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European Reference Network for rare or low prevalence complex diseases

Network Neuromuscular Diseases (ERN EURO-NMD)

Working Group Neuropathies

Inter-ERN Working Group Gene Therapies

8th ERN EURO-NMD Annual Meeting

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Landscape of gene therapy practices across Europe

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SURVEY ON CURRENT PRACTICES REGARDING GENETIC THERAPIES IN EUROPE

- Proposed by **Holm Graessner** and developed within the framework of **the inter-ERN working group on Gene Therapy** led by the **ERN EURO-NMD,** including **ERN-RND** and **EpiCARE**
- ERN-EYE and MetabERN were also invited to contribute to the initiative *with the objectives*:
- **Aim to investigate the current landscape of GTs in Europe** (*data applicable for year 2023*)
  - ✓ **Access conditions** and **availability** of approved therapies **by center and country**
  - ✓ **Organizational aspects**, **approval process** and **clinical decision-making** around Europe when gene therapy is considered for treating a patient **in specified disease pathways**

Discussed May-Oct 2023 → **Finalized early 2024** → **Conducted June-July 2024** → **Results collected Sep 2024**

➢Following this mapping process, ultimately, we aim to improve and harmonize access to genetic and cellular therapies for all eligible patients across Europe

5 participating ERNs:

1. **EURO-NMD**
2. **ERN-RND**
3. **EpiCARE**
4. **MetabERN**
5. **ERN-EYE**

SURVEY DESIGN

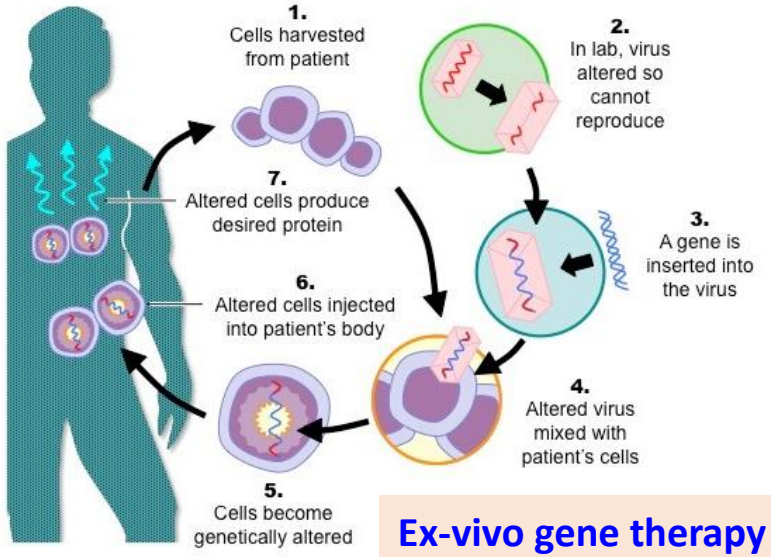
- **Set of information collected from all participating ERNS:**
  - **List of HCPs invited by the respective ERN, country, status,** name of the HCP representative (**contact person**)
    1. **List of gene therapies approved in the EU (EMA marketing authorization)** for the **diseases falling under each ERN scope**
    2. **List of diseases with ongoing gene therapy clinical trials**
  - **One EMA-approved gene/cell therapy selected as the focus of a section of the survey exploring:**
    - **country-specific GT practices**
    - **genetic screening practices**

Survey created online using EU Survey

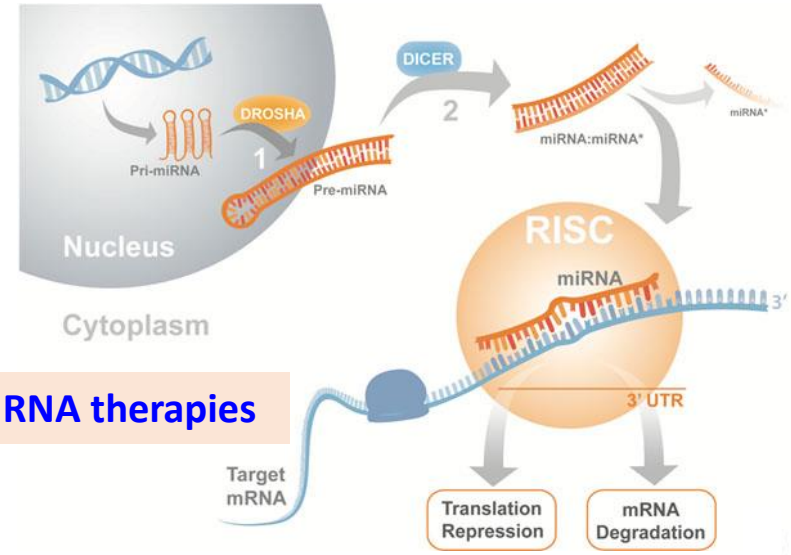
- *Made necessary **modifications and corrections** as discussions progressed*
- *Checked content consistency, adapted survey parameters for accurate visibility*

ERN	Persons involved THANK YOU!
EURO-NMD	• **Houda Ali (Project manager)** • Kleopas Kleopa (inter-ERN WG chair) • **Teresinha Evangelista (EURO-NMD coordinator**)
ERN-RND	• **Holm Graessner (ERN-RND coordinator)** • Sophie Anne Gabrielle Ripp (Project manager)
EpiCARE	• Sébile Tchaicha (Project manager) • Alexis Arzimanoglou (EpiCARE coordinator)
MetabERN	• Cinzia Bellettato (Project manager)
ERN-EYE	• Isabella Anna Vacchi (Project manager)

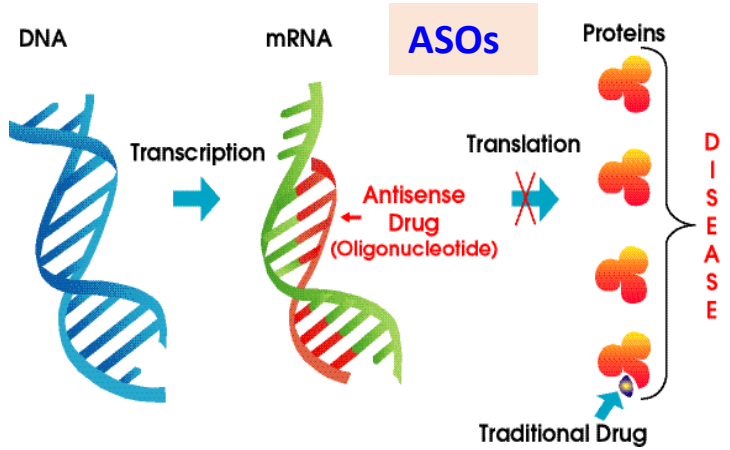
INTER-ERN WORKING GROUP GENE THERAPY

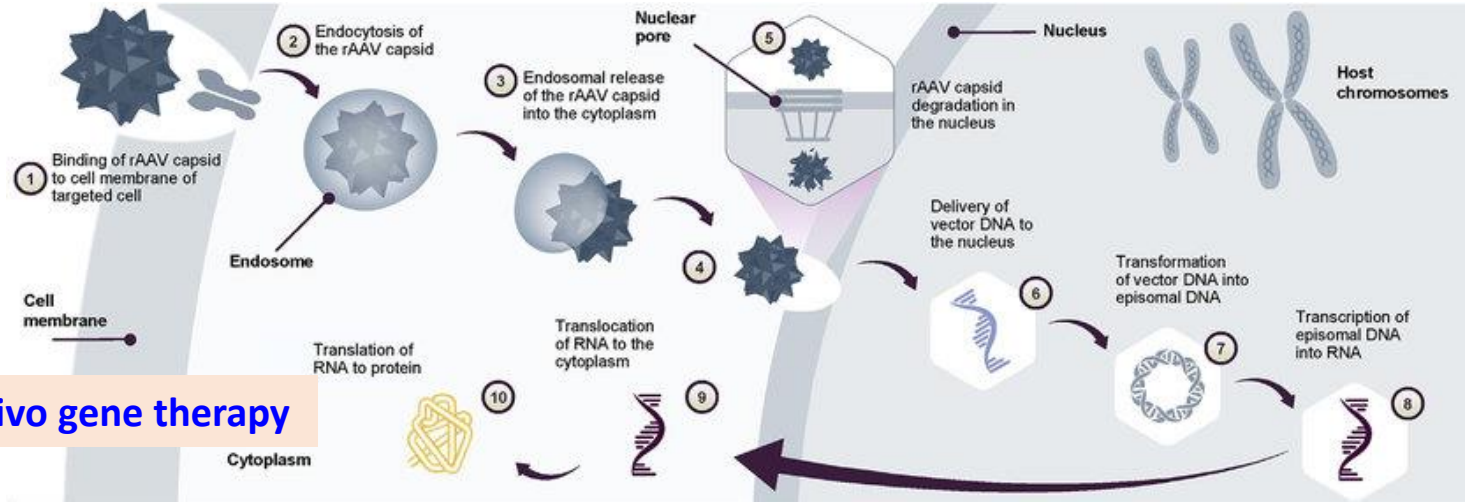


Ex-vivo gene therapy

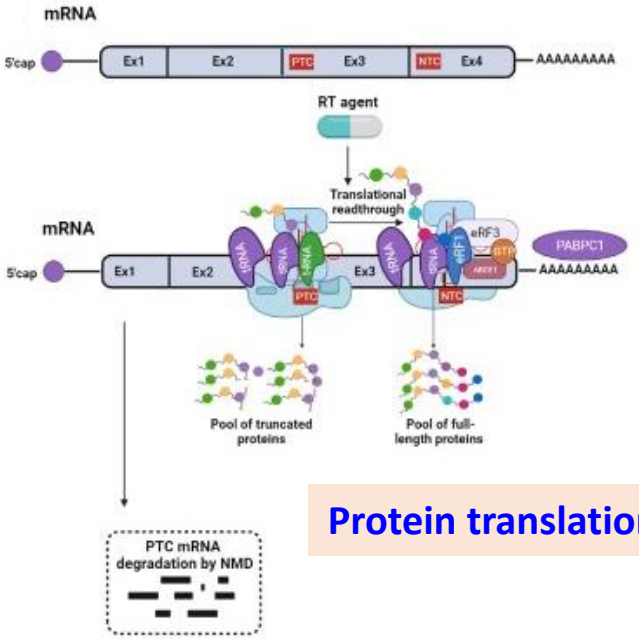


RNA therapies





In-vivo gene therapy



Protein translation

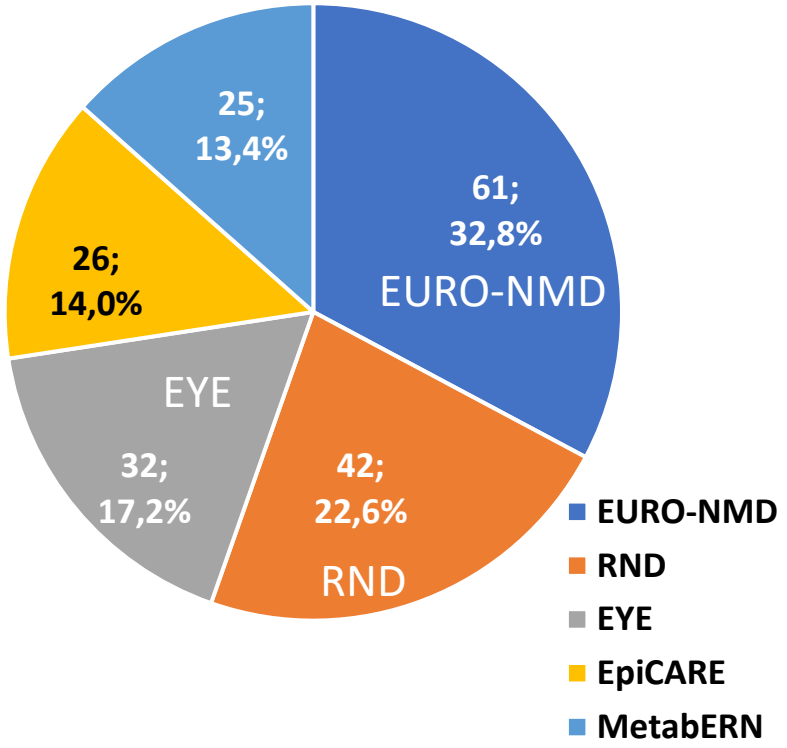
Survey scope: Inclusive questionnaire encompassing **all therapies relating to modifying genes or genetic information**

Survey instructions and completion

Instructions provided to target participants:

- ***Own experience*** *to fill out the questionnaire.*
- ***Questionnaire is ERN-specific and center-specific****. Please fill out the questionnaire on behalf of the ERN you have received it from.*
- *If* ***center belongs to more than one ERN****, then the* ***survey should be filled for each ERN separately****, by the appropriate person in your center.*
- ***1 filled survey per center per ERN****.*
- ***HCP representatives*** *to fill the survey on behalf of center,* ***involving other colleagues, when needed****, to help you with questions whose answers you don't know or that require specific expertise.*

Total HCP responses by ERN (% of all responses)



- **HCPs that responded from all ERNs**

	EURO-NMD	RND	EYE	EpiCARE	MetabERN	ALL ERNs
HCPs responded per ERN	61 (33,2%)	42 (22,8%)	32 (16,8%)	26 (13,6%)	25 (13,6%)	186

Response rates for ERN-EURO-NMD

	ERN-EURO NMD Centers*	Countries
Contacted	91	27
Responses received	61	23
Response rate	67,0%	85,2%

*includes former UK members and external collaborators

- In total, **61 EURO-NMD centers participated** in the survey, out of the 91 centers contacted (**67%**)
- **23 countries are represented (85%** of all 27 countries in EURO-NMD)
- **No responses from**: **BU, GR, LU, UK**

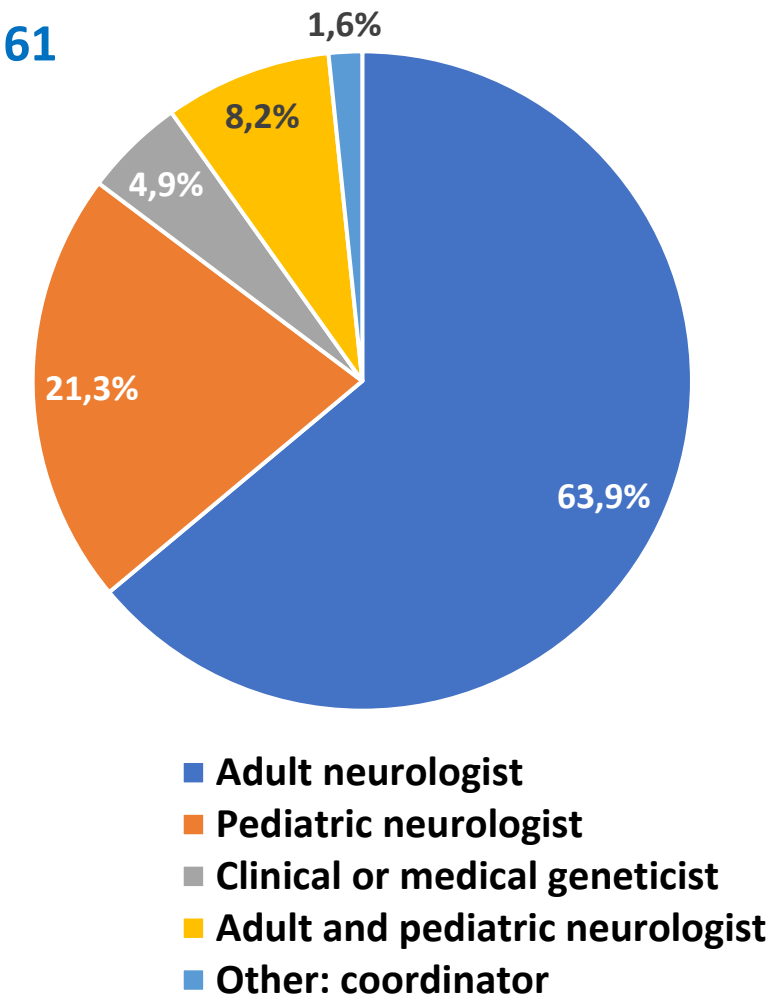
Responders by country

Country	Contacted (EURO-NMD centers)	Responses (EURO-NMD centers)	Response rate (%)
Austria	2	2	100
Belgium	5	5	100
Bulgaria	1	0	0
Cyprus	1	1	100
Czech Republic	2	2	100
Denmark	2	1	50
Estonia	1	1	100
Finland	2	2	100
France	9	6	67
Germany	10	8	80
Greece	1	0	0
Hungary	2	1	50
Ireland	1	1	100
Italy	20	14	70
Latvia	1	1	100
Lithuania	1	1	100
Luxembourg	1	0	0
Malta	1	1	100
Netherlands	6	3	50
Norway	1	1	100
Poland	1	1	100
Portugal	1	1	100
Slovenia	1	1	100
Spain	7	4	57
Sweden	2	1	50
Ukraine	4	2	50
United Kingdom	5	0	0
ALL COUNTRIES	91	61	67

Represented specialties among EURO-NMD Responders

*Q: What is your expertise/function?

n = 61



Specialty	Number	%	incl. Clinical or medical geneticist	incl. Metabolic diseases specialist
Adult neurologist	39	63,9	1	
Pediatric neurologist	13	21,3	1	1
Clinical or medical geneticist	3	4,9	3	
Adult and pediatric neurologist	5	8,2		1
Other: coordinator	1	1,6		
TOTAL	61	100,0	5	2

Part 1: EMA-approved therapies for rare neuromuscular diseases

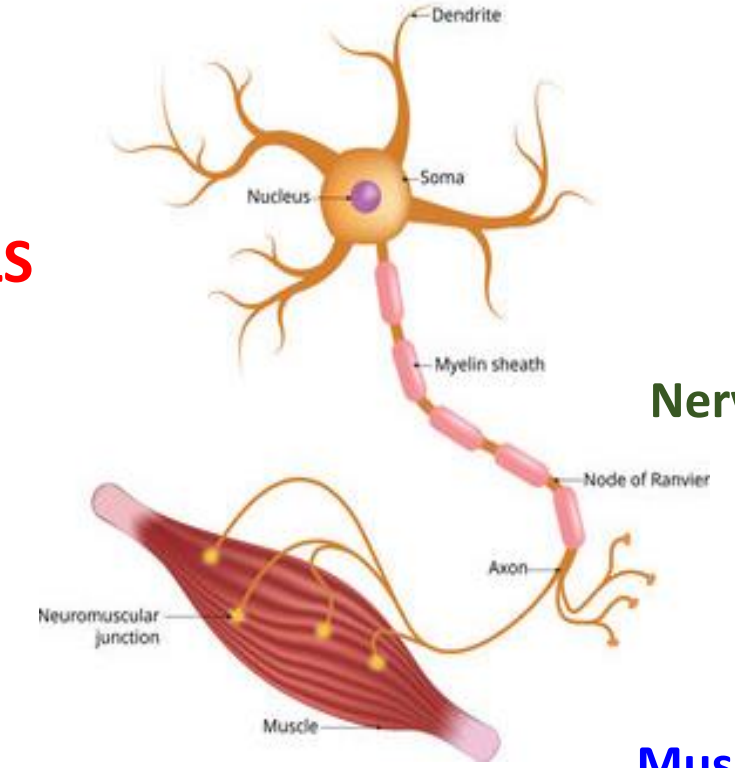
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Nusinersen
Evrysdi
Zolgensma → SMA

Qalsody → SOD1-FALS

Amvuttra
Tegsedi
Onpattro → ATTRv

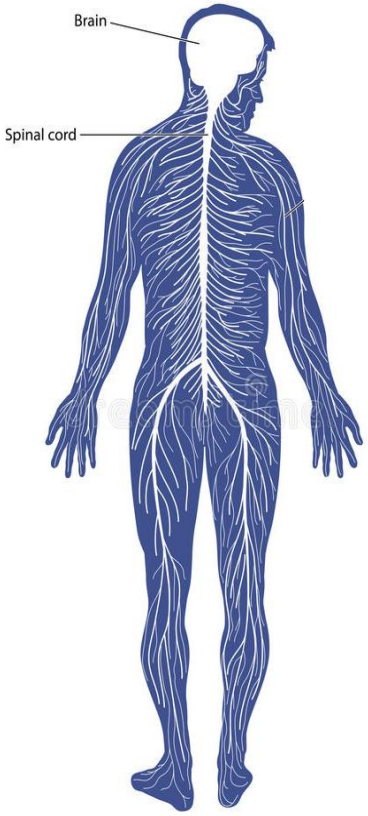
Translarna → DMD



Motor Neuron

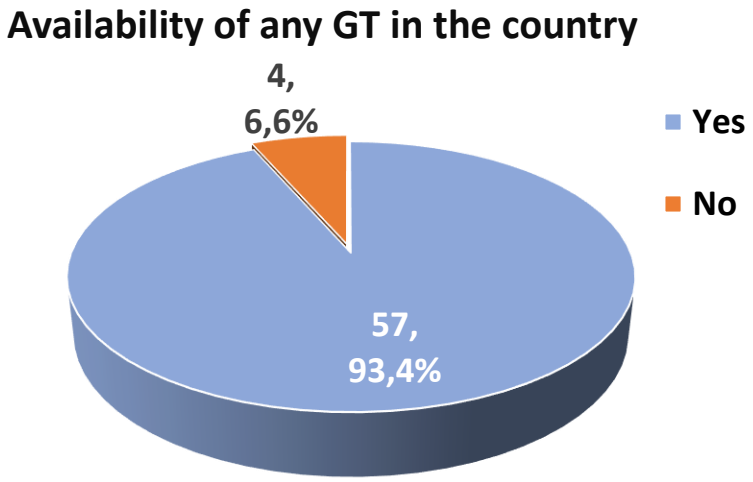
Nerve

Muscle



Availability of GTs by country

***Q: Are any EMA-approved gene or cell therapies for neuromuscular diseases covered by the ERN EURO-NMD available *in your country* at all?**



- ***If answer here was no, then participants were taken directly to the clinical trials section***
- *We received **discrepant results between Centers** in France and Italy*
  - Might show a **lack of awareness of some participants** regarding access and practices in their country
- ***Latvia and Estonia appear to have no availability** for approved therapies*

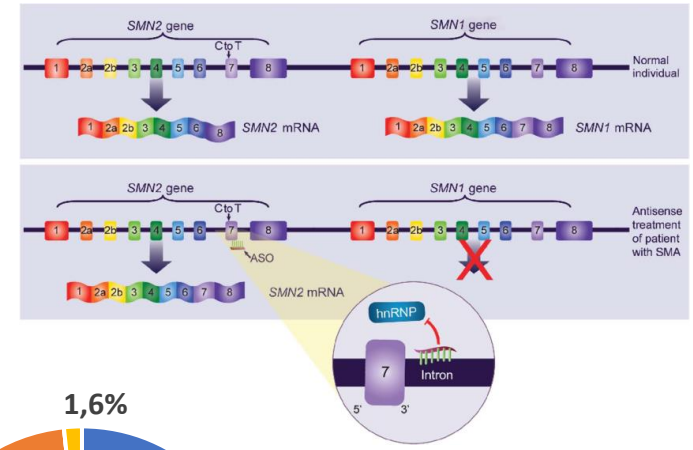
Country	Yes	No	Total
ALL COUNTRIES	57 (93,4%)	4 (6,6%)	61
Austria	2	0	2
Belgium	5	0	5
Cyprus	1	0	1
Czech Republic	2	0	2
Denmark	1	0	1
Estonia	0	1	1
Finland	2	0	2
France	5	1	6
Germany	8	0	8
Hungary	1	0	1
Ireland	1	0	1
Italy	13	1	14
Latvia	0	1	1
Lithuania	1	0	1
Malta	1	0	1
Netherlands	3	0	3
Norway	1	0	1
Poland	1	0	1
Portugal	1	0	1
Slovenia	1	0	1
Spain	4	0	4
Sweden	1	0	1
Ukraine	2	0	2

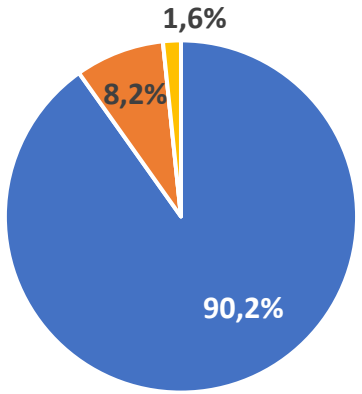
➢ Availability of SMA therapies by country:

SPINRAZA

➢ **Modifies pre-mRNA splicing of the *SMN2***

→ improvement in motor-milestone response and increased survival rate (*Finkel et al., NEJM 2017*)





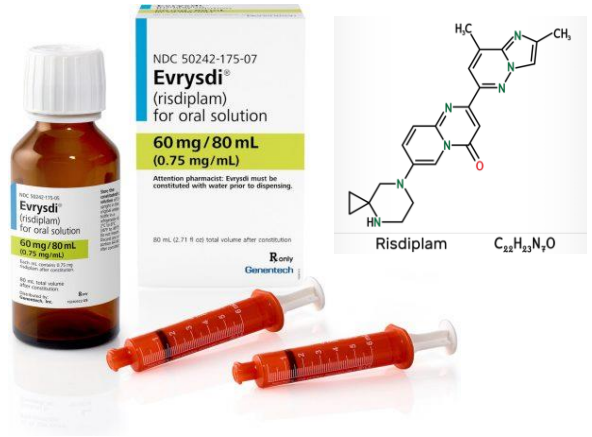
- Available in my centre
- Available in my country but not in my center
- Not available in my country
- Not sure

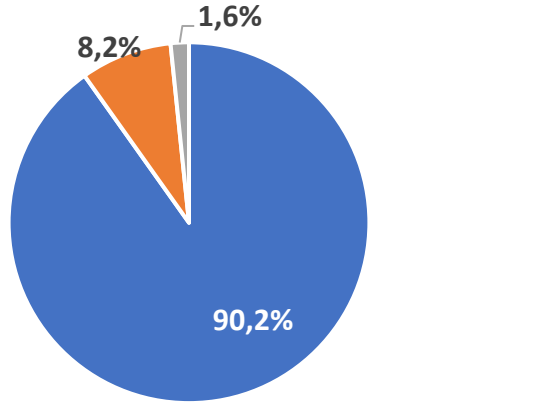
SPINRAZA	Available in my center	Available in my country, but not in my center	Not available in my country	I'm not sure	TOTAL responses
ALL COUNTRIES	51 (89,5%)	5 (8,8%)	0 (0%)	1 (1,8%)	57
Austria	2				2
Belgium	5				5
Cyprus	1				1
Czech Republic	2				2
Denmark	1				1
Finland	2				2
France	5				5
Germany	8				8
Hungary	1				1
Ireland	1				1
Italy	11	2			13
Lithuania	1				1
Malta				1	1
Netherlands	1	2			3
Norway	1				1
Poland	1				1
Portugal	1				1
Slovenia	1				1
Spain	3	1			4
Sweden	1				1
Ukraine	2				2

➢ Availability of SMA therapies by country:

EVRYSDI

- small molecule that modifies *SMN2* pre-mRNA splicing *(Baranello et al., NEJM 2021)*



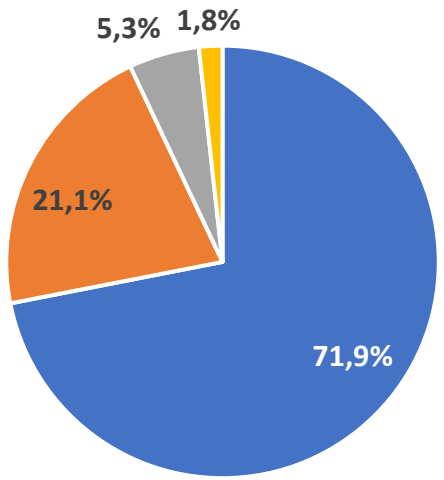


EVRYSDI	Available in my center	Available in my country, but not in my center	Not available in my country	I'm not sure	TOTAL responses
ALL COUNTRIES	51 (89,5%)	5 (8,8%)	1 (1,8%)	0 (0%)	57
Austria	2				2
Belgium	5				5
Cyprus	1				1
Czech Republic	2				2
Denmark	1				1
Finland	2				2
France	5				5
Germany	8				8
Hungary	1				1
Ireland		1			1
Italy	11	2			13
Lithuania	1				1
Malta			1		1
Netherlands	1	2			3
Norway	1				1
Poland	1				1
Portugal	1				1
Slovenia	1				1
Spain	4				4
Sweden	1				1
Ukraine	2				2

➢ Availability of SMA therapies by country - ZOLGENSMA

- ❑ AAV9-mediated SMN gene replacement in neurons
- ❑ Prolongs survival and motor function (*Mendell et al., NEJM 2017*)

(scAAV9.CB.hSMN)

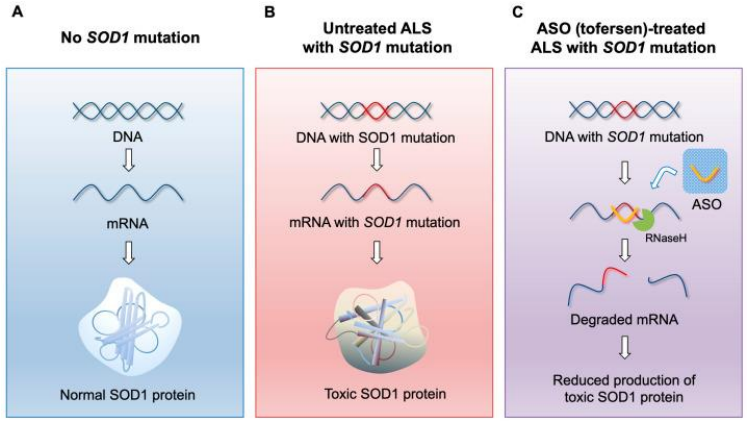


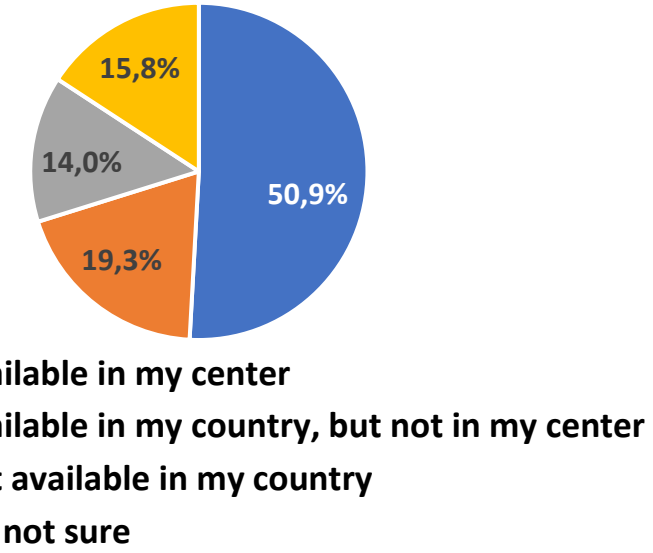
- discrepant answers from: Germany, Ukraine

ZOLGENSMA	Available in my center	Available in my country, but not in my center	Not available in my country	I'm not sure	TOTAL responses
ALL COUNTRIES	41 (71,9%)	12 (21,1%)	3 (5,3%)	1 (1,8%)	57
Austria	2				2
Belgium	4	1			5
Cyprus	1				1
Czech Rep	2				2
Denmark	1				1
Finland	2				2
France	5				5
Germany	6	1	1		8
Hungary		1			1
Ireland		1			1
Italy	9	3		1	13
Lithuania	1				1
Malta			1		1
Netherlands	1	2			3
Norway	1				1
Poland		1			1
Portugal	1				1
Slovenia	1				1
Spain	2	2			4
Sweden	1				1
Ukraine	1		1		2

Availability of Qalsody (Tofersen) for SOD1-related FALS

- ASO reducing the toxic SOD1 gene product *(Miller et al, NEJM 2022)*

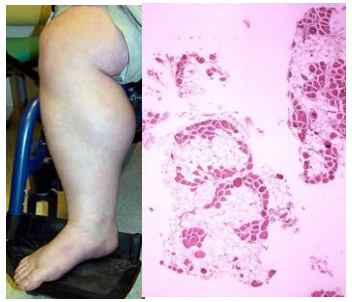


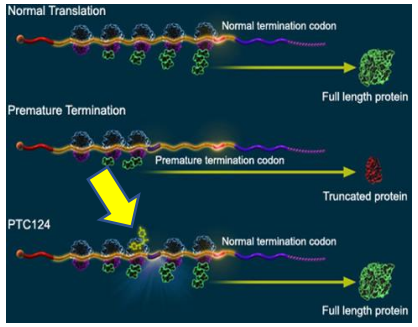


- discrepant answers from: Belgium, Germany and Ukraine

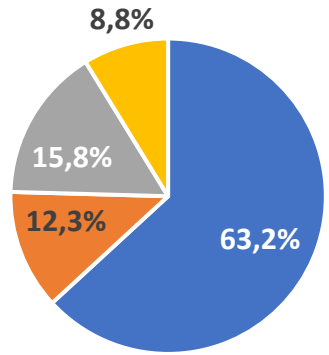
QALSODY (Tofersen)	Available in my center	Available in my country, but not in my center	Not available in my country	I'm not sure	TOTAL responses
ALL COUNTRIES	29 (50,9%)	11 (19,3%)	8 (14%)	9 (15,8%)	57
Austria		2			2
Belgium	3	1	1		5
Cyprus				1	1
Czech Republic	2				2
Denmark			1		1
Finland			1	1	2
France	4	1			5
Germany	5	1	1	1	8
Hungary		1			1
Ireland			1		1
Italy	10	2		1	13
Lithuania	1				1
Malta			1		1
Netherlands	1	1		1	3
Norway			1		1
Poland		1			1
Portugal				1	1
Slovenia	1				1
Spain	1	1		2	4
Sweden				1	1
Ukraine	1		1		2

Availability of Translarna (Ataluren) for DMD





- Small molecule suppressing use of premature stop codon mutations found in 10% of DMD patients *(McDonald et al., Lancet 2017, Neurology 2023)*



- Available in my centre
- Available in my country but not in my center
- Not available in my country
- Not sure

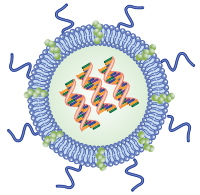
- discrepant answers from: Belgium, Spain

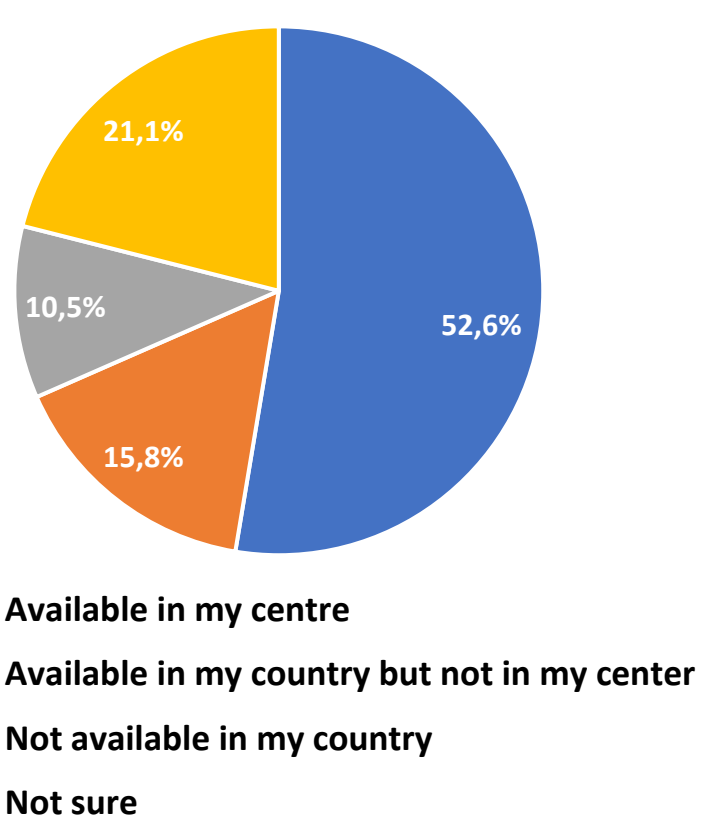
TRANSLARNA	Available in my center	Available in my country, but not in my center	Not available in my country	I'm not sure	TOTAL responses
ALL COUNTRIES	36 (63,2%)	7 (12,3%)	9 (15,8%)	5 (8,8%)	57
Austria	2				2
Belgium	1		4		5
Cyprus	1				1
Czech Republic	2				2
Denmark			1		1
Finland	2				2
France	5				5
Germany	7			1	8
Hungary		1			1
Ireland		1			1
Italy	8	5			13
Lithuania	1				1
Malta			1		1
Netherlands			1	2	3
Norway			1		1
Poland	1				1
Portugal	1				1
Slovenia	1				1
Spain	1		1	2	4
Sweden	1				1
Ukraine	2				2

➢ Availability of ATTRv amyloidotic PN therapies by country - AMVUTTRA

s.c. siRNA therapeutic to suppress TTR synthesis

Adams et al. Amyloid 2023



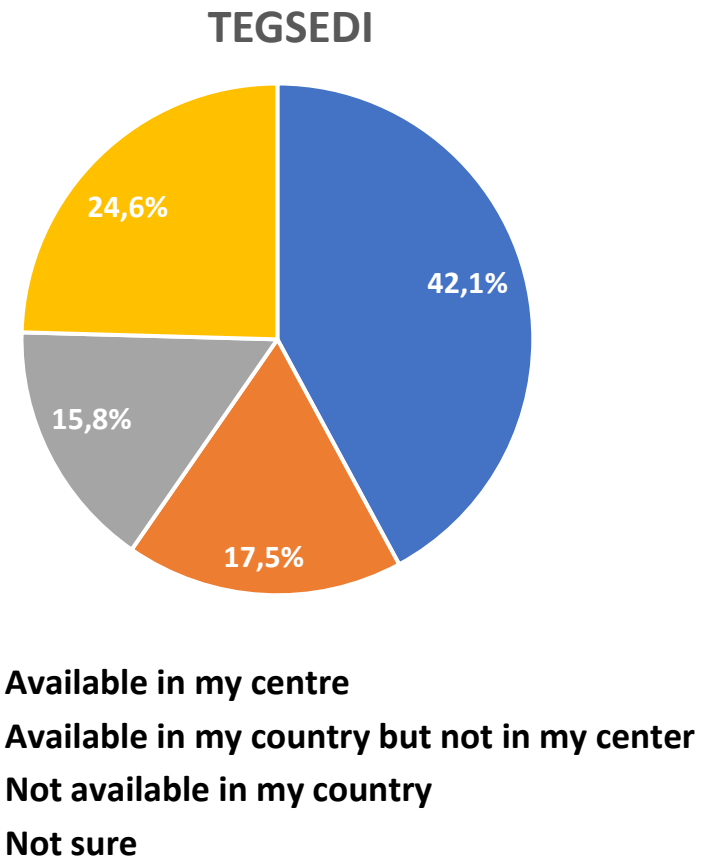


AMVUTTRA	Available in my center	Available in my country, but not in my center	Not available in my country	I'm not sure	TOTAL responses
ALL COUNTRIES	30 (52,6%)	9 (15,8%)	6 (10,5%)	12 (21,1%)	57
Austria		2			2
Belgium	5				5
Cyprus	1				1
Czech Republic	2				2
Denmark			1		1
Finland			1	1	2
France	4	1			5
Germany	6	1		1	8
Hungary			1		1
Ireland		1			1
Italy	7	3		3	13
Lithuania				1	1
Malta			1		1
Netherlands				3	3
Norway			1		1
Poland		1			1
Portugal	1				1
Slovenia	1				1
Spain	3			1	4
Sweden				1	1
Ukraine	1		1		2

➢ Availability of ATTRv amyloidotic PN therapies by country - TEGSEDI

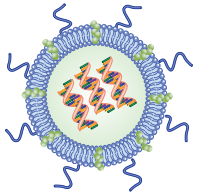
Anti-sense oligonucleotide (inotersen) to suppress TTR expression

Benson et al. N Engl J Med 2018



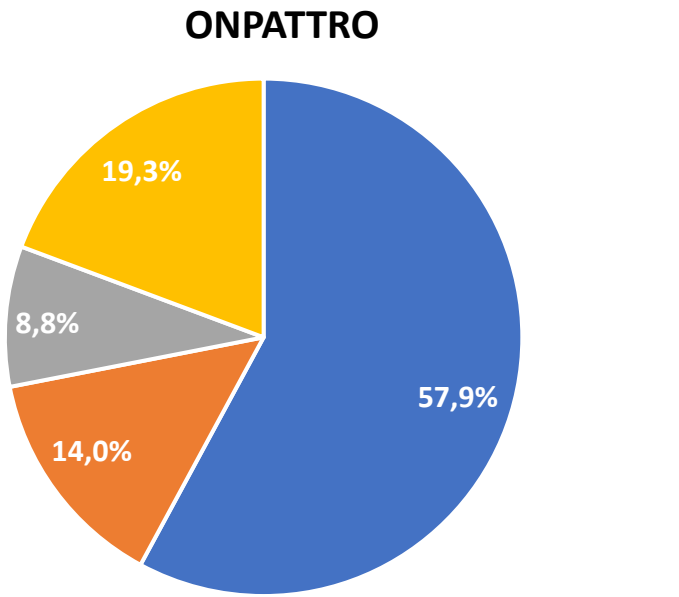
TEGSEDI	Available in my center	Available in my country, but not in my center	Not available in my country	I'm not sure	TOTAL responses
ALL COUNTRIES	24 (42,1%)	10 (17,5%)	9 (15,8%)	14 (24,6%)	57
Austria		2			2
Belgium			3	2	5
Cyprus	1				1
Czech Republic	1			1	2
Denmark			1		1
Finland			1	1	2
France	4	1			5
Germany	6	1		1	8
Hungary				1	1
Ireland		1			1
Italy	5	5		3	13
Lithuania				1	1
Malta			1		1
Netherlands	1			2	3
Norway			1		1
Poland			1		1
Portugal	1				1
Slovenia	1				1
Spain	3			1	4
Sweden				1	1
Ukraine	1		1		2

- **Availability of ATTRv amyloidotic PN therapies by country – ONPATTRO**



i.v. siRNA therapeutic to suppress TTR

Adams et al. N Engl J Med 2018

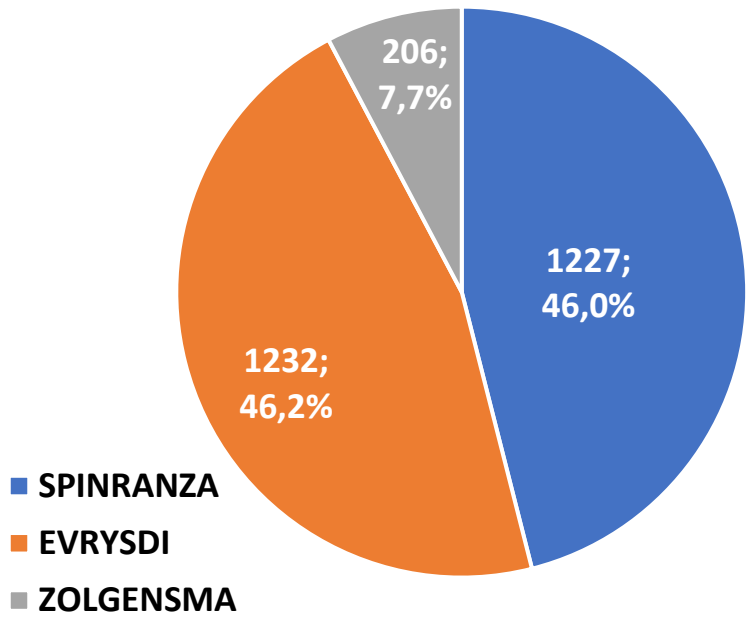


ONPATTRO	Available in my center	Available in my country, but not in my center	Not available in my country	I'm not sure	TOTAL responses
ALL COUNTRIES	33 (57,9%)	8 (14%)	5 (8,8%)	11 (19,3%)	57
Austria		2			2
Belgium	5				5
Cyprus	1			1	1
Czech Republic	2				2
Denmark	1				1
Finland			1	1	2
France	4	1			5
Germany	6	1		1	8
Hungary	1				1
Ireland		1			1
Italy	7	3		3	13
Lithuania				1	1
Malta			1		1
Netherlands	1			2	3
Norway			1		1
Poland			1		1
Portugal	1				1
Slovenia	1				1
Spain	3			1	4
Sweden				1	1
Ukraine	1		1		2

Total number of patients received each gene therapy within ERN EURO-NMD

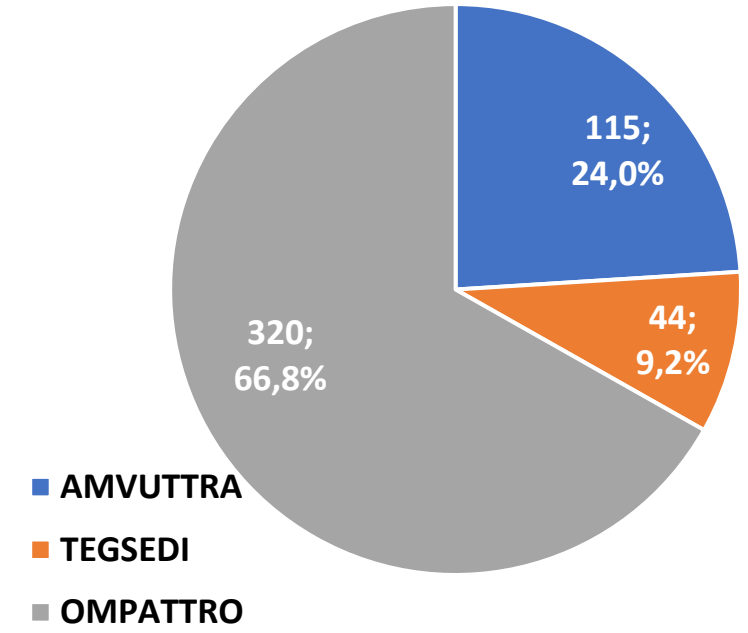
THERAPY	SPINRAZA	EVRYSDI	ZOLGENSMA	QALSODY	TRANSLARNA	AMVUTTRA	TEGSEDI	OMPATTRO
Total patients in all HCPs	1227	1232	206	105	142	115	44	320
Patients treated per HCP (range)	1-128	1-97	1-33	1-15	1-12	1-22	1-9	1-25

PATIENTS ON SMA THERAPIES*



* Some patients may be on combination therapies

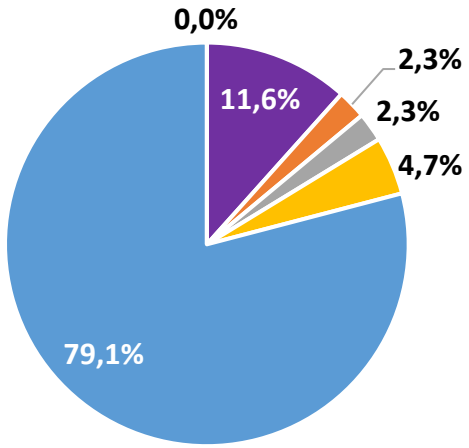
PATIENTS ON ATTRv THERAPIES**



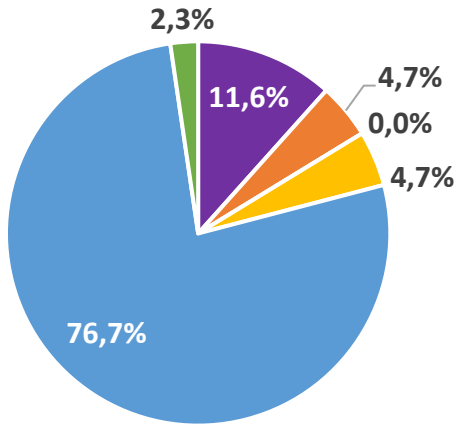
**AMVUTTRA approved in 2022, OMPATTRO in 2018

*Q: In your country, how many centers offer treatment with the following approved therapies?

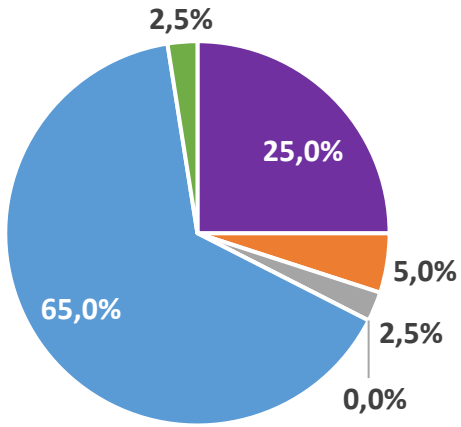
SPINRANZA



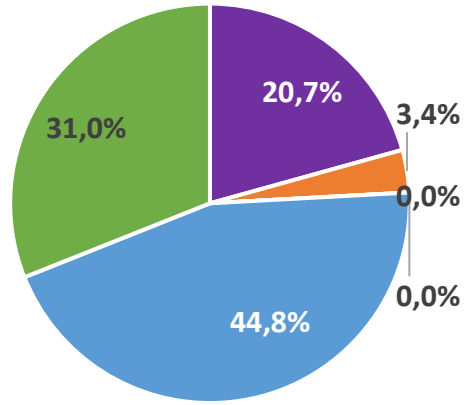
EVRYSDI



ZOLGENSMA

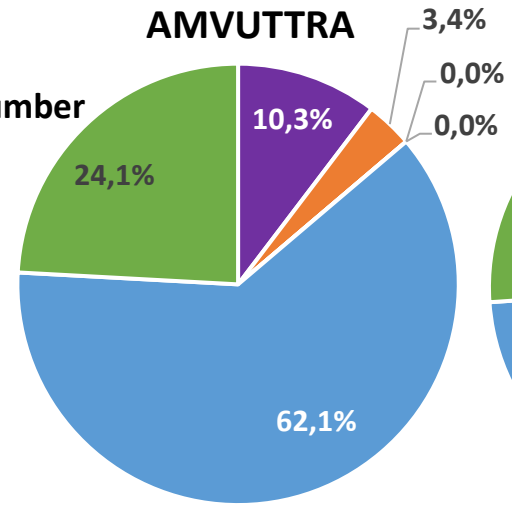


QALSODY

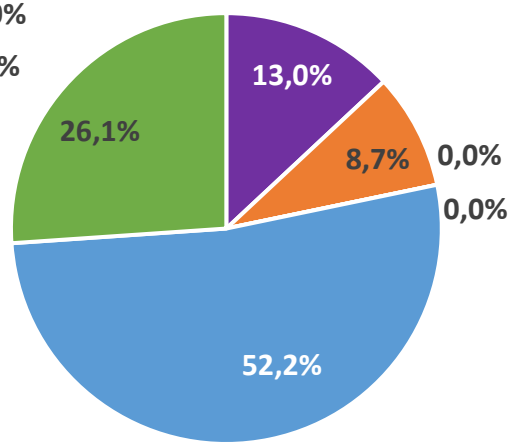


- Centralized in 1 center
- 2 centers
- 3 centers
- 4 centers
- 5+ centers
- More than 1, but unsure number

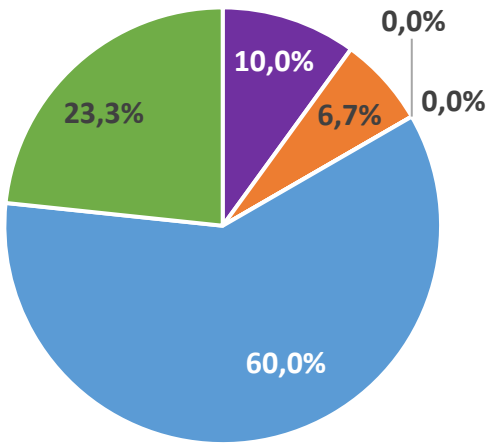
AMVUTTRA



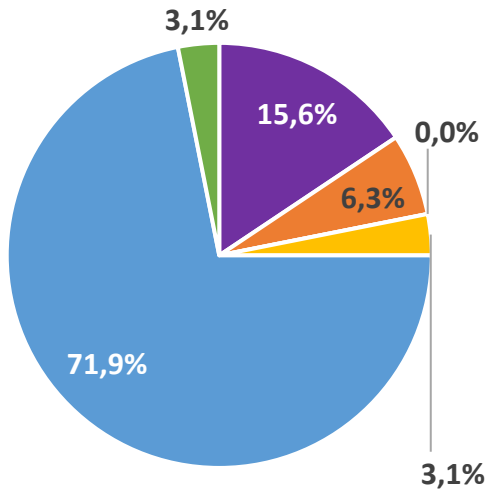
TEGSEDI



OMPATTRO



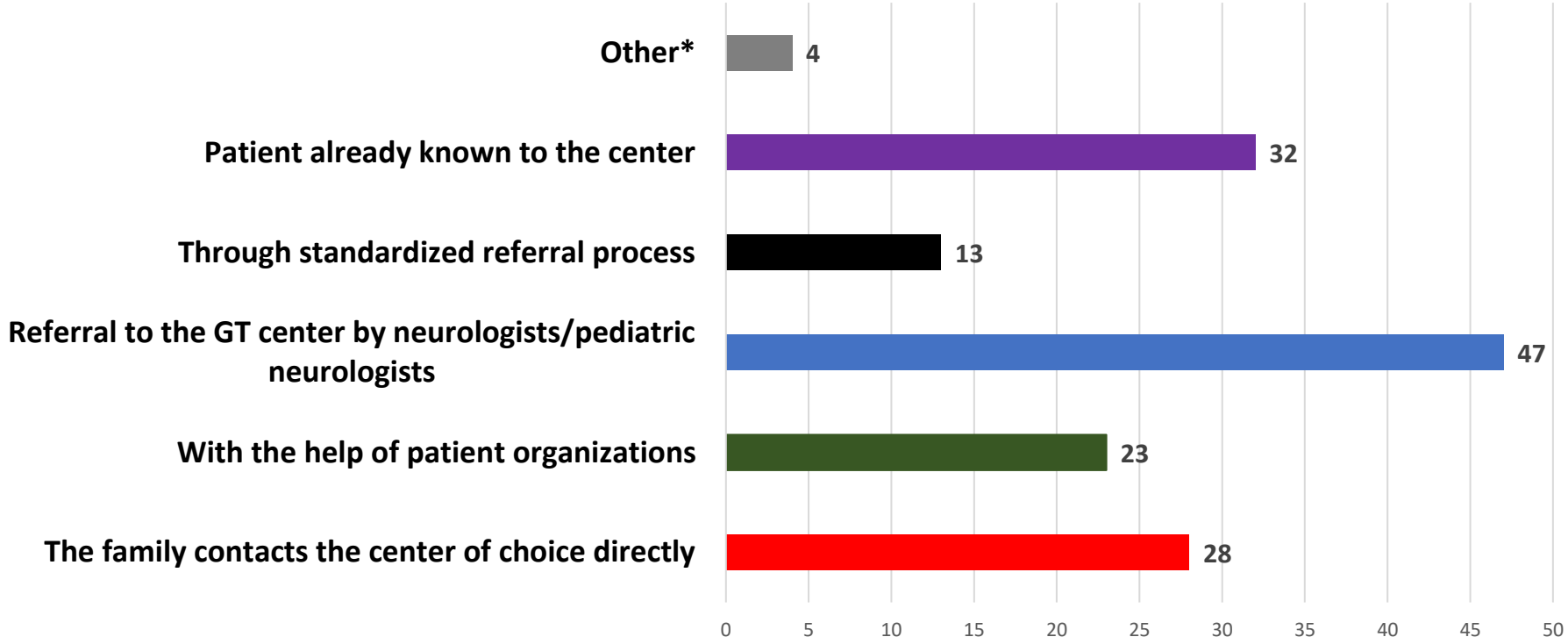
TRANSLARNA



Pathway to GT treatment by country

***Q: In your country, how do patients usually arrive at the gene/cell therapy center to receive treatment?**

- *57 respondents selected 147 items in total (more than one options per HCP)*



***Q: Please describe briefly the standardized referral process:**

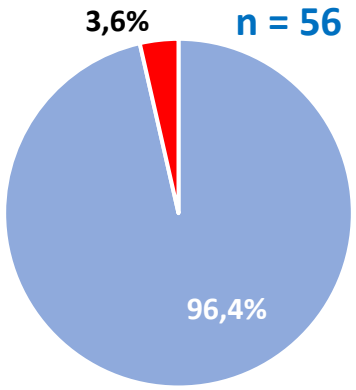
- Through Newborn screening for SMA (AT, CZ)
- Referred to a neuromuscular reference center (http://filnemus.fr) (FR) / Examined at University Hospitals (FI)
- National Center of Expertise (NL) / reference centre for neuromuscular diseases CSUR (ES)
- Referrals by pediatric/adult Neurologist (IT, NO)

REIMBURSEMENT OF GENE/CELL THERAPIES for rare NMDs

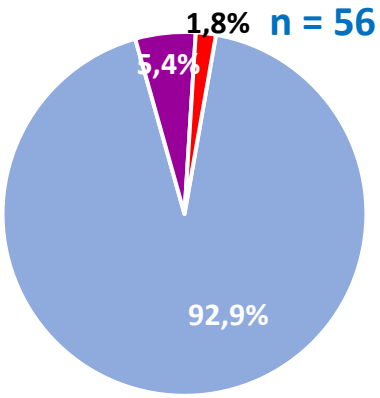
***Q: In your country, are the following approved medicinal products for gene/cell therapy reimbursed by the national healthcare system?**

Restrictions, conditional, partial or budget limitations (IT, FI, NL, Ukraine)…

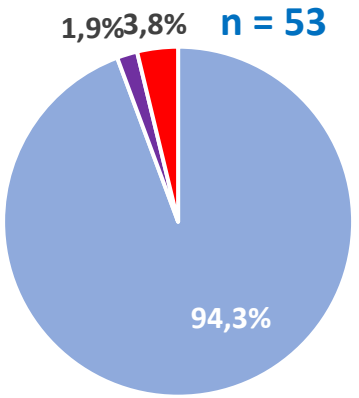
SPINRAZA



EVRYSDI



ZOLGENSMA

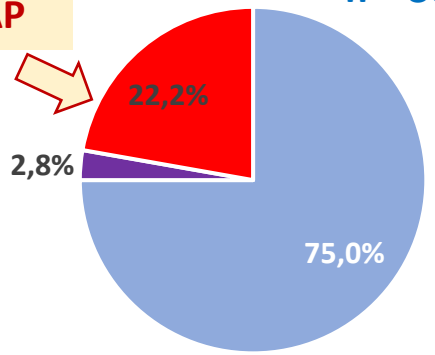


REIMBURSEMENT

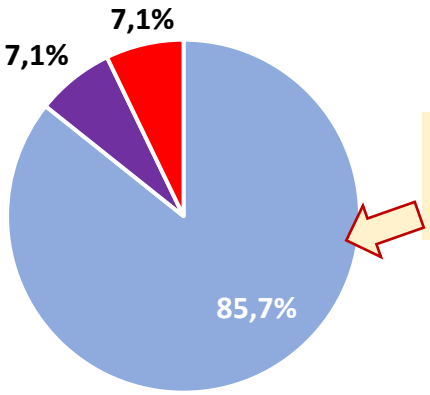
Fully reimbursed
Partially reimbursed
Not reimbursed

Mostly on EAP

QALSODY

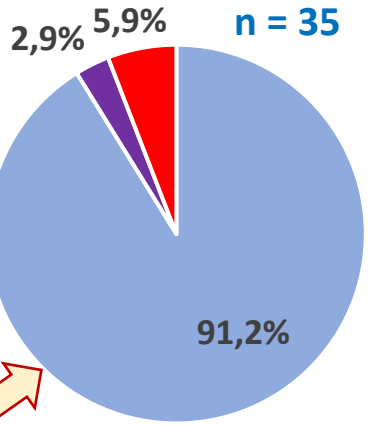


TRANSLARNA



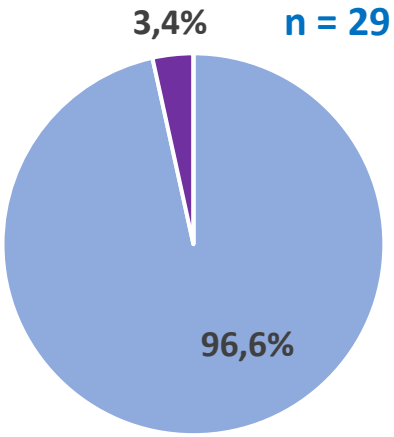
D/C in: IT, FR

AMVUTTRA

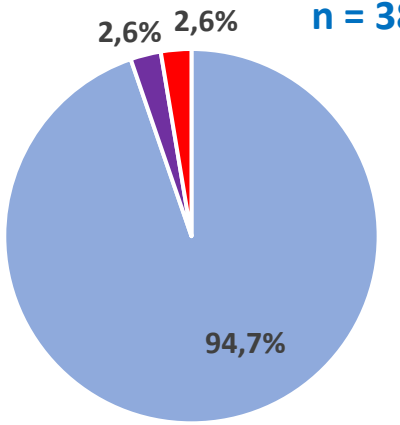


Compassionate use (PT)

TEGSEDI

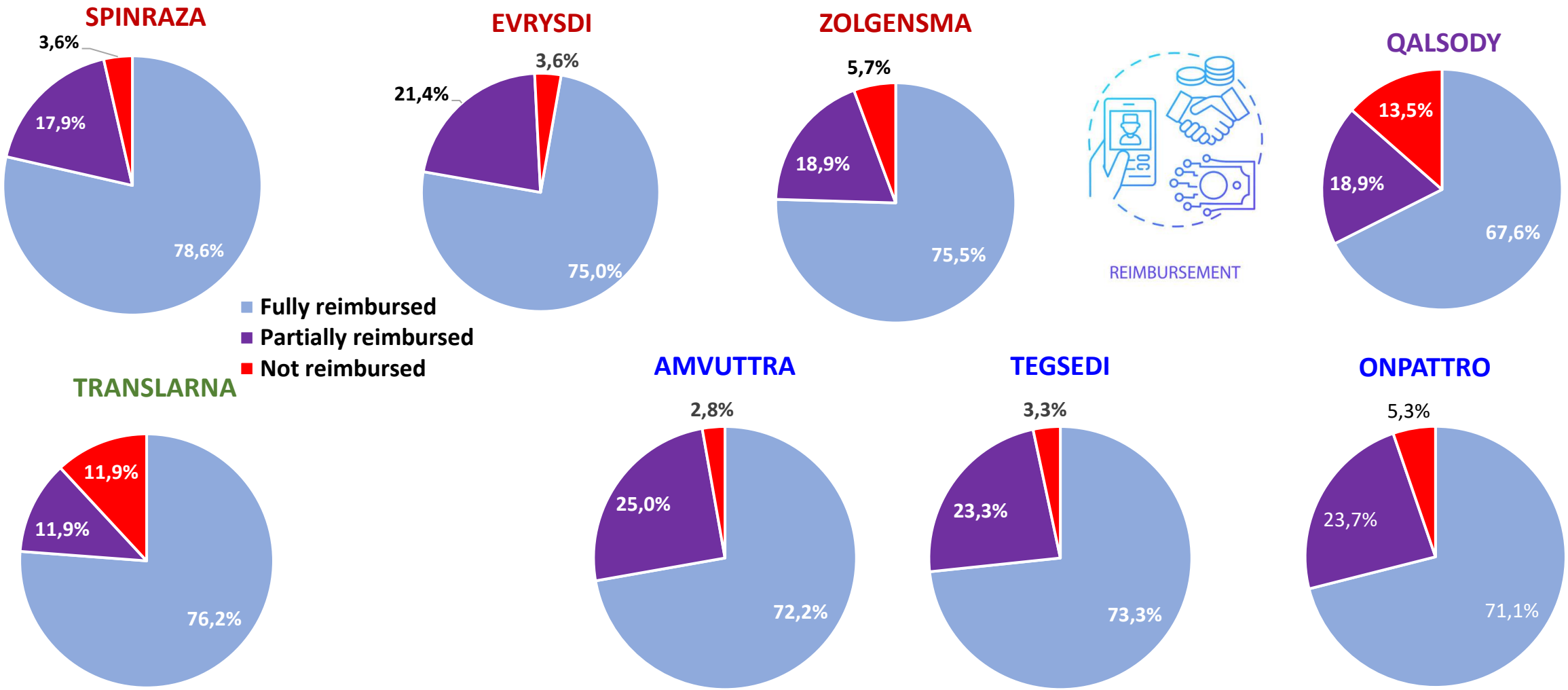


ONPATTRO



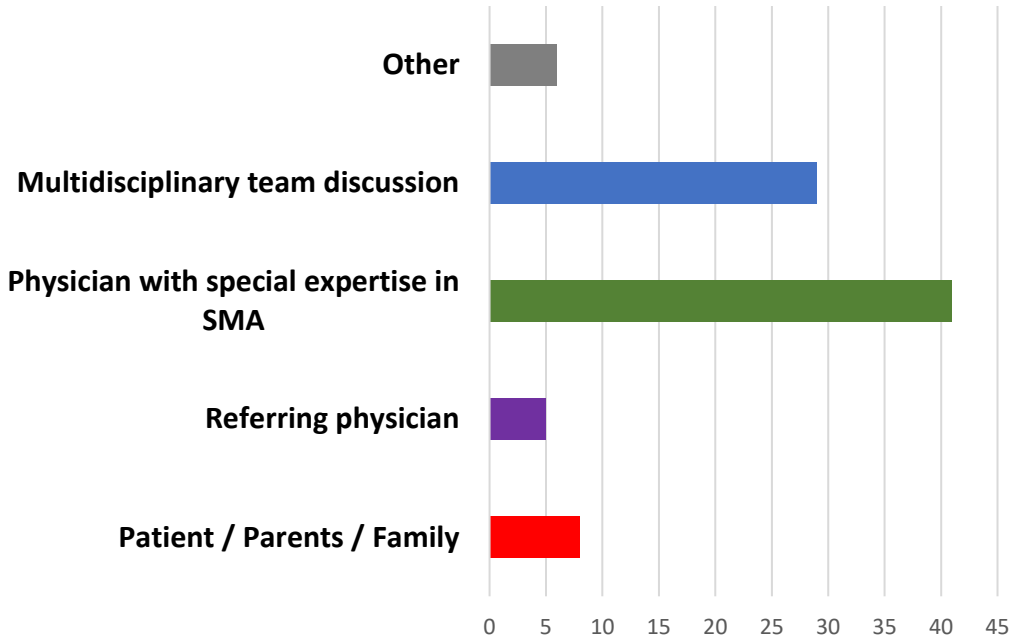
Reimbursement of costs related to care services/infrastructure

***Q: In your country, does the national healthcare system reimburse the costs related to care services/infrastructures needed before and after treatment of a patient with a gene/cell therapy?**



❑ **In some countries and centers limitations in coverage of: NBS, logistics, rehabilitation, outpatient follow up…**

*Q: In your country, who decides if a patient affected by SMA is eligible to be treated with Zolgensma?



	Patient /parents/ family	Referring physician	Physician with special expertise in SMA	Multidisciplinary team discussion	Other	TOTAL
ALL COUNTRIES	8	5	41	29	6	89
Austria (2)			2	1		3
Belgium (5)	2	1	5	4		12
Cyprus (1)					1	1
Czech Republic (2)	1		2	1		4
Denmark (1)			1	1		2
Finland (2)	1		2			3
France (5)			1	4	1	6
Germany (7)	1		6	3		10
Hungary (1)				1		1
Ireland (1)			1			1
Italy (12)	2	3	11	6		22
Lithuania (1)					1	1
Netherlands (3)			2	1	1	4
Norway (1)			1	1		2
Poland (1)	1	1	1		1	4
Portugal (1)			1	1		2
Slovenia (1)			1			1
Spain (4)			3	4		7
Sweden (1)					1	1
Ukraine (1)			1	1		2

*Q: Other- specify

CY: Evaluation by a special **committee** of neurologists and pharmacists belonging to the **Cyprus Pharmaceutical Services/Ministry of Health**.

FR: National therapeutic commission constituted by neuropediatricians expert in SMA (**SFNP- Filnemus**)

NL: Reimbursement

SE: Reimbursement criteria. Most parents of SMA **babies identified in NBS with no more than 3 SMN2 copies** choose Zolgensma, not other DMT.

Country-specific practices in the treatment of SMA patients with Zolgensma

***Q: What is the typical decision-making process for determining whether to administer Zolgensma…** *open text*

- **Medical diagnosis-indication confirmed**
- **Parental consent**
- **Application for approval** and reimbursement of costs
- **Standardized process, national treatment committee** for SMA
- **Multidisciplinary consensus** -expert neuromuscular neurologist and national expertise team (paediatric neurologist with expertise of SMA)
- **National commission/multidisciplinary team** (virtual sessions every 2 weeks or on-line mailing discussions if urgent)
- **Multidisciplinary discussion within experts** muscle team.
- **Team discussion**, insurance company decision
- **Eligible based on the indications according to EMA**
- **NMD centre that provides the therapy can decide**
- Treatment options are discussed with the family and the **decision is made together with the family**
- **Contraindications excluded, Assessments:** AAV9 antibodies; motor test (CHOP intend, HINE2), head and thorax perimeter, video recording (mobility, feeding and breathing movements)

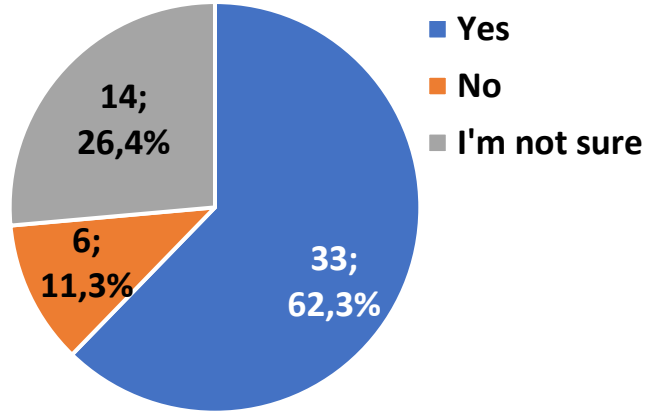
***Q: What are the (clinical) eligibility criteria applied for determining whether a patient can receive Zolgensma? …** *open text*

- **1-3 copies of SMN2 gene**; **up to 21 kg BW** (**AT**)
- **SMA-I, up to the age of 2 years or up to a BW 13.5 kg**, no permanent invasive ventilatory assistance (**BE, NL**)
- **EMA indications** (**CY, PT**) *
- **< 13.5 kg, < 3 years of age** (**CZ**)
- **2 SMN2 copies** (**FI**)
- **SMA type I or II and up to 3 SMN2 copies, <13 Kg** (**FR, IT**)
- **No major respiratory failure**: no paradoxal respiration, head /thoracic ratio (>0.85) (Ropars et al 2019), CMAP (median nerve) (>0.5 mV), CHOP-Intend scale (>15 points) (**FR**)
- **SMA 1, regardless of the number of SMN2 gene copies**, **no restriction on age and/or weight** established so far (**DE**)
- **AAV9 Ab of <1:50** (**DE, ES**)
- **CHOP-Intend scale** >12 points (**PL**)
- < 9 months of age, <13.5 Kg (**ES**)

*** EMA:** "*There is **limited experience in patients 2 years of age and older or with body weight above 13.5 kg**. The safety and efficacy of onasemnogene abeparvovec in these patients have not been established*"

***Q: In your country, are there specific processes and/or predefined criteria that a center must adhere to in order to administer Zolgensma treatment to patients affected by SMA?**

Criteria about Zolgensma Center



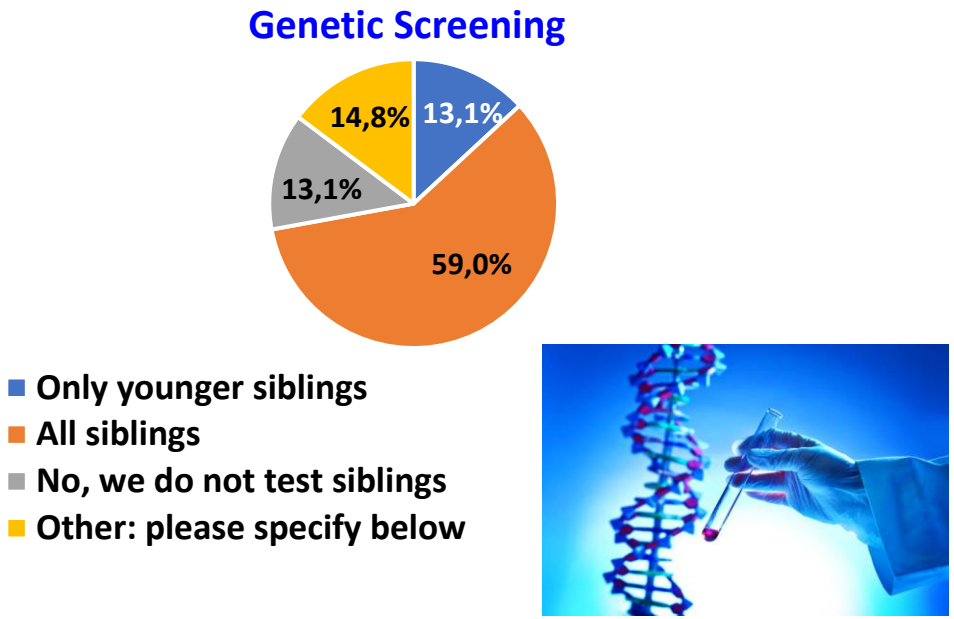
Criteria examples

- ✓ **Sufficient experience with SMA-patients, expertise, number of patients**,
- ✓ **Training in the application of vector-based gene therapy**
- ✓ **Paediatric intensive care facility**, **pharmacy**
- ✓ **Center must comply with expert based guidelines** defined criteria/equipment
- ✓ **Personal resources, multidisciplinary approach** possible, expertise also in **care, physiotherapy**, **follow-up possible for the first year** at the center
- ✓ Center has to be **nominated by Health Ministry**

	Yes	No	I'm not sure	TOTAL
ALL COUNTRIES	33 (62,6%)	6 (11,3%)	14 (26,4%)	53
Austria	2			2
Belgium	3	1	1	5
Cyprus		1		1
Czech Republic	1		1	2
Denmark	1			1
Finland		1	1	2
France	2		3	5
Germany	7			7
Hungary			1	1
Ireland			1	1
Italy	9	1	2	12
Lithuania			1	1
Netherlands	2		1	3
Norway	1			1
Poland	1			1
Portugal		1		1
Slovenia	1			1
Spain	2		2	4
Sweden	1			1
Ukraine		1		1

GENETIC SCREENING PRACTICES FOR SMA PATIENTS

***Q: Regardless of the availability of gene/cell therapy for SMA at your center, do you routinely conduct genetic screening for asymptomatic siblings of an index SMA patient, either onsite or off-site?**

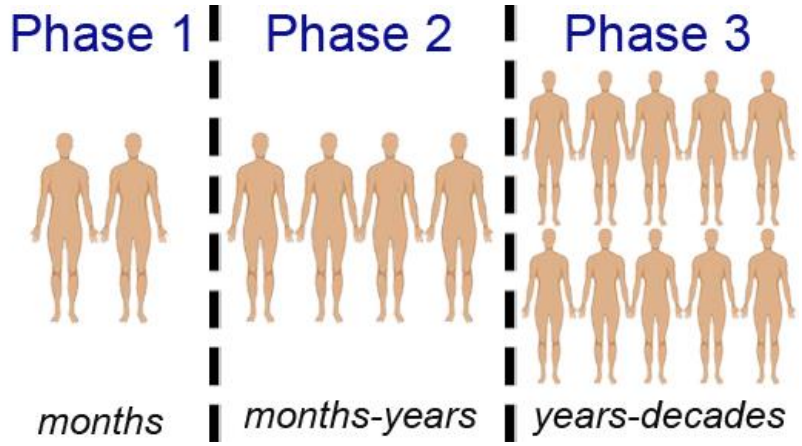


***Other: please specify:**

NO: Depends on what the family and treating physician decides
NL: Only after extensive counseling by a clinical geneticist
FR: The genetic counseling will perform such test
SE: all siblings tested if reasonable suspicion
DE: just in symptomatic older siblings // the younger receive gNBS

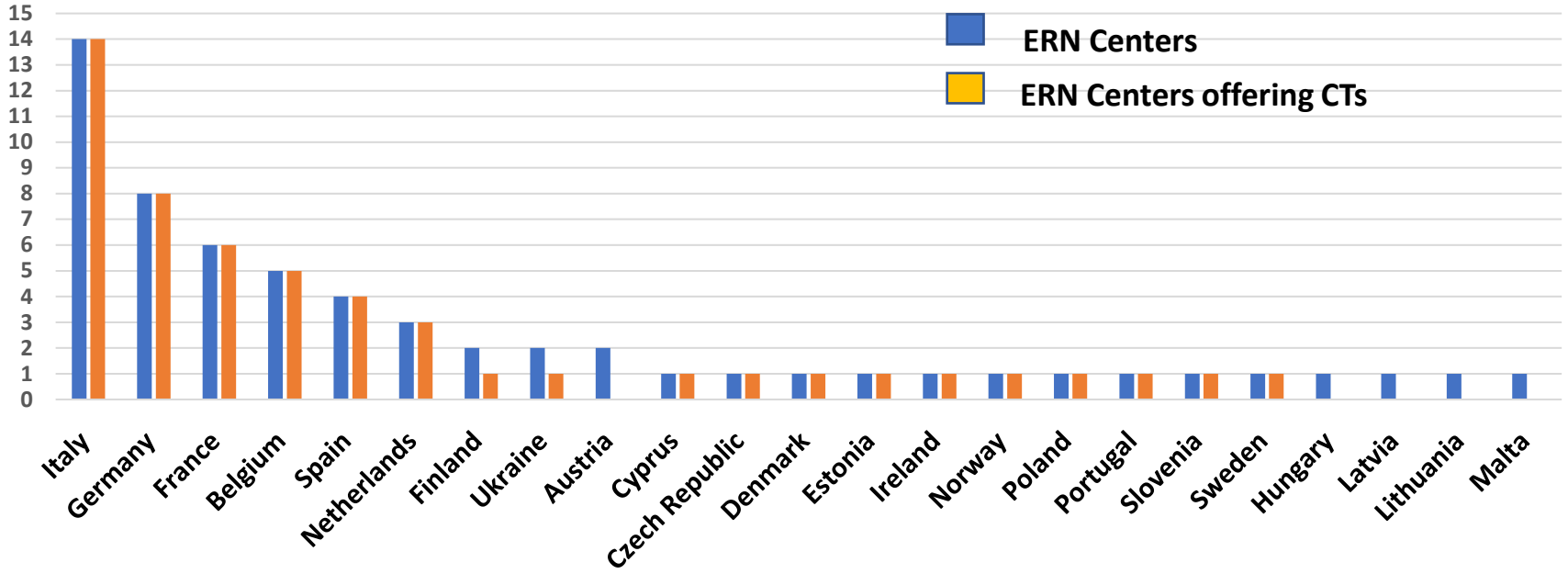
Country	Only younger siblings	All siblings	No, we do not test siblings	Other: please specify below	TOTAL
ALL COUNTRIES	8 (13,1%)	36 (59%)	8 (13,1%)	9 (14,8%)	61
Austria	1		1		2
Belgium		5			5
Cyprus		1			1
Czech Republic		2			2
Denmark	1				1
Estonia				1	1
Finland	1			1	2
France		4		2	6
Germany	2	3	2	1	8
Hungary		1			1
Ireland			1		1
Italy	2	9	3		14
Latvia			1		1
Lithuania		1			1
Malta		1			1
Netherlands		2		1	3
Norway				1	1
Poland		1			1
Portugal		1			1
Slovenia		1			1
Spain		3		1	4
Sweden				1	1
Ukraine	1	1			2

Part 2: Clinical trials for gene/cell therapies for Rare Neuromuscular Diseases

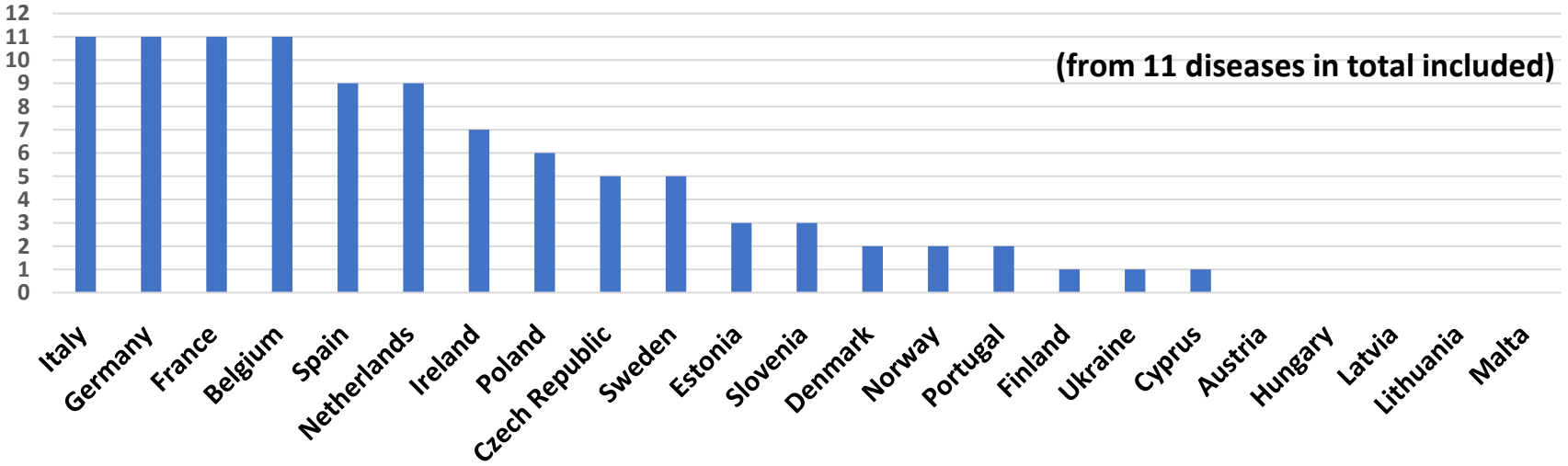


***Q: In your country, do patients have access to clinical trials investigating gene/cell therapies for the following neuromuscular diseases?**

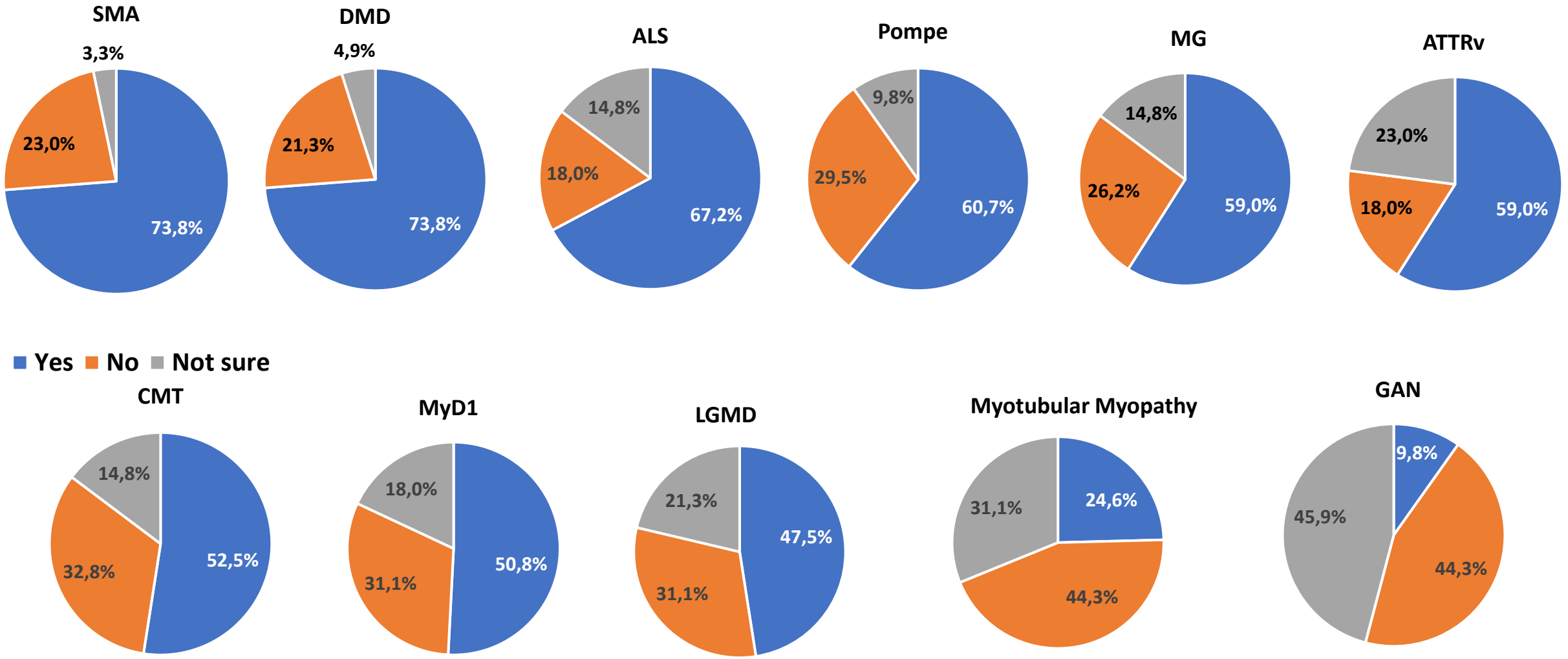
Access to clinical trials by ERN Center and country across Europe



Number of NMD diseases for which CTs are offered per country

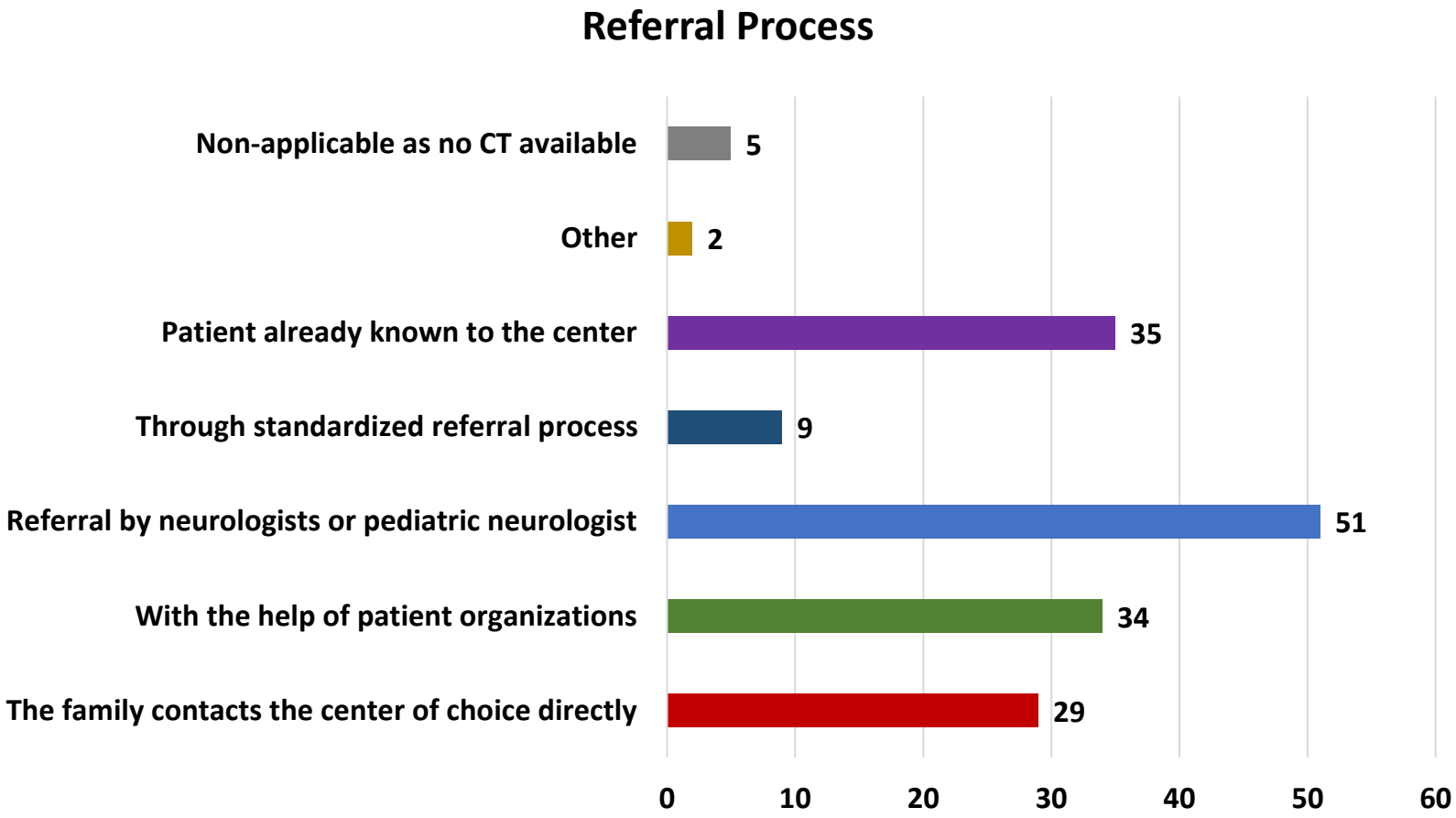


Access to clinical trials by NMD indication across Europe



❑ Other NMDs for which HCPs participate in clinical trials: FSHD, Myositis, Mitochondrial Disorders

*Q: In your country, how is a patient usually referred to a gene/cell therapy center to participate in a clinical trial?



➢ *61 respondents selected 166 items in total (more than one options per HCP)*

*Q: Please describe briefly the standardized referral process:

- **BE:** interaction between Belgian NRMC
- **FI:** Our center serves as a primary center for pediatric neurology/neurology
- **FR:** Neuromuscular patients are usually followed in the referent centers
- **IT:** The sites chosen by the industry for trials are previously discussed by a central network commission (COMET)
- **NL:** All the other centers may sent them their patients if interested and compatible with the inclusion criteria/ profile
- **ES:** clinical and anamnestic examination

*Q: Please specify Other:

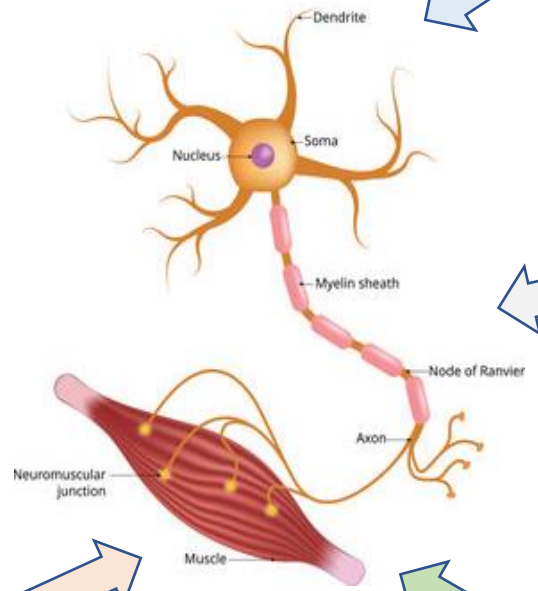
- **DE:** Information **through patient registries**

***Q: Please list all clinical trials - addressing cell/gene therapies for rare NMDs - that your center has participated in since 2020:**

Indicative clinical trials in which ERN Members participate (*selection by disease group*)

Myopathies:

- **DMD:** Exon skipping- Casimersen or Golodirsen microdystrophin, ataluren, Idebenone
- **DM1:** gene therapy, Metformin
- **FKRP:** gene therapy
- **Myotubular myopathy:** gene therapy
- **Centronuclear myopathy**
- **Pompe - late onset:** NeoGAA (GZ402666) and Alglucosidase Alfa
- **Mitochondrial Myopathy:** Elamipretide
- **FSHD:** Antimiostatina, ARO-DUX4



Motor neuron disorders:

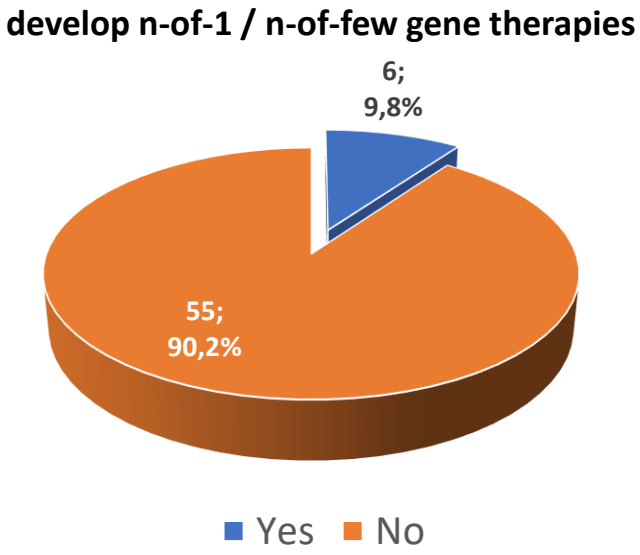
- **Amyotrophic Lateral Sclerosis ALS:** AMX0035, TUDCA, Edaravone, Dazucorilant, Reldesemtiv
- **C9orf72 - ALS/FTD**
- **SOD1-FALS**
- **SMA:** Spinraza, Risdiplam, Zolgensma

Neuropathies:

- **ATTRv:** Amvuttra, Patisiran, Eplontersen, CRISPR-Based Treatment
- **CIDP:** Efgartigimod

- **Myasthenia:** Efgartigimod, amifampridine phospate

*Q: If your center develops n-of-1/n-of-few investigational gene/cell therapies – specify

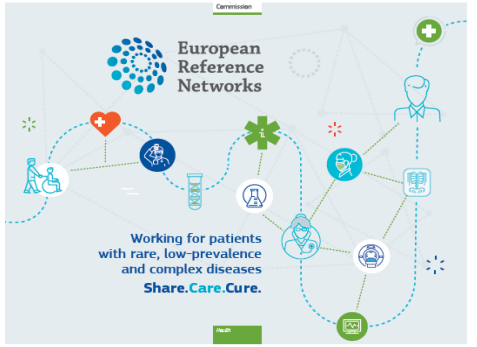


➢ **Mostly for ALS and DMD**

Country	HCP name	For which therapies/diseases
France	HCP16 - Garches - APHP Raymond Poincaré Hospital, University Hospitals Paris-Ouest (University Hospital France)	NCT05753462 - Pr H Amthor, for DMD Only worldwide centre: Raymond Poincaré Hospital, **Phase 1/2a for Safety, PK and PD of SQY51 in Paediatric and Adult Patients DMD** (AVANCE1): 15 patients Sponsor: SQY Therapeutics
France	HCP17 - Nantes - Nantes University Hospital (University Hospital France)	**DMD Cell therapy**
Germany	HCP20 - Göttingen - Neuromuscular Center of the University Medical Center	**CRISPR/CAS9 for DMD**
Germany	HCP21 - Ulm - Universitätsklinikum Ulm (UKU) in cooperation with the Universitätsund Rehabilit	**ALS**
Italy	HCP74 - Milan - IRCCS Ospedale San Raffaele di Milano	**cell therapy for Duchenne Muscular Dystrophy**
Italy	HCP77 - Novara - Azienda Ospedaliero Universitaria Maggiore della Carità	**fetal neuronal stem cells in ALS**

Funded by the European Union

Interim survey conclusions



- **The survey provides a detailed map of current NMD gene therapy practices in Europe**
- **Initial review indicates disparities in most aspects of GT availability and procedures across Europe**
- Overall **gene therapies for Rare NMD are widely available throughout Europe** and mostly **fully reimbursed**
- **Mostly limited and centralized access to approved therapies, with variable criteria used**
- **Several clinical trials ongoing for promising future therapies, but access of patients to clinical trials for Rare NMD is not possible throughout Europe**
- **Most ERN EURO-NMD Centers participate in Clinical trials**
- There seems to be a **gap in knowledge and awareness among HCPs** regarding different gene therapies available –? due to **adult vs child neurology background/experience**, or **certain HCPs not being involved in certain diseases management**
- **Some inconsistencies between HCPs in the same country, may indicate lack of awareness or collaboration**

Funded by
the European Union

Action Plan: INTER-ERN SURVEY GENE THERAPY

European Reference Network
for rare or low prevalence complex diseases

Network Neuromuscular Diseases (ERN EURO-NMD)

- Need to have **better communication between HCPs within same country and across ERN throughout Europe - bridge awareness gaps**
- More **interaction and awareness between adult and paediatric neurologists (coordination and transition)**
- **Harmonize procedures and policies and apply uniform criteria to access gene therapies**

Expert Panel to analyse survey results has been formed with representation of all 5 ERNs

Scope

- Focus on **country comparison** (not ERN specific)
- **Overarching themes** common to all ERNs.
- **Decisions making process** regarding GT access
- **Comparison adult-paediatric** input and practices

Next steps for the data analysis

Vigorous methodology to **prepare a position paper**

Results need to be cross-validated with official sources:

- ❑ **Health Authorities** in each country
- ❑ **Companies** marketing gene therapies

THANK YOU!