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SMA NBS programme learnings from Germany

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Speaker disclosures

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- Advisory Board member and speaker for: Audentes, AveXis (Novartis Gene Therapies), Biogen, Roche, PTC, Sanofi-Genzyme, Sarepta
- PI in studies sponsored by: Audentes, Biogen, Italfarmaco, Roche, Sarepta

LMU, Ludwig Maximilian University; PI, Principal Investigator.

Acknowledgements

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Important questions to be addressed for the successful implementation of SMA NBS

Wilson and Jungner classic screening criteria[1]

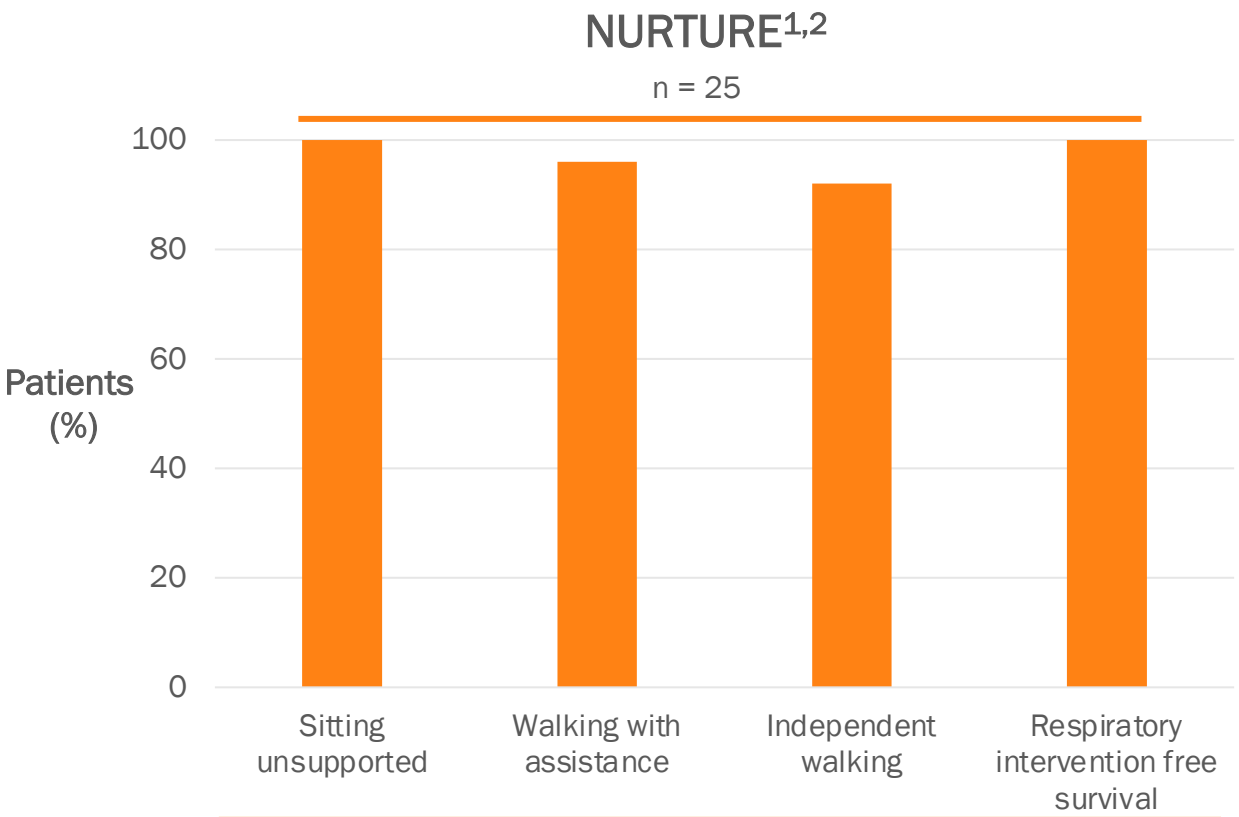
- Important health problem
- Known natural history
- Recognizable latent or early symptomatic stage
- Treatment available
- Suitable and acceptable test or examination
- Cost/benefit ratio favours screening
- Existing process, from identification of suspected condition to treatment

We asked...[2]

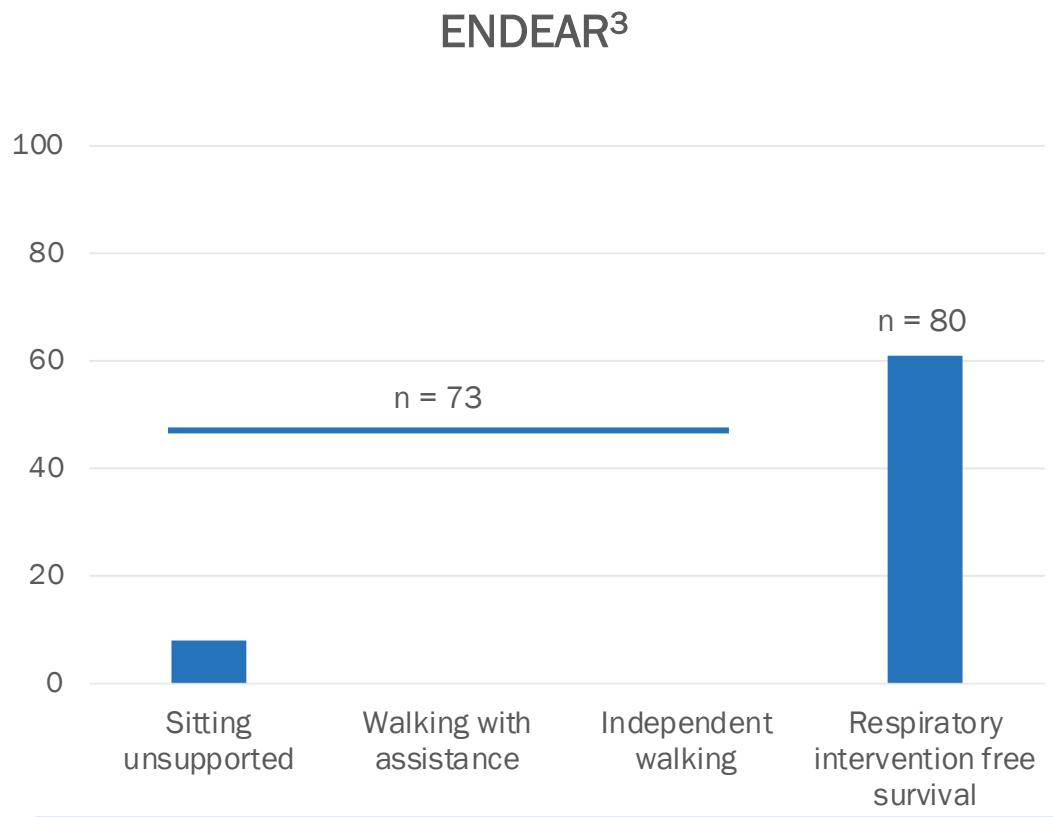
- Can it be performed in a timely manner?
- Are the methods reliable?
- Does it improve the outcome?

NBS, newborn screening; SMA, spinal muscular atrophy.
1. Wilson JMG, Jungner G. Principles and practice of screening for disease. World Health Organization: Geneva; 1968. p.7-168. 2. Based on Prof Müller-Felber's clinical experience.

Presymptomatic screening for SMA is necessary for better treatment outcomes



Median follow-up period after nusinersen: 4.9 years



Follow-up period after nusinersen: 1 year (approximately)

The studies NURTURE and ENDEAR cannot be directly compared to each other. NURTURE is an ongoing Phase 2, open-label study aimed to evaluate the safety and efficacy of nusinersen in preventing or profoundly attenuating the severity of SMA when initiated prior to the onset of symptoms. ENDEAR was a randomized, double-blind, sham-controlled, phase 3 efficacy and safety trial of nusinersen in infants with spinal muscular atrophy. The study population as well as the primary and secondary endpoints differ from each other. The primary endpoints in ENDEAR were a motor-milestone response (defined according to results on the HFMSE) and event-free survival (time to death or the use of permanent assisted ventilation). In the final analysis, a higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (37 of 73 infants [51%] vs. 0 of 37 [0%]), and the likelihood of event-free survival was higher in the nusinersen group than in the control group (hazard ratio for death or the use of permanent assisted ventilation, 0.53; P=0.005). The most common adverse reactions associated with the administration of nusinersen were headache, vomiting and back pain. These reactions can be considered manifestations of post-lumbar puncture syndrome. HFMSE, Hammersmith Functional Motor Scale-Expanded; SMA, spinal muscular atrophy.

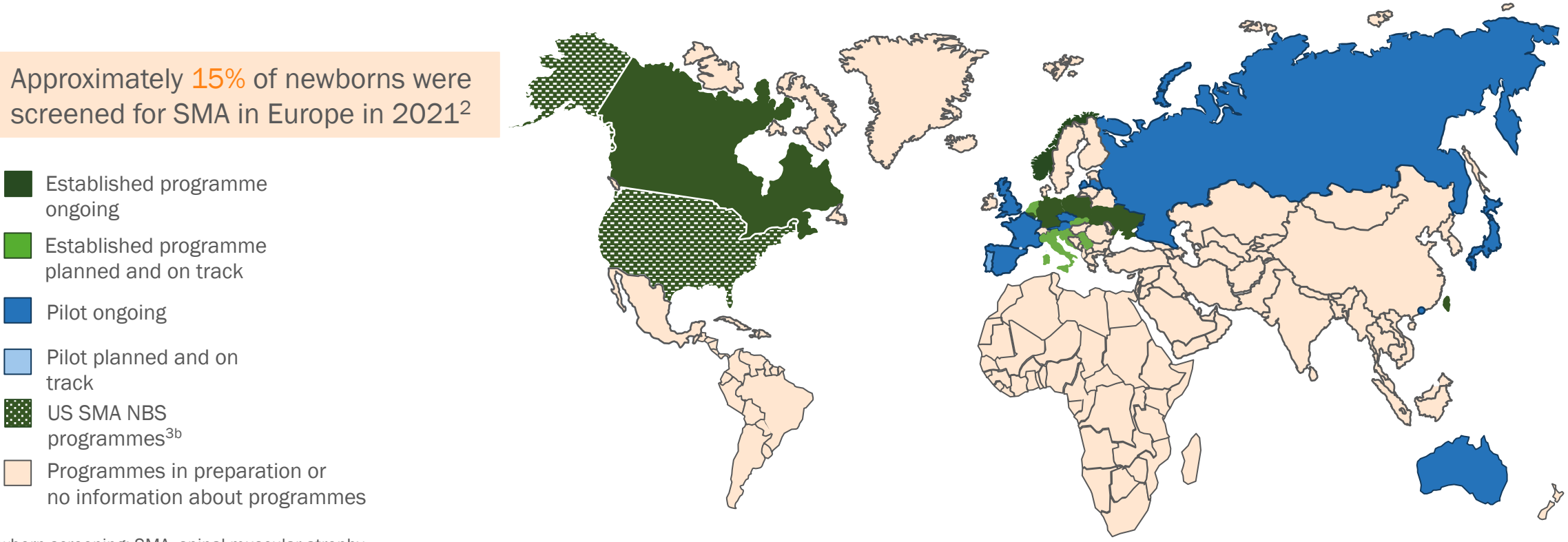
1. NCT02386553. https://clinicaltrials.gov/ct2/show/NCT02386553. Accessed April 2022. 2. Crawford TO, et al. Presented at MDA 2022. 3. Finkel RS, et al. N Engl J Med. 2017;377:1723-32.

Several countries around the world aim to implement SMA into their national NBS programmes

95 countries have been surveyed and 70 countries provided information about SMA NBS programmes:[a]

- 25 countries had established or pilot SMA NBS programmes, ongoing or planned
- 14 countries had established and 11 had pilot SMA NBS programmes

Approximately 15% of newborns were screened for SMA in Europe in 2021[2]



NBS, newborn screening; SMA, spinal muscular atrophy.

[a] Information about the status of SMA NBS programmes in different countries comes from a survey conducted among colleagues from medical, patient advocacy, and public policy and government affairs groups[1].

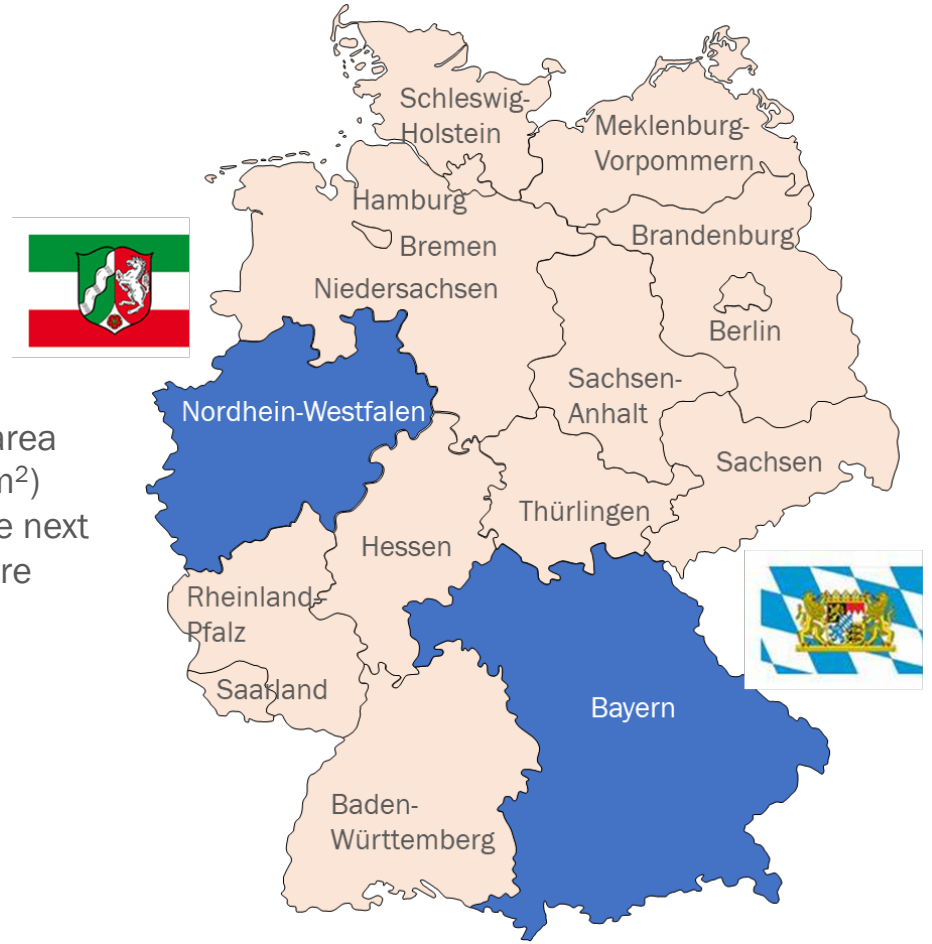
[b] In the USA, the programmes are slightly different to those in other countries and differ per state within the USA.

1. Additional information on status. Available from: https://www.sma-screening-alliance.org/map/. There is no published information on some countries. 2. SMA Europe and European Alliance for Newborn Screening. Unpublished data. April 2022. 3. USA: States and Screening Status. Available from: https://www.curesma.org/newborn-screening-for-sma/#:~:text=The%20Cure%20SMA%20Newborn%20Screening,time%2C%20and%20develop%20new%20treatments. All links accessed April 2022.

Best practices from our SMA NBS pilot project in Germany

January 2018 to September 2021

Treatment centres in
Munich, Essen, Münster



- Densely populated area (526 inhabitants/km^2)
- Short distance to the next neuromuscular centre

- Sparsely populated area (185 inhabitants/km^2).
- Long distance to the next neuromuscular centre.

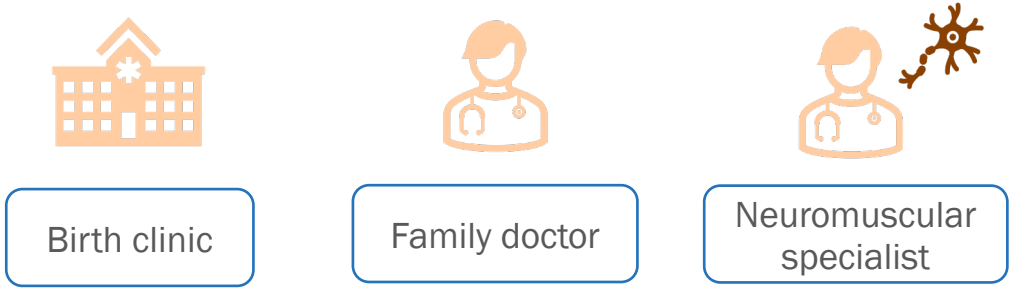
NBS, newborn screening; SMA, spinal muscular atrophy.
Based on Prof Müller-Felber's clinical experience.

The challenges following positive screening

Who should inform the parents?

- Practical issues
- Legal aspects
- Experience with the disease

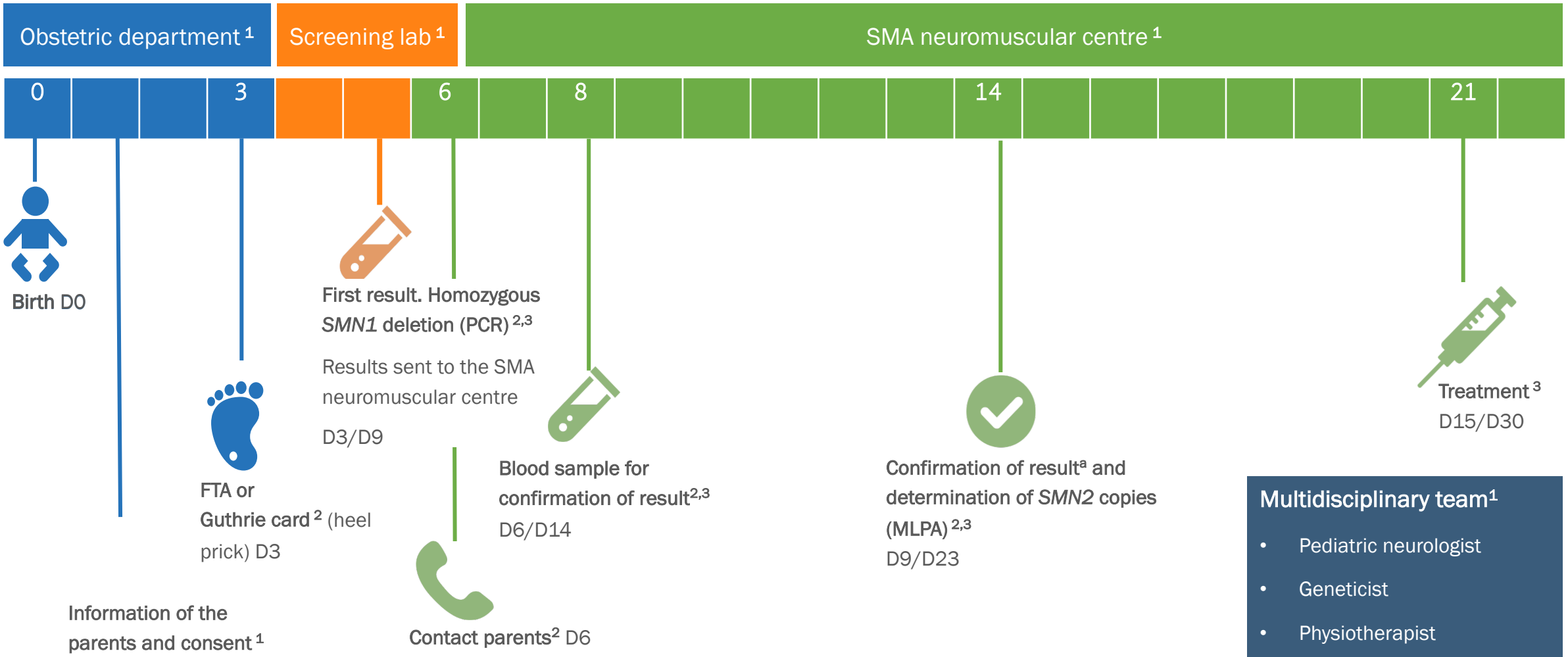
Who should perform the confirmatory blood test?



- Rapid availability of confirmation and *SMN2* copy number
- Appointment at a neuromuscular clinic within a few days
- Start of treatment as necessary

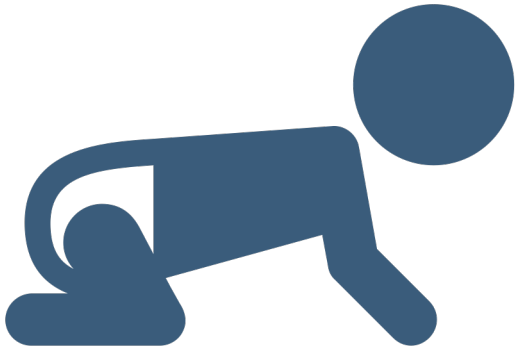
SMN, survival of motor neuron.
Based on Prof. Müller-Felber's clinical experience.

The screening process in the pilot project

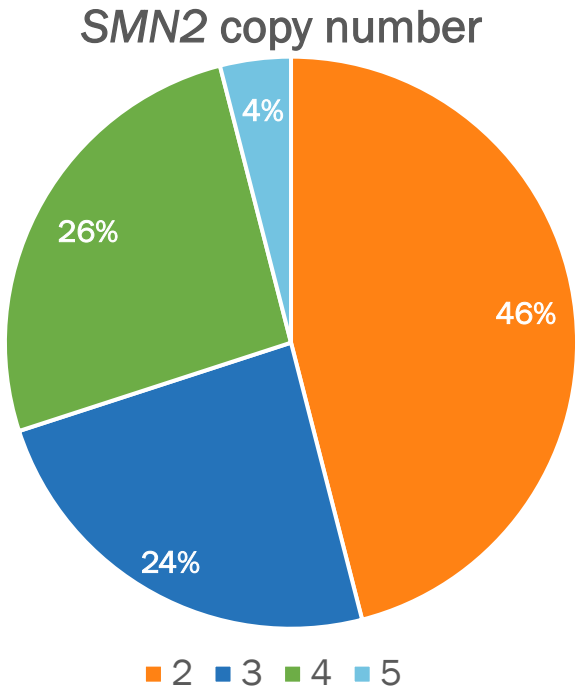


D, day; FTA, Flinders Technology Associates (special card to conserve DNA); LGL, The Bavarian Health and Food Safety Authority; MLPA, multiplex ligation-dependent probe amplification; PCR, polymerase chain reaction; SMN, survival of motor neuron.
1. Based on Prof. Müller-Felber's clinical experience. 2. Nennstiel-Ratzel U, LGL Bayern. Unpublished data, Jan 2021.
3. Vill K, et al. Orphanet J Rare Dis 2021:16;153.

Sensitivity and specificity of the SMA NBS



Newborns screened	N = 553,690
Patients with *SMN1* deletion	n = 67
Confirmed cases	n = 67

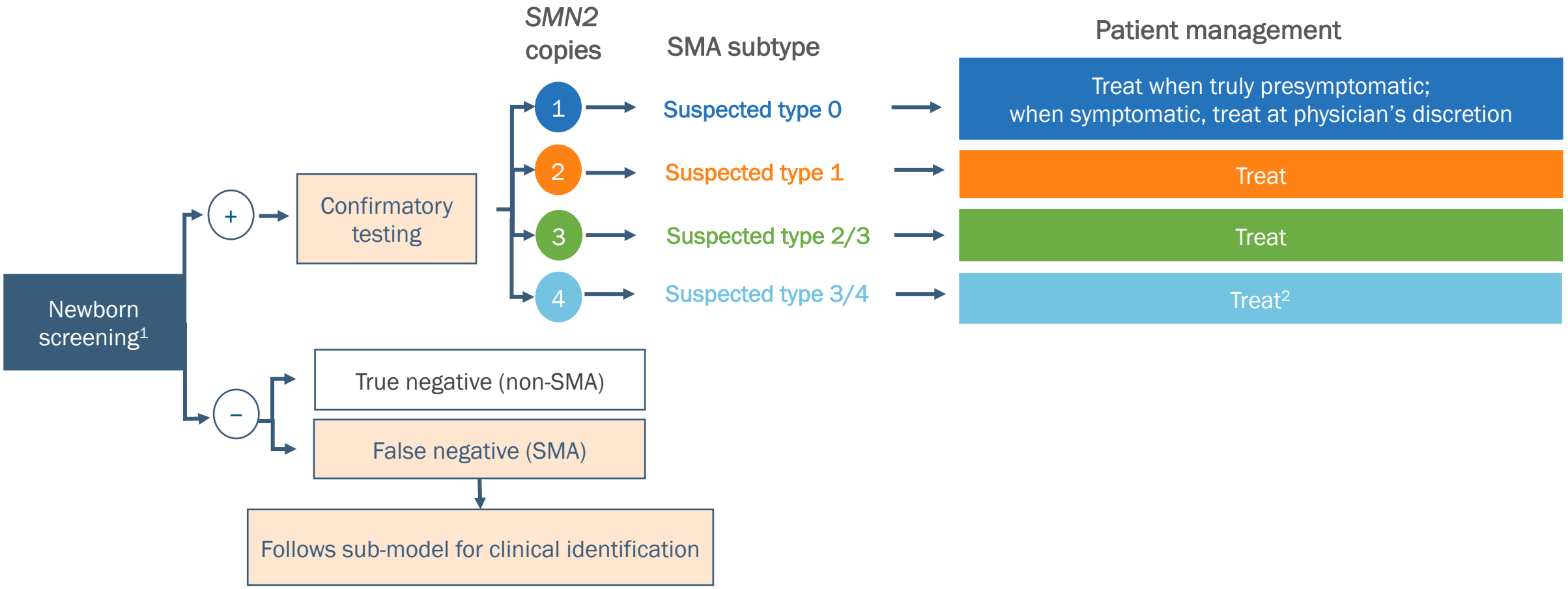


- < 5% of children will not be identified (compound heterozygotes)
- Technical issues are possible when numerous laboratories are involved
- Feedback system is necessary

NBS, newborn screening; SMA, spinal muscular atrophy; SMN, survival of motor neuron.
Vill K, Müller-Felber W. Unpublished data. Sep 2021.

Deciding about treatment

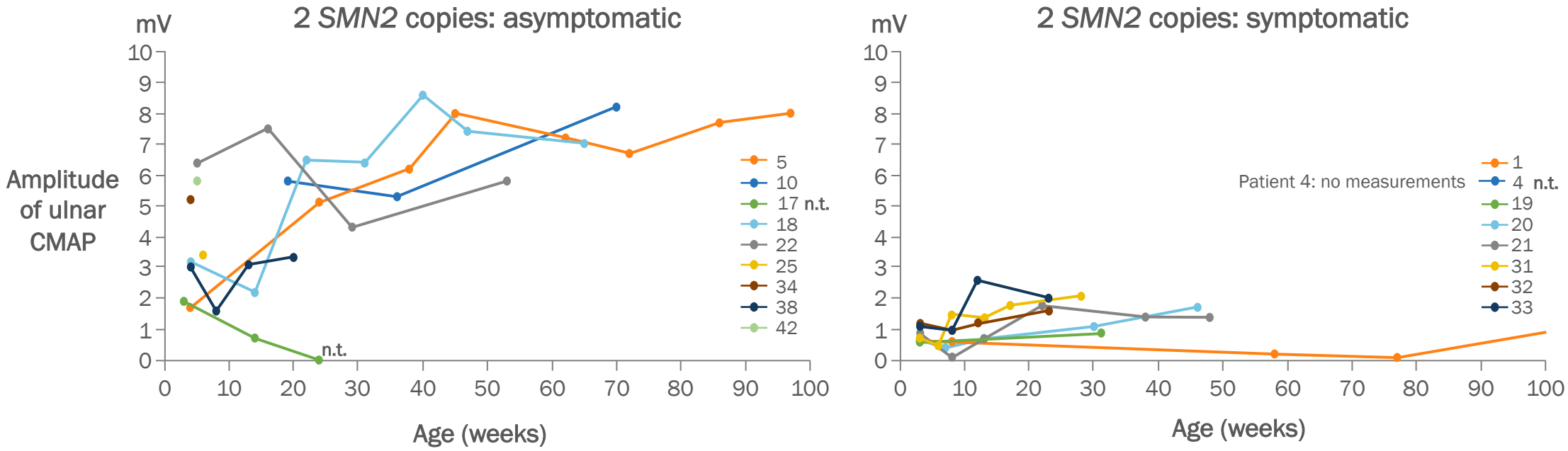
Treatment guidelines by Cure SMA working group, 2020



SMA, spinal muscular atrophy; SMN, survival of motor neuron.
1. Adapted from Glascock, J, et al. J Neuromuscul Dis. 2018;5:145-58. 2. Glascock J, et al J Neuromuscul Dis. 2020;7:97-100.

CMAP: an indicator of motor neuron loss

15/17 children with 2 *SMN2* copies were treated with nusinersen; age at treatment initiation: 14–39 days



All children with 2 *SMN2* copies who eventually turned out to be early symptomatic had low ulnar CMAP amplitudes

CMAP, compound muscle action potential; n.t, not treated; SMA, spinal muscular atrophy; SMN, survival of motor neuron.
Adapted from Vill K, et al. Orphanet J Rare Dis 2021:16;153.

Symptoms and signs in children with 2 *SMN2* copies

Children with first symptoms of SMA (4/21)

- 20 % reduced muscle tone lower extremities
- 33 % decreased/absent DTR
- 35 % CMAPs < 1mV

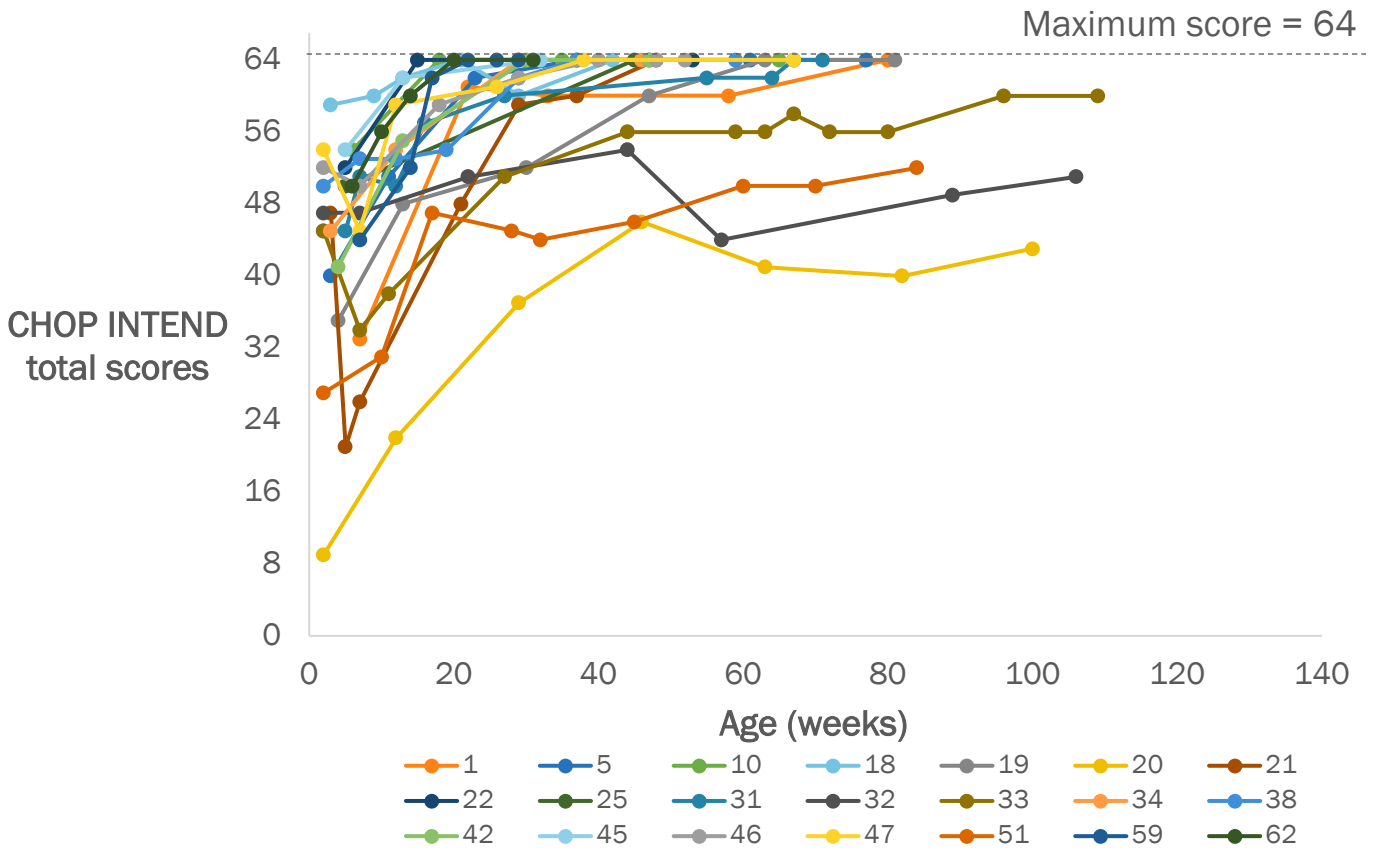
Children without symptoms of SMA (3/21)

- 15 % developed reduced muscle tone and weakness within 4 weeks after first visit

Treatment should be started as soon as possible.

DTR: deep tendon reflexes; SMA, spinal muscular atrophy; SMN, survival of motor neuron.
Schwartz O. J Neuromuscul Dis. 2022 Apr 12. Online ahead of print.

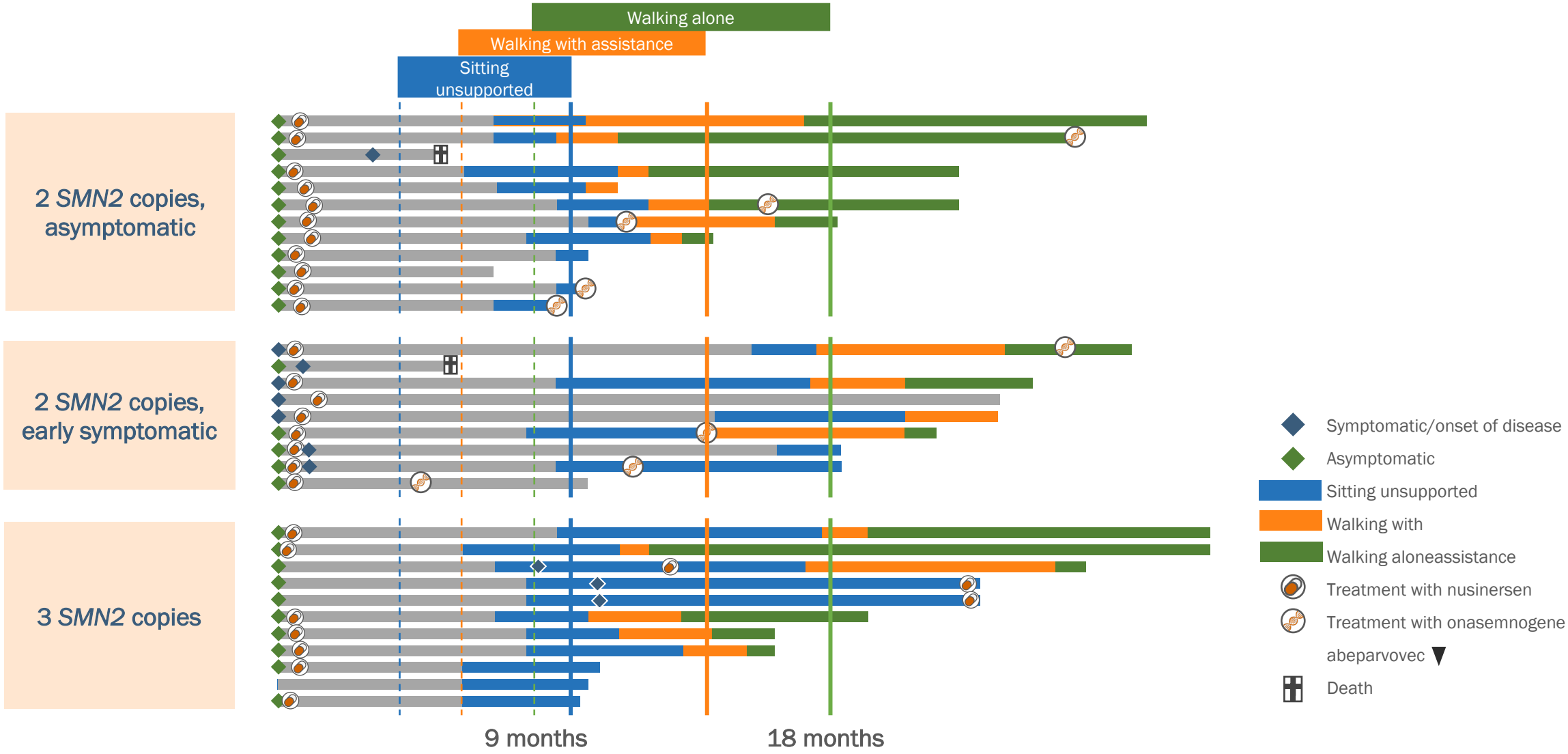
Motor outcome in children with 2 *SMN2* copies after treatment



	Patients, % (n/N)
Motor system	
Proximal weakness	29 % (6/21)
Walking with support	14.5 % (3/21)
Able to sit (SMA type 2)	14.5 % (3/21)
Respiratory	
Respiratory problems	5 % (1/21)
NIV overnight	5 % (1/21)
Nutrition	
Mild chewing problems	14.5 % (3/21)
Tube feeding (gastrostomy)	9.5 % (2/21)

CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; NIV, non-invasive ventilation; SMA, spinal muscular atrophy; SMN, survival of motor neuron.
Adapted from Schwartz O. J Neuromuscul Dis. 2022 Apr 12. Online ahead of print.

WHO motor milestones in children with 2 or 3 *SMN2* copies



SMN, survival of motor neuron; WHO, World Health Organization.
Müller-Felber W, Vill K, Kölbel H, Schwartz O. Unpublished data.

Motor development in children with 2 *SMN2* copies after 3 years of therapy

Therapy started at age 2.5 months

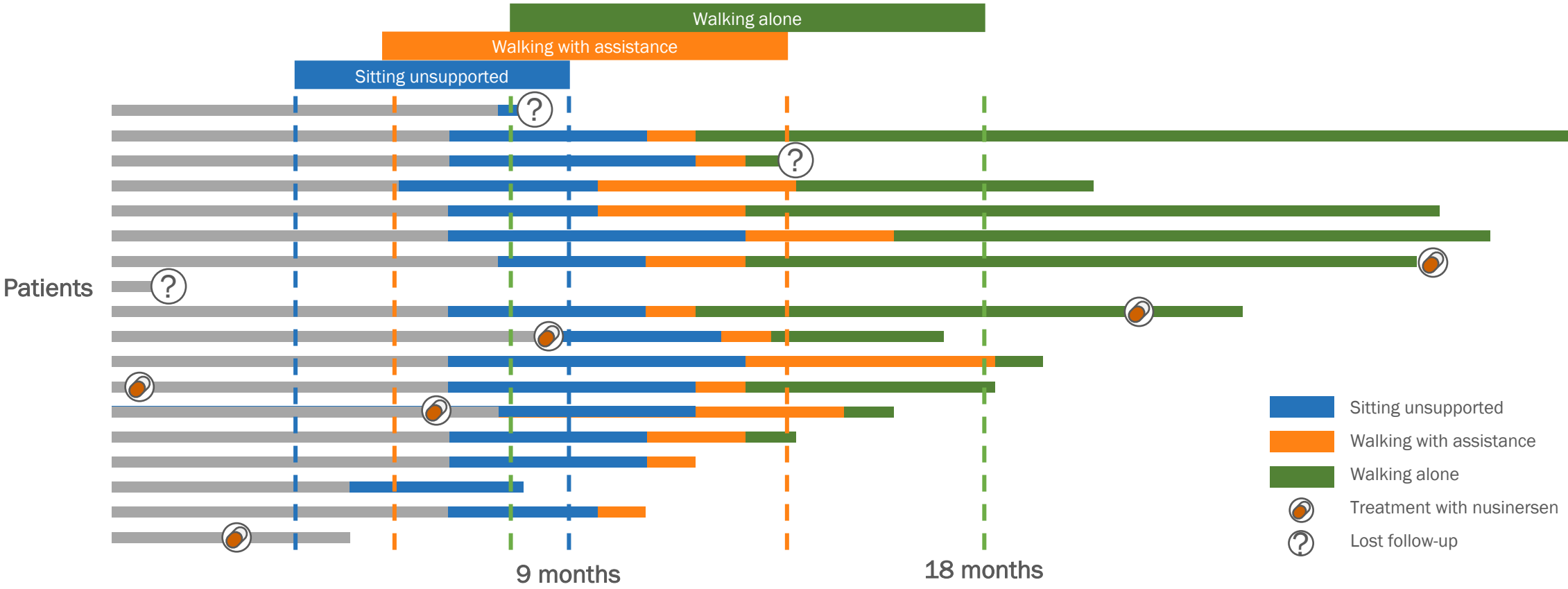
Therapy started at age 2 weeks

Patient outcomes after treatment may differ among individuals. SMN, survival of motor neuron.
Based on Prof Müller-Felber's personal archive.

Patients with 4 *SMN2* copies: to treat or not to treat…

Patient outcomes after treatment may differ among individuals. SMN, survival of motor neuron.
Based on Prof Müller-Felber's personal archive.

WHO motor milestones in children with 4 *SMN2* copies identified by SMA NBS



N = 18

- 3 symptomatic children
- 3 lost follow-up
- 2 with affected relatives with the same *SMN2* copy number

Data from clinical trials ENDEAR[2] and CHERISH[3] show treatment efficacy of nusinersen in patients with infantile and later-onset SMA respectively. Patients who were included in in CHERISH and received nusinersen (n = 84) had 2 to 4 *SMN2* copies. Only 2% of these patients had 4 *SMN2* copies[3]. Patients who were included in ENDEAR and received nusinersen (n=81) had 2 *SMN2* copies2. The incidence and severity of adverse events in both studies were similar between the control and nusinersen group[2,3].

SMA, spinal muscular atrophy; SMN, survival of motor neuron; WHO, World Health Organization.

1. Müller-Felber W, Vill K. Unpublished data. Jan 2021. 2. Finkel RS, et al. N Engl J Med. 2017;377:1723-32. 3. Mercuri E, et al. N Engl J Med. 2018;378:625-35.

No increase in the incidence of SMA due to SMA NBS

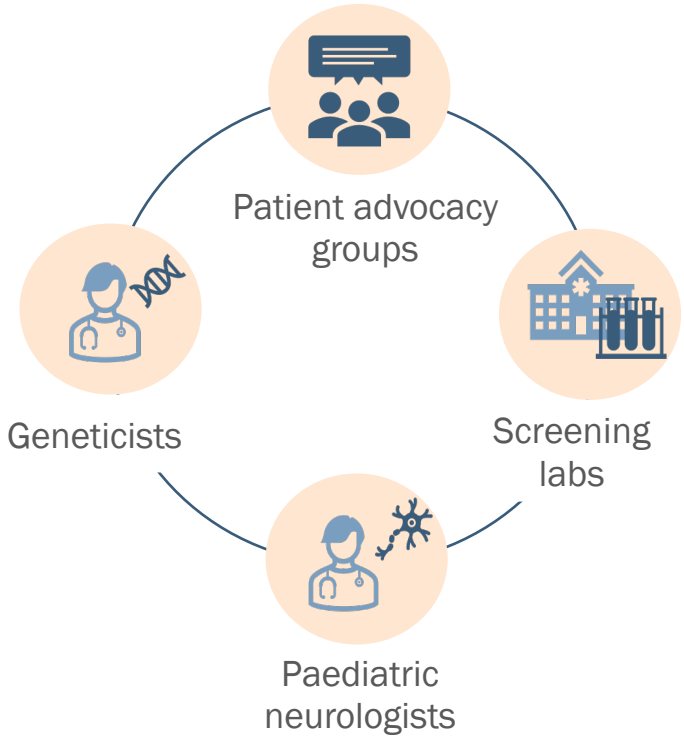
- 1:7,353 = incidence of persons actually affected in Germany 2014[1]
- 1:7,637 = incidence of affected persons according to genetic criteria in screening in 2021- 2022[2]
- Most of the children will develop the disease[2]

NBS, newborn screening; SMA, spinal muscular atrophy.
1. Konig, K, et al. Orphanet J Rare Dis. 2019;14:152. 2. Based on Prof Müller-Felber's clinical experience.

From pilot project to nationwide screening

A national SMA NBS programme was implemented in Germany in 2021[1]

Definition of necessary structures[2]



Feedback systems[2]

- Regular telephone conference with participating neuromuscular centres
- Feedback between the geneticist and screening laboratory
- Benchmarking of the screening process

G-BA, Gemeinsamer Bundesausschuss (The Federal Joint Committee); NBS, newborn screening; SMA, spinal muscular atrophy.
1. G-BA Press Release. Available from: https://www.g-ba.de/presse/pressemitteilungen-meldungen/919/. Accessed April 2022. 2. Based on Prof Müller-Felber's clinical experience. Map available from: https://dgm-behandlungszentren.org. Accessed April 2022.

Concluding remarks

Screening for SMA is technically and organizationally feasible

- Regular communication between neuromuscular centres and clinicians is important
- Network for further care of families is needed

We recommend the implementation of SMA NBS in countries where therapy is available

- Prognosis of children with SMA has been improved dramatically by screening

Careful decisions about treatment

- Children with 2 *SMN2* copies urgently need treatment
- “Wait and see” strategy in cases of patients with 4 *SMN2* copies has to be critically evaluated

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

Prescribing information: Spinraza® (nusinersen) 12 mg solution for injection

Please refer to the Summary of Product Characteristics (SmPC) for further information. Indication: For treatment of 5q Spinal Muscular Atrophy (SMA). **Dosage and administration:** Initiate treatment under supervision of a physician experienced in SMA. The decision to treat should be based on an individualised expert evaluation of the expected benefits and risks for the individual. Recommended dose is 12 mg (5 ml) per administration. Initiate as early as possible after diagnosis with 4 loading doses (days 0, 14, 28 and 63). A maintenance dose should be administered every 4 months thereafter. Continuation of therapy should be reviewed regularly as limited information is available for long term efficacy beyond 3 years of treatment. Spinraza is administered as an intrathecal bolus over 1 to 3 minutes by lumbar puncture using a spinal anaesthesia needle. Treatment should be administered by professionals experienced in the procedure. Sedation and imaging techniques may be required to aid administration. **Contraindications:** Hypersensitivity to nusinersen or any of the excipients. **Special warnings and precautions:** Lumbar puncture: Adverse reactions and complications including serious infection, such as meningitis, may occur as part of the lumbar puncture procedure. Thrombocytopaenia and coagulation abnormalities, including acute severe thrombocytopaenia, have been observed after administration of other subcutaneous or intravenous antisense oligonucleotides. Appropriate testing is recommended prior to administration if clinically indicated. Renal toxicity observed after administration of other subcutaneous or intravenous antisense oligonucleotides. Appropriate testing is recommended prior to administration if clinically indicated. Further evaluation should be considered for persistent elevated urinary protein. Hydrocephalus not related to meningitis or bleeding has been reported. In patients with decreased consciousness, evaluation for hydrocephalus should be considered. The benefits and risks of treatment maintenance/ use of ventriculo-peritoneal shunt should be carefully considered. Excipients: Contains less than 1 mmol sodium and potassium per vial, i.e. essentially sodium and potassium free **Drug interactions:** No interaction studies have been performed. **Pregnancy and lactation:** As a precaution, avoid use in pregnancy. A benefit-risk evaluation of the use during breastfeeding should be undertaken. There are no data on the potential impacts on fertility in humans. **Undesirable effects:** In clinical trials, the most commonly reported side effects were associated with lumbar puncture (headache, vomiting and back pain). Aseptic meningitis, meningitis and hypersensitivity have also been reported with unknown frequency. The incidence of treatment-emergent anti-drug antibodies was low (4%); no AEs of interest were identified from review of the individual treatment-emergent ADA-positive cases. See SmPC for full list of side effects. **Legal classification:** POM. **Pack size and basic NHS price:** Spinraza 12 mg solution for injection: 1 box containing 1 vial £75,000. **Marketing Authorisation number:** *Ireland/Northern Ireland:* EU/1/17/1188/001; *Great Britain:* PLGB 22407/0018. **Marketing Authorisation Holder:** Biogen Netherlands B.V., Prins Mauritslaan 13, 1171 LP Badhoevedorp, The Netherlands. **Date of last revision of Prescribing Information:** March 2022

Adverse events should be reported.

For the UK, reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or via the Yellow Card app available from the Apple App Store or Google Play Store.

Adverse events should also be reported to Biogen Idec on 1800 812 719 in Ireland and 0800 008 7401 in the UK.

European Medicines Agency Summary of Product Characteristics for nusinersen. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/spinraza. Accessed April 2022.

To watch this webinar on demand please visit the Biogen Scientific Lounge

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Biogen-164705. April 2022