Taking the next steps to improve patient outcomes in SMA: Early diagnosis and treatment

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Expert panel

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Agenda

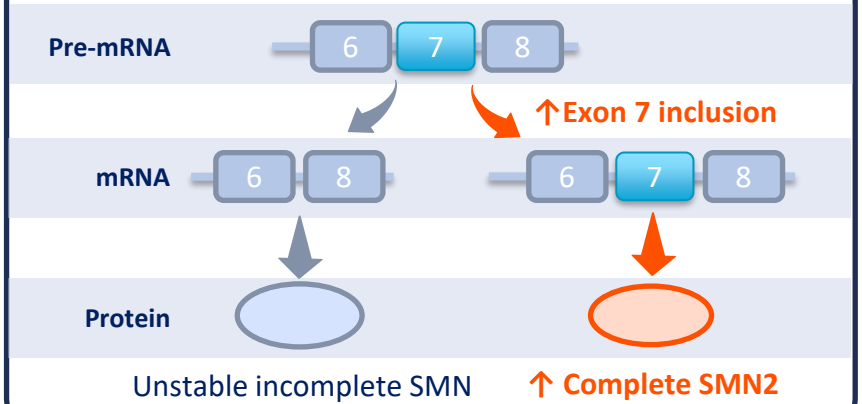
- What is the evidence for initiating treatment early in patients with SMA?
- How can SMA be diagnosed at the earliest opportunity?
- How close are we to new biomarkers for SMA?

SMA, spinal muscular atrophy.

Available treatments in SMA and their mechanisms of action

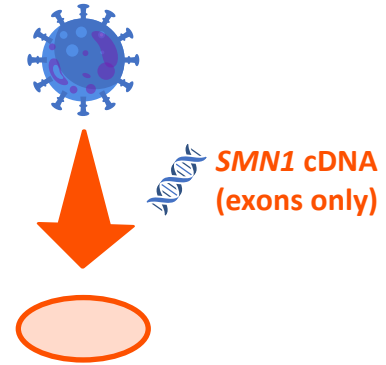
Nusinersen and risdiplam

Modify *SMN2* pre-mRNA splicing increasing full-length SMN2 protein



Onasemnogene abeparvovec

***SMN1* gene replacement using adenovirus vector AAV9-SMN**



AAV, adeno-associated virus; cDNA, complementary deoxyribonucleic acid; micro-ribonucleic acid; SMA, spinal muscular atrophy; SMN, survival motor neuron.

Messina S, Sframeli M. *J Clin Med*. 2020;9:2222.

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SMA treatments: Approvals and indications

Agent	Approval date and indication	
	FDA	EMA
Nusinersen	**2016** SMA in paediatric and adult patients[1]	**2017** Patients with 5q SMA[2]
Onasemnogene abeparvovec	**2019** Patients <2 years with SMA with bi-allelic mutations in the *SMN1* gene[3]	**2020** Patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and: • A clinical diagnosis of SMA Type 1 **or** • ≤3 copies of the *SMN2* gene[4]
Risdiplam	**2020** SMA in patients ≥2 months of age[5,6]	**2020** Marketing authorization application accepted[7]

EMA, European Medicines Agency; FDA, Food and Drug Administration; SMA, spinal muscular atrophy; SMN, survival motor neuron.

1. Nusinersen. Prescribing Information. Revised June 2020; 2. Nusinersen Summary of Product Characteristics. Updated 31 January 2020;
3. Onasemnogene abeparvovec. Prescribing Information. Revised: May 2019; 4. Onasemnogene abeparvovec. Summary of Product Characteristics. Updated 06 November 2020;
5. FDA Press release. Available at: www.fda.gov/news-events/press-announcements/fda-approves-oral-treatment-spinal-muscular-atrophy (accessed 25 November 2020);
6. Risdiplam Prescribing Information. Revised August 2020; 7. PTC announcement. Available at: https://ir.ptcbio.com/node/13116/pdf (accessed 25 November 2020).

Summary of clinical trials in SMA

Key registration trials

Agent	Trials	Study design and patients
Nusinersen	ENDEAR[1]	• **Phase III, randomized, double-blind, placebo-controlled** • **Infantile-onset** • SMA Type 1, N=121, age ≤7 months
	CHERISH[2]	• **Phase III, randomized, double-blind, placebo-controlled** • **Late-onset** • SMA Type 2/3, N=126, age=2–9 years
Onasemnogene abeparvovec	START[4]	• **Phase I, open-label, dose-finding** • SMA Type 1, N=15
	STR1VE[5]	• **Phase III, open-label, single-arm** • SMA Type 1, N=22
Risdiplam	FIREFISH[7]	• **Phase II/III, open-label, two-part pivotal trial** • SMA Type 1, N=62
	SUNFISH[8]	• **Phase II/III, two-part, double-blind, placebo-controlled pivotal trial** • SMA Type 2/3, N=231, age=2–25 years old

Studies in pre-symptomatic children

NURTURE[3]
- Phase II, open-label, single-arm
- Infants genetically diagnosed as likely to develop SMA Type 1/2
- N=25, age ≤6 weeks

SPR1NT[6]
- Phase III, open-label, single-arm, multicentre
- SMA Type 1, N=30, age ≤6 weeks

RAINBOWFISH (recruiting)[9]
- Open-label, single-arm, multicentre
- SMA Type 1, age ≤6 weeks

SMA, spinal muscular atrophy.

1. Finkel RS, et al. *N Engl J Med*. 2017;377:1723–32; 2. Mercuri E, et al. *N Engl J Med*. 2018;378:625–35; 3. De Vivo DC, et al. *Neuromuscul Disord*. 2019;11:842–56; 4. Mendell JR, et al. *N Engl J Med*. 2017;377:1713–22; 5. NCT03306277; 6. NCT03505099; 7 NCT02913482; 8. NCT02908685; 9. NCT03779334.
Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed 25 November 2020).

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Outcomes in children with SMA treated with nusinersen when symptomatic vs those treated pre-symptomatically

ENDEAR: Nusinersen treatment initiated when symptomatic[1]

SMA Type 1
N=121
Age ≤7 months

Outcomes

- **51%** in the nusinersen vs **0%** in control group were **motor milestone responders at 9 months**

In the nusinersen group:

- 22% achieved head control, 10% rolling, 8% independent sitting, 1% standing
- 63% reduced risk of mortality vs control group (HR, 0.37; 95% CI, 0.18–0.77; P=0.004)

By the end of the ENDEAR trial, 31/80 (39%) nusinersen-treated infants with infantile-onset SMA died or required permanent ventilation

NURTURE: Nusinersen treatment initiated pre-symptomatically[2]

Infants genetically diagnosed as likely to develop SMA Type 1 or 2
N=25, age ≤ 6 weeks

Outcomes

At 2.9 years:

- **100% did not require permanent ventilation**
- 100% achieved sitting without support
- 92% achieved walking with assistance
- 88% achieved walking independently

CI, confidence interval; HR, hazard ratio; SMA, spinal muscular atrophy.

1. Finkel RS, et al. *N Engl J Med*. 2017;377:1723–32; 2. De Vivo DC, et al. *Neuromuscul Disord*. 2019;11:842–56.

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Outcomes in children treated with onasemnogene abeparvovec when symptomatic vs those treated pre-symptomatically

STR1VE-US: Onasemnogene abeparvovec initiated when symptomatic[1]

SMA Type 1
N=22
Age ≤6 months

US study

Outcomes (among 19 patients who had reached, or would have reached, 13.6 months at data cut off)

- **17 (89%)** were surviving without permanent ventilation vs 25% survival in untreated natural history
- **5/6 (83%) patients** ≥18 months old sat independently for ≥30 seconds
- Mean (range) baseline CHOP-INTEND score was 32 (18–52) and increased by 6.9, 11.7, and 14.3 points at months 1, 3, and 5, respectively

SPR1NT: Onasemnogene abeparvovec treatment initiated pre-symptomatically[2]

Age ≤6 weeks

Two *SMN2* copies, n=14
Three *SMN2* copies, n=15

Outcomes (interim data as of 31 December 2019)

- Mean age at last follow-up visit: 11.2 months (two *SMN2* copies) and 9.7 months (three *SMN2* copies)
- **All patients were alive and none required ventilation support as of last visit**

Among patients with two *SMN2* copies:

- 8/14 infants achieved independent sitting within the normal age interval
- 4/14 walked independently within a normal age range
- All patients achieved a CHOP-INTEND score of ≥50 points

Among patients with three *SMN2* copies:

- 4/15 achieved independent standing within the WHO reference window; 3 of these also achieved independent walking

CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SMA, spinal muscular atrophy; SMN, survival motor neuron; WHO, World Health Organization.

1. Day JW, et al. Abstract 40. Presented at: 2020 MDA Clinical & Scientific Conference (virtual); 2. Strauss KA, et al. *Neurology*. 2020;94(Suppl. 15):2384.

Evidence for diagnostic delay in SMA

2015 systematic literature review[1]

SMA studies published between 2000–2014

	SMA Type		
	1	2	3
Time from symptom onset to diagnosis (months)	**3.6**	14.3	43.6
Mean age at diagnosis (months)	**6.3**	20.7	50.3

2018 analysis of Cure SMA database[2]

Worldwide patient-reported database of SMA patients

2010–2016

N=1,966 patients
(n=1,021 with SMA Type 1)

	SMA Type 1
Mean age at diagnosis (months)	**5.2**

2020 Italian study of SMA[3]

Italy

N=480 patients
(n=191 with SMA Type 1)

	SMA Type 1
Mean age at onset of symptoms (months)	**2.75**
Time from symptom onset to diagnosis (months)	**1.94**
Mean age at diagnosis (months)	**4.7**

SMA, spinal muscular atrophy.

1. Lin CW, et al. *Pediatr Neurol*. 2015;53:293–300; 2. Belter L, et al. *J Neuromuscul Dis*. 2018;5:167–76; 3. Pera MC, et al. *PLoS One*. 2020;15:e0230677.

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Newborn screening for SMA

NBS in the USA[1]

33 States currently screen for SMA

68% of newborn babies are screened

German pilot project[2]

Germany, Bavaria and North Rhine Westphalia

165,525 children screened

22 cases of SMA identified

Jan 2018–Feb 2019

Incidence rate of SMA=1:7,524

7/10 patients with two or three *SMN2* copies were treated pre-symptomatically, and showed no muscle weakness by age 1 month to 1 year

NBS pilot study in Belgium[3]

Launch of new NBS programme in Belgium

To cover 17,000 neonates/year

Coverage extension to all of Southern Belgium to screen **55,000 babies/year** is underway

Three-year pilot study in a Belgian neonatal screening laboratory

NBS method to detect homozygous deletions of exon 7 in the *SMN1* gene

NBS in Australia[4]

Australia

- 103,903 infants screened
- 10 cases of SMA identified
- 9/10 genetically confirmed
- 4/10 had clinical signs of SMA within 4 weeks
- Median time to implementation of care plan=26.5 days from birth

1 Aug 2018–31 July 2019

The European Alliance for Newborn Screening in SMA seeks NBS in all European countries by 2025[5]

NBS, newborn screening; SMA, spinal muscular atrophy; SMN, survival motor neuron.

1. CureSMA. Available at: www.curesma.org/newborn-screening-for-sma/ (accessed 25 November 2020); 2. Vill K, et al. *J Neuromuscul Dis.* 2019;6:503–15;
3. Boemer F, et al. *Neuromuscul Disord.* 2019;29:343–9; 3; 4. Kariyawasam D, et al. *Genet Med.* 2020;22:557–65;
5. SMA Europe. Available at: www.sma-europe.eu/opening-a-new-horizon-for-children-born-with-sma/ (accessed 25 November 2020.

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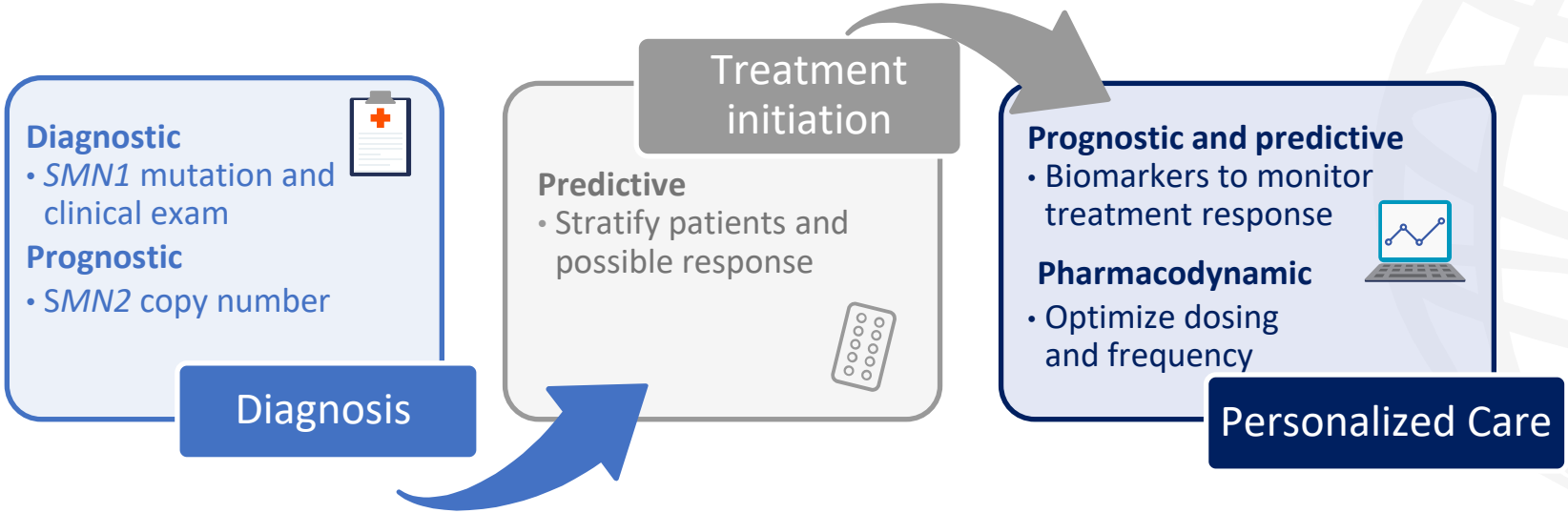
Potential role of biomarkers in a personalized approach for diagnosing and managing patients with SMA



SMA, spinal muscular atrophy; SMN, survival motor neuron.
Kariyawasam DST, et al. *Front Neurol*. 2019;10:898.

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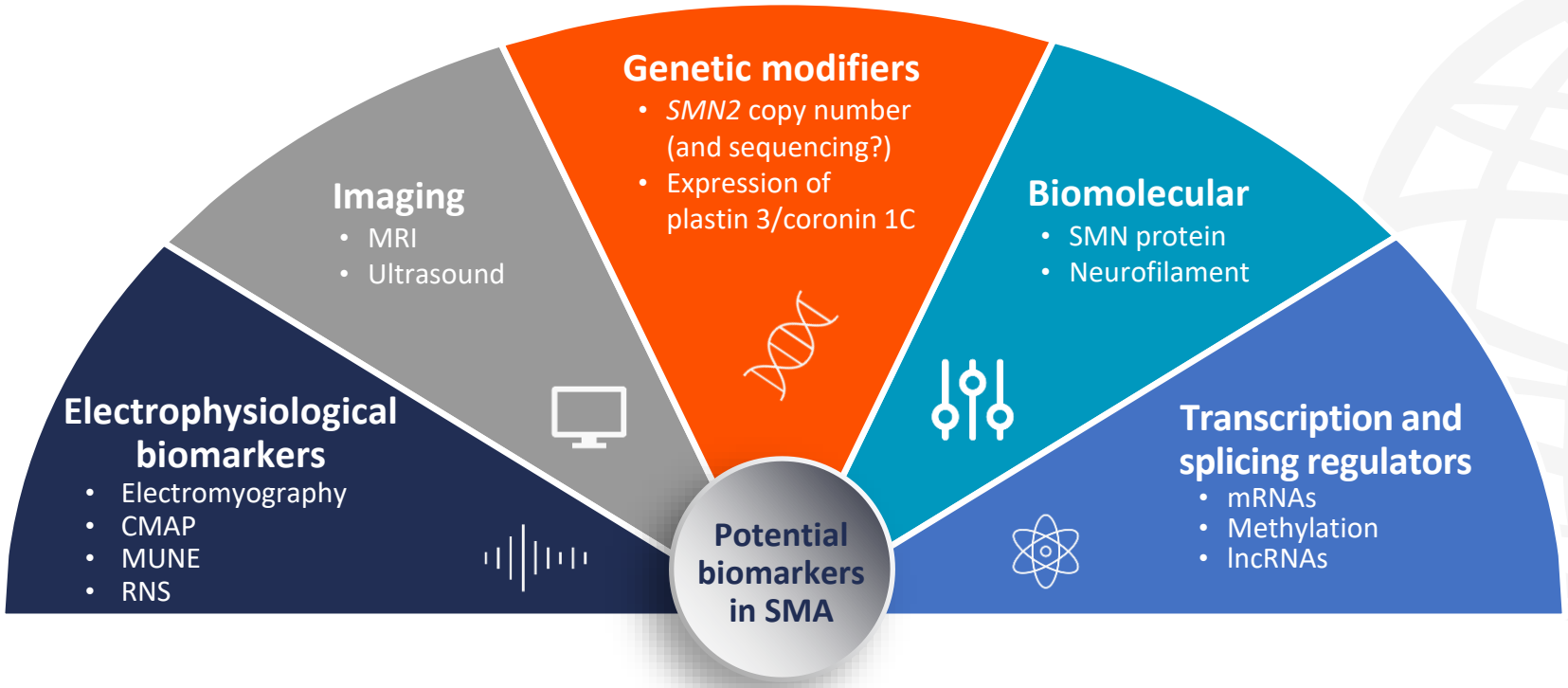
Potential biomarkers in SMA



CMAP, compound muscle action potential; lncRNA, long non-coding ribonucleic acid; MRI, magnetic resonance imaging; mRNA, micro-ribonucleic acid; MUNE, motor unit number estimation; RNS, repetitive nerve stimulation; SMA, spinal muscular atrophy; SMN, survival motor neuron.

Kariyawasam DST, et al. *Front Neurol*. 2019;10:898.

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