What is SMA?

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- Schorling, David C et al. "Advances in Treatment of Spinal Muscular Atrophy - New Phenotypes, New Challenges, New Implications for Care." Journal of neuromuscular diseases vol. 7,1 (2020): 1-13. doi:10.3233/JND-190424

Mom defines SMA as **S**onsuz **M**ücadelenin **A**dı

BUT it stands for **S**pinal **M**uscular **A**trophy

Atrophy vs Dystrophy

Autosomal Recessive Inheritance

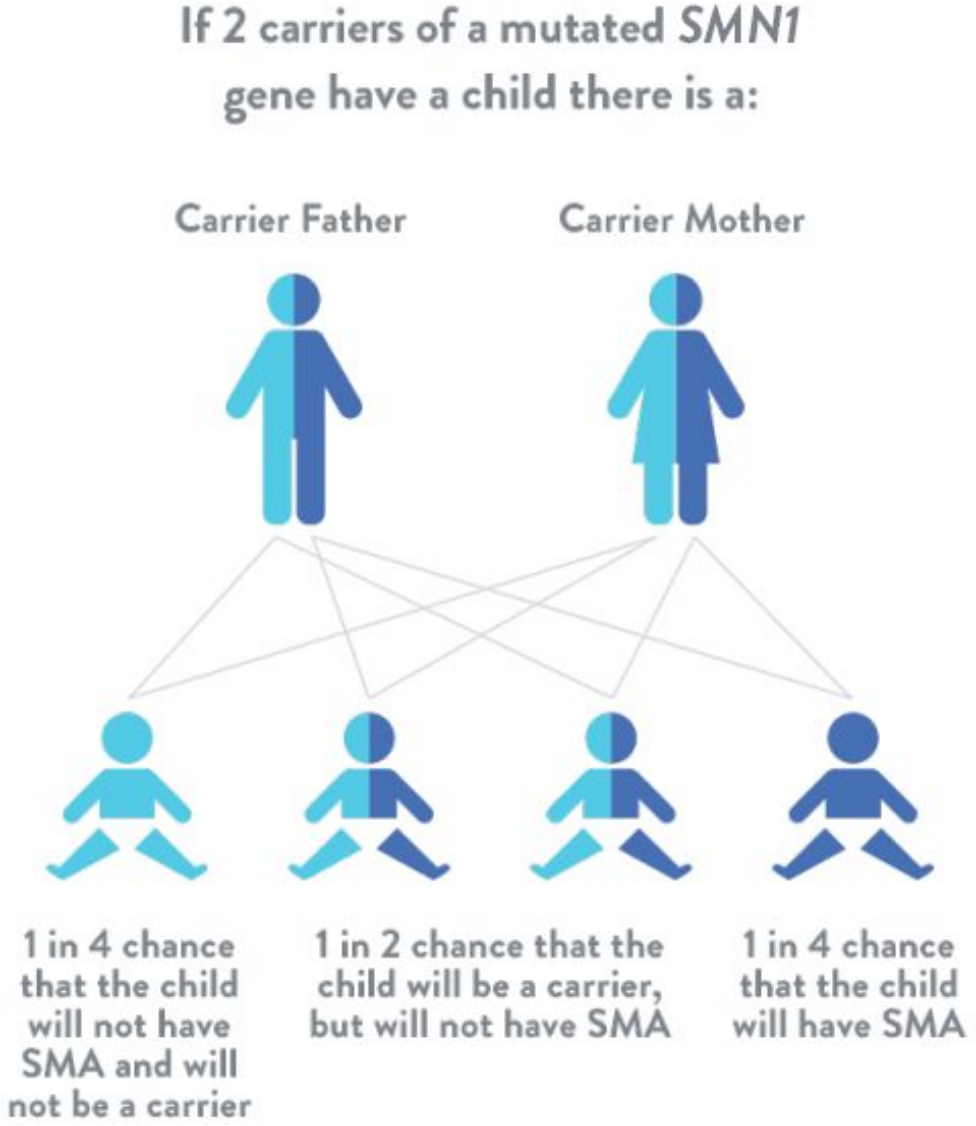
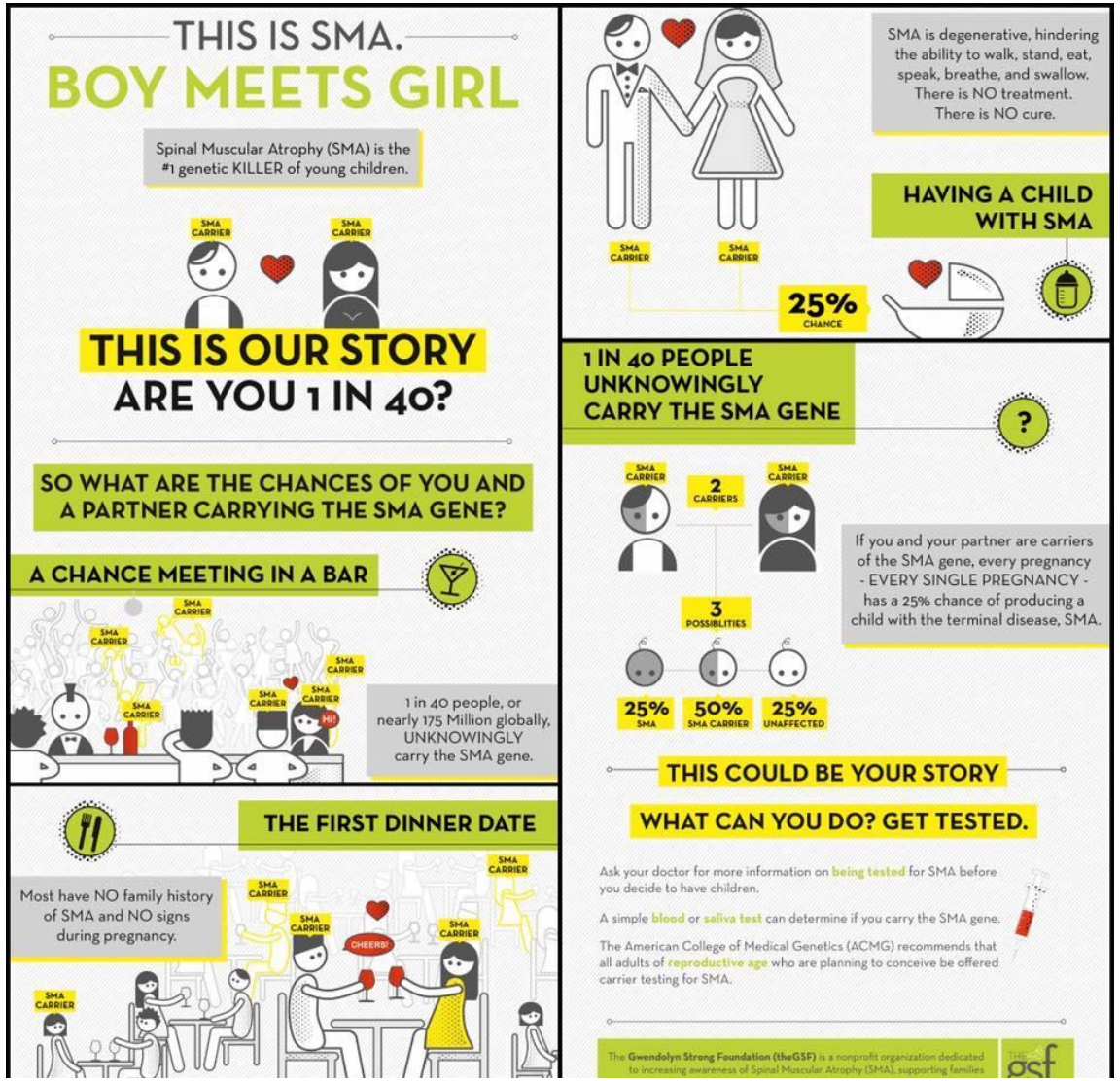


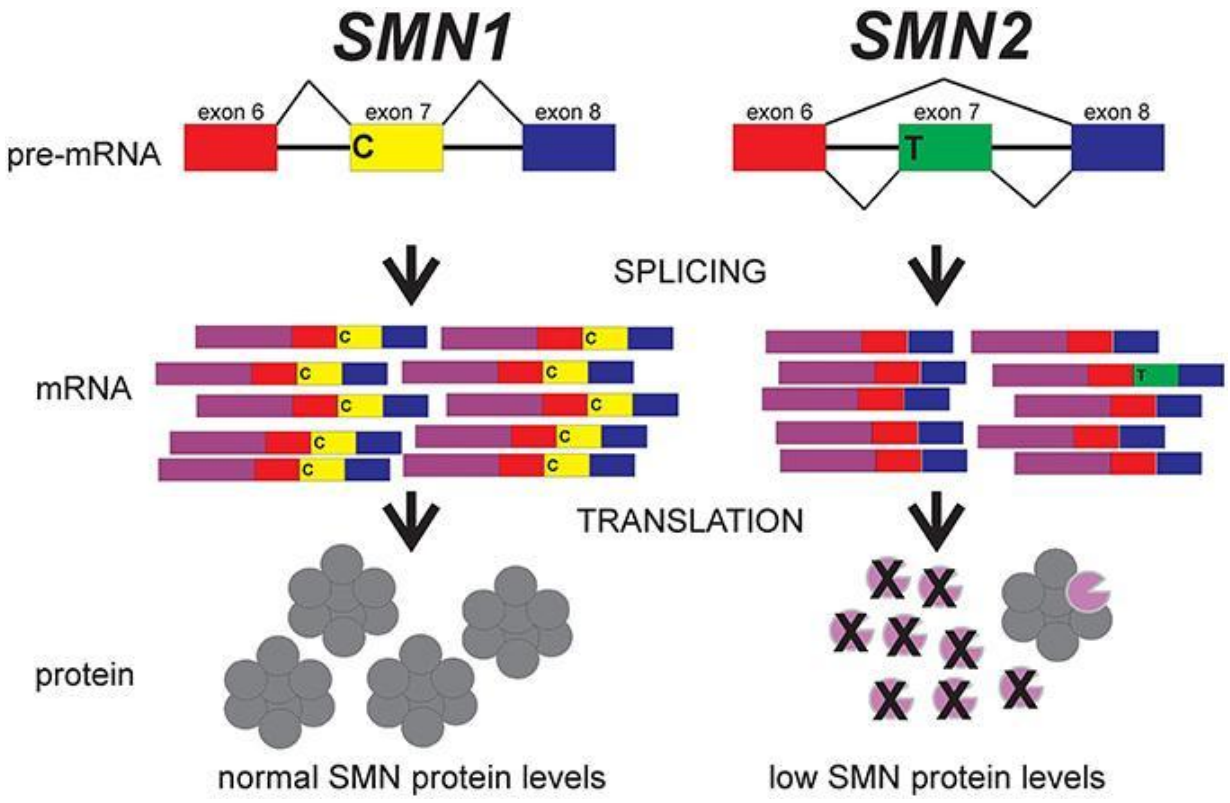
Image is from *Together in SMA* program website:
https://www.togetherinsma.com/en_us/home/introduction-to-sma/smn1-gene.html

- Approximately 1 in 40 people is a carrier.

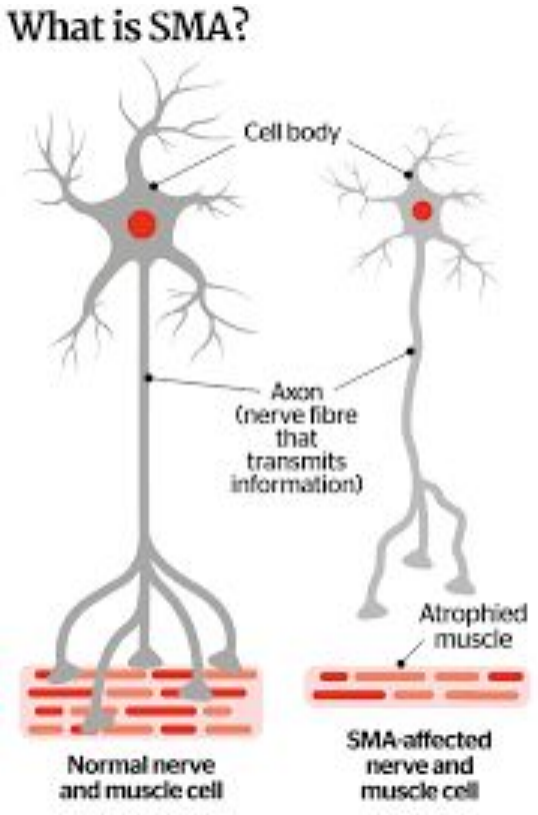


Picture is from Gwendolyn Strong Foundation

What is SMA?



Butchbach, M. (2016, February 25). Copy Number Variations in the Survival Motor Neuron Genes: Implications for Spinal Muscular Atrophy and Other Neurodegenerative Diseases. Retrieved October 21, 2020, from https://www.frontiersin.org/articles/10.3389/fmolb.2016.00007/full



Aubusson, K. (n.d.). Baby Aviana's heartbreaking fate. Retrieved October 21, 2020, from https://www.smh.com.au/interactive/2017/baby-aviana/

SMA Types

- SMA is a motor-neuron disease – degeneration of lower motor neurons.

❖ Prenatal-onset SMA	(Type 0)
❖ Werdnig Hoffmann Disease (0-6 months)	(Type 1)
❖ Dubowitz Disease (6-10 months)	(Type 2)
❖ Kugelberg Welander Disease (>18 months)	(Type 3)
❖ Adult-onset (Adulthood)	(Type 4)

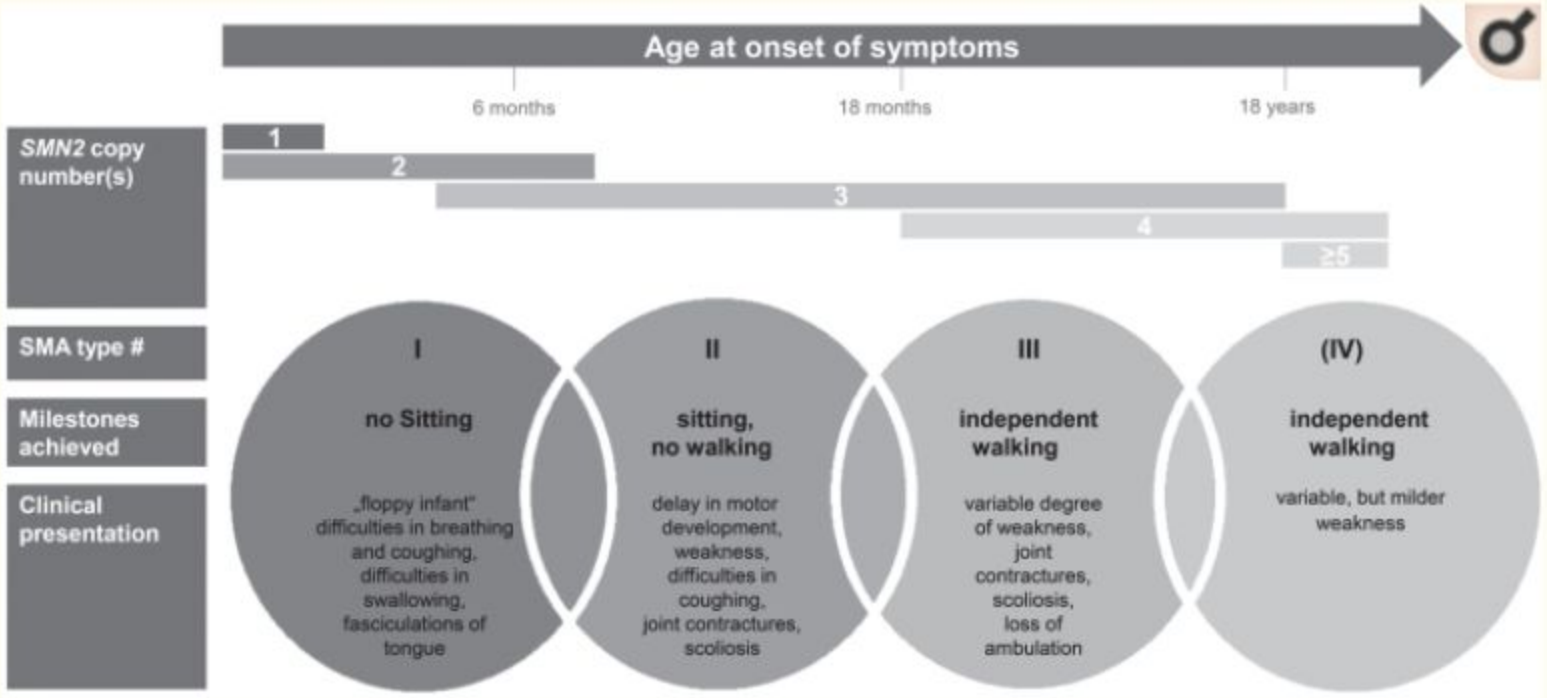


Fig.1

Clinical classification of SMA subtypes according to onset, milestones achieved, and clinical presentation. Typically associated *SMN2* copy numbers are displayed.

Schorling, David C et al. “Advances in Treatment of Spinal Muscular Atrophy - New Phenotypes, New Challenges, New Implications for Care.” *Journal of neuromuscular diseases* vol. 7,1 (2020): 1-13. doi:10.3233/JND-190424

NAIP gene

Table 4

Comparison of clinical characteristics in patients with *SMN1* deletions only and those with both *SMN1* and *NAIP* deletions

	(*n*=24)	deletions (*n*=6)		CI)
Males (*n*=11)	9	2	NS	
Age at symptom onset, mean±SD (range), months	18.4±20.4 (0.1–96.0)	1.9±1.7 (0.1–4.0)	0.007	
Clinical type (*n*=30)			0.005	
Type 1	8	6		
Types 2+3	16	0		
Initial presentation (*n*=30)			0.003	3.33 (1.53–7.27)
Respiratory difficulty and hypotonia	6	5		
Developmental delay and gait disturbance	18	1		
Clinical outcome (*n*=16)			0.009	4.68 (1.48–14.8)
Survivors without ventilator	10/12	0/4		
Died or on ventilator	2/12	4/4		

Ahn, E., Yum, M., Kim, E., Yoo, H., Lee, B., Kim, G., & Ko, T. (2017, January). Genotype-Phenotype Correlation of SMN1 and NAIP Deletions in Korean Patients with Spinal Muscular Atrophy. Retrieved October 21, 2020, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5242148/

SMN2 copy number and SMA Types (Not only factor, but important!)

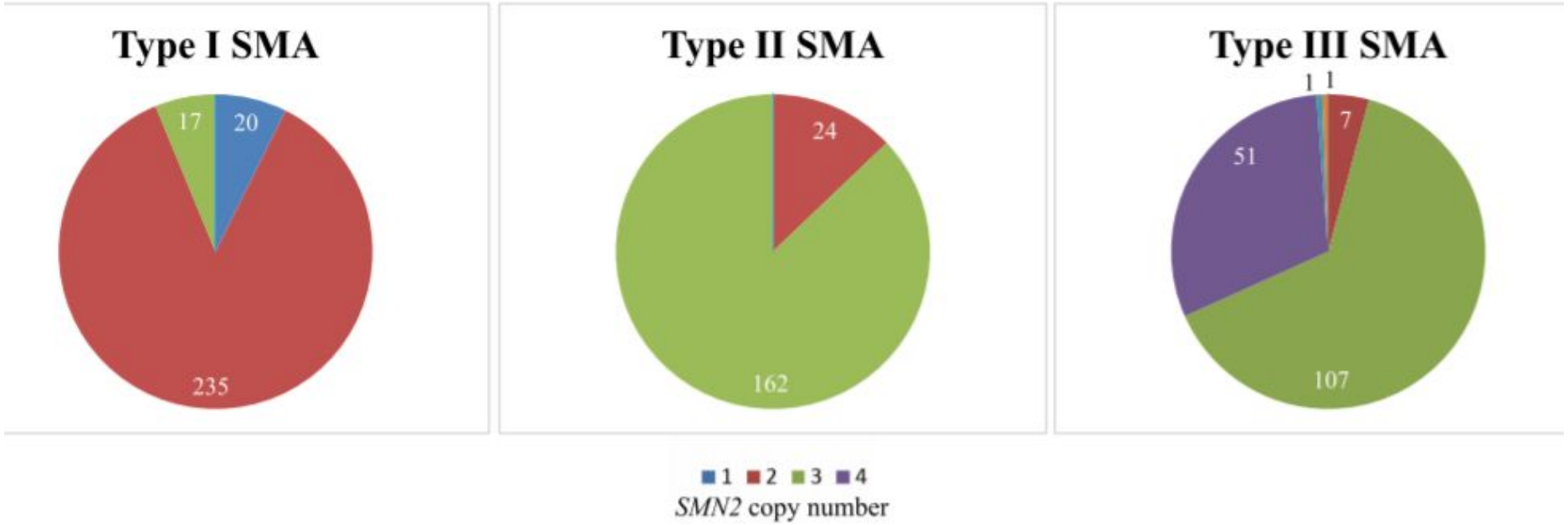


Fig. 1. Distribution of *SMN2* copy numbers according to SMA type. Number of Spanish SMA patients studied from our cohort of 625 index cases.

Calucho M, Bernal S, Alías L, March F, Venceslá A, Rodríguez-Álvarez FJ, Aller E, Fernández RM, Borrego S, Millán JM, Hernández-Chico C, Cuscó I, Fuentes-Prior P, Tizzano EF. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscul Disord. 2018 Mar;28(3):208-215. doi: 10.1016/j.nmd.2018.01.003. Epub 2018 Jan 11. PMID: 29433793.

Treatments

- Spinraza (Nusinersen) FDA approval in December 2016, EMA approval in 2017,in TITCK's list of the drugs that can be imported in 2017, SGK covered for Type 1 in 2017 summer, SGK covered for type 2 and 3 on 1st of Febraury, 2019.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

R.S. Finkel, E. Mercuri, B.T. Darras, A.M. Connolly, N.L. Kuntz, J. Kirschner, C.A. Chiriboga, K. Saito, L. Servais, E. Tizzano, H. Topaloglu, M. Tulinius, J. Montes, A.M. Glanzman, K. Bishop, Z.J. Zhong, S. Gheuens, C.F. Bennett, E. Schneider, W. Farwell, and D.C. De Vivo, for the ENDEAR Study Group*

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Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study

Darryl C. De Vivo[a,*], Enrico Bertini[b], Kathryn J. Swoboda[c], Wuh-Liang Hwu[d], Thomas O. Crawford[e], Richard S. Finkel[f], Janbernd Kirschner[g,h], Nancy L. Kuntz[i], Julie A. Parsons[j], Monique M. Ryan[k], Russell J. Butterfield[l], Haluk Topaloglu[m], Tawfeg Ben-Omran[n,o], Valeria A. Sansone[p,q], Yuh-Jyh Jong[r], Francy Shu[s], John F. Staropoli[t,l], Douglas Kerr[t,l], Alfred W. Sandrock[t], Christopher Stebbins[t], Marco Petrillo[t], Gabriel Braley[t], Kristina Johnson[t], Richard Foster[u], Sarah Gheuens[t], Ishir Bhan[t], Sandra P. Reyna[t,l], Stephanie Fradette[t], Wildon Farwell[t], on behalf of the NURTURE Study Group

Neuromuscular
Original research

Nusinersen safety and effects on motor function in adult spinal muscular atrophy type 2 and 3

Lorenzo Maggi[1], Luca Bello[2], Silvia Bonanno[1], Alessandra Govoni[3, 4], Claudia Caponnetto[5], Luigia Passamano[6], Marina Grandis[5, 7], Francesca Trojsi[8], Federica Cerri[9], Manfredi Ferraro[10], Virginia Bozzoni[2], Luca Caumo[2], Rachele Piras[11], Raffaella Tanel[12], Elena Saccani[13], Megi Meneri[3], Veria Vacchiano[14], Giulia Ricci[4], Gianni Soraru'[2], Eustachio D'Errico[15], Irene Tramacere[16], Sara Bortolani[10], Giovanni Pavesi[17], Riccardo Zanin[18], Mauro Silvestrini[19, 20], Luisa Politano[6], Angelo Schenone[5, 7], Stefano Carlo Previtali[9], Angela Berardinelli[21], Mara Turri[22], Lorenzo Verriello[23], Michela Coccia[20], Renato Mantegazza[1], Rocco Liguori[14, 24], Massimiliano Filosto[25, 26], Gianni Marrosu[27], Gabriele Siciliano[4], Isabella Laura Simone[15], Tiziana Mongini[10], Giacomo Comi[3, 28], Elena Pegoraro[2]

Author affiliations +

Abstract

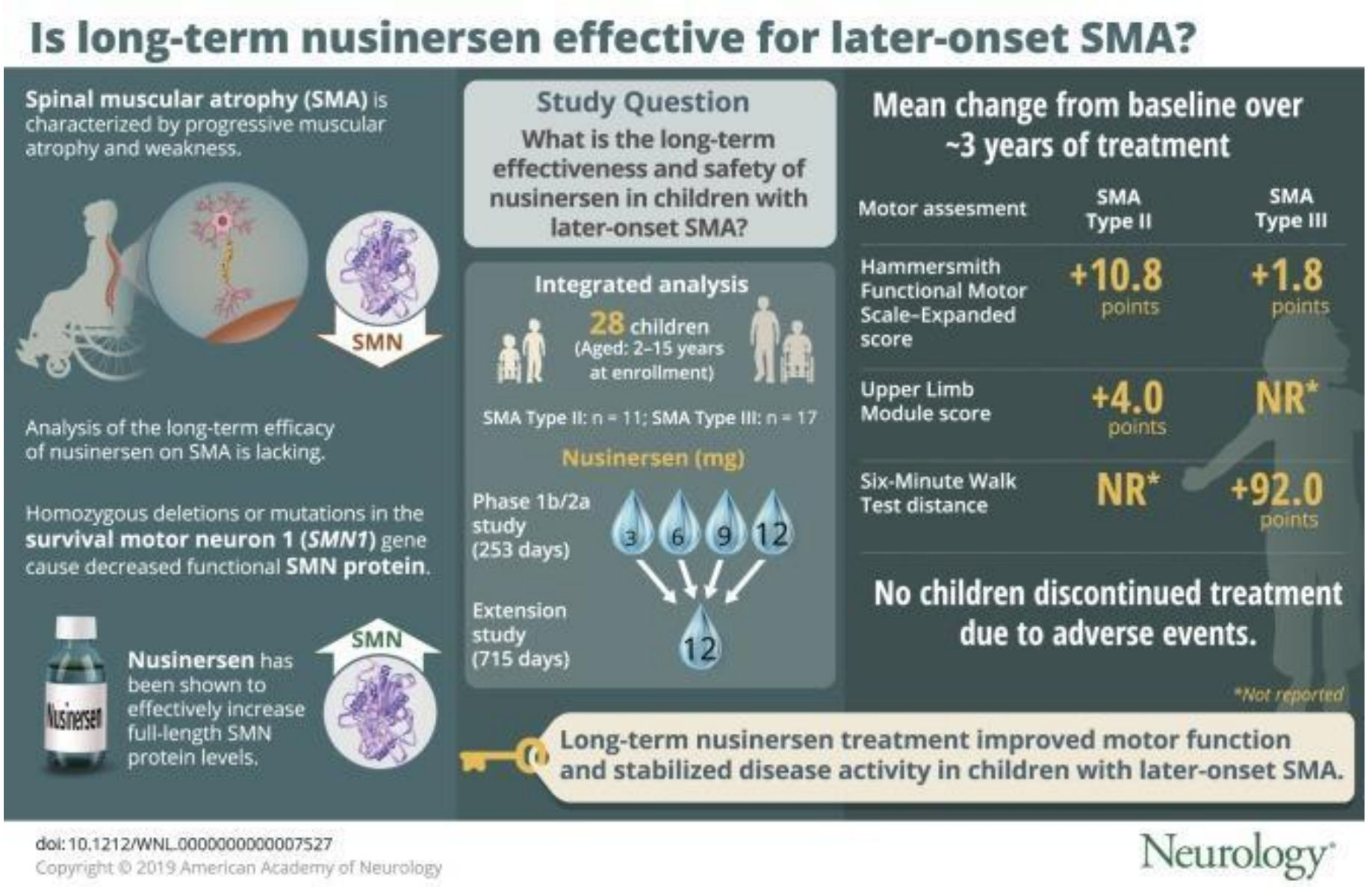
Objective To retrospectively investigate safety and efficacy of nusinersen in a large cohort of adult Italian patients with spinal muscular atrophy (SMA).

Methods Inclusion criteria were: (1) clinical and molecular diagnosis of SMA2 or SMA3; (2) nusinersen treatment started in adult age (>18 years); (3) clinical data available at least at baseline (T0-beginning of treatment) and 6 months (T6).

Results We included 116 patients (13 SMA2 and 103 SMA3) with median age at first administration of 34 years (range 18–72). The Hammersmith Functional Rating Scale Expanded (HFMSE) in patients with SMA3 increased significantly from baseline to T6 (median change +1 point, p<0.0001), T10 (+2, p<0.0001) and T14 (+3, p<0.0001). HFMSE changes were independently significant in SMA3 sitter and walker subgroups. The Revised Upper Limb Module (RULM) in SMA3 significantly improved between T0 and T14 (median +0.5, p=0.012), with most of the benefit observed in sitters (+2, p=0.018). Conversely, patients with SMA2 had no significant changes of median HFMSE and RULM between T0 and the following time points, although a trend for improvement of RULM was observed in those with some residual baseline function. The rate of patients showing clinically meaningful improvements (as defined during clinical trials) increased from 53% to 69% from T6 to T14.

Conclusions Our data provide further evidence of nusinersen safety and efficacy in adult SMA2 and SMA3, with the latter appearing to be cumulative over time. In patients with extremely advanced disease, effects on residual motor function are less clear.

View Full Text



doi:10.1212/WNL.0000000000007527

Neurology

Darras, Basil T et al. “Nusinersen in later-onset spinal muscular atrophy: Long-term results from the phase 1/2 studies.” *Neurology* vol. 92,21 (2019): e2492-e2506. doi:10.1212/WNL.0000000000007527

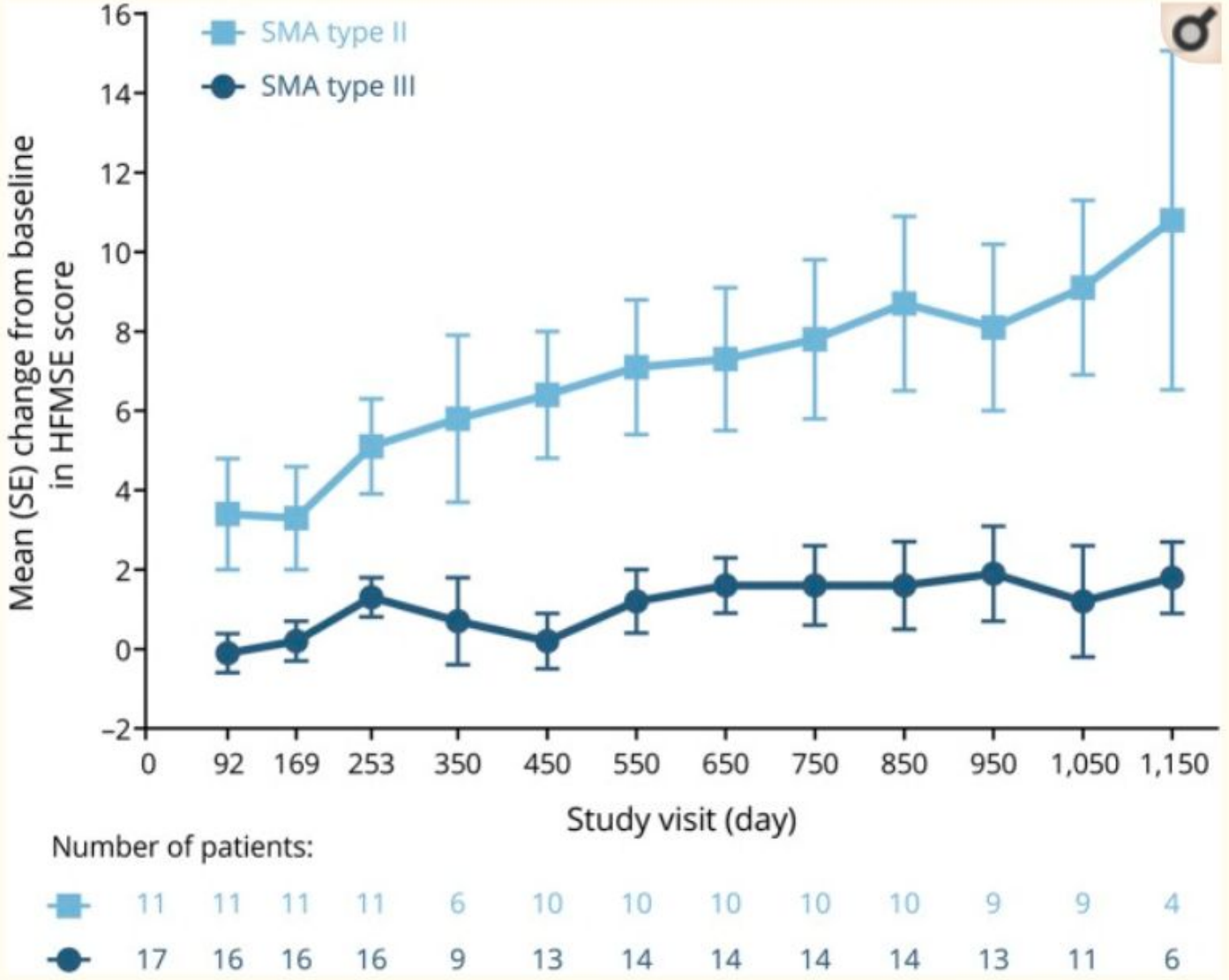


Figure 2

Mean change from baseline in Hammersmith Functional Motor Scale–Expanded (HFMSE) score

Darras, Basil T et al. “Nusinersen in later-onset spinal muscular atrophy: Long-term results from the phase 1/2 studies.” *Neurology* vol. 92,21 (2019): e2492-e2506. doi:10.1212/WNL.0000000000007527

Cold Spring Harbor Laboratory

From Instagram page of SMA Benimle Yürü Derneği @smabenimleyuru

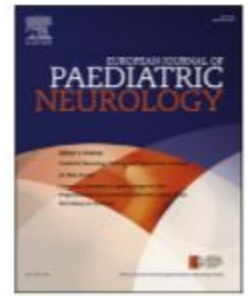
Zolgensma (onsamnogene abeparvovec-xioi)
 FDA approval in 2019, EMA approval in 2020

Evrysdi (Risdiplam) FDA approval in August 2020, submission to EMA is done, decision is waited. It is in TITCK’s list of the drugs that can be imported since August 2020 but SGK does not cover the expanses at this moment.

European Journal of Paediatric Neurology 28 (2020) 38–43

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology



European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy

Janbernd Kirschner [a, *], Nina Butoianu [b], Nathalie Goemans [c], Jana Haberlova [d], Anna Kostera-Pruszczyk [e], Eugenio Mercuri [g, h], W. Ludo van der Pol [k], Susana Quijano-Roy [i], Thomas Sejersen [j], Eduardo F. Tizzano [f], Andreas Ziegler [l], Laurent Servais [m, n, 1], Francesco Muntoni [o, 1]

Ongoing Studies

There are many preclinical and clinical studies.

Please visit the webpage: www.clinicaltrials.gov

- SRK-015 - TOPAZ trial
- AVXS-101 (FDA hold)
- and other studies…

- DEVOTE trial (Nusinersen in higher doses)
- RESPOND trial (Nusinersen after gene therapy)
- Trials of presymptomatic babies
- Extension studies of approved drugs.

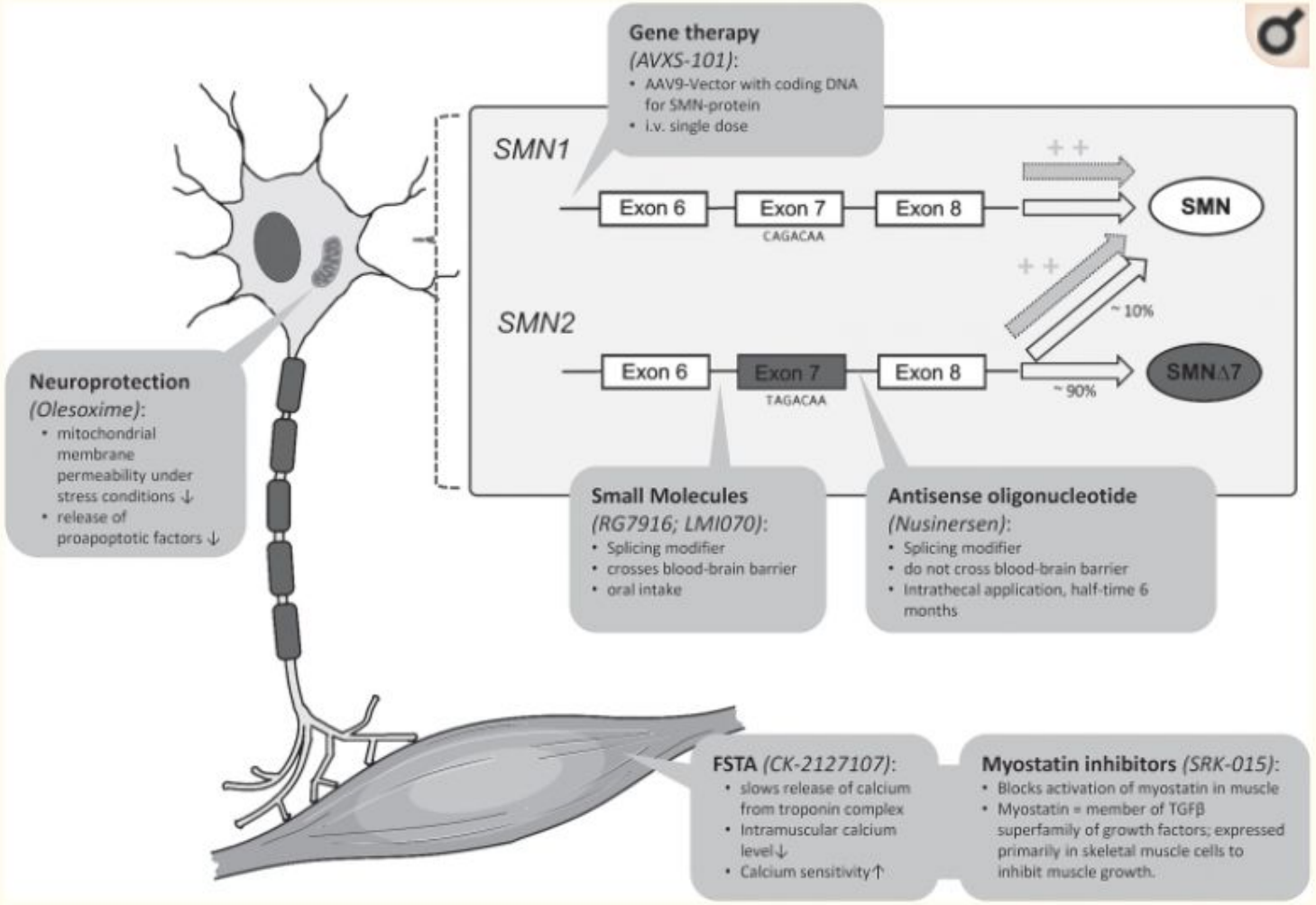


Fig.2

Illustration of therapeutic approaches in SMA involving molecular mechanisms of action (modified illustration based on Farrar et al. 2017 [101] and Pechmann et al. 2017 [102]). FSTA=Fast Troponin Activator.

Schorling, David C et al. “Advances in Treatment of Spinal Muscular Atrophy - New Phenotypes, New Challenges, New Implications for Care.” Journal of neuromuscular diseases vol. 7,1 (2020): 1-13. doi:10.3233/JND-190424

Some scoring tests to evaluate SMA patients

- Hammersmith Motor Functional Scale
- CHOP-Intend Scale
- Revised Upper Limb Module (RULM) Scale
- MFM-32 Scale
- HINE (Hammersmith Infant)
- 6-minute walking test
- 10 meter walking test

To support us…

- In order to watch news, see improvements with Spinraza, read newspapers about me and my brother, here is the instagram page that our mom created: **@ayca_burak_annesi**

- SMA Benimle Yürü Derneği

Twitter and Instagram: @smabenimleyuru

Facebook Page: SMA Benimle Yürü

YouTube: SMA Benimle Yürü

Website: www.smabenimleyuru.org.tr

Hashtags frequently used in social media:
#spinalmuscularatrophy , #smatype1 , #smatype2 , #smatype3, #spinraza , #nusinersen , #zolgensma , #evrysdi , #risdiplam , #smaawareness

Thank you!
Any questions?