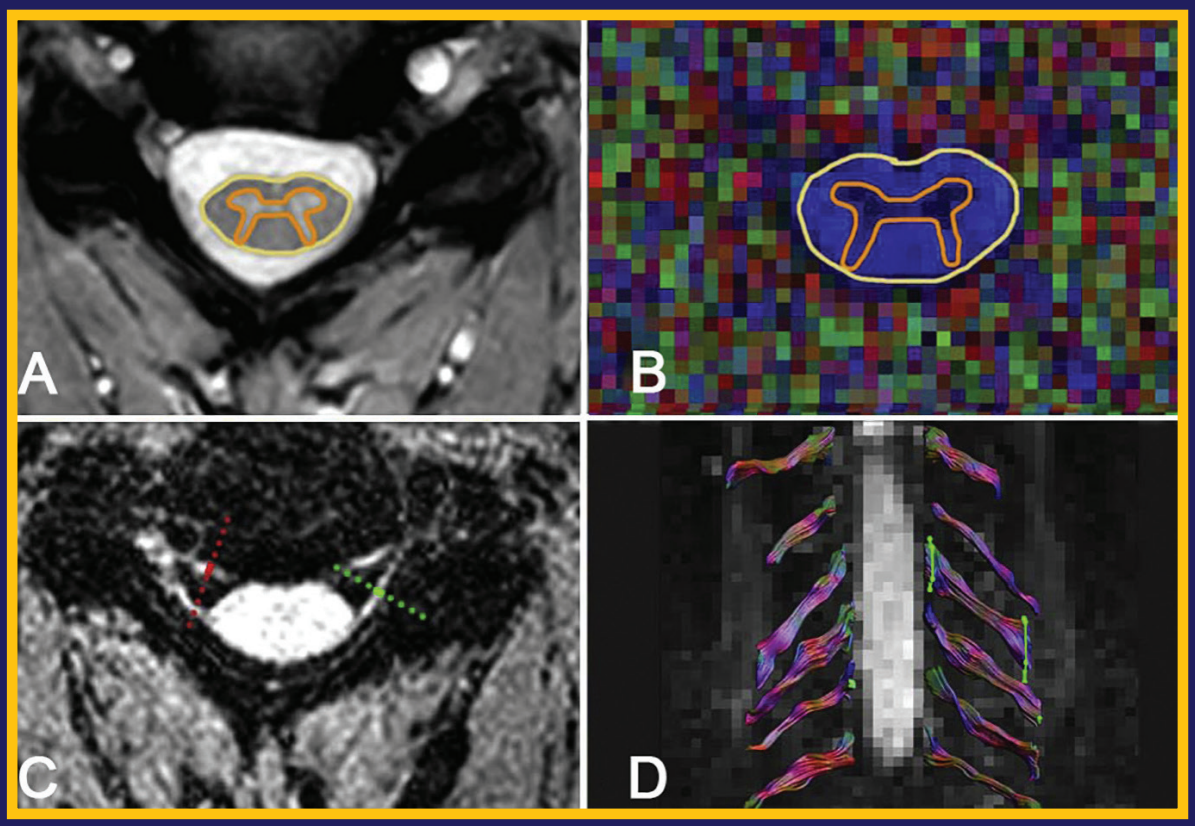
Advances and Challenges in Treating Spinal Muscular Atrophy in Federal Medicine



U.S. Medicine
THE VOICE OF FEDERAL MEDICINE

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Proven to provide efficacy in infants, children, and adults with spinal muscular atrophy (SMA)

IN TWO ONGOING PIVOTAL TRIALS, PARTICIPANTS WHO RECEIVED EVRYSDI EXPERIENCED BENEFITS IN MOTOR FUNCTION[1*†]

IN INFANTILE-ONSET SMA

(n=21; age range, 3-7 months for Part 1)

- After 12 months of treatment with Evrysdi, 90% (19/21) of all infants were alive without permanent ventilation, and 81% (17/21) were alive without permanent ventilation at 23 months[1‡]
- At 12 months, 41% (7/17) of infants who received the recommended dosage of Evrysdi were able to sit without support for at least 5 seconds, as measured by Item 22 on the BSID-III gross motor scale[§]

IN LATER-ONSET SMA

(n=180; age range, 2-25 years)

Significant improvement in motor function with Evrysdi (n=115) from baseline at 12 months versus placebo (n=59) in children and adults, as measured by MFM-32 (1.55-point difference between the means; 95% CI: 0.30, 2.81; *P*=0.0156)[1]

- Evrysdi demonstrated a 1.36-point mean change from baseline (95% CI: 0.61, 2.11) versus a –0.19-point mean change from baseline for placebo (95% CI: –1.22, 0.84)[1]

Learn more at www.Evrysdi-HCP.com/NowApproved

BSID-III=Bayley Scales of Infant and Toddler Development-Third Edition; MFM-32=Motor Function Measure-32 items.

*FIREFISH is a 2-part, multicenter, open-label trial to investigate the efficacy, safety, and tolerability of Evrysdi in infants between 2 and 7 months at the time of enrollment, diagnosed with Type 1 SMA. No data are available for patients under 2 months. Part 1 was a dose-finding portion in 21 infants; efficacy was established on the basis of achievement of a key motor milestone, as measured by the BSID-III gross motor scale, and on the basis of survival without permanent ventilation. Efficacy and safety were assessed at the 12-month time point, after which all infants were switched to the recommended dosage (0.2 mg/kg/day) and will continue to be monitored for an additional 12 months.

†SUNFISH is a 2-part, multicenter trial to investigate the efficacy, safety, and tolerability of Evrysdi in children and adults between 2 and 25 years, diagnosed with Type 2 or Type 3 SMA. Part 2 was the randomized, double-blind, placebo-controlled portion in 180 nonambulatory patients with Type 2 (71%) or Type 3 (29%) SMA. Patients were randomized 2:1 to receive either Evrysdi at the recommended dosage or placebo. The primary efficacy endpoint was mean change from baseline in motor function as measured by MFM-32.

‡Permanent ventilation was defined as requiring a tracheostomy or more than 21 consecutive days of either noninvasive ventilation (≥16 hours per day) or intubation, in the absence of an acute reversible event.

§Results from the recommended-dosage cohort (n=17/21), which included patients whose dosage was adjusted to 0.2 mg/kg/day before 12 months of treatment.

Indication

Evrysdi is indicated for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older.

Important Safety Information

Interactions with Substrates of MATE Transporters

- Based on in vitro data, Evrysdi may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K, such as metformin
- Avoid coadministration of Evrysdi with MATE (multidrug and toxin extrusion) substrates. If coadministration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction of the coadministered drug if needed

Pregnancy

- In animal studies, administration of Evrysdi during pregnancy or throughout pregnancy and lactation resulted in adverse effects on development
- Based on animal data, advise pregnant women of the potential risk to the fetus. Pregnancy testing is recommended for females of reproductive potential prior to initiating Evrysdi. Advise female patients of reproductive potential to use effective contraception during treatment with Evrysdi and for at least 1 month after the last dose

Breastfeeding

- There is no data on the presence of Evrysdi in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Evrysdi and any potential adverse effects on the breastfed infant

Potential Effects on Male Fertility

- Male fertility may be compromised by treatment with Evrysdi. Counsel male patients on the potential effects on fertility. Male patients may consider sperm preservation prior to treatment

Hepatic Impairment

- The safety and efficacy of Evrysdi in patients with hepatic impairment have not been studied
- Because Evrysdi is predominantly metabolized in the liver, hepatic impairment may potentially increase the exposures to Evrysdi. Avoid use of Evrysdi in patients with impaired hepatic function

Most Common Adverse Reactions

- The most common adverse reactions in later-onset SMA (incidence in at least 10% of patients treated with Evrysdi and more frequent than control) were fever, diarrhea, and rash
- The most common adverse reactions in infantile-onset SMA were similar to those observed in later-onset SMA patients. Additionally, adverse reactions with an incidence of at least 10% were upper respiratory tract infection, pneumonia, constipation, and vomiting

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see Brief Summary of Prescribing Information on adjacent pages.

Reference: 1. Risdiplam (EVRYSDI™) Prescribing Information. South San Francisco, CA; Genentech, Inc; 2020.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION
EVRYSDI™ (risdiplam) for oral solution
Initial U.S. Approval: 2020
This is a brief summary of information about EVRYSDI. Before prescribing, please see full Prescribing Information.

1 INDICATIONS AND USAGE

EVRYSDI is indicated for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older.

4 CONTRAINDICATIONS

None.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials including patients with infantile-onset SMA and later-onset SMA, a total of 337 patients (52% female, 72% Caucasian) were exposed to EVRYSDI for up to a maximum of 32 months, with 209 patients receiving treatment for more than 12 months. Forty-seven (14%) patients were 18 years and older, 74 (22%) were 12 years to less than 18 years, 154 (46%) were 2 years to less than 12 years, and 62 (18%) 2 months to less than 2 years.

Clinical Trial in Later-Onset SMA

The safety of EVRYSDI for later-onset SMA is based on data from a randomized, double-blinded, placebo-controlled study (Study 2 Part 2) in patients with SMA Type 2 or 3 (n = 180) *[see Clinical Studies (14.2)]*. The patient population in Study 2 Part 2 ranged in age from 2 to 25 years at the time of treatment start.

The most common adverse reactions (reported in at least 10% of patients treated with EVRYSDI and at an incidence greater than on placebo) in Study 2 Part 2 were fever, diarrhea, and rash. Table 2 lists the adverse reactions that occurred in at least 5% of patients treated with EVRYSDI and at an incidence ≥ 5% greater than on placebo in Study 2 Part 2.

Table 2 Adverse Reactions Reported in ≥ 5% of Patients Treated with EVRYSDI and with an Incidence ≥ 5% Greater Than on Placebo in Study 2 Part 2

Adverse Reaction	EVRYSDI (N = 120) %	Placebo (N = 60) %
Fever[1]	22	17
Diarrhea	17	8
Rash[2]	17	2
Mouth and aphthous ulcers	7	0
Arthralgia	5	0
Urinary tract infection[3]	5	0

[1] Includes pyrexia and hyperpyrexia.
[2] Includes rash, erythema, rash maculo-papular, rash erythematous, rash papular, dermatitis allergic, and folliculitis.
[3] Includes urinary tract infection and cystitis.

Clinical Trial in Infantile-Onset SMA

The safety of EVRYSDI therapy for infantile-onset SMA is based on data from an open-label study in 62 patients (Study 1) *[see Clinical Studies (14.1)]*. In Study 1 Part 1 (n = 21) and Part 2 (n = 41), 62 patients received EVRYSDI for up to 30 months (31 patients for more than 12 months). The patient population ranged in age from 2 to 7 months at the time of treatment start (weight range 4.1 to 10.6 kg).

The most frequent adverse reactions reported in infantile-onset SMA patients treated with EVRYSDI in Study 1 were similar to those observed in later-onset SMA patients in Study 2. Additionally, the following adverse reactions were reported in ≥ 10% of patients: upper respiratory tract infection (including nasopharyngitis, rhinitis, respiratory tract infection), pneumonia, constipation, and vomiting.

7 DRUG INTERACTIONS

7.1 Effect of EVRYSDI on Substrates of Multidrug and Toxin Extrusion (MATE) Protein Transporters

Based on in vitro data, EVRYSDI may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K *[see Clinical Pharmacology (12.3)]*, such as metformin. Avoid coadministration of EVRYSDI with MATE substrates. If coadministration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction of the coadministered drug (based on the labeling of that drug) if needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of EVRYSDI in pregnant women. In animal studies, administration of risdiplam during pregnancy or throughout pregnancy and lactation resulted in adverse effects on development (embryofetal mortality, malformations, decreased fetal body weights, and reproductive impairment in offspring) at or above clinically relevant drug exposures *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Based on animal data, advise pregnant women of the potential risk to the fetus.

Data

Animal Data

Oral administration of risdiplam (0, 1, 3, or 7.5 mg/kg) to pregnant rats throughout organogenesis resulted in decreased fetal body weights and increased incidences of fetal structural variations at the highest dose tested, which was not associated with maternal toxicity. The no-effect level for adverse effects on embryofetal development (3 mg/kg/day) was associated with maternal plasma exposure (AUC) approximately 2 times that in humans at the maximum recommended human dose (MRHD) of 5 mg.

Oral administration of risdiplam (0, 1, 4, or 12 mg/kg) to pregnant rabbits throughout organogenesis resulted in embryofetal mortality, fetal malformations (hydrocephaly), and structural variations at the highest dose tested, which was associated with maternal toxicity. The no-effect dose for adverse effects on embryofetal development (4 mg/kg/day) was associated with maternal plasma exposure (AUC) approximately 4 times that in humans at the MRHD.

When risdiplam (0, 0.75, 1.5, or 3 mg/kg/day) was orally administered to rats throughout pregnancy and lactation, gestation was prolonged in the dams, and delayed sexual maturation (vaginal opening) and impaired reproductive function (decreased numbers of corpora lutea, implantation sites, and live embryos) were observed in female offspring at the highest dose. The no-effect dose for adverse effects on pre- and postnatal development in rats (1.5 mg/kg/day) was associated with maternal plasma exposure (AUC) similar to that in humans at the MRHD.

8.2 Lactation

Risk Summary

There are no data on the presence of risdiplam in human milk, the effects on the breastfed infant, or the effects on milk production. Risdiplam was excreted in the milk of lactating rats orally administered risdiplam.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EVRYSDI and any potential adverse effects on the breastfed infant from EVRYSDI or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Studies of risdiplam in juvenile and adult rats and in monkeys demonstrated adverse effects on the reproductive organs, including germ cells, in males at clinically-relevant plasma exposures *[see Use in Specific Populations (8.4) and Nonclinical Toxicology (13.1)]*.

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating EVRYSDI *[see Use in Specific Populations (8.1)]*.

Contraception

EVRYSDI may cause embryofetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Female Patients

Advise female patients of reproductive potential to use effective contraception during treatment with EVRYSDI and for at least 1 month after her last dose.

Infertility

Male Patients

Male fertility may be compromised by treatment with EVRYSDI *[see Nonclinical Toxicology (13.1)]*.

Counsel male patients of reproductive potential receiving EVRYSDI about the potential effects on fertility. Male patients may consider sperm preservation prior to treatment.

8.4 Pediatric Use

The safety and effectiveness of EVRYSDI in pediatric patients ≥ 2 months of age have been established *[see Clinical Studies (14)]*. Safety has not been established in pediatric patients < 2 months of age.

Juvenile Animal Toxicity Data

Oral administration of risdiplam (0, 0.75, 1.5, 2.5 mg/day) to young rats from postnatal day (PND) 4 through PND 31 resulted in decreased growth (body weight, tibia length) and delayed sexual maturation in males at the mid and high dose. The skeletal and body weight deficits persisted after cessation of dosing. Ophthalmic changes consisting of vacuoles in the anterior vitreous were seen at the high dose. Decreases in absolute B lymphocyte counts were observed at all doses after cessation of dosing. Decreases in testis and epididymis weights, which correlated with degeneration of the seminiferous epithelium in the testis, occurred at the mid and high doses; the histopathology findings were reversible, but organ weight persisted after cessation of dosing. Impaired female reproductive performance (decreased mating index, fertility index, and conception rate) was observed at the high dose. A no-effect dose for adverse developmental effects on preweaning rats was not identified. The lowest dose tested (0.75 mg/kg/day) was associated with plasma exposures (AUC) lower than that in humans at the maximum recommended human dose (MRHD) of 5 mg/day.

Oral administration of risdiplam (0, 1, 3, or 7.5 mg/day) to young rats from PND 22 through PND 112 produced a marked increase in micronuclei in the bone marrow, male reproductive organ histopathology (degeneration/necrosis of the seminiferous tubule epithelium, oligo/aspermia in the epididymis, spermatic granulomas), and adverse effects on sperm parameters (decreased sperm concentration and motility, increased sperm morphology abnormalities) at the highest dose tested. Increases in T lymphocytes (total, helper, and cytotoxic) were observed at the mid and high doses. The reproductive and immune effects persisted after cessation of dosing. The no-effect dose (1 mg/kg/day) for adverse effects on postweaning juvenile rats was associated with plasma exposures (AUC) lower than that in humans at the MRHD.

8.5 Geriatric Use

Clinical studies of EVRYSDI did not include patients aged 65 years and over to determine whether they respond differently from younger patients.

8.6 Hepatic Impairment

The safety and efficacy of EVRYSDI in patients with hepatic impairment have not been studied. Because risdiplam is predominantly metabolized in the liver, hepatic impairment may potentially increase the exposures to risdiplam *[see Clinical Pharmacology (12.3)]*. Avoid use of EVRYSDI in patients with impaired hepatic function.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Pregnancy and Fetal Risk

Inform pregnant women and women of reproductive potential that, based on animal studies, EVRYSDI may cause fetal harm *[see Use in Specific Populations (8.1)]*. Discuss with women of childbearing age whether they are pregnant, might be pregnant, or are trying to become pregnant. Advise women of childbearing potential to use effective contraception during treatment with EVRYSDI and for at least 1 month after stopping EVRYSDI. Advise a female patient to immediately inform the prescriber if she is pregnant or planning to become pregnant *[see Use in Specific Populations (8.3)]*.

Potential Effects on Male Fertility

Advise male patients that their fertility may be compromised while on treatment with EVRYSDI *[see Use in Specific Populations (8.3)]*.

Instructions for Preparation of Oral Solution

Advise patients to ensure that EVRYSDI is in liquid form when received from the pharmacy. Instruct patients/caregivers to take EVRYSDI after a meal or after breastfeeding at approximately the same time each day. However, instruct caregivers to not mix EVRYSDI with formula or milk. Instruct patients/caregivers to take EVRYSDI immediately after it is drawn up into the reusable oral syringe *[see Dosage and Administration (2.1)]*.

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New Discoveries Dramatically Alter Understanding of Spinal Muscular Atrophy

Military Parents Keep the Faith With Son's SMA Diagnosis

FORT BENNING, GA—Kanaan and Kari Merriken had never heard of spinal muscular atrophy until their son was diagnosed with the disease in 2010. At the time, Kanaan was a staff sergeant with the 75th Ranger Regiment at Fort Benning, GA. Since then, Kanaan, now a first sergeant, and Kari have focused on raising public awareness of SMA while providing the care their son needs.

"No parent ever wants to be told that their child has SMA," said Mary Schroth, MD, chief medical officer of the advocacy group Cure SMA. "Not that long ago, parents of newly-diagnosed SMA babies were told to take them home and love them and that their lives will be short—usually less than two years."

The Merrikens were up to the challenge. Kanaan had already survived extensive wounds including a damaged carotid artery and brain injury from an improvised explosive device attack in Baghdad in 2003. Not expected to live, he was medevaced to Landstuhl Regional Medical Center in Germany and medically retired. To the surprise of his physicians, he recovered, then returned to the Army and the Rangers in 2005—and competed in the Best Ranger Competition in 2011. Throughout, Kari has relied on her deep faith.

First described nearly 130 years ago, SMA remains the leading genetic cause of death for infants. That grim fact and the classic categorization of the disease may soon fade into history as new therapies and increased awareness of the genetic underpinnings of SMA revolutionize treatment.

In nearly all cases of SMA, a deletion of or mutation in both copies of the survival motor neuron 1 *(SMN1)* gene in chromosome 5 prevents production of the SMN protein essential to maintaining healthy motor neurons, nerve cells in the brainstem and spinal cord that send signals to the muscles in the tongue, throat, face, chest, legs and arms. Without the protein, the neurons die. Without signals from the neurons, the muscles they control weaken and atrophy. As the muscles weaken, activities such as breathing, swallowing, speaking and walking become more difficult.

About 1 in 40 individuals carry the recessive mutation primarily responsible for SMA, which affects between 1 in 6,000 and 1 in 10,000 live births. Mutations in other genes, including *IGHMBP2, VAPB, DYNC1H1, BICD2* and *UBA1* can cause rarer forms of SMA and SMA-like diseases through different mechanisms.

Classic SMA

SMA traditionally has been divided into four main types. Type 1 manifests before six months of age. Also called infantile-onset SMA or Werdnig-Hoffman disease, neonates with the disease appear to be "floppy infants" with reduced movement, lack of tendon reflexes, muscle contractures and difficulty swallowing and feeding. Without treatment, these children never sit on their own and typically die before age two of respiratory failure.

"It's not as rare as you might think," Kanaan Merriken told *The Bayonet,* Fort Benning's newspaper, shortly after his son's diagnosis. "My co-worker's son has spinal muscular atrophy Type 1. He can't move his legs. He can't roll over. They have to have him on oxygen."

The Merriken's son was diagnosed with Type 2 SMA (Dubowitz disease), which develops between six and two years of age. At the time of his diagnosis, there was no way to stop disease progression. These children typically manage to sit without support but do not stand or walk without assistance. In time, they may lose the ability to sit unaided. Curvature of the spine is common. They often have respiratory challenges and reduced life expectancy without treatment.

Type 3 SMA or Kugelberg-Welander disease develops after 18 to 24 months, sometimes first appearing in older children or adolescents. Individuals with this type can generally walk independently, though they may have trouble running or climbing stairs. Scoliosis and muscle contractures are common. Life expectancy is not reduced, but affected individuals often experience increased instability and reduced mobility that may require a wheelchair as they age.

Individuals with Type 4 SMA develop symptoms as adults, often after age 35. They have the mildest course, with the disease primarily affecting the leg muscles. Fatigue is common, as is mild tremor or occasional muscle cramping.

Sgt. 1st Class Kanaan Merriken recites the oath of enlistment as wife Kari and son Caleb look on. Merriken and his wife have focused on raising public awareness of SMA while providing the care their son needs. —75th Ranger Regiment photo by Tracy A. Bailey

Some schemas include a Type 0, in which infants suffer prenatal onset and live just a short time.

A New View

For years, the Merrikens and other families affected by SMA held 5K runs and other programs to raise money to fund development of treatments that would change the trajectory of the disease—and they succeeded.

Researchers discovered a crucial factor in the speed and severity of development of SMA: the number of copies of a second gene that can also produce the SMN protein. All patients with SMA have at least one copy of this back-up gene, *SMN2,* which is 99% similar to the *SMN1* gene. Typically, however, *SMN2* produces just 10% of the amount of full-length SMN protein that a functional copy of *SMN1* would.

Generally, infants with Type 1 SMA have two *SMN2* genes, while those with Type 2 usually have three copies, and individuals with Type 3 have three or four copies. Patients with Type 4 SMA have from three to eight copies of the back-up gene. Because these genes produce some of the critical protein, more copies often mean later development of the symptoms.

SMN-enhancing therapies that modify *SMN2* so that the existing copies produce more full-length proteins or insert functional *SMN1* genes have been shown to fundamentally change the progression of the disease, making typing based on timing of manifestation of symptoms or limitations arguably moot for treated patients.

As an example, one study showed that enhancing *SMN2* function in presymptomatic infants with two copies of the gene who were treated before six weeks of age enabled 100% of them to sit, 88% to walk and 77% to walk independently. None needed permanent ventilation, and all lived.[1] In the traditional classification of SMA, those patients would primarily have been classified as Type 1, in which none of those milestones would have ever been achieved. Studies with other approved agents have also produced improvements that call into question the usual typing.

As a result of this shift, some in the field suggest that classification of SMA phenotypes should be updated to include the number of *SMN2* copies, the age at treatment initiation and age of symptom onset.[2]

With the emergence of disease-modifying therapies, many experts have urged states to incorporate

Table 2.

Spectrum of SMA Phenotypes at Presentation

Phenotype	Age of Onset	Life Span[1]	Motor Milestones[1]	Other Findings[1]
SMA 0	Prenatal	A few weeks, <6 mos	None achieved	• Severe neonatal hypotonia • Severe weakness • Areflexia • Respiratory failure at birth • Facial diplegia • fetal movements • Atrial septal defects • Arthrogryposis
SMA I	<6 mos	Median survival 8-10 mos	Some head control, sit w/support only	• Loss of head control • Mild joint contractures • Normal or minimal facial weakness • Variable suck & swallow difficulties
SMA II	6-18 mos	70% alive at age 25 yrs	Independent sitting when placed	• Developmental delay w/loss of motor skills • or absent deep tendon reflexes • Proximal muscle weakness • Postural tremor of fingers
SMA III	>18 mos	Normal	Independent ambulation	• Proximal muscle weakness (i.e., difficulty w/stairs, running) • Loss of motor skills • Fatigue • Postural tremor of fingers • Loss of patellar reflexes
SMA IV	Adulthood	Normal	Normal	• Fatigue • Proximal muscle weakness

[1] With supportive care only

Source: Spinal Muscular Atrophy; GeneReviews® [Internet]; Initial Posting: February 24, 2000; Last Update: November 14, 2019; www.ncbi.nlm.nih.gov/books/NBK1352

SMA into newborn screening tests. So far, 31 states covering 65% of U.S. babies have adopted or are piloting the test.

An expert consensus-based SMA treatment algorithm recommends using the results of newborn screening to enable initiation of the life-changing treatment in infants with two to four copies of *SMN2* immediately.[3] In infants with Type 1 SMA, an estimated 90% of motor neurons die within the first six months of life without treatment and they do not regenerate, so time is of the essence.

The panel concluded that infants born with just one copy of *SMN2* were likely to be symptomatic at birth, and the decision whether to treat should be left to the physician and family based on the child's disease state.[4]

Children who were born before the new treatments were available, and patients not treated in the first few months of life may also benefit from therapies approved for these older groups, with studies demonstrating positive results ranging from stabilization of symptoms to significantly enhanced motor skills and even attainment of normal motor milestones.[5]

[1] Finkel R, Chiriboga C, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet*. 2016;388(10063):3017-3026.

[2] Schorling DC, Pechmann A, Kirschner J. Advances in treatment of spinal muscular atrophy—new phenotypes, new challenges, new implications for care. *J Neuromusc Dis*. 2020;7(1):1-13. doi:10.3233/JND-190424

[3] Glascock J, Sampson J, Haiet-Phillips A, et al. Treatment algorithm for infants diagnosed with spinal muscular atrophy through newborn screening. *J Neuromusc Dis*. 2018;5(2):145-158. doi:10.3233/JND-180304

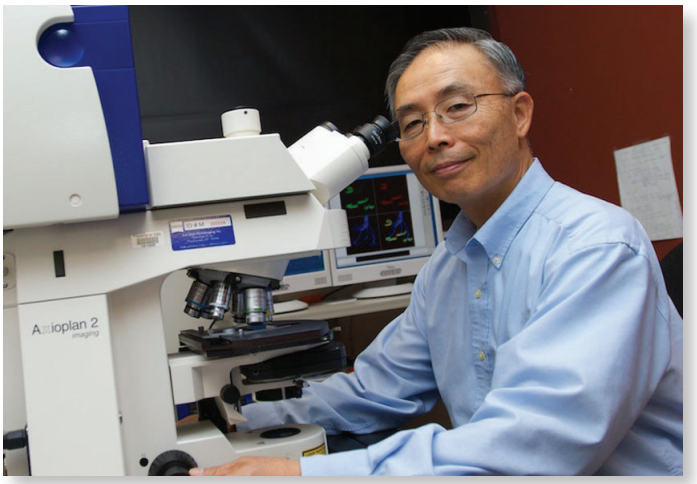
[4] Glascock J, Sampson J, Connolly AM, et al. Revised recommendations for the treatment of infants diagnosed with spinal muscular atrophy via newborn screening who have 4 copies of SMN2. *J Neuromusc Dis*. 2020;7(2):97-100. doi:10.3233/JND-190468

[5] Mercuri E, Barisic N, Boespflug-Tanguy O, et al. SUNFISH Part 2: Efficacy and safety of risdiplam (RG7916) in patients with Type 2 or non-ambulant Type 3 spinal muscular atrophy (SMA) Presented at the American Academy of Neurology Conference 2020. *Neurology*. 2020;94:1260.

Novel Treatments Offer Hope for Spinal Muscular Atrophy Patients

LOS ANGELES—Four years ago, individuals with spinal muscular atrophy (SMA) had no therapies that could slow the disease. Today, three disease-modifying drugs have approval from the U.S. Food and Drug Administration, and at least five more have begun clinical trials.

The dramatic shift may be attributed to two transformative trends. Turbocharged by social media platforms, efforts by patients, caregivers, advocacy organizations and rare disease research foundations to connect with each other, give greater voice to their issues and attract researchers and investment have seen unprecedented success over the last decade. At the same time, breakthroughs in genetic analysis have provided insights into rare inherited diseases that illuminate pathways to mitigation or a cure for the first time.



Chien-Ping Ko's work contributed to the development of the drug risdiplam, approved to treat spinal muscular atrophy. —Photo by Dietmar Quistorf for a University of Southern California press release

For one scientist, these two developments intersected in a way that changed the course of his research and many patients' lives. Chien-Ping Ko, PhD, a neuroscientist at the University of Southern California in Los Angeles, had focused for years on neuromuscular connections. That work led him to study the neuromuscular junction, the path from particular neurons to specific muscles, in mice with SMA to better understand why the disease severely affected some muscles and largely spared others.

Ko's view of the work suddenly took a personal turn when a family with two daughters with SMA visited his lab. Both girls used wheelchairs and had limited ability to move on their own. "The mother said, 'If we could help them just comb their hair, that would be a big relief.' I didn't even think about such a simple thing, how one minor improvement could make such a big difference," Ko said.

Ultimately, Ko figured out why muscles and nerve connections fail quickly in some children with SMA—keeping them from not just combing their hair, but from even breathing on their own—and why those connections work in others for years. Then he shared that knowledge with pharmaceutical companies to enable them to make more effective and more targeted drugs. Throughout, the National Institutes of Health and several rare disease research organizations provided critical funding.

In a rare experience for a scientist who labors in basic research and preclinical studies, Ko saw his work culminate in an FDA-approved drug. With his colleagues at USC and researchers from the SMA Foundation and two pharmaceutical companies, Ko discovered risdiplam.[1]

Disease-Modifying Agents

Approved in August 2020, risdiplam contains a survival of motor neuron 2 *(SMN2)*-directed RNA splicing modifier that increases the production of full-length *SMN2* mRNA, which increases SMN protein levels in the central nervous system and peripheral organs and tissues. Higher protein levels mitigate the muscle atrophy and other complications caused by having no functional *SMN1* gene. Risdiplam (Evrysdi) is indicated for SMA patients two months of age and older. Studies are in progress for use of the drug in infants younger than six weeks at first dose.

"Evrysdi is the first drug for this disease that can be taken orally, providing an important treatment option for patients with SMA, following the approval of the first treatment for this devastating disease less than four years ago," said Billy Dunn, MD, director of the

Office of Neuroscience in the FDA's Center for Drug Evaluation and Research.

The daily therapy leads to significant improvement. After one year of treatment, 41% of the 21 infants in the study with Type 1 SMA could sit without support for at least five seconds, "a meaningful difference from the natural progression of the disease because almost all untreated infants with infantile-onset SMA cannot sit up independently," the FDA noted. After 24 months, 81% of children taking risdiplam required no permanent ventilation, also a notable improvement compared to typical disease progression.

Among 180 patients enrolled in the ongoing randomized, placebo-controlled SUNFISH study of risdiplam in patients aged 2 to 25 with later-onset SMA, those on risdiplam achieved an average 1.36 point increase in the MFM32 test of motor function after one year compared to an 0.19 decrease in those on placebo. This is the only placebo-controlled trial in adults with Types 2 and 3 SMA conducted to date.

An update to the SUNFISH results presented at the virtual Cure SMA Annual Conference in June 2020 found a 3.99-point improvement in patients receiving risdiplam at 24 months and a doubling of blood SMN protein levels after four weeks that was maintained for at least two years.

The first drug approved for SMA, nusinersen, also modifies the alternative splicing of *SMN2* seen in SMA. Approved in December 2016, nusinersen is an antisense oligonucleotide administered via spinal injection. Treatment with the drug starts with four loading doses within two months, followed by maintenance doses every four months.

Approved in 2019, the third treatment, onasemnogene abeparvovec-xioi, is a gene therapy indicated for use in babies under age two with SMA Type 1 (infantile-onset). Onasemnogene abeparvovec-xioi is administered as a one-time intravenous injection. An adeno-associated virus vector delivers a fully functional copy of the *SMN* gene to the target motor neuron cells, correcting the primary cause of SMA and leading to expression of the SMN protein in the neurons.

[1] Ratni H, Ebeling M, Baird J, Bendels S,et. Al. Discovery of Risdiplam, a Selective Survival of Motor Neuron-2 (SMN2) Gene Splicing Modifier for the Treatment of Spinal Muscular Atrophy (SMA). *J Med Chem*. 2018 Aug 9;61(15):6501-6517. doi: 10.1021/acs.jmedchem.8b00741. Epub 2018 Jul 25. PMID: 30044619.

VA's Multidisciplinary Approach Proves to Be Best for Adult SMA

STANFORD, CA—While much of the research on spinal muscular atrophy has focused on children, adults make up more than one-third of all SMA cases.

Most adults with SMA have Type 3, with symptoms that began in childhood or teens, but some have Type 4 disease and may not have experienced any symptoms until their 30s. Because their presentations can vary substantially, sometimes a person with Type 3 or 4 SMA may join the service before symptoms appear.

These individuals may receive care through the VA, particularly as progressive spinal muscular atrophy is considered a presumptive service-connected disability as an organic disease of the nervous system if it develops during active duty or within the applicable time limit.

The VA's multidisciplinary patient-aligned care teams (PACTs) are particularly well suited to providing care for patients with SMA, as adult patients are likely to experience multiple organ system involvement, requiring the coordination of multiple specialists. Optimal management of SMA requires integrated acute care, physical therapy, cardiology, neurology, pulmonology, gastroenterology, orthopedics, nutrition and pharmacy.

Pharmacological Approach

Adult patients with SMA might benefit from drugs that increase the production of full-length SMN protein. The first clinical trial of an SMN-enhancing drug in adults, found that the oral agent risdiplam stabilized disease progression in 57.1% of young adult patients vs. 37.5% for participants receiving placebo. Anecdotally, adult patients have also reported recovering the ability to move to a upright sitting position using only core muscles. The level of SMN protein increased four-fold and was detectable in tissues throughout the body, which may help with some of the nonmotor complications of SMA. The intrathecally injected nusinersen is also approved for use in adults.

Patients also could benefit from combining one of the SMN-enhancers with treatments that act on other affected parts of the body, particularly muscles. One drug in development blocks the production of myostatin, a molecule that inhibits muscle growth. Another slows the release of calcium from the regulatory troponin complex, which may increase the ability of muscles to contract. A clinical trial of the second investigational agent demonstrated an increased aerobic capacity and endurance as well and improved maximal expiratory pressure. Increasing function by protecting and building muscle may be especially useful for older SMA patients with milder forms of the disease.

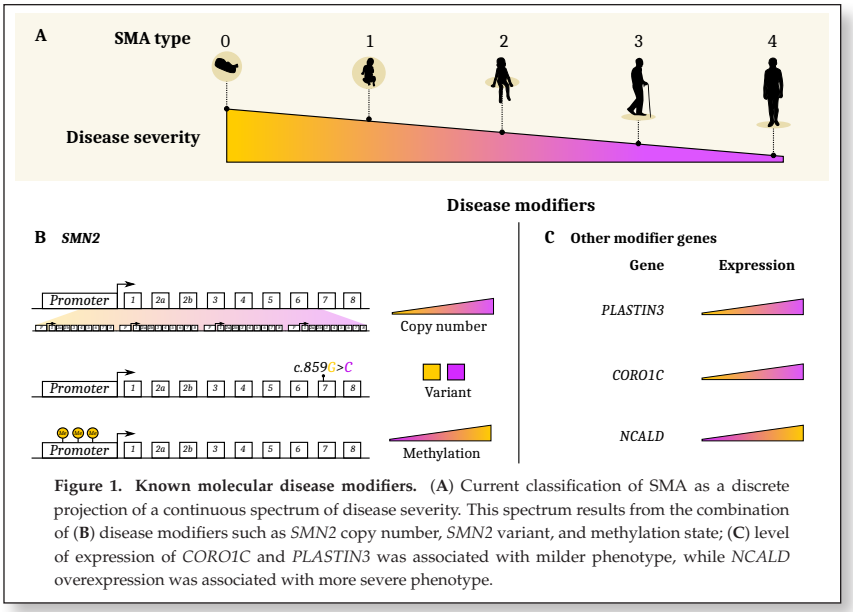


Figure 1. Known molecular disease modifiers. (**A**) Current classification of SMA as a discrete projection of a continuous spectrum of disease severity. This spectrum results from the combination of (**B**) disease modifiers such as *SMN2* copy number, *SMN2* variant, and methylation state; (**C**) level of expression of *CORO1C* and *PLASTIN3* was associated with milder phenotype, while *NCALD* overexpression was associated with more severe phenotype.

Source: The Identification of Novel Biomarkers Is Required to Improve Adult SMA Patient Stratification, Diagnosis and Treatment; J. Pers. Med. *2020, 10(3), 75; https://doi.org/10.3390/jpm10030075*

Nonpharmacological Considerations

The provider team can provide ongoing support to patients with SMA by working together to ensure healthy habits and appropriate nonpharmacological interventions.

While many patients with neuromuscular disorders have historically been advised to refrain from exercise to avoid muscle injury, current evidence supports regular activity to maintain flexibility and strength. Swimming or water exercise, weight-bearing aerobic activities, yoga and resistance therapy have been found to be useful in moderation, according to recommendations from Tina Duong, MPT, PhD, of Stanford University School of Medicine, and Bakri Elsheikh, MD, of The Ohio University Wexner Medical Center in Columbus, OH, who recommend about a half-hour of exercise two to five times a week.

They caution to "watch for fatigue and overuse weakness from overwork" with aerobic exercise, which can lead to decreased intensity. They also advise incorporating exercise into daily activities. While strengthening and aerobic exercise are not shown to improve strength, they do improve aerobic capacity and have no deleterious effects.

In addition, regular exercise helps patients maintain an optimal weight, an important consideration in individuals with reduced mobility. Excess weight can strain joints, increase pressure on the back and further reduce movement. Overweight may also increase the risk of cardiovascular disease and sleep apnea.

Sleep-disordered breathing occurs in 40%, and obstructive sleep apnea affects nearly one-quarter of individuals with neuromuscular disease. As the symptoms of sleep apnea may be mistaken for progression of SMA, physicians at the James H. Quillen VA Healthcare System in Mountain Home, TN, encouraged providers to "be watchful for reversible conditions that are associated with or are a complication of their primary disorder." They noted that "early diagnosis and therapy directed toward these treatable disorders can contribute to an improved quality of life and may lengthen patient survival."[2]

The International Standard of Care Committee for SMA recommends physical therapy for patients with SMA. Physical therapy can preserve walking ability, prevent joint contractures and strengthen muscles. Physical therapists may also recommend mobility aids, orthotics and assistive devices.

Many patients with SMA suffer from some degree of scoliosis, and many will ultimately require back surgery to ensure that the spinal curvature does not threaten proper respiratory function. Surgeons, pulmonologists and neurologists will need to work together with physical therapists to achieve the best outcomes.

Women with SMA planning or managing a pregnancy may also need the support of high-risk obstetricians working in tandem with a neurologist and a pulmonologist familiar with SMA. Elsheikh and colleagues found that nearly three-quarters of women reported increased weakness during pregnancy that continued into the post-partum period for 42% of the mothers.[1]

Struggling with SMA day in, day out and concerns about losing mobility or independence increases the risk of depression and anxiety. Primary care providers may recommend a mental health specialist to help patients work through emotions associated with SMA, identify coping mechanisms and select other treatment options. Some patients find that connecting with other adults with SMA through online groups or local organizations that meet in person can mitigate feelings of isolation and facilitate sharing of management techniques.

[1] Elsheikh BH, Zhang X, Swoboda KJ, et al. Pregnancy and delivery in women with spinal muscular atrophy. *Int J Neurosci*. 2017; 127(11): 953–957.

[2] Puruckherr M, Mehta JB, Girish MR, Byrd RP Jr, Roy TM. Severe obstructive sleep apnea in a patient with spinal muscle atrophy. *Chest*. 2004 Nov;126(5):1705-7. doi: 10.1378/chest.126.5.1705. PMID: 15539750.

Federal Funds Are Critical to Advances in Spinal Muscular Atrophy Research

BETHESDA, MD—For decades, federal grants have provided critical support for research on the causes and potential cures for spinal muscular atrophy (SMA), with ongoing funding from the National Institutes of Health (NIH) and the DoD.

The NIH's National Institute of Neurological Disorders and Stroke (NINDS) conducts basic, translational and clinical research on SMA at its own laboratories and through grants to major medical institutions across the country.

Researchers at those labs continue to build the critical understanding of the cellular and molecular mechanisms that cause degeneration of motor neurons in the hope that elucidation of the pathways will point the way to new therapies for SMA and, perhaps, other neuromuscular disorders.

So far, NIH-funded studies have developed multiple models of the disease in animals and cells that reveal the steps involved in the disease process and speed evaluation of potential therapies. The work in this area contributed significantly to the development of and clinical trials for the therapies approved in the last four years that have changed the lives of SMA patients by stopping motor neuron destruction and slowing disease progression. Additional therapeutic candidates targeting other avenues are in the pipeline.

Early funding for animal models of SMA in zebrafish, mice and pigs, continue to help researchers explore potential therapeutic targets and new therapies for SMA, not just for Type 1 disease but also for the older children and adults less severe SMA Types 2 and 3. At the same time, longitudinal studies that track pre-symptomatic and recently-diagnosed children with SMA and their siblings builds an invaluable foundation for genetic counseling of carriers of the critical mutation underlying the disease and provides objective information on SMA progression, therapeutic advances and clinical trial opportunities for parents of recently-diagnosed children.

NINDS has also created a network of clinical trials, NeuroNext (NINDS Network for Excellence in Neuroscience Clinical Trials), to facilitate investigation of potential therapies for neurological disorders in children and adults. Among its current goals, the network aims to develop early-phase trials focused on identifying biomarkers that can indicate likely severity of SMA in infants and predict responses to new therapies to maximize their benefits while minimizing potential harms for adverse events. The natural history data NINDS gained through these efforts has been critical in the approval decisions for SMN-enhancing therapies and continues to improve the design of additional clinical trials in SMA.

In addition, the NIH launched the BRAIN Initiative to bring together discoveries that promise to unravel some of the enduring mysteries of the brain, including the underlying causes of many neuromuscular

diseases. Through 2019, the NIH had made 700 awards totaling $1.3 billion to the program.

DoD Funding

SMA became an approved research topic in the DoD's Peer-Reviewed Medical Research Program in 2016, "opening up a whole new level of funding from a completely new source," said FightSMA co-founder Martha Slay at the time. That opened up consideration by the DoD's Congressionally Directed Medical Research Programs.

According to the DoD, "the vision and mission of the PRMRP is to improve the health, care and well-being of all military servicemembers, veterans and beneficiaries by encouraging, identifying, selecting and managing medical research projects of clear scientific merit and direct relevance to military health." While the funding clearly benefits veterans and beneficiaries who develop SMA, the immediate relevance to military health might be less obvious.

An approved grant to Columbia University in New York succinctly explained the importance of SMA research to the DoD. "Department of Defense investment in this initiative would increase the chances of finding treatments for current members of the armed forces and veterans who otherwise remain paralyzed or die from combat-related conditions," it said. "Since SMA research focuses on dying neurons, how to keep them alive and how to stimulate them to regenerate, discoveries in this area should have impact for treatment of traumatic injuries to the brain and spinal cord, and this has specific relevance to the armed forces in Iraq."

Further, the grant application noted, greater understanding of disease mechanisms and advances in treatment in SMA could be applicable to other degenerative diseases, including Alzheimer's disease and amyotrophic lateral sclerosis (ALS). Clinicians anticipate that advances in treatment of SMA will be applicable to other degenerative diseases such as ALS, appears to have developed at increased rates in veterans who served in the Gulf War.

Continued Funding

Federal funding for research in SMA remains critical. While the recently-developed SMN-enhancing therapies have transformed the outlook for many newly-diagnosed SMA patients and improved the prognosis for many others. Still, a cure remains elusive, and not all patients respond equally to the available therapies.

Further, the long-term trajectory of patients with Type 1 SMA is just now coming into view, and the impact of new treatments on Type 2 and Type 3 patients over time remains unknown. More critically, the precise details of the pathogenesis of SMA and the disease's impact on the brain, liver, pancreas and other organs continues to be unclear.

Here's how the National Institute of Neurological Disorders and Stroke defines Spinal Muscular Atrophy and its subtypes:

Spinal Muscular Atrophy refers to a group of hereditary diseases that damages and kills specialized nerve cells in the brain and spinal cord (called motor neurons). Motor neurons control movement in the arms, legs, face, chest, throat and tongue, as well as skeletal muscle activity including speaking, walking, swallowing and breathing. The most common form of SMA is caused by an abnormal or missing gene known as the survival motor neuron gene 1 (SMN1), which is responsible for the production of a protein essential to motor neurons. This form of SMA has four types:

- Type 1, also called Werdnig-Hoffman disease or infantile-onset SMA, is usually evident before 6 months of age. The most severely affected children will have reduced movement and chronic shortening of muscles or tendons (called contractures). Other children may have symptoms including reduced muscle tone, lack of tendon reflexes, twitching, skeletal abnormalities and problems swallowing and feeding. Without treatment, many affected children die before age 2.
- SMA Type 2 is usually first noticed between 6 and 18 months of age. Children can sit without support but are unable to stand or walk unaided. Children also may have respiratory difficulties. Life expectancy is reduced, but most individuals live into adolescence or young adulthood.
- SMA Type 3 (Kugelberg-Welander disease) is seen after age 18 months. Children can walk independently but may have difficulty walking or running, rising from a chair or climbing stairs. Other complications may include curvature of the spine, contractures and respiratory infections. With treatment, most individuals can have a normal life span.
- Individuals with SMA Type 4 develop symptoms after age 21 years, with mild to moderate leg muscle weakness and other symptoms.

Despite these uncertainties and the continued need for development of therapies that address the nonmotor aspects of SMA, many funding organizations and charities in the U.S. and abroad have experienced greater challenges in raising money to continue research since the approval of the disease-modifying therapies.

Ensuring that these therapies can provide maximum benefit and that new ones will be discovered to address unanswered issues, "can only occur with a steady flow of funding from both charities and federal/government funding bodies," argued Melissa Bowerman, PhD, of Keele University School of Medicine in the UK, in an editorial in *Future Neurology*. "Thus, while we have changed the course of the disease for the better, it is important that we continue funding fundamental, preclinical and clinical SMA research, to keep us on an upward trajectory, in the hopes that, one day, no one has to succumb to SMA."[1]

[1.] Bowerman M. Funding for spinal muscular atrophy research must continue. *Future Neurology*. 5 June 2019;14(2). Published online.

Quality of Life Remains Extremely Low For Some SMA Patients, Caregivers

ELK GROVE VILLAGE, IL—With several new drugs approved for treatment of spinal muscular atrophy, patients and caregivers of patients now have reason to measure progress and to assess quality of life.

Historically, spinal muscular atrophy (SMA), a genetic neuromuscular disease characterized by progressive muscle atrophy and weakness, often led to paralysis and premature death. SMA usually is first diagnosed in infants and toddlers, but also can be initially identified in children and, less commonly, adults.

The online 2019 Cure SMA Community Update Survey, with results published recently in the *Orphanet Journal of Rare Diseases,* assessed health-related quality of life (HRQoL), loss of work productivity and fatigue using the Health Utilities Index Questionnaire (HUI), the Work Productivity and Activity Impairment Questionnaire (WPAI) and the Patient Reported Outcomes Measurement Information System Fatigue Short Form (PROMIS Fatigue SF), respectively, among SMA patients and caregivers.[1]

The goal was to collect baseline quality of life results using the above Patient-Reported Outcome Measures (PROMs).

"The 2019 Community Update Survey dataset provides an important benchmark from which to begin assessing year-over-year change in HRQoL for affected individuals and their caregivers," the authors explained. "Cure SMA will conduct follow up annual surveys using the WPAI and HUI instruments to evaluate the impact that new therapies are making on the overall experience of affected individuals and their families. It is anticipated that these future survey activities will also add in other HRQoL measurements (including the EQ-5D and the Fatigue Impact Scale to broaden the picture of SMA impact among the community, evaluate which tools are most sensitive to each subtype of the diverse SMA population, can assess treatment affects and determine the health utility among a large sample of affected individuals with SMA."

Researchers received 666 surveys completed between March and May 2019 and included 478 in the analysis, taking into account duplicates, missing data, or deaths. Most of the responses involved SMA Type 2, 47%, which is less severe than Type 1: with 25% for Type 1, the most severe, with 25%, and 28% for Type 3, which is considered milder.

Current functional status/milestones were used to categorize the responses, with subsets for "permanent ventilation," "nonsitters," "sitters," "walk with support" and "walk alone." While WPAI and HUI respondents included affected adults and caregivers, the PROMIS Fatigue SF was completed by the primary caregiver of affected children.

Results indicated a highly-rated burden of SMA across all three assessments, in line with findings from previous qualitative studies that assessed the burden of SMA across phenotypes. As measured by the HUI, the quality-of-life scores fell under the category of "severe disability:" work productivity lost due to having SMA or caring for someone with SMA was also significant; and the fatigue levels of children affected with SMA was greater than that of the general population, regardless of type.

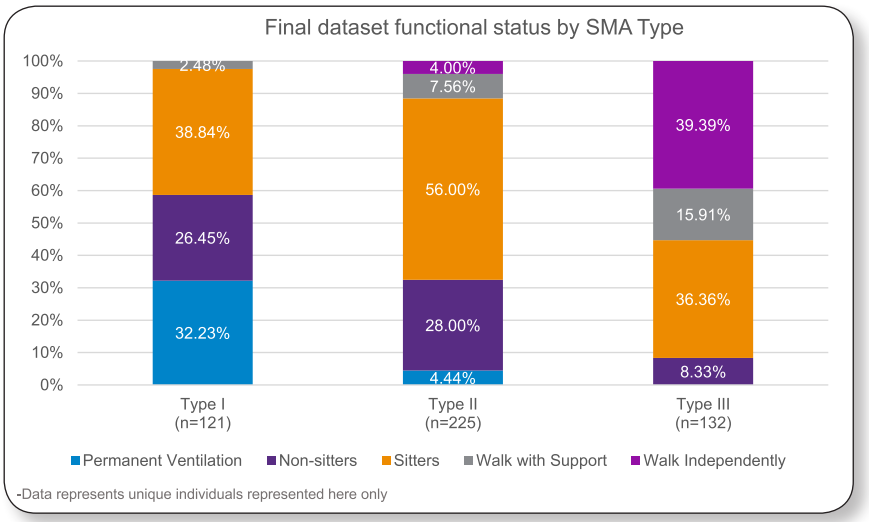
"Overall, those affected by a less severe form of SMA and with a higher functional status reported

higher HRQoL and lower work productivity and activity impairment," the authors reported. "All affected individuals reported higher fatigue levels than the general population."

Baseline Snapshot

The authors noted that the study offered essential insights into the burden of SMA among affected individuals and their caregivers. A key advantage is that the results provide a "baseline picture of the patient and caregiver experience with SMA in a post-treatment era from which to measure year-over-year changes in quality of life scores from new therapies and improved care," they pointed out.

Fig.2 Final dataset functional status by SMA type



Source: Quality-of-life data for individuals affected by spinal muscular atrophy: a baseline dataset from the Cure SMA Community Update Survey; Orphanet Journal of Rare Diseases; https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-01498-2

Some of the measurements were problematic, however. "The WPAI demonstrates the significant impact of work productivity among SMA populations," the researchers explained. "Aspects of the HUI seem more appropriate to certain SMA sub-populations than others. Measures from the PROMIS Fatigue SF appear to under-represent the burden of fatigue often reported by SMA individuals and caregivers; this may, perhaps be due to a lack of sensitivity in the questions associated with fatigue in the SMA affected population, when compared with other studies on this topic. Overall, these results suggest the need for SMA-specific quality of life outcome measures to fully capture clinically meaningful change in the SMA population."

The bottom line, according to the study, is the immense challenges faced by patients and their families. "Often this odyssey begins with a prolonged and traumatic process to confirm diagnosis and a lifelong journey of overwhelming physical, emotional, psychosocial and financial strains associated with managing and living with a progressive, debilitating and incurable disease."

The study described the situation as "critical" when it comes to quantifying outcomes that are meaningful from the patient perspective and how those are affected by new therapies.

Researchers also advised that both patients and healthcare providers do not believe that factors being assessed in pharmacoeconomic analyses are sensitive enough to capture the overall effects on quality of life. impact on quality of life. "Thus, it has been proposed for SMA (and for rare disease more generally) that focusing on generating evidence that translates therapy benefit from clinical trials to patient and family relevant outcomes such as quality of life, independence and productivity impact might be more appropriate when analyzing cost effectiveness," according to the authors. "Encompassing these additional dimensions would provide a more complete picture of the burden of disease and the potential overall impact of a new therapy."

They noted that similar efforts have recently been undertaken in other rare, pediatric diseases such as Duchenne muscular dystrophy (DMD).

The authors concluded that the 2019 Community Update Survey dataset provides an important benchmark from which to begin assessing year-over-year change in HRQoL for affected individuals and their caregivers. Cure SMA said it will conduct follow-up annual surveys using the WPAI and HUI instruments to evaluate how new therapies are affecting the overall experience of affected individuals and their families.

"Ultimately, we anticipate learning through this process, that different instruments will be more appropriate for assessing HRQoL within SMA, and among the various SMA subpopulations, ages of affected individuals and functional milestone status," the researchers wrote.

[1] Belter L, Cruz R, Jarecki J. Quality of life data for individuals affected by spinal muscular atrophy: a baseline dataset from the Cure SMA Community Update Survey. *Orphanet J Rare Dis*. 2020 Aug 24;15(1):217. doi: 10.1186/s13023-020-01498-2. PMID: 32838797;

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