MDA® For Strength, Independence & Life

Highlights of the MDA U.S. Neuromuscular Disease Registry (2013–2016)

Muscular Dystrophy Association · **mda.org**

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Registry Overview

In 2013, MDA launched the U.S. Neuromuscular Disease Registry (the "registry") for four diseases — amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) — in 26 Care Centers in diverse locations throughout the United States. The registry captures clinical information on a subset (approximately 2,700) of the more than 100,000 individuals with neuromuscular diseases who are registered with MDA.

The four diseases, ALS, SMA, DMD and BMD, were chosen for this pilot project because at the time of the pilot launch, there were multiple experimental therapies in development for them and because national working groups of clinical and research specialists already had identified and standardized much of the information that is important to collect in clinical trials. In addition, formal "standards of care" for individuals with these diseases already were defined, providing a unique opportunity to demonstrate how a registry could be used to measure the implementation of these care standards and their impact on patient outcomes.

The registry collects a wide range of clinical data from individuals seen in MDA Care Centers including diagnostic tests, clinical measures and interventions. MDA's registry is a clinician-entered database, which means information is typically entered or uploaded by the physician or a study coordinator, as opposed to data being entered by individual patients and/or their caregivers or families.

Participation in the registry is voluntary. An independent committee called an Institutional Review Board (IRB) protects the rights and welfare of participants involved in the registry and ensures all research conducted is held to the highest ethical standards. Data from the registry used for research purposes is de-identified, meaning that the identity of the individuals enrolled in the registry is protected and not able to be connected to the clinical data.

MDA's intent in establishing the registry is to optimize the clinical management of individuals with neuromuscular diseases in order to improve survival and quality of life, and to help advance drug development for these diseases.

What is a registry?

A registry is a database of information — typically about individuals diagnosed with a specific disease or condition — that enables tracking or measuring of any number of health-related or quality-of-life outcomes.

As the only organization in the neuromuscular disease field that supports multiple neuromuscular diseases and maintains a nationwide network of more than 150 Care Centers providing multidisciplinary care to more than 50,000 individuals annually — MDA is uniquely positioned to establish a neuromuscular disease registry.

Registry Goals for the Pilot Phase

- Gain a better understanding of the course of illness for specific neuromuscular diseases.
- Collect data about genotype-phenotype correlations to allow for better prediction of disease progression based on genetic information.
- Collect longitudinal patient data that will allow benchmarking of best clinical practices.
- Use registry data as a platform to develop and implement a clinical quality improvement program for MDA Care Centers across the country.
- Provide outcome-related information about MDA Care Centers for families seeking medical care.
- Establish a database of individuals eligible for clinical trials in neuromuscular diseases to ease the burden of clinical trial recruitment and accelerate drug development.

**The above goals were set out for the pilot phase of the registry. These goals may be amended as the pilot phase concludes and the registry is evaluated further.*

We are deeply grateful to all who have contributed to launching the MDA registry, especially the individuals living with ALS, SMA, BMD and DMD, the health care professionals who have entered data, and the MDA Registry Advisory Board and Clinical Advisory Committee for their insight and guidance.

Clinical Advisory Committee

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Participating Pilot MDA Care Centers

Ann & Robert H. Lurie Children's Hospital of Chicago (Chicago, Ill.)

California Pacific Medical Center (San Francisco, Calif.)

Carolinas Medical Center (Charlotte, N.C.)

Children's Healthcare of Atlanta at Scottish Rite (Atlanta, Ga.)

Children's Hospital Colorado (Aurora, Colo.)

Children's Hospital of Philadelphia (Philadelphia, Pa.)

Children's Medical Center of Dallas (Dallas, Texas)

Columbia University Medical Center (New York, N.Y.)

Gillette Children's Specialty Healthcare (St. Paul, Minn.)

Hospital for Special Care (New Britain, Conn.)

Le Bonheur Children's Hospital (Memphis, Tenn.)

Massachusetts General Hospital (Boston, Mass.)

Methodist Neurological Institute (Houston, Texas)

MetroHealth Medical Center (Cleveland, Ohio)

Monmouth Medical Center (Long Branch, N.J.)

Nationwide Children's Hospital (Columbus, Ohio)

Nemours Children's Hospital (Orlando, Fla.)

Ohio State University Wexner Medical Center (Columbus, Ohio)

Rady Children's Hospital — San Diego (San Diego, Calif.)

Shriners Hospital for Children — Portland (Portland, Ore.)

Texas Neurology P.A. (Dallas, Texas)

UCSF Benioff Children's Hospital (San Francisco, Calif.)

UCSF Fresno (Fresno, Calif.)

University of Michigan (Ann Arbor, Mich.)

University of Minnesota (Minneapolis, Minn.)

Wesley Neurology Clinic (Cordova, Tenn.)

Use of the Registry Data to Support Research

MDA invites researchers to use the registry data to accelerate improvements in drug development and health services research. Requests for access to de-identified data are welcomed from academic investigators, clinicians and industry. Requests are reviewed internally by MDA and the Registry Advisory Board, both of which are eager to support research proposals that show promise to advance our understanding and treatment of neuromuscular diseases. Publication and presentation of results from the analyses of MDA registry data are encouraged. MDA prohibits the use of registry data for marketing purposes related to the purchase or use of medical products. Please email **MDARegistry@mdausa.org** to receive a Request for Data Access Form and the Data and Publication Guidelines.

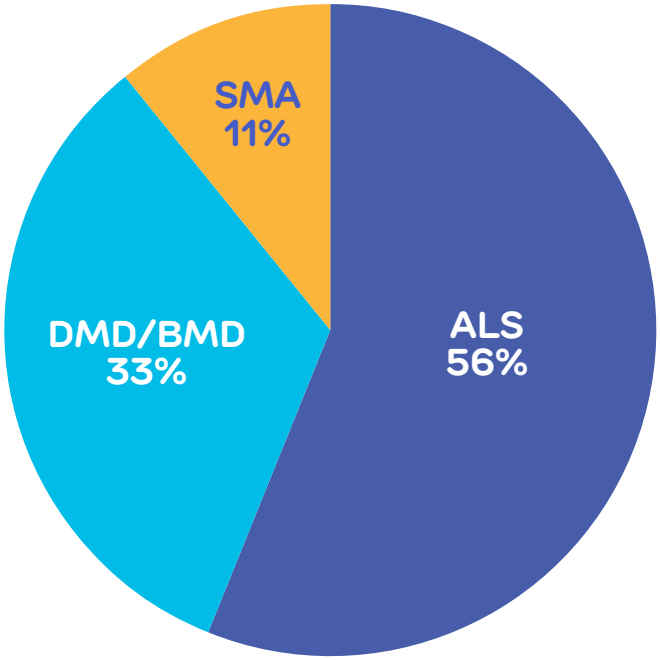
MDA Care Centers

MDA provides care for children and adults from day one through our network of more than 150 MDA Care Centers across the United States and Puerto Rico. These multidisciplinary clinics, located at leading hospitals and health care institutions, bring health care specialists from a variety of disciplines together so that families can receive the care they need in one place. To ensure the best possible health outcomes for families, MDA supports the Care Centers through funding grants with the goal to strengthen and expand multidisciplinary care, which is proven to improve and prolong life.

Introduction to the MDA Registry

The registry contains information on individuals with ALS, SMA, DMD and BMD who received care at select MDA Care Centers between 2013 and 2016. As of September 2016, there was a total of 2,685 individuals enrolled in the registry.

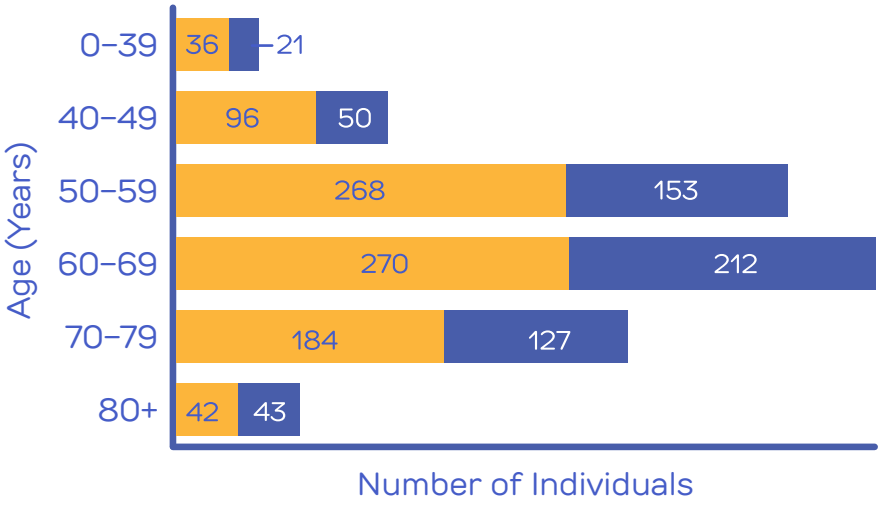
Individuals Enrolled in the Registry



Age and Sex Distribution

Male Female

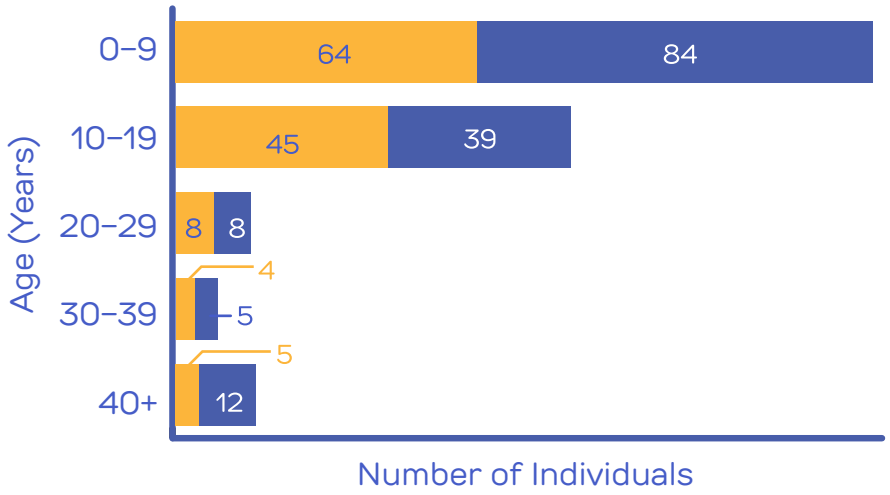
ALS



*Age unspecified for 2; Sex unspecified for 1

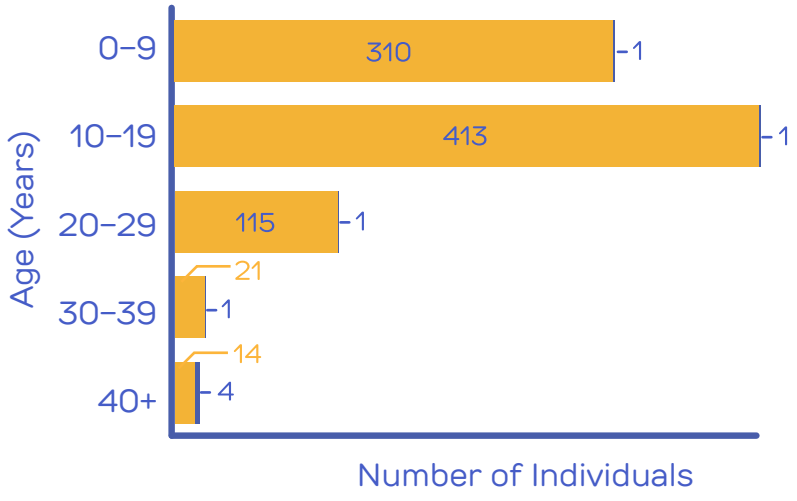
There are more males with ALS than females enrolled in the registry, consistent with the knowledge that **ALS strikes men slightly more often than women**.

SMA



The most common forms of SMA are typically diagnosed during the **infant, toddler or early childhood years**, while less severe forms may not present until later in childhood or even adulthood.

DMD/BMD

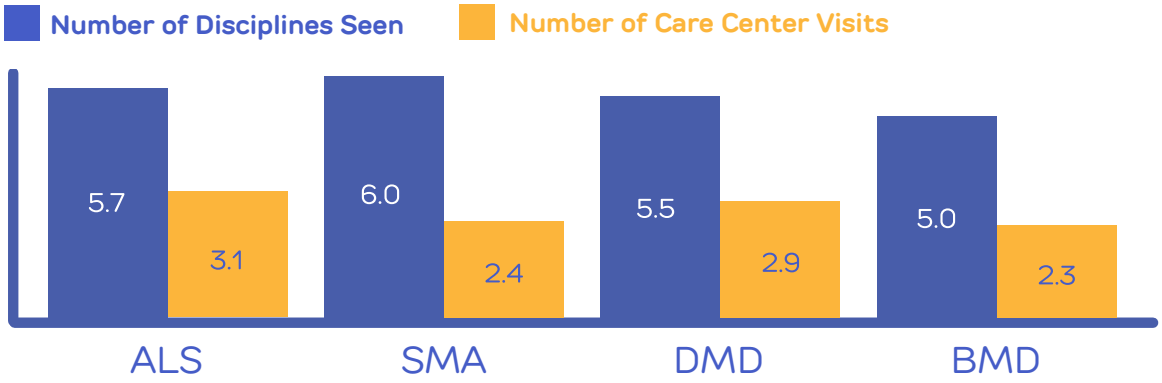


* Age unspecified for 2; Sex unspecified or unknown for 2

DMD and BMD are diseases caused by alterations in the *DMD* gene found on the X chromosome. The *DMD* gene encodes a protein called **dystrophin**.

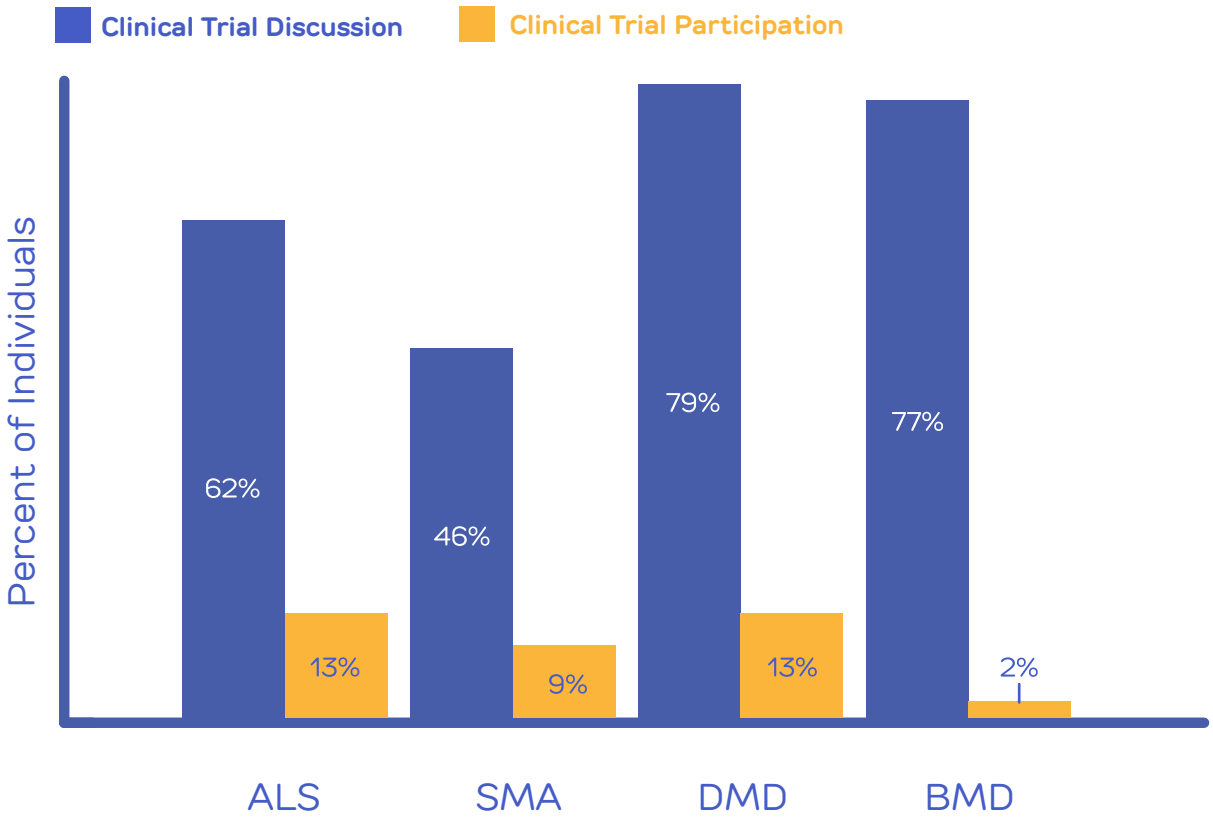
DMD and BMD affect males, although females can be "carriers" who have a normal *DMD* gene on one X chromosome and an abnormal *DMD* gene on the other X chromosome. Most female carriers do not have signs or symptoms of DMD or BMD.

Average Experience at MDA Care Centers Between 2013–2016



On average, individuals in the registry visited their MDA Care Center **two to three times** between 2013 and 2016 and saw specialists in **five to six different health care disciplines** at each visit.

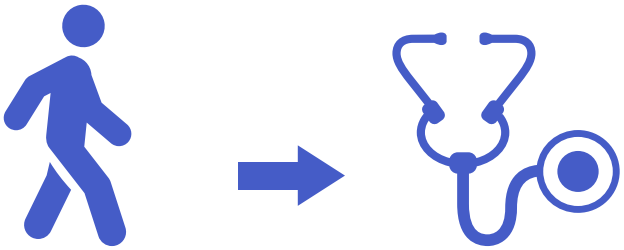
Clinical Trial Participation and Education



About half or more of the individuals in the registry discussed participating in clinical trials with their doctor. Only **9 to 13 percent** of individuals with ALS, SMA and DMD enrolled in a clinical trial.

Amyotrophic Lateral Sclerosis (ALS)

In ALS (also known as Lou Gehrig's disease), the motor neurons that control voluntary movement of muscles degenerate, leading to progressive muscle weakness, paralysis and death without mechanical ventilation intervention. Some individuals also develop mild dementia or difficulty with making executive decisions.



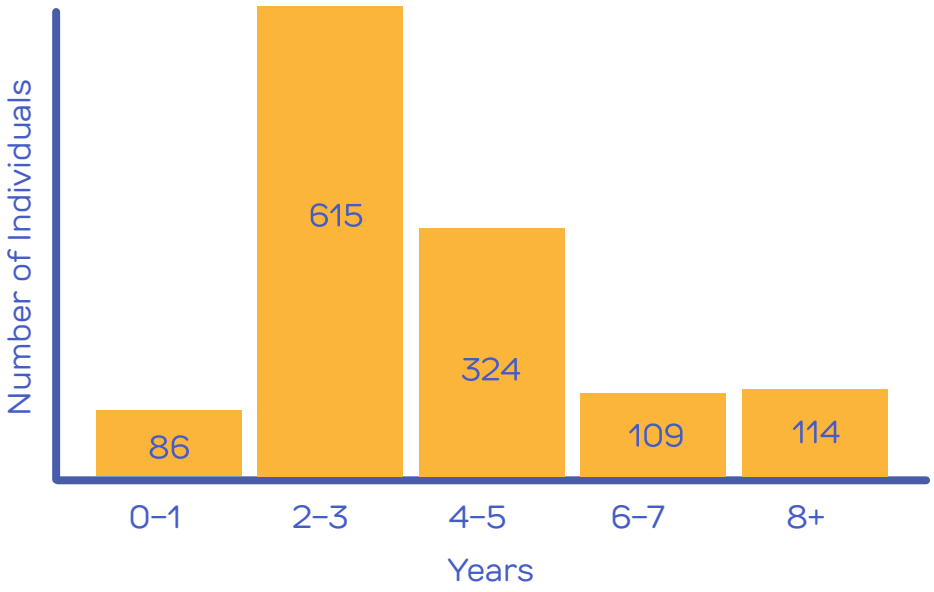
59.3 years
median age at reported symptom onset

1+ year

60.9 years
median age at diagnosis

On average, it takes more than a year following symptom onset for an individual to receive a diagnosis of ALS.

Years Post-Diagnosis for Individuals with ALS



The majority of individuals with ALS in the registry have received their ALS diagnosis **within the last two to five years**.

ALS Genetics

Approximately 5 to 10 percent of ALS is familial — meaning it arises in families in which there is a history of ALS. The other 90 to 95 percent of ALS cases are sporadic, meaning the disease occurs without a family history (in other words, "sporadically").

Many of the genes that cause familial ALS have been recently identified. However, a common misconception is that only familial ALS is "genetic." Both familial and sporadic ALS can stem from genetic causes, and some individuals with sporadic ALS may carry ALS-causing genetic mutations that can be passed on to the next generation. A genetic counselor can help people with ALS understand inheritance and any associated risks for family members.

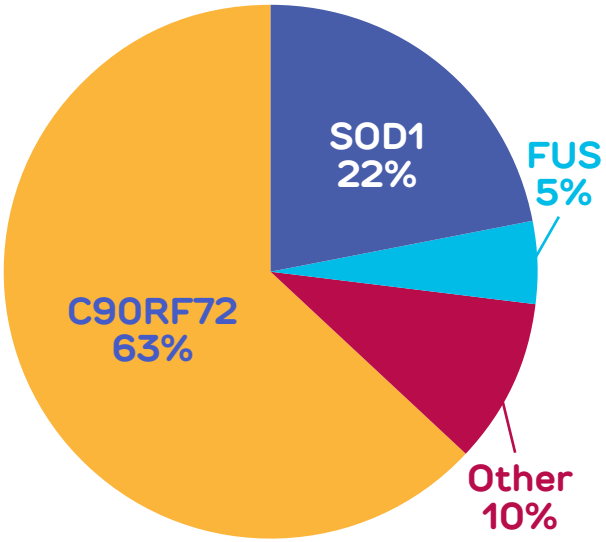
8%
of individuals with ALS in the registry report a family history of ALS

9%
of individuals with ALS in the registry underwent genetic testing

37%
of individuals with ALS in the registry who underwent genetic testing had a causative gene identified

Genes Identified to Cause ALS

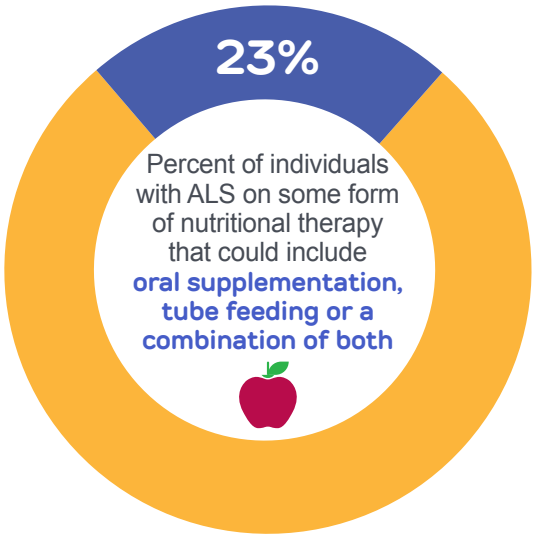
Out of those individuals with an identified genetic alteration causing their ALS, the most common alteration was an expansion (a longer-than-normal section of DNA) in the ***C9ORF72*** gene.



*Data from 41 individuals with genetic alterations identified.

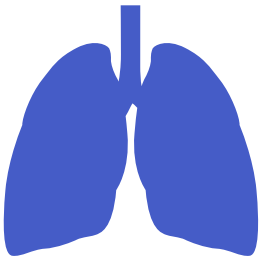
Individuals with ALS Taking Nutritional Therapy

Placement of a gastrointestinal tube to assist with feeding is more common when disease progresses and individuals are no longer able to swallow food. The 80 percent of individuals using tube feeds may represent those in the registry with more advanced disease.



80%

of those individuals using some form of nutritional therapy are taking nutrition either partially or completely through a gastrointestinal tube

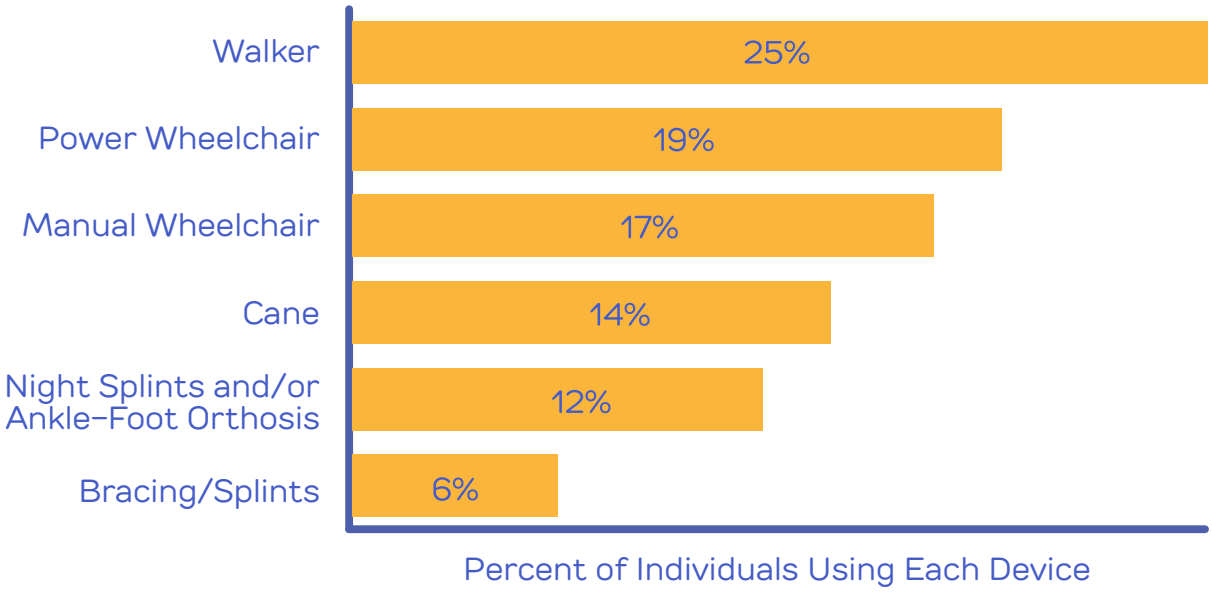


33%

of the individuals with ALS in the registry are using noninvasive ventilation (NIV).

Individuals with ALS typically initiate or increase use of NIV as their disease progresses; thus, the 33 percent using NIV may represent those in the registry with more advanced disease.

Top Assistive Devices Used by Individuals with ALS



65% of individuals with ALS enrolled in the registry use an assistive device for **mobility**

Use of assistive devices typically increases as disease progresses; therefore, the 65 percent of individuals using assistive mobility devices may represent those in the registry with more advanced disease.

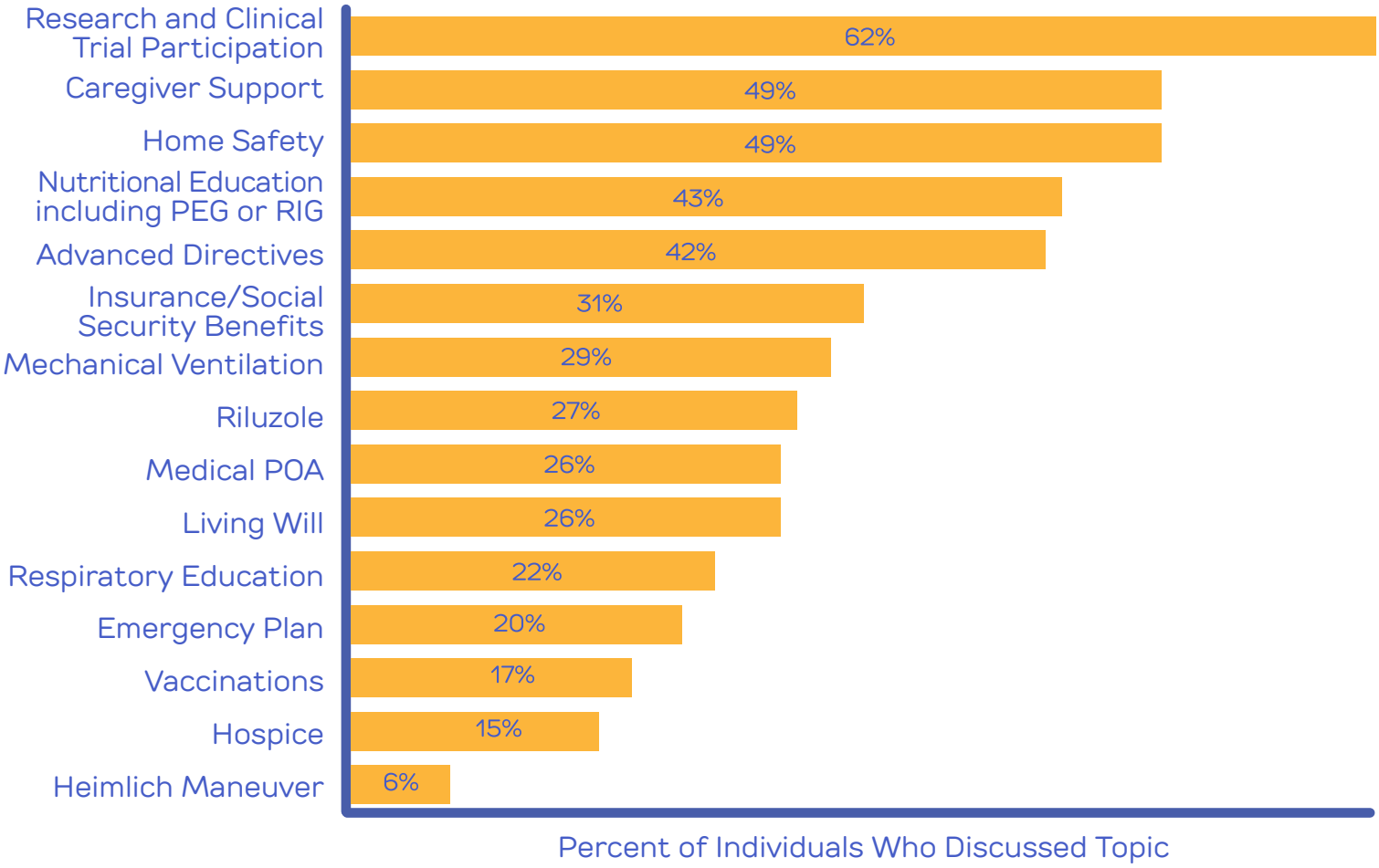
Medications Used	Percent Using Medication
riluzole	38%
baclofen	21%
dextromethorphan/quinidine (Nuedexta)	16%
gabapentin	9%

38% of individuals with ALS in the registry were taking **riluzole**

Common medications taken to manage disease symptoms include baclofen, dextromethorphan/quinidine (brand name Nuedexta) and gabapentin.

At the time of data collection for the registry, edaravone (brand name Radicava) was not yet approved by the U.S. Food and Drug Administration for the treatment of ALS. Radicava was approved in May 2017.

Education Topics Discussed During Care Center Visits



Health care providers at MDA Care Centers report discussing various topics during a typical visit for an individual with ALS. These types of conversations are important to ensuring individuals and families receive the necessary support to make informed decisions regarding their care. This ongoing communication from providers who are knowledgeable with the disease course allows individuals to stay informed about the options available to them (such as the opportunity to participate in research), and ensure they are adequately prepared for the future when difficult decisions may need to be made related to mobility, nutrition or ventilation needs. The topics discussed during an MDA Care Center visit may vary depending on an individual's stage of disease.

PEG (percutaneous endoscopic gastrostomy)

RIG (radiologically inserted gastrostomy)

PEG and RIG are surgical procedures whereby a feeding tube is passed into a patient's stomach through the abdominal wall, allowing food to be directly placed into the stomach when it is difficult or unsafe to swallow food through the mouth.

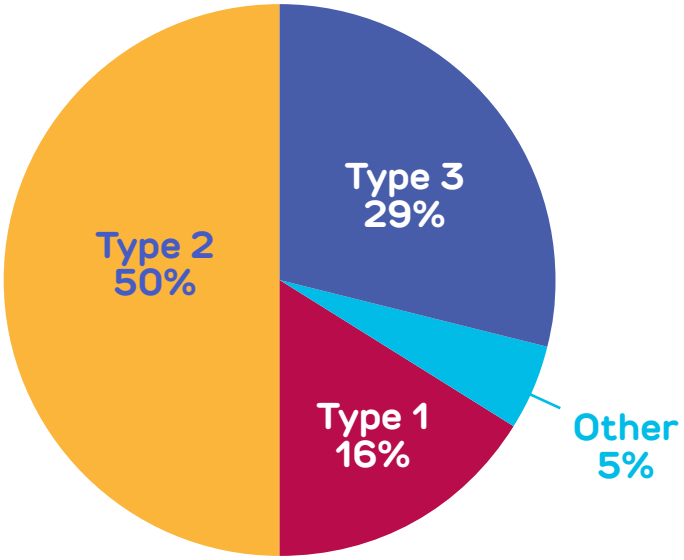
Medical POA (power of attorney)

POA is a written authorization whereby an individual gives rights to another person to make medical decisions on their behalf should they become unable to make such decisions.

Spinal Muscular Atrophy (SMA)

SMA is caused by the death of specialized motor neurons in the spinal cord that normally control voluntary muscle movement. SMA is the most common genetic cause of death in babies.

Individuals with SMA in the Registry

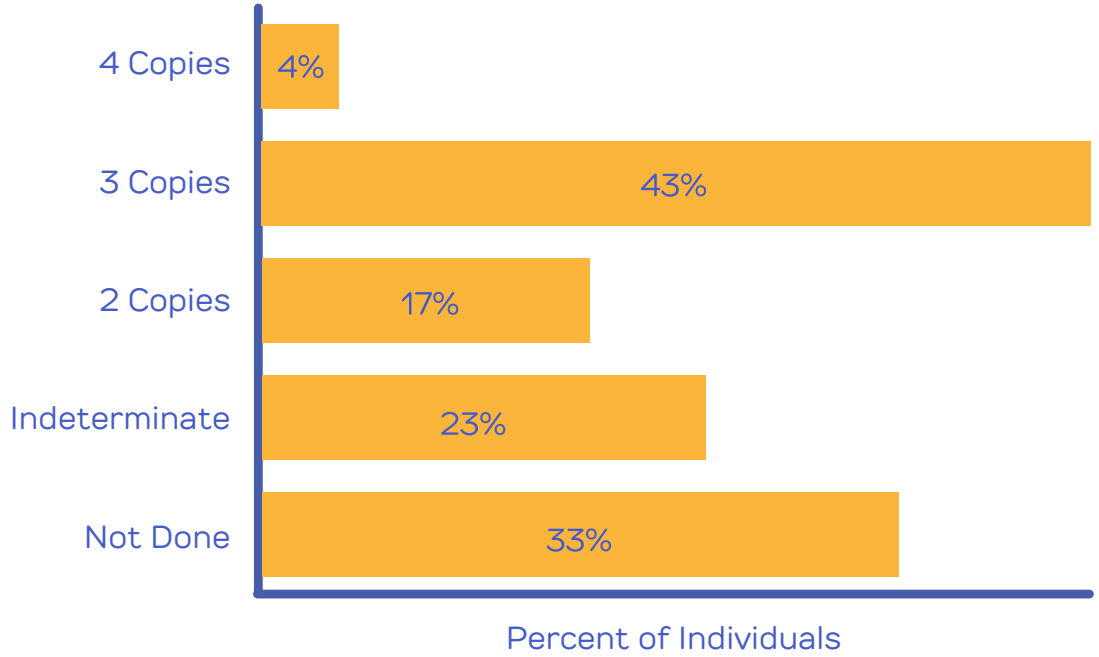


The most common form of SMA is type 1; however, the largest proportion of individuals with SMA in the registry are diagnosed with **type 2 SMA**. Because type 1 SMA is diagnosed earlier and can be rapidly progressive, these individuals are less likely to be captured in the registry. Considering the recent development of disease-modifying therapeutics for SMA as well as the recent progress toward implementation of newborn screening for SMA, the percentage of individuals with type 1 SMA captured in the registry may increase in the future.

SMA is caused by an abnormal or missing gene called survival motor neuron gene 1 (*SMN1*), which is responsible for producing a protein critical for motor neurons. Individuals carry two copies of the *SMN1* gene and loss of both copies results in disease, whereas individuals with loss of only one copy are said to be SMA carriers who typically show no symptoms.

88% of the individuals in the registry have a genetic confirmation of SMA

SMN2 Copy Number



The best predictor of SMA disease severity is the number of copies of a backup gene called *SMN2* that a person carries in his/her DNA. Typically, individuals with more *SMN2* copies develop less severe forms of SMA.

Top 10 SMA Medications

1. albuterol
2. budesonide
3. gabapentin
4. valproic acid (Depakote)
5. diazepam (Valium)
6. albuterol (inhaled)
7. ipatropium
8. lorazepam
9. amitriptyline
10. sertraline (Zoloft)

Medications are used by individuals with SMA for a variety of reasons. Medications such as albuterol, ipratropium and budesonide address **respiratory symptoms** while diazepam (brand name Valium), lorazepam, amitriptyline and sertraline (brand name Zoloft) are used to manage **anxiety and depression**. Gabapentin is thought to have **potential neuroprotective action** while valproic acid (brand name Depakote) may **alter splicing** of the backup SMN2 gene, resulting in increased levels of the missing SMN protein.

Although both gabapentin and Depakote are used off-label for SMA, neither has been shown to be effective in randomized controlled trials.

In December 2016, the **first** disease-modifying drug for SMA called **nusinersen (brand name Spinraza)** was approved by the U.S. Food and Drug Administration.

Spinraza is a disease-modifying antisense drug, one of a class of experimental therapeutic molecules designed to target genetic instructions at the RNA stage (an intermediate step between DNA and the protein manufacturing stage inside cells). It is designed to increase production of the needed SMN protein.

Data for this registry was collected prior to the approval of Spinraza.

49%
of individuals with SMA in the registry are using noninvasive ventilation (NIV)

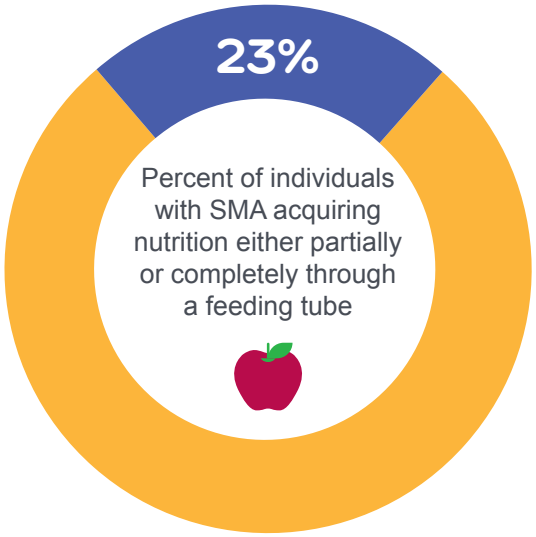
Individuals with SMA typically initiate or increase use of NIV as their disease progresses; thus, the 49 percent of individuals using NIV may represent those in the registry with more severe and/or more advanced disease.

10%
of individuals with SMA in the registry have had tracheostomies

Most of the individuals with tracheostomies were **type 1 SMA**, but there were also three individuals with **type 2 SMA** who underwent a tracheostomy to manage their respiratory needs.

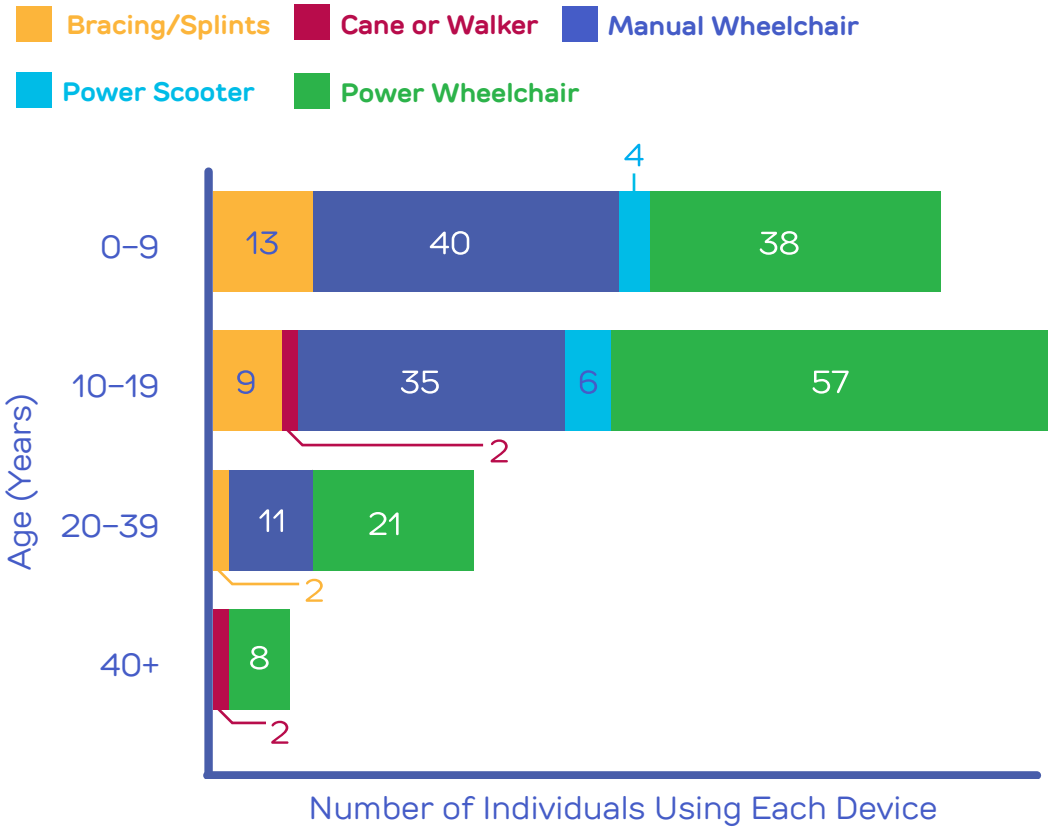
A tracheostomy is a surgical procedure whereby an opening is created through the neck into the trachea (windpipe) to allow direct placement of a breathing tube.

32% of individuals with SMA have undergone surgery to address scoliosis, including rod placement or fusion surgery



It is more common for individuals with type 1 SMA to use a feeding tube as compared to those with other types of SMA in the registry.

Commonly Used Mobility Devices by Individuals with SMA



Use of mobility devices by individuals with SMA is predicted to vary depending on whether the individual is affected by type 1, type 2 or type 3 SMA, as well as the stage of disease or how far along in progression the disease is for that individual.

Duchenne and Becker Muscular Dystrophy (DMD and BMD)

DMD and BMD are muscular dystrophies characterized by progressive muscle wasting and weakness leading to decreases in muscle strength.

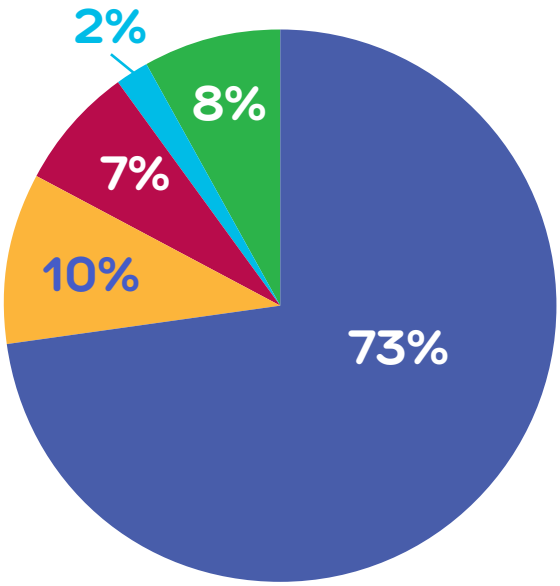
DMD and BMD are both caused by deleterious alterations in the ***DMD* gene**, which encodes a protein called **dystrophin**. While DMD mutations cause virtually **no functional** dystrophin to be made, individuals with BMD make dystrophin that is **partially functional**, which protects the muscles of those with BMD from degenerating as completely or as quickly as those with DMD.

Genetic Alterations in Individuals with DMD and BMD

Various types of disease-causing gene alterations include exon deletion, exon duplication or small point mutations such as nonsense or missense mutations. The type of mutation in an individual can influence how much dystrophin protein is produced and impact disease severity.

Deletions or duplications **Nonsense mutation** **Other** **None detected** **No response**

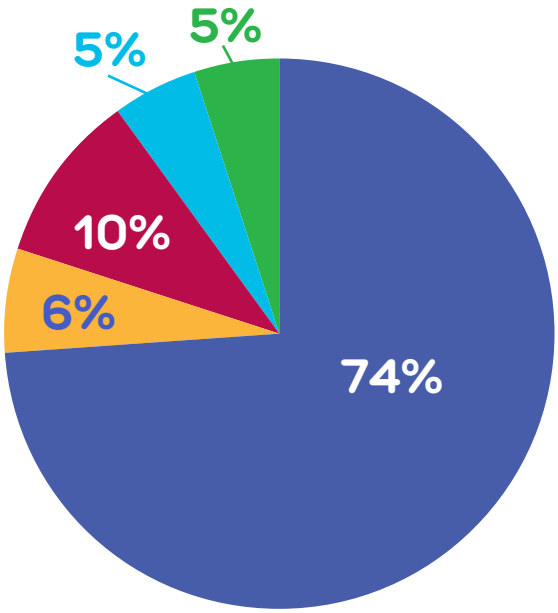
DMD



93%
have a genetic confirmation of DMD

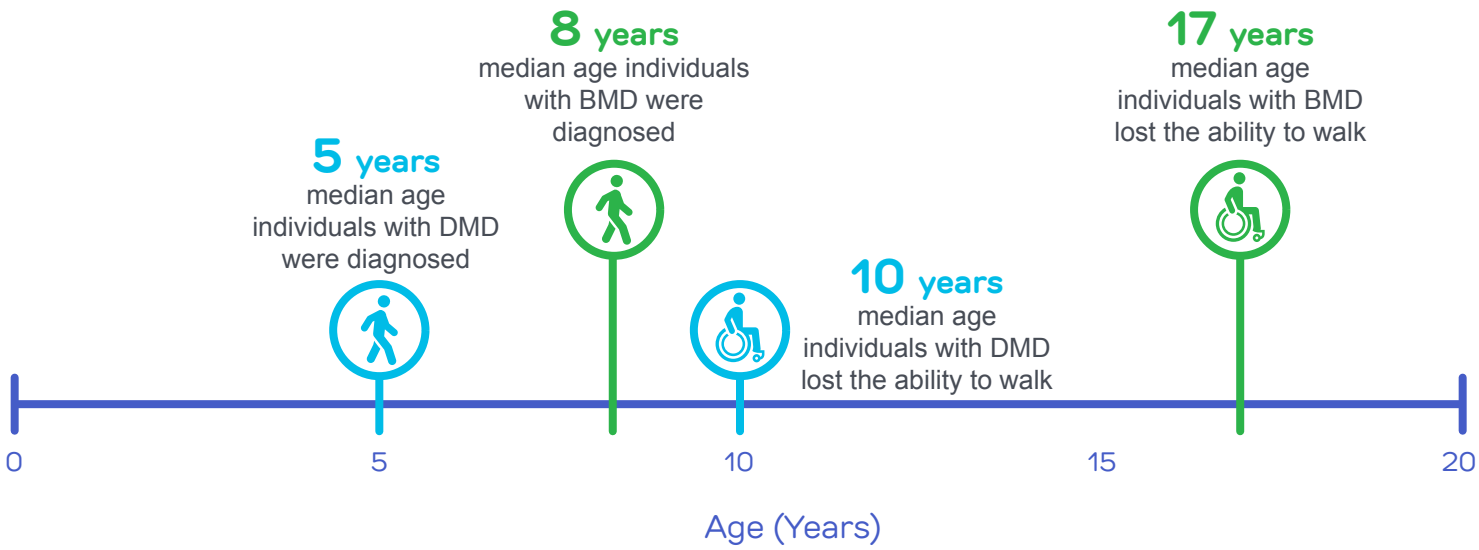
28%
have had a muscle biopsy

BMD



97%
have a genetic confirmation of BMD

39%
have had a muscle biopsy



Top 10 DMD and BMD Medications

DMD

1. prednisone
2. lisinopril
3. deflazacort (Emflaza)
4. albuterol
5. enalipril
6. losartan
7. sertraline (Zoloft)
8. amphetamine/ dextroamphetamine (Adderall)
9. fluoxetine (Prozac)
10. paroxetine (Paxil)

48% of individuals with DMD are on a daily steroid regimen

29% have never used steroids

BMD

1. lisinopril
2. prednisone
3. albuterol
4. deflazacort (Emflaza)
5. sertraline (Zoloft)
6. enalipril
7. losartan
8. guanfacine (Intuniv)
9. aripiprazole (Abilify)
10. amphetamine/ dextroamphetamine (Adderall)

11% of individuals with BMD are on a daily steroid regimen

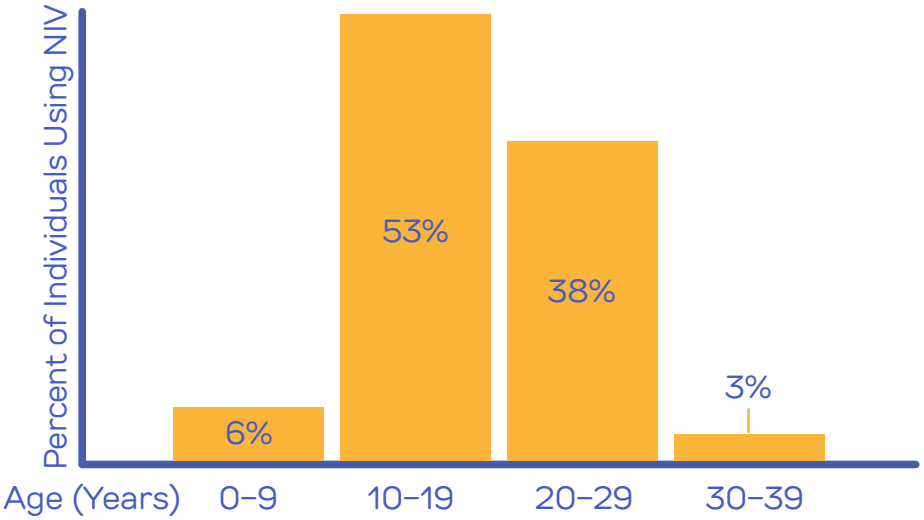
71% have never used steroids

Medications are used for a variety of reasons by individuals with DMD and BMD. **Corticosteroids** such as prednisone and deflazacort (brand name Emflaza) are used to transiently **improve strength** without repairing the underlying genetic defect. Other common medications address respiratory symptoms, help to **manage blood pressure**, and **relieve anxiety** and **depression**.

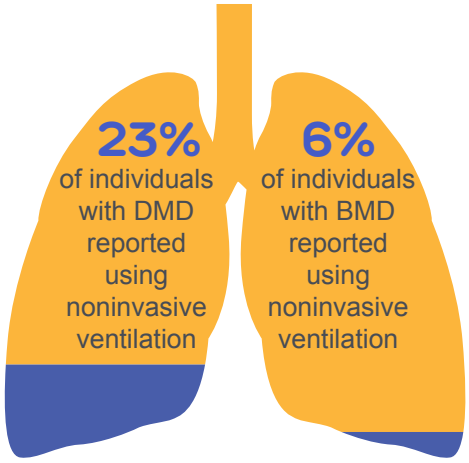
Although individuals with BMD use similar medications to those living with DMD, fewer take corticosteroids such as prednisone or Emflaza to manage their disease.

At the time of data collection, neither **eteplirsen (brand name Exondys 51)** nor **deflazacort (brand name Emflaza)** were approved for the treatment of DMD in the U.S. Some individuals with DMD and BMD ordered Emflaza from other countries prior to approval. Emflaza was approved in February 2017 and Exondys 51 was granted accelerated approval in September 2016. Exondys 51 is the only currently approved medication that **targets the underlying genetic defect** in a subset of boys with DMD. None of the medications approved for use in BMD address the underlying genetic defect.

Noninvasive Ventilation (NIV) Usage by Age Group for Individuals with DMD

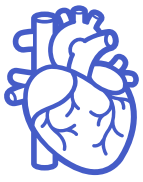


The Centers for Disease Control (CDC) guidelines for diagnosis and management of DMD recommend individuals with DMD who are ambulatory and are 6 years of age or older undergo a respiratory assessment at least annually, while nonambulatory individuals are recommended to be assessed at least every six months.



39% of individuals with DMD have undergone surgery to address scoliosis, including rod placement or fusion surgery (no individuals with BMD reported these surgeries)

30%
of individuals with DMD have a history of cardiomyopathy

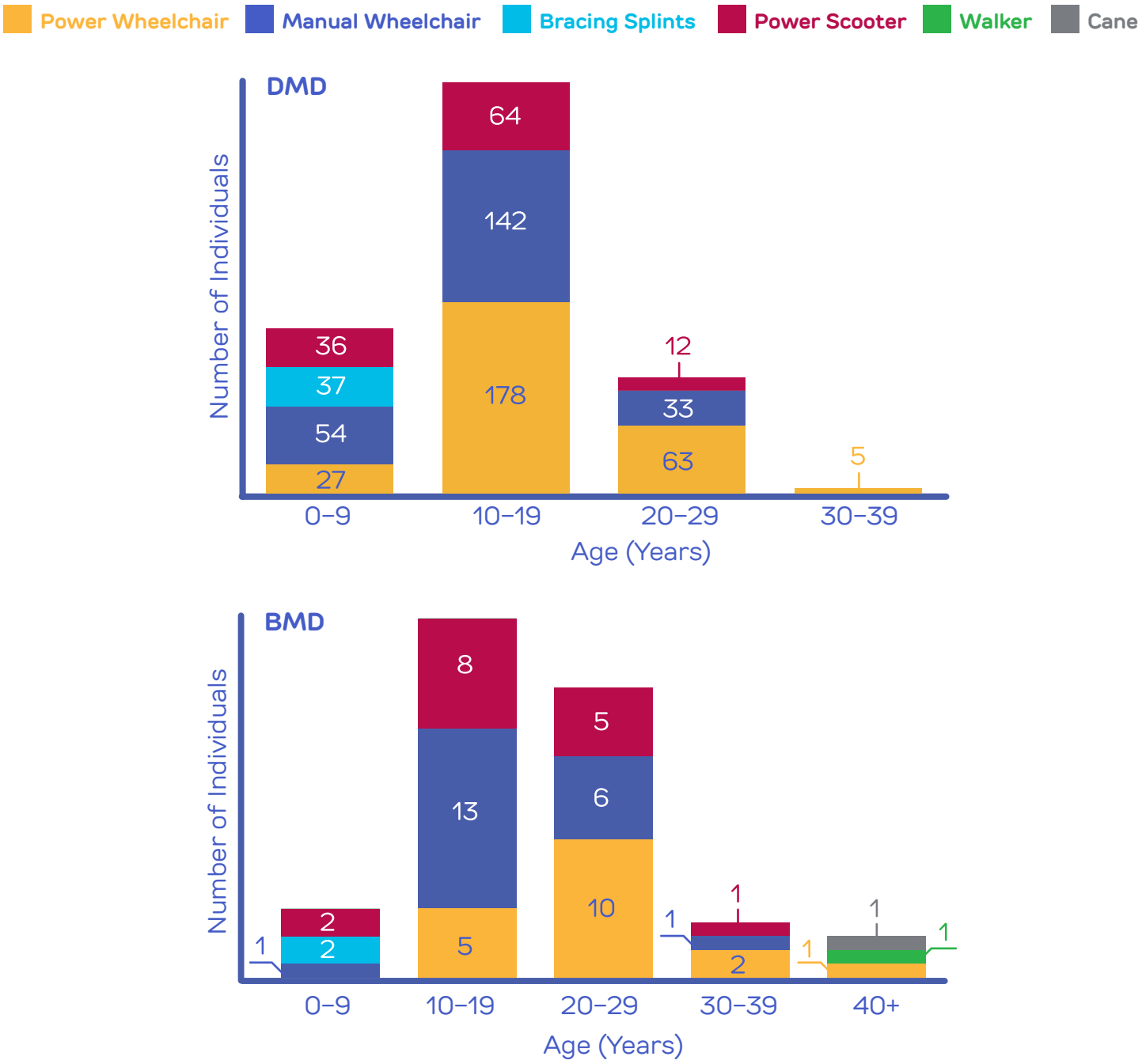


23%
of individuals with BMD have a history of cardiomyopathy

The Centers for Disease Control and Prevention (CDC) guidelines for diagnosis and management of DMD recommend that individuals with DMD have a cardiac evaluation at diagnosis or by age 6 and again at least every other year until age 10 when evaluations should be done yearly.

The American Academy of Pediatrics recommends that individuals with BMD have cardiac evaluations at least every other year beginning at age 10.

Top Mobility Devices by Age Group

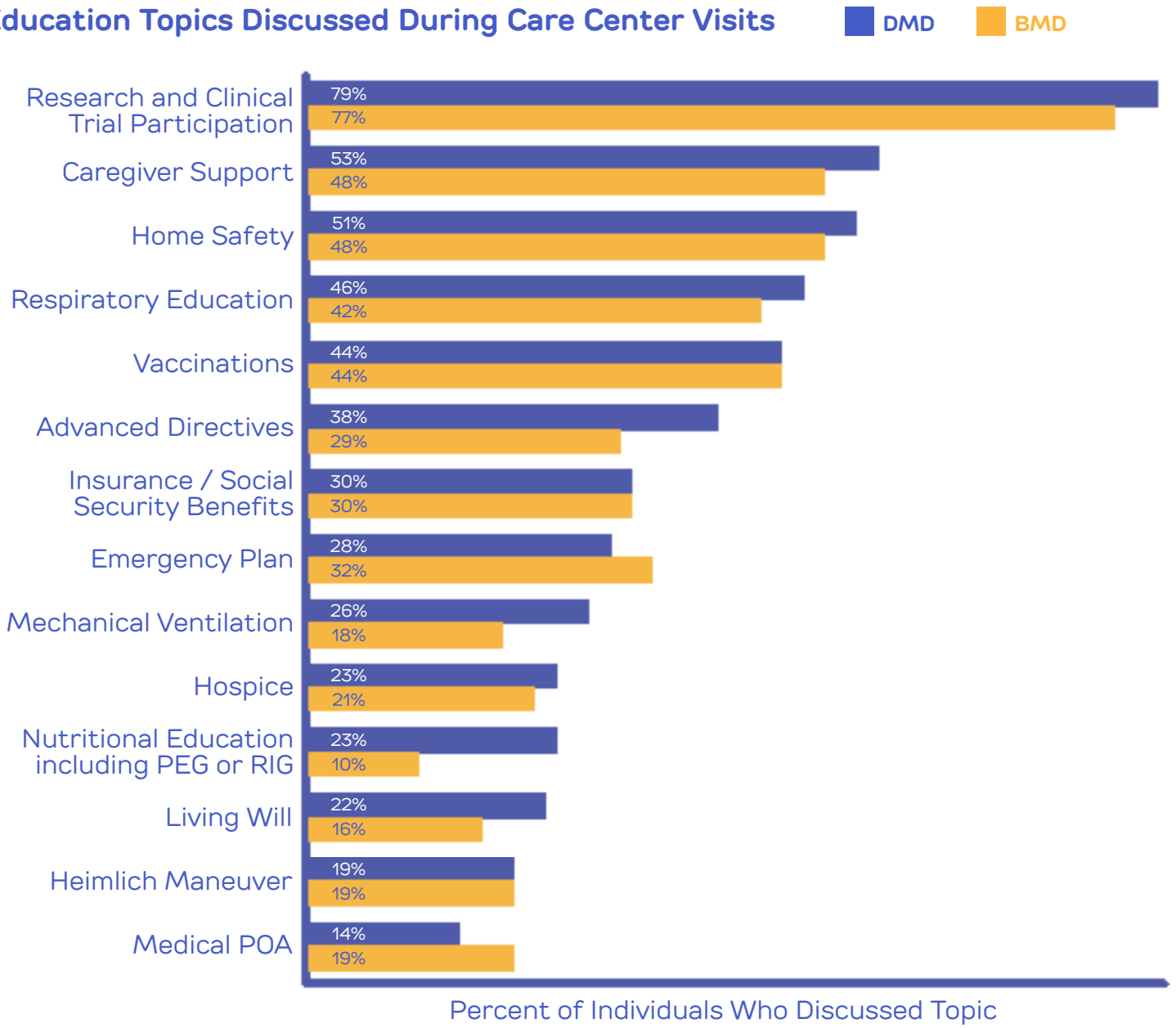


78%
of individuals with DMD report use of an assistive device

39%
of individuals with BMD report use of an assistive device

The mobility devices reported to be used by individuals with DMD and BMD in the registry **varied by age group**, which is likely due to the severity of disease and the degree of physical impairment. The most commonly used devices were **power or manual wheelchairs**.

Education Topics Discussed During Care Center Visits



Health care providers at MDA Care Centers report discussing various topics during a typical visit for an individual with DMD or BMD. These types of conversations are important to ensuring individuals and families receive the necessary support to make informed decisions regarding their care. This ongoing communication from providers who are knowledgeable of the disease course allows individuals to stay informed about the options available to them (such as the opportunity to participate in research) and ensure they are adequately prepared for the future when difficult decisions may need to be made related to mobility, nutrition or ventilation needs. The topics discussed during an MDA Care Center visit may vary depending on an individual's stage of disease.

PEG (percutaneous endoscopic gastrostomy)

RIG (radiologically inserted gastrostomy)

PEG and RIG are surgical procedures whereby a feeding tube is passed into a patient's stomach through the abdominal wall, allowing food to be directly placed into the stomach when it is difficult or unsafe to swallow food through the mouth.

Medical POA (power of attorney)

POA is a written authorization whereby an individual gives rights to another person to make medical decisions on their behalf should they become unable to make such decisions.

Community Impact

MDA is committed to ensuring children and adults living with neuromuscular disease receive high-quality care, as well as to understanding how this care can be improved. Working closely with 26 MDA Care Center pilot sites, nearly 2,700 ALS, DMD, BMD and SMA families were enrolled in the MDA U.S. Neuromuscular Disease Registry from 2013-2016. Data from this registry has provided a more informed understanding of the health of individuals visiting MDA Care Centers and offered potential directions for improving care in this population.

Building a registry has been a community effort, and MDA intends for the data collected in this registry to be a community resource. De-identified data from the pilot phase of the registry are being shared and analyzed by professional societies and industry partners, in addition to MDA, with the goal of better understanding disease, improving care and furthering research that will lead to new treatments.

MDA is grateful for those individuals living with neuromuscular disease who have participated in the pilot phase of the registry and for the commitment of the Care Center sites and health care providers involved. These efforts have been crucial for building and initiating the registry and completing data collection during this pilot phase. The data analyses underway already have started to identify trends in care received by our families, enabling us to recognize opportunities for improvement as we look toward the future.

MDA is grateful to our corporate partners including:

Biogen and Cytokinetics

for their support of the MDA U.S. Neuromuscular Disease Registry.

For Strength,
Independence & Life

Muscular Dystrophy Association

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