European Reference Network
for rare or low prevalence complex diseases

Network Neuromuscular Diseases (ERN EURO-NMD)

7th ERN EURO-NMD ANNUAL MEETING

21st – 23rd February 2024

NBS
Neuromuscular Disorders

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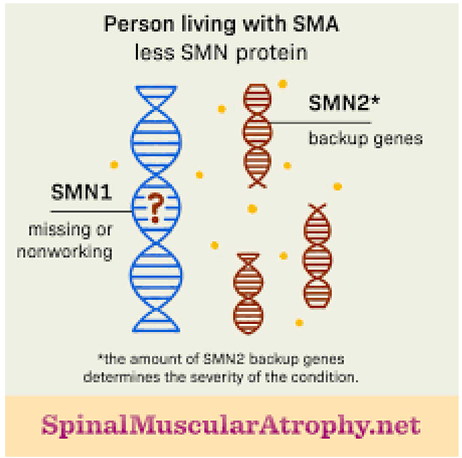
Disclosures

- Tecnifar, EISAI, Angelini, Bial, PTC, Roche, Biogen, Novartis, Sanoffi, Biomarin

Points

- NBS – Disease modifiers
- Spinal Muscular Atrophy
- Other neuromuscular disorders – DD
- Comments

Spinal Muscular Atrophy



Progressive – weakness: axial, proximal and lower limbs, bulbar
Tipo 0 – severe. death

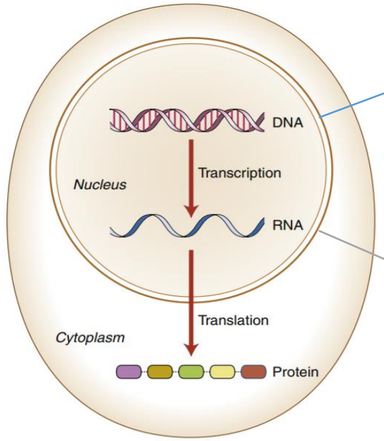
Tipo 1 – 60% Onset 1- 6 meses. Death<2Y

Tipo 2 – > 6M. Seat, not walkers

Tipo 3 – >2Y, majority second decade . Walk – loss ambulation

Tipo 4 – later

SMA - New drugs + Care teams



Target: *SMN1* mutation[1]
DNA-based strategy: gene therapy (onasemnogene abeparvovec)

Target: *SMN2* splicing[1]
RNA-based strategy: antisense oligonucleotides (nusinersen) and small molecules (risdiplam)

1. Mercuri E, et al. *Nat Rev Neurol*. 2020;16:706–15; 2.Eduardo F. Tizzano and Richard S. Finkel. «Spinal muscular atrophy: A changing phenotype beyond the clinical trials" Neuromuscular Disorders 2017

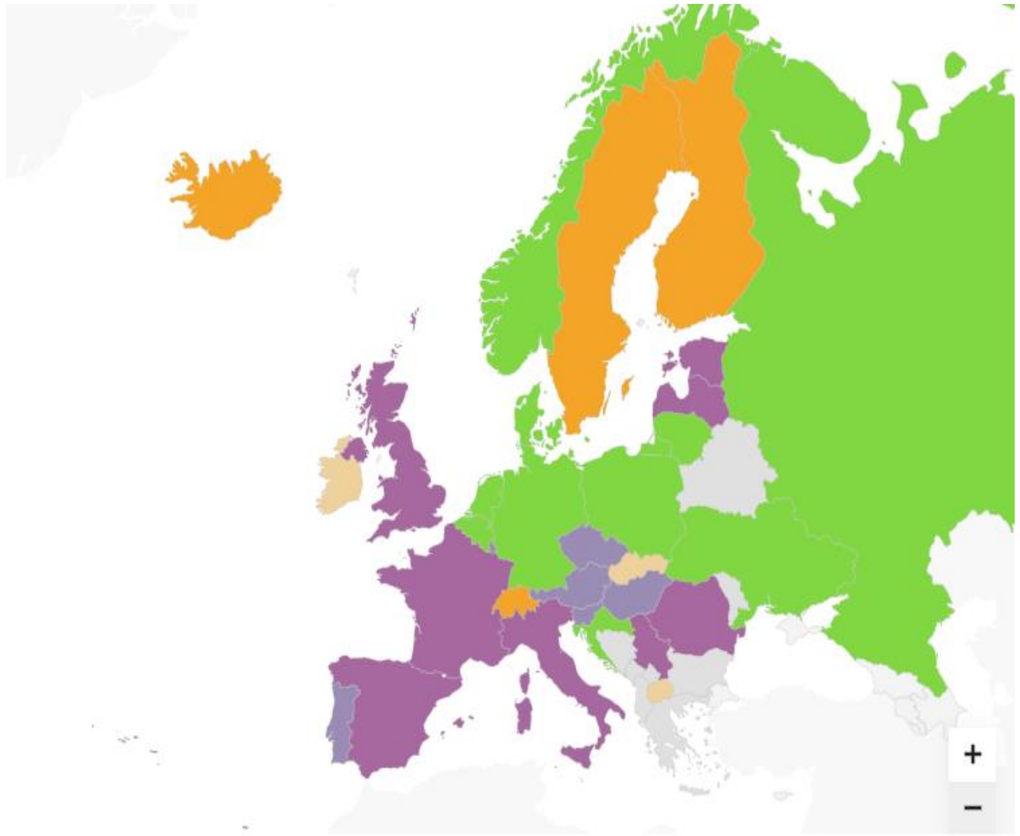
New drugs

- What we learned :
  - The sooner the better
  - Not all patient have same results
  - Pre symptomatic treatment

NBS

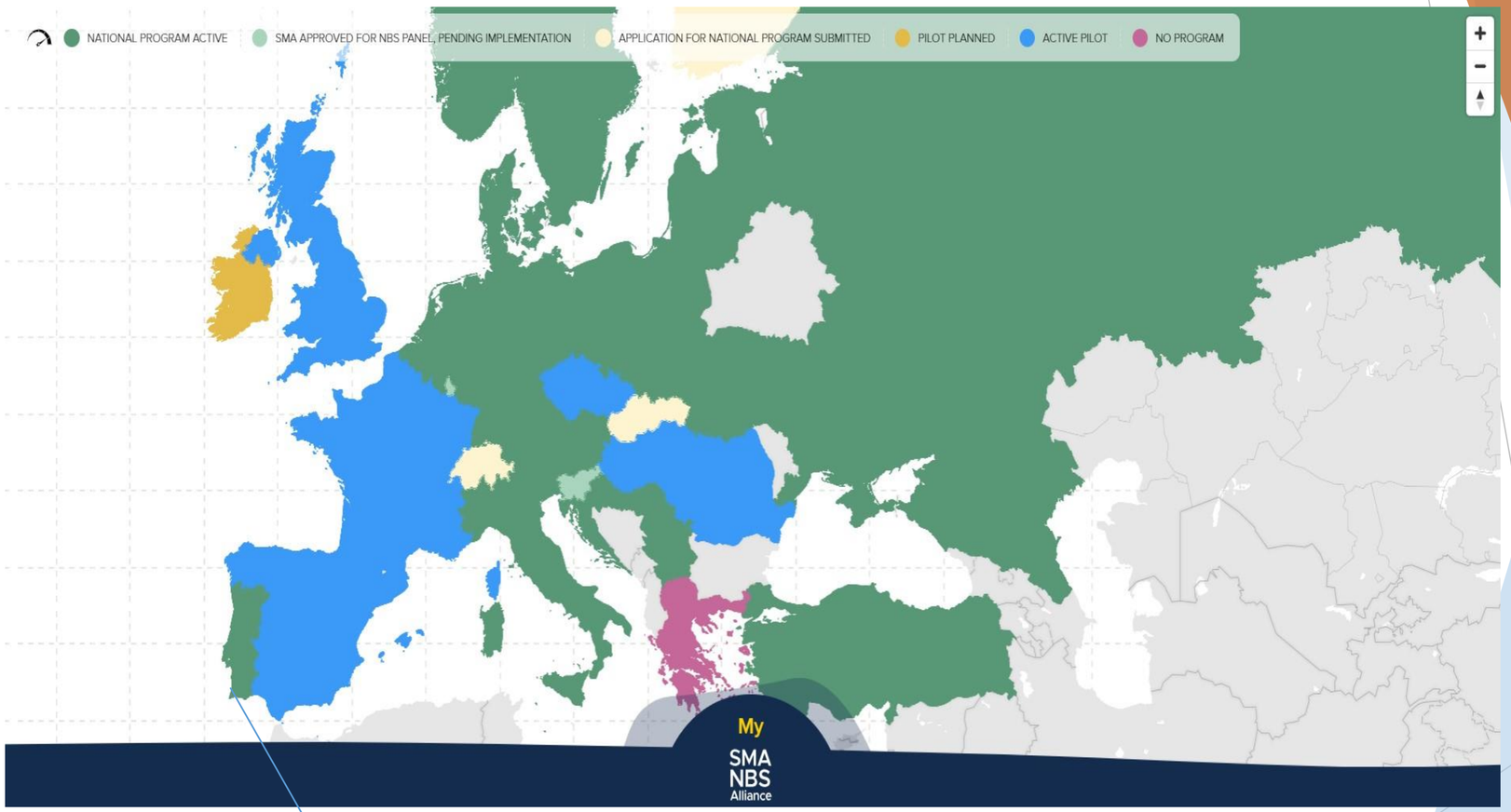
2018 – Belgium, Germany

NBS – SMA in Europe mars 2023



1. Map – SMA Newborn Screening Alliance (sma-screening-alliance.org

NBS – SMA in Europe nov 2023



Ireland, - starting

Pilot

2024 slovakia,
luxemburg, Greece

NBS in SMA

But: 40 to 55% of patients with 2 copies are symtomatic at first observation/treatment

Journal of Neuromuscular Diseases 9 (2022) 389–396
DOI 10.3233/JND-220789
IOS Press

Research Report

Spinal Muscular Atrophy – Is Newborn Screening Too Late for Children with Two *SMN2* Copies?

Oliver Schwartz[a], Heike Kölbel[b], Astrid Blaschek[c], Dieter Gläser[d], Siegfried Burggraf[e], Wulf Röschinger[e], Ulrike Schara[b], Wolfgang Müller-Felber[c] and Katharina Vill[c,*]

Greenway for SMA treatment

Different from country to country , center to center

NBS in neuromuscular disorders: D Duchenne

Duchenne Muscular Dystrophy
X linked
High Ck

Symptoms 2-3Y.
Loss ambulation 11-12Y
Motor+Cardiac. **Cognition**
Diagnosis: 2-2,5 Y – 4-4,5 Y

NBS in neuromuscular disorders: D Duchenne

	Route	Mechanism of action	Completed clinical trials	Ongoing clinical trials	Comments
Gene therapy					
PF-06939926 (fordadistrogene movaparvovec)	Intravenous	AAV-9-mediated micro-dystrophin replacement; exclusion of patients with mutations in any exon between 9 and 13 inclusive, or a deletion affecting exons 29 and 30	NA	NCT03362502 (phase 1) NCT04281485 (phase 3; CIFFREO)	A hold was placed in December, 2021, after one reported death, but the trials are now resuming; no peer-reviewed publication available at the point of this Review
SGT-001	Intravenous	AAV-9-mediated micro-dystrophin replacement; for all mutations	NA	NCT03368742 (phase 1/2; IGNITE DMD)	A hold was placed in 2018 and 2019 after serious adverse events, but the trial is now resuming; no peer-reviewed publication available at the point of this Review
SRP-9001 (rAAVrh74.MHCK7.micro-dystrophin)	Intravenous	AAVrh74-mediated micro-dystrophin replacement; for frameshift or premature stop codon mutation between exons 18–58	NA	NCT04626674 (phase 1; ENDEAVOR), NCT03375164 (phase 1/2), NCT03769116 (phase 2), NCT05096221 (phase 3; EMBARK)	Results from the one-year follow-up of NCT03375164 reported in Mendell et al (2020)[6]
rAAVrh74.MCK.micro-dystrophin	Intramuscular	AAVrh74-mediated micro-dystrophin replacement; for mutations compatible with micro-dystrophin cDNA	NCT02376816 (phase 1)	NA	No peer-reviewed publication available at the point of this Review
Stop codon readthrough					
Ataluren (PTC-124)	Oral	Ribosome readthrough of stop codons; for non-sense mutation Duchenne muscular dystrophy	NCT00592553 (phase 2), NCT01826487 (phase 3; ACT DMD), NCT01557400 (phase 3), NCT02819557 (phase 2), NCT03796637 (phase 2), and NCT03648827 (phase 2)	NCT04336826 (phase 2), NCT01247207 (phase 3), NCT03179631 (phase 3 OLE), NCT02369731 (registry; STRIDE)	Has conditional EMA approval (brand name Translarna, NS Pharma, Paramus NJ, USA)[7–12]
Exon skipping					
Eteplirsen (AVI-4658)	Intravenous	Exon 51 skipping; for amenable mutations	NCT01396239, NCT01540409, NCT02420379, NCT02286947, and NCT03218995 (all phase 2), NCT02255552 (phase 3; PROMOVI)	NCT03992430 (phase 3; MIS51ON), NCT03985878 (phase 2), NCT04179409 (phase 2, duplications*)	Has FDA approval (brand name Exondys 51, Sarepta Therapeutics, Cambridge MA, USA)[13–16]
SRP-5051	Intravenous	Exon 51 skipping; for amenable mutations	NCT03375255 (phase 1)	NCT04004065 (phase 2; MOMENTUM)	No peer-reviewed publication available at the point of this Review
Casimersen (SRP-4045)	Intravenous	Exon 45 skipping; for amenable mutations	NCT02530905 (phase 1)	NCT03532542 (phase 3 LTE†), NCT02500381 (phase 3; ESSENCE‡), NCT04179409 (phase 2, duplications*)	Has FDA approval (brand name Amondys 45, Sarepta Therapeutics, Cambridge MA, USA)[17]
Golodirsen (SRP-4053)	Intravenous	Exon 53 skipping; for amenable mutations	NCT02310906 (phase 1/2)	NCT04179409 (phase 2, duplications*), NCT03532542 (phase 3 LTE†), NCT02500381 (phase 3; ESSENCE‡)	Has FDA approval (brand name Vyondys 53, Sarepta Therapeutics, Cambridge MA, USA)[18–20]

NBS in neuromuscular disorders: D Duchenne

- **FDA Approves First Gene Therapy for Treatment of Certain Patients with Duchenne Muscular Dystrophy**
- June 22, 2023

- Today, the U.S. Food and Drug Administration approved Elevidys, the first gene therapy for the treatment of pediatric patients 4 through 5 years of age with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene who do not have a pre-existing medical reason preventing treatment with this therapy.

NBS in neuromuscular disorders: D Duchenne

- Older studies in some EU contries, USA, China, Canada, N Zealand
- Pilot studies ongoing in US (.. New York), Taywan, South Corea, Belgium..

International Journal of *Neonatal Screening*

MDPI

Article

Newborn Screening for Duchenne Muscular Dystrophy: First Year Results of a Population-Based Pilot

Michael J. Hartnett [1], Michele A. Lloyd-Puryear [1], Norma P. Tavakoli [2], Julia Wynn [3], Carrie L. Koval-Burt [3], Dorota Gruber [4,5], Tracy Trotter [6], Michele Caggana [2], Wendy K. Chung [3], Niki Armstrong [7] and Amy M. Brower [1,*]

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ANNALS of Clinical and Translational Neurology — Open Access — ANA American Neurological Association

RESEARCH ARTICLE

Newborn screening for Duchenne muscular dystrophy: A two-year pilot study

Norma P. Tavakoli[1,2], Dorota Gruber[3,4], Niki Armstrong[5], Wendy K. Chung[6], Breanne Maloney[1], Sunju Park[1], Julia Wynn[6], Carrie Koval-Burt[6], Lorraine Verdade[3], David H. Tegay[3,7], Lilian L. Cohen[8], Natasha Shapiro[9], Annie Kennedy[10], Garey Noritz[11], Emma Ciafaloni[12], Barry Weinberger[13,14], Marty Ellington Jr[14,15], Charles Schleien[3,14], Regina Spinazzola[14,16], Sunil Sood[14,17], Amy Brower[18], Michele Lloyd-Puryear[19], Michele Caggana[1,2] & the Duchenne Muscular Dystrophy Pilot Study Group

NBS in neuromuscular disorders: D Duchenne

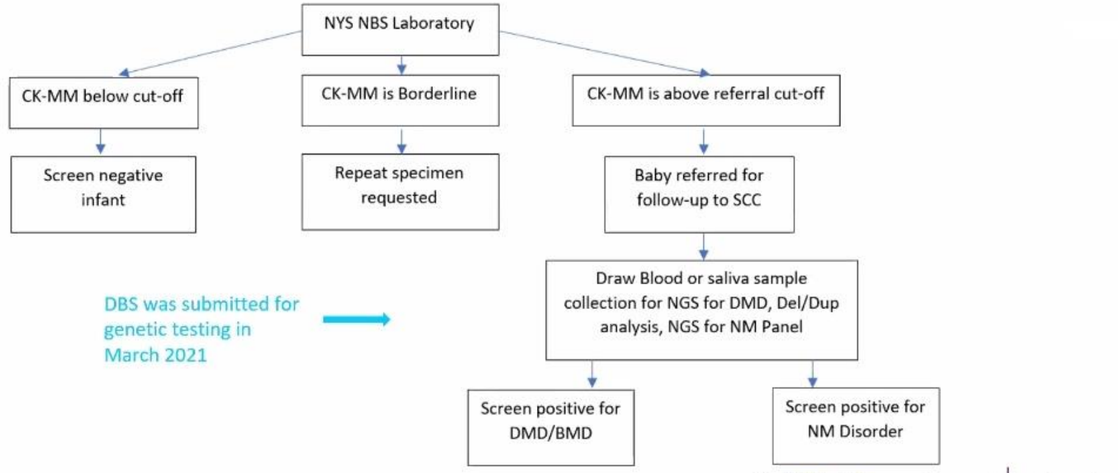
NEW YORK STATE | Department of Health | Wadsworth Center

A Consented Pilot Study in NYS to Screen Newborns for Duchenne Muscular Dystrophy

Norma Tavakoli, PhD
Research Scientist, NYSDOH

June 2, 2023

Screening Strategy



NEW YORK STATE | Department of Health | Wadsworth Center

NBS in neuromuscular disorders: high CK

1. *DMD Sequencing and Microarray-based Comparative Genomic Hybridization (aCGH) Analysis*: In solution hybridization of the 79 coding exons, the muscle promoter as well as the region surrounding several known deep intronic pathogenic variants, within the *DMD* gene. Direct sequencing of the amplified captured regions performed using next generation short base pair read sequencing. A custom aCGH for the *DMD* gene was used to detect deletions and/or duplications.
2. *If needed, perform neuromuscular disorders panel (47 genes):* In solution hybridization of the targeted coding exons within the genes tested.* The genes on this panel were chosen through evidence-based analysis and direct sequencing of the amplified captured regions was performed using next generation short base pair read sequencing.
3. *If needed, perform additional analysis (90 to 104 genes):* These gene panels include sequencing and deletion/duplication testing by NGS of up to 103 additional genes associated with neuromuscular disorders and related neurological disorders.**

**ACTA1, AMPD1, ANO5, CAPN3, CAV3, COL6A1, COL6A2, COL6A3, CRPPA, DES, DMD, DYSF, EMD, FKRP, FKTN, GAA, GNE, ISPD, ITGA7, LAMA2, LARGE1, LMNA, MYOT, NEB, PLEC, PMM2, POMGNT1, POMT1, POMT2, PYGM, RYR1, RYR2, SELENON, SGCA, SGCB, SGCD, SGCE, SGCG, SIL1, TCAP, TNNI2, TNNT1, TPM2, TPM3, TRIM32, TTN, VCP*

***ADSSL1, AGRN, ALG14, ALG2, ATP2A1, B3GALNT2, B4GAT1, BAG3, BIN1, CACNA1S, CASQ1, CCDC78, CFL2, CHAT, CHKB, CHRNA1, CHRNB1, CHRND, CHRNE, CLCN1, CNTN1, COL12A1, COL13A1, COLQ, CPT2, CRYAB, DAG1, DNAJB6, DNM2, DOK7, DPAGT1, DPM1, DPM2, DPM3, FHL1, FKBP14, FLNC, GFPT1, GMPPB, GOSR2, GYG1, GYS1, HACD1, HNRNPA2B1, HNRNPDL, ISCU, KBTBD13, KCNJ2, KLHL40, KLHL41, KLHL9, LAMB2, LAMP2, LDB3, LIMS2, LMOD3, LRP4, MAP3JK20, MATR3, MEGF10, MICU1, MTM1, MTMR14, MUSK, MYH2, MYH7, MYL2, MYO18B, MYPN, ORAI1, PNPLA2, POMGNT2, POMK, PREPL, PYROXD1, RAPSN, RXYLT1, SCN4A, SLC18A3, SLC5A7, SMCHD1, SMN1, SMN2, SNAP25, SPEG, SQSTM1, STAC3, STIM1, SUN1, SUN2, SYNE1, SYNE2, SYT1, TAZ, TIA1, TK2, TMEM43, TNNT3, TNPO3, TOR1AIP1, TRAPPC11, TTN, VAMP1, VMA21*

NBS in neuromuscular disorders: D Duchenne

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IOS Press

Review

Newborn Screening for the Diagnosis and Treatment of Duchenne Muscular Dystrophy

First Workshop Report: Establishing Australian health system readiness for the implementation and evaluation of a pilot program in New South Wales and the Australian Capital Territory

- Multidisciplinary care measures
- Access to emerging therapies
- Familly counselling

NBS - Comments

Magnifico *et al. Rare Dis Orphan Drugs J* 2023;2:16
DOI: 10.20517/rdodj.2023.17

Rare Disease and
Orphan Drugs Journal

Systematic Review

Open Access

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A systematic review of real-world applications of genome sequencing for newborn screening

Giuditta Magnifico, Irene Artuso, Stefano Benvenuti

Fondazione Telethon ETS, Milan IT 20129, Italy.

(..)published recently; however, this evidence is not yet sufficient to put an end to the broad and animated debate on the use of GS for NBS. Ethical, legal, and social issues still constitute great challenges and major barriers to wide and uniform adoption of GS in NBS (..)

NBS - Comments

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Review

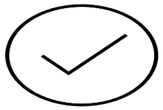
Newborn Screening for the Diagnosis and Treatment of Duchenne Muscular Dystrophy

First Workshop Report: Establishing Australian health system readiness for the implementation and evaluation of a pilot program in New South Wales and the Australian Capital Territory

WORKSHOP STRUCTURE

Twenty attendees including clinicians, geneticists, scientists, patient advocates, and government representatives convened on 31st May 2021 for the *Newborn Screening for the Diagnosis and Treatment of Duchenne Muscular Dystrophy- Australian Health System Readiness Workshop*. The stakeholder committee consisted of individuals with expertise in newborn screening, neuromuscular diseases, implementation science, practice and health policy, funding bodies and consumer facing (advocate) roles. This

NBS - Comments

- NBS for patients on “greenway” modifier of disease 
- NBS for diagnosis of disorders without treatment? and later (adult) onset ??
- NGS versus awareness ?

NBS – Comments

- Large discussion: etical, legal, clinical, organization, economical issues
- Discuss within centres of our contry and network → consensus
- Health systems, economy …. different

Questions