« Safety and Monitoring in Trials: pharmacovigilance in pediatrics, off-label use and side-effect monitoring »

Pr Isabelle Desguerre

Hôpital Necker

Clinical trials are differents of real life

Efficacy in a short time >2 years

- Motor scores
- Improvement of mobility
- New functions?
- Maintain of function ?
- Release of a symptom (epilepsy)
- Quality of live

Adverse events during the clinical trials

- Severe or Not
- Biological abnormalities only
- Event not linked to the treatment

Real life is different of clinical trials

Benefit

- Long term>15 years
- What means improvement of a motor score?
- Improvement of Autonomy in the day life
- Supports? Hospitalisation?
- Schooling? Pregnancy?
- QOL?

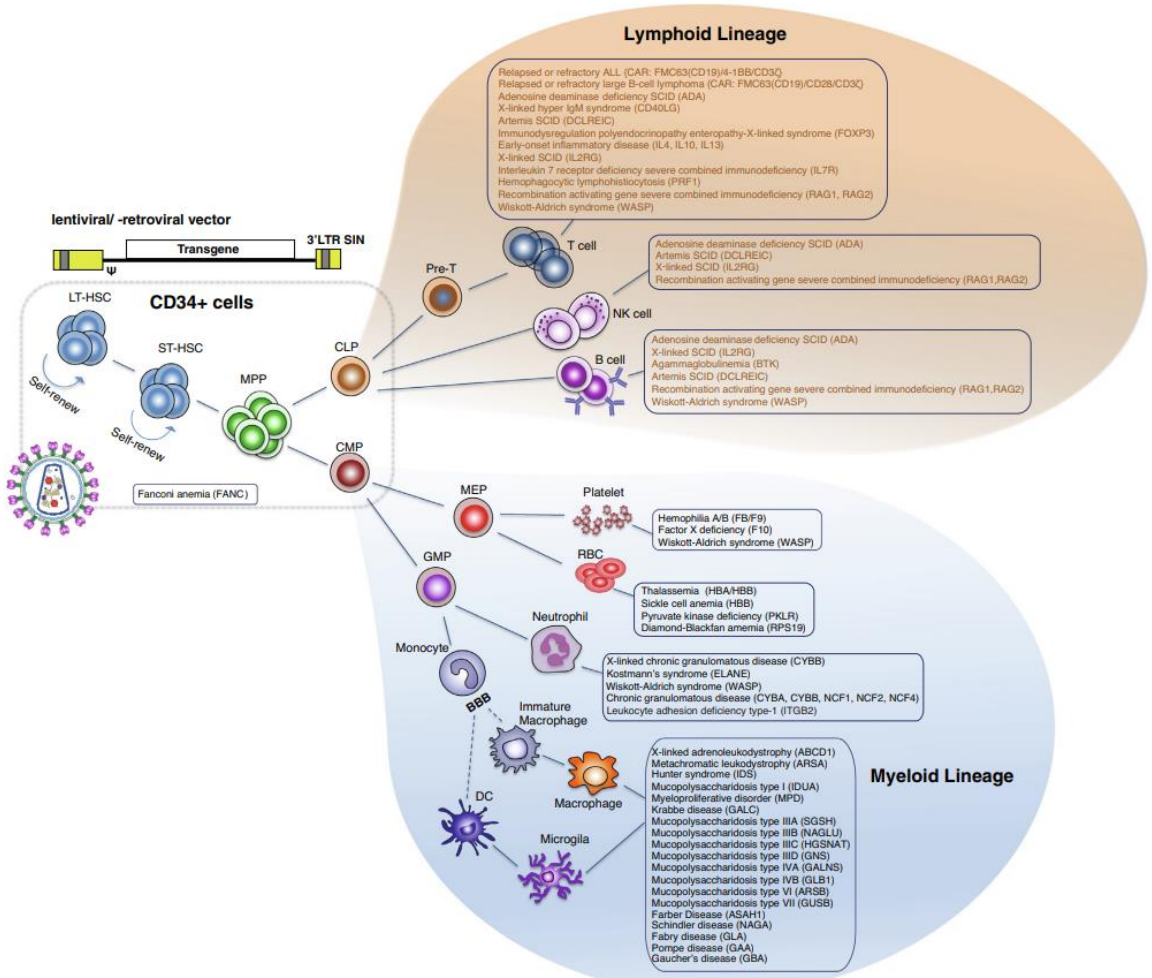
Adverse event

- Long term >15 years
- What means toxicity ?
- Necessity of Registry

Gene therapy and Antisens Oligonucleotides

- One shot or repeated treatments
- Different ways to deliver
  - In vivo and ex vivo
  - Intraveinous, intrathecal, intracérébral, intraocular, intrahepatic, cutaneous….
- Expert centers
- Expansive treatments

Ex vivo: hematopoietic cells



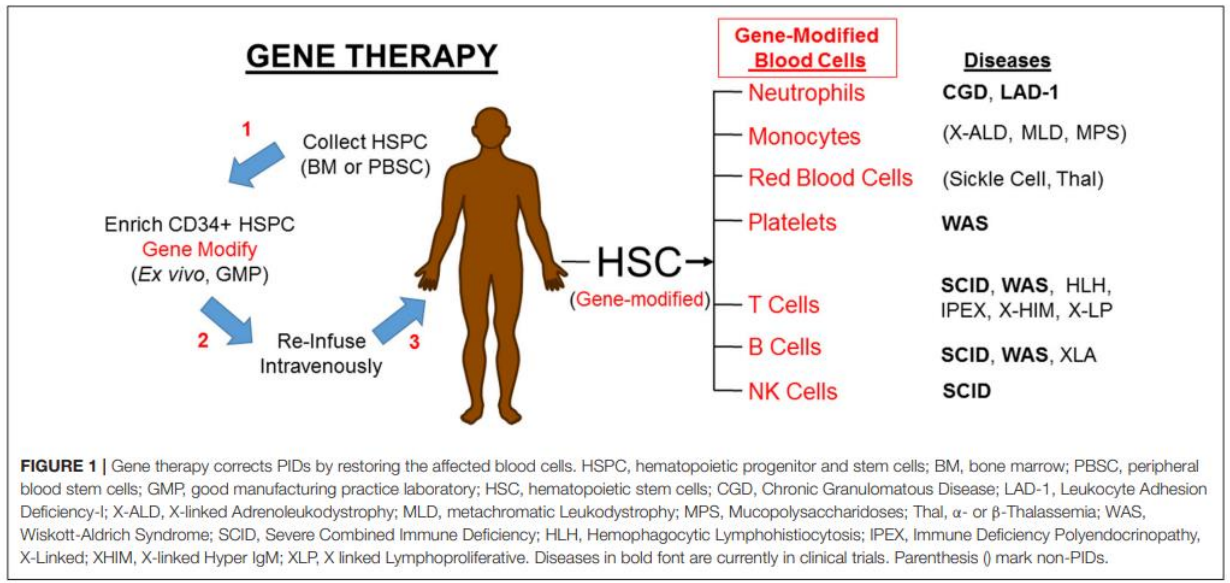
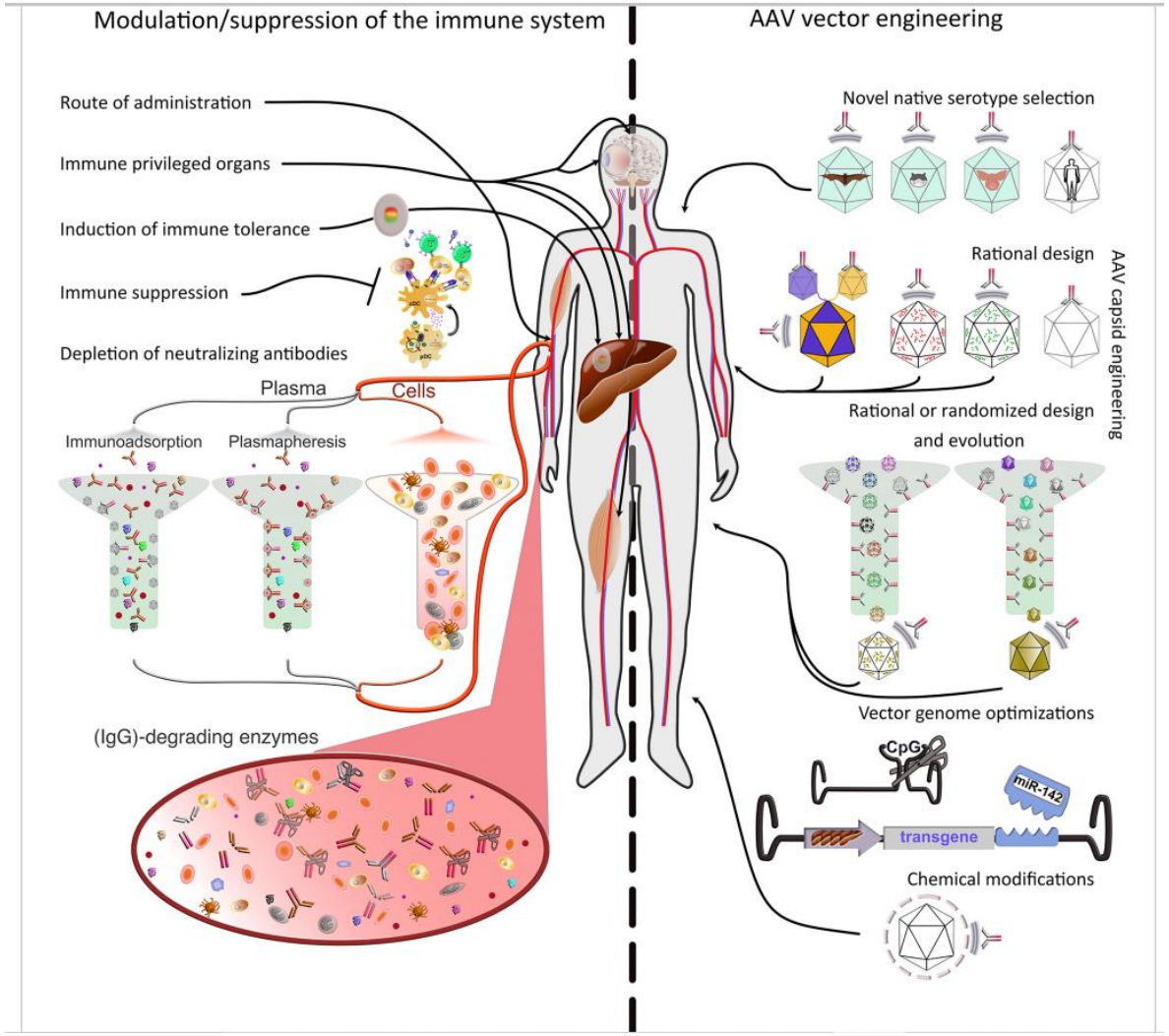


FIGURE 1 | Gene therapy corrects PIDs by restoring the affected blood cells. HSPC, hematopoietic progenitor and stem cells; BM, bone marrow; PBSC, peripheral blood stem cells; GMP, good manufacturing practice laboratory; HSC, hematopoietic stem cells; CGD, Chronic Granulomatous Disease; LAD-1, Leukocyte Adhesion Deficiency-I; X-ALD, X-linked Adrenoleukodystrophy; MLD, metachromatic Leukodystrophy; MPS, Mucopolysaccharidoses; Thal, α- or β-Thalassemia; WAS, Wiskott-Aldrich Syndrome; SCID, Severe Combined Immune Deficiency; HLH, Hemophagocytic Lymphohistiocytosis; IPEX, Immune Deficiency Polyendocrinopathy, X-Linked; XHIM, X-linked Hyper IgM; XLP, X linked Lymphoproliferative. Diseases in bold font are currently in clinical trials. Parenthesis () mark non-PIDs.

In vivo



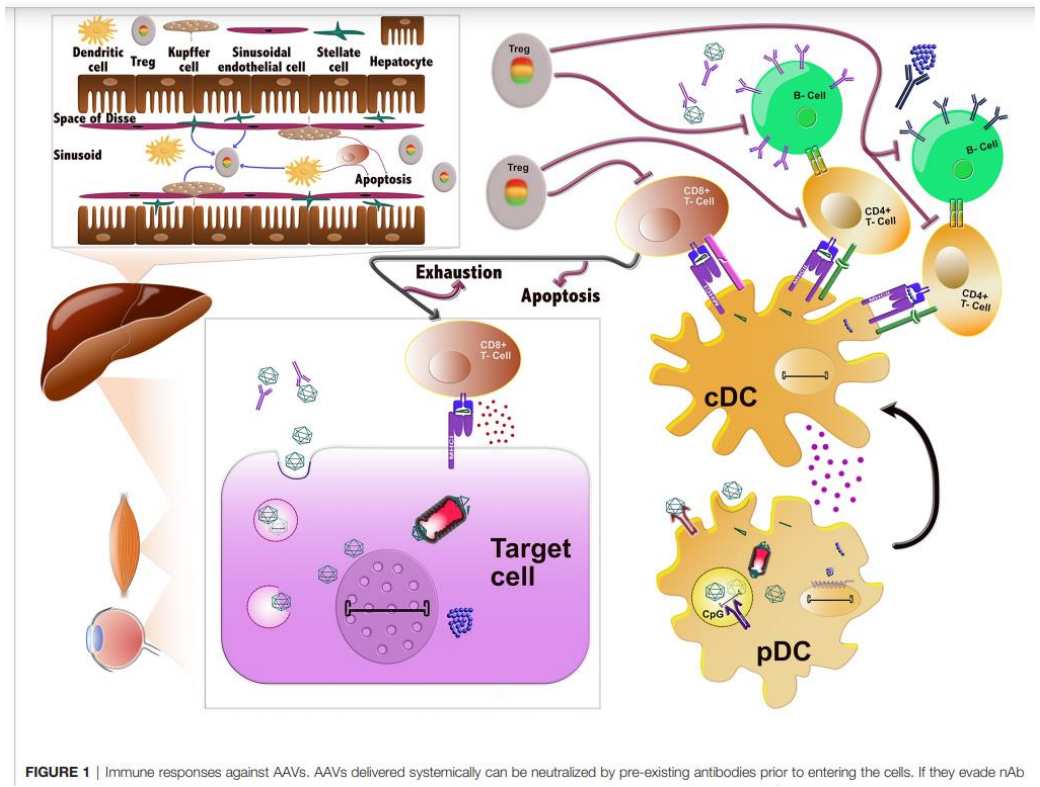


FIGURE 1 | Immune responses against AAVs. AAVs delivered systemically can be neutralized by pre-existing antibodies prior to entering the cells. If they evade nAb

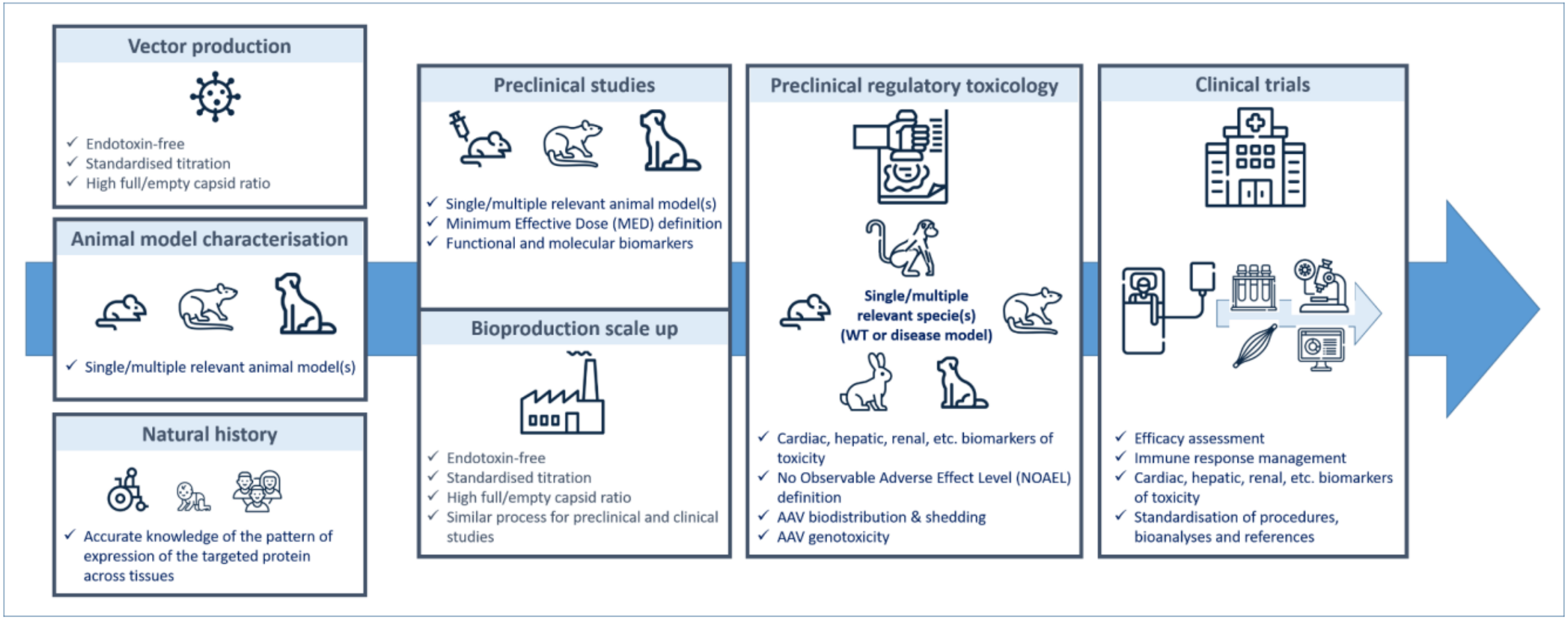
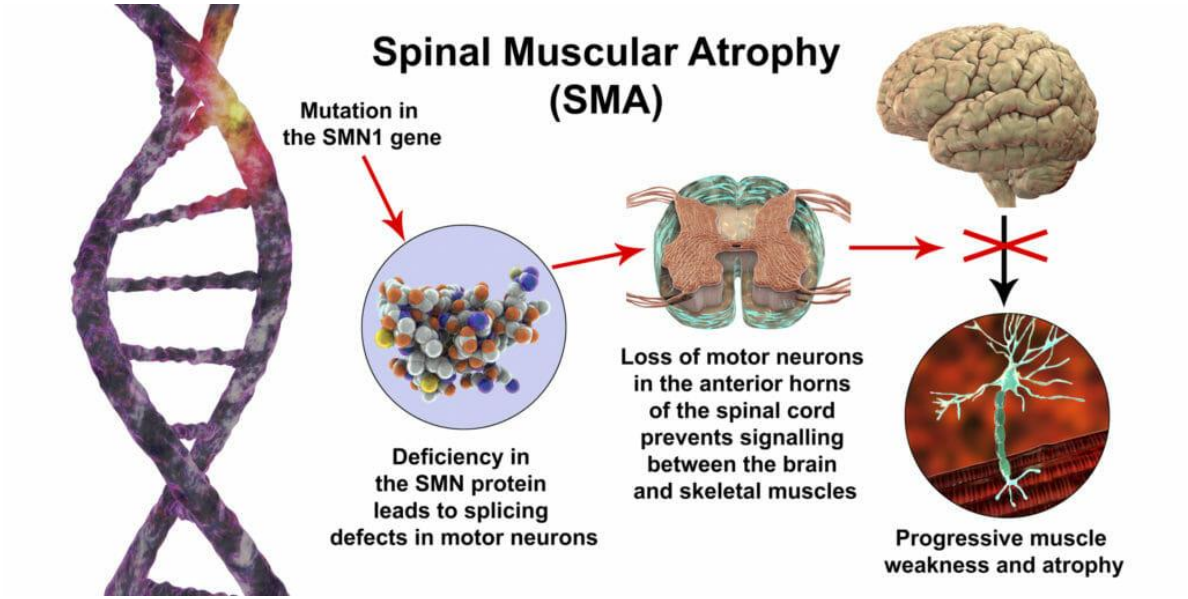


Figure 1. Of rAAV and men: the ideal journey.

One example

Spinal Muscular atrophy

Physiopathology of SMA: death of motoneurons: an emergency



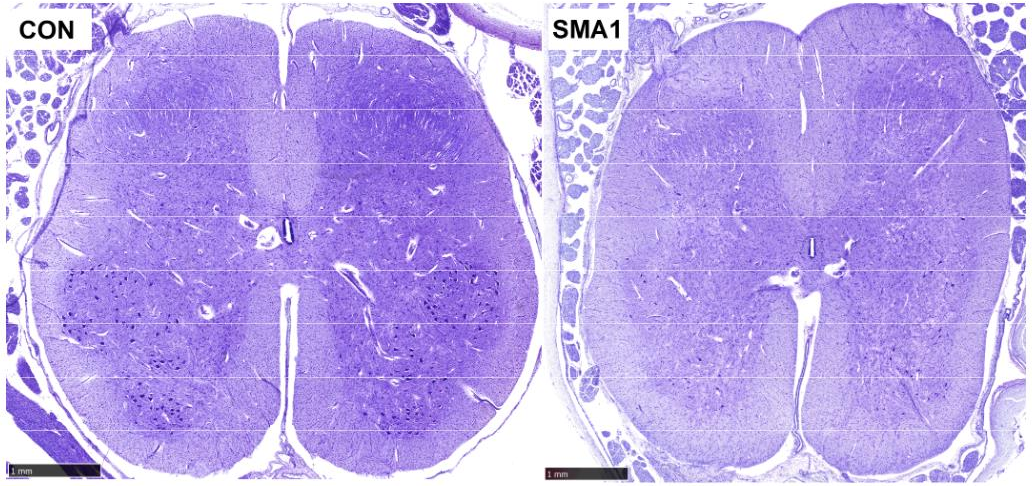


Figure 1. The normal spinal cord of a 4-month-old infant (**left**) and spinal cord of a 5-month-old infant with SMA type 1 due to homozygous deletion of *SMN1* exon 7 (**right**). Both are transverse sections through the cervical part of the spinal cord. SMA1 is characterized by a significant loss of anterior horn a-motoneurons. CON, control; SMA1, spinal muscular atrophy type 1. Cresyl violet

SMA before MTI

Type 1
No head control
death before 2 years



Type 2
Sitter
Scoliosis
Ventilatory support



Type 3
Walker
Risk of loss ambulation



Multidisciplinary approach

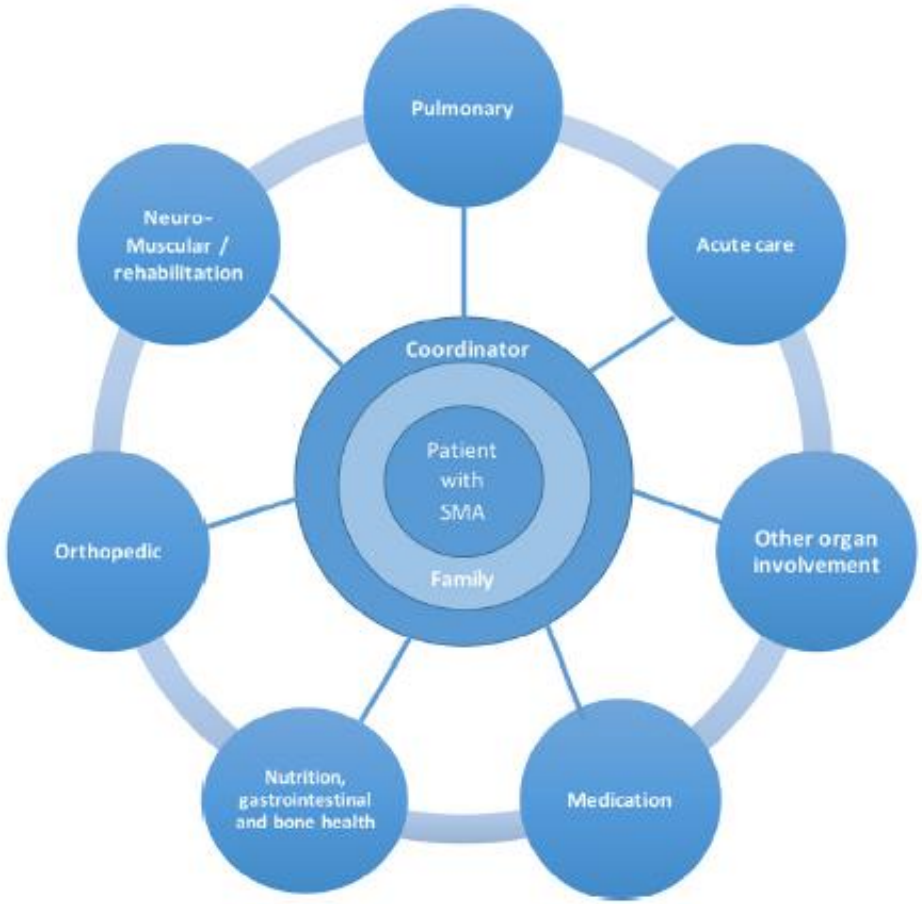
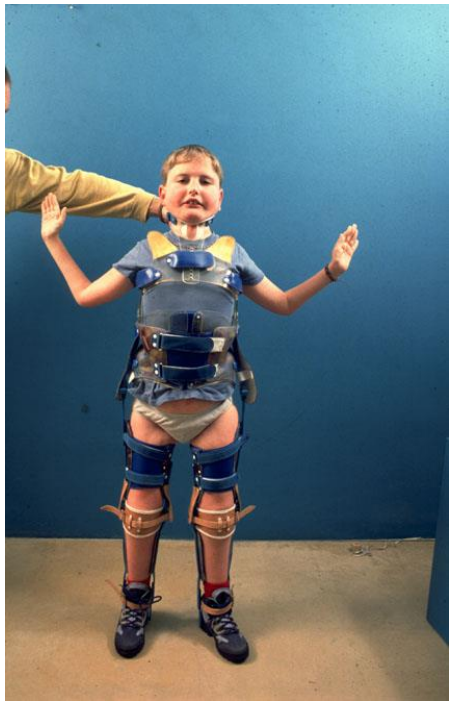


Fig. 2. Multidisciplinary approach.

scoliosis

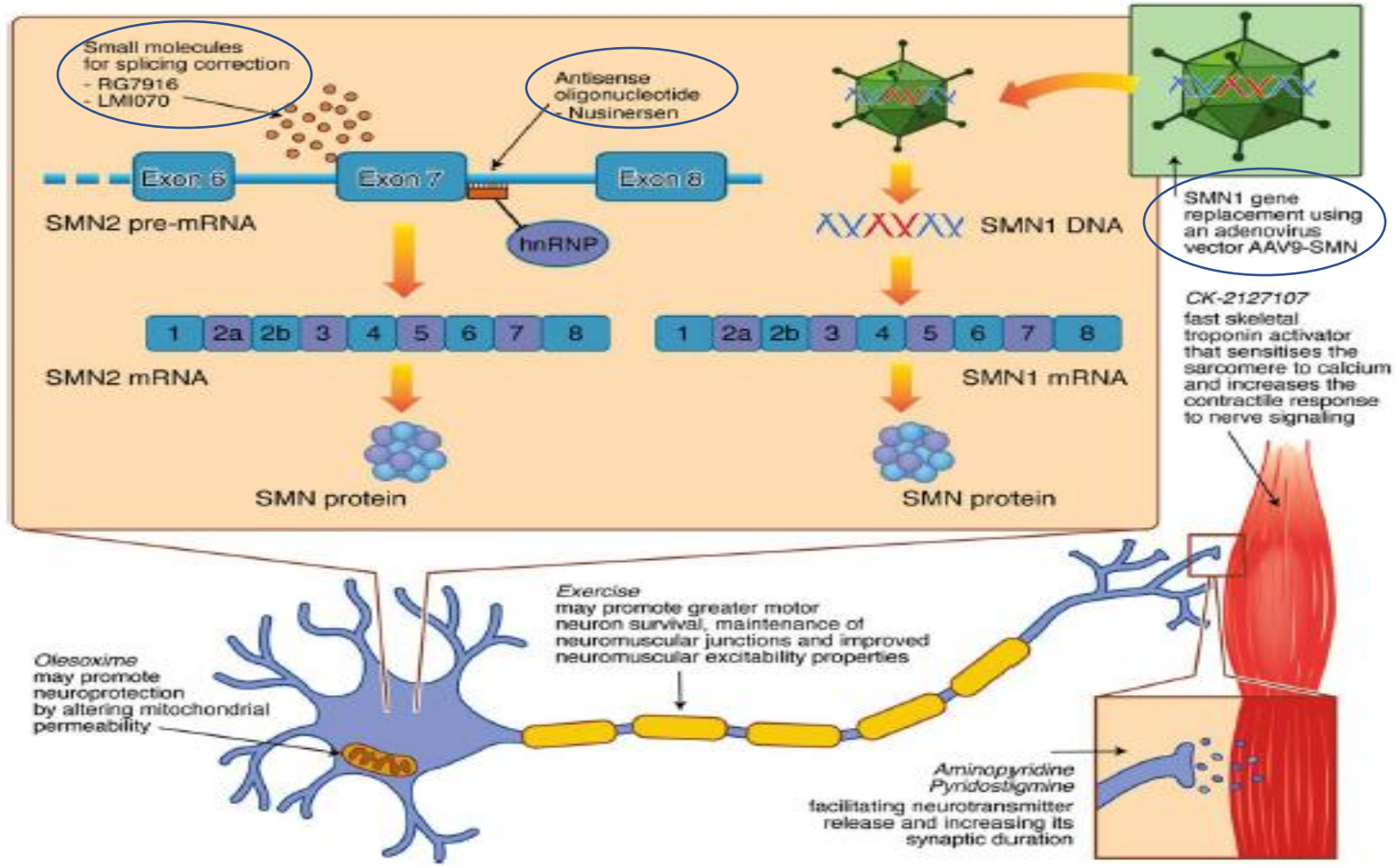


Standing



Respiratory support



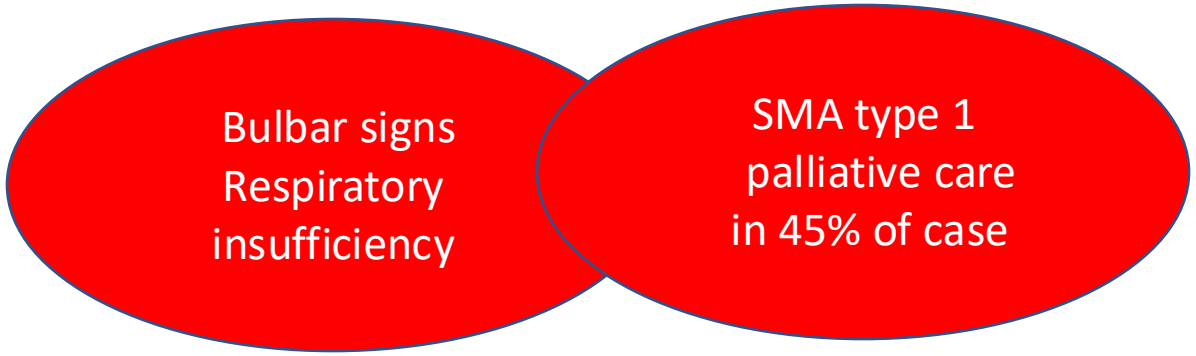


1995: SMN1 gene discover in Necker Judith Melki

2017 : First therapies

Gene therapy since 2019 in France
National meeting every 15 days (RCP)

- 35 referral centers of the network FILNEMUS
- GT for age <24 months
  - Résultat génétique et AC anti AAV
  - motor scores
  - Vidéos
  - Nutritional status
  - Respiratory function: ratio PT/HC
  - Electromyogramm: CMAP
- Choice for the therapeutic center (N=8)
- Survey and monitorring of the adverse events
- Long term evaluation in the real life





Improvement of the motor and respiratory scores

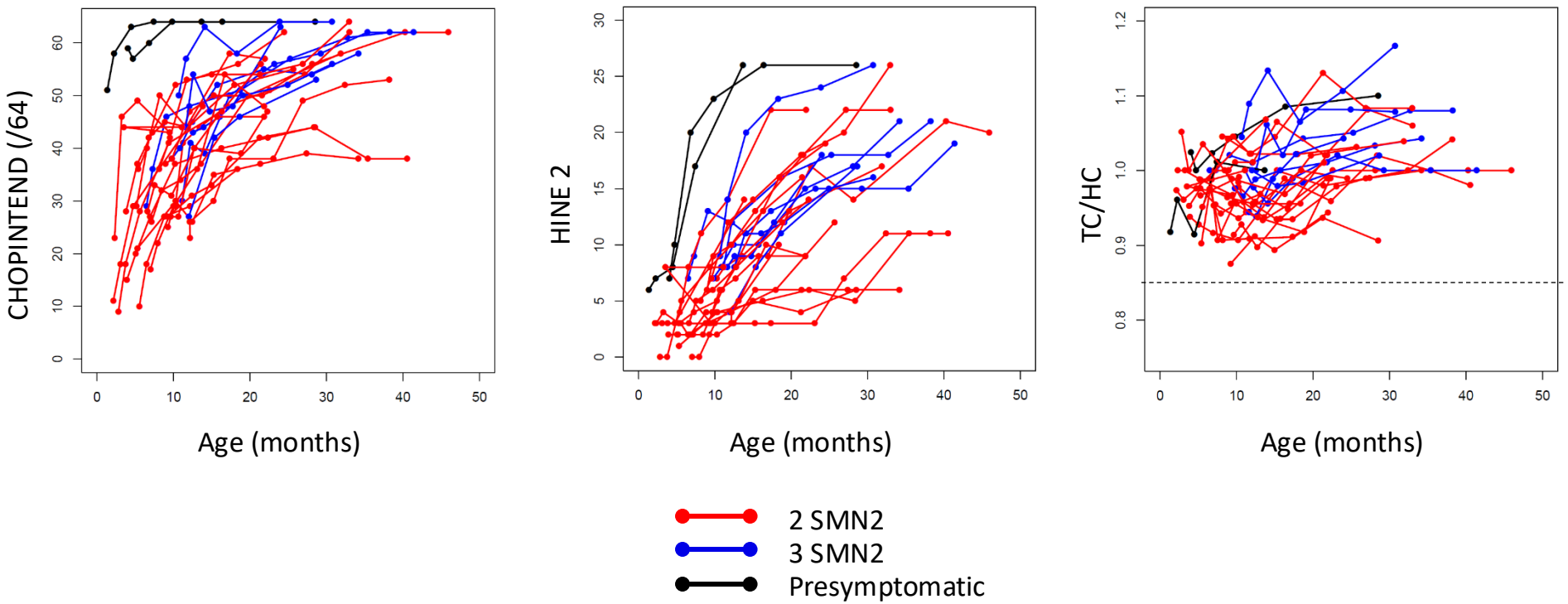


Figure 1

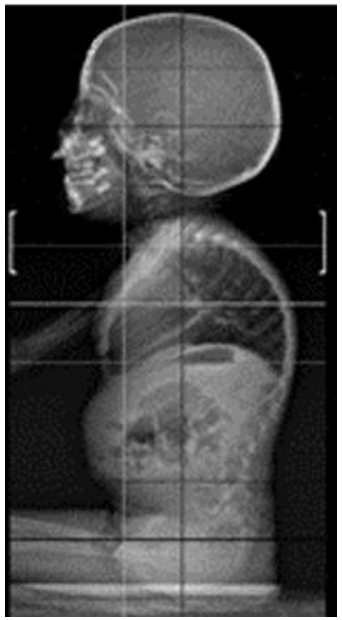
		2 SMN2 copy number																				3 SMN2							presympt.	
Initial	Numero	30	21	23	2	31	28	33	32	6	10	29	17	12	19	11	1	15	14	8	9	22	4	5	7	13	18	26	20	3
	Age Gene therapy	2,8	5,5	2,1	3,9	7	5,3	2,3	12	9,3	7,1	9,2	9,6	3,8	6,6	5,2	10	9	5,4	8,1	9	12	6,5	11	9,8	13	12	11	1,3	4
	ASI type	1b	a/b	1a	1b	1b	té 1b	té 1a	b/1c	1b	1b	é 1 b	1c	1b	1b	1b	1c	1b	1b	1c	1c	1c	1c	1c	1c	2/1c	1c	1c		
	gender	f	f	f	m	f	m	m	m	m	m	m	f	f	f	f	m	f	f	f	f	m	m	f	f	f	f	f	m	f
	initial CHOP	9	10	11	15	17	21	23	23	25	26	27	27	28	28	29	29	35	36	36	37	27	29	30	38	43	44	50	51	59
M0 (N=29)	VNI	-	-	-	-	-	-	-	-	●	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Gastrotomie	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Corset	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Head holding	-	-	-	-	-	-	-	-	-	-	●	●	●	●	-	●	●	●	●	●	●	-	●	●	●	●	●	-	●
M12 (N=29)	VNI	-	●	-	-	-	●	-	●	●	-	●	-	-	-	-	-	●	-	-	-	-	-	-	-	-	-	-	-	-
	Gastrotomie	-	-	-	-	-	-	-	-	-	-	-	●	-	-	-	-	●	-	-	-	-	-	-	-	-	-	-	-	-
	Corset	-	●	-	●	-	●	-	●	●	-	-	●	-	●	●	-	●	-	●	-	-	-	-	-	●	-	-	-	-
	Head holding	●	●	●	●	●	●	●	●	-	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
	Sitting 30 s	●	-	●	-	●	-	-	-	-	●	-	●	-	●	-	●	-	●	●	●	●	●	●	●	●	●	●	●	●
	Supporting	-	-	-	-	-	-	-	-	●	●	-	-	-	-	-	-	-	●	-	-	-	-	-	-	-	-	●	-	●
M24 (N=18)	VNI	-	-		-	-		●	●	●	-		-			-	-			-	-		-	-	-		-			-
	Gastrotomie	-	-		-	-		-	●	-	-		●			-	-			-	-		-	-	-		-			-
	Corset	-	●		●	-		●	●	●	●		●			●	●			●	●		●	●	●		●			-
	Head holding	●	●		●	●		●	●	●	●		●			●	●			●	●		●	●	●		●			●
	Sitting 30 s	●	●		-	●		●	●	-	●		●			●	●			●	●		●	●	●		●			●
	Supporting	●	●		-	-		-	●	-	●		●			-	●			●	●		●	●	●		●			●

data not available
- absent
● VNI or gastrostomy or corset present
● head holding or 30s unaided sitting or supporting present

SMA1 treated after 2 years

Early scoliosis







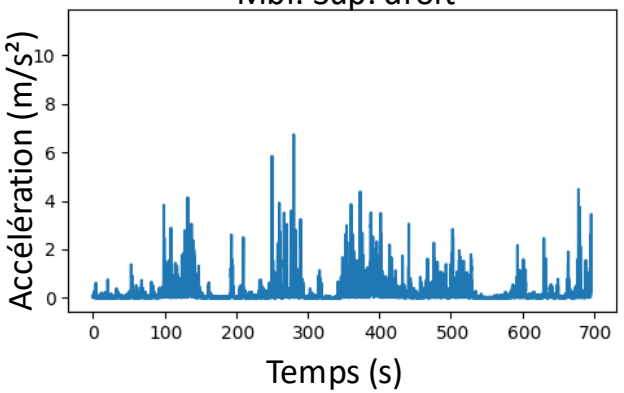






Non invasive evaluation

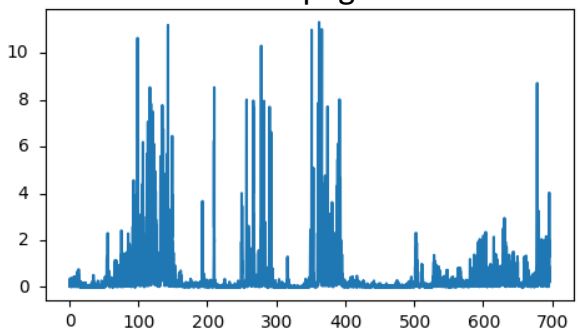
Mbr. Sup. droit



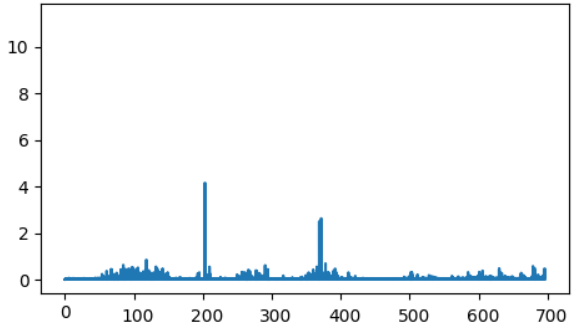
Sans portique



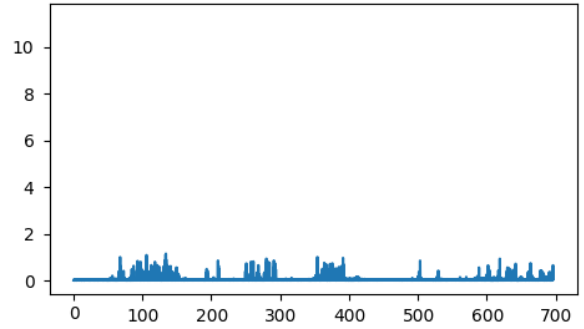
Mbr. Sup. gauche



Mbr. inf. droit



Mbr. inf. gauche



Protocole de mesure par capteurs inertiels avec et sans portique de jeux.

Non invasive measure of improvement

Barrois *et al.*
Journal of NeuroEngineering and Rehabilitation (2024) 21:183
https://doi.org/10.1186/s12984-024-01477-9

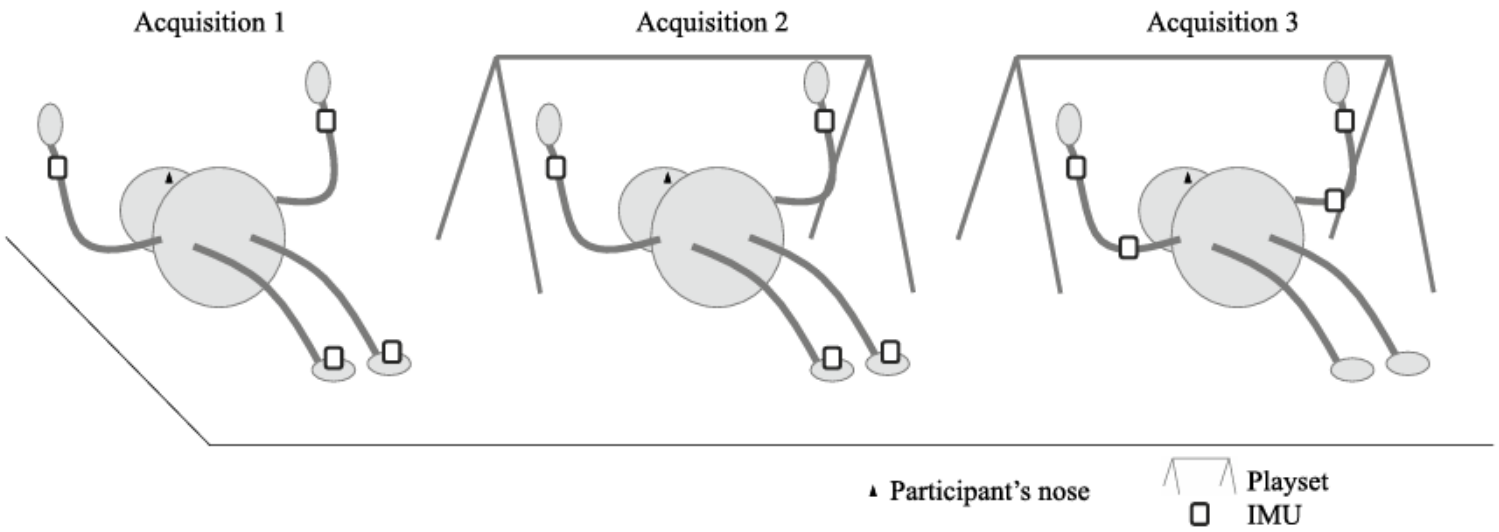
Journal of NeuroEngineering and Rehabilitation

RESEARCH Open Access

Acceptability, validity and responsiveness of inertial measurement units for assessing motor recovery after gene therapy in infants with early onset spinal muscular atrophy: a prospective cohort study

R. Barrois[1,2,3,10*], B. Tervil[3], M. Cacioppo[4,5], C. Barnerias[1], E. Deladrière[1], V. Leloup-Germa[1], A. Hervé[1], L. Oudre[3], D. Ricard[3,6], P. P. Vidal[3], N. Vayatis[3], S. Quijano Roy[7], S. Brochard[5,8], C. Gitiaux[1,2] and I. Desguerre[1,9]

Acquisition nbr.	Nbr. of IMU	IMU's position	Duration (min)	Playset	Child's position
1	4	Wrist x 2 Foot x 2	10	no	lying on the back
2	4	Wrist x 2 Foot x 2	10	yes	lying on the back
3	4	Wrist x 2 Elbow x 2	5	yes	lying on the back



STIMULUS REPORT

blood advances

Fatal thrombotic microangiopathy case following adeno-associated viral *SMN* gene therapy

Julia Guillou,[1,*] Alice de Pellegars,[2,*] Florence Porcheret,[1] Véronique Frémeaux-Bacchi,[3] Emma Allain-Launay,[1] Camille Debord,[4] Manon Denis,[5,6] Yann Péréon,[7] Christine Barnérias,[8] Isabelle Desguerre,[8,*] Gwenaëlle Roussey,[1,*] and Sandra Mercier,[6,9]

Received: 11 December 2020 | Revised: 22 June 2021 | Accepted: 27 June 2021

DOI: 10.1002/mus.27363

ISSUES & OPINIONS

MUSCLE&NERVE WILEY

Expert recommendations and clinical considerations in the use of onasemnogene abeparvovec gene therapy for spinal muscular atrophy

Elizabeth A. Kichula MD, PhD[1] | Crystal M. Proud MD[2] | Michelle A. Farrar PhD, MBBS[3] | Jennifer M. Kwon MD[4] | Kayoko Saito MD, PhD[5] | Isabelle Desguerre MD, PhD[6] | Hugh J. McMillan MD, MSc[7]

Sleep Medicine 119 (2024) 335–341

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Sleep Medicine

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

ELSEVIER





Polysomnography findings and respiratory muscle function in infants with early onset spinal muscular atrophy after gene replacement as monotherapy: A prospective study

Rémi Barrois [a,b,c,*], Lucie Griffon [d,e], Christine Barnerias [f], Cyril Gitiaux [a,c,f], Isabelle Desguerre [f,g,h], Brigitte Fauroux [d,e], Sonia Khirani [d,e,i]

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 21 December 2022
DOI 10.3389/fped.2022.1062390

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Olivier Putois,
Université de Strasbourg, France

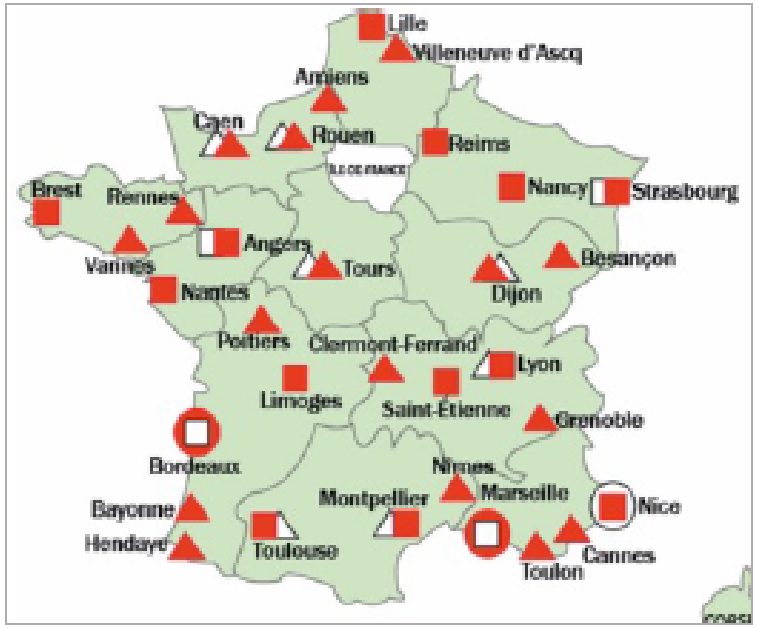
REVIEWED BY
Raphael Minjard,
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Parents' dilemma: A therapeutic decision for children with spinal muscular atrophy (SMA) type 1

Sophie Boursange[1,2,3]*, Marco Araneda[4], Caroline Stalens[5], Isabelle Desguerre[6,7,8], Christine Barnerias[6,7,8], Marie-

French SMA – Registry

- Registry of all patients followed in France (treated and non-reated).
- Start of the registry in **January 2020**.
- Data collection:
  - **Retrospective**: September 2016 - January 2020.
  - **Prospective:** from January 2020.
- Follow-up for **10 years**.
- **64 participating centres**: 32 paediatric, 29 adult, 3 mixed.



Research article

REGISTRE SMA FRANCE: A nationwide observational registry of patients with spinal muscular atrophy in France

Journal of Neuromuscular Diseases
1–11
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Lamiae Grimaldi[1], Rocio Garcia-Uzquiano[2], Marta Gomez-Garcia de la Banda[2], Amal Oulhissane-Omar[2], Celine Tard[3], Pascale Saugier-Veber[4], Vincent Laugel[5], Isabelle Desguerre[6], Pascal Cintas[7], Carole Vuillerot[8], Frederic Audic[9], Claude Cances[10], Tanya Stojkovic[11], Jon Andoni Urtizberea[12], Shahram Attarian[9], Juliette Ropars[1,13], Susana Quijano-Roy[2,14] and the Registre SMA France Study Group

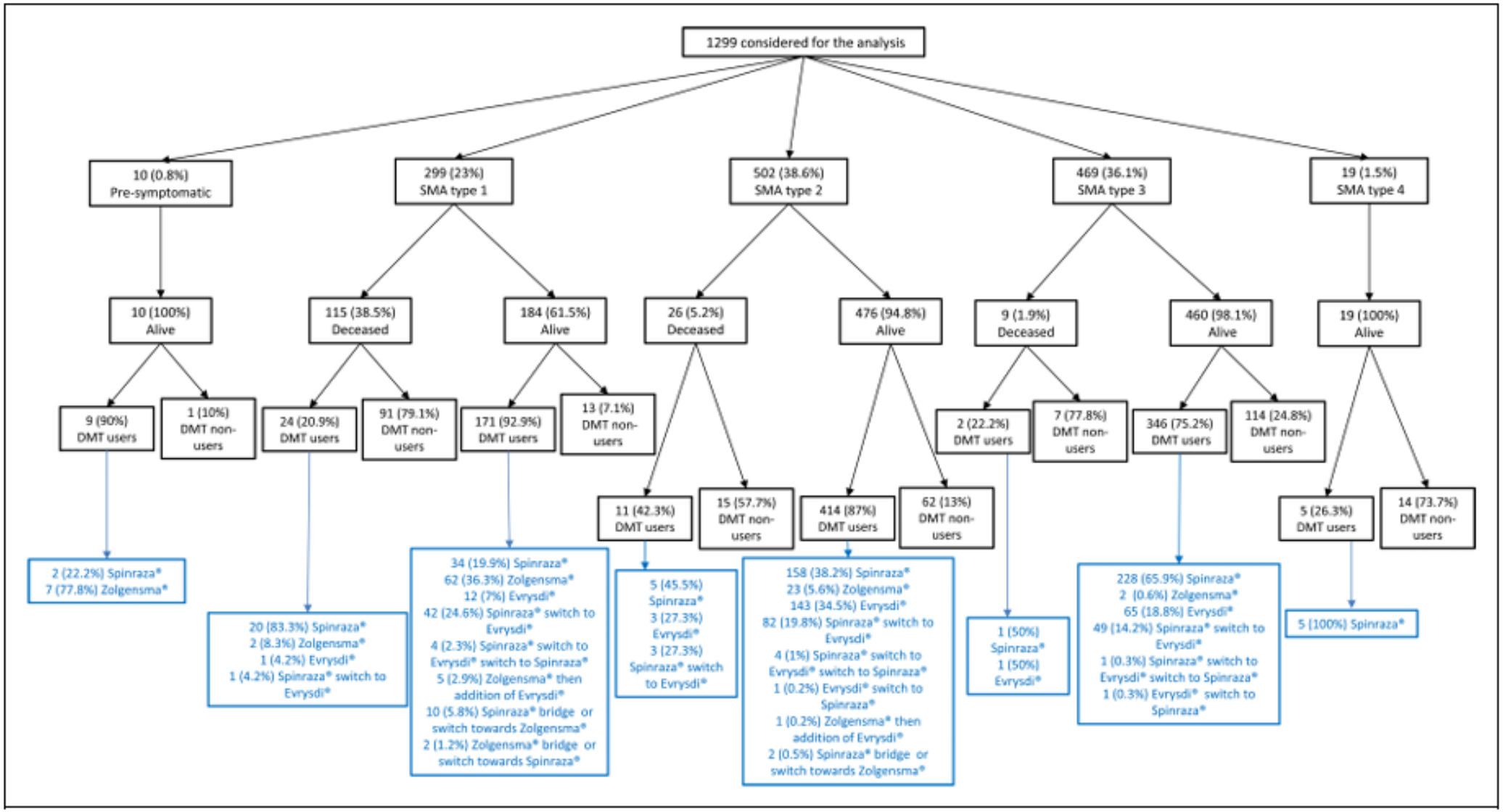
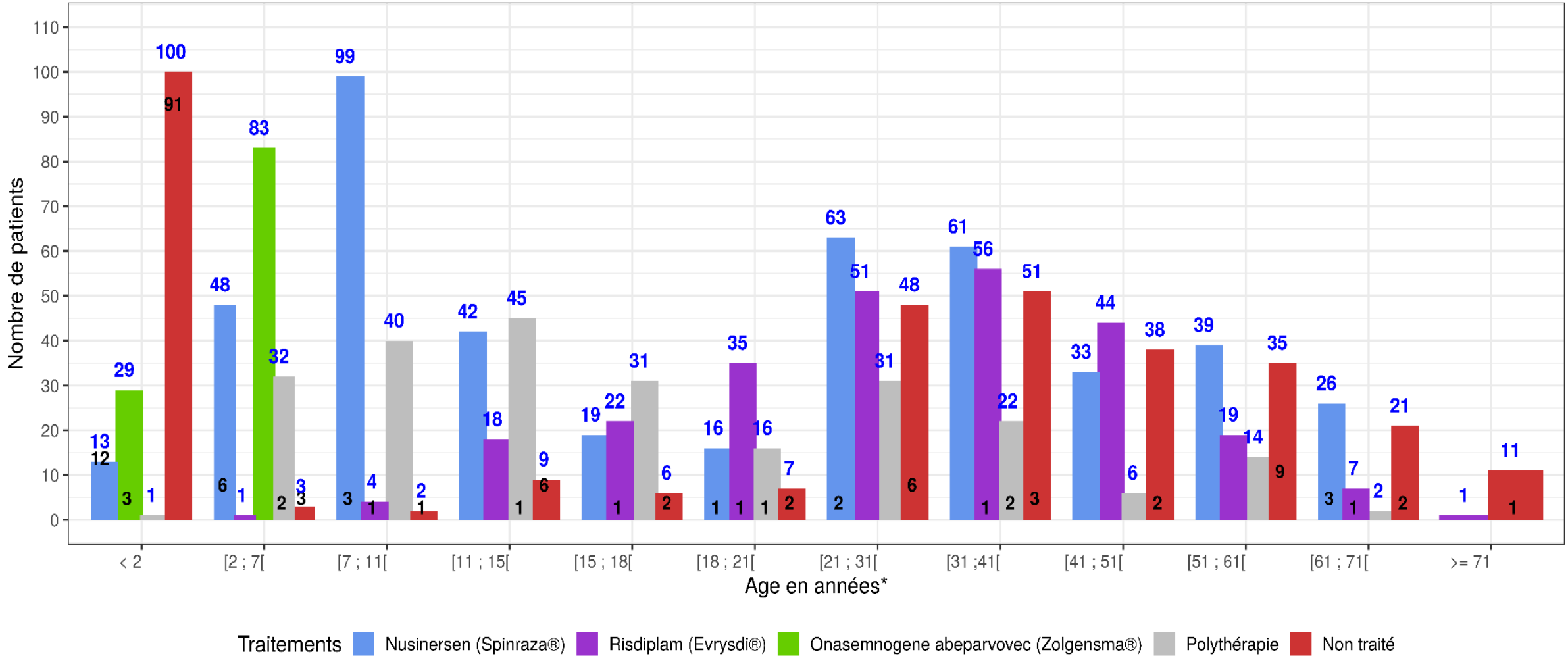


Figure 2. Distribution of patients with SMA according to SMA type, vital status, and DMT use.
DMT, disease-modifying therapy; SMA, spinal muscular atrophy.

Répartition des traitements par tranche d'âge chez les 1400 patients

** Nombre de décès en noir



*Age = Age à la date d'extraction de la base de données, pour les patients vivants à cette date

*Age = Age au décès, pour les patients décédés

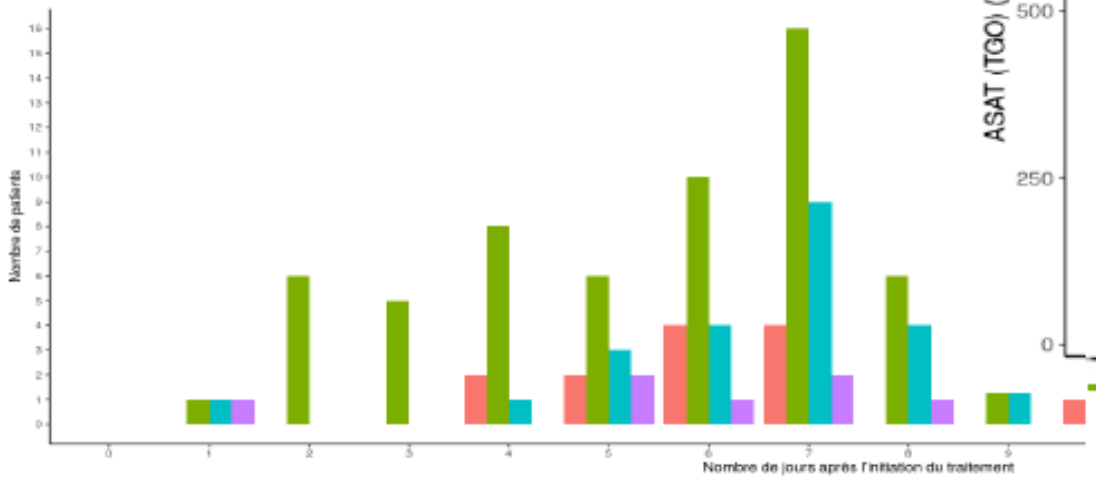
Gene therapy cohort

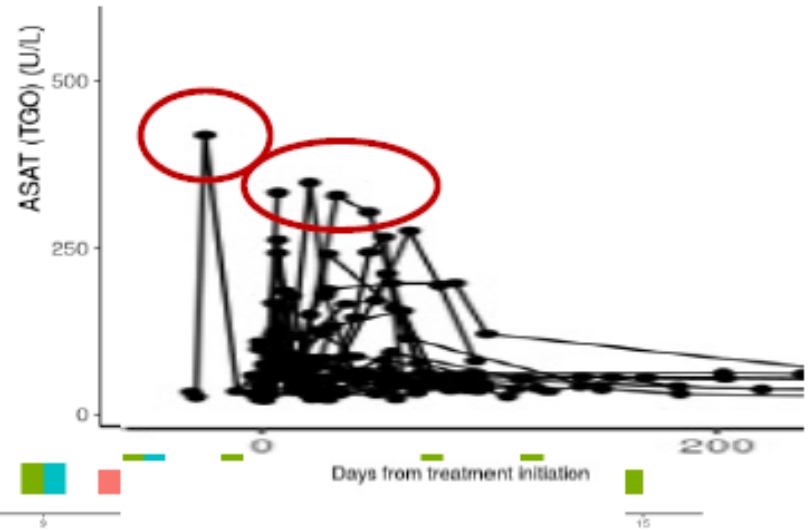
Adverse events during the first two weeks

- **ASAT > 50 U/L** : 34 patients (**87%**).
- **ASAT > 150 U/L**: 16 patients (**41%**).

- **Platelets < 150 G/L**: 17 patients (**44%**).
- **Platelets < 65 G/L:** 5 patients (**13%**).

2 <u>deceased</u> patients:
- 1 in the context of **TMA, 2 months post GT**
- 1 in the context of **respiratory infection, 4 months post GT**



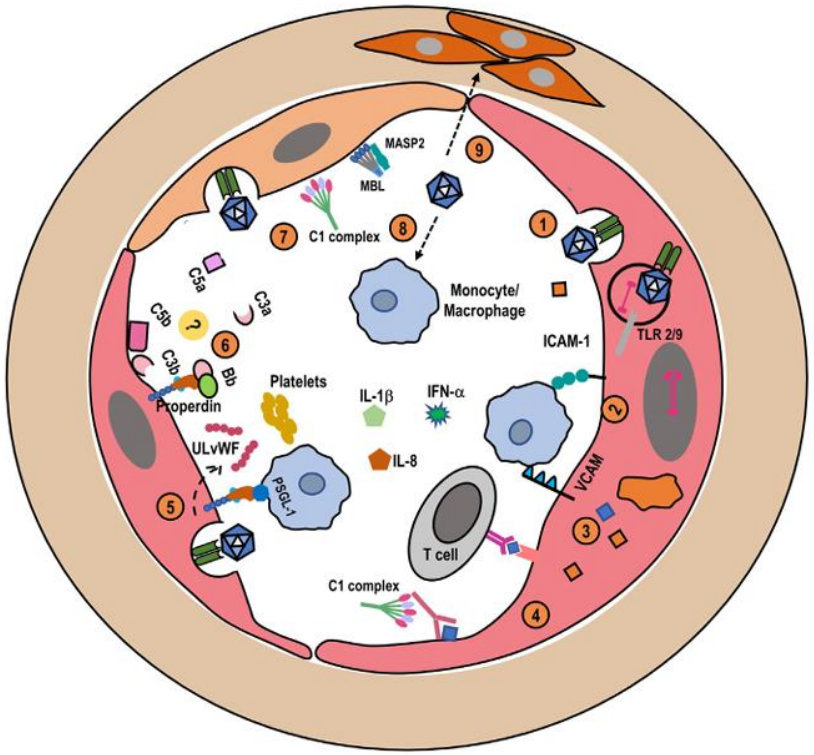


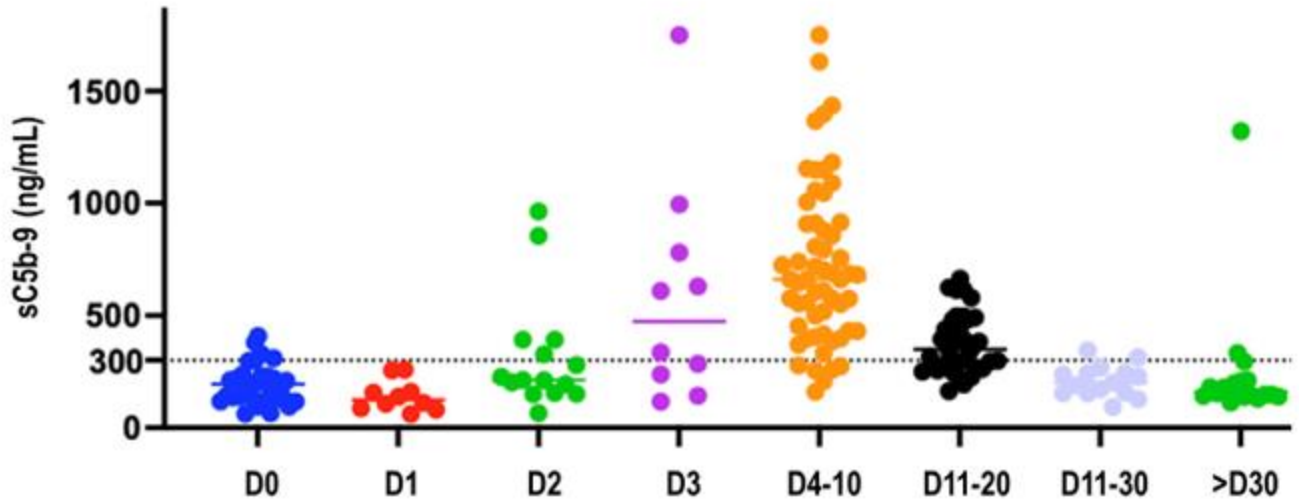
Thrombotic Microangiopathy as an Emerging Complication of Viral Vector–Based Gene Therapy

Check for updates

Nora Schwotzer[1,7], Carine El Sissy[2,3,7], Isabelle Desguerre[4], Véronique Frémeaux-Bacchi[2,3], Laurent Servais[5,6] and Fadi Fakhouri[1]

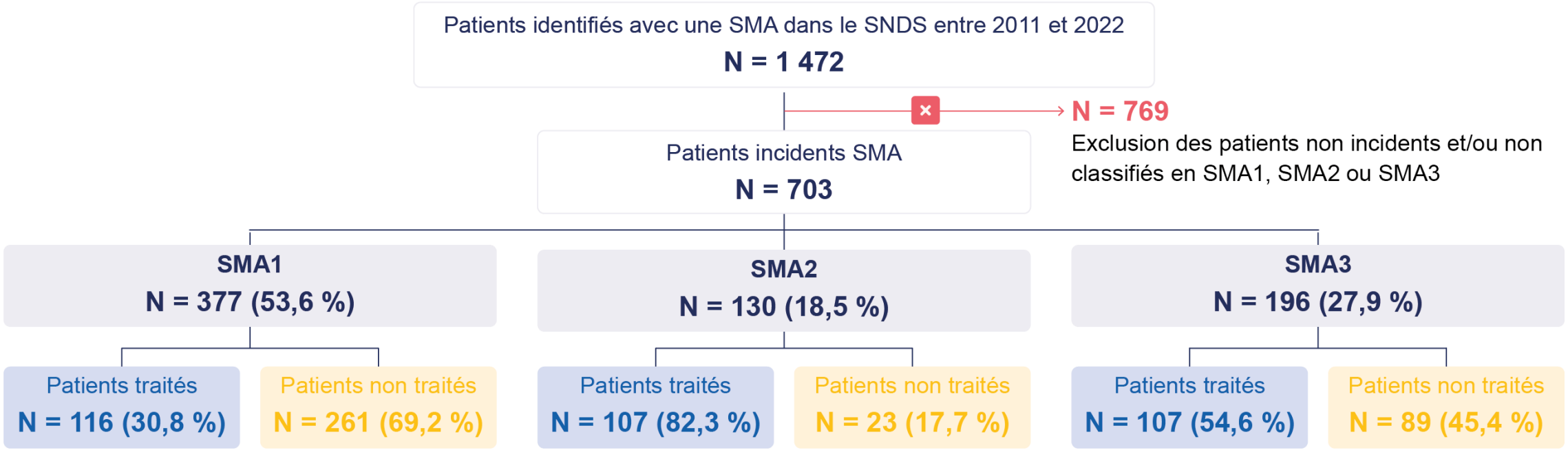
[1]Service of Nephrology and Hypertension, Department of Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; [2]Department of Immunology, Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Paris, France; [3]Paris University, Paris, France; [4]Paediatric Neurology Department, Necker Hospital, APHP Centre, Université Paris Cité, Paris, France; [5]MDUK Oxford Neuromuscular Center and NIHR Oxford Biomedical Research Center, University of Oxford, Oxford, UK; and [6]Neuromuscular Center, Department of Pediatrics, University of Liege and University Hospital of Liege, Belgium



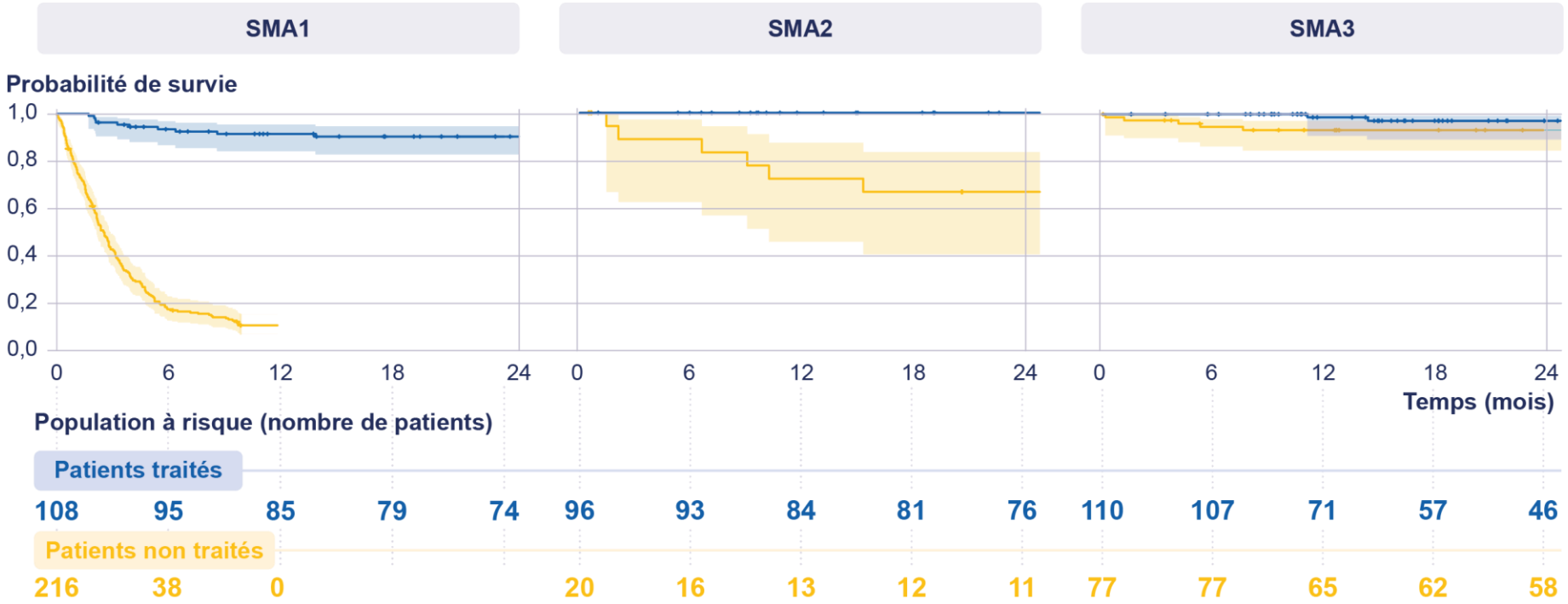


ics of complement final pathway activation in patients receiving viral-based gene therapy. Serum levels of sC5b-9, a r

Résults of analysis of National Health insurance in France over 11 years Medico-economic analysis



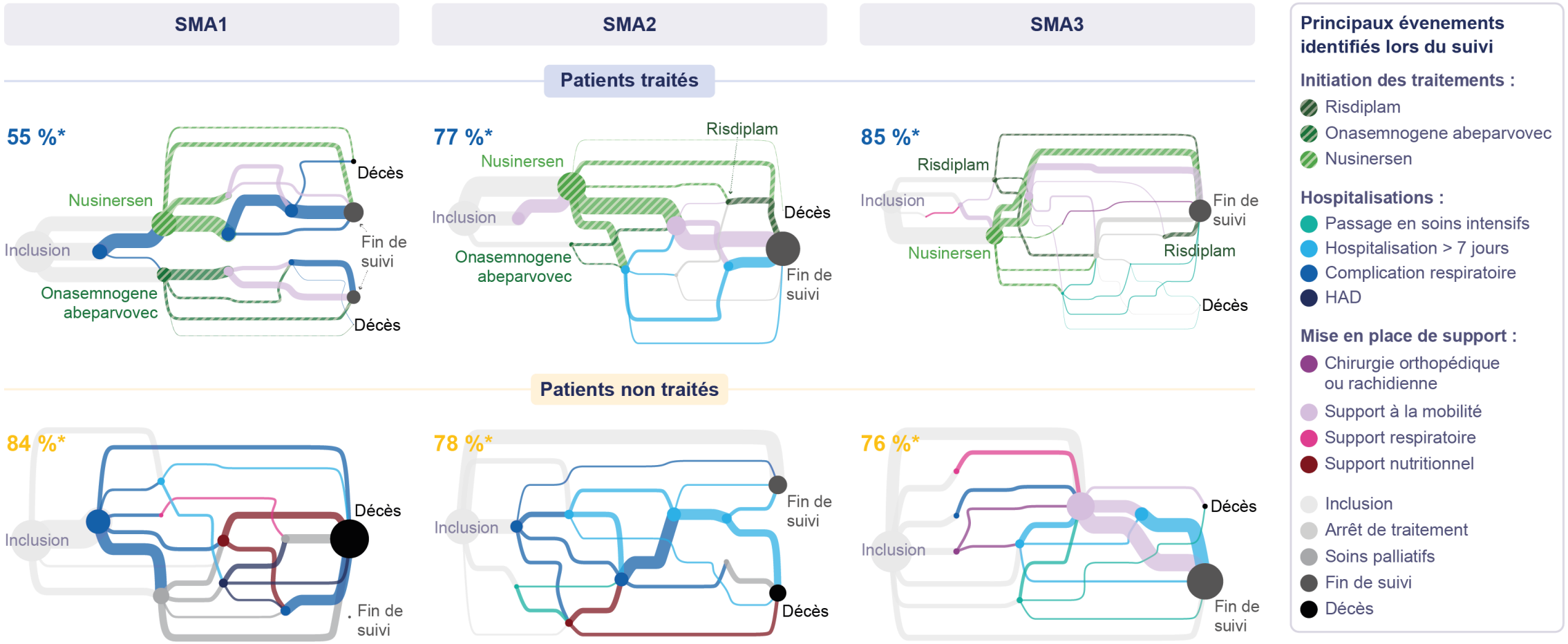
Résults- life expectancy



- Probability of life at 12 months

SMA1		SMA2		SMA3	
Patients traités	Patients non traités	Patients traités	Patients non traités	Patients traités	Patients non traités
91 %	11 %	100 %	72 %	99 %	93 %

Care trajectory -Data mining analysis



*Pourcentage des parcours de soins des patients représentés par chaque graphique (score de rejouabilité)

Benefit of presymptomatic treatment : neonatal screening since september 2025 in France

Vill et al. Orphanet J Rare Dis (2021) 16:153
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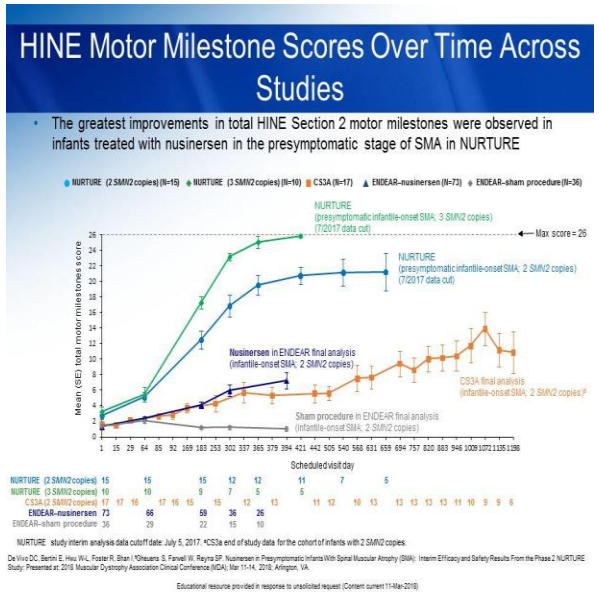
Newborn screening for spinal muscular atrophy in Germany: clinical results after 2 years

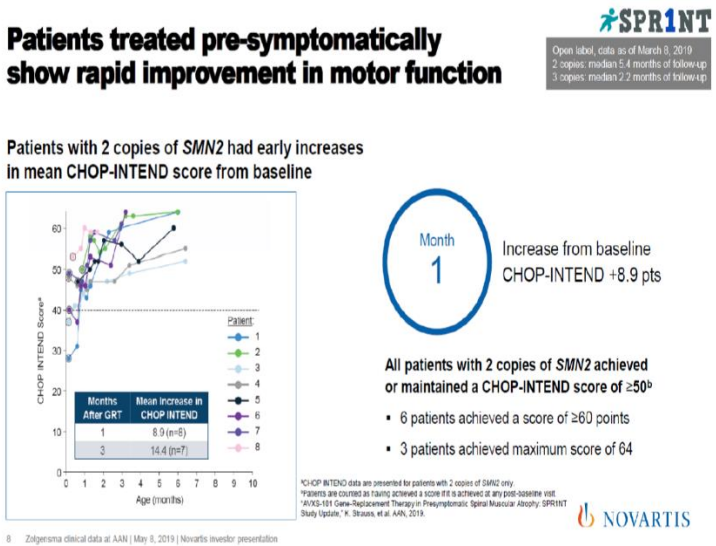
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Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study

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New treatments for serious conditions: Ethical implications

N M P King, C E Bishop

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(1) Uncertain and unknown effects of a newly approved treatment and the necessity of long-term follow-up

(2) Causes and consequences of overoptimism and hype (Network, Parent Association)

(3) Implications of high treatment costs (price of the medication but also recurrent hospitalisations and medical time consuming)

(4) Implications for newborn screening: presymptomatic treatment for SMA type 1, 2, 3

(5) Changing the standard of care with more invasive cares (place of ventilatory support , gastrostomy).

Quality of life? New needs?

- ***Longer life span*** increases the needs for financial support, equipment, and assistance in activities of daily living
- It also has important ***existential and social implications,*** as those living longer with disabling conditions share the human desire to live independently, participate in the workforce, and have their own families.

Ethical purposes

- Principes: respect parent, patient’s autonomy, safety, legacy, quality of life
- Multidisciplinary team and decision making process
- Implication of the family in the discussion but the decision is medical in accordance with the parents…..most of the time
- First or best interest of the child
  - Sometimes against the whishes of the parents
  - Dilemna for the medical team , for the parents

4 Axis: *M Hully*

