALS is clearly "familial," or "inherited," only 5 to 10 percent of the time, genetic factors probably play a role in ALS in many people in whom the disorder does not appear to be inherited. It may be that genes that aren't directly involved in causing ALS can contain variations that increase or decrease the likelihood of developing the disease in the presence of as-yet-uncertain environmental factors.

Protein misfolding

A common feature in ALS is the presence in nerve cells of improperly folded proteins that clump together, forming "aggregates." In people with ALS, misfolded versions of proteins known as SOD1, FUS and TDP43 are frequently seen, even when there is no genetic abnormality in the DNA for these proteins. (If there is a genetic abnormality, they're even more likely to misfold.)

Free radicals

Free radicals are molecules that carry electrical charges that make them unstable and liable to damage cellular structures. They're a normal part of cellular life, and cells are usually able to neutralize most of them and keep their numbers in check. But in ALS, free radicals may build to toxic levels and damage cells, through an attack process called "oxidative stress."

Excess glutamate

Glutamate is a common chemical in the nervous system, which neurons use to send signals to other neurons. But, like many things, glutamate has to be present in the right amount to work: Too little leads to a lack of signaling and too much to the death of nearby nerve cells.

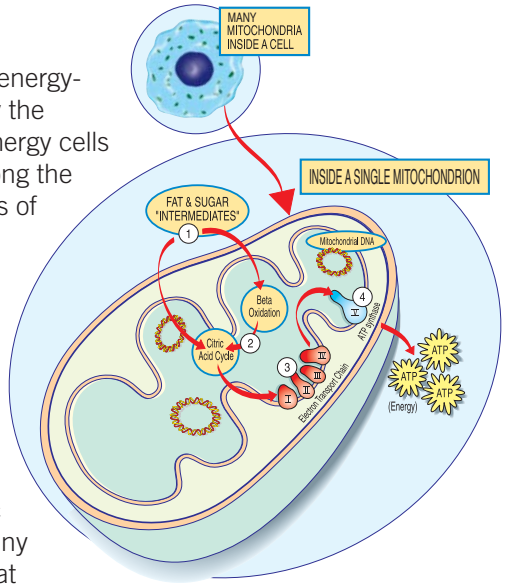
Evidence from studies of people with ALS points to an overabundance of glutamate in the nervous system. This may result from inadequate transport of glutamate away from nerve cells after it has finished its signaling work.

Defects in mitochondria

Of all the working parts of a cell, the energy-producing mitochondria are arguably the most crucial — especially for high-energy cells like motor neurons. They're also among the most complex and most studied parts of the cell.

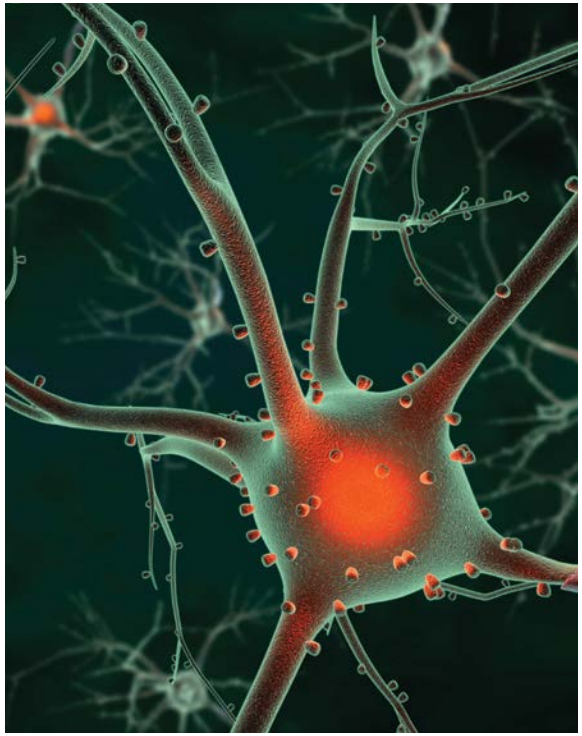
Mitochondria have their own genetic material (DNA). It bears some resemblance to the cell's other DNA, which is organized into chromosomes in the cell nucleus.

But mitochondrial DNA is organized differently, packaged into microscopic rings of genetic material that lack many of the protections against damage that chromosomes in the nucleus possess.



Mitochondria have their own DNA, and they produce much of a cell's needed energy through complex biochemical processes.

For this reason, and because processes inside the mitochondria produce potentially dangerous chemicals, mitochondrial DNA is always in danger of being damaged. Some amount of damage occurs naturally as part of the aging process, but in ALS there may be more damage to mitochondria than the average aging cell sustains.



Counteracting a "cell suicide" program could help preserve nerve cells in ALS.

Cell suicide

Most cells have a built-in "suicide" program known as "programmed cell death," or "apoptosis." Under some circumstances, programmed cell death is normal. But in ALS and other degenerative diseases, it's possible that the cell death program is activated inappropriately.

Immune system abnormalities

Many disorders that affect the nervous system are "autoimmune" in nature, meaning they occur when the body's immune system mistakenly attacks its own tissues. Microglia, immune system cells found in the nervous system, appear to play a role in ALS. None of the medications that are helpful for other autoimmune diseases has been effective against ALS so far, but some are being tested now, and new ones are in development.

Viruses and other infectious agents

For decades, scientists have guessed that viruses may play a role in ALS and other disorders that involve degeneration of nerve cells. So far, however, there's no proof of an ALS-related viral trigger.

Viruses may play a role in ALS, but there's no proof of this.

Toxins

The heavy metals lead, mercury and arsenic, although they can be toxic to the nervous system, haven't been shown to be causative agents in ALS.

Lead can damage upper and lower motor neurons, but, in the United States, exposure to lead has been monitored and limited for most people for several decades. In some circumstances, it may be worth testing for these exposures.

ALS can be inherited.

Prolonged contact with agricultural chemicals, such as pesticides, may be an ALS trigger in some cases. Other possible environmental risk factors include smoking and exposure to formaldehyde.

The association of ALS with service in the Gulf War of 1990-91 may yield some clues. Some studies suggest that service in the military in general is a risk factor, in which case a broad range of factors will need investigation.

A high incidence of ALS on the island of Guam following World War II has led to the idea that the cycad seed, ingested by people on the island, could be an ALS trigger.

Does It Run in the Family?

ALS is "familial" — that is, there is a family history of the disease — about 5 to 10 percent of the time. Since the early 1990s, more than 20 genes that, when flawed, cause ALS, have been identified, many by MDA-supported researchers.

Familial ALS can be inherited in an "autosomal dominant" pattern, meaning only one gene flaw (mutation) from one parent is needed to cause the disease. It can also be inherited in an "autosomal recessive" pattern, meaning two gene flaws (mutations), one from each parent, are needed before symptoms occur. People with one gene flaw of this type are said to be "carriers" of the disorder.

The familial nature of ALS can be complicated. For one thing, there may be genetic variants (not exactly flaws, just normal variations) that predispose people to develop or not develop ALS, perhaps in the presence of certain toxic exposures, such as those that may have ben present during the Gulf War in the 1990s.

And, when the disease is recessively inherited, it may exist only in the carrier state in a family until someone conceives a baby with another carrier.

Also, since ALS usually occurs in middle age or later, family histories can be misleading. If a parent died from other causes (for instance, an accident, heart attack or cancer) at an age younger than that at which ALS usually develops, the genetic component in the family may go unnoticed.

People who have close relatives with ALS are more likely to develop the disease than those who don't.

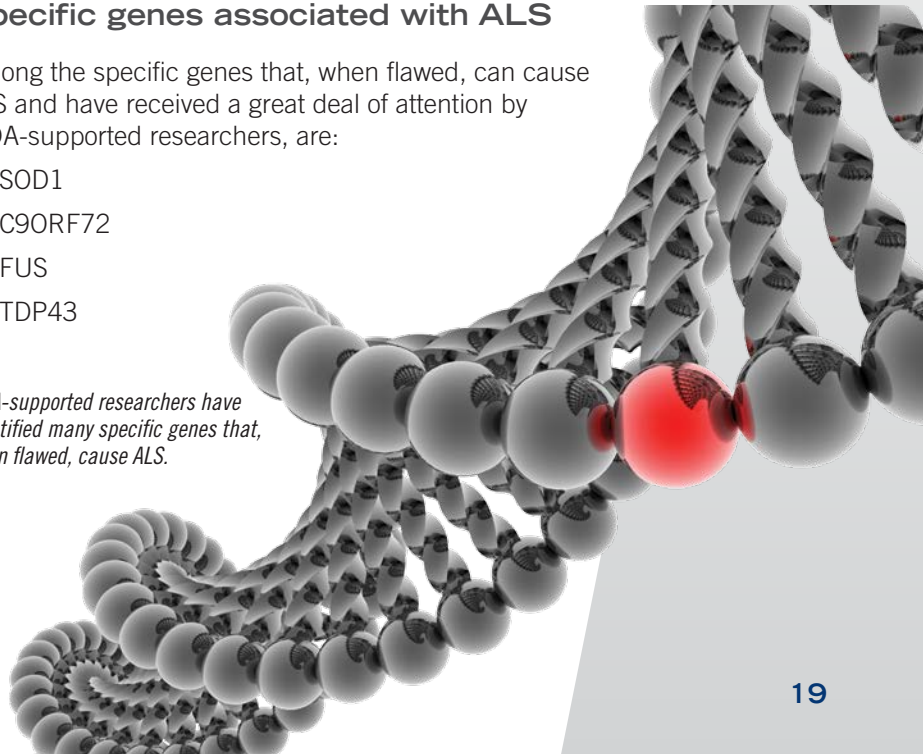
Many laboratories now test for ALS-causing genetic mutations, generally requiring only a blood sample. If the particular gene involved in a family is known, the testing is easier and less expensive. If it is not known, a panel of genetic tests for ALS can be ordered, but this is expensive.

Ask your MDA clinic physician or genetic counselor for guidance on genetic testing. Laboratories providing genetic testing for ALS can be found on genetests.org.

Specific genes associated with ALS

Among the specific genes that, when flawed, can cause ALS and have received a great deal of attention by MDA-supported researchers, are:

- SOD1
- C9ORF72
- FUS
- TDP43



MDA-supported researchers have identified many specific genes that, when flawed, cause ALS.

MDA's Search for Treatments and Cures

MDA has sponsored more ALS research than any other nonprofit health organization in the world, and our "umbrella" organization status — covering more than 40 neuromuscular disorders — puts us in a unique position. We leverage the advances in research and best practices for clinical care from one disease to inform progress in others.

We support ALS research projects worldwide and many drugs in development through industry sponsors had their early development in MDA-funded basic science research.

There are several types of clinical trials and studies currently being conducted. Here are some examples.

Combatting misfolded proteins

- Arimoclomol, an experimental compound that may activate molecular "chaperones," which help proteins fold into their correct shape
- Pyrimethamine (Daraprim), a drug used to treat malaria and toxoplasmosis that appears to target the SOD1 protein
- ISIS-SOD1-Rx, an experimental compound directed against SOD1
- HSP104, a "clump-busting" molecule in early-stage development that appears to break up aggregates and help misfolded proteins such as TDP43 and FUS re-fold into their proper shape

Modulation of the immune system

- A combination of five existing immunosuppressant drugs (basiliximab, methylprednisolone, prednisone, tacrolimus and mycophenolate mofetil)
- Fingolimod (Gilenya), a drug approved for use in multiple sclerosis
- Acthar, a drug used to treat multiple sclerosis and other disorders in which autoimmunity plays a role
- NP001, an experimental compound in development that may restore normal function of immune system cells called macrophages

Protection of nerve cells (neuroprotection)

- GM604, an experimental compound that may protect nerve cells via control and regulation of numerous genes and pathways
- NurOwn, stem cells derived from the bone marrow and coaxed to develop into cells that secrete nerve cell protectants
- Neuralstem NSI-566, stem cells derived from early-stage spinal cord cells
- Ozanezumab, an experimental compound that may protect neuromuscular junctions, where nerve and muscle fibers interact

Improving mitochondrial function

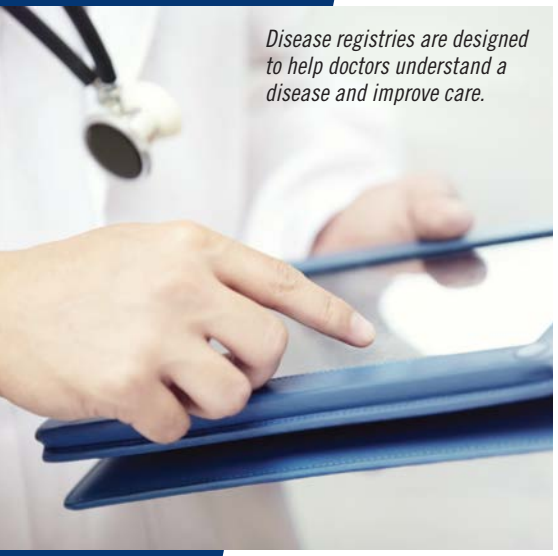
- Rasagiline (Azilect), a drug used in Parkinson's disease

Improving muscle function

- Tirasemtiv, an experimental compound that may make muscles more sensitive to weak signals from the nervous system
- Nuedexta, a drug used to treat uncontrolled emotional expression in people with ALS and multiple sclerosis that also may help with speech and swallowing

Supporting respiratory function

- NeuRx Diaphragm Pacing System, a surgically implanted device that stimulates the respiratory diaphragm and may help ALS patients live longer and sleep better



Disease registries are designed to help doctors understand a disease and improve care.

Understanding ALS causes and improving care

- The MDA U.S. Neuromuscular Disease Registry, a registry to record data about care in ALS and other disorders now being piloted in some 25 MDA clinics
- The National ALS Registry (cdc.gov/ALS), a registry being overseen by ATSDR (Agency for Toxic Substances & Disease Registry) that is collecting data about who develops ALS and possible risk factors for ALS

MDA Is Here to Help You

The Muscular Dystrophy Association offers an array of services to help you and your family deal with ALS. The staff at your local MDA office is there to assist you in many ways:

- nationwide network of clinics staffed by top neuromuscular disease specialists, including a number of clinics designated as MDA/ALS centers
- help with locating durable medical equipment through its national equipment program
- financial assistance with repairs or modifications to all types of durable medical equipment
- annual occupational, physical, respiratory or speech therapy consultations
- annual flu shots
- support groups for people with ALS and their families
- online support services through *my*MuscleTeam at mda.org/services/finding-support/mymuscle-team, a program that helps recruit and coordinate in-home help

MDA-sponsored support groups help people with ALS, their families and caregivers.

MDA helps you stay abreast of research news, medical findings and disability information at mda.org — which features an ALS-specific disease center at mda.org/disease/amyotrophic-lateral-sclerosis — as well as through the MDA/ALS Newsmagazine (alsn.mda.org), its quarterly magazine, Quest (quest.mda.org), and other publications, videos and seminars.

If you have any questions about ALS, someone at MDA will help you find the answer. To reach your local MDA office, call (800) 572-1717, or go to mda.org and enter your ZIP code in the "MDA in Your Community" box.

Six Decades of Progress Against ALS

MDA provides more support to ALS patients than any other nonprofit group.

MDA pioneered the use of historical controls in ALS clinical trial design, reducing the number of patients needed for trials

13,500

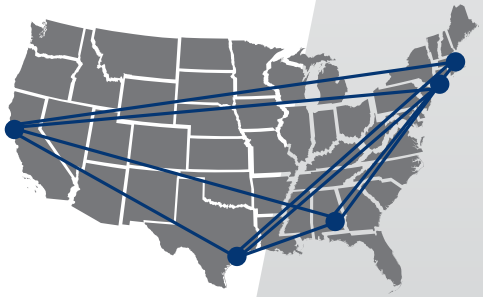
Registered ALS patients with access to MDA clinics

Over 40

ALS centers at 200 MDA clinics

MDA funds more ALS research than any other voluntary health organization in the United States.

MDA operates an ALS clinical research network housed at five of the largest ALS research centers in the country.



MDA's advocacy efforts influence public policy and therapy development.

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