

NeuRx® Diaphragm Pacing System (DPS)®: Product technical manual must be reviewed prior to use for detailed disclosure.

INTENDED USE

The NeuRx Diaphragm Pacing System (DPS)® is a percutaneous, intramuscular, diaphragm motor point stimulating device intended for use in amyotrophic lateral sclerosis (ALS) patients with a stimlatable diaphragm (both right and left portions) as demonstrated by voluntary contraction or phrenic nerve conduction studies, and who are experiencing chronic hypoventilation (CH), but not progressed to an FVC less than 45% predicted. For use only in patients 21 years of age or older.

CONTRAINDICATIONS

None known.

PRECAUTIONS

If you think the device is not providing enough stimulation, then call your healthcare provider. Some patients may feel skin irritation or sensitivity because of the NeuRx DPS™. Call your healthcare provider if this occurs. Avoid touching the patient cable or electrode wires to other metal objects. To avoid damage to the device, keep this device out of the reach of children. Do NOT attempt to open the NeuRx™ External Pulse Generator (EPG). Do NOT drop the NeuRx™ EPG. Do NOT allow the NeuRx® EPG to get wet. Do NOT get wet while using the NeuRx® EPG. This includes bathing, showering, swimming, or any other activity in which you could get wet. Do NOT have the EPG connected during any type of electrical diagnostic test such as an electromyogram (EMG) or electrocardiogram (ECG). Electromagnetic Interference: When using your NeuRx® EPG around electrical equipment, check the NeuRx® EPG screen to make sure the EPG is working. Do NOT use cables or accessories with your NeuRx® EPG other than those specified.

ADVERSE EVENTS

In 86 clinical trial patients, 3 patients (3.5%) experienced a serious adverse effect which was related or possibly related to the surgical implantation procedure: i.e., capnothorax (in 2 patients or 2.3%) requiring catheter placement or an extended hospital stay; and respiratory failure following complications from surgery (in 1 patient or 1.2%) after the migration outside of the stomach of a percutaneous endoscopic gastrostomy (PEG) tube placed following electrode implantation. There were no reports of any serious adverse effects related to the patients' use of the device following discharge. The most commonly reported non-serious adverse effects were capnothorax, mild to moderate discomfort from stimulation, infection where the electrode wire passes through the skin (exit site), and malfunction of device components resulting in a loss or diminution of conditioning therapy until resolution.

HUMANITARIAN USE DEVICE

Authorized by Federal Law for use in the treatment of chronic hypoventilation in ALS patients. The effectiveness of this device for this use has not been demonstrated.

Caution: Federal law (USA) restricts this device to sale by or on the order of a physician.



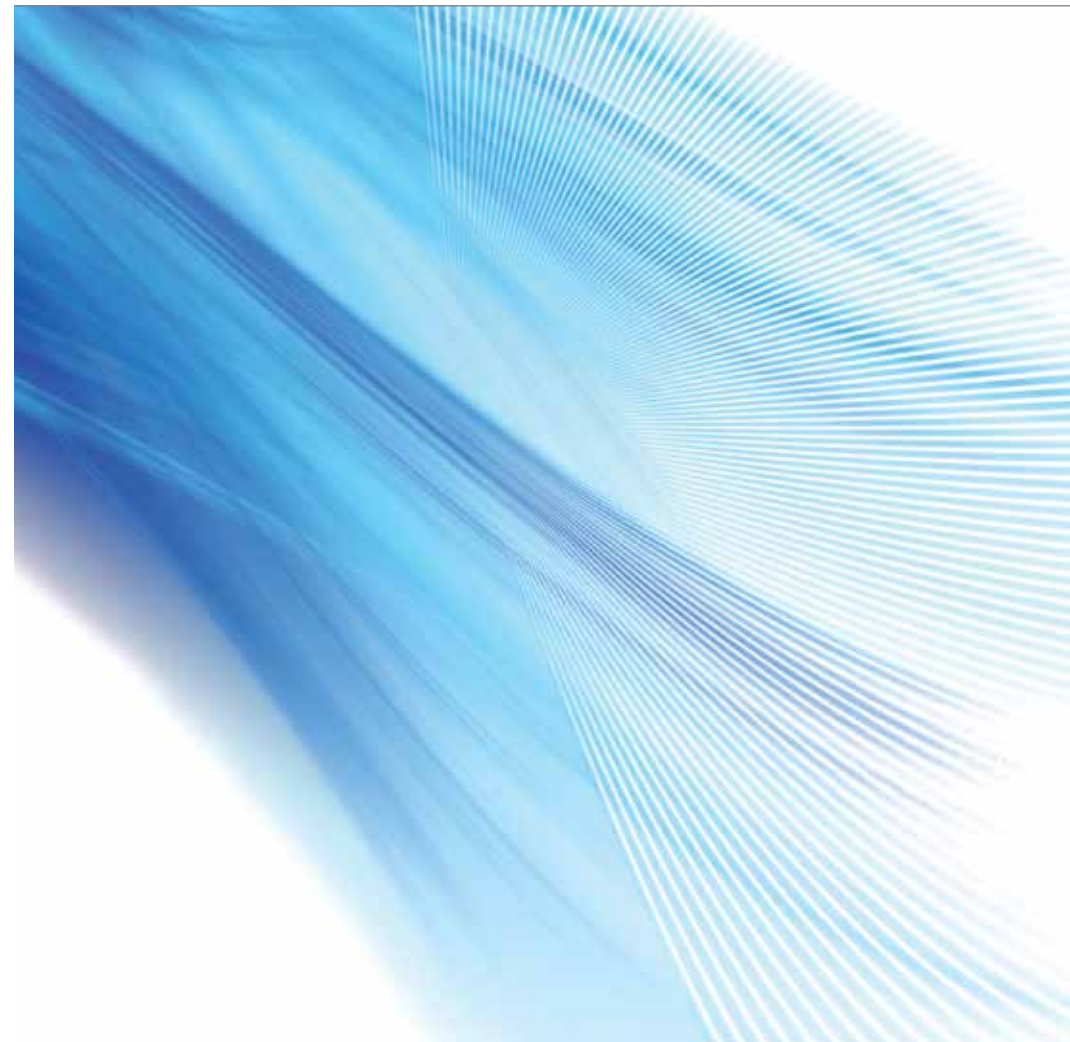
Your ALS Center staff can help answer questions and offer guidance regarding treatment options available to you. For more information about the NeuRx Diaphragm Pacing System®, or to submit a patient inquiry, contact us at:

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The ALS patient's guide to the NeuRx Diaphragm Pacing System®



PACING THE DIAPHRAGM:

The NeuRx DPS® for people with Amyotrophic Lateral Sclerosis



Q What is ALS?

Amyotrophic lateral sclerosis (ALS) is a disease that affects nerve cells in the brain and the spinal cord. Certain nerve cells called motor neurons reach from the brain to the spinal cord and from the spinal cord to the muscles throughout the body. When the motor neurons die because of ALS, the ability of the brain to start and control muscle movement is lost. Patients in the later stages of the disease may become totally paralyzed. Often ALS affects the motor neurons which reach to the muscles used in breathing.

For more about ALS see the website of the ALS Association: www.alsa.org/about-als

Q How can the NeuRx Diaphragm Pacing System (DPS)® help you?

Life is about savoring moments and sharing them with people you love. Holding hands with your significant other. Building a Pinewood Derby racer with your son for Cub Scouts. Watching your grandchildren take their first steps and traveling to places you never thought you'd visit. Moments and memories to create, enjoy, share and cherish.

The NeuRx DPS® can help you experience memorable moments in ways you thought no longer possible. The NeuRx DPS® may:

- Help you to breathe and live longer
- Condition diaphragm muscle to improve fatigue resistance during normal exertion
- Delay your time until reliance on a ventilator
- Improve your sleep

With no moving parts, noiseless operation and small size, the state-of-the-art NeuRx DPS® is engineered to help you to breathe and live longer.

Q What are the main tradeoffs and risks?

In order to obtain the potential benefits of NeuRx DPS®, you will need to undergo a routine laparoscopic surgical procedure with four short incisions to have the electrodes implanted in your diaphragm (breathing muscle). All surgery involves risks including the risks of anesthesia, respiratory complications and infection. With this procedure, there is a risk of abdominal air getting through the diaphragm and going into the chest cavity during the surgery (*capnothorax*). Most of the time, the problem goes away on its own but sometimes it requires placement of a small tube in the chest for a short time and extra time in the hospital.

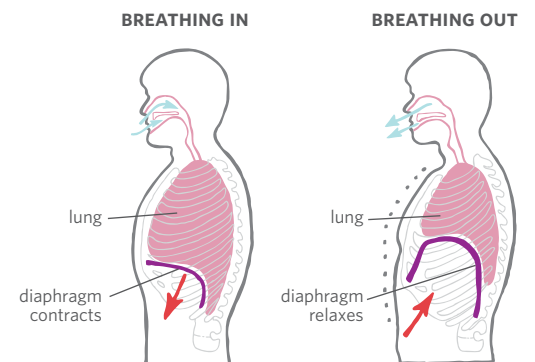
Q How do the lungs work?

When you breathe, oxygen is drawn into the lungs and absorbed into your veins. The veins carry the oxygen to your heart, which pumps it through your arteries so it can nourish your organs and tissues. At the same time, carbon dioxide is taken out of your veins by the lungs and exhaled from your body.

Q What is the diaphragm, and how does it work to create respiration?

The diaphragm is the body's most important breathing muscle. It is a sheet of tissue that separates your abdomen from your chest. When you breathe in, your brain sends a signal along the phrenic nerve to your diaphragm. The signal causes the diaphragm muscle to contract and push down into your abdomen. This creates negative pressure in your lungs, which causes air to rush in.

When the diaphragm contracts, the chest cavity enlarges, reducing the pressure inside. To equalize the pressure, air rushes into the lungs. When the diaphragm relaxes, the elasticity of the lungs and chest wall pushes air out of the lungs.



"The Diaphragmic Pacer has been the single best decision I have made since my diagnosis. My diaphragm is the one muscle in my body that not only stays the same, but has gotten stronger. 90% of ALS patients choose not to go on a ventilator. The pacer will help extend the decision while we help find a cure."

- Augie Nieto
MDA's ALS Division Co-Chairperson



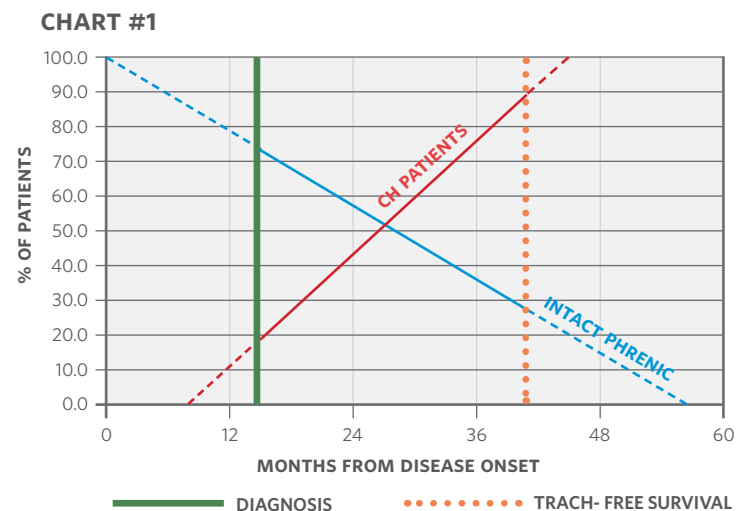
AUGIE AND LYNNE NIETO & FAMILY WITH NANCY O'DELL, ENTERTAINMENT TONIGHT CO-HOST, AT MDA TELETHON

Q How is the diaphragm affected by ALS?

With ALS, your nerves' ability to signal your muscles decreases over time. This also affects your breathing nerves (phrenic nerves), which lose their ability to carry the message from your brain to your diaphragm. Ultimately, ALS weakens your diaphragm. See the blue line on Chart #1. As your diaphragm weakens, you develop a condition called chronic hypoventilation, which means you're no longer drawing enough oxygen into your lungs. See the orange line on Chart #1. Additional information, including the Synapse Biomedical Patient Manual, can be provided to you during a consultation with an ALS treatment center physician

Your ALS physician determines when you have developed chronic hypoventilation by using standard breathing tests. These tests include:

- Forced Vital Capacity (FVC)
- Maximum Inspiratory Pressure (MIP)
- Arterial Blood Gas (ABG)
- Oxygen Saturation (SaO₂)



Q What is the NeuRx DPS®?

The NeuRx DPS® is a groundbreaking neurostimulation technology approved by the U.S. Food and Drug Administration (FDA) for treating people with ALS who have breathing problems.

The NeuRx DPS® consists of:

- Four electrodes implanted in the diaphragm
- A fifth electrode implanted under the skin
- An electrode connector, which groups the five electrodes exiting the skin into a socket
- A holder to hold the electrode connector in place on the skin
- An external pulse generator (EPG)

NeuRx® EPG is a stimulator box that sends electrical signals to the diaphragm, replacing the signals normally sent by your brain along your nerves. The signals cause the diaphragm to contract, which exercises and conditions the muscle. The EPG settings are adjusted by your doctor to match your natural and comfortable breathing pattern.

You control the NeuRx DPS® EPG. You can turn it on and off by pressing the two buttons on the front of the EPG. Because the EPG is about the size of a TV remote, it can be easily concealed.

Q What is the rationale for using electrical stimulation in ALS?

The rationale for the use of electrical stimulation in ALS includes the research done by Dr. Handa in the 1990s. Handa studied the effects of electrical stimulation on ALS-affected extremity muscles via percutaneous implanted indwelling intramuscular electrodes. He reported short- and long-term therapeutic effects and concluded that electrical stimulation may slow the progression of muscle deterioration in ALS patients. Handa did not study the effects of electrical stimulation on the diaphragm, but his research was part of the rationale for conducting a clinical trial of NeuRx DPS® in ALS. The results of that trial are discussed in the following section.

Handa, I., et al., A clinical trial of therapeutic electrical stimulation for amyotrophic lateral sclerosis. Tohoku J Exp Med, 1995. 175(2): p. 123-34.

Handa, I., et al., Short-Term And Long-Term Effects Of Therapeutic Electrical Stimulation On Amyotrophic Lateral Sclerosis. Proceedings of the International Functional Electrical Stimulation Society, 1996.

Handa, I.S.; Mimami, H.; Ihashi, K.; Yagi, R.; Matsushita, N.; Itoyama, Y.; Handa, Y. Long-term Effects of Therapeutic Electrical Stimulation for ALS Patients. In 8th World Congress of the International Rehabilitation Medicine Association. 1997. Kyoto (Japan).

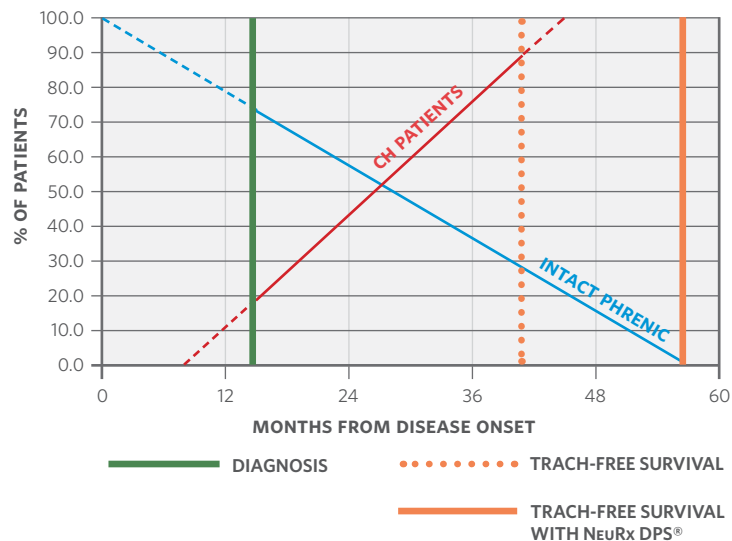
Q What were the outcomes of the clinical trial?

The NeuRx DPS® was evaluated in a clinical study, <http://clinicaltrials.gov/ct2/show/NCT00420719> at 9 clinical centers (8 in the U.S. and 1 in France). In the study, 86 patients with ALS had breathing problems like those described in the NeuRx DPS® Indications for Use. The risks and benefits of NeuRx DPS® are based on the results of these 86 patients compared to matched patient groups in two other published studies.

The trial identified average probable benefits for patients;

- Those who used NeuRx DPS® plus non-invasive ventilation (NIV), such as BIPAP®, survived 16 months longer from the time they were diagnosed than patients who just used NIV alone;
- Those who used NeuRx DPS® plus NIV survived 9 months longer from the time they started using NIV than patients who just used NIV alone;
- Those who used NeuRx DPS® and could not tolerate NIV survived 16 months after starting treatment;
- Those whose sleep was tested after using the NeuRx DPS® for 4 months slept better than before they received treatment.

CHART #2



Survival time was measured until death or need for full-time ventilator with tracheostomy tube.

To obtain the Humanitarian Device Exemption approval from FDA, it was necessary to demonstrate that “the probable benefit to health from the use of the device outweighs the risk of injury or illness, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.” The main risks identified in the trial were the risks associated with the surgery to implant the electrode wires into the diaphragm:

- Problems caused by abdominal air getting through the diaphragm and going into the chest cavity during the surgery (capnothorax). Two patients (in about 1 out of every 43 patients) needed special treatment to resolve this problem. In another 13 patients (in about 1 out of every 7 patients), the problem occurred but went away on its own.
- Reaction to anesthesia. One patient had a serious reaction to anesthesia. The surgery was then cancelled before any incision was made.

Q Can I have a feeding tube placed at the same time of surgery?

Yes. Your surgeon may recommend that you receive both the NeuRx DPS® and a feeding tube to supplement your nutrition. In the clinical trial of 86 people with ALS and chronic hypoventilation, a PEG was placed in 24 of the patients at the same time as the DPS implant. There was a remarkable improvement in the survival rate at 30 days, 6 months and 12 months following the PEG and DPS placement, when compared to other published studies of PEG alone.

However, there are still risks associated with PEG placement. One of the 24 patients in the study experienced a fever about one week post implant, and it was found that the PEG had moved out of the stomach, causing an abscess. Those problems led to the patient needing breathing support, through a tube in their throat (tracheostomy), from a breathing machine (ventilator).

Q What concerns should I have about the implant surgery?

As mentioned above, there are risks of the surgery to implant the electrode wires. The most serious include capnothorax, respiratory failure and general risks of all surgery such as anesthesia reaction. The full list of device risks, warnings and precautions is available in the NeuRx DPS® Patient/Caregiver Information and Instruction Manual, which can be provided to you during a consultation with an ALS treatment center physician. For a summary, see the statement of intended use, precautions and adverse events in the box on the back of this brochure.

Q So can I use BiPAP® (Bilevel Positive Airway Pressure) with NeuRx DPS®?

Yes. In the clinical trial of 86 people with ALS and chronic hypoventilation, the NeuRx DPS® demonstrated an ability to enhance the benefit over NIV (e.g., BiPAP®) alone.

This is because NIV and NeuRx DPS® work in different ways. NIV helps rest the accessory breathing muscles while NeuRx DPS® works to maintain diaphragm condition by maintaining diaphragm fatigue-resistant muscle fibers.

Q How is the NeuRx DPS® implanted?

The device's five biocompatible electrodes are implanted during a minimally invasive laparoscopic procedure. During the procedure, your surgeon tests a number of areas on your diaphragm to find the best locations to implant the electrodes. Only a few stitches are needed to close the small incisions. You will see 1 or 2 inches of wire from each electrode outside your body. You may feel sore after your surgery as your body heals. Your doctors can prescribe pain medications, if appropriate.

Q I've heard the NeuRx DPS® was found to positively impact sleep.

Yes. The NeuRx DPS® demonstrated an ability to increase sleep efficiency, reduction in sleep arousal index, decrease of wake-after-sleep onset and a decrease in apneas and hypopneas during REM sleep.

Q I'm concerned about making things worse. Do you wrap or cut the phrenic nerve?

Unlike traditional phrenic nerve technologies that require wrapping the nerve, the NeuRx DPS® wires are placed in the diaphragm muscle and do not physically touch the nerve. If you wish, you may discontinue use of the device at any time. If you decide to stop using NeuRx, your doctor may decide to either remove the wires or cut the wires at the skin.

Q What about muscle fatigue?

Unlike respiratory accessory muscles which benefit from resting, the diaphragm is partially composed of fatigue-resistant muscle. When the brain signal to a muscle is reduced, the underutilized muscle loses its endurance. The NeuRx DPS® substitutes ultra-short electrical pulses for the brain's signals to establish a more fatigue-resistant diaphragm muscle than when left untreated.

Q What happens after surgery?

Your NeuRx DPS® may be implanted as a same-day surgery. Depending on your condition before and after surgery, you may need to spend the night. While you are recovering from surgery, a healthcare provider will adjust the settings on your NeuRx® EPG. The purpose is to give the right amount of stimulation to your diaphragm. If the stimulation makes you uncomfortable, tell your healthcare provider. He or she can change the settings which usually reduces or eliminates the discomfort.

Before you leave the hospital, you will receive the Patient/Caregiver Information and Instruction Manual and instructions on how to use the NeuRx DPS® to condition your diaphragm. In conditioning, the NeuRx® EPG sends a small amount of electricity through the wires to your diaphragm. Typically, you will start conditioning with at least 30-minute sessions at least three times a day. Over time, you may find it helpful to use the NeuRx® EPG for longer periods to help with breathing. You may also sleep with the NeuRx® EPG if you find that it helps with breathing difficulties at night. The NeuRx® EPG may be used at the same time as non-invasive ventilation.

Your physician may ask you to return to your ALS clinic every two to three months for evaluations. Follow-up evaluations may include diagnostic testing and possible adjustment of your device settings to optimize the conditioning benefit. The device settings can be adjusted only by a trained clinician.

Phil Carlo, Author of "The Iceman," speaks on sleep apnea

"When you have ALS you get headaches in your sleep. Every morning I woke up with a headache. Every morning I had to take aspirins. After I got the pacer that stopped. I never get headaches any more. I attribute that to the pacer."

- Phil Carlo



LAURA AND PHIL CARLO

Q Who is eligible to use the NeuRx DPS®?

To be a candidate for treatment, you must have chronic hypoventilation as a result of ALS, you must be able to tolerate a surgical procedure, and your diaphragm must demonstrate the ability to respond to stimulation. A NeuRx DPS® treatment center neurologist will go over the list of candidate requirements, explain the benefits and risks, and coordinate preoperative testing.

Q How long does the device's battery power last?

The NeuRx DPS® operates on two batteries: a disposable lithium battery with 500 hours of life and a permanent, rechargeable back-up battery that lasts eight to 24 hours. The device will sound a tone every 10 seconds when the disposable battery needs replacing.

Q Where can I learn about people who have used the NeuRx DPS®?

You can access patient testimonials on the Synapse Biomedical website: www.synapsebiomedical.com/als/alstestimonials.shtml

You also may view ALS patients blogs on NeuRx DPS® users like www.patientslikeme.com
www.patientslikeme.com/treatments/show/297-diaphragm-pacing-implant?brand=f

Q Where can I get evaluated and treated?

The NeuRx DPS® is available at select ALSA, MDA/ALS and other neurological treatment centers in the United States listed at www.synapsebiomedical.com/als/usneurx-centers.shtml. Our European centers can be found at www.synapsebiomedical.com/eu/euneurx-centers.shtml.

Q Are the costs of the NeuRx DPS® and its implantation surgery covered by my health insurance?

Coverage related to the NeuRx DPS® program will depend upon your benefit plan. You'll need to coordinate preapproval with your healthcare provider and insurance company. Synapse Biomedical has established Medicare and private insurance reimbursement guidance to help treatment centers in getting pre-approved patient coverage.

Additionally, you can find on our website Medicare Eligibility Guidance for people with ALS at www.synapsebiomedical.com/als/reimbursement.shtml

Should an issue arise with a private insurer:

- A. Contact Patient advocacy at www.patientadvocate.org/index.php.
- B. Get consumer guides for your state on getting and keeping health insurance: www.healthinsuranceinfo.net/.
- C. Obtain a copy of your full (not abbreviated or summarized) explanation of insurance benefits. Read your policy carefully and thoroughly, including fine print, definitions, exclusions, etc., to discover which type of dispute resolution mechanism (appeals process) is available to you.
- D. Find out if you have been assigned a case manager and contact that individual. If not, request you be assigned a case manager or benefits advisor. You should educate this individual about your needs to preserve the integrity of your body and health. Explain that the NeuRx DPS® is a Humanitarian Use Device (HUD) approved by the FDA as a Humanitarian Device Exemption (HDE) and is not experimental (IDE).
- E. All health insurance plans have some form of appeals procedure. Aggressively follow the appeals process. If you need to, be sure the doctor writes thorough documentation in support of the need for treatment. It is not unusual for procedures to be denied to individuals covered by healthcare plans. Contact your insurance representative immediately and ask for an explanation of the action.
 - a. If needed information was not provided with the original request, resubmit your request with the necessary information. Most appeals have a strict appeal time window.
 - b. If the action is a denial, request the reason(s) for each denial in writing.
- F. Document/record all conversations with your insurance company: include date of the call, the reason for the call, the person with whom you spoke and the outcome of the call.
- G. Keep all correspondence that has anything to do with your health insurance coverage. All written communications should include your name, insurance Identification (ID) and/or Group Number, Social Security Number and your date of birth. Require that all actions regarding health benefits coverage be in writing.
- H. Contact the Insurance Commissioner www.naic.org/state_web_map.htm for your state if an appeal is denied. Inquire if the state has a Health Insurance Ombudsman who could be helpful with your appeals process. Insurance companies should have a medical review committee that can review a request for coverage.

Q

Do you have ongoing research on NeuRx DPS® and ALS?

Yes. Synapse Biomedical is conducting a post-approval study at a few sites in the U.S. The intent of the study is to expand the safety and benefit knowledge for NeuRx DPS® including the relationship between survival time and onset type (bulbar and limb), the time from onset to treatment, as well as use of the device with NIV, riluzole, or PEG.

Additionally, Synapse Biomedical, in cooperation with Motor Neuron Disease (MND) Association, (www.mndassociation.org/get_involved/donations/2011_clinical.html), is supporting a 108-person, randomized clinical trial in the United Kingdom (www.controlled-trials.com/ISRCTN53817913) to determine if NeuRx DPS® treatment prolongs life and maintains quality of life when given in addition to current standard care with non-invasive ventilation.

Q

How long has the NeuRx DPS® been in development?

The NeuRx DPS® has been developed over a 20-year period at University Hospitals and Case Western Reserve University in Cleveland, Ohio. This innovative research has led to significant advances in state-of-the-art electrical stimulation for the treatment of chronic respiratory insufficiency, enabling patients to enhance their independence and quality of life. The first clinical implant of the NeuRx DPS® was performed for a person with spinal cord injury in March 2000. As of September 2011, that patient continues to use the NeuRx DPS® successfully.



Q

How long has Synapse Biomedical been in business?

Synapse Biomedical Inc., headquartered in Oberlin, Ohio, was founded in 2002 to develop and advance the NeuRx platform technology, and make it commercially available for all those who suffer from respiratory insufficiency. In January 2008 the NeuRx DPS® was approved for sale in Europe (CE Registration #CE 518356). In June 2008, the NeuRx DPS® was approved in the U.S. for treating ventilator dependency as a result of spinal cord injury.

"As a caregiver to my husband Pat, anything that helps make living with ALS easier is huge. The diaphragm pacer has allowed Pat to sleep in his bed instead of the recliner chair. During the day when Pat 'paces,' he feels like it rejuvenates him, helps him to get a deeper breath, and gives him more daytime energy."



PAT AND JENNY DWYER

Glossary of Terms

ALS (amyotrophic lateral sclerosis, Lou Gehrig's disease) – a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. Motor neurons reach from the brain to the spinal cord, and from the spinal cord to the muscles throughout the body. When the motor neurons die, the ability of the brain to initiate and control muscle movement is lost. With voluntary muscle action progressively affected, patients in the later stages of the disease may become totally paralyzed. www.alsa.org/about-als/ (March 2011)

Arterial Blood Gas (ABG) – a blood test that measures the amount of oxygen and carbon dioxide in the blood.

BiPAP® (Bilevel Positive Airway Pressure) – a machine that helps users breathe more easily. BiPAP is a registered trademark of Respironics Inc. Other manufacturers make machines that provide similar features.

Capnothorax – a complication caused by abdominal air penetrating the diaphragm and going into the chest cavity during the surgical procedure.

Chronic Hypoventilation – Reduction in the amounts of air entering the lung's air sacs, causing below-normal oxygen levels and above-normal carbon dioxide levels in the blood.

Conditioning – the process of sending a small amount of electricity through the electrode wires placed in the diaphragm to cause contraction of the diaphragm muscle.

Diaphragm – the main muscle in your chest that is responsible for breathing.

ECG (electrocardiogram) – test to assess the electrical activity of your heart. If you have had a heart attack or an irregular heartbeat, the changes in electrical activity in your heart will show up on the ECG, allowing the heart problem to be diagnosed.

EPG (NeuRx DPS® External Pulse Generator) (stimulator) – the battery-powered external device (box) that generates the electrical signal that causes the diaphragm muscle to contract. The EPG is outside the body and is connected (through the electrode connector) to the electrode wires, which are implanted in the diaphragm.

Forced Vital Capacity (FVC) – a measurement of the amount of air you can forcibly exhale from your lungs.

Maximum Inspiratory Pressure (MIP or PImax) – a measure of how well you breathe in (inhale).

NeuRx DPS® (Diaphragm Pacing System) – device that delivers a small amount of electricity to the diaphragm muscle to cause it to contract. Major parts include the electrode wires, which are implanted in the diaphragm during surgery, the external pulse generator (“EPG”) box, and the patient cable (described below).

Non-Invasive Ventilation (NIV) – breathing assistance provided by a small machine that uses a tightly-fitting mask that fits over the nose, or nose and mouth.

Oxygen saturation (SaO2) test - This test is performed with a small monitor placed over your finger, which can detect oxygen levels in your blood. This test is done during sleep.

Percutaneous Endoscopic Gastrostomy (PEG) – a tube that is inserted through the abdominal wall and into the stomach to allow nutrition to be delivered.

Phrenic Nerves – the nerves responsible for telling your diaphragm to either inhale or exhale.

Progressive Neurodegenerative Disease – diseases such as Alzheimer's, Parkinson's and ALS can cause a rapid breakdown in a nerve's ability to function properly (transmit a signal). This breakdown can affect your speech, balance, movement, breathing and heart function.

Pulmonary Function Test (PFT) – a series of breathing tests that show how well your lungs are working (exhaling and inhaling).

Stimulator – See EPG (External Pulse Generator).