targeting genes

Researchers look to treat genetic disease at its source

ACCESSIBLE AIR TRAVEL
How to get your travel plans off the ground

FLIP OVER TO READ SPECIAL EDITION: 2019 MDA CLINICAL & SCIENTIFIC CONFERENCE
Together we are united in the fight to End Duchenne

Sarepta is inspired daily by the Duchenne community and is committed to making a profound difference in the lives of those affected by rare neuromuscular diseases.

DuchenneMosaic.com
Progress in Motion

We are pleased to share content from our 2019 Clinical & Scientific Conference, themed “Progress in Motion,” in this special issue of Quest. The conference, which was our largest ever, was held April 14–17 in Orlando, Fla. More than 1,200 people attended, including academic scientists, clinical researchers, clinical practitioners, industry scientists, regulatory scientists and leaders from other funding organizations, such as patient advocacy groups and government institutions.

This was the first time MDA has convened both our scientific and clinical communities for one large event. We merged these previously separated meetings because both fields have matured, and our community of experts is increasingly meeting in the center on therapy development. MDA’s conference serves as a call to action for all stakeholders and an opportunity to facilitate collaboration across disciplines.

The major themes highlighted at this year’s conference included genetic medicine, clinical trials, emerging use of technology and newborn screening. Each of the conference sessions was designed to illustrate common lessons that cut across the different disease states and fields that we serve. Presenters traded learnings across diseases on common features of biology, approaches to drug development, laboratory and clinical techniques, and other rapidly evolving topics.

Other conference highlights included a keynote speech by Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research at the U.S. Food and Drug Administration (FDA); a panel discussion by additional FDA experts; an introduction to MDA’s 2019 National Ambassadors; and an exhibit hall featuring a Technology Row and a Patient Advocacy Pavilion.

This year’s conference was the largest and most comprehensive of its kind in MDA’s history. And for 2020, we’re aiming even higher.

Sincerely,

Lianna Orlando, Ph.D.
Interim Head of Research
Muscular Dystrophy Association

Liana Orlando, Ph.D.
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On May 24, the U.S. Food and Drug Administration (FDA) approved Zolgensma (onasemnogene abeparvovac-xioi), a one-time gene-replacement therapy for the treatment of children younger than 2 with spinal muscular atrophy (SMA). This approval marks another historic achievement for the SMA community.

MORE ONLINE
Go to strongly.mda.org and search for “Zolgensma.”
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We believe in the power of community and the importance of building relationships with others going through similar experiences. If you are living with a neuromuscular disease, we invite you and your loved ones to attend our MDA Engage education events taking place across the country. MDA Engage Community Education Seminars and Disease Specific Symposia are one-day events empowering individuals and families with knowledge and resources. Information is shared by experts in the field and individuals living with neuromuscular disease.

EVENT SPOTLIGHT
On April 12, the spinal muscular atrophy (SMA) community came together for the MDA Engage SMA Symposium in Orlando, Fla. Event Chair Richard S. Finkel, M.D., the chief of Neurology at Nemours Children’s Hospital, shared updates on research within SMA. Participants also heard about managing scoliosis and contractures and the importance of multidisciplinary care within MDA Care Centers. A family panel discussed care and social needs while living with SMA. Representatives from Biogen, Genentech and AveXis joined a panel with physicians to discuss developing drugs for SMA.

UPCOMING MDA ENGAGE EVENTS
- Aug. 3, 2019 MDA Engage Community Education Seminar, Dallas, TX
- Sept. 7, 2019 MDA Engage Community Education Seminar, Oklahoma City, OK
- Sept. 14, 2019 MDA Engage Community Education Seminar, San Diego, CA
- Oct. 5, 2019 MDA Engage Community Education Seminar, Nashville, TN
- Nov. 2, 2019 MDA Engage MG Symposium, Durham, NC
- Nov. 9, 2019 MDA Engage DMD Symposium, Sacramento, CA
- Nov. 9, 2019 MDA Engage CMT Symposium, Philadelphia, PA
- Nov. 9, 2019 MDA Engage Myotonic Symposium, Rochester, NY

Find an Event
For a complete list of MDA Engage events and to register, visit mda.org/care/mda-engage.
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Amyotrophic lateral sclerosis (ALS)

Stem Cell Study Participants Needed

Researchers at Brainstorm Cell Therapeutics are looking for individuals with ALS to participate in a phase 3 study to help researchers evaluate the effects of mesenchymal stromal stem cells secreting neurotrophic factors (MSC-NTF cells) on disease progression.

In ALS, motor neurons degenerate or die and stop sending messages to muscles, which gradually weaken and waste away. MSC-NTF cells are the patient’s own (autologous) cells harvested from the bone marrow in an outpatient procedure. The cells are cultured to secrete higher levels of chemicals that protect neurons, or neurotropic factors. The cells are transplanted back into the patient, where they can potentially benefit the health and survival of neurons, slowing the progression of the disease.

Trial participants will be randomly assigned to groups receiving either MSC-NTF cells or placebo. Researchers will use the ALS Functional Rating Scale-Revised to determine whether the treatment is associated with slowing the rate of the disease.

Throughout the study, participants will continue to see their regular doctor for routine care.

In order to be eligible to participate, adults 18-60 years old with ALS must have a disease duration from symptom onset of 24 months or fewer; if taking riluzole, have a stable dose or not have taken the drug for 30 days prior to first study visit; and meet additional criteria.

To learn more about this study, visit ClinicalTrials.gov and enter NCT03280056 in the “Other Terms” search box.
MDA MVP Grant Supports AcuraStem ALS Drug
AS2015 may help prevent motor neuron death

MDA awarded an MDA Venture Philanthropy (MVP) grant totaling $300,000 over two years to California-based biotechnology company AcuraStem to support preclinical development of a new small molecule therapeutic for ALS. MVP grants are awarded to researchers developing therapeutics for neuromuscular diseases to make drug development easier and less risky.

The grant will allow AcuraStem to undertake proof-of-concept studies in mouse models of ALS, as well as develop biomarkers for its orally delivered, blood-brain-penetrating, preclinical development candidate, AS2015.

"With this funding, we’ll continue to move forward our novel approach aimed at transforming outcomes for ALS." —AcuraStem Co-Founder and Board Chairman Paul August, Ph.D.

The investigational treatment has the potential to be transformative for a broad range of ALS patients. AcuraStem aims to begin clinical trials in ALS patients by 2020.

Learn more about MDA’s ALS research efforts at mda.org/science.

ORARIALS-01
Now Enrolling
Phase 3 clinical trial will assess effects of arimoclomol on ALS disease progression

Researchers at Orphazyme are looking for participants with ALS for the ORARIALS-01 phase 3 study to evaluate the effects of arimoclomol on disease progression.

Arimoclomol is designed to work by helping the body clear abnormally aggregated proteins from cells.

The trial aims to determine whether treatment with arimoclomol is associated with slowing the rate of functional and respiratory decline and extending survival as measured by Combined Assessment of Function and Survival (CAFS).

Trial participants will randomly be assigned to groups that will receive either arimoclomol or placebo. Total study duration for each participant will be up to 82 weeks, with a clinic visit approximately every two months to assess patient function using ALS-specific assessment scales. Throughout the study, participants will continue to see their regular doctor for routine care.

To participate, adults ages 18 and older must have an ALS diagnosis, with disease duration from symptom onset of 18 months or fewer, and meet additional study criteria.

For more information on this study, go to ClinicalTrials.gov and enter NCT03491462 in the “Other Terms” search box. Visit orphazyme.com/about-arimoclomol to learn more about arimoclomol.

Biogen to License and Develop BIIB067
Antisense drug may block production of flawed SOD1 protein

Following its announcement of positive phase 1 clinical trial results, Biogen Inc. will license and develop partner Ionis Pharmaceuticals’ BIIB067 (IONIS-SOD1RX). BIIB067 is an investigational therapy for ALS caused by superoxide dismutase 1 (SOD1) mutations, a subtype of familial ALS.

BIIB067 is an antisense oligonucleotide (ASO), a molecule that is composed of short segments of synthetic genetic material (nucleic acid) that bind to RNA, the chemical step between DNA and the protein that it manufactures. When an antisense molecule like BIIB067 binds to RNA, it prevents or decreases protein production.

The study was designed to evaluate the safety and tolerability of BIIB067, as well as how the drug is absorbed, distributed and metabolized in the body. Participants who received the highest dose over three months showed significantly lower levels of SOD1 protein in the cerebrospinal fluid and reduced clinical decline, as measured by the ALS Functional Rating Scale-Revised, when compared to the placebo group.

To learn more about this trial, visit ClinicalTrials.gov and enter NCT02623699 in the “Other Terms” search box.
Charcot-Marie-Tooth disease (CMT)

MDA and CMTA Co-Fund Research

Studies will assess gene delivery paradigms in CMT1X

The Charcot-Marie-Tooth Association (CMTA) and MDA have jointly awarded a research grant totaling $276,430 over three years to Kleopas Kleopa, M.D., professor and senior consulting neurologist at the Cyprus Institute of Neurology and Genetics, Cyprus School of Molecular Medicine, in Nicosia, Cyprus.

Mutations in the gene coding for the gap junction beta-1 protein (GJB1), also known as connexin 32 (Cx32), are associated with the X-linked form of CMT (CMT1X), which affects approximately 1 in 25,000 people. Using this grant funding, Dr. Kleopa will perform critical proof-of-concept studies to test whether delivery of the Cx32 gene using an adeno-associated virus (AAV) vector (delivery vehicle) can improve symptoms in a mouse model of CMT1X as well as determine the optimal route for delivery of the therapy.

Learn more about MDA-supported CMT research at mda.org/science.

Duchenne muscular dystrophy (DMD)

Vamorolone Study Seeks Participants

Researchers will assess drug safety and efficacy

Researchers at ReveraGen BioPharma are looking for ambulatory boys with DMD to participate in a phase 2b study to evaluate the safety and efficacy of vamorolone. Researchers hope this therapy will improve muscle strength and endurance with a more favorable safety profile compared to the current standard of care.

Participants will randomly be assigned to groups that will receive either vamorolone or placebo during treatment period No. 1 (lasting 24 weeks); all participants will receive vamorolone in treatment period No. 2.

The total study duration for each patient will be about one year, with approximately 16 clinic visits. Throughout the study, participants will continue to see their regular doctor for routine care.

To be eligible to participate, candidates must have a confirmed diagnosis of DMD, be between the ages of 4 and 7, and meet additional study criteria.

Travel support for the participant and one travel companion for each visit is available. Contact Suzanne Gaglianone at suzanne.gaglianone@reveragen.com for more information about travel support.

To learn more or to inquire about participation, contact Andrea D’Alessandro at adalessandro@trinds.com.

Encouraging Preliminary Results for IGNITE DMD

Gene therapy trial tests dosages of SGT-001

Solid Biosciences has announced preliminary results from its phase 1/2 clinical trial, called IGNITE DMD, which is designed to assess the safety and efficacy of its lead drug candidate, SGT-001, in children and adolescents with DMD.

DMD is caused by a mutation in the dystrophin gene on the X chromosome that results in little or no production of dystrophin, a protein that is essential for keeping muscle cells intact. SGT-001 is a type of gene therapy that delivers an engineered replacement gene called “microdystrophin” via intravenous (IV) infusion, which enables production of a functional protein to substitute for the missing dystrophin.

Learn about the study design and encouraging results reported at the MDA Clinical & Scientific Conference. Flip this issue and turn to page 5.

For more information on IGNITE DMD, go to ClinicalTrials.gov and enter NCT03368742 in the “Other Terms” search box.
**Innovative Exon Skipping Trial**

WVE-210201 moves to phase 2/3 trial

Wave Life Sciences’ phase 2/3 clinical trial of suvodirsen (WVE-210201), an investigational therapy for boys with DMD who are amenable to exon 51 skipping, has been selected by the U.S. Food and Drug Administration (FDA) for its complex innovative trial designs (CID) pilot program.

The FDA’s CID pilot program aims to improve clinical trial design and help streamline and advance drug development and regulatory approval. Wave’s application included a plan to leverage DMD historical control data to effectively reduce the number of patients needed in the placebo group, potentially accelerating the completion of the study.

Learn about the promising results of Wave's phase 1 study reported at the MDA Clinical & Scientific Conference. Flip this issue and turn to page 8.

For more information on WVE-210201, visit wavelifesciences.com.

**Positive Results for MYO-101 Gene Therapy**

Trial aims to enroll more symptomatic individuals between ages 4 and 15

Sarepta Therapeutics has announced positive interim results of a phase 1/2a clinical trial for MYO-101, a gene therapy candidate developed by Myonexus Therapeutics for people living with LGMD type 2E (LGMD2E). Also known as beta-sarcoglycanopathy, LGMD2E is characterized by insufficient levels of beta-sarcoglycan protein.

The first three trial participants dosed demonstrated significant increased production of beta-sarcoglycan protein in the muscle fiber. Individuals also demonstrated a marked reduction in an enzyme (creatine...
kinase, or CK) that muscles release in response to damage. This trial was the first LGMD gene therapy trial to use a single, intravenous infusion to restore expression and functionality of beta-sarcoglycan in skeletal and cardiac muscle. Based on data reported from the first, low-dose cohort, Sarepta indicated it is moving ahead with cohort 2, which will include three individuals treated with a higher dose and three placebo subjects. Placebo subjects will have the option to be treated with the experimental therapy once biopsy results have been taken after one year of participation.

Mitochondrial myopathy (MM)

**MMPOWER-3 Recruiting Participants**

Phase 3 trial will assess effects of elamipretide

Stealth BioTherapeutics is looking for participants with primary mitochondrial myopathy (PMM) to participate in the MMPOWER-3 phase 3 trial. This trial is designed to evaluate the efficacy and safety of daily subcutaneous (under-the-skin) injections of elamipretide, an investigational drug that has been shown to improve mitochondrial function in preclinical and early clinical studies.

Participants will randomly be assigned to groups that will receive treatment with either elamipretide or placebo for six months. Researchers will assess whether treatment with elamipretide is associated with increased distance in the six-minute walk test and decreased patient-reported fatigue.

Participants who complete the six-month study may elect to extend their treatment and receive elamipretide for the remaining duration of the trial.

To participate in MMPOWER-3, individuals must:
- Have previous genetic testing results available
- Be able to walk
- Be between ages 16 and 80
- Be diagnosed with PMM in the opinion of the investigator
- Be able to meet additional study criteria

Learn more about the study at stealthbt.com. For questions, or to inquire about participation, contact Cristy Balcells R.N., M.S.N., at cristy.balcells@stealthbt.com or 423-914-8322.

Myasthenia gravis (MG)

**Firdapse Trial**

Drug was shown to be safe and effective in phase 2 trial

Results from a phase 2b clinical trial to evaluate Firdapse (amifampridine phosphate) for the treatment of muscle-specific kinase antibody positive myasthenia gravis (MuSK-MG) showed the drug to be safe and effective in treating people with this rare disease.

MuSK is a protein that plays an important role in the formation and maintenance of the connection between nerve and muscle. Patients with MuSK-MG produce antibodies that attack this protein, resulting in a reduced ability of nerves to communicate with muscles.

In the range of a 30 to 60 mg daily dose, Firdapse was found to be safe and effective for treating patients with MuSK-MG. All 10 enrolled participants showed statistically significant changes in both Quantitative Myasthenia Gravis (QMG) and Myasthenia Gravis-Activities of Daily Living (MG-ADL) scores, as well as improved assessments of quality of life (using the Myasthenia Gravis Quality of Life scale) and fatigue (using the Fatigue Severity scale). The only adverse event was a burning or prickling sensation (paresthesia) in 60 percent of patients.

Recruitment is ongoing for a phase 3 clinical trial (identifier NCT03579966) testing Firdapse in MuSK-MG patients.

Elamipretide is administered by subcutaneous injection.

Firdapse is an oral potassium channel inhibitor designed to prolong signals released from nerves and allow greater stimulation of muscles.

Firdapse is administered by subcutaneous injection.
Positive Results

Rozanolixizumab associated with improvement in health and quality of life

Pharmaceutical company UCB has announced positive results in its phase 2 trial of rozanolixizumab (also known as UCB7665), a potential treatment for MG.

Investigators found that rozanolixizumab, a neonatal Fc receptor monoclonal antibody, performed well in the study, achieving improvement in multiple disease-related endpoints and a satisfactory safety profile.

The randomized study enrolled 43 participants living with MG and evaluated patients who received the drug vs. placebo based on the following pre-specified disease-related endpoints: Quantitative Myasthenia Gravis (QMG) score, Myasthenia Gravis Composite (MGC) responder rate and Myasthenia Gravis-Activities of Daily Living (MG-ADL) score.

Recipients of rozanolixizumab saw improvements in both qualitative outcomes and biomarkers.

To learn more about the phase 2 trial of rozanolixizumab, visit ucb.com.

Study for Adults with Pompe Disease

Combination therapy targets late-onset Pompe disease

Researchers at Amicus Therapeutics are looking for adults with late-onset Pompe disease (LOPD) to participate in a phase 3 study called PROPEL. The study aims to evaluate the safety and efficacy of ATB200/AT2221, which researchers hope may improve muscle function and respiratory function compared to the current standard of care.

Learn about interim trial results reported at the MDA Clinical & Scientific Conference. Flip this issue and turn to page 9.

To learn more, visit pompestudy.com. To inquire about participation, contact patientadvocacy@amicusrx.com.

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EMFLAZA is indicated for the treatment of Duchenne muscular dystrophy in patients 5 years of age and older.

Do not use if you are allergic to deflazacort or any of the inactive ingredients in EMFLAZA.

Please see Indication and Important Safety Information on the next page and accompanying brief summary.
SELECTED IMPORTANT SAFETY INFORMATION

What is EMFLAZA?
EMFLAZA® is a corticosteroid indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 5 years of age and older.

When should I not use EMFLAZA?
• Do not use if you are allergic to deflazacort or any of the inactive ingredients in EMFLAZA

What should I tell my healthcare provider before taking EMFLAZA?
It is important to tell your healthcare provider if you have had recent or ongoing infections, develop a fever, have recently received a vaccine or are scheduled for a vaccination, or experience any other side effects.

What warnings should I know about EMFLAZA?
Do not stop taking EMFLAZA, or change the amount you are taking, without first checking with your healthcare provider, as there may be a need for gradual dose reduction to decrease the risk of adrenal insufficiency and steroid “withdrawal syndrome”. Acute adrenal insufficiency can occur if corticosteroids are withdrawn abruptly, and can be fatal. A steroid “withdrawal syndrome”, seemingly unrelated to adrenocortical insufficiency, may also occur following abrupt discontinuance of corticosteroids.

For patients already taking corticosteroids during times of medical stress, the dosage may need to be increased.

Cushing's Syndrome: Cushing's syndrome occurs with prolonged exposure to exogenous corticosteroids, including EMFLAZA. Symptoms include high blood pressure, truncal obesity and thinning of the limbs, purple striae, facial rounding, facial plethora, muscle weakness, easy and frequent bruising with thin fragile skin, posterior neck fat deposition, osteopenia, acne, amenorrhea, hirsutism, and psychiatric abnormalities.

Hyperglycemia: Corticosteroids can increase blood glucose, worsen pre-existing diabetes, predispose those on long-term treatment to diabetes mellitus, and may reduce the effect of anti-diabetic drugs. Monitor blood glucose at regular intervals. For patients with hyperglycemia, anti-diabetic treatment should be initiated or adjusted accordingly.

Increased Risk of Infection: Medical advice should be sought immediately if you develop a fever or other signs of infection as some infections can potentially be severe and fatal. Avoid exposure to chickenpox or measles, but if you are exposed, medical advice should be sought without delay.

Alteration in Cardiovascular/Kidney Function:
EMFLAZA can cause an increase in blood pressure and water retention or a decrease in your potassium or calcium levels. If this occurs, dietary salt restriction and potassium supplementation may be needed.

Behavioral and Mood Disturbances: There is a potential for severe behavioral and mood changes with EMFLAZA and you should seek medical attention if psychiatric symptoms develop.

Effects on Bones: There is a risk of osteoporosis or decrease in bone mineral density with prolonged use of EMFLAZA, which can potentially lead to vertebral and long bone fractures.

Effects on Growth and Development: Long-term use of corticosteroids, including EMFLAZA may slow growth and development in children.

Ophthalmic Effects: EMFLAZA may cause cataracts or glaucoma and you should be monitored if corticosteroid therapy is continued for more than 6 weeks.

Vaccination: The administration of live or live attenuated vaccines is not recommended. Killed or inactivated vaccines may be administered, but the responses cannot be predicted.

Serious Skin Rashes: Seek medical attention at the first sign of a rash.

What are the side effects that could occur with EMFLAZA?
• facial puffiness or Cushingoid appearance
• weight increased
• increased appetite
• upper respiratory tract infection
• cough
• frequent daytime urination
• unwanted hair growth
• central obesity
• colds

What other medications might interact with EMFLAZA?
Certain medications can cause an interaction with EMFLAZA. Tell your healthcare provider of all the medication you are taking, including over-the-counter medicines (such as insulin, aspirin, or other NSAIDS), dietary supplements, and herbal products. Alternate treatment, dosage adjustment, and/or special test(s) may be needed during treatment. Do not take EMFLAZA suspension with grapefruit juice.

The information presented is not comprehensive. Talk to your healthcare provider for more information or see www.EMFLAZA.com for the full FDA-approved product information.

For medical information, product complaints, or to report an adverse event, please call 1-866-562-4620 or email at usmedinfo@ptcbio.com.

You may also report adverse events directly to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
The Ups and Downs of Accessible Air Travel

A little knowledge and preparation can get your travel plans off the ground

BY BARBARA AND JIM TWARDOWSKI

Cory Lee, who lives with spinal muscular atrophy (SMA), has explored 32 countries in the past five years. While traversing the globe in his 300-pound power wheelchair, Lee writes about accessible travel on his blog curbfree withcorylee.com, which has garnered thousands of followers. The No. 1 topic people ask him about is air travel.

For passengers with neuromuscular diseases — especially those who use wheelchairs — air travel requires knowledge and preparation. Lee, who wrote a book on the subject, “Air Travel for Wheelchair Users,” emphasizes that travelers with disabilities should be familiar with the Air Carrier Access Act (ACAA).

Passed in 1986, the ACAA prohibits discrimination on the basis of disability and requires airlines to provide certain accessible facilities and accommodations. The ACAA applies to all U.S. airlines and flights on foreign carriers to or from the United States.

“Knowing the rules and regulations gave me more confidence about flying,” Lee says.

Being familiar with airport procedures and airline policies is also vital for a smooth flight.

TRAVELING WITH EQUIPMENT

The ACAA requires newer airplanes to have space in the cabin to store a folded wheelchair or other compact mobility equipment. A power wheelchair or other bulky equipment will fly in the baggage compartment. Lee removes the headrest and seat cushion from his power wheelchair and carries them onto the plane for safekeeping.

“Know the dimensions of the plane’s cargo hold in advance,” advises John Morris, the founder of Wheelchair-Travel.org. This helps you determine if your wheelchair will have to be disassembled, which the ACAA requires airline staff to assist with at the airport. Morris, a triple amputee who uses a power wheelchair, provides a list of airplanes and their cargo hold dimensions on his website.

It’s a good idea to ask your wheelchair manufacturer how to properly disassemble or fold the seatback for storage during flight. Attach written instructions to your chair before you check it. “Otherwise, your chair will be loaded on its side, which is the No. 1
way it is broken and damaged,” Morris says.

Always carefully inspect your equipment upon landing. If it is damaged, immediately report it to the airline and the U.S. Department of Transportation. (See “Informed Consumers.”)

GETTING ONBOARD

One of the most stressful aspects of flying is boarding the plane. The ACAA states that passengers with disabilities who need assistance or extra time to board should go before all other passengers, but Morris sees this regulation violated often. Speak with a gate agent before boarding starts to make sure you can pre-board.

Airlines are required to provide assistance with boarding for those who need it. If you cannot walk to your seat, airline staff will roll you to your seat in a narrow, high-backed wheelchair and assist with a transfer. Select a roomier bulkhead seat for easier transfers or confirm that your row has armrests that can be raised.

BATHROOM CONCERNS

Perhaps the biggest obstacle to air travel is knowing what to do when nature calls at 30,000 feet. Only wide-body aircraft (those with two aisles) are required to have accessible lavatories. However, the ACAA does require most flights to have a wheelchair on board to help a passenger reach the lavatory if the passenger requests it at least 48 hours in advance.

THE WORLD AWAITS

While long security lines and cramped airplane seats may be unavoidable, a little knowledge and advance planning can ensure that accessibility issues don’t keep you grounded.

“It’s too bad that people who are capable of traveling are staying home because they are afraid of the experience they might have with air travel,” Morris says. “Air travel is a barrier that can be overcome. The world is waiting for you.”

Barbara Twardowski lives with Charcot-Marie-Tooth disease (CMT) and uses a power wheelchair. Jim, her husband, is a registered nurse. The couple writes about accessible travel, health and lifestyle.

INFORMED CONSUMERS

In December 2018, a new law, championed by MDA, went into effect requiring airlines to report to the U.S. Department of Transportation (DOT) how many wheelchairs and motorized scooters they break, lose or damage each month. This rule gives airline consumers more information to compare airlines and make informed decisions about their equipment.

Find information about mishandled equipment, as well as flight delays and consumer complaints, in the DOT’s Air Travel Consumer Reports at transportation.gov/individuals/aviation-consumer-protection/air-travel-consumer-reports.

To learn more about consumer rights and how to file a complaint, visit transportation.gov/airconsumer.

READY FOR TAKE-OFF

When planning your travel, follow these tips for a smooth flight:

› Before you purchase a ticket, review the airline’s accessibility services and policies on its website.
› At least 48 hours before departing, call your airline’s disability assistance phone line and request the specific assistance you will need.
› Build extra time into your flight plan, especially if you are catching a connecting flight, using large and busy airports, or traveling internationally. Remember, wheelchair users are the last passengers to exit the plane.
› Review the Transportation Security Administration (TSA) screening process at tsa.gov/travel/passenger-support. For questions, call TSA (855-787-2227) at least 72 hours before flying.
Researchers look to treat genetic disease at its source

BY AMY MADSEN
Until the 1980s, little was known about the cause of any neuromuscular disease. In 1986, MDA-supported researchers identified a single gene on the X chromosome that leads to Duchenne muscular dystrophy (DMD) when it is mutated (flawed). In 1987, the protein associated with that gene was identified and named dystrophin. Lack of the dystrophin protein in muscle cells causes them to be fragile and easily damaged.
Many more discoveries have been made since then, and scientists have identified thousands of genes that, when mutated, cause disease in humans. Identifying the gene that causes a certain disease — and how the mutation leads to disease — gives hope for treatments and cures where none existed before. Without knowing the root cause of a disease, medical professionals can only treat the symptoms. But when the gene causing the disease is identified and the mechanism behind the disease is understood, researchers have a potential target at which to aim treatments and cures.

In recent years, drug developers have been able to pair the ever-expanding pool of gene identifications with advances in technologies for delivering gene-targeted therapies. These therapies hold a great deal of promise for treating neuromuscular diseases, including many of the rare diseases under MDA’s umbrella.

**IT STARTS WITH GENES**

*Genes* are made up of *DNA*. Some genes contain instructions for making *proteins* that the body needs to function properly.

Most neuromuscular diseases are caused by *genetic mutations*. These mutations can result in the destruction, malfunction or absence of proteins needed for muscles to develop and function properly.

Gene-targeted therapies seek to treat a genetic disease at its source. A therapy may do this by replacing a mutated gene with a working gene, repairing a flawed gene.
or altering how a gene is controlled.

“Gene therapy is an opportunity to directly impact patients with neuromuscular disease,” says Barry Byrne, M.D., Ph.D., director of the Powell Gene Therapy Center at the University of Florida and a former MDA grantee. “Replacing the causative gene for a given condition seems to have a major effect where conventional therapies may not have an impact.”

**GENE-REPLACEMENT THERAPY**

Currently, the most exciting area of gene-targeted therapy is gene-replacement therapy, which aims to introduce a working copy of a missing or defective gene into target cells.

Zolgensma, a gene-replacement therapy for the treatment of children younger than 2 with spinal muscular atrophy (SMA), was recently approved by the U.S. Food and Drug Administration (FDA). Zolgensma is the second-ever approved gene-replacement therapy for any disease and the first for a neuromuscular disease. (To learn more about studies of Zolgensma and how the drug works, flip this issue and turn to page 7.)

In gene-replacement therapy, scientists create the new gene in a laboratory and then package it in a delivery vehicle called a **vector**, which transports the gene into the nucleus of targeted cells. The cells can “read” the code carried within the new gene and produce the needed protein.

There are two ways to introduce the vector to cells. In **ex vivo** gene therapy, cells are removed from a person’s body and treated in a lab. The altered cells are then transferred back into the person. In **in vivo** gene therapy involves delivering genes directly into a person’s body through an injection or intravenous (IV) tube inserted in a vein.

**DELCERRY THE GOODS**

An area of intense focus for researchers is the vector, which can determine whether a replacement gene integrates itself into the cell’s existing DNA or remains separate inside the nucleus.

Many scientists are working with adeno-associated viral (AAV) vectors. These small viruses don’t cause diseases in people, but they can insert genetic material into cells. AAVs are designed to allow a new gene to enter the cell nucleus and work on its own, without integrating into the cell’s DNA, where it can trigger unintended consequences, such as other diseases.

The downside of not integrating into the cell’s DNA is that as cells divide, the transferred gene — and its effects — are gradually lost.

**MDA’S GENE CATALYST INITIATIVE DRIVES ADVANCES IN GENETIC MEDICINE**

MDA recently launched our Gene Catalyst Initiative (GCI), a multi-faceted effort to ensure that MDA families benefit from all the promise genetic medicine has to offer.

The GCI comprises a number of initiatives:

- Working to provide genetic diagnoses to individuals with neuromuscular disease — the first step to making it possible for them to utilize genetic medicine
- Driving MDA Care Centers to become leading experts in genetic medicine
- Providing public education about genetic medicine
- Continuing to fund cutting-edge research to advance knowledge and develop safe and effective gene-targeted therapies

“This important initiative builds upon MDA’s long history of supporting research aimed at the development of genetic medicines, with an appreciation and understanding that the best way to move toward treatments and cures is to understand the root cause of the disease and target that as closely as possible,” says Lianna Orlando, Ph.D., MDA’s interim head of research.

Through the multi-pronged approaches embodied in the GCI, MDA will continue to work with its large community of partners — including families, donors, researchers and clinicians — to keep up the momentum and pave the way to more treatments and cures.
Some strategies using anti-sense oligonucleotides (ASOs) to alter the genetic machinery in different ways have made it to late-stage human clinical trials or even through regulatory approval in the United States and/or Europe.

One promising way of using ASOs is through antisense gene therapy that aims to “turn off” a defective gene’s effect. This involves altering a strand of DNA or RNA to effectively tell cells to ignore part of the genetic information.

In contrast to AAVs, lentiviral vectors insert their genetic cargo into the target cell’s DNA. This means that the new gene will be passed on as cells divide, making lentiviruses useful when targeting tissues that have high rates of cell turnover.

“The most promising current approach for gene therapy to treat neuromuscular disease is the use of AAV’s,” says Michele Calos, Ph.D., an MDA grantee and immediate past president of the American Society of Gene & Cell Therapy. “But there are limitations to the AAV approach, such as size limit for the therapeutic gene and many patients’ pre-existing immunity to AAV, so additional approaches are needed.”

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The National ALS Registry: Get The Facts

The National Amyotrophic Lateral Sclerosis (ALS) Registry enables persons with ALS to fight back and help defeat ALS (Lou Gehrig’s Disease). By signing up, being counted, and answering brief questions about your disease, you can help researchers find answers to critical questions.

Learn more at www.cdc.gov/als or (800) 232-4636

Who can sign-up?
Anyone with ALS

What do I need?
- A computer with an internet connection
- An email address

What if I need help?
Caregivers and others can help you in person or even over the phone

What kind of information is collected?
- Basic demographics (e.g., age, sex, height, weight)
- Military history
- Physical activity
- Family history

Do I need to update my information?
YES! Every six months – you’ll get an email reminder

Will my information be private?
- YES! Only approved registry scientists can see it, NOT employers or insurers
- You CANNOT be looked up in the registry by name

More information for research
A better understanding of ALS
The chance to help create a better future for persons with ALS

YOU JOINING
instructions during protein manufacturing. This is called exon skipping and can cause cells to produce shortened but functional protein.

Nonsense mutations are changes in DNA sequence that introduce a premature stop codon, which acts like a cellular stop sign, causing cells to stop partway through the protein-making process. This results in shortened protein that does not work because it is missing critical parts. With stop codon read through technology, cells can be coaxed into running the erroneous stop sign, allowing them to produce functional protein.

Gene editing permits scientists to go into a cell and delete or replace a targeted section of DNA in the mutated gene. This approach allows for a precise method of targeting genetic mutations, but because it permanently changes the genome, it raises greater safety concerns.

Currently, gene editing is usually done ex vivo. Eventually, scientists hope to use viral vectors to transport tools, such as CRISPR–Cas9, into the body to edit genes, but more work is needed to determine if this is safe in humans.

**THERE ARE RISKS**

Research and development of gene-targeted therapies are being conducted with a sharp focus on patient safety, but there are still risks associated with efforts to alter a person’s genetic code. Some of the risks are:

“For many years MDA has invested in basic and translational research that has contributed to gene discovery and therapeutic strategies using gene therapy. In the era of clinical implementation of gene therapy, the MDA Care Center network will play an important role in establishing best practices for providing gene therapy treatments to the patient community.”

—Barry Byrne, M.D., Ph.D.
• The body’s immune system may mount a response to the viral vector, which could lead to inflammation and, possibly, organ failure.
• The immune system may mount a response to proteins previously not expressed in a person that are now expressed with gene-targeted therapy.
• The therapy may not work as predicted. In this case, there is no way to “turn off” a new gene once it is introduced to cells.

ERA OF HOPE

We are in an unprecedented era of therapy development for neuromuscular diseases. “For the first time, we have seen the development of genetic therapies in the last few years, and we’ll likely see more successful applications of new gene therapy technologies in the near future,” says MDA grantee Kleopas Kleopa, M.D., professor and senior consulting neurologist at the Cyprus Institute of Neurology and Genetics, Cyprus School of Molecular Medicine, in Nicosia, Cyprus.

Over the last few decades, MDA-supported researchers have discovered the gene-causing mutations for many neuromuscular disorders, developed and refined gene delivery tools and methods, and devised creative and groundbreaking solutions to the problems created by genetic defects. Those efforts have contributed to the FDA approval of Zolgensma, as well as approvals for other types of gene-targeted therapies, such as Spinraza for SMA and Exondys 51 for DMD. Many more experimental therapies are in clinical trials for diseases including limb-girdle muscular dystrophy (LGMD) and Pompe disease.

“As we learn more from the ongoing preclinical and clinical studies, the approaches for treating these disorders will continue to improve,” Dr. Kleopa says.

The outlook for gene-targeted therapies is hopeful, as a robust pipeline of gene therapy candidates and new technologies could soon benefit individuals and families living with neuromuscular diseases.

Amy Madsen is a science writer and frequent contributor to Quest.
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IMPORTANT SAFETY INFORMATION
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Before taking SPINRAZA, tell your healthcare provider if you are pregnant or plan to become pregnant.

For additional Important Safety Information, please see brief summary of full Prescribing Information on the next page.

This information is not intended to replace discussions with your healthcare provider.
Individual results may vary based on several factors, including severity of disease, initiation of treatment, and duration of therapy.

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Myotonic dystrophy (DM) is the most common form of muscular dystrophy in adults. This is a complex disease, affecting not just the muscles but nearly every other organ system in the body. The signature manifestation is myotonia, an inability to consciously relax the muscles, coupled with progressive muscle weakness.

There are two types of DM, each caused by a different genetic mutation.

DM1 is the most common form, with three subtypes:

- Adult onset, also called “classical DM,” is the most common type, affecting about 75 percent of those with DM. It begins in adolescence or adulthood, typically with myotonia. Over time, the muscles throughout the body become weaker and other organs are affected.
- Juvenile onset begins between ages 1 and 10. It is characterized by cognitive and behavioral symptoms, including attention deficit disorder and anxiety, as well as muscle weakness and myotonia.
- Congenital onset begins at or before birth and features severe muscle weakness, cognitive impairment and other developmental abnormalities.

DM2, sometimes called proximal myotonic myopathy (PROMM), typically begins in adulthood and tends to be less severe than DM1.

Numerous medical conditions occur with both forms, including cardiovascular complications, gastrointestinal symptoms (in DM1), a higher risk of certain cancers, male infertility and low testosterone, high cholesterol and low blood pressure, and insulin resistance.

We turned to Tetsuo Ashizawa, M.D., a professor of neurology and director of the Neurosciences Research Program at Houston Methodist and Weill Cornell Medical College, and a leading expert in DM, for an update on treatment and efforts to find a cure for the disease. Most of what you’ll read here refers to DM1.

Can you explain the genetic component of DM?

DM1 results from a mutation in the DMPK gene and DM2 from a mutation in the CNBP gene.

The mutation in the DMPK gene leads to an expansion of a cytosine-thymine-guanine (CTG) trinucleotide repeat in the DNA. (Nucleotides are molecules that make up DNA and RNA.) Normally, we have up to 37 CTG repeats at this location. But most of those with DM have a much higher number of repeats, sometimes in the thousands. In DM1, the larger the repeat, the earlier the symptoms appear and the more severe they are. Also, the number of repeats in DM1 may increase with each generation. So while a grandparent may have few symptoms, a grandchild may have many. This is called “genetic anticipation.”

The mutated gene, in turn, produces an expanded version of messenger RNA, which is responsible for reading the DNA “code.” These RNA molecules become toxic and interfere with the production of other proteins, preventing normal cell functioning.

Is there any treatment for DM?

We can treat the symptoms. There are some medications...
that can help improve myotonia and muscle pain (which primarily occurs in DM2).

People with DM may develop problems with arrhythmias, or irregular heartbeats, which can lead to heart failure and sudden death. Thus, people with DM often receive a pacemaker or defibrillator.

Exercise is a good idea. We used to think that DM muscles are fragile and break down easily, but it turns out that regular physical activity may prevent muscle atrophy. However, it is important that people with DM check with their doctor before beginning any exercise program.

Are there guidelines for diagnosing and treating DM?
The first-ever Consensus-Based Care Recommendations for Adults with Myotonic Dystrophy Type 1 were published last year. Currently, there are no evidence-based guidelines to establish a standard of care for patients with DM because the rigorous clinical studies needed to gather the necessary data have yet to be conducted. Thus, many patients report difficulty finding and accessing quality care and informed clinicians. The newly published recommendations are intended to help standardize and elevate care for people living with DM.

Where is the research on finding a cure for DM?
A better understanding of the disease is driving research into new targets for treatment, most directed at the toxic RNA. These include antisense oligonucleotides (ASOs). The ASO binds to the target RNA and destroys it, thus restoring function. While successful in animal models, the one human clinical trial so far didn’t show any clinically detectable therapeutic effects. Now researchers are working on a better delivery system for humans. If ASOs can be delivered to muscles and other organs, it may address many of the complications of the disease.

Another option is to use a genetic tool called CRISPR to remove the expanded DNA repeat from the gene itself. But that is 10 to 20 years down the road.

What can those with DM do today to help advance research?
They can enroll in a registry that helps recruit people for clinical studies. They also can participate in longitudinal natural history studies. Understanding the natural history of the disease is important for future clinical trials in order to track the efficacy of drugs and understand ethnic, gender and age-related differences in the disease. There are two registries: Myotonic Dystrophy Family Registry, managed by the Myotonic Dystrophy Foundation, and the Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Registry, run by the National Institute of Neurological Diseases and Stroke. People with DM can enroll in both.

They can also volunteer for clinical studies. There are numerous ongoing clinical trials investigating everything from drugs that target the disease itself to treatments for the complications and genetic studies to better understand how the disease manifests in families.

Find a Trial
Learn what to expect in a clinical trial and find out if there is a study you can enroll in at mda.org/research/clinical-trials.
The moment you become a parent of a child with spinal muscular atrophy (SMA), everything changes.

My daughter, Nella, was diagnosed with SMA when she was 11 weeks old, and the doctors warned me and my husband that she would only get weaker over time since her condition was terminal. We cherished every moment that we had with Nella, and it was important to us to spend time seeking out possible treatment and care, even though we were told treatment for SMA was not available at the time of her diagnosis. For months, Nella struggled to swallow or move unaided. She had to sleep with a ventilator to help her breathe throughout the night. For such a young life, it seemed unfair that she had so many challenges to face.

In 2016, we first heard about a clinical trial for SPINRAZA® (nusinersen), a potential treatment for SMA. The trial was taking place in Orlando, Florida, and would have required our family to move across the country, so we did not have Nella participate. Instead, I decided to immerse myself in the SMA community and follow the journeys of those accessing treatment. It was through this community that I learned the trial would be expanding its access to a hospital near our home in St. Louis, Missouri. We consulted with our doctor to discuss the risks and benefits, and in December 2016, Nella received her first loading dose of SPINRAZA as part of the trial. Weeks later, SPINRAZA was approved by the FDA for treatment in adults and children. I get chills thinking about the enormous feelings of hope and gratitude I felt as Nella received her first injection of SPINRAZA. At her diagnosis, doctors had told us that there was no treatment and to prepare for our daughter to pass. And yet, here she is – alive, receiving treatment, and reaching milestones we never thought possible. In June 2018, Nella completed her eighth SPINRAZA injection and shortly afterwards, she celebrated her fifth birthday. She continues to surprise us – recently during physical therapy she turned her head almost 180 degrees all on her own. Some may consider this to be a small movement, but it isn’t small for us – it’s everything!

Every caregiver has their own unique experience, but despite these different experiences I know there is one thing we all have in common – it’s that we make the most of every moment with our loved ones.

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Biogen is compensating Grace for sharing her and Nella’s story. This content has been reviewed for compliance with FDA guidelines. Please keep in mind these are Nella’s experiences with SMA Type 1 and SPINRAZA, and others may have different experiences. For more information about SPINRAZA, visit SPINRAZA.com.
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QUESTIONS?
The risk information provided here is not comprehensive. To learn more, talk about SPINRAZA with your healthcare provider or pharmacist. The FDA-approved product labeling can be found at www.spinraza.com or 1-844-4SPINRAZA (1-844-477-4672).

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Above and Beyond
One doctor gives his all at MDA Summer Camp

From the moment neurologist Heeren Patel, M.D., was asked to be a volunteer on-call physician at MDA Summer Camp in northern Illinois, he already wanted to do more to help. Rather than just being called in the event of an emergency, he had another idea.

“I asked, ‘What if I came and provided care on-site?’” Dr. Patel says.

That’s exactly what he did. For the past five summers, he has eagerly spent one week of his vacation time at MDA Summer Camp.

“It is such a life-changing experience,” says Dr. Patel, who works for Northwestern Medicine in the Chicago area. “It’s changed the way I practice with my patients on a daily basis. I understand them better.”

By donating his time, Dr. Patel has helped keep down camp medical costs, and he has helped with recruitment and retention of volunteer medical staff. Within his local medical community, he has worked to make it easier for doctors and nurses to take time off for volunteer opportunities like these.

For all of his efforts, he was awarded a Humanitarian Award by Northwestern Medicine in January. Given in honor of Martin Luther King Jr., the award recognizes Dr. Patel’s contributions to the MDA Summer Camp program.

True to his humble nature, Dr. Patel is most proud of this award because it has motivated his peers to help.

“So many nurses and doctors have said they want to get involved,” he says. “Now we have a nice cohort of medical staff we can lean on if we need it at the camp.”

For this summer, Dr. Patel already has four new volunteer nurses, and he says he is excited for them to have the experience.

“Once you do it, you realize the impact it makes on you, all while providing a safe, impactful environment for the campers to have fun and build their confidence,” he says. “It almost feels selfish because of how good it feels to help. It’s humbling and a privilege.”

Marathon Momentum

Nura Maali (fourth from left), a mother of two kids with limb-girdle muscular dystrophy (LGMD), gathered a team of eight and joined MDA Team Momentum for the TCS New York City Marathon last November.

Her team raised nearly $30,000, and she’s excited to fundraise again for the Bank of America Chicago Marathon in October.

“My kids, raising awareness and seeing their faces as I crossed the finish line meant more to me than anything,” Maali says.
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For more information about this study, please contact:

www.dmdstudy041.com
After six long days, I’m tired. It’s the middle of the night, I’m wearing five layers of clothing and I know I have several more hours to go in the frigid air before I reach the 19,341-foot summit. “Mom believes in you. Dad believes in you. All of your friends and family believe in you. You are strong,” are the words that echo through my mind with every step.

I am not one who believes in chance. Everything happens for a reason. For the past decade, facioscapulohumeral muscular dystrophy (FSHD) has been part of my story. It has never been who I am. In fact, it has only served to enhance the whole person that I am, gradually putting up hurdles that I work to jump over and grow from.

Pushing Limits

A hiker proves she is stronger than FSHD by taking on the toughest trek of her life

BY NEENAH WILLIAMS

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Just after Christmas in 2017, I decided I wanted to do something spontaneous and unforgettable in 2018. A couple of weeks later (somewhat on a whim), I booked a trip to climb Mount Kilimanjaro, Africa’s tallest mountain.

In the months following my decision, FSHD unexpectedly began to affect my lower limbs. When hiking, I began to fall on the trails. When I planned the trip, I had no idea the timeline was going to correspond so closely with this gradual decline in muscle. I quickly learned that the trek was going to be challenging.

Falling Into Place

In August 2018, I moved to Colorado. The elevation of my city is more than a mile high. Living at this altitude took a lot of getting used to, but it turned out to be a major benefit during my trek. On top of that, I took my first hot yoga class, which quickly turned into a habit that helped improve my lung efficiency. My yoga teacher was an expert on the effects of high altitude on the body, and he provided me with diet tips to help give my muscles more endurance.

Approximately three weeks before my climb, I found a group of local hiking buddies, and together we summited Pikes Peak (14,115 feet). This gave me an idea of how my body would react as I ascended Kilimanjaro.

It is as if all of these things fell into place at the perfect time, one right after the other. Isn’t it beautiful how things work out?

On Top of the World

Each day of the Kilimanjaro journey came with its own challenges. Not only was the climate different from one day to the next — the trek begins in a rainforest and ends in a frozen desert — but the altitude gain and steep inclines make it tough to breathe while carrying a full day pack.

On day four, we spent several hours climbing up the side of a daunting cliff known as Barranco Wall. The wall is more than 800 feet tall, and my hips were throbbing by the time I made it to the top. At one point mid-climb, I was overcome with emotion. Tears flowed as I sat on a rock, overwhelmed by gratefulness, pride and the reality of how FSHD has changed my body over the years.

On Oct. 8, 2018, I made it to the summit of Mount Kilimanjaro, known as Uhuru Peak. I have never felt as strong or as equal as I did on that day.

I say “equal” because the night I began my trek from base camp, I was climbing alongside several hundred complete strangers, all contending with their own internal struggles. No one knows anything about your story, yet there’s this one goal that aligns everyone there. I wasn’t known as Neenah, the girl with FSHD. Instead, I was simply one in a group of people who all saw in each other the same resilient spirit and desire to keep pressing forward, no matter how much our bodies begged us to quit.

To all my friends, this condition does not define us. It is only one of many factors that shape our mind, body and spirit. The strength within is a powerful force. Keep pushing your limits, and soon you will be on top of the world.

Neenah Williams, 27, was diagnosed with FSHD in 2007. She lives in Colorado and is an avid hiker and yogi.
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For Captain Mike Vasile, a member of San Marcos, Calif., Local 4184, Fill the Boot is personal.

Vasile’s younger brother, Cole, was diagnosed with Duchenne muscular dystrophy (DMD) at age 5. Although doctors expected him to live only into his mid-20s, Cole is now 32.

“Unfortunately, I have seen quite a few people succumb to the disease — good people who were taken way too early,” Vasile says. “I always enjoy raising awareness and funds for MDA to help support those with the disease and to hopefully someday find a cure.”

Each year, Vasile organizes his local Fill the Boot Drive. He and about 35 of his fellow off-duty fire fighters gather at an intersection for eight hours to collect donations for MDA. Cole always comes out to motivate the fire fighters, and an enthusiastic community rallies behind the event.

In 2018, they raised $22,514.

“Our event wouldn’t be successful without the participation and support of our local members and those who are passing through making the donations,” Vasile says.

Vasile is already busy planning the 2019 San Marcos Fill the Boot, which will take place on Friday, Oct. 4.

“We are looking forward to another successful year and helping to achieve a common goal, which is to make a difference,” Vasile says.