Approach to the floppy infant

SAPA WEBINAR
29TH
SEPTEMBER @
5PM

Approach to a floppy child

Prof Ronald Van Toorn

Update on the management of Status Epilepticus

Dr Rajeshree Govender

Register in advance for this meeting:

https://uct-za.zoom.us/meeting/register/tJApc-Grqz8sH9CO-aQEoMhF5g9vBbd5RVG1

South African Paediatric Association

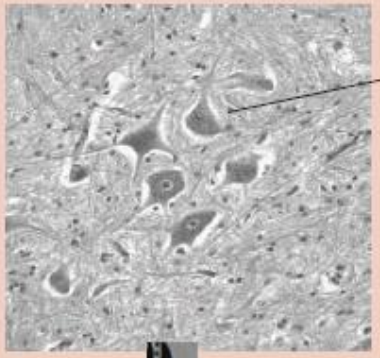
Clinical clues from the history

Antenatally : Quality of fetal movements, Breach presentation, Oligo or polyhydramnious
Evidence to support perinatal asphyxia (HIE)
Arthrogryposis multiplex congenita
Onset of the hypotonia from birth (congenital) or acquired.
Familial consanguity
Mother: Myasthenia / early cataract surgery / myotonia (shake her hand)

Lower motor neuron	Upper motor neuron
Floppy weak	Floppy strong
Tongue Fasciculation's	
Tendon reflexes likely to be reduced absent	Tendon reflexes increased
Alert. Gross and fine motor delay.	Higher function likely to be affected. Obtundation. Global developmental delay
Low pitched progressively weaker cry	
Weakness in anti-gravitational limb muscles.	Axial weakness a significant feature
Arthrogryposis	

LMN weakness= Floppy weak

Ability to cough and clear airway secretions
(“ cough test”)
Swallowing function
The character of the cry
Paradoxical breathing pattern
Frog-like posture
Quality of spontaneous movements.



Anterior horn cell:

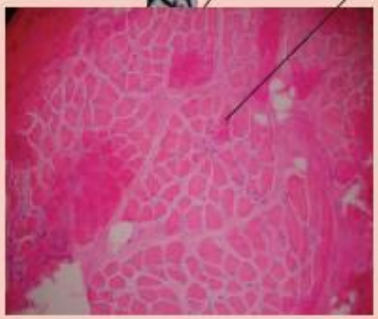
Spinal muscular atrophy
Poliomyelitis

Nerve fibre: neuropathies

(Demyelinating or axonal)
Acquired: Guillain-Barré syndrome
Infectious: diphtheria, syphilis, coxsackie, HIV
Toxic: drugs, heavy metals
Nutritional: Vit B_1, B_6, B_{12}, E, folate
Endocrine: Diabetes, uraemia
Metabolic neurodegenerative causes
Hereditary: Charcot-Marie-Tooth disease

Neuromuscular junction

Myasthenia gravis
Botulism



Muscle

Dystrophinopathies (lack of specific muscle protein): Duchenne, Becker's fascioscapular humeral, limb girdle and congenital muscular dystrophies

Congenital myopathies (abnormal muscle structure)

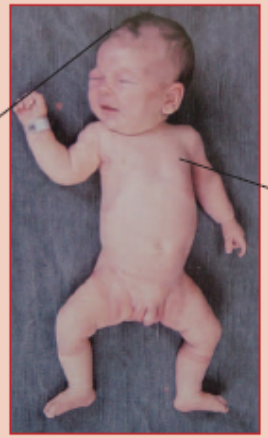
Muscle membrane disorders: congenital myotonias, congenital myotonic dystrophies

Inflammatory myopathies: dermatomyositis, poliomyositis

Metabolic myopathies: lipid glycogen storage diseases

Endocrine myopathies: hypothyroidism

Energy depletion within muscle: mitochondrial, free-fatty acid oxidatation and carnitine disorders



Floppy strong

Increased tendon reflexes
Extensor plantar response
Sustained ankle clonus
Global developmental delay
Microcephaly or suboptimal head growth
Obtundation convulsions
Axial weakness a significant feature

Floppy weak

Hypo- to areflexia
Selective motor delay
Normal head circumference and growth
Preserved social interaction
Weakness of antigravitational limb muscles
Low pitched weak cry
Tongue fasciculations
Paradoxical chest wall movement

Upper motor neuron disorder
Central hypotonia

Lower motor neuron disorder
Peripheral hypotonia

Creatine kinase assay
EMG
Nerve conduction studies

Genetic studies
Karotyping
FISH methylation studies
VLCFA

Triosomy 21
Prader-Willi syndrome
Zellweger syndrome

CT/MRI

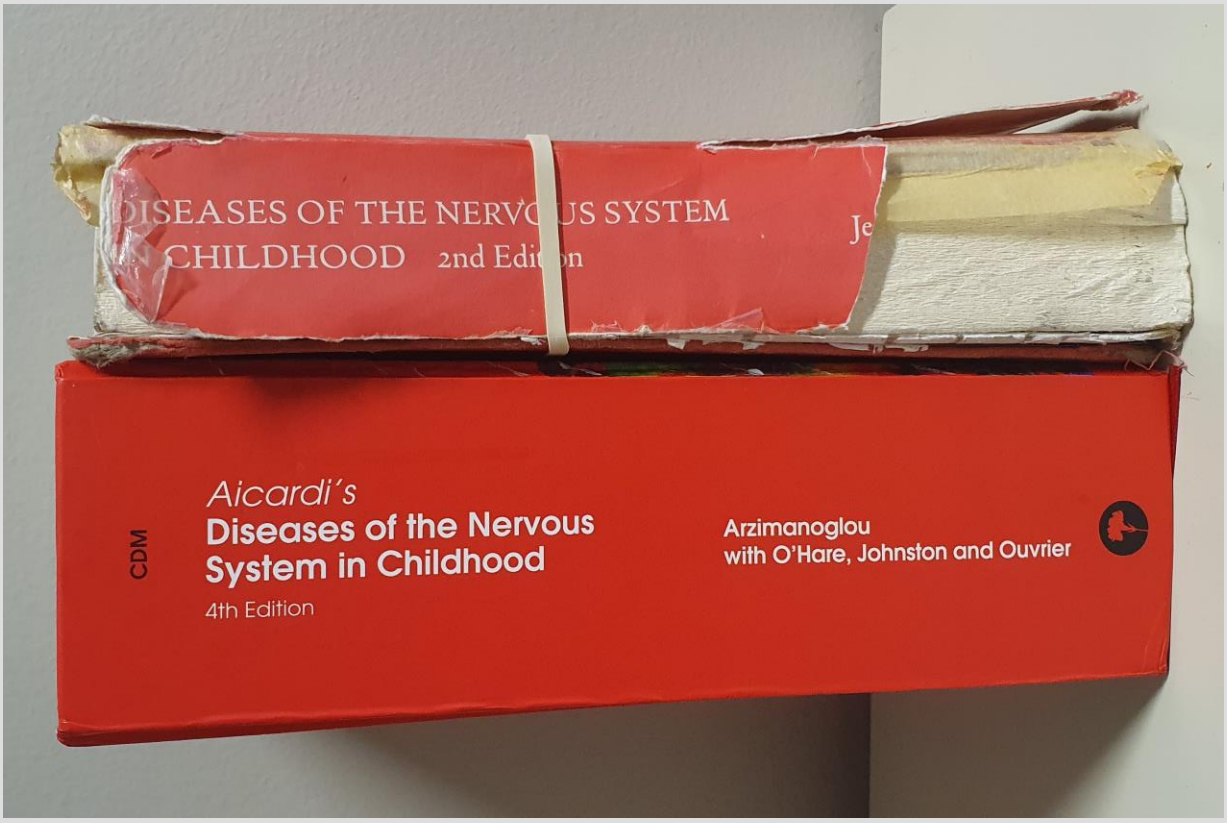
Hypoxic ischaemic encephalopathy
Cerabral malformations

DNA-based mutation analysis if available

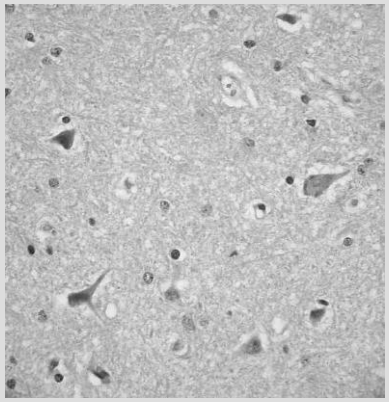
Spinal muscuar dystrophy
Congenital myotonic dystrophy
Congenital muscular dystrophies

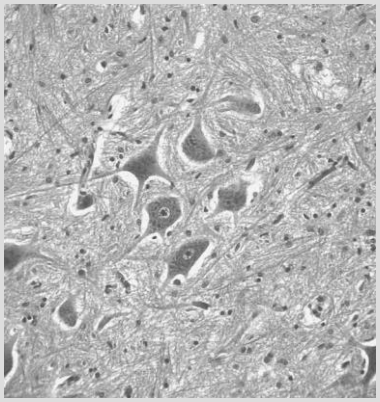
Muscle or nerve biopsy

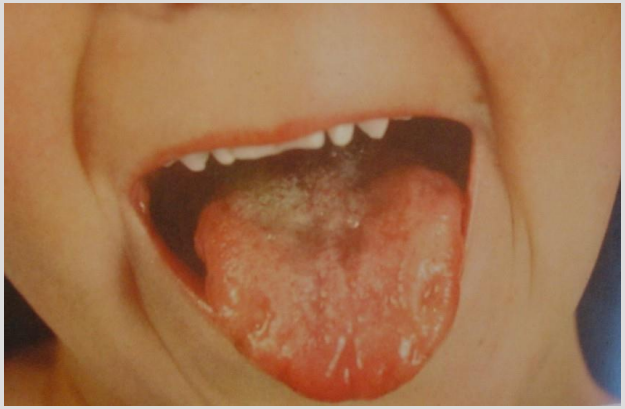
Congenital structural myopathies

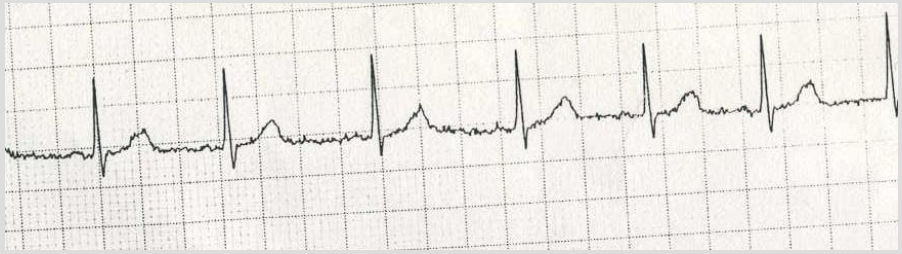

DISEASES OF THE NERVOUS SYSTEM
IN CHILDHOOD 2nd Edition
CDM
Aicardi's
Diseases of the Nervous System in Childhood
4th Edition
Arzimanoglou
with O'Hare, Johnston and Ouvrier

Spinal muscular atrophy

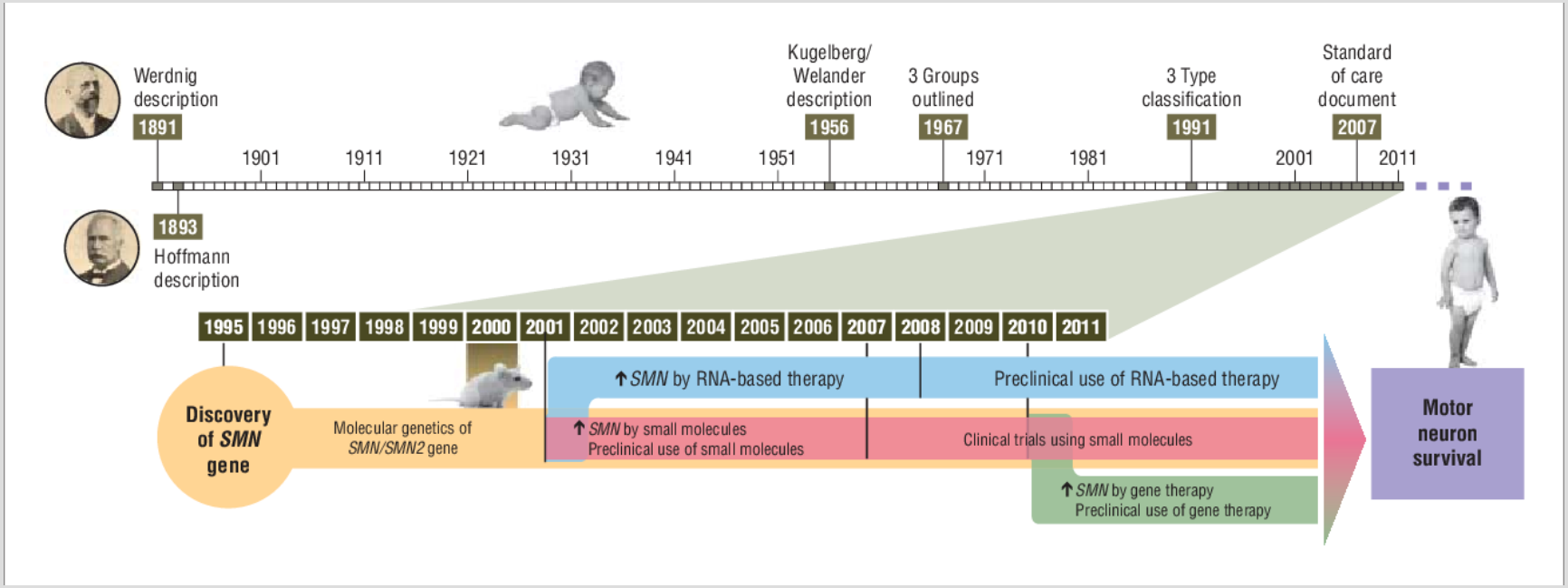




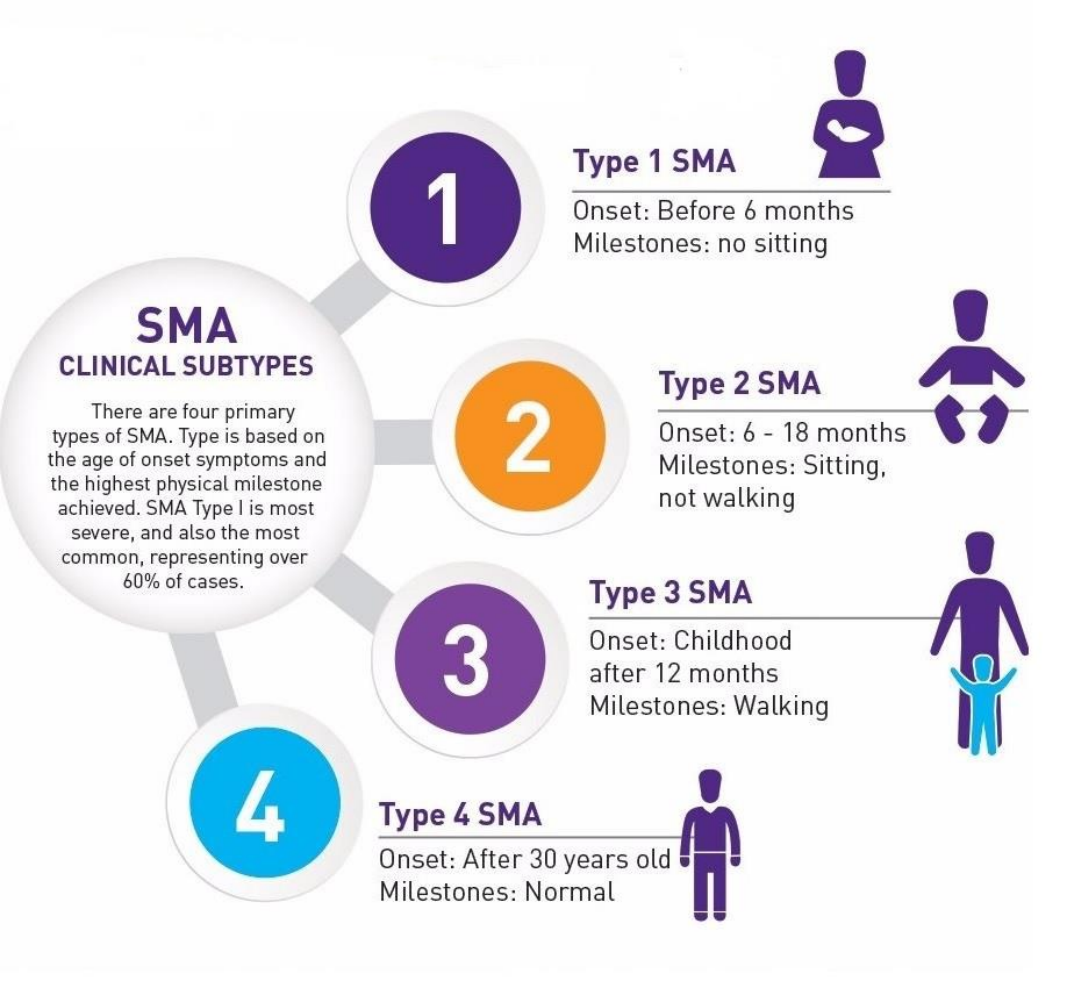




History of SMA



Historical classification of SMA

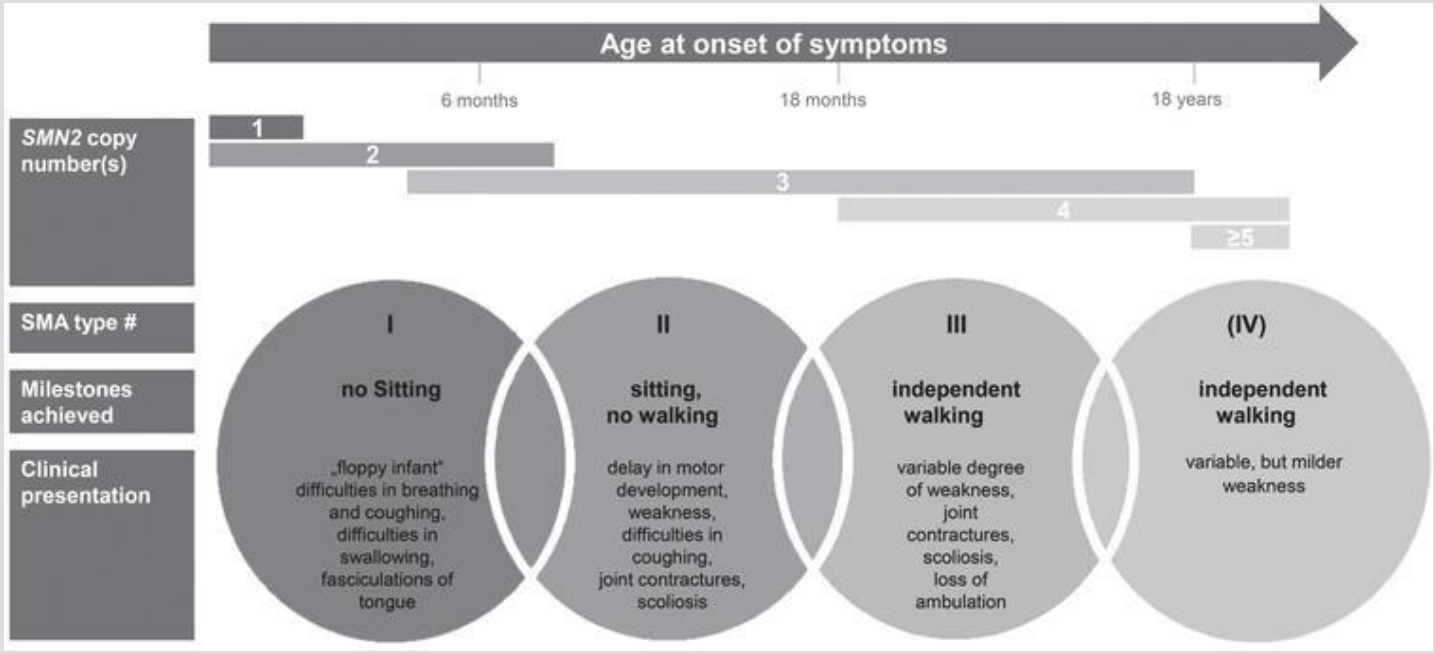


Updated Classification of SMA

SMA type	Age at onset	Maximum function	Prognosis	Proposed classification	*SMN2* copy no.
Type 0 (very severe)	Neonatal with prenatal signs	Never sits	If untreated no survival beyond first months after birth	–	–
Type 1 (severe)	0–6 months	Never sits	If untreated life expectancy <2 years	1a, head control never achieved, symptomatic in neonatal period 1b, head control never achieved, onset after neonatal period 1c, head control achieved, onset after neonatal period	One or two copies of *SMN2* in 80% of patients
Type 2 (intermediate)	7–18 months	Sits but never stands	Survival into adulthood expected	Decimal classification according to functional level from 2.1 to 2.9	Three copies of *SMN2* in >80% of patients
Type 3 (mild)	>18 months	Stands and walks	Normal life expectancy	3a, onset of weakness before 3 years 3b onset of weakness after 3 years	Three or four copies of *SMN2* in 96% of patients
Type 4 (adult)	10–30 years	Stands and walks	Normal life expectancy	–	Four or more copies of *SMN2*

SMN2 copy numbers determine severity

SMA Type	*SMN2* Copy Number	Disease Severity
0	1	Most Severe
1	1-3	
2	3	
3	3-4	
4	4+	Least Severe



Clinical features

Facial expression and attentiveness are good (bright alert facies).
Weakness symmetrical; proximal more than distal; legs more affected than arms
Poor head control & typical “frog-like” posture
Weakness of the intercostals with relative sparing of the diaphragm
Bell shaped chest & paradoxical breathing pattern
Tongue fasciculation's
Bulbar weakness, difficulty swallowing, risk of aspiration
Cranial nerves spared & cognition is normal
Deep tendon reflexes absent

Standard of care

Regular examination to assess cough effectiveness, work of breathing, paradoxical breathing, chest deformity.
Physiotherapist: intermitted chest percussion, appropriate positioning
Cough assist machine, clearing of secretions
Speech and language therapist: assessment of feeding and swallowing
Standard immunizations
Regular sleep studies (fatigue, headaches, disturbed sleep)
Non-invasive ventilation

Treatment of SMA

Drug	Sponsor	Mechanism of action	Route of application	Phase I	Phase II	Phase III	FDA Approval	Comment
Splicing modification of SMN2:								
Nusinersen	Biogen-Ionis	Antisense-oligonucleotide	IT	x	x	x	x	Approval by FDA (Dec. 2016) and EMA (Jul. 2017) for all subtypes of SMA
RG7916 (Risdiplam)	Roche	Small molecule/splicing modifier	PO	x	x	(x)		SMA type 1: After 15 months of treatment inde-pendent sitting in 33%
LMI070 (Branaplam)	Novartis	Small molecule/splicing modifier	PO	x	x			Recruitment temporarily halted (safety concerns), now completed
Replacement of SMN1-gene								
AVXS-101 (Zolgensma)	Avexis/Novartis	AAV-9-Vector	IV	x	x	x	x	FDA approval for SMA patients <2 years of age (May 2019)
AVXS-101 (Zolgensma)	Avexis/Novartis	AAV-9-Vector	IT	x				Study in children <6 years of age with 3 *SMN2*-copies
Upregulation of muscle growth								
CK-2127107 (Reldesemtiv)	Cytokinetics	FSTA	PO	x	x			Mild improvement in 6MWT after 4–8 weeks of treatment in SMA 2 and 3
SRK-015	Scholar Rock	Myostatin Inhibotor	IV	x	x			Positive results in animal models
Neuroprotection								
Olesoxime	Hoffmann-La Roche	Apoptosis-inhibitor	PO	x	x			Development stopped in 2018

NHS England strikes deal on life-saving gene-therapy drug that can help babies with rare genetic disease move and walk

8 March 2021

Children and young people
Genomics
Long term conditions
Medicine
Specialised commissioning

A life-saving drug that can enable mobility in babies and young children suffering from a rare genetic condition will be available on the NHS, chief executive Sir Simon Stevens announced today.

Zolgensma, which has a reported list price of £1.79 million per dose and is labelled the most expensive drug in the world, will be available to patients at a price that is fair to taxpayers after a landmark confidential deal struck by NHS England.

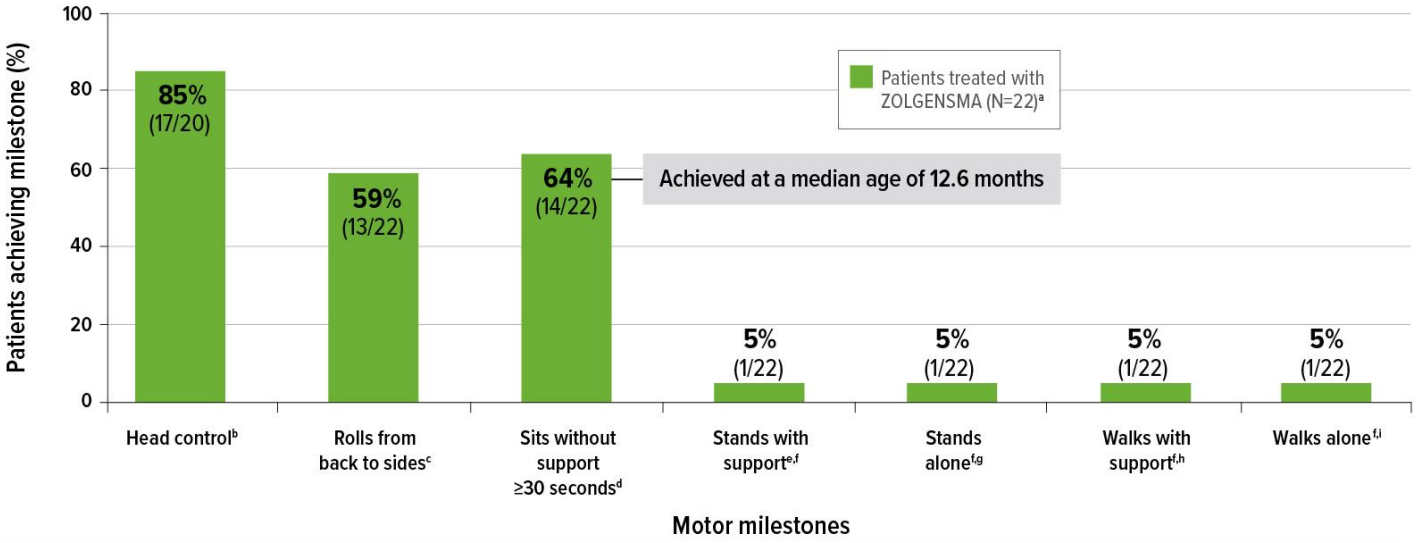
Babies born with severe type 1 SMA – the most common form of the condition – have a life expectancy of just two years.

In studies Zolgensma, manufactured by Novartis Gene Therapies, has helped babies to reach milestones such as breathe without a ventilator, sit up on their own and crawl and walk after a single infusion treatment.

NHS England Chief Executive Sir Simon Stevens said: "This deal is a life-changer for youngsters with this cruel disease and for their families.

STR1VE: New motor milestones were achieved with ZOLGENSMA[2]

Video-confirmed milestones achieved at any point during the STR1VE trial



59% (13/22) of patients achieved sitting without support for ≥30 seconds at the 18-months-of-age-study visit, a primary endpoint[2]

[a] One patient was initially classified as presymptomatic and removed from the intent-to-treat (ITT) data set included in the Prescribing Information. The patient has been confirmed to be symptomatic at the time of gene therapy and included in the final ITT analysis.[2]

[b] Bayley-III, gross motor subtest item 4. Two patients were excluded as they had already achieved head control before the study commenced.[2]

[c] Bayley-III, gross motor subtest item 20.[2]

[d] Bayley-III, gross motor subtest item 26.[2]

[e] Bayley-III, gross motor subtest item 33 (supports own weight ≥2 seconds).[2]

[f] These milestones were achieved by the same patient.[2]

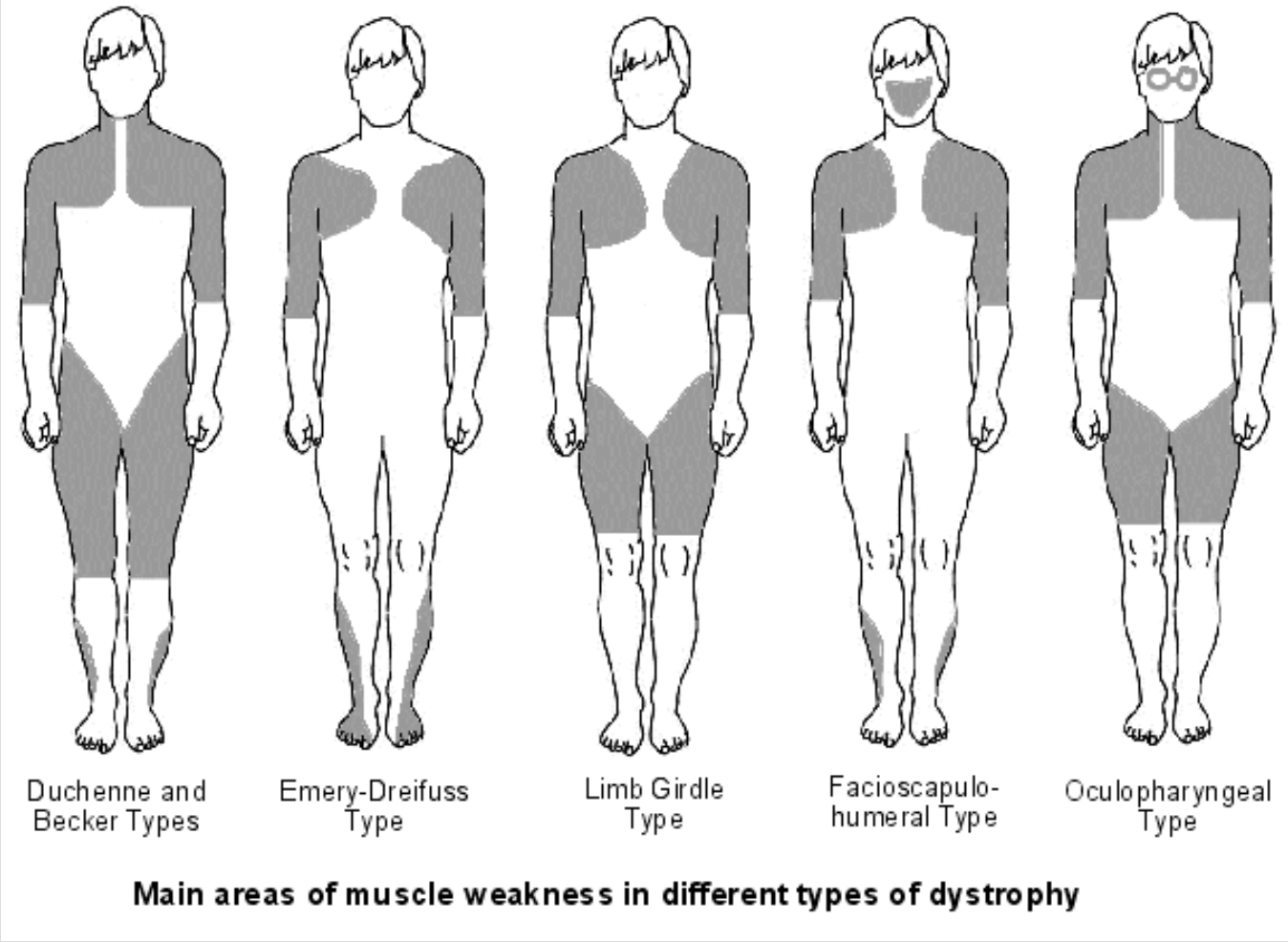
[g] Bayley-III, gross motor item 40.[2]

[h] Bayley-III, gross motor item 37.[2]

[i] Bayley-III, gross motor item 43.[2]

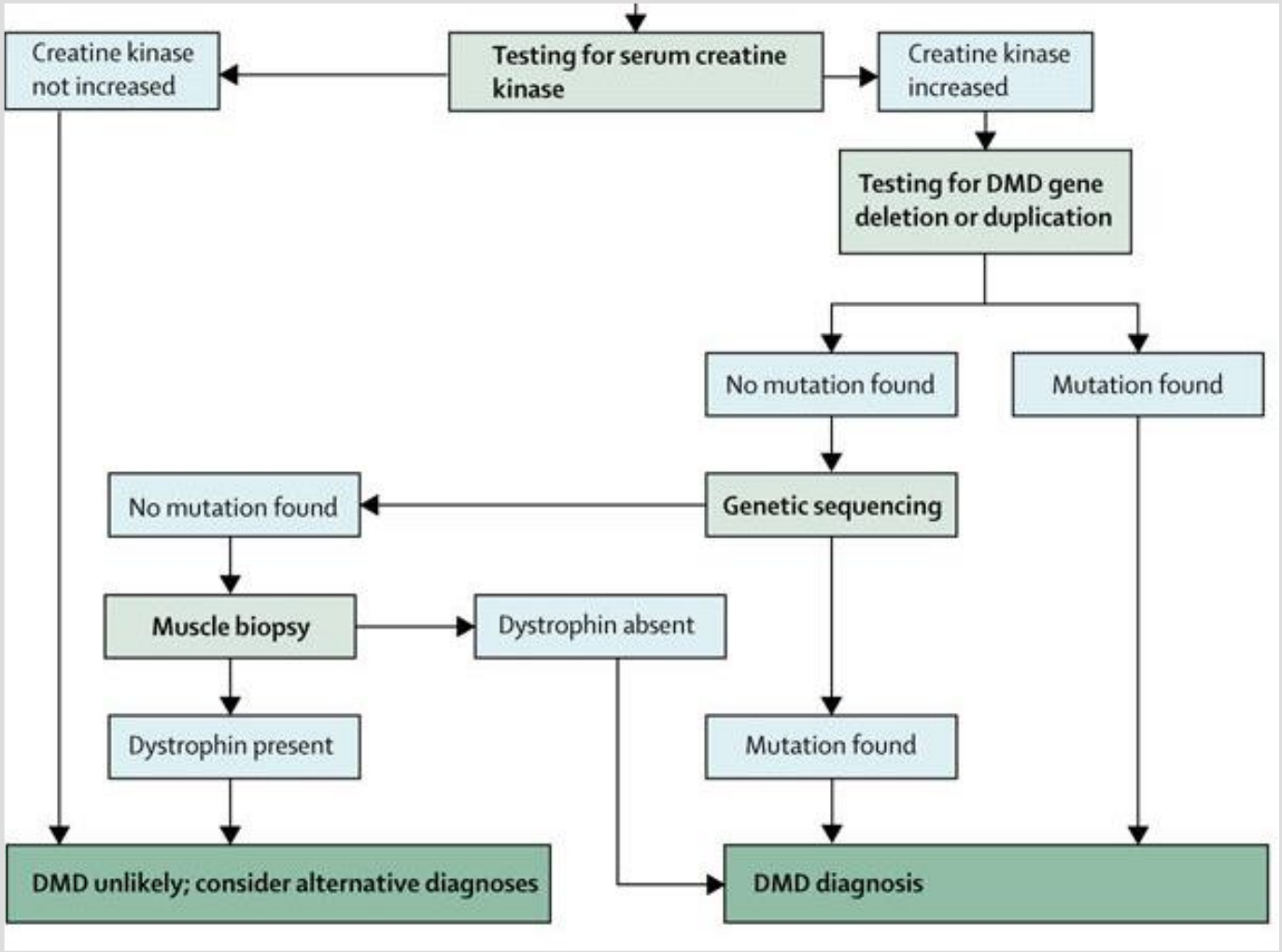
A randomized, sham-controlled, double-blind study to evaluate the efficacy and safety of intrathecal (IT) OAV101 in patients with later onset Type 2 spinal muscular atrophy (SMA) who are ≥ 2 to < 18 years of age, treatment naive, sitting, and never ambulatory

Duchenne & Becker muscular dystrophy



Main areas of muscle weakness in different types of dystrophy

Investigations

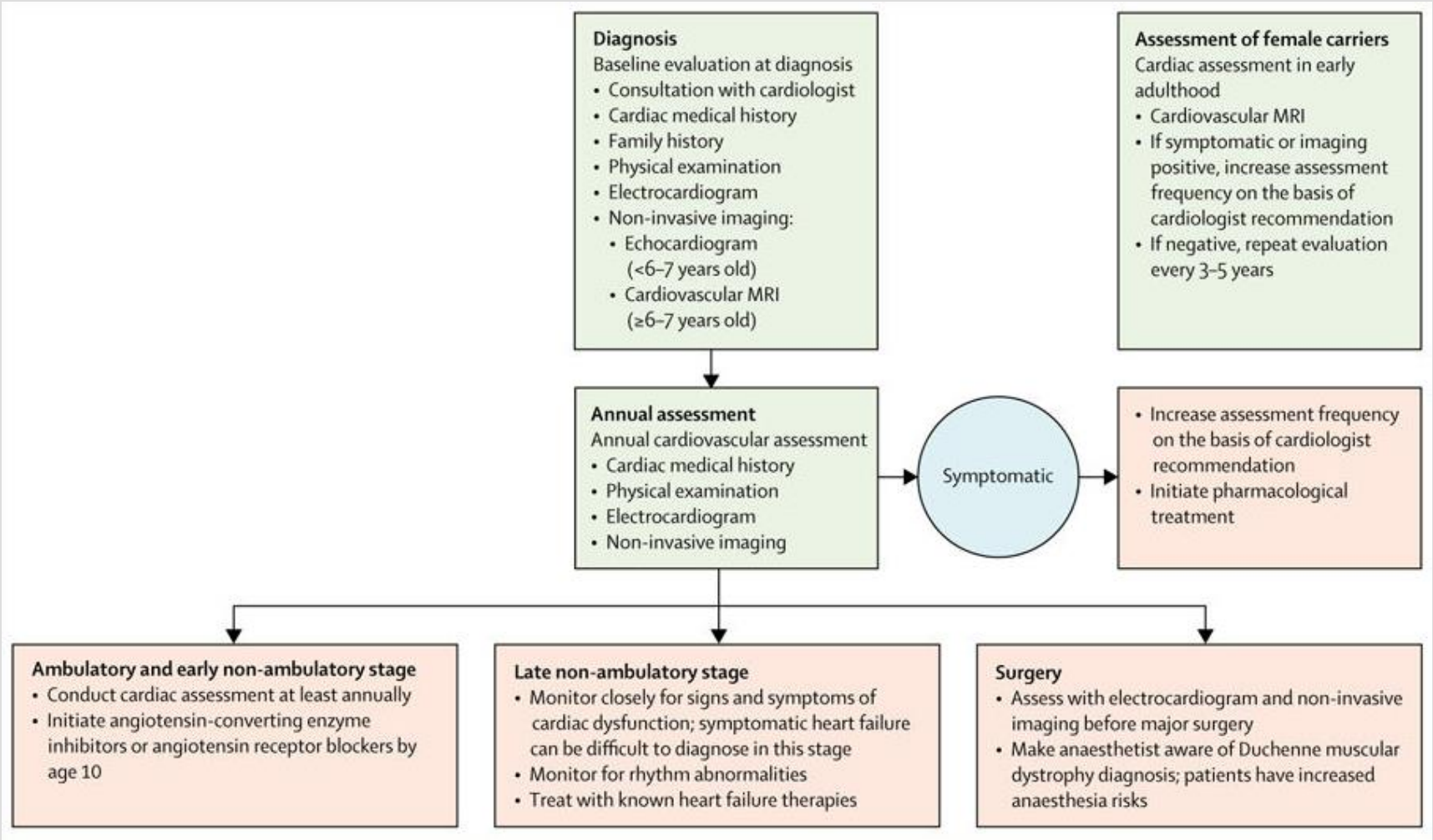


Corticosteroids in DMD

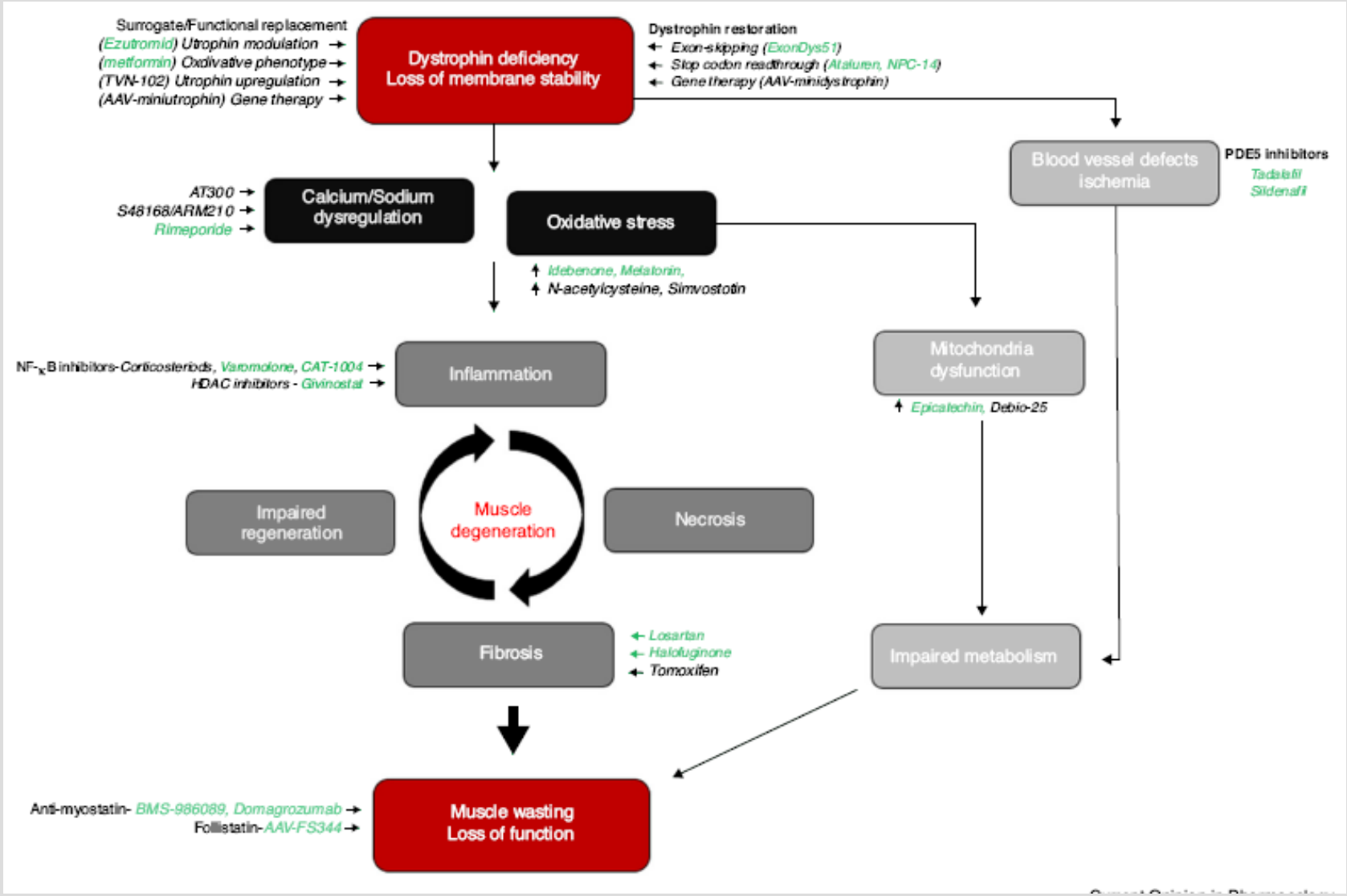
Benefit: ambulatory 2-3 years & improved pulmonary function [B]
When should treatment be initiated: 2-4 years (6 months)
Show long should patient remain on treatment? uncertainty

Optimal dosage regimen: uncertainty optimal dosing regimen
Prednisone 0.75 mg/kg/day or deflazacort 0.9 mg/kg/day
Prednisone 10 mg/kg/weekend equally effective

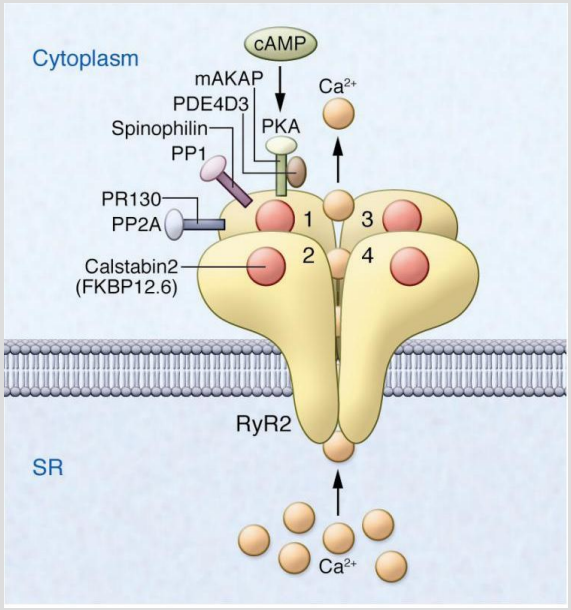
Cardiac Surveillance

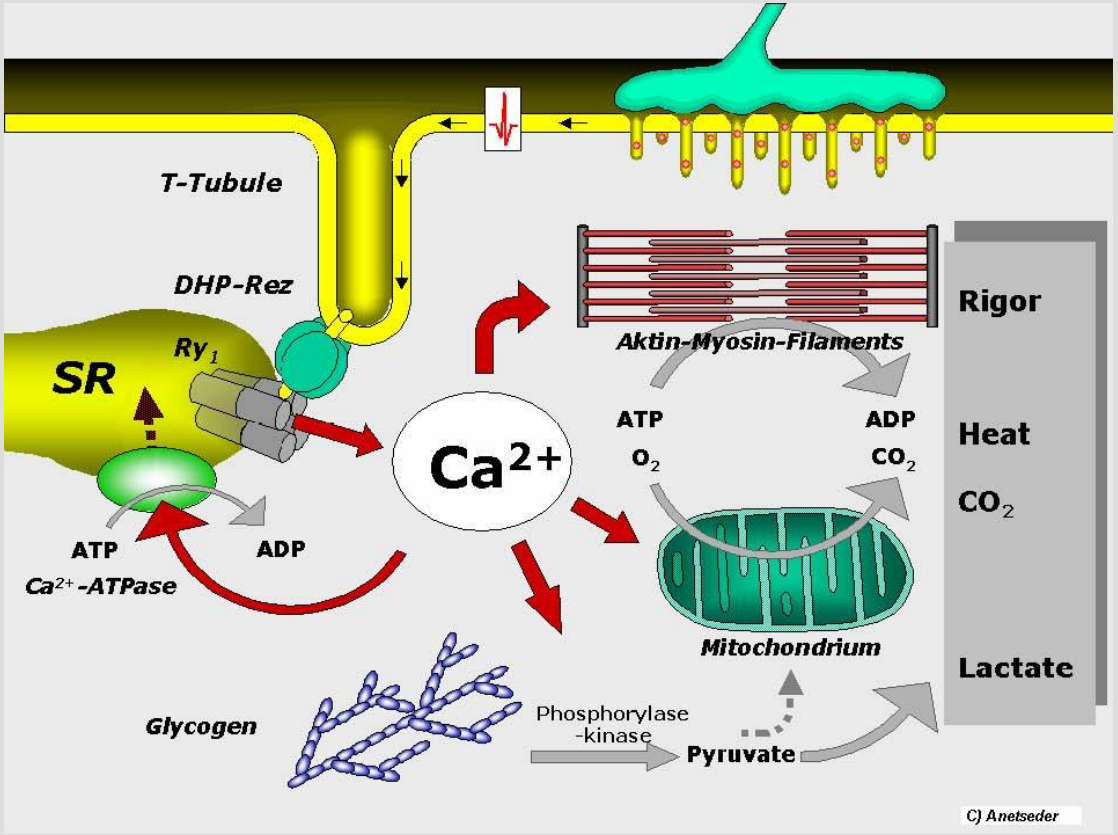


Treatment of DMD



Ryanodine receptor 1 (RYR1) mutations





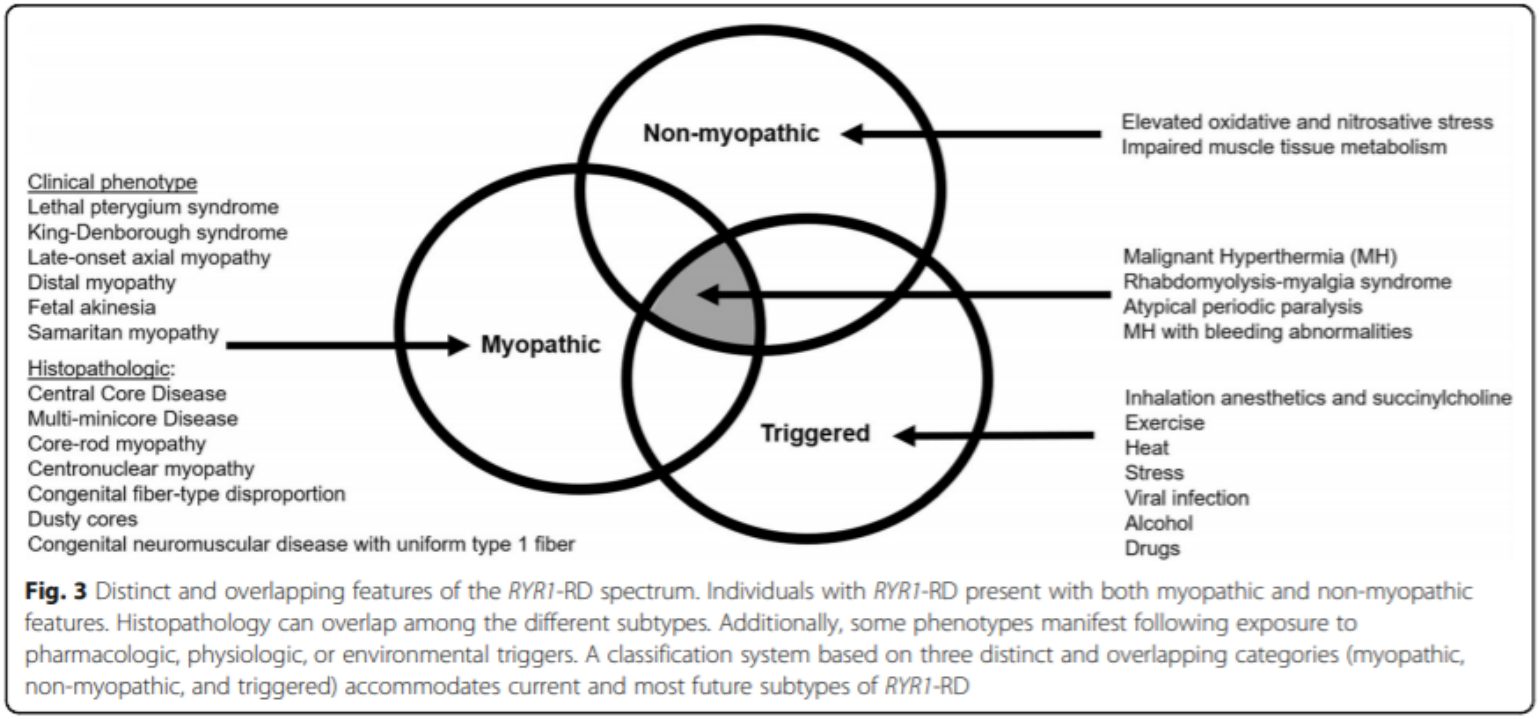


Fig. 3 Distinct and overlapping features of the *RYR1*-RD spectrum. Individuals with *RYR1*-RD present with both myopathic and non-myopathic features. Histopathology can overlap among the different subtypes. Additionally, some phenotypes manifest following exposure to pharmacologic, physiologic, or environmental triggers. A classification system based on three distinct and overlapping categories (myopathic, non-myopathic, and triggered) accommodates current and most future subtypes of *RYR1*-RD

	Central core disease	Multiminicore disease	Core–rod myopathy	Centronuclear myopathy	Congenital fiber type disproportion
Clinical features	Hypotonia and motor development delay	Hypotonia	Axial hypotonia		Static or slowly progressive generalized muscle weakness
	Respiratory, bulbar, and cardiac involvement are uncommon	Early respiratory impairment with or without cardiac complications	Respiratory impairment	Mild respiratory involvement	Respiratory weakness
	Proximal weakness pronounced in hip girdle	Distal weakness	Diffuse muscle weakness	Diffuse and progressive muscle weakness	Proximal axial weakness
		Extraocular muscle involvement and ophthalmoplegia in severe cases		Ptosis/extraocular involvement	Ophthalmoplegia
			Mild facial involvement	Facial dysmorphism	Facial muscle weakness
	Orthopedic deformities (scoliosis) and ligamentous laxity	Spinal rigidity and scoliosis	Multiple joint contractures and scoliosis	Joint contractures	
		Moderate bulbar involvement		Bulbar weakness	Dysphagia
	Myalgia and/or exertional weakness with or without rhabdomyolysis	Exercise-induced myalgia			
	High malignant hyperthermia susceptibility	Malignant hyperthermia rarely reported			

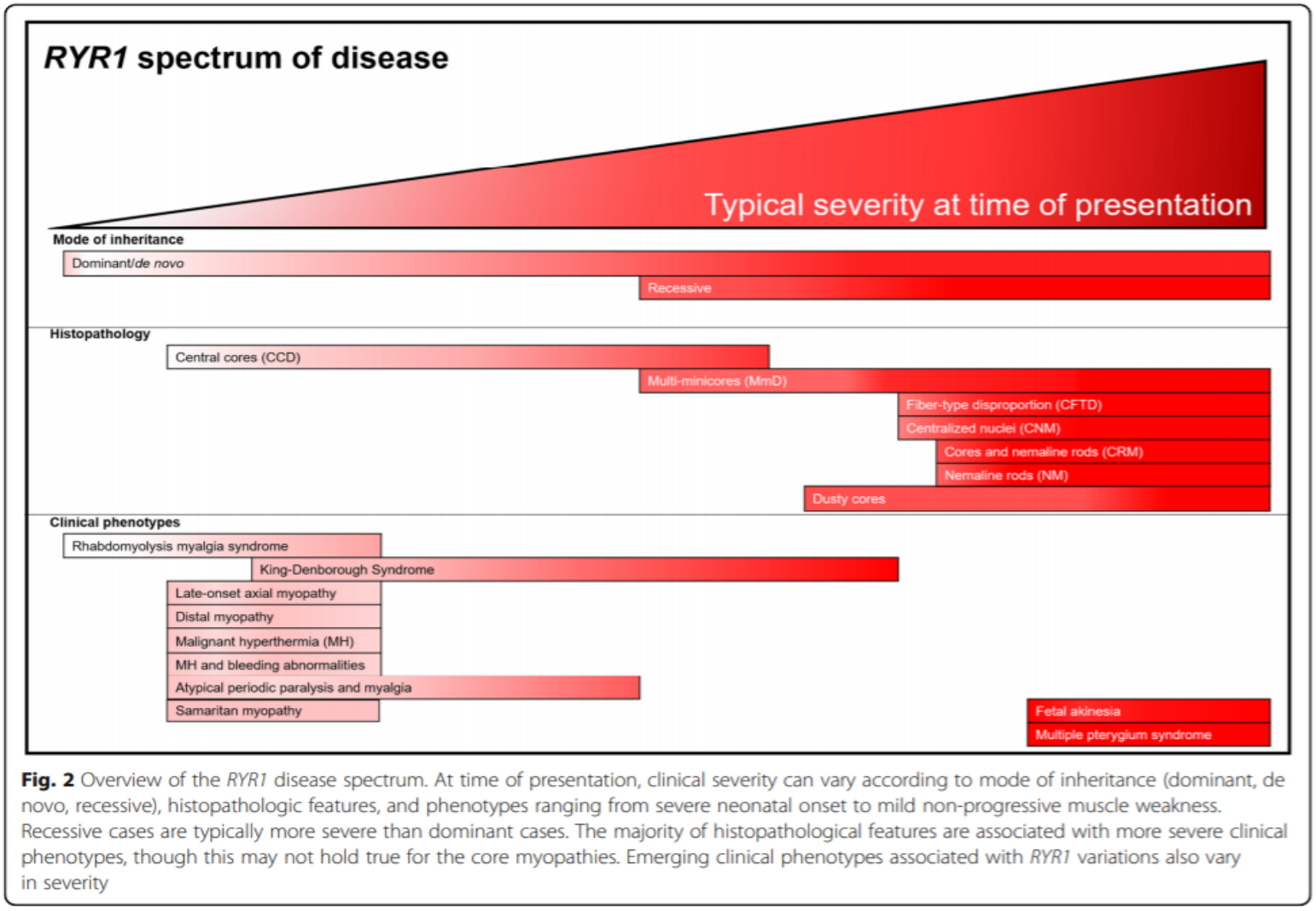


Fig. 2 Overview of the *RYR1* disease spectrum. At time of presentation, clinical severity can vary according to mode of inheritance (dominant, de novo, recessive), histopathologic features, and phenotypes ranging from severe neonatal onset to mild non-progressive muscle weakness. Recessive cases are typically more severe than dominant cases. The majority of histopathological features are associated with more severe clinical phenotypes, though this may not hold true for the core myopathies. Emerging clinical phenotypes associated with *RYR1* variations also vary in severity

State patients

DISORDER	LABS	LIMITATIONS	TAT	~ COST
SMA (Diag/PD)	GSH, WITS (MLPA/PCR)	Homozygous Exon 7 deletion only	6 weeks (8-24)	
BMD/DMD (Diag/CD/PD)	GSH, WITS (MLPA)	Deletions/ Duplications only	8-10 weeks (8-24)	
FKRP-related muscular dystrophy (Diag/CD/PD)	WITS (Sanger)	Founder mutations only State patients only	8 weeks	
Myotonic Dystrophy (Diag/PD)	WITS (Triplet repeat, PCR)		6-12 weeks	
CMT 1A (Diag/PT)	WITS	PMP22 duplication only	8-12 weeks	
RYR1	GSH	Founder variants		

(Mitochondrial, MPV17): GSH

Diag: Diagnostic testing
CD: Carrier Detection
PD: Prenatal diagnosis
PT: Presymtomatic Testing

South African participation in International Centre for Genomic Medicine in Neuromuscular Disease (ICGNMD) – a call for collaboration with MDSA

By Francois H van der Westhuizen, PhD
Professor of Biochemistry
Deputy Director: School of Physical and Chemical Sciences North-West University

Neuromuscular diseases (NMDs) affect approximately 20 million children and adults globally. They cause either premature death or are chronic diseases causing lifelong disability with economic impact. They include many different disorders affecting muscle and nerve function and account for 20% of all neurological diseases. Examples include muscular dystrophies, motor neuron diseases, and mitochondrial diseases. Most NMDs are genetic single gene disorders, with many genes being discovered. In developed countries, a precise genetic diagnosis and gene discoveries are already having an important impact on patient care and health outcomes. Unfortunately in developing countries, such as SA, this is not the case and the great strides in research that are required to develop such genetic diagnoses in our country have not been forthcoming in recent decades.

The newly established International Centre for Genomic Medicine in Neuromuscular Disease (ICGNMD) - partly funded by the MRC (UK) for five years from July 2019 - has the mission to harness genomics to understand disease mechanisms and improve the health outcomes of children and adults with serious NMDs on a global scale. It is led by the University College London & Cambridge University and include partners from five developing countries: South Africa, Brazil, India, Zambia and Turkey. The main objectives are to build NMD cohorts in these countries, identify the genes involved in the disease in each population, and build human capacities in each country and international networks that are sustainable. Reaching these objectives will greatly help to address the treatment of the various NMDs.

For SAs participation, experienced researchers and clinicians at the following universities have formed a core team:

- Prof Francois H van der Westhuizen (coordinator and NMD researcher), Centre for Human Metabolomics, North-West University (NWU), Potchefstroom
- Prof Izelle Smuts (paediatric neurologist). Department of Paediatrics, University of Pretoria (UP).
- Prof Jo Wilmshurst (paediatric neurologist). School of Child and Adolescent Health, Red Cross War Memorial Children's Hospital, University of Cape Town (UCT).
- Dr Franclo Henning (neurologist). Division of Neurology, Stellenbosch University (SU).
- Prof Jeannine Heckmann (neurologist). Division of Neurology, Groote Schuur Hospital, UCT.
- Prof Soraya Bardien (geneticist), Division of Molecular Biology and Human Genetics, Stellenbosch University.

The success of this ambitious study for SA will greatly depend on the extent in which patients can recruited and how well the complex, population-specific clinical and genomic data can be scrutinized. It will also depend on collaborations with all stake holders in SA. The centres already participating have NMD clinics a base of patients that are visiting these clinics, as well as established collaborations (e.g. contact with local MDSA branches) and networks. We would like to expand the knowledge of this study so that broader access of patients with a NMD and other collaborations with these clinics can be established over the next 5 years.

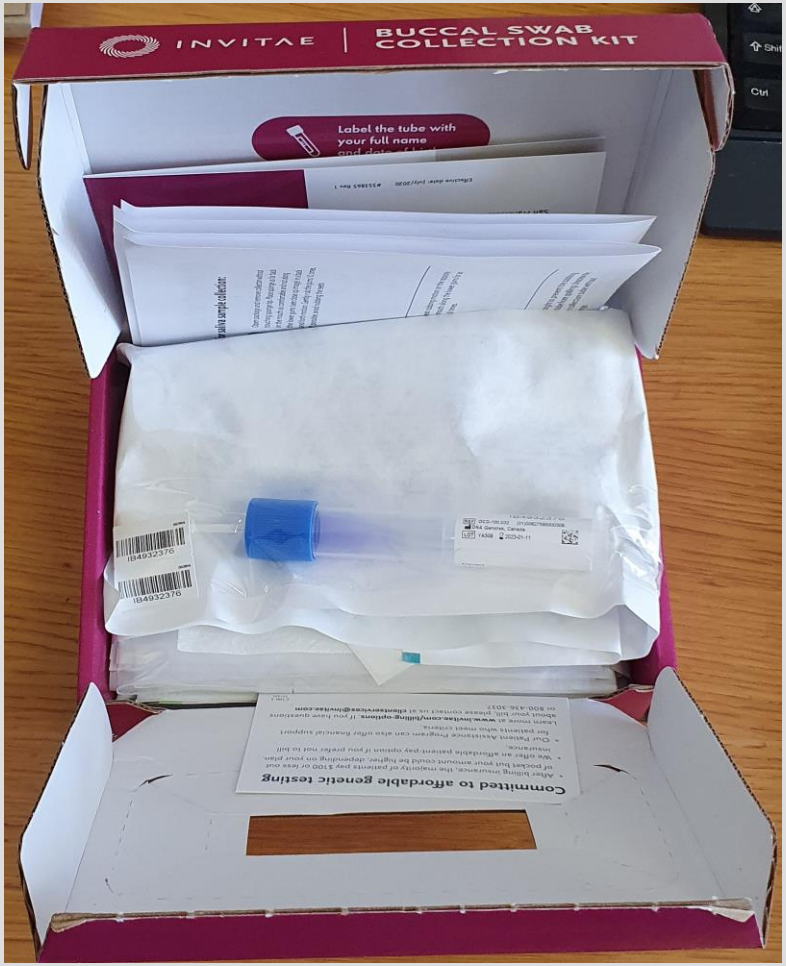
Private patients

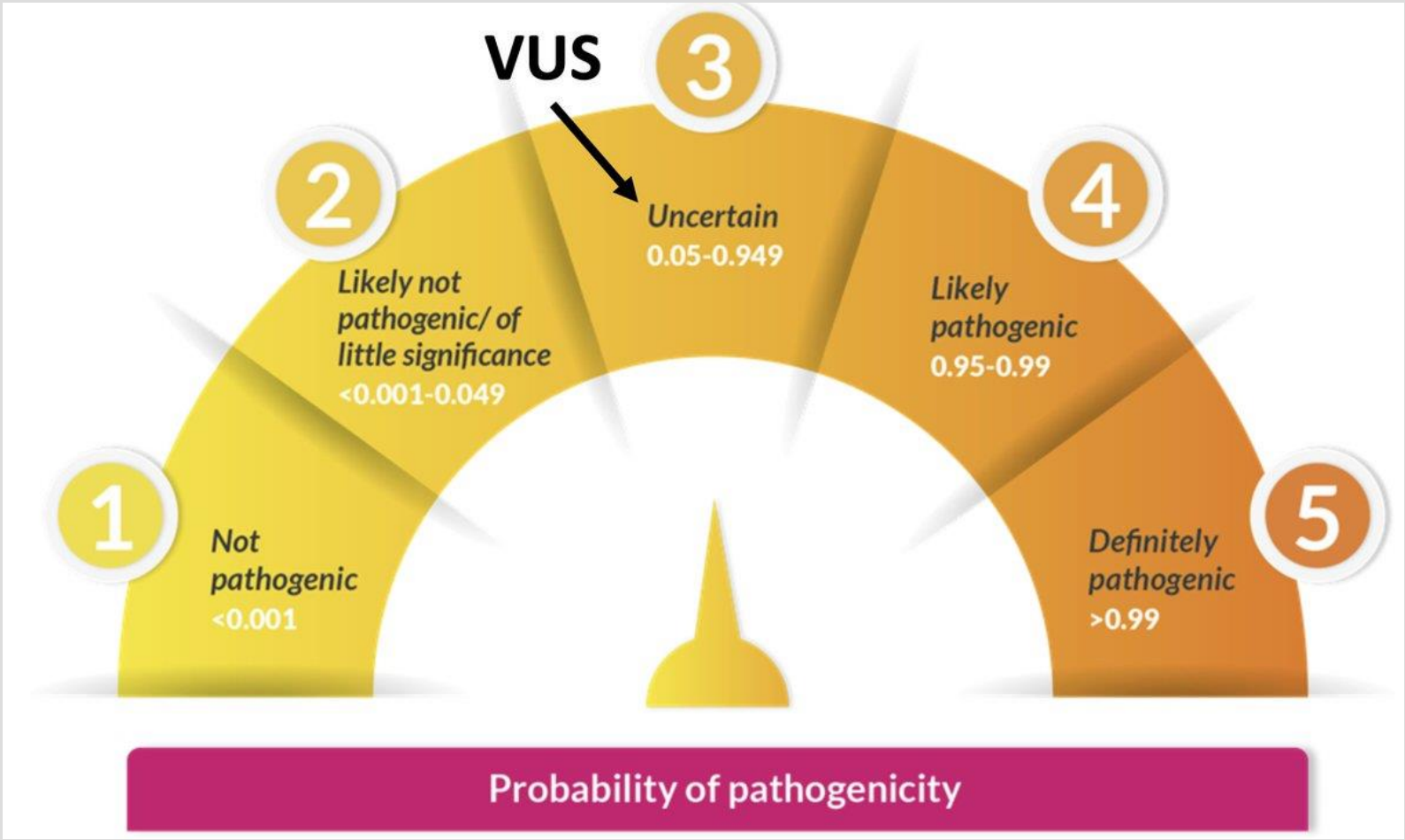
***SMA, DMD, DM1 performed at NHLS for Private patients as for State patients

DISORDER/ PHENOTYPE	LOCAL/ O/SEAS	LABS	COMMENT	TAT	COST
Myopathies (Diag, PD)	Local	Ampath	MH NGS panel (**RYR1, STAC3**, CACNAS, BCHE)	12w	
CMT 1A (Diag, PT)	Local	Ampath	PMP22 duplication (MLPA)		
Congenital muscular dystrophy	O	Invitae	29 gene NGS panel	3w	$250
Comprehensive muscular dystrophy	O	Invitae	52 gene NGS panel Includes DMD	3w	$250
Limb Girdle muscular dystrophy	O	Invitae	37 gene panel	3w	$250
Congenital myopathy	O	Invitae	36	3w	$250
Comprehensive myopathy	O	Invitae	71	3w	$250
Myotonia/paramyotonia Congenita	O	Invitae	CLCN1, SCN4A	3w	$250
SMA / SMA stat	O	Invitae	SMN1, SMN2	3w	$250
Congenital myasthenic	O	Invitae	21 gene panel	3w	$250

DISORDER/ PHENOTYPE	LOCAL/ O/SEAS	LABS	COMMENT	TAT	COST
Comprehensive Neuromuscular Disorders	O	Invitae	131 gene panel	3w	$250 = R3500
Hereditary Rhabodomyolysis	O	Invitae	101 gene panel	3w	$250
Comprehensive Neuropathies	O	Invitae	101 gene panel	3w	$250
CMT Comprehensive	O	Invitae	57 gene panel	3w	$250
HSAN	O	Invitae	15 gene panel	3w	$250
HMN	O	Invitae	27 gene panel	3w	$250
Hereditary Spastic Paraplegia	O	Invitae	62 gene panel	3w	$250
Whole exome sequencing	O	Invitae/ Centogene	Proband only Trio	6w	($1250/€820) ($2500/€2045)
Whole genome sequence	O	Centogene	Proband/Trio		SQ

Invitae collection kits




VUS
1
Not pathogenic
<0.001
2
Likely not pathogenic/ of little significance
<0.001-0.049
3
Uncertain
0.05-0.949
4
Likely pathogenic
0.95-0.99
5
Definitely pathogenic
>0.99
Probability of pathogenicity

RESULT: POTENTIALLY POSITIVE

One Pathogenic variant and two Variants of Uncertain Significance identified in RYR1. RYR1 is associated with autosomal dominant and recessive myopathies and autosomal dominant malignant hyperthermia susceptibility.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
RYR1	c.10348-6C>G (Intronic)	heterozygous	PATHOGENIC
RYR1	c.14524G>A (p.Val4842Met)	heterozygous	Uncertain Significance
RYR1	c.9001-12A>G (Intronic)	heterozygous	Uncertain Significance
AGRN	c.4313C>T (p.Ser1438Leu)	heterozygous	Uncertain Significance
COL12A1	c.2422G>A (p.Ala808Thr)	heterozygous	Uncertain Significance
COL12A1	c.4781G>A (p.Arg1594His)	heterozygous	Uncertain Significance
FKTN	c.1250A>T (p.Glu417Val)	heterozygous	Uncertain Significance
GAA	c.2110G>A (p.Ala704Thr)	heterozygous	Uncertain Significance
ISPD	c.1218T>G (p.Ile406Met)	heterozygous	Uncertain Significance
LAMA2	c.358G>A (p.Glu120Lys)	heterozygous	Uncertain Significance
LAMA2	c.535C>G (p.Leu179Val)	heterozygous	Uncertain Significance
MICU1	c.987T>G (p.Phe329Leu)	heterozygous	Uncertain Significance

Conclusion

Implementation of NGS into routine clinical practice will some of the diagnostic algorithms in patients with neuromuscular diseases.

Nonetheless, clinical evaluation, neurophysiological and histopathological information is still essential for precise phenotype to select the most appropriate genetic test.

There are challenges and limitations of NGS among others the interpretation of some of the VUS.