European Reference Network
for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

Newborn Screening in Neuromuscular Diseases

Satellite Scientific Symposium organized by ERN EURO-NMD
March, 6th 2025

Newborn screening for spinal muscular atrophy

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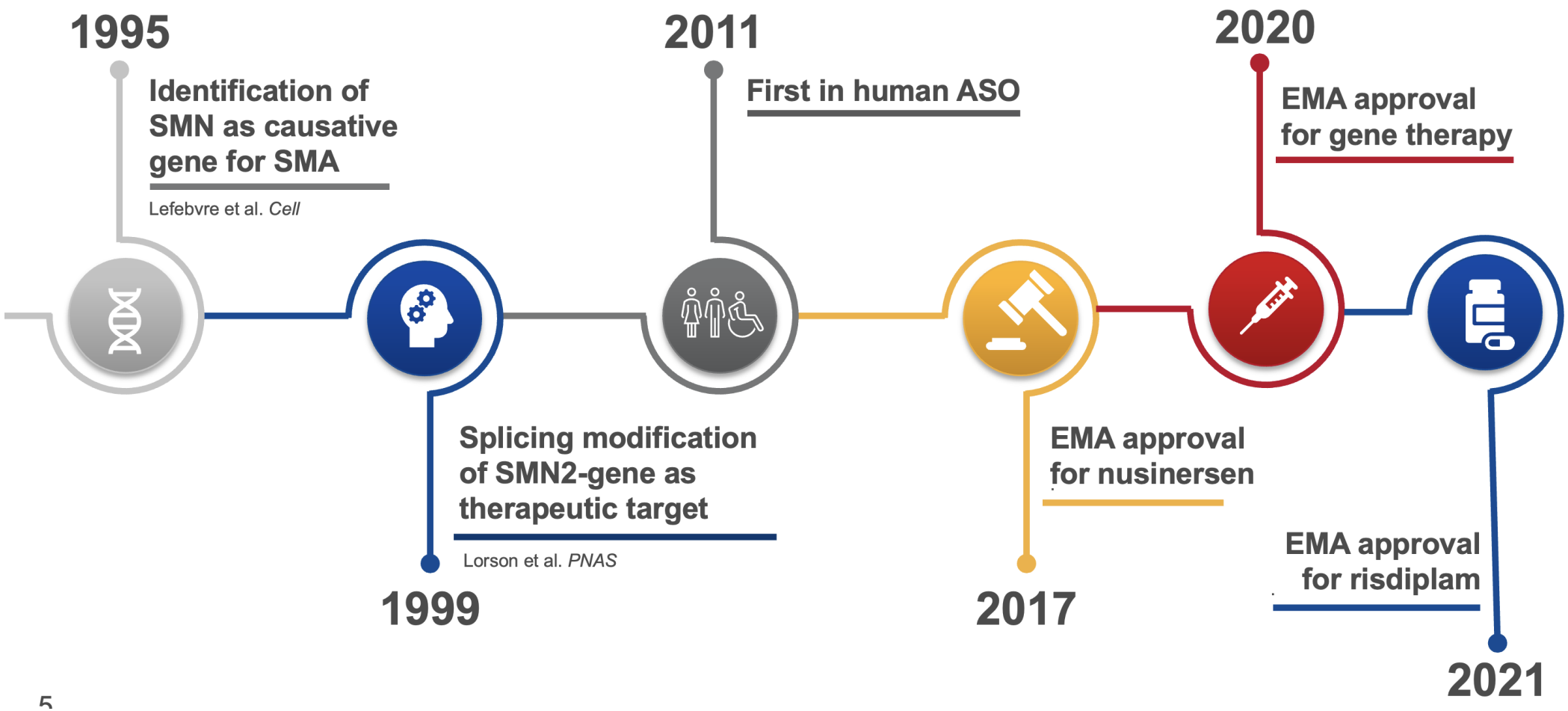
Freiburg Zentrum für Seltene Erkrankungen

DGM Deutsche Gesellschaft für Muskelkranke e. V.

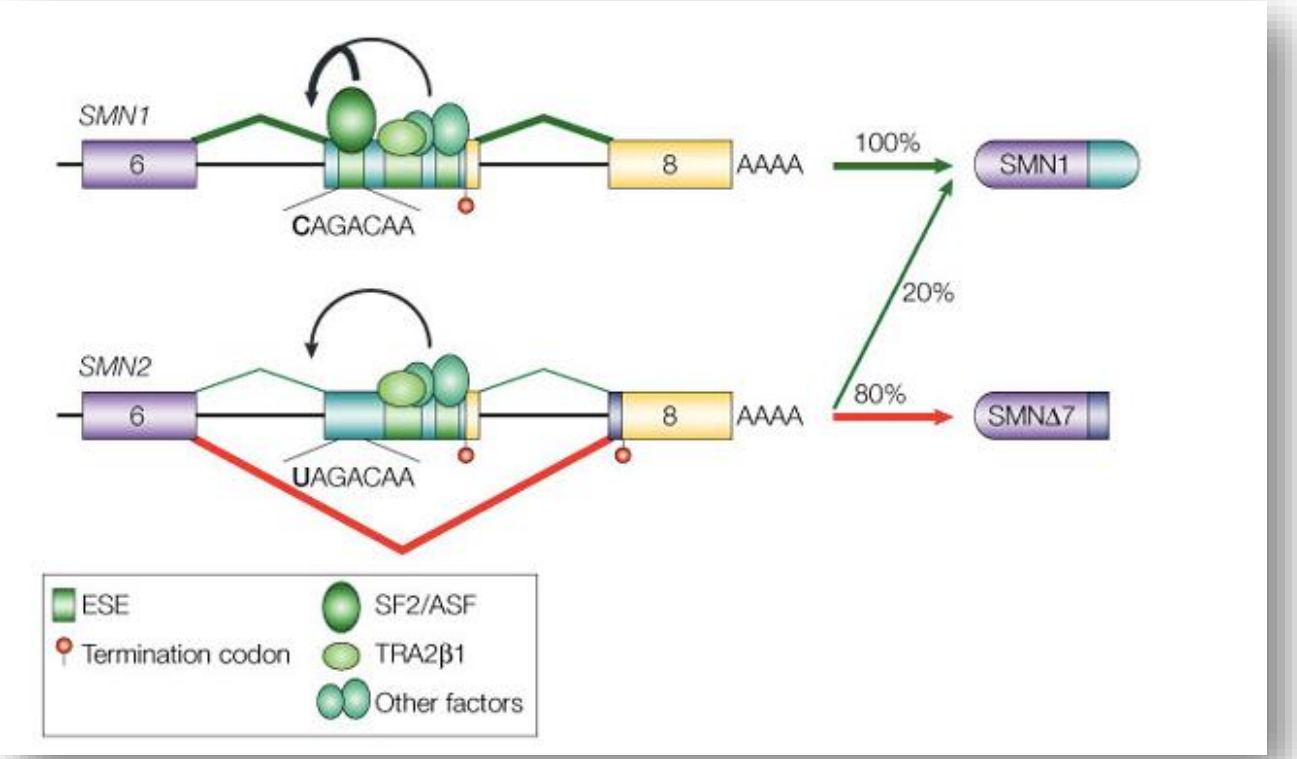
Disclosures

- Investigator for clinical trials sponsored by Biogen, Biohaven, Novartis, Roche, ScholarRock
- Financial support received for the SMArtCARE registry from Biogen, Novartis, and Roche
- Consultancy and educational activities for Biogen, Novartis, and Roche
- Chair of the Data Safety Monitoring Board for Biogen and Genethon

History and Drug Development for SMA



Spinal Muscular Atrophy (SMA) – Therapeutic Approaches



Cartegni et al. Nature Rev Genet 2002

Splicing modification of *SMN2* to increase production of full-length SMN protein

- **Antisense oligonucleotide** (Nusinersen, Spinraza®)
  Intrathecal administration every 4 month
- **Small molecule** (Risdiplam, Evrysdi®)
  Oral application once daily

Addition of intact *SMN1* gene

- **AAV9 based gene therapy**
  Onasemnogene abeparvovec, Zolgensma®
  one-time intravenous application

Clinical trials for pre-symptomatic treatment

- **NUTURE study** started 2015 and enrolled 15 presymptomatic infants with 2 and 10 infants with 3 copies of SMN2 treated pre-symptomatically with nusinersen (Crawford et al. Musc Nerve 2023)
- **SPR1NT study** started 2018 and enrolled 14 infants with 2 copies and 15 children with 3 copies of SMN2 treated pre-symptomatically with onasemnogene abeparvovec (Strauss et al. Nat Med 2022)
- **RAINBOWFISH study** started 2019 and enrolled 5 infants with 2 copies of SMN2 and 18 infants with 3 or more copies of SMN2 treated pre-symptomatically with risdiplam (Servais et al. WMS 2024)

Clinical trials for pre-symptomatic treatment

Table 4. Summary of results from clinical trials.

	Study (Drug)	*N*	Mean Follow-Up (mo)	Follow-Up Range (mo)	Mean Age at Treatment (Days)	Age Range (Days)	Sitter < 9 Months	Sitter < 18 Months	Walker < 18 Months	Walker < 3 Years
Two copies of *SMN2*	NURTURE (nusinersen)	15	59	47–68	19	8–41	11 (73%)	15 (100%)	6 (40%)	13 (87%)
	SPR1NT (gene therapy)	14	18	18	20	8–34	11 (76%)	14 (100%)	5 (36%)	9 (64%) [a]
	Rainbowfish (risdiplam)	4	12	12–15	26	16–40	1 (33%)	4 (100%)	1 (33%)	1 (33%) [a]
	Total	33	36	12–68	22	8–41	23 (70%)	33 (100%)	12 (36%)	23 (70%) [a]
Three copies of *SMN2*	NURTURE (nusinersen)	10	59	47–68	22	3–42	10 (100%)	10 (100%)	10 (100%)	10 (100%)
	SPR1NT (gene therapy)	15	24	24	32	9–43	11 (78%)	15 (100%)	11 (78%)	14 (93%) [a]
	Rainbowfish (risdiplam)	3 [b]	13	12–15	26	16–40	3 (100%)	3 (100%)	3 (100%)	3 (100%) [a]
	Total	28	35	12–68	27	3–42	24 (86%)	28 (100%)	24 (86%)	27 (96%) [a]

Abbreviation: *n*, number of patients, [a] Follow-up shorter than 3 years. [b] One patient was reported as having atypical 2–3 copies.

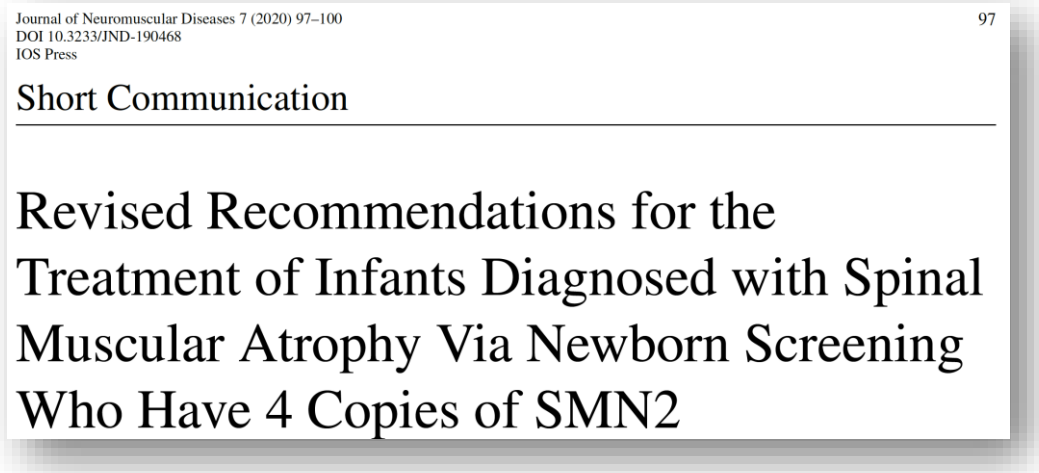
Aragon-Gawinska et al., Genes 2023

Newborn screening for SMA – technical approach

- Genetic test for homozygous deletions of *SMN1* (sensitivity about 95%)
- Quantitative PCR of DNA extracted from dry blood spot (DBS)
- Heterozygous carriers are not detected
- Specificity of the assays almost 100%
- Costs per sample around 5 EUR (about 50 000 EUR to detect a single case)

Newborn screening for SMA – approach for positive cases

- **Positive Screening confirmed by MLPA with determination of SMN2 copy number**
- **Treatment initiation dependent on *SMN2* copy number**
  - Patients with ≤ 3 *SMN2* copies → immediate treatment initiation
  - Patients with 4 *SMN2* copies → recommendation revised to timely treatment
  - Patients with >4 *SMN2* copies → watch and wait strategy


Journal of Neuromuscular Diseases 7 (2020) 97–100
DOI 10.3233/JND-190468
IOS Press

Short Communication

Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2

Newborn screening for SMA – 4 copies of *SMN2*

RESEARCH ARTICLE

Clinical Phenotype of Pediatric and Adult Patients With Spinal Muscular Atrophy With Four *SMN2* Copies: Are They Really All Stable?

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Giorgia Coratti, PhD,[1,2] Stefania Fiori, MLT,[3] Costanza Cutrona, MD,[1]
Adele D'Amico, PhD,[4] Valeria A. Sansone, PhD,[5] Claudio Bruno, PhD,[6]
Sonia Messina, PhD,[7] Tiziana Mongini, PhD,[8] Michela Coccia, MD,[9]
Gabriele Siciliano, PhD,[10] Elena Pegoraro, PhD,[11] Riccardo Masson, MD,[12]
Massimiliano Filosto, PhD,[13] Giacomo P. Comi, PhD,[14,15] Stefania Corti, PhD,[14,15]
Dario Ronchi, PhD,[14,15] Lorenzo Maggi, MD,[16] Maria G. D'Angelo, PhD,[17]
Veria Vacchiano, MD,[18] Chiara Ticci, MD
Lorenzo Verriello, MD,[21] Federica S. Ricci, M
Maria Antonietta Maioli, PhD,[23] Matteo Garibald
Stefano C. Previtali, PhD,[27] Maria Carmela Per
Marika Pane, PhD,[1,2] Francesco Danil
Eugenio Mercuri, PhD,[1,2‡] on behalf o

Journal of Neurology (2024) 271:2787–2797
https://doi.org/10.1007/s00415-024-12188-5

ORIGINAL COMMUNICATION

Check for updates

5qSMA: standardised retrospective natural history assessment in 268 patients with four copies of *SMN2*

Katharina Vill[1,2] · Moritz Tacke[1] · Anna König[1] · Matthias Baumann[3] · Manuela Baumgartner[4] · Meike Steinbach[5] · Guenther Bernert[6] · Astrid Blaschek[1] · Marcus Deschauer[7] · Marina Flotats-Bastardas[8] · Johannes Friese[9] · Susanne Goldbach[37] · Martin Gross[11] · René Günther[12] · Andreas Hahn[13] · Tim Hagenacker[14] · Erwin Hauser[15] · Veronka Horber[16] · Sabine Illsinger[17] · Jessika Johannsen[18] · Christoph Kamm[19] · Jan C. Koch[20] · Heike Koelbel[21] · Cornelia Koehler[22] · Kirsten Kolzter[23] · Hanns Lochmüller[24,25] · Albert Ludolph[26,53] · Alexander Mensch[27] · Gerd Meyer zu Hoerste[28] · Monika Mueller[29] · Wolfgang Mueller-Felber[1] · Christoph Neuwirth[30] · Susanne Petri[31] · Kristina Probst-Schendzielorz[32] · Manuel Pühringer[33] · Robert Steinbach[34] · Ulrike Schara-Schmidt[21] · Mareike Schimmel[35] · Bertold Schrank[36] · Oliver Schwartz[10] · Kurt Schlachter[38] · Annette Schwerin-Nagel[39] · Gudrun Schreiber[40] · Martin Smitka[41] · Raffi Topakian[42] · Regina Trollmann[43] · Matthias Tuerk[44,45] · Manuela Theophil[46] · Christian Rauscher[47] · Mathias Vorgerd[48] · Maggie C. Walter[49] · Markus Weiler[50] · Claudia Weiss[51] · Ekkehard Wilichowski[52] · Claudia D. Wurster[53] · Gilbert Wunderlich[54,55] · Daniel Zeller[56] · Andreas Ziegler[57] · Janbernd Kirschner[22] · Astrid Pechmann[22] · SMArtCARE study group

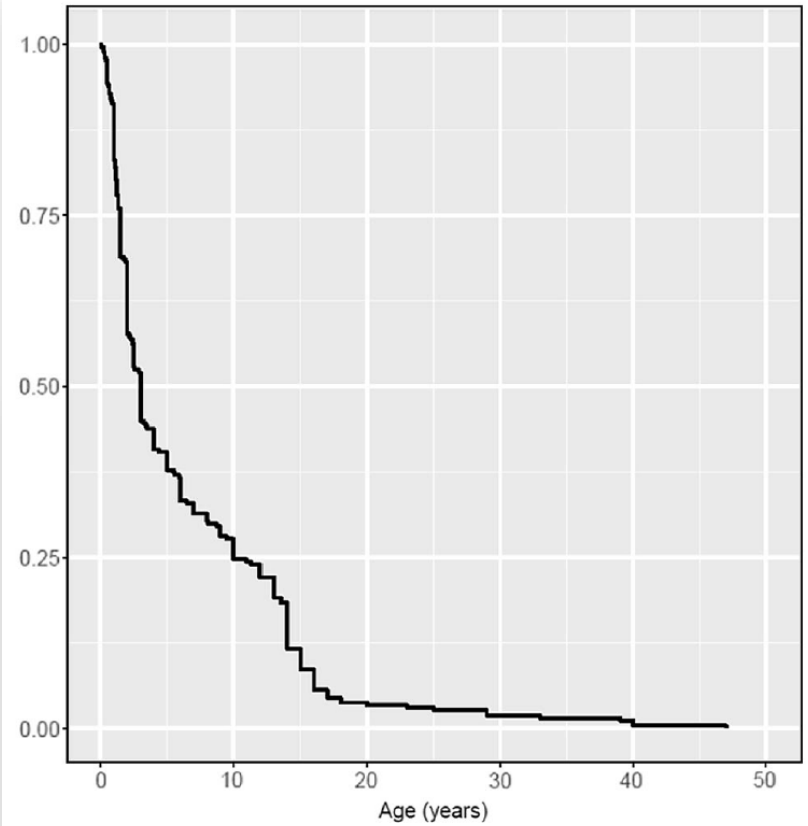

Fig. 1 Kaplan–Meier curve for age at disease onset: by the age of 18 years, approximately 95% of patients with four copies of *SMN2* was affected by the disease

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Newborn Screening for SMA – real world experience

JAMA Pediatrics | Original Investigation

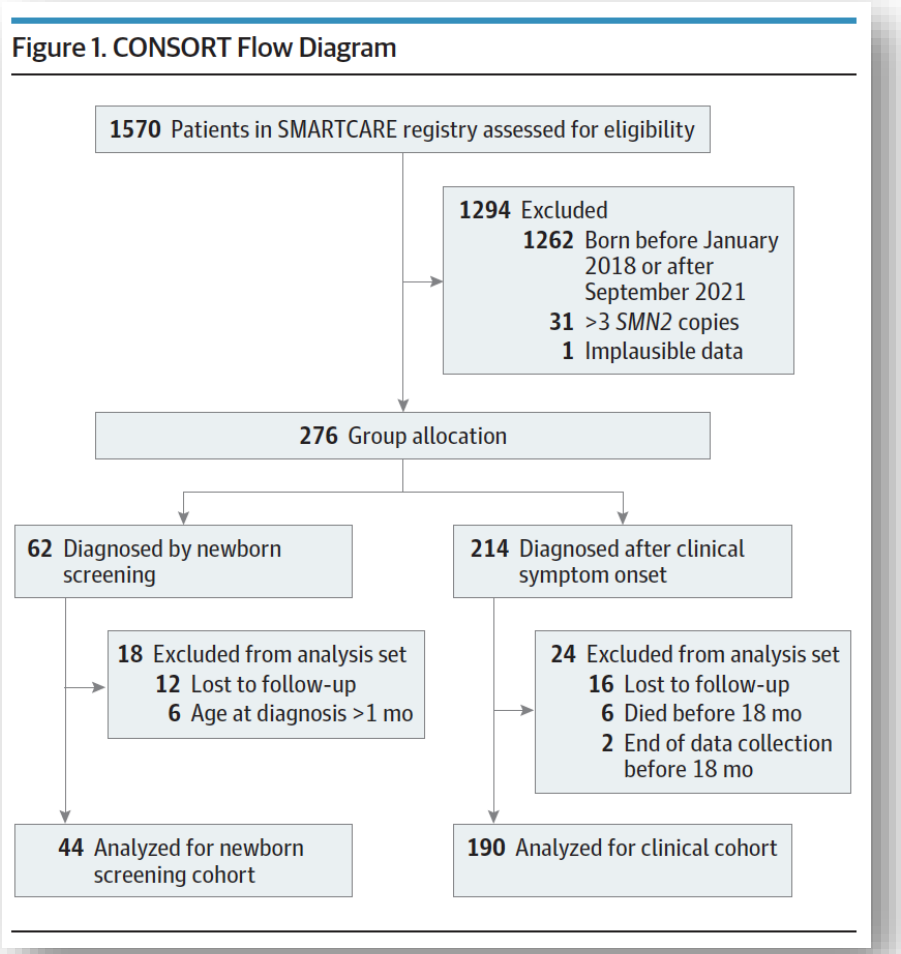
Clinical Effectiveness of Newborn Screening for Spinal Muscular Atrophy
A Nonrandomized Controlled Trial

Oliver Schwartz, MD; Katharina Vill, MD; Michelle Pfaffenlehner, MS; Max Behrens, MS; Claudia Weiß, MD; Jessika Johannsen, MD; Johannes Friese, MD; Andreas Hahn, MD; Andreas Ziegler, MD; Sabine Illsinger, MD; Martin Smitka, MD; Arpad von Moers, MD; Heike Kölbel, MD; Gudrun Schreiber, MD; Nadja Kaiser, MD; Ekkehard Wilichowski, MD; Marina Flotats-Bastardas, MD; Ralf A. Husain, MD; Matthias Baumann, MD; Cornelia Köhler, MD; Regina Trollmann, MD; Annette Schwerin-Nagel, MD; Astrid Eisenkölbl, MD; Mareike Schimmel, MD; Martin Fleger, MD; Birgit Kauffmann, MD; Gert Wiegand, MD; Manuela Baumgartner, MD; Christian Rauscher, MD; Sebahattin Cirak, MD; Dieter Gläser, MD; Günther Bernert, MD; Tim Hagenacker, MD; Susanne Goldbach, BA; Kristina Probst-Schendzielorz, PharmD; Hanns Lochmüller, MD; Wolfgang Müller-Felber, MD; Ulrike Schara-Schmidt, MD; Maggie C. Walter, MD; Janbernd Kirschner, MD; Astrid Pechmann, MD; for the SMARTCARE study group

Regional pilot project for newborn screening

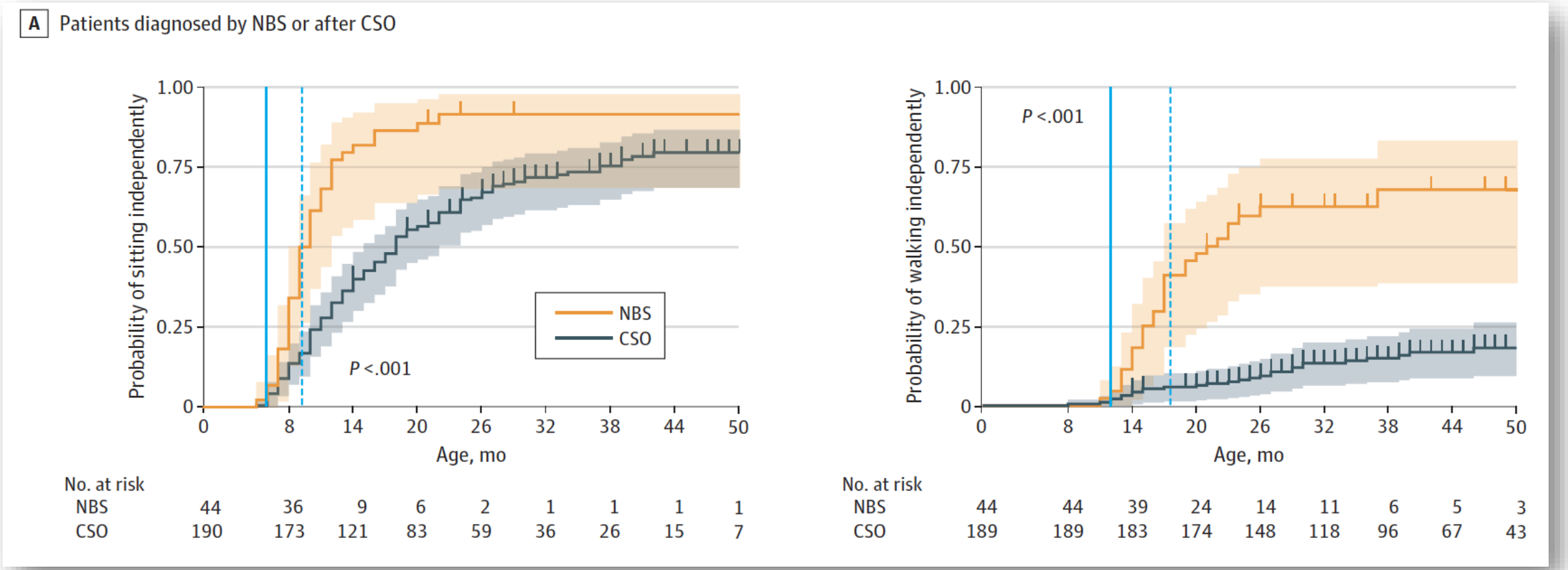
276 infants born between Jan 2018 and Sept 2021

Parallel control group comparing patients diagnosed by screening and those diagnosed clinically



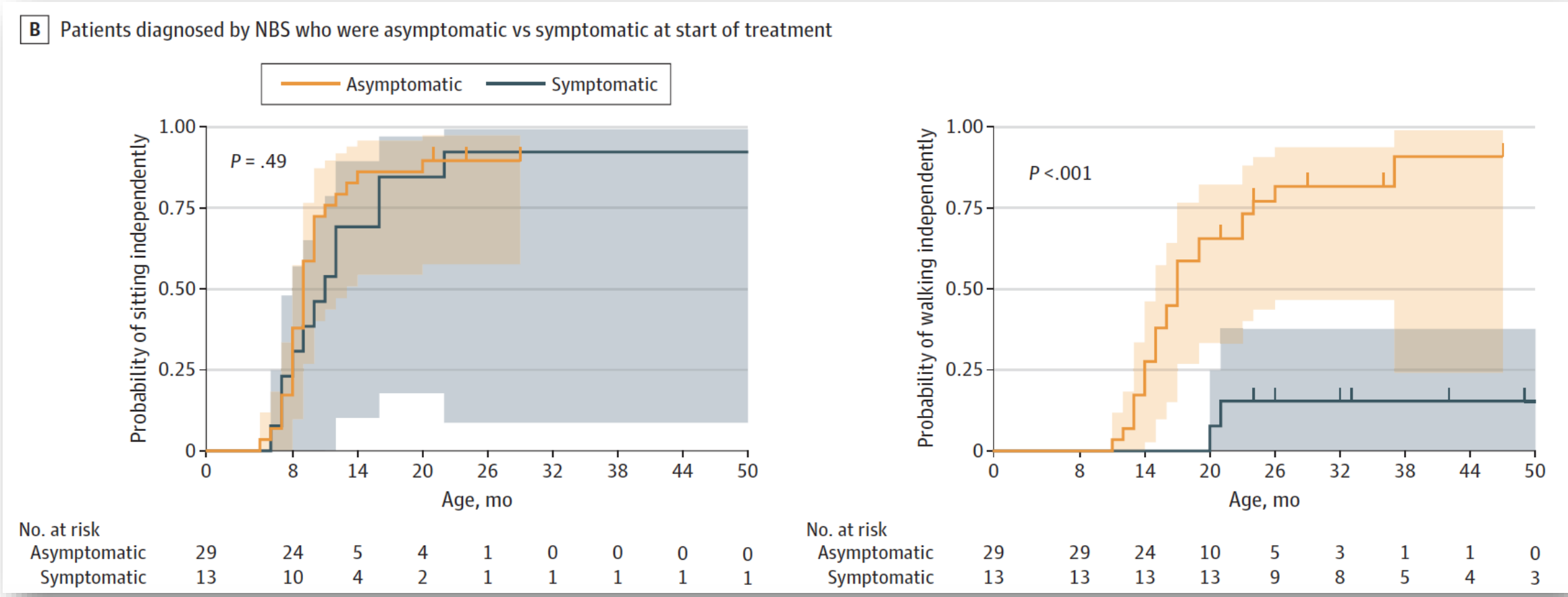
Schwarz et al. JAMA Pediatrics 2024

Newborn Screening for SMA – real world experience



Schwarz et al. JAMA Pediatrics 2024

Newborn Screening for SMA – real world experience



Schwarz et al. JAMA Pediatrics 2024

Newborn screening for SMA – cost effectiveness

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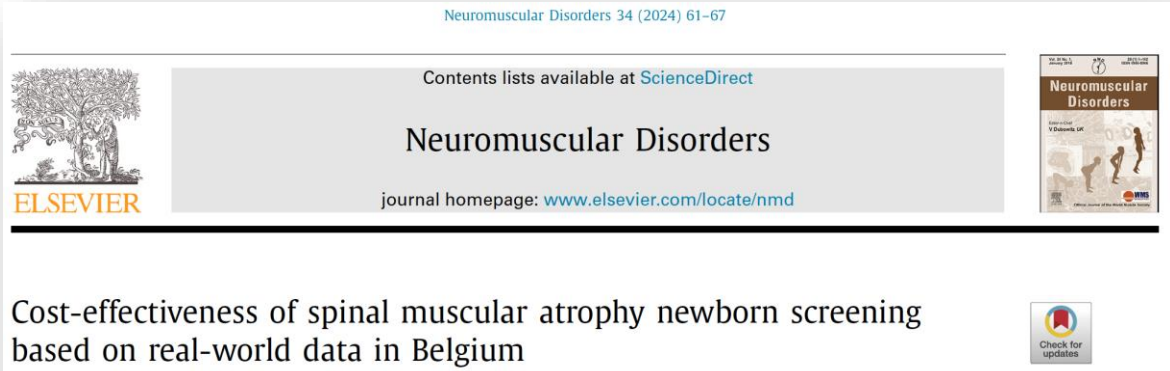
Journal homepage: www.elsevier.com/locate/jval

Economic Evaluation

Cost-Effectiveness of Newborn Screening for Spinal Muscular Atrophy in The Netherlands

Rimma Velikanova, MSc, Simon van der Schans, MSc, Matthias Bischof, PhD, Rudolf Walther van Olden, MD, PhD, Maarten Postma, PhD, Cornelis Boersma, PhD



Neuromuscular Disorders 34 (2024) 61–67

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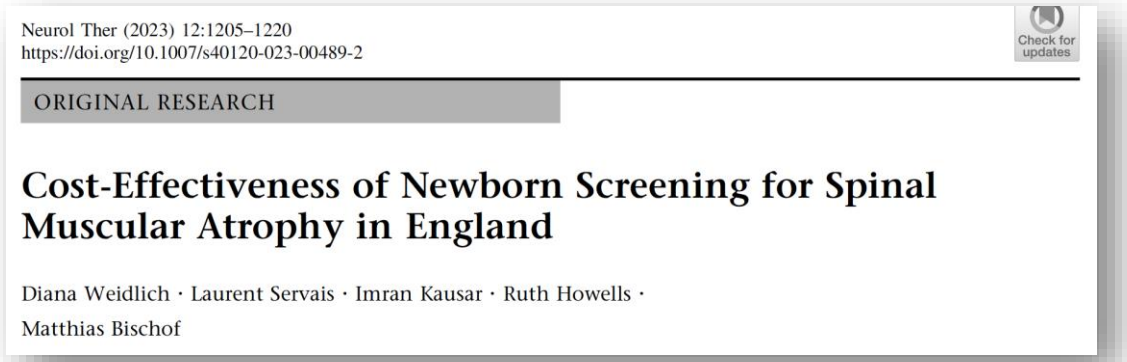
Contents lists available at ScienceDirect

Neuromuscular Disorders

journal homepage: www.elsevier.com/locate/nmd

Cost-effectiveness of spinal muscular atrophy newborn screening based on real-world data in Belgium

Tamara Dangouloff[a,*], Praveen Thokala[b], Matthew D Stevenson[b], Nicolas Deconinck[c], Adèle D'Amico[d], Aurore Daron[a], Stephanie Delstanche[a], Laurent Servais[a,e], Mickael Hiligsmann[f]

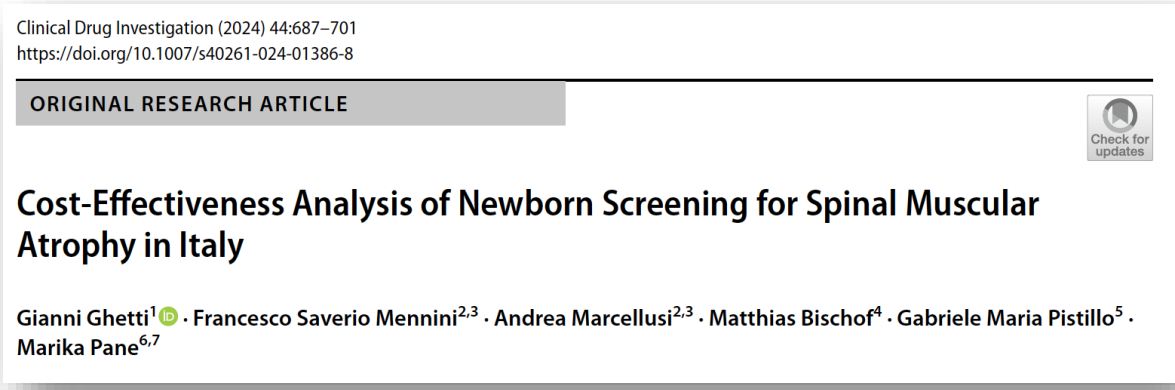


Neurol Ther (2023) 12:1205–1220
https://doi.org/10.1007/s40120-023-00489-2

ORIGINAL RESEARCH

Cost-Effectiveness of Newborn Screening for Spinal Muscular Atrophy in England

Diana Weidlich · Laurent Servais · Imran Kausar · Ruth Howells · Matthias Bischof



Clinical Drug Investigation (2024) 44:687–701
https://doi.org/10.1007/s40261-024-01386-8

ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness Analysis of Newborn Screening for Spinal Muscular Atrophy in Italy

Gianni Ghetti[1] · Francesco Saverio Mennini[2,3] · Andrea Marcellusi[2,3] · Matthias Bischof[4] · Gabriele Maria Pistillo[5] · Marika Pane[6,7]

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Newborn screening for SMA – implementation

Research Article

Newborn screening programs for spinal muscular atrophy worldwide in 2023

Journal of Neuromuscular Diseases
2024, Vol. 11(6) 1180–1189

DOI: 10.1177/22143602241288095
journals.sagepub.com/home/jnd

Eva Vrščaj[1,*], Tamara Dangouloff[2,*], Damjan Osredkar[1,3,#], Laurent Servais[2,4,#] and the SMA NBS World Study Group

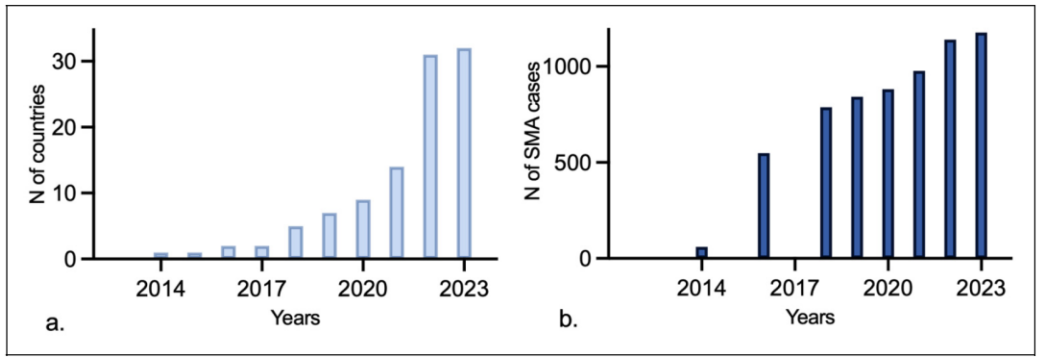

Figure 3. A: Number of countries with SMA NBS programs by year. b: Number of SMA cases identified by SMA NBS worldwide by year.

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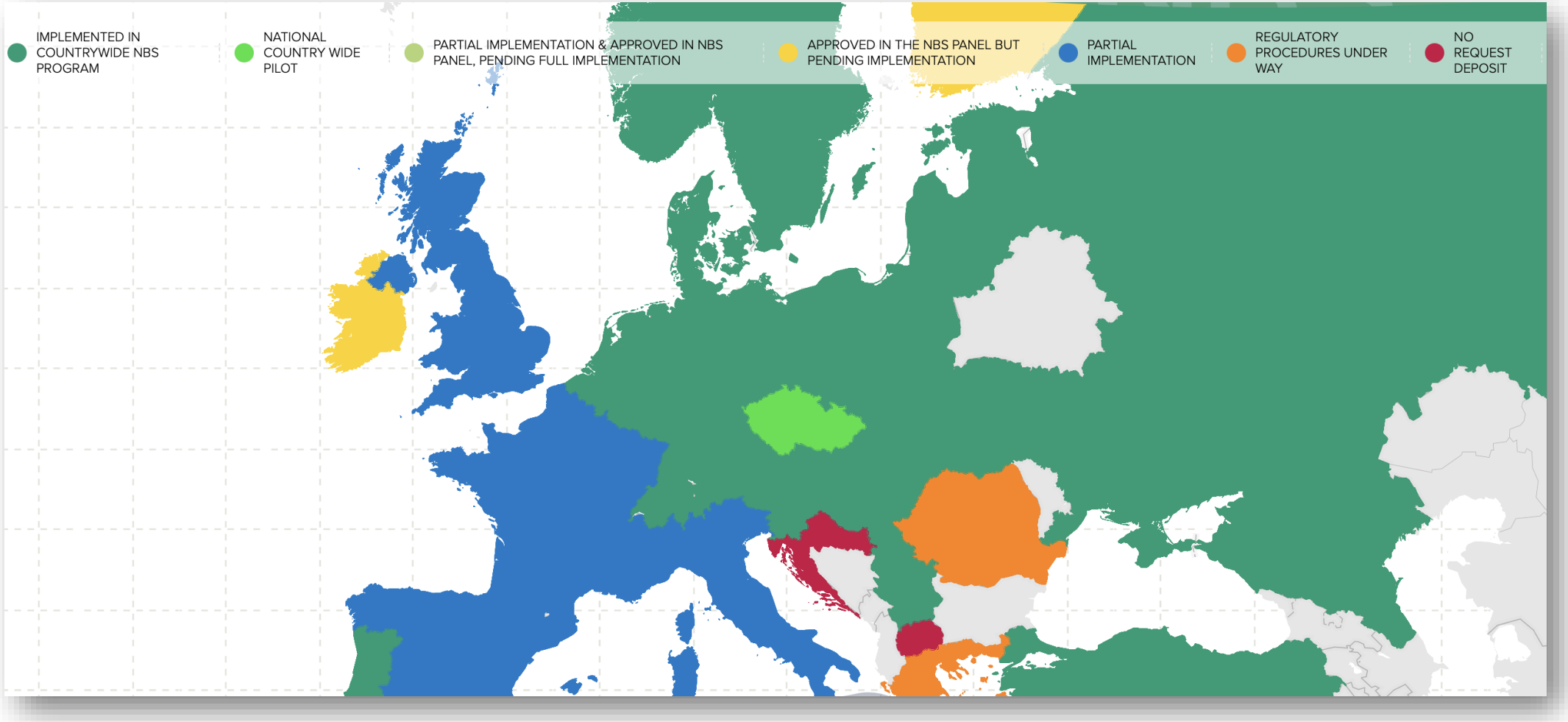
Newborn screening for SMA – implementation



https://www.sma-screening-alliance.org/map

Conclusions and Challenges

- Clinical trials for all three disease modifying treatments have shown that **treatment initiation in the pre-symptomatic phase is associated with significantly better outcome.**
- *Real-world experience with newborn screening has shown that about **30-40% of patients with 2 SMN2 copies are already symptomatic** when diagnosed and this is associated with **poorer outcome.***
- ***Cost effectiveness of newborn screening for SMA** has been shown for several European countries.*
- *Additional efforts are needed to further make **NBS and treatments available to all infants** and to reduce the **time between diagnosis and treatment** initiation.*
- *Patients with **2 copies of SMN2 often remain with significant disease burden.** Additional efforts are needed to **improve outcome** (e.g. early/prenatal tx, bridging tx).*
- ***Long term observational studies are needed** to monitor long-term effectiveness and safety of NBS and pre-symptomatic treatment initiation in different cohorts.*

Thank you!

SMArtCARE study team Freiburg

Members of the SMArtCARE Steering Committee

Investigators and evaluators at participating centres

Clinical Trials Unit Freiburg

Harald Binder, Michelle Pfaffenlehner, Max Behrens
Institute of Medical Biometry and Statistics (IMBI)

All contributing patients and families

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