INHERITED NEUROMUSCULAR DISORDERS

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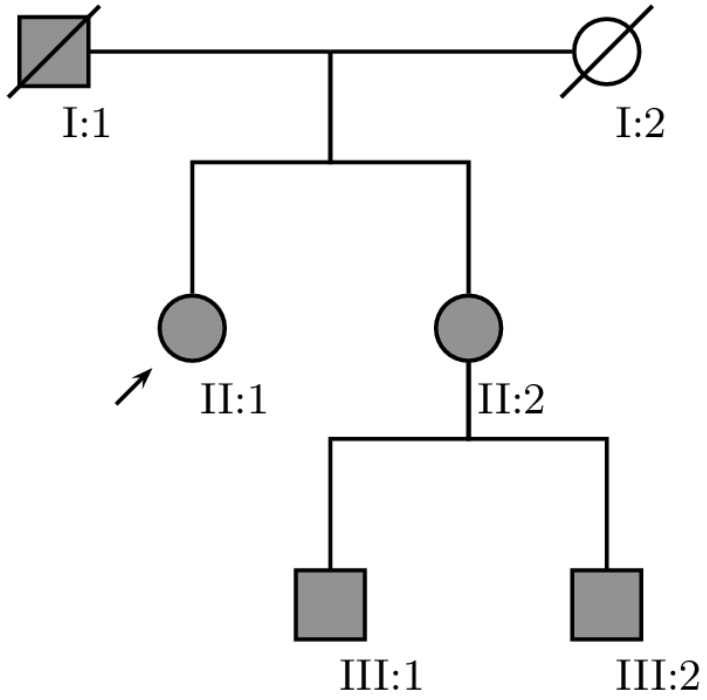
Photo of patients

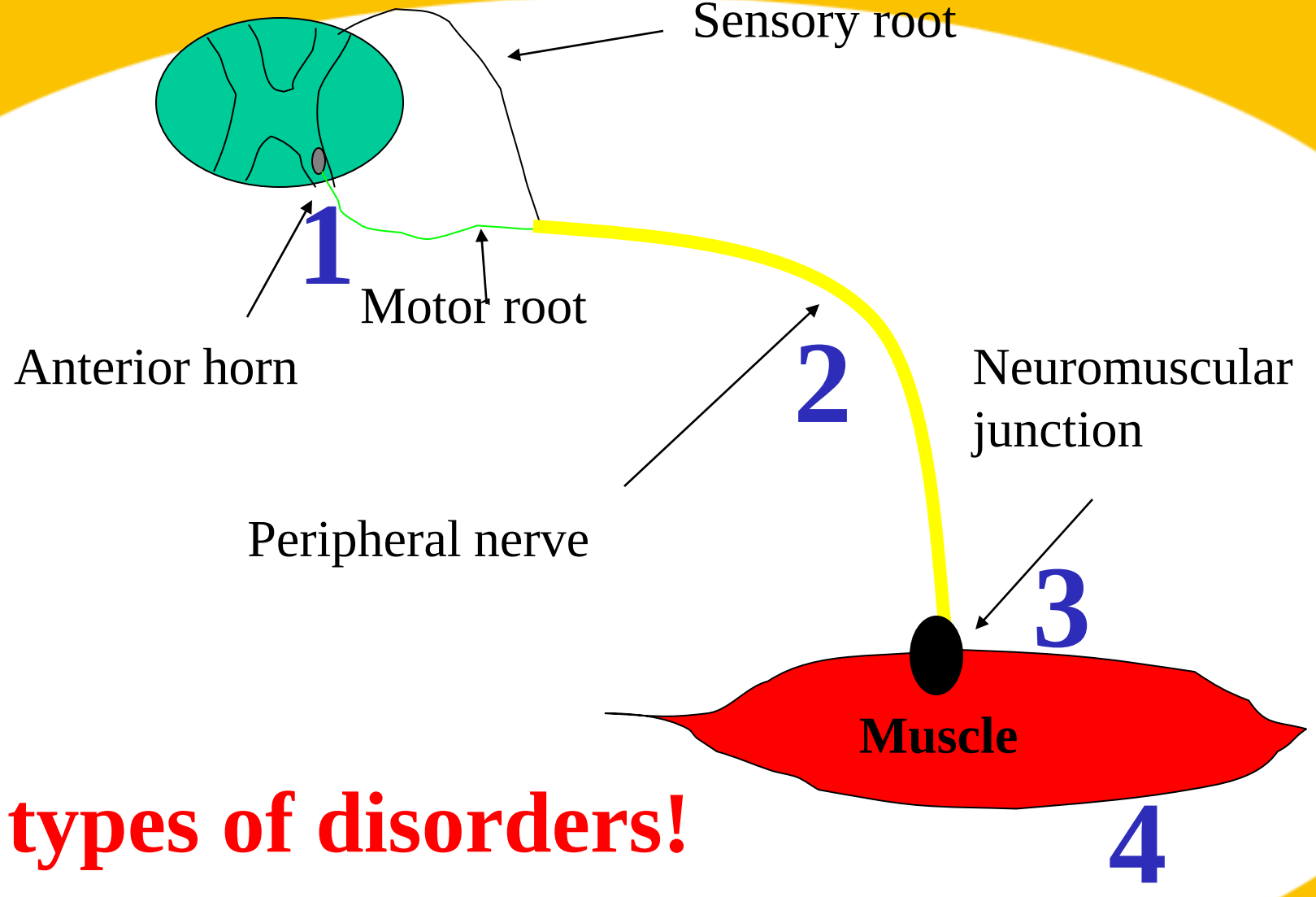

I:1
I:2
II:1
II:2
III:1
III:2

The objectives today

- To discuss the main concept
- To give several examples of recognizing specific disorders and their management

Myths

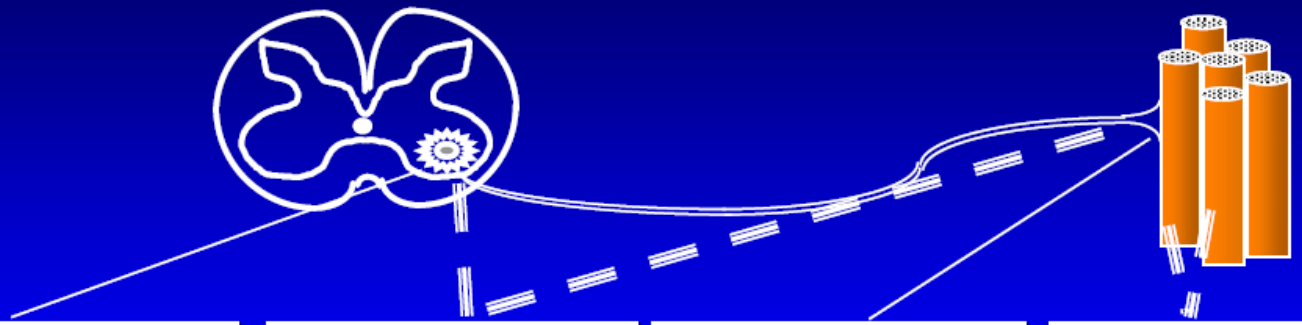
- Rare disorders?
- Difficult to recognize?
- Incurable disorders?



4 types of disorders!

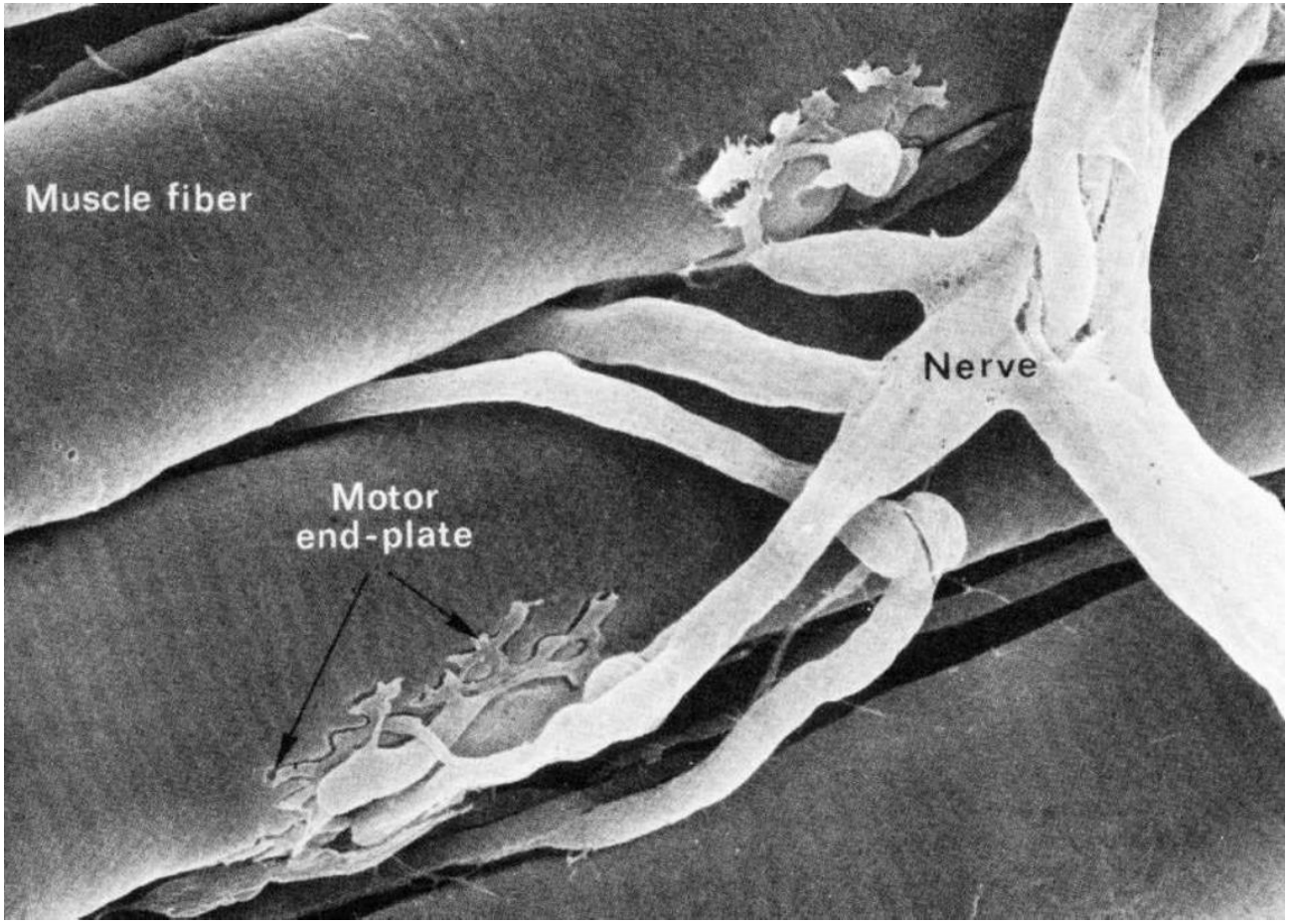
D.Hilton-Jones, Oxford, 2000

Anatomical classification of Neuromuscular Dis.

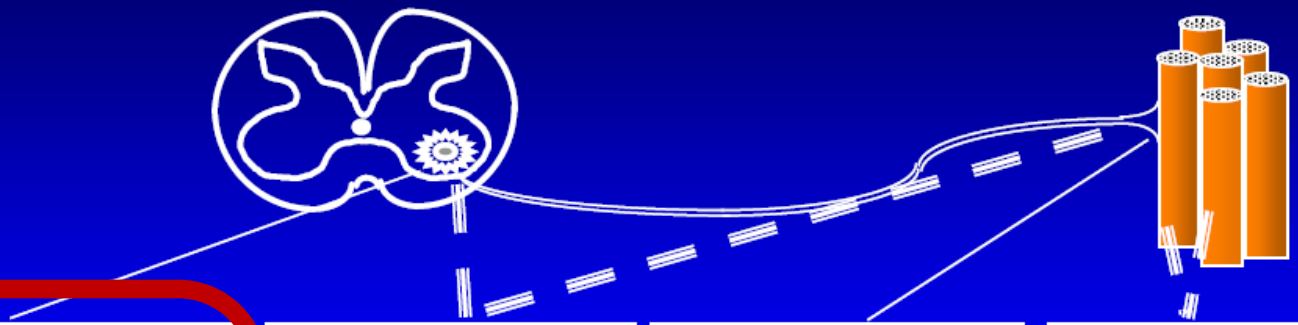


ANTERIOR HORN	NERVE	NM JUNCTION	MUSCLE FIBER
SPINAL MUSCULAR ATROPHIES *(SMA)* Types 1-4 **ALS** **KENNEDY Sd** **FAZIO-LONDE sd** **BROWN-VIALETTO** **Distal SMA**	**NEUROPATHIES** **H.S.M.N.** ***(Charcot-Marie-Tooth, Déjerine-Sotas, others)*** **H.M.N.** **H.N.A.**	**MYASTHENIAS** **Myasthenia gravis** *-AChR+* *- MusK+* *- others* **Congenital myasthenic synd.**	**DYSTROPHIES** **Duchenne / Becker** **Limb girdle (LGMD)** **Emery-Dreifuss / FSHD** **MYOTONIC Sd** **Steinert (DM1) / DM2** **Thomsen, others** **MISCELLANEOUS** **Mitochondrial** **Congenital** **Metabolic** **Dysimmune**

A.Urtizberea, Paris, 2019


Muscle fiber
Nerve
Motor
end-plate

Anatomical classification of Neuromuscular Dis.



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UpToDate®

spinal muscular atrophy

Contents | Calculators | Drug Interactions | UpToDate Pathways

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Spinal muscular atrophy

Author: Olaf A Bodamer, MD, PhD, FAAP, FACMG
Section Editors: Douglas R Nordli, Jr, MD, Helen V Firth, DM, FRCP, FMedSci, Richard Martin, MD
Deputy Editor: John F Dashe, MD, PhD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Jan 2022.** | This topic last updated: **Jan 13, 2022.**

Spinal muscular atrophy (SMA) is characterized by degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem, which results in progressive muscle weakness and atrophy.

The inheritance pattern of the common forms of SMA is autosomal recessive.

These forms are caused by biallelic deletions or mutations in the SMN1 gene on chromosome 5q13.

SMA phenotypes are classified as types 0 through 4 depending upon the age of onset and clinical course.

Normal Baby

Floppy Baby

Clinical classification of spinal muscular atrophy (SMA)

Type	Age of onset	Requires respiratory support at birth	Able to sit	Able to stand	Able to walk	Life expectancy	Predicted *SMN2* copy number
0	Prenatal	Yes	No	No	No	<6 months	1
1	<6 months	No	No	No	No	<2 years	2
2	6 to 18 months	No	Yes	No	No	10 to 40 years	3
3	>18 months	No	Yes	Yes	Assisted	Adult	3 to 4
4	>5 years	No	Yes	Yes	Yes	Adult	>4

From: Butchbach ME. Copy Number Variations in the Survival Motor Neuron Genes: Implications for Spinal Muscular Atrophy and Other Neurodegenerative Diseases. Front Mol Biosci 2016; 3:7. Copyright © 2016 Butchbach. Available at: http://journal.frontiersin.org/article/10.3389/fmolb.2016.00007/full (Accessed on March 27, 2017). Reproduced under the terms of the Creative Commons Attribution License.

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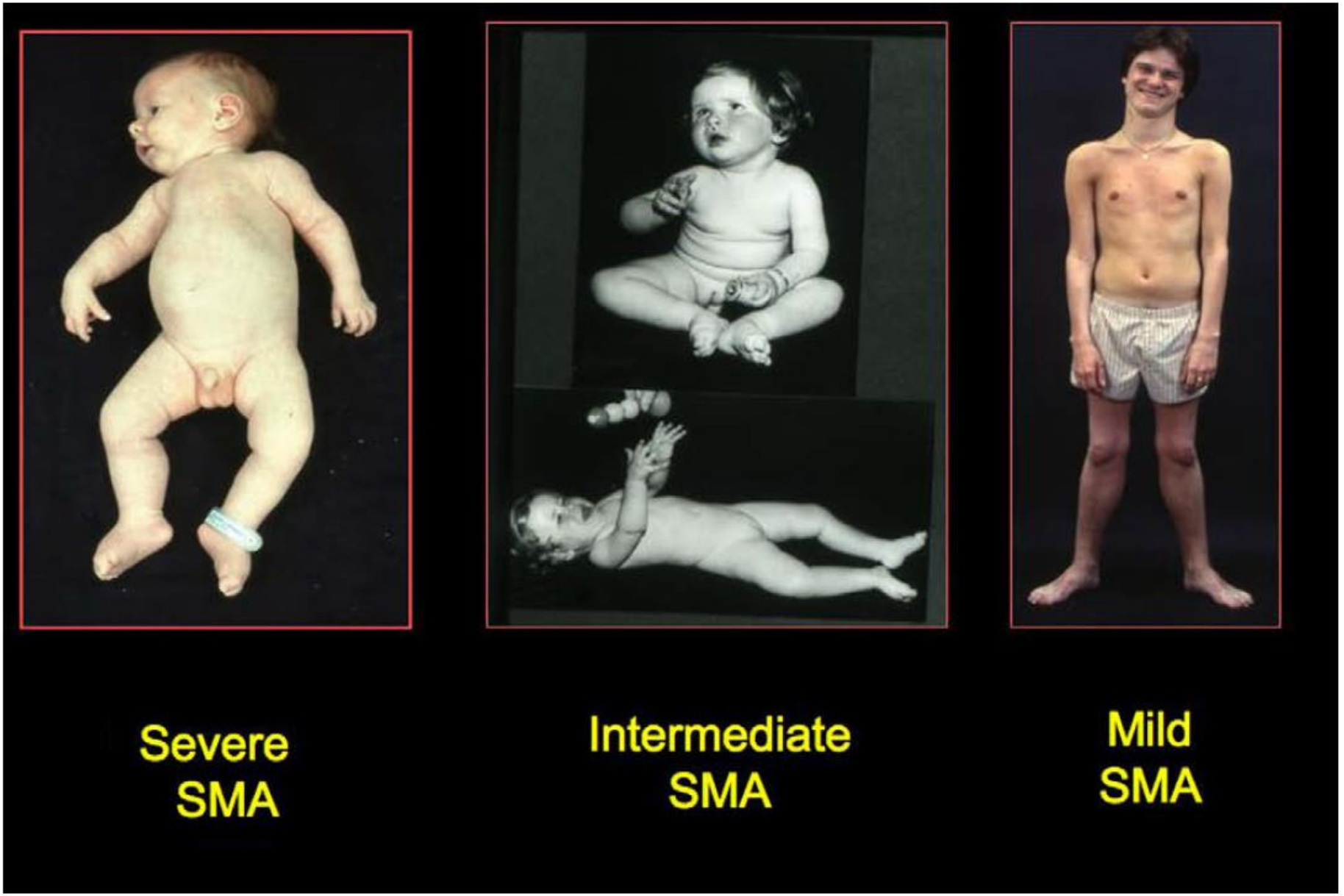
•SMA type 0 designates prenatal onset of SMA, which presents at birth with severe weakness and hypotonia, and often with areflexia. No motor milestones are achieved. Death occurs from respiratory failure by age six months, and usually by one month.
•SMA type 1 (infantile spinal muscular atrophy or Werdnig-Hoffmann disease) typically presents after birth but before age six months. Symptoms progress rapidly, and the majority of infants die before two years of age from respiratory failure.


Severe
SMA
Intermediate
SMA
Mild
SMA

- SMA type 2 (intermediate form) and SMA type 3 (Kugelberg-Welander disease) have a less severe course. SMA type 2 presents between 3 and 15 months of age. SMA type 3 typically presents from 18 months of age until adulthood and progresses to a chronic course.

- SMA type 4 is notable for adult onset and is the mildest form.

SMA III

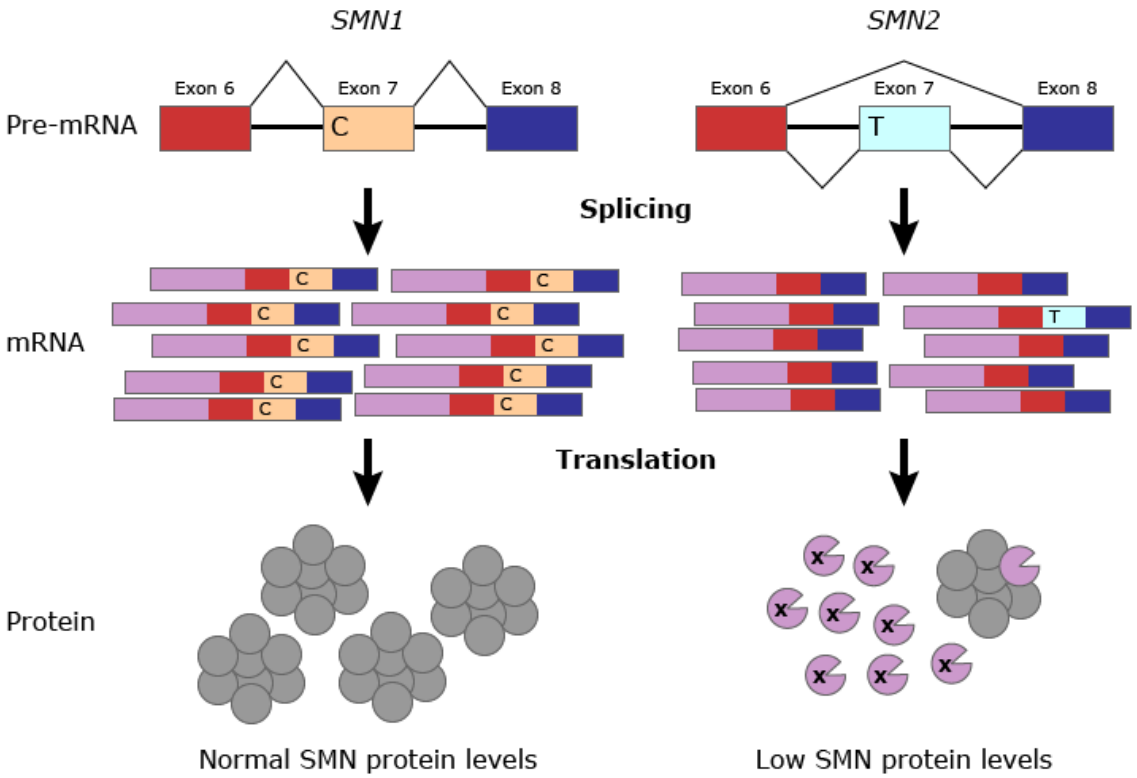
Photo of patients

Patients with all forms of SMA have diffuse symmetric proximal muscle weakness that is greater in the lower than upper limbs and absent or markedly decreased deep tendon reflexes.

Infants with SMA type 1 have a severe symmetric flaccid paralysis and are unable to sit unsupported. All SMA types, particularly SMA type 1, may be associated with restrictive lung disease.

Molecular genetic testing can confirm the diagnosis in infants and children with suspected SMA by detection of homozygous deletions of exons 7 of the *SMN1* gene.

The effect of the C-to-T transition in exon 7 between *SMN1* and *SMN2* on splicing



SMN1: survival motor neuron 1 gene; *SMN2*: survival motor neuron 2 gene.

Original figure modified for this publication. Butchbach ME, Burghes AH. Perspectives on models of spinal muscular atrophy for drug discovery. Drug Discov Today Dis Models 2004; 1:151. Illustration used with the permission of Elsevier Inc. All rights reserved. From: Butchbach ME. Copy Number Variations in the Survival Motor Neuron Genes: Implications for Spinal Muscular Atrophy and Other Neurodegenerative Diseases. Front Mol Biosci 2016; 3:7. Copyright © 2016 Butchbach. Available at: http://journal.frontiersin.org/article/10.3389/fmolb.2016.00007/full (Accessed March 27, 2017). Reproduced under the terms of the Creative Commons Attribution License.

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Therapeutic interventions

- Curative :
  - *pharmacotherapy*
  - *cell therapy*
  - *gene therapy*
- Supportive :
  - *orthopaedic*
  - *respiratory*
  - *cardiac, others…*
- Prevention :
  - *prenatal testing, genetic counseling*
  - *others*

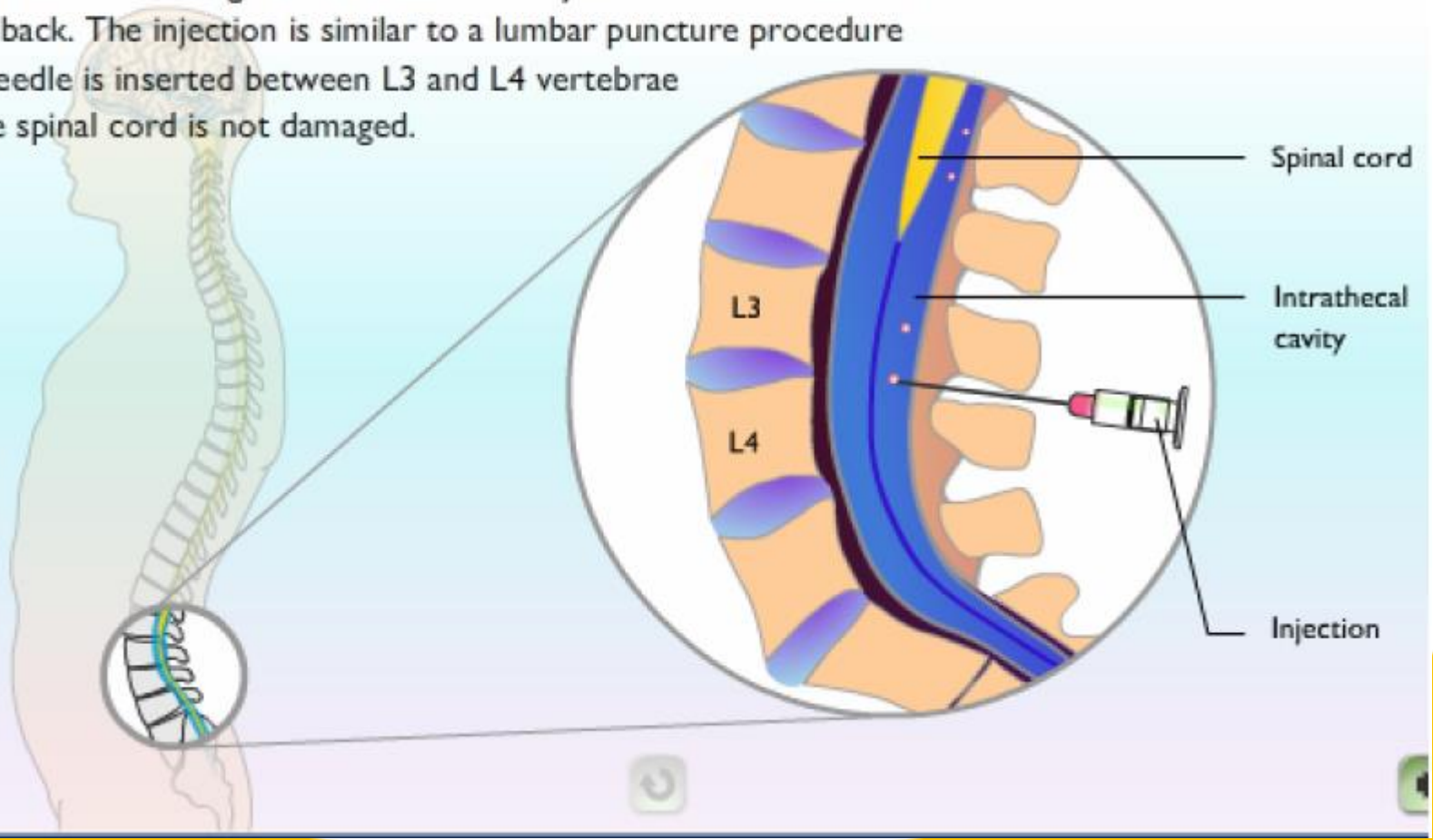
Disease-modifying therapy for SMA is available; nusinersen is approved in the United States and several other regions and countries around the world; onasemnogene abeparvovec and risdiplam are approved in the United States. Direct comparisons between nusinersen, onasemnogene abeparvovec, and risdiplam are lacking. Nusinersen is given by intrathecal injection with maintenance dosing every four months after the initial four loading doses, which are given over eight weeks. Onasemnogene abeparvovec is given as a one-time intravenous infusion. Risdiplam is given daily by mouth using a syringe.

SPINRAZA™

(nusinersen) injection 12 mg/5 mL

Intrathecal drug delivery

In a technique called intrathecal drug delivery, a drug can be injected into the CSF, where it flows through the intrathecal cavity between the vertebrae of the lower back. The injection is similar to a lumbar puncture procedure where a needle is inserted between L3 and L4 vertebrae so that the spinal cord is not damaged.



- manufactured and sold by Biogen Inc.
- approved by FDA (Dec. 23th, 2016)
- for all types of SMA
- pending approval by European Medical Agency
- very much debated pricing policy
  - stratospheric range
  - 125,000 USD per injection
  - ~ 750,000 USD per year and per patient (first year)
  - 375,000 USD the following years

- intrathecally injected
- first year: 6 injections, then 1 injection x 4 months
- French experience:
  - EAP (expanded access program)
  - drug provided for free by the company
  - 40 type I patients injected to date
  - good safety profile
  - good and poor responders
  - most remain ‘bulbar’: ethical issues raised
  - hot debate about embarking on type 2 patients
- a potential technical issue for type 2s who underwent spine fusion

●For infants and very young children with SMA who are not ventilator-dependent, we recommend treatment with disease-modifying therapy using either nusinersen, onasemnogene abeparvovec, or risdiplam where available (Grade 1B). The efficacy of onasemnogene abeparvovec for children two years of age and older is unknown. For older children (age ≥2 years) and adults with moderate symptoms of SMA, we suggest treatment with nusinersen or risdiplam (Grade 2C). The choice among these treatments should be individualized according to drug cost, availability, adverse effect profile, burden of administration, and patient values and preferences, using a process of shared decision-making. Short-term trials have shown modest efficacy for these treatments in a disease that, left untreated, leads to profound disability and death. However, these therapies are extraordinarily expensive.

●Affected individuals with SMA and their parents should be referred for genetic counseling.

CURE?!

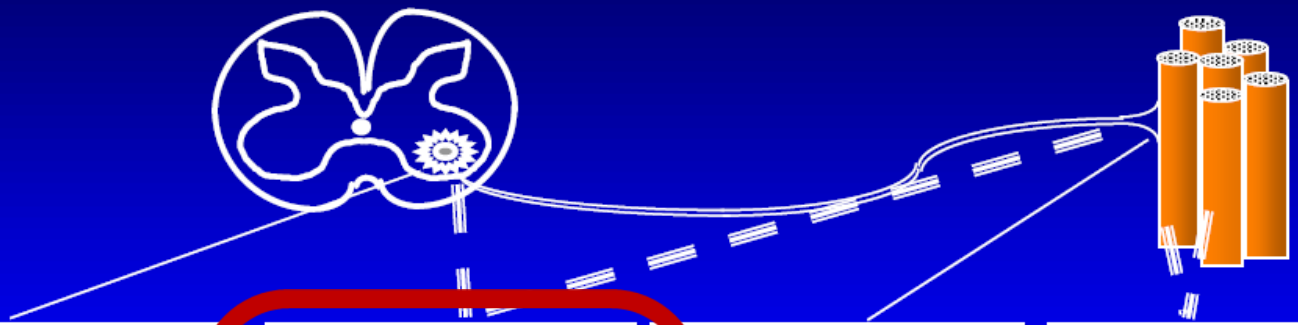
AveXis receives FDA approval for Zolgensma®, the first and only gene therapy for pediatric patients with spinal muscular atrophy (SMA) on May 24, 2019

https://www.novartis.com/news/media-releases/avexis-receives-fda-approval-zolgensma-first-and-only-gene-therapy-pediatric-patients-spinal-muscular-atrophy-sma

CURE?!

The approval of Zolgensma is based on data from the ongoing Phase 3 STR1VE trial and the completed Phase 1 START trial evaluating the efficacy and safety of a one-time IV infusion of Zolgensma in patients with SMA Type 1 who showed symptoms of SMA at <6 months of age, with one or two copies in the STR1VE trial or two copies in the START trial of the *SMN2* backup gene and who have bi-allelic *SMN1* gene deletion or point mutations.These data show Zolgensma provides unprecedented rates of survival never seen in the natural history of the disease; rapid motor function improvement, often within one month of dosing; and, durable milestone achievement, including the ability to sit without support, a milestone never achieved in untreated patients. Safety observations in STR1VE were comparable to those seen in the START trial. The most commonly observed adverse events were elevated aminotransferases and vomiting.

Anatomical classification of Neuromuscular Dis.



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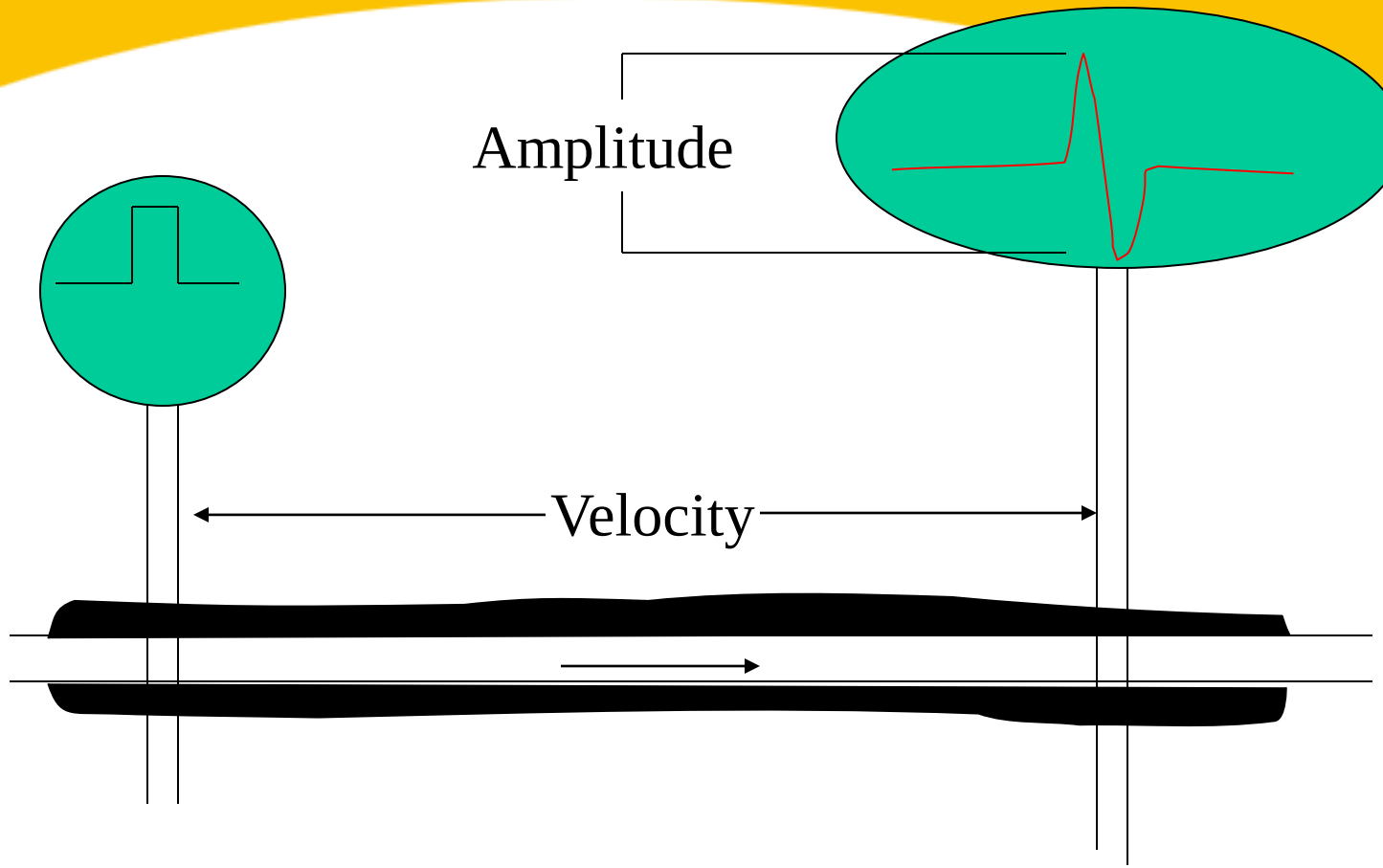
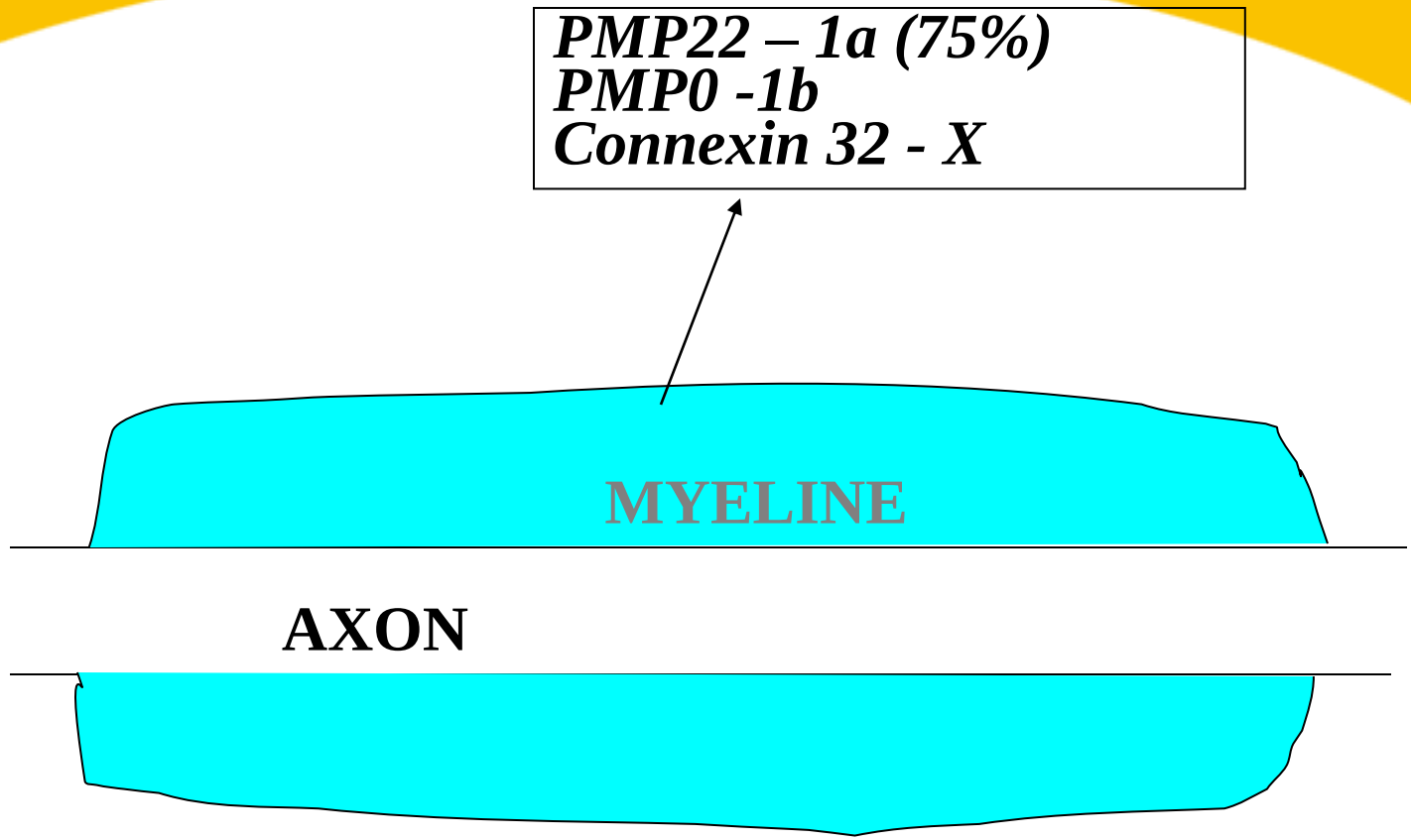
HMSN

Photo of patients

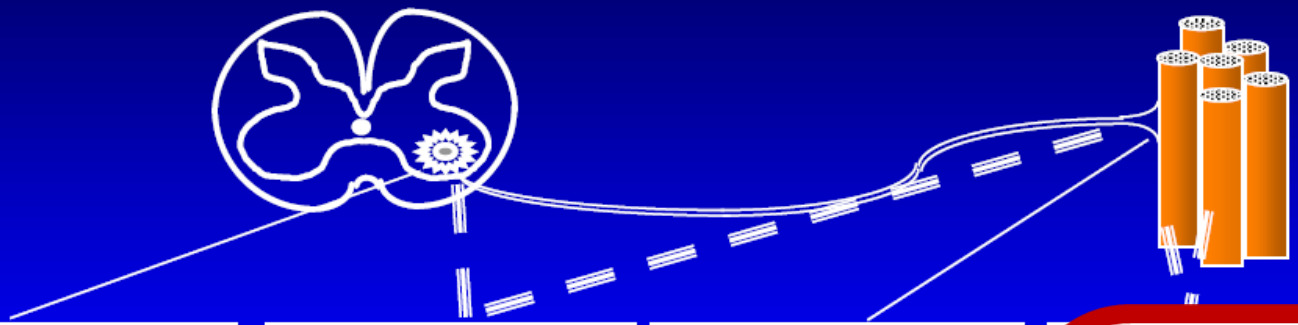

Amplitude
Velocity

HMSN

- Type1
  - Normal amplitude
  - Velocity <38 m/s
  - = demyelinating neuropathies
- Type2
  - Low amplitude
  - Velocity >38 m/s (often normal)
  - = axonal type


PMP22 – 1a (75%)
PMP0 -1b
Connexin 32 - X
MYELINE
AXON

Anatomical classification of Neuromuscular Dis.



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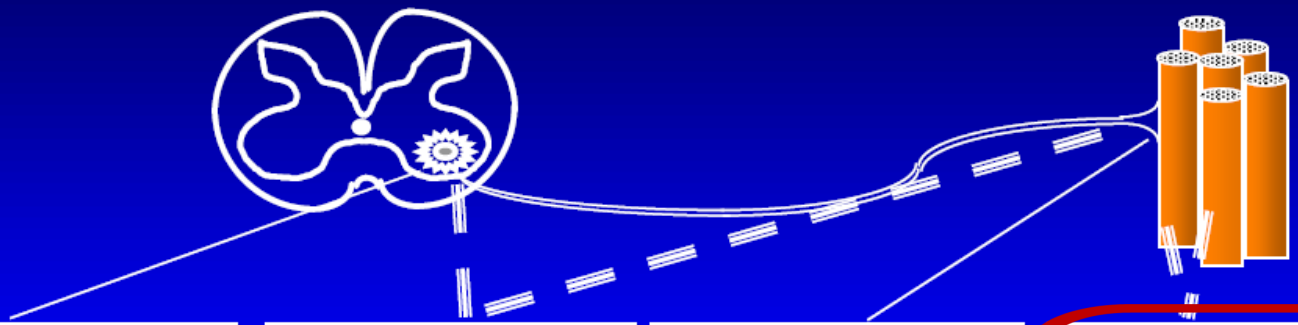
Muscular dystrophies

- X-linked recessive
  - Duchenne/Becker
  - Emery-Dreifuss
- Autosomal dominant
  - Facio-scapulae-humeral
  - Limb-girdle muscular dystrophies
  - Emery-Dreifuss
- Autosomal recessive
  - Limb-girdle muscular dystrophies

Anatomical classification of Neuromuscular Dis.



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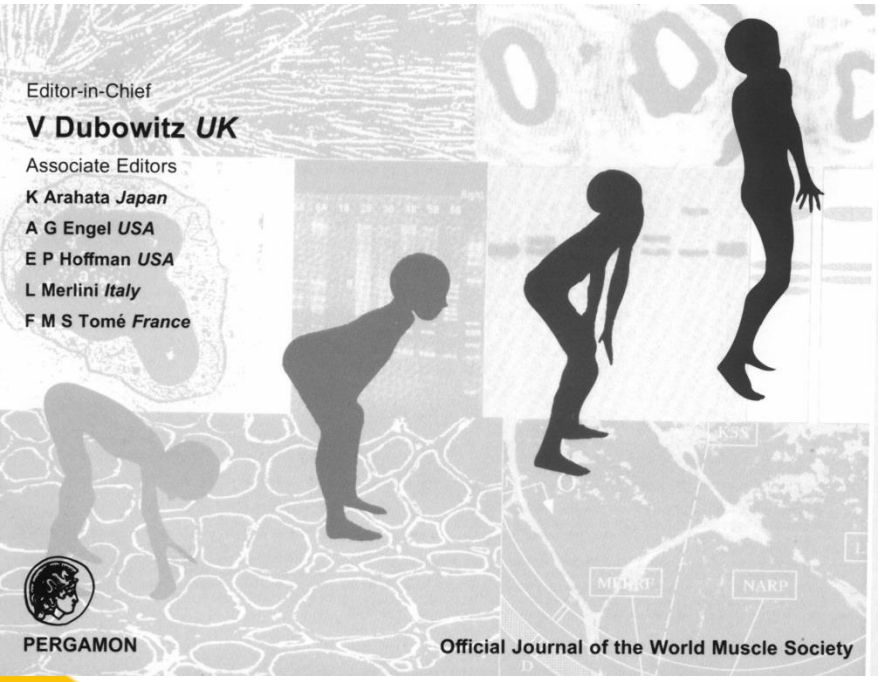
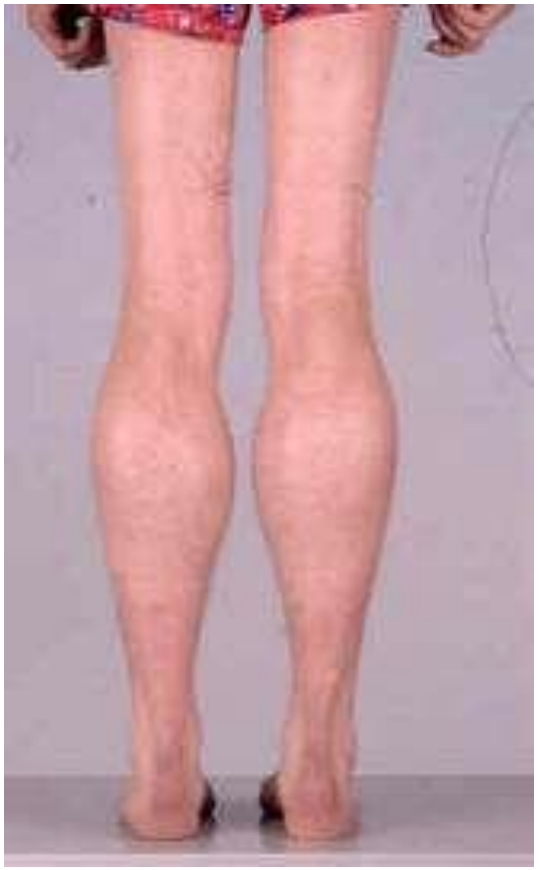
Type	Chr	Protein
LGMD 2A	15q	Calpain
LGMD 2B	2p	Dysferlin
LGMD 2C	13q	γ-sarcoglycan
LGMD 2D	17q	α-sarcoglycan
LGMD 2E	4q	β-sarcoglycan
LGMD 2F	5q	δ-sarcoglycan
LGMD 2G	17q	Telethonin

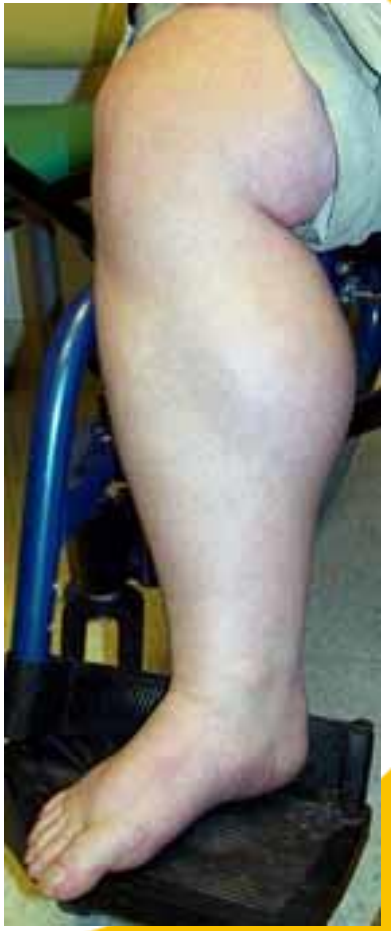
Duchenne/Becker muscular dystrophy (DMD)

- **X-linked recessive – Xp21 (boys affected) – dystrophin gene**
- **Most aggressive**
- **Clinical signs:**
  - **Proxymal muscle weakness**
  - **Pseudohypertrophies**
  - **Cardiomyopathy**
  - **Endocrinal disorders**

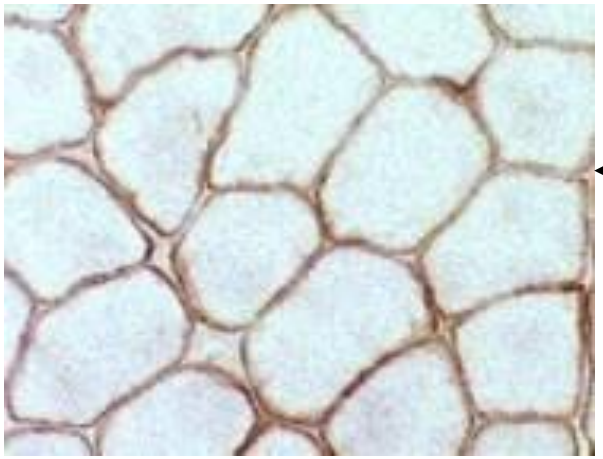
Duchenne/Becker muscular dystrophy (DMD)





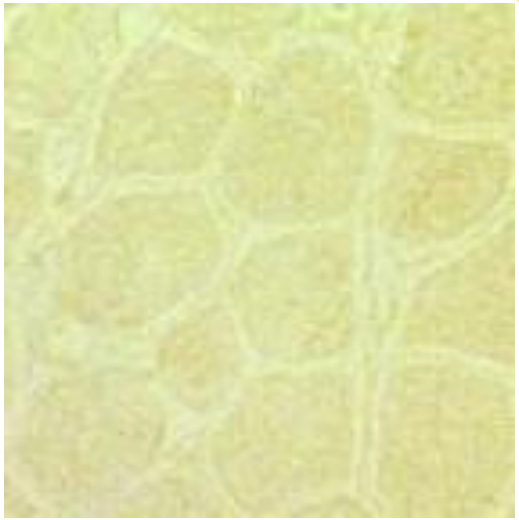


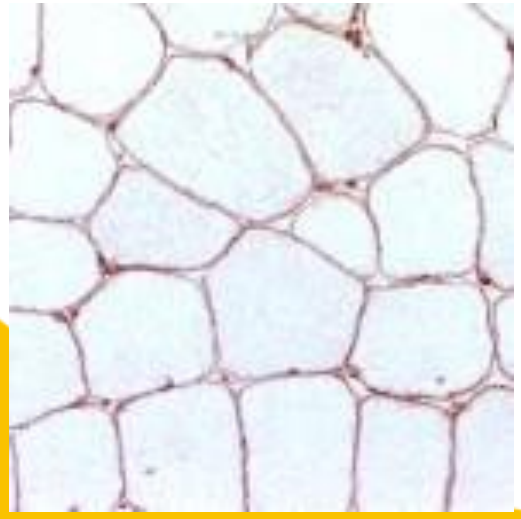
Duchenne/Becker muscular dystrophy (DMD)



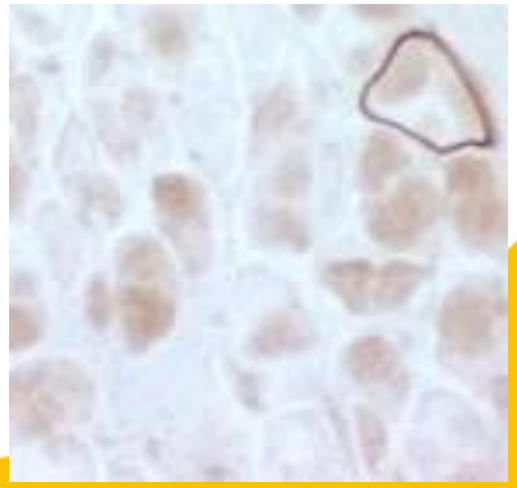
Normal dystrophin

Duchenne type



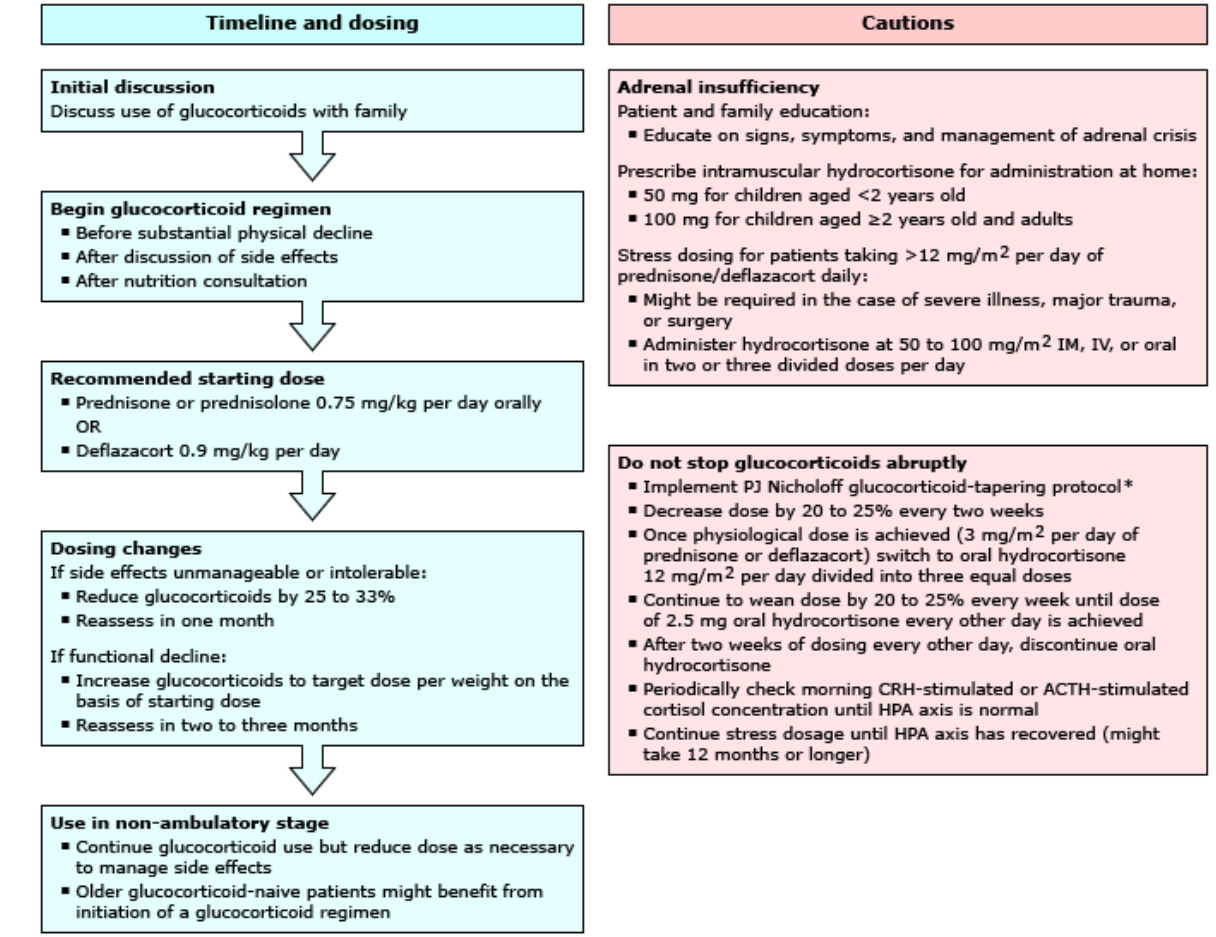


Becker type



- Glucocorticoids are the mainstay of pharmacologic treatment for Duchenne muscular dystrophy (DMD)

Care considerations for glucocorticoid (steroid) initiation and use for patients with Duchenne muscular dystrophy



CRH: corticotropin-releasing hormone; ACTH: adrenocorticotropic hormone; HPA: hypothalamic-pituitary-adrenal; IM: intramuscular; IV: intravenous.

* The PJ Nicholoff tapering protocol is available online.

Original figure modified for this publication. From: Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol 2018; 17:251. Illustration used with the permission of Elsevier Inc. All rights reserved.

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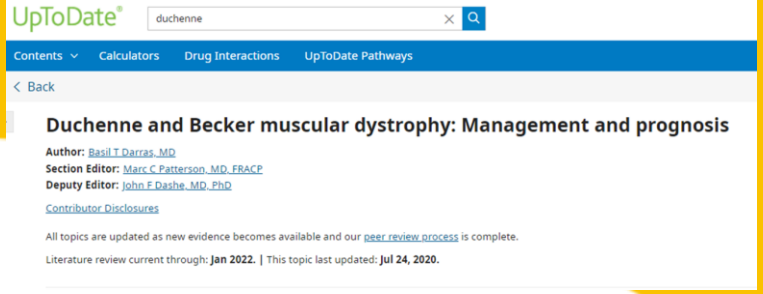


- Rehabilitation for DMD requires multidisciplinary care to coordinate the multiple specialized assessments and interventions needed to maximize function and quality of life for affected individuals
- Orthopedic interventions are specifically aimed at maintaining function and preventing contractures. For boys with DMD who are ambulatory or in the early nonambulatory stage of the disorder, we suggest regular submaximum (ie, gentle) exercise to avoid disuse muscle atrophy and other complications of inactivity.
- Attention to nutrition, bone health, fracture and fall prevention, growth and endocrine management, and routine immunizations is important for optimizing function and quality of life for patients with DMD.
- Weight and growth should be monitored, and evaluation by a dietician/nutritionist is indicated at diagnosis and at every clinic visit. For all patients with DMD, we suggest dietary calcium and vitamin D supplementation in the form of dairy products, other foods rich in calcium and vitamin D, and sunshine exposure (Grade 2C). For children with diminished intake of calcium-containing foods, we suggest calcium supplementation (500 to 1000 mg/day). Children with a serum concentration of vitamin D <30 ng/mL should receive vitamin D supplementation.
- A decrease in growth trajectory, an annual height velocity of <4 cm year, or height less than the third percentile should prompt referral to an endocrinologist. Lack of pubertal development by age 14 years for boys should also trigger referral to an endocrinologist.
- Patients with DMD often have risk factors for poor bone health that may include decreased mobility, muscle weakness, and side effects of glucocorticoid therapy. The approach to monitoring bone health focuses on identifying the earliest signs of bone fragility with periodic spine imaging and measurement of bone mineral density. Proactive guidance and home environment assessment and modification may reduce the risk of vertebral and long bone fractures.

Intervention: Adolescence and Transition to Adulthood

$400

$3,000

Intervention: Adolescence and Transition to Adulthood

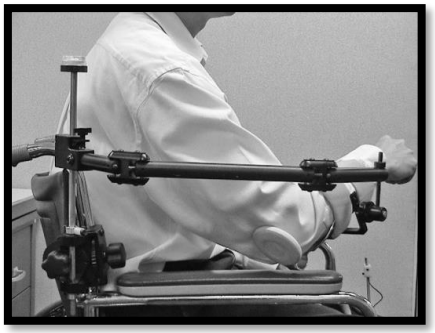
$100-$200

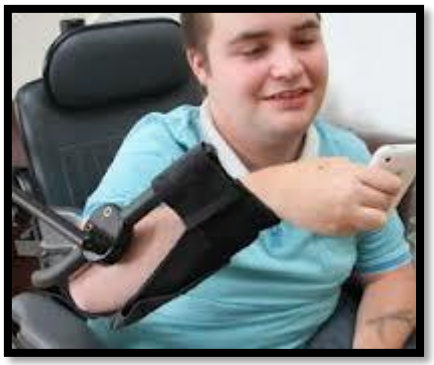
Bedside commode with drop arm to facilitate transfer

Intervention: Adolescence and Transition to Adulthood

Roll-in shower chair with commode seat

Intervention: Adolescence and Transition to Adulthood





Mobile arm supports prolong independent self-care and facilitate participation

Intervention: Adolescence and Transition to Adulthood

Light weight
manual wheelchair
with reclining back rest
$700

Tilt-in-space manual wheelchair
Cannot be propelled by patient
due to small rear wheels
$2,000

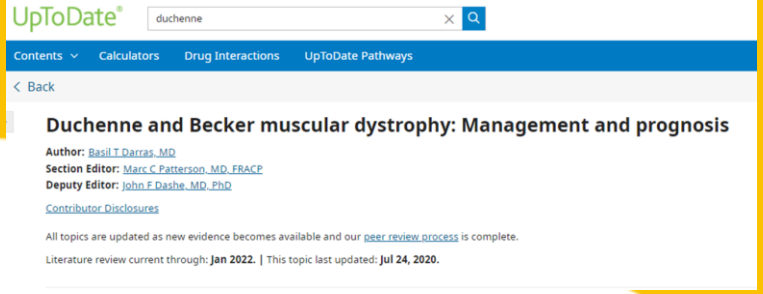
Tilt in space power
Wheelchair
$3,000-$35,000

Custom molded seating system
to manage scoliosis

Intervention: Adolescence and Transition to Adulthood

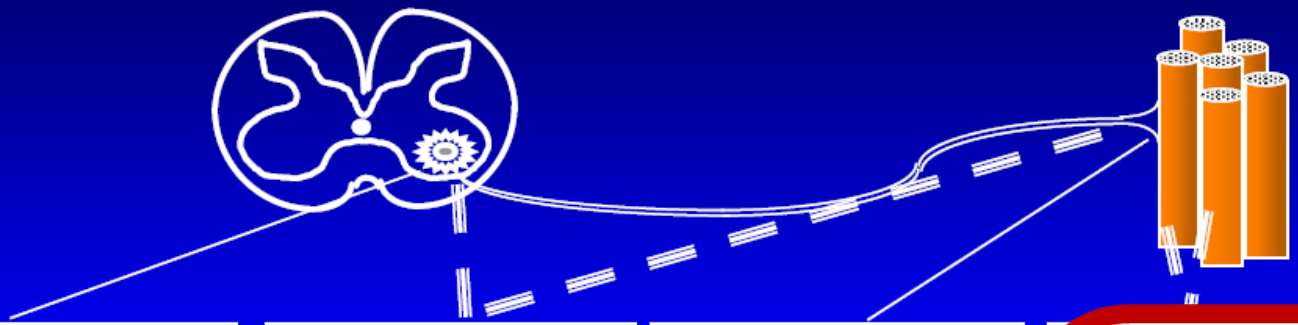
Manually operated hospital bed
$1000

Fully electric hospital bed
allows patient independence
$3,000-$4,000



- For patients with DMD, a baseline assessment of cardiac function, including electrocardiogram and noninvasive cardiac imaging, is recommended at the time of diagnosis and at least annually thereafter. Female DMD carriers should have a baseline cardiac assessment in early adulthood. For boys with DMD, we recommend initiation of an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) beginning by age 10 years (Grade 1B).
- Respiratory management is a critical component of DMD care. Serial monitoring of vital capacity should begin when the individual is five to six years of age and followed yearly during the ambulatory stage. When patients become nonambulatory, more extensive monitoring should occur at least every six months. The core respiratory therapies for DMD are lung volume recruitment, assisted coughing, nocturnally assisted ventilation, and subsequent daytime ventilation. In most cases, the need for these interventions arises after loss of ambulation. Detailed indications are listed above.
- Psychosocial care for DMD and Becker muscular dystrophy (BMD) includes routine assessment of the mental health of the patient and family at every clinic visit, with ongoing support and referrals to a psychiatrist or psychologist if needed. Multidisciplinary care should include educational support, vocational training, and planning for adult roles. Clinicians should sensitively engage patients and families in discussions about treatment options, advanced care planning, advanced directives, palliative care, and other end-of-life issues, as guided by patient values and preferences.
- Patients with DMD have a high risk of complications when they undergo surgery or procedures requiring anesthesia or sedation, and should have preoperative evaluations by pulmonary, anesthesia, and cardiac specialists prior to any surgery. Total intravenous anesthesia is indicated for patients with DMD. Succinylcholine (a depolarizing neuromuscular blocking agent) is absolutely contraindicated because it carries an unacceptable risk of life-threatening hyperkalemia and rhabdomyolysis.

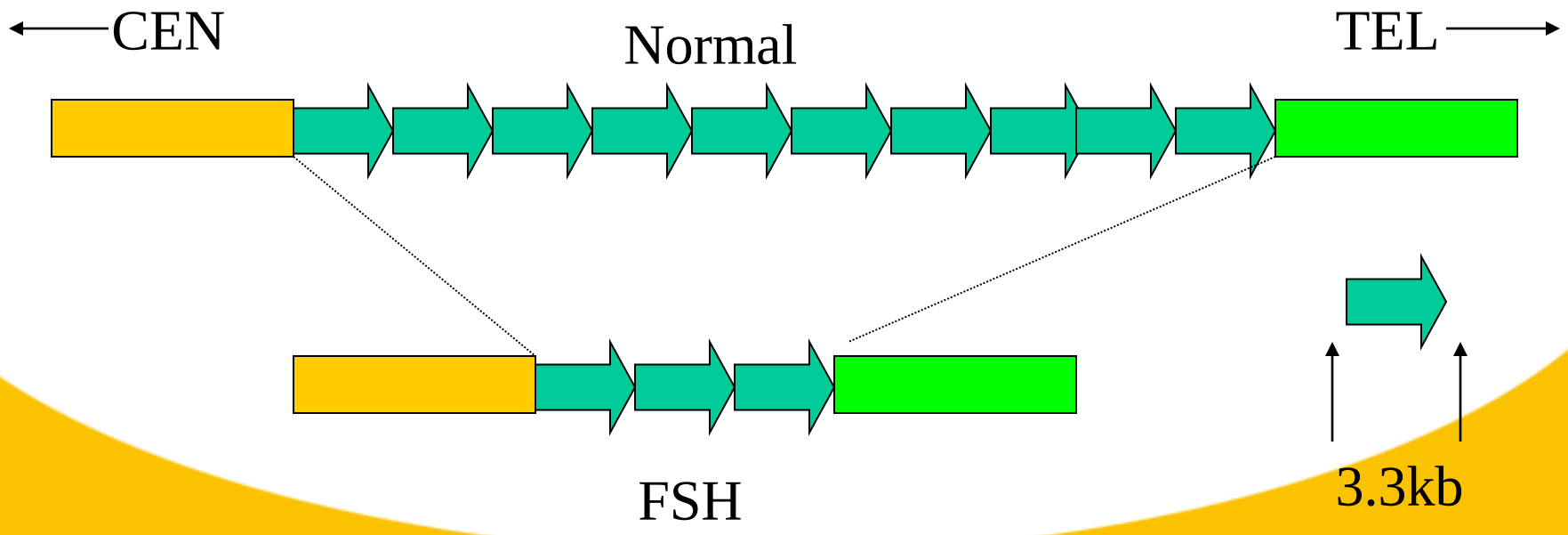
Anatomical classification of Neuromuscular Dis.



ANTERIOR HORN	NERVE	NM JUNCTION	MUSCLE FIBER
SPINAL MUSCULAR ATROPHIES *(SMA)* Types 1-4 **ALS** **KENNEDY Sd** **FAZIO-LONDE sd** **BROWN-VIALETTO** **Distal SMA**	**NEUROPATHIES** **H.S.M.N.** ***(Charcot-Marie-Tooth, Déjerine-Sotas, others)*** **H.M.N.** **H.N.A.**	**MYASTHENIAS** **Myasthenia gravis** *-AChR+* *- MusK+* *- others* **Congenital myasthenic synd.**	**DYSTROPHIES** **Duchenne / Becker** **Limb girdle (LGMD)** **Emery-Dreifuss / FSHD** **MYOTONIC Sd** **Steinert (DM1) / DM2** **Thomsen, others** **MISCELLANEOUS** **Mitochondrial** **Congenital** **Metabolic** **Dysimmune**

FSH

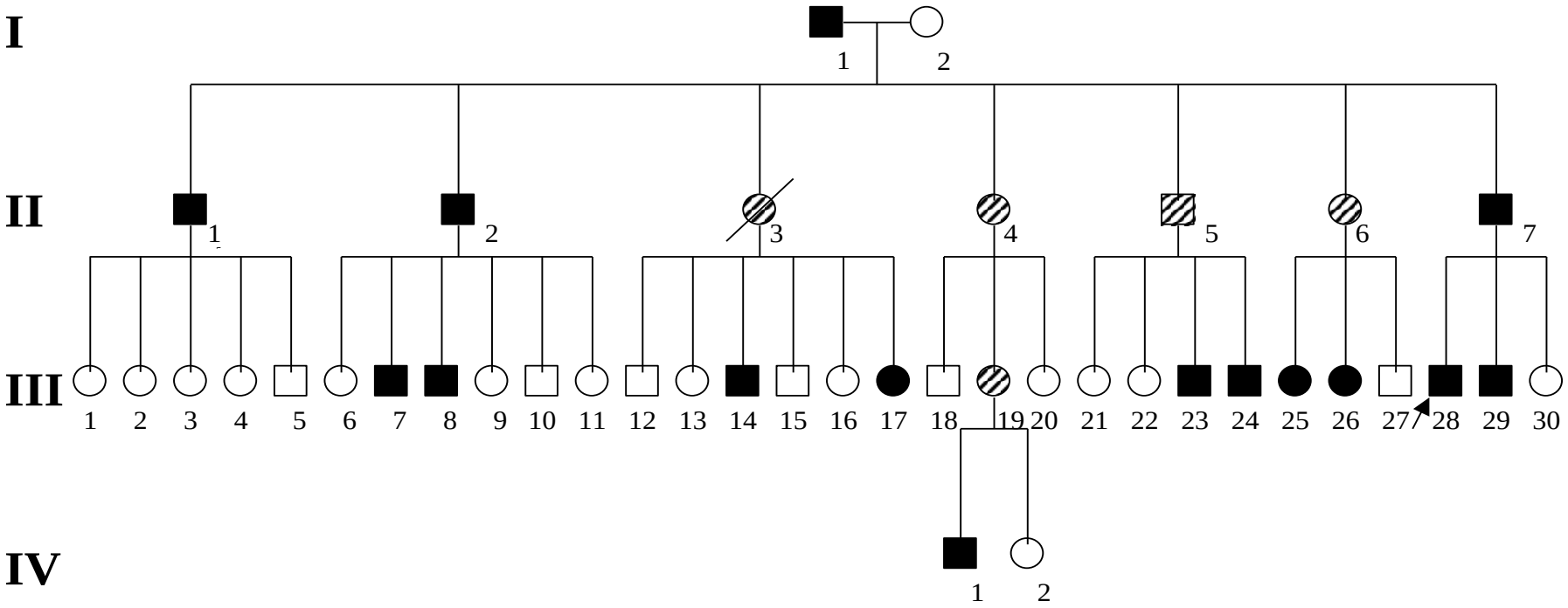
- Molecular genetics
  - 4q35
  - deletion



FSH

Photo of patients

FSH


I
II
III
IV
1
2
1
2
3
4
5
6
7
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
1
2

FSH

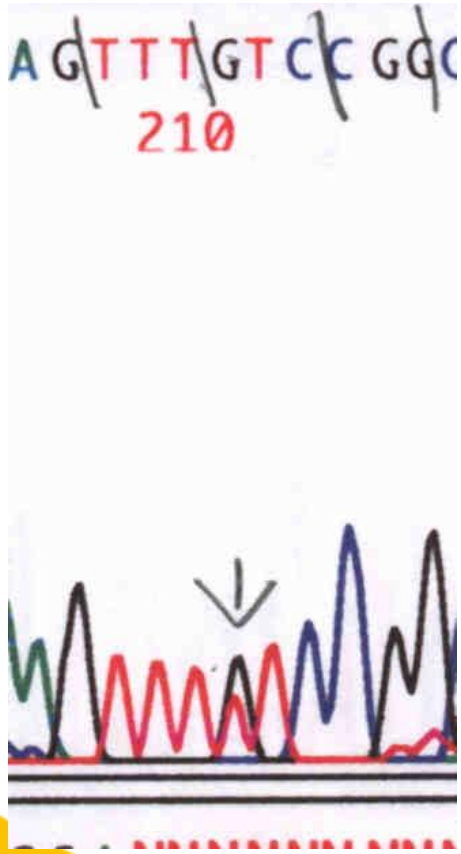
Photo of patients

Emery-Dreifuss

- Inheritance
  - Usually X-linked recessive
    - (Xq28 - emerin)
  - AD
    - (1q11-q23 - lamin A/C)
  - AR (extremely rare)

AD Emery-Dreifuss

Photo of patients



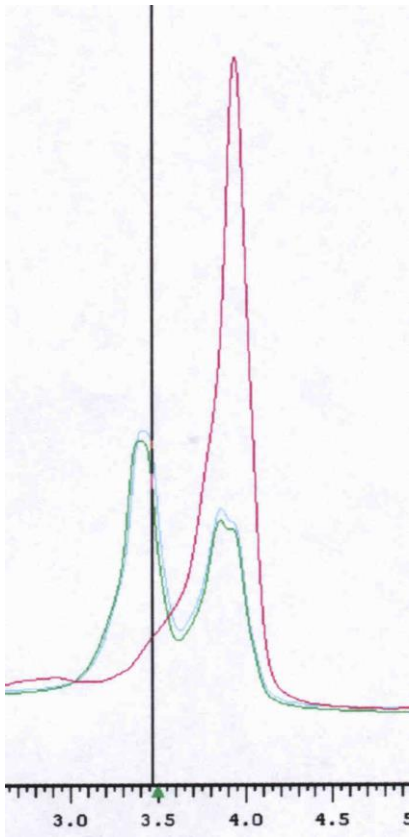
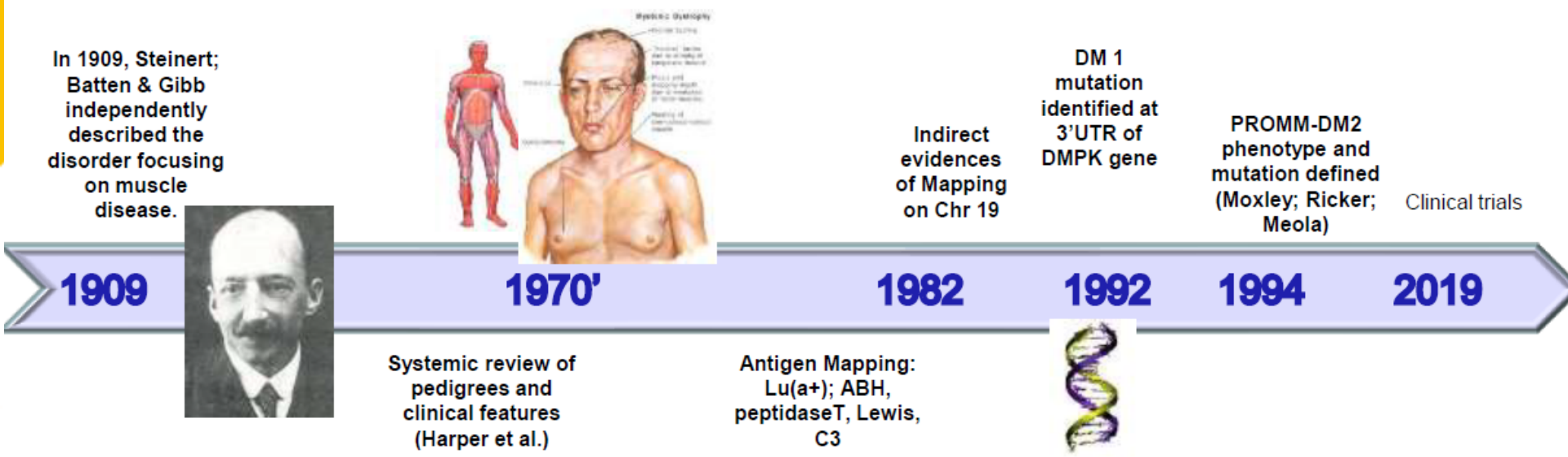


Photo of patients

GTC 452 TTC

Val Phe

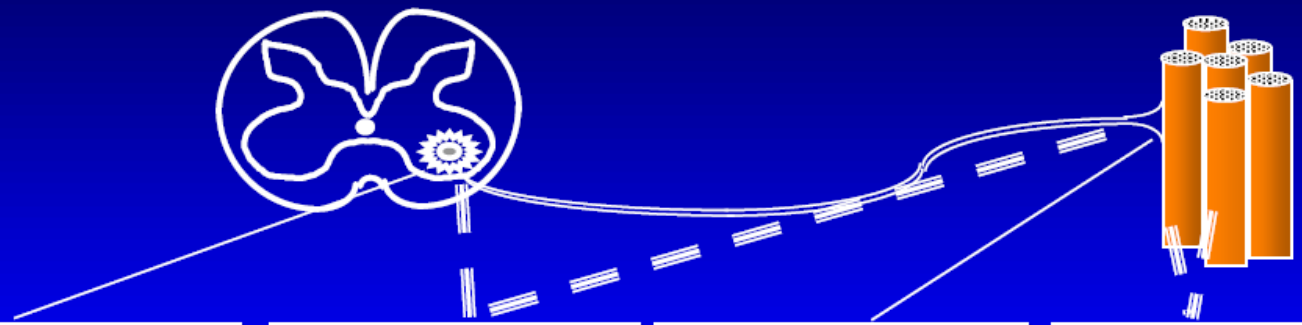
Myotonic dystrophies, the timeline



- In 1909, Steinert, Batten & Gibb, independently describe the disorder focusing on muscle disease.
- Complex multisystemic phenotype (eyes, heart, endocrine, CNS) (see Harper 2001).
- Argument: one disease or many?
- Up to 1986 or so, no presymptomatic, or prenatal tests.

A.Urtizberea, Paris, 2019

Anatomical classification of Neuromuscular Dis.



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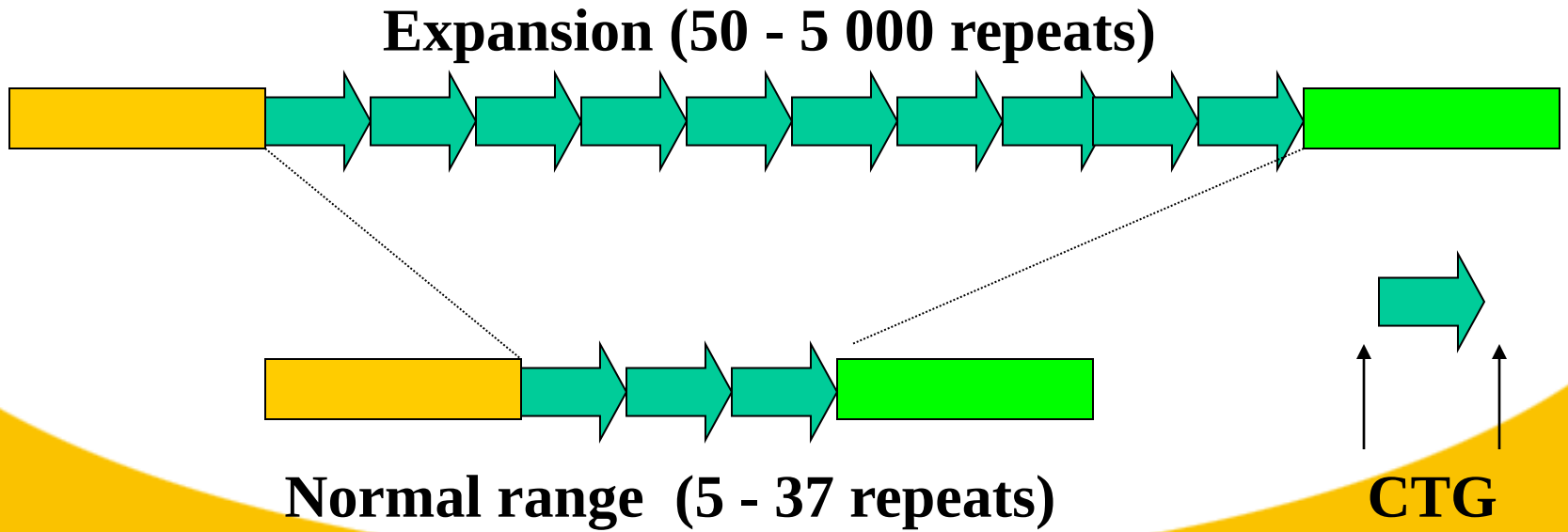
Steinert's Myotonic Dystrophy

- Molecular genetics
  - 19q13.3 - 3' UTR – gene MtPK
  - Expansion CTG-repeats (over 50)



Steinert's Myotonic Dystrophy

- Steppage gait
- Muscles:
  - Dystal limbs
  - Ptosis
  - Face muscles
  - Bulbar muscles
  - M. sternocleidomastoideus

Photo of patients

Myotonic dystrophy (DM1) is the most common form of adult muscular dystrophy. It is a multisystem disorder with a complex pathophysiology. Although inheritance is autosomal dominant, disease variability is attributed to anticipation, a maternal expansion bias, variable penetrance, somatic mosaicism, and a multitude of aberrant pre-mRNA splicing events. Patient presentations range from asymptomatic or mild late onset adult to severe congenital forms. Multiple organ systems may be affected. Patients may experience early cataracts, myotonia, muscle weakness/atrophy, fatigue, excessive daytime sleepiness, central/obstructive apnea, respiratory failure, cardiac arrhythmia, insulin resistance, dysphagia, GI dysmotility, cognitive impairment, Cluster C personality traits, and/or mood disorders. At present, there is no curative or disease-modifying treatment, although clinical treatment trials have become more promising. Management focuses on genetic counseling, preserving function and independence, preventing cardiopulmonary complications, and symptomatic treatment (e.g., pain, myotonia, hypersomnolence, etc.). Currently, there is an increasing international consensus on monitoring and treatment options for these patients which necessitates a multidisciplinary team to provide comprehensive, coordinated clinical care.

Curr Treat Options Neurol (2016) 18: 52
DOI 10.1007/s11940-016-0434-1

CrossMark

Neuromuscular Disorders (SA Rudnicki, Section Editor)

Myotonic Dystrophy Type 1 Management and Therapeutics

Cheryl A. Smith, MD, PhD
Laurie Gutmann, MD[*]

Ho G *et al*. Congenital and childhood myotonic dystrophy

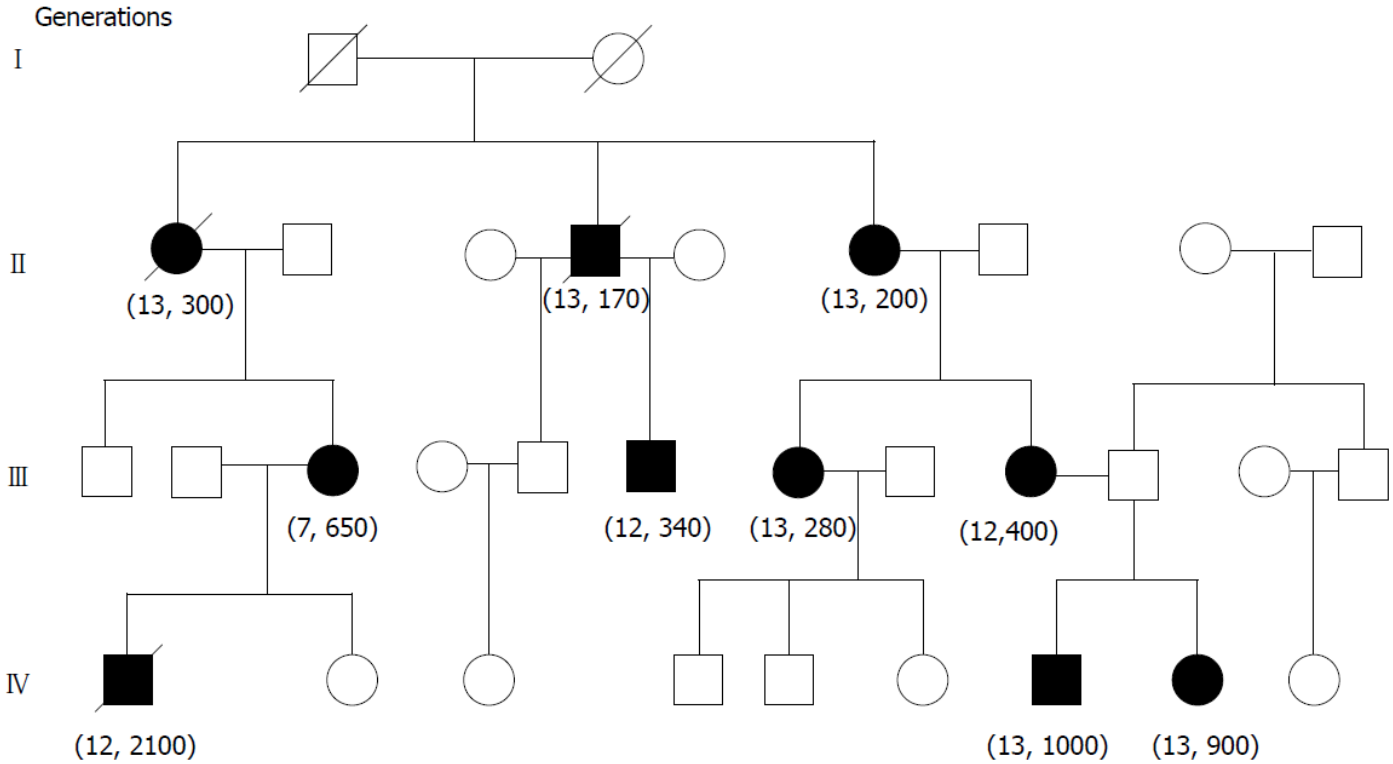


Figure 1 Genogram of family with myotonic dystrophy type 1 illustrating autosomal dominant inheritance. The numbers in brackets indicate the number of CTG triplet repeats in the 3' untranslated portion of the *DMPK* gene of affected individuals. Square = male; Circle = female; Black symbol = DM1 affected individuals; Strikethrough symbol = deceased.

2011

1999

2005

Photo of patients

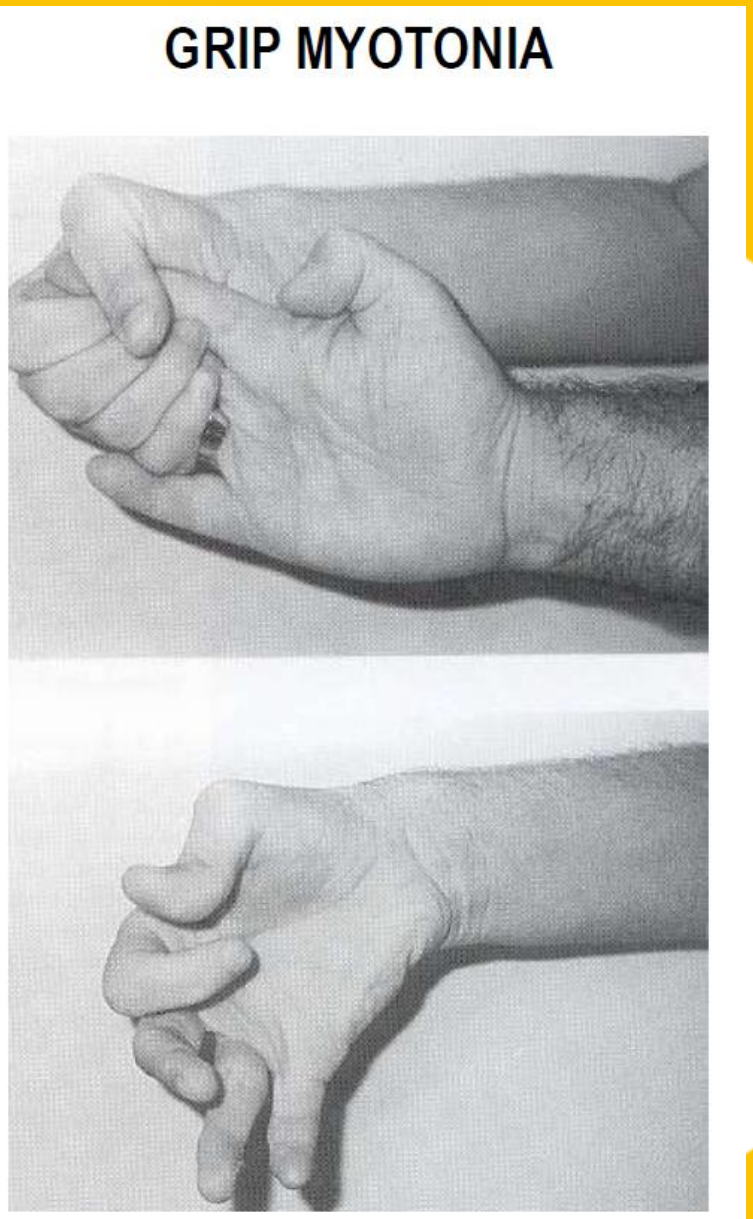
Multisystemic disorder

Affected functions:

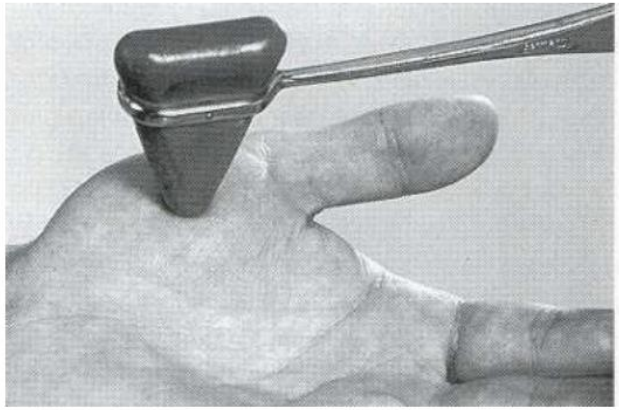
- Movement (weakness)
- Mental (cognitive impairment)
- Cardiac (slow heart rate, low blood pressure)
- Endocrinal (sexual, thyroid, pancreatic)

Myotonia

Photo of patients



PERCUSSION MYOTONIA



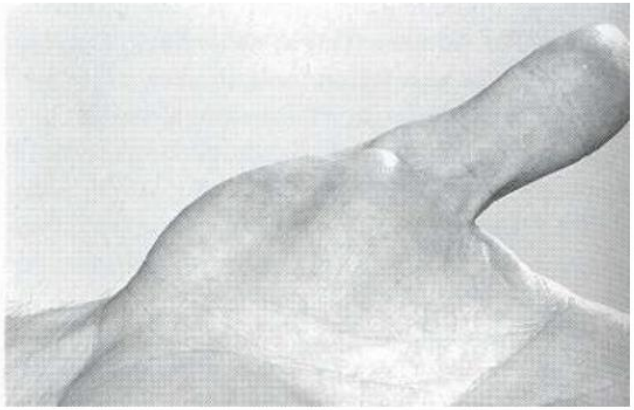
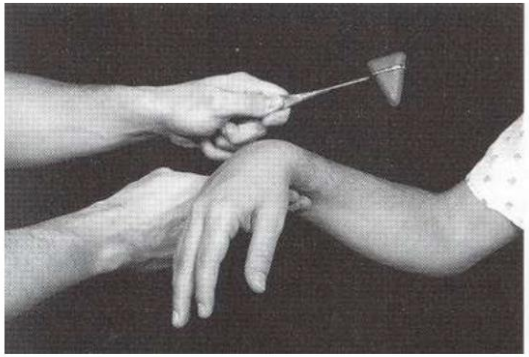
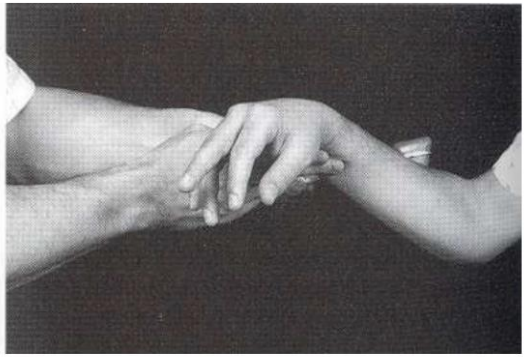
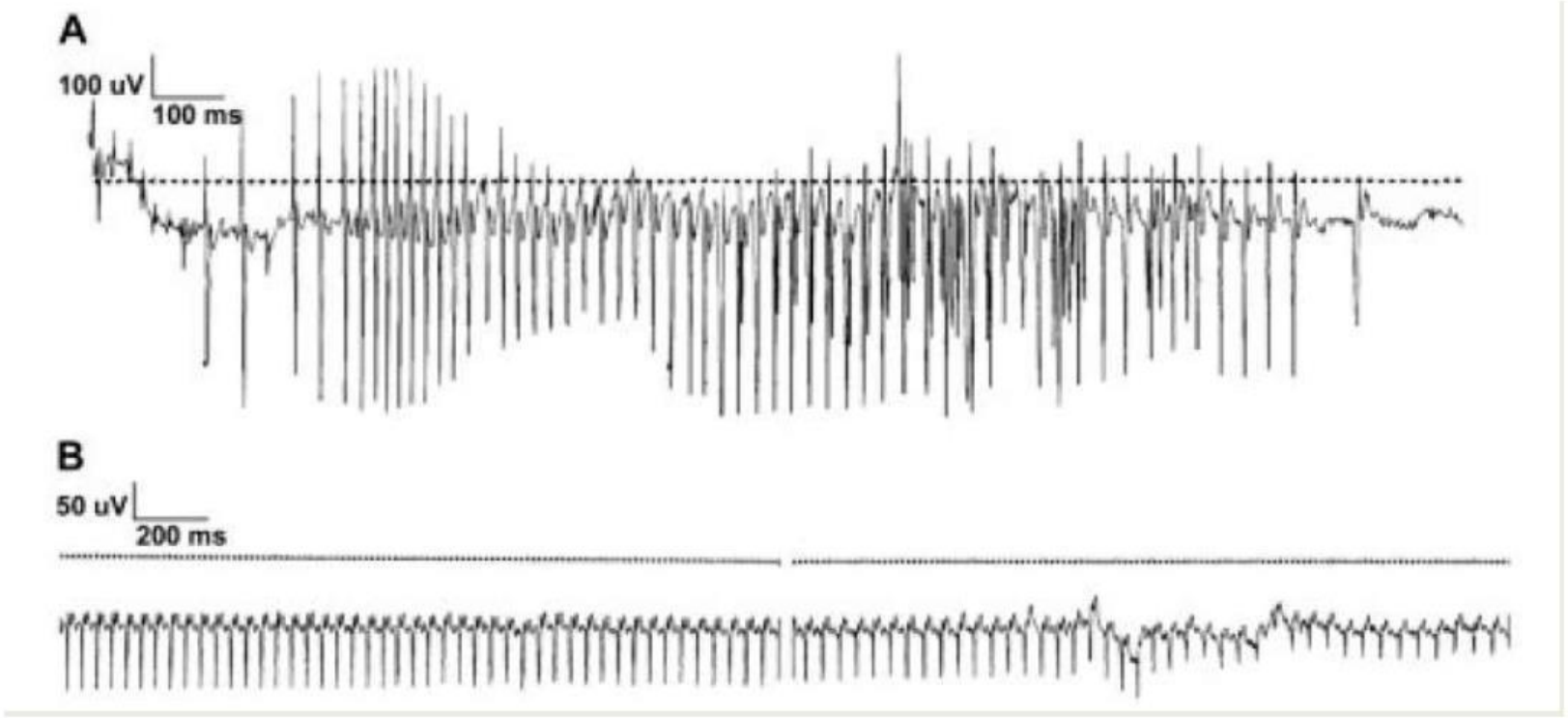


Photo of patients





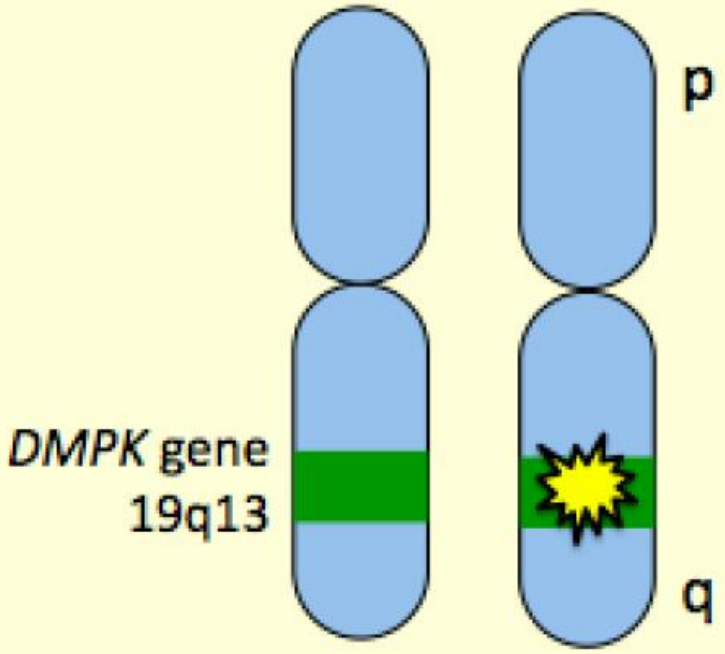


(A) Two-second myotonic discharge in a DM1 patient with typical waxing and waning frequency and amplitude; maximal frequency about 60 HZ, minimal about 8 HZ. **(B)** Four-second myotonic discharge (two successive oscilloscope sweeps) in a DM2 patient in which frequency and amplitude gradually decline with no waxing component; maximal frequency toward onset about 23 HZ, minimal toward termination about 19 HZ.

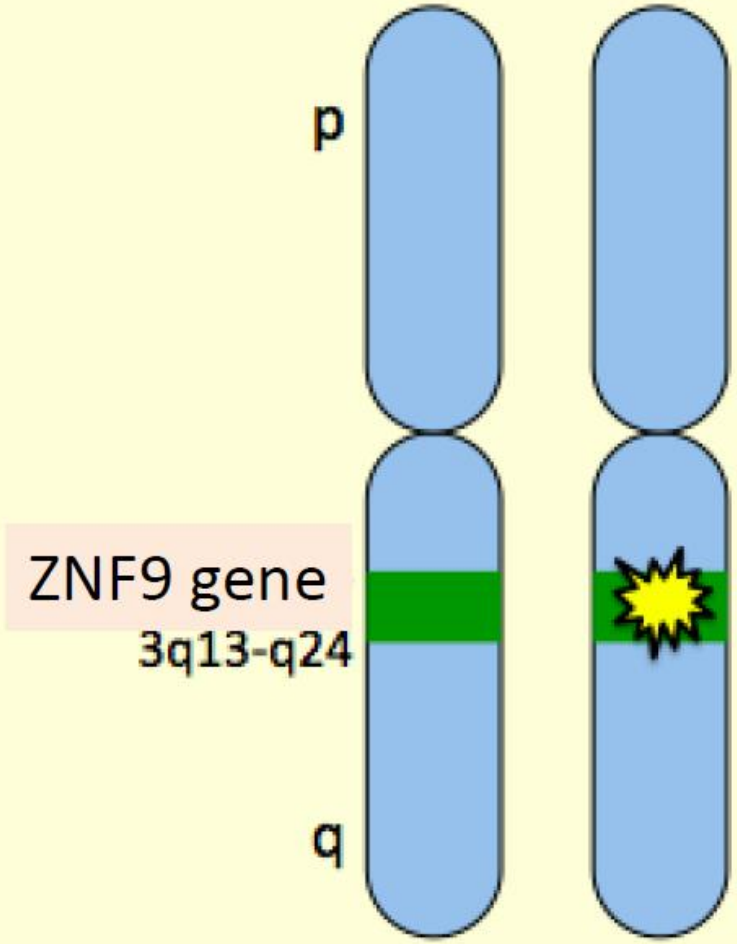
FIG.2

Logigian et al. Muscle & Nerve 2007;35:479-485

DM Type 1

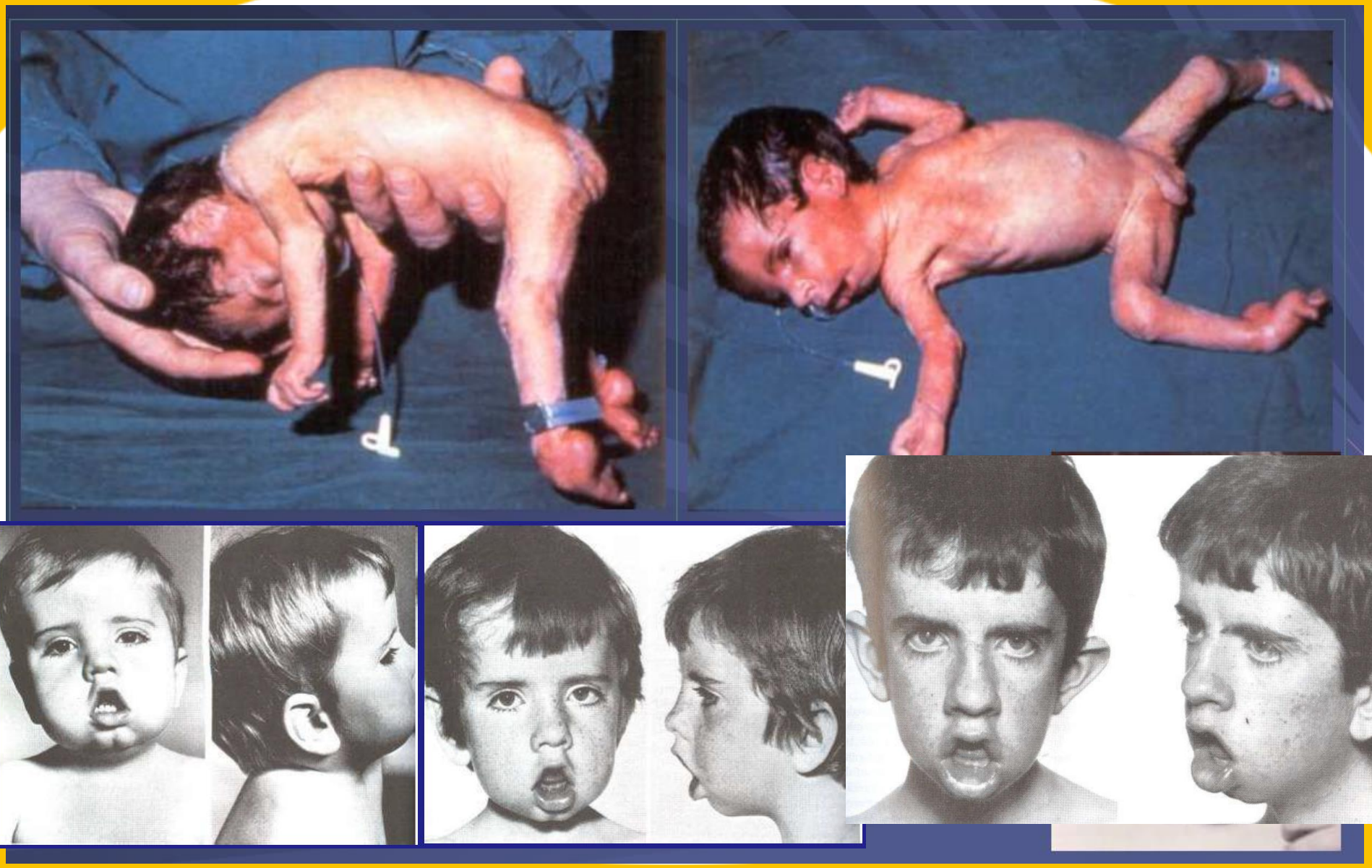


DM Type 2



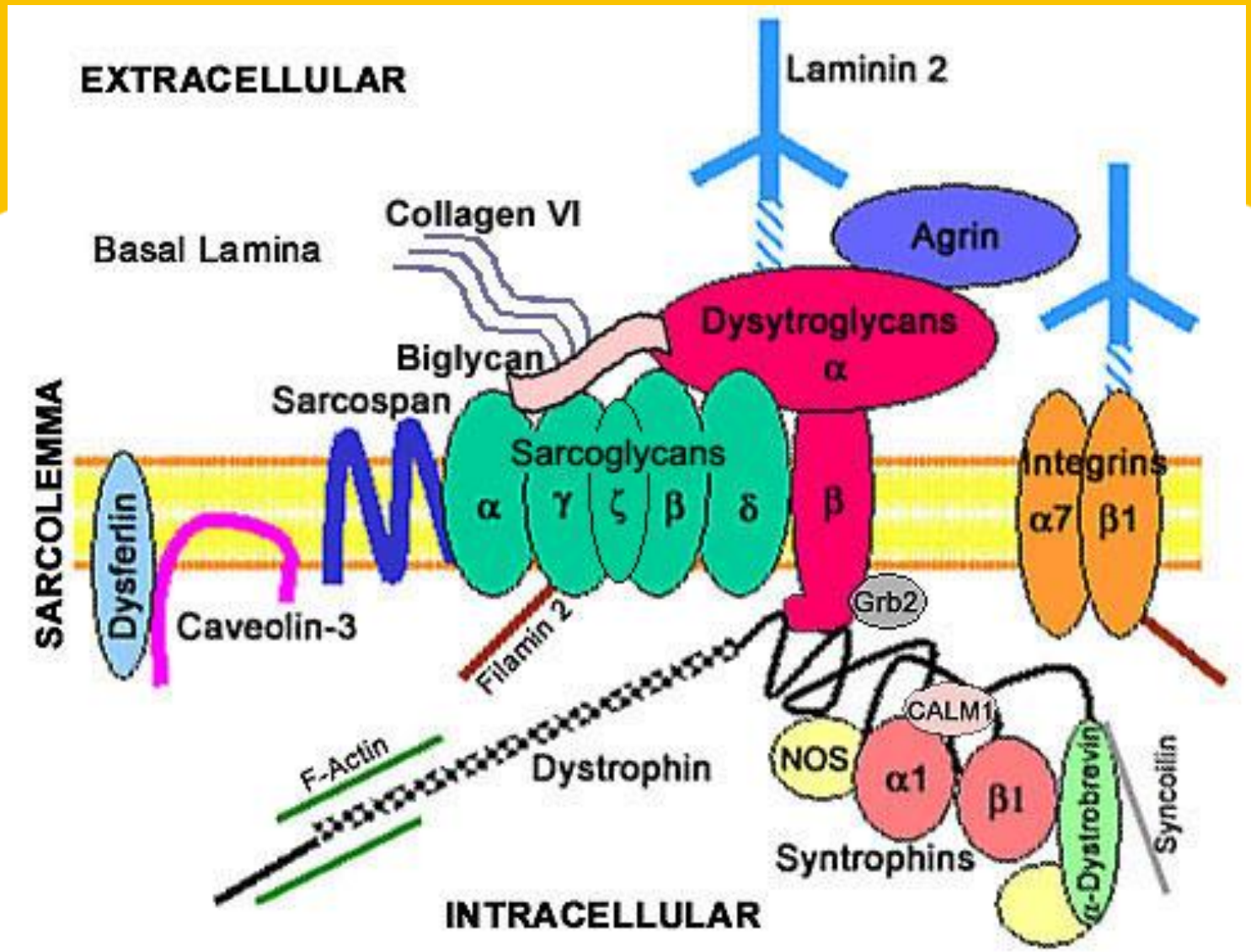
http://www.genetics4medics.com/myotonic-dystrophy.html

Congenital DM 1



Advances in neuromuscular disorders

1986	2019
40 recognized entities	Over 800 loci or genes *(see Gene Table - NMD)*
First gene cloned by reverse genetics (dystrophin)	90 % of NMD genes are mapped or cloned
Supportive approach almost exclusively	multiple therapeutic avenues being explored *(gene & cell therapies, pharmacology)*

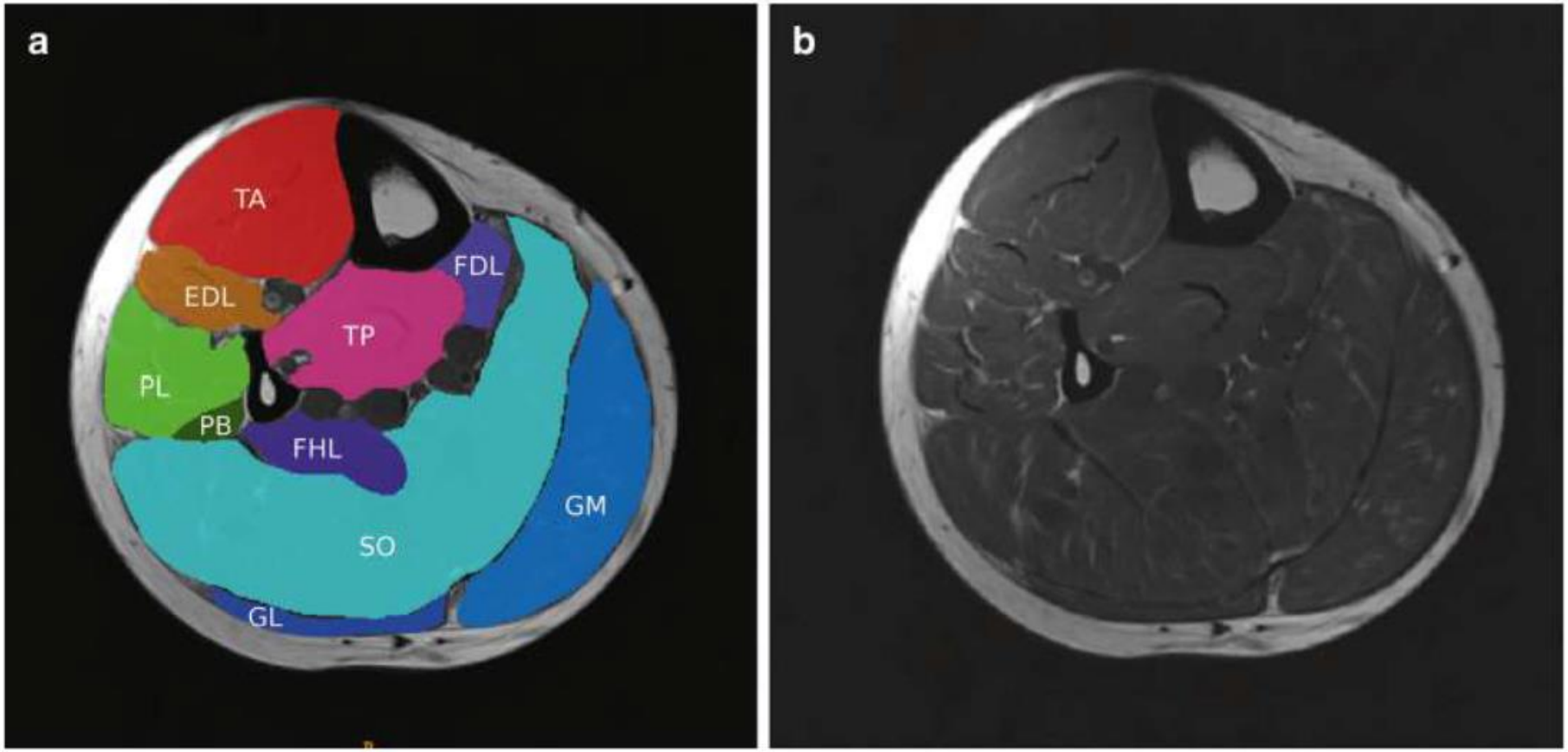


https://neuromuscular.wustl.edu/musdist/dag2.htm

Muscle Imaging

- several techniques
  - *Ultrasound tomography*
  - *Computerized Tomography (CT-scan)*
  - *Magnetic Resonance Imaging (MRI) +++*
- potentially useful
  - *to select the site of muscle biopsy*
  - *to demonstrate muscle involvement selectivity*
  - *and therefore to point towards a diagnosis*
  - *to monitor disease progression*

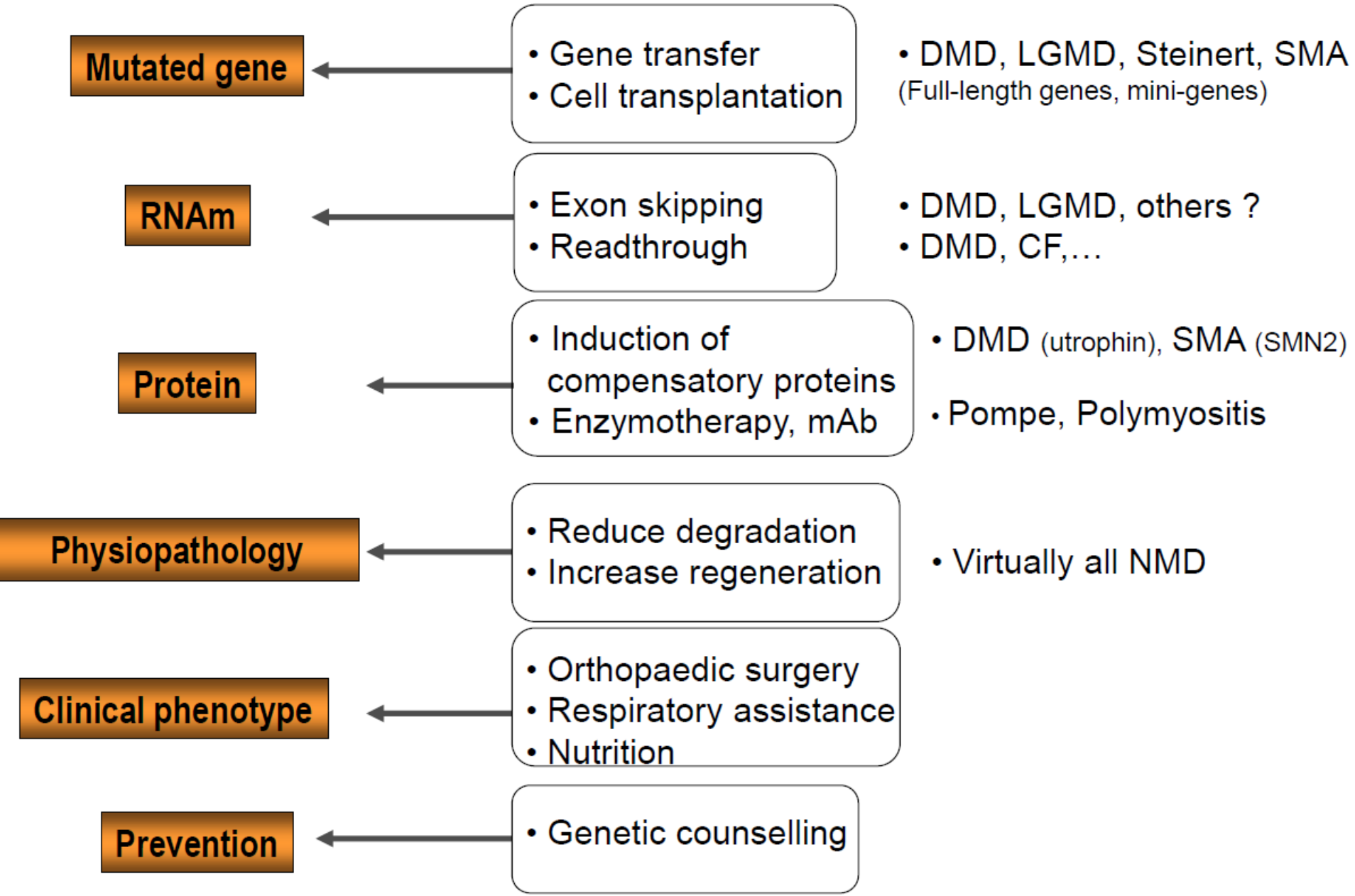
Muscle MRI of the LOWER LEG



Terminology

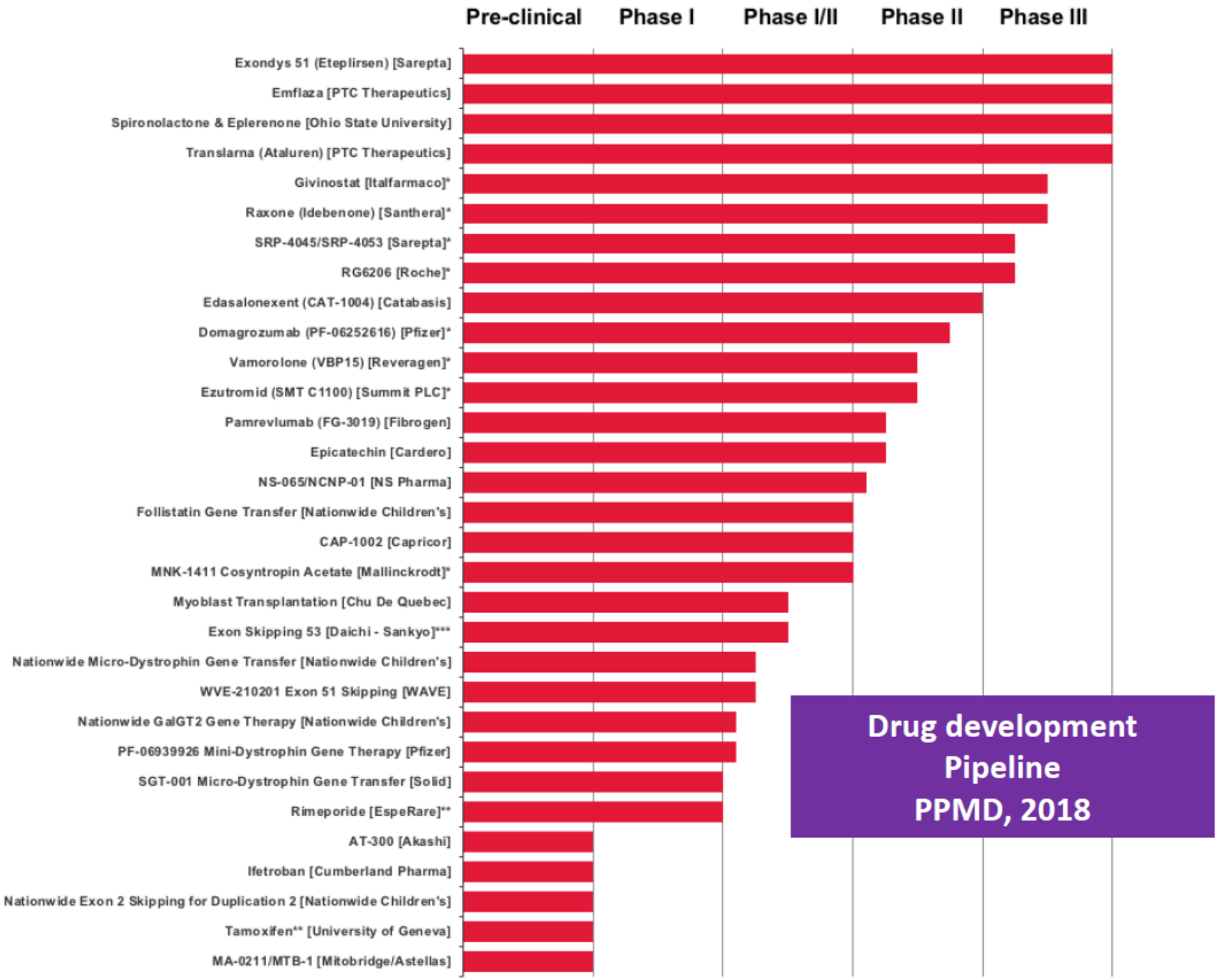
- **cure** : something able to lead to full recovery
- **therapy** : something able to improve the condition
- or to modify substantially the disease course

THERAPEUTIC STRATEGIES IN NMD

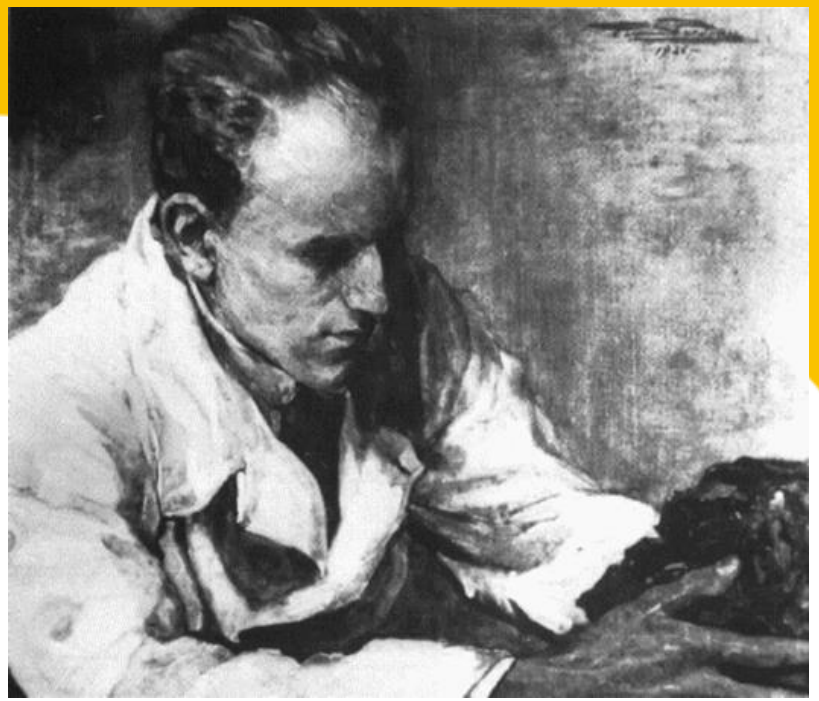


Examples of curable/treatable NM disorders

- IOPD : *infantile onset Pompe disease*
- LOPD : *late-onset Pompe disease*
- MADD: *multiple-acyl-coA dehydrogenase*
- CPT1: *primary creatine deficiency*
- BVVL – FL: *Brown-Vialetto-Van Laere, Fazio-Londe*
- AGAT: *creatine deficiency*
- MNAI: *autoimmune necrotizing myopathy*
- Immune-mediated neuropathies (GBS, CIDP, MMN,…)
- CMS: *congenital myasthenic syndromes*
- DM: *dermato-myositis*
- SMA: *5q-related spinal muscular atrophies*
- DMD: *Duchenne muscular dystrophy*
- Many others to come

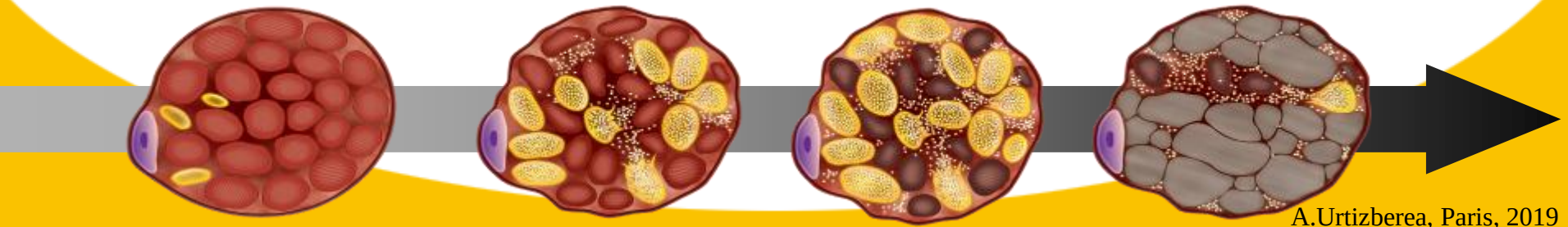

Pre-clinical
Phase I
Phase I/II
Phase II
Phase III
Exondys 51 (Eteplirsen) [Sarepta]
Emflaza [PTC Therapeutics]
Spironolactone & Eplerenone [Ohio State University]
Translarna (Ataluren) [PTC Therapeutics]
Givinostat [Italfarmaco]*
Raxone (Idebenone) [Santhera]*
SRP-4045/SRP-4053 [Sarepta]*
RG6206 [Roche]*
Edasalonexent (CAT-1004) [Catabasis]
Domagrozumab (PF-06252616) [Pfizer]*
Vamorolone (VBP15) [Reveragen]*
Ezutromid (SMT C1100) [Summit PLC]*
Pamrevlumab (FG-3019) [Fibrogen]
Epicatechin [Cardero]
NS-065/NCNP-01 [NS Pharma]
Follistatin Gene Transfer [Nationwide Children's]
CAP-1002 [Capricor]
MNK-1411 Cosyntropin Acetate [Mallinckrodt]*
Myoblast Transplantation [Chu De Quebec]
Exon Skipping 53 [Daichi - Sankyo]***
Nationwide Micro-Dystrophin Gene Transfer [Nationwide Children's]
WVE-210201 Exon 51 Skipping [WAVE]
Nationwide GalGT2 Gene Therapy [Nationwide Children's]
PF-06939926 Mini-Dystrophin Gene Therapy [Pfizer]
SGT-001 Micro-Dystrophin Gene Transfer [Solid]
Rimeporide [EspeRare]**
AT-300 [Akashi]
Ifetroban [Cumberland Pharma]
Nationwide Exon 2 Skipping for Duplication 2 [Nationwide Children's]
Tamoxifen** [University of Geneva]
MA-0211/MTB-1 [Mitobridge/Astellas]
Drug development
Pipeline
PPMD, 2018

- POMPE disease =
- Acid Maltase deficiency
- AMD
- Glycogen storage disease type II
- GSD type II
- Alpha-glucosidase deficiency
- GAA deficiency



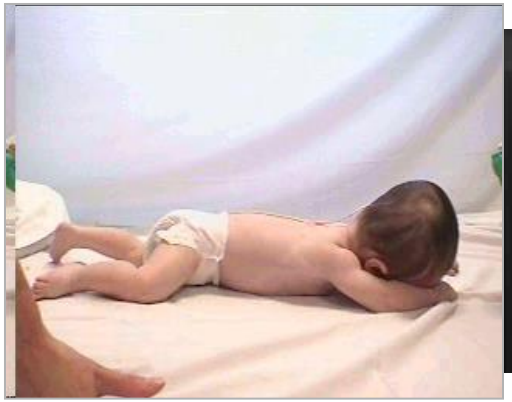
Johannes C. Pompe, 1901-1945

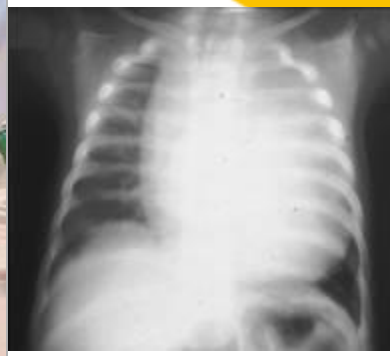
- IOPD : infantile-onset Pompe disease (newborns and infants)
- LOPD : late-onset Pompe disease (children, adolescents, and adults)

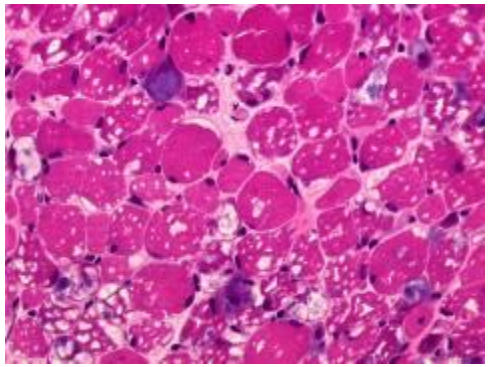


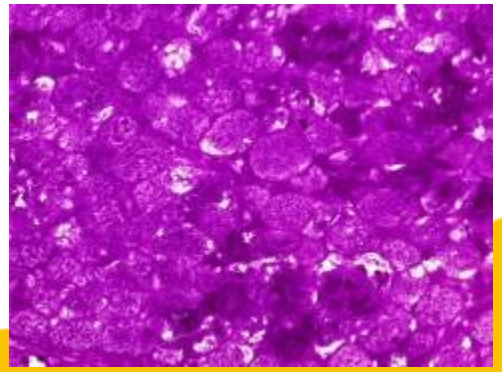
Pompe disease = IOPD

- Age at first symptoms: *1,6 months*
- Age at diagnosis: *5,3 months*
- Age of death: *6,3 months*
  (98% of death before age 18 months)
- Delay diagnosis / death: *2 mths*
  (van den Hout et al., Pediatrics, 2003)
- Diagnostic clues:
  - Stereotyped clinical presentation
  - High CK levels
  - Acid α-glucosidase activity in blood (dried bloodspots+++)
  - Muscle biopsy*: vacuolar myopathy*
  - Molecular analysis : *GAA mutation*









MUST BE REGARDED AS AN EMERGENCY +++

A.Urtizberea,
Paris, 2019

http://www.myozyme.com/

Google

Genzyme Websites | Genzyme Corporate

Myozyme® (alglucosidase alfa)

Text Size A A A | Search This Site | GO

Important Safety Information | Prescribing Information including boxed warning

Patients & Families | Healthcare Professionals

What is Myozyme? | Myozyme Treatment | Disease Management | Resources | Patient Services

Important Safety Information

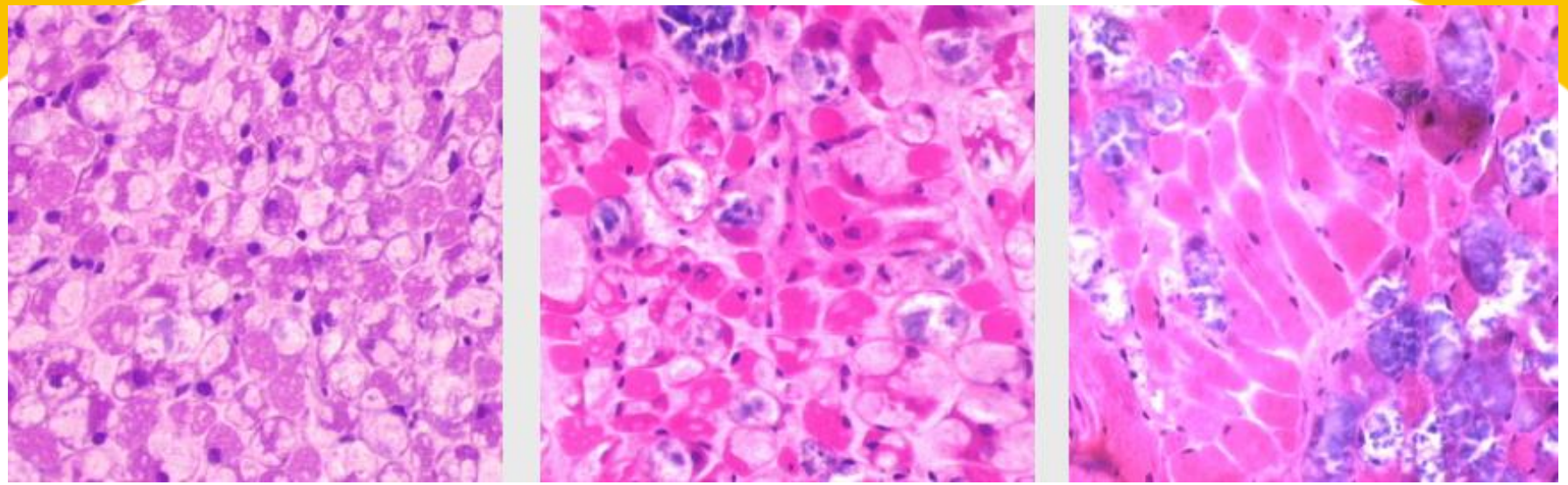
Life-threatening anaphylactic reactions have been observed in some patients during MYOZYME infusions. Patients with compromised cardiac or respiratory function may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to infusion reactions.

View additional Important Safety Information

Myozyme is the first specific treatment for Pompe disease.

Learn More

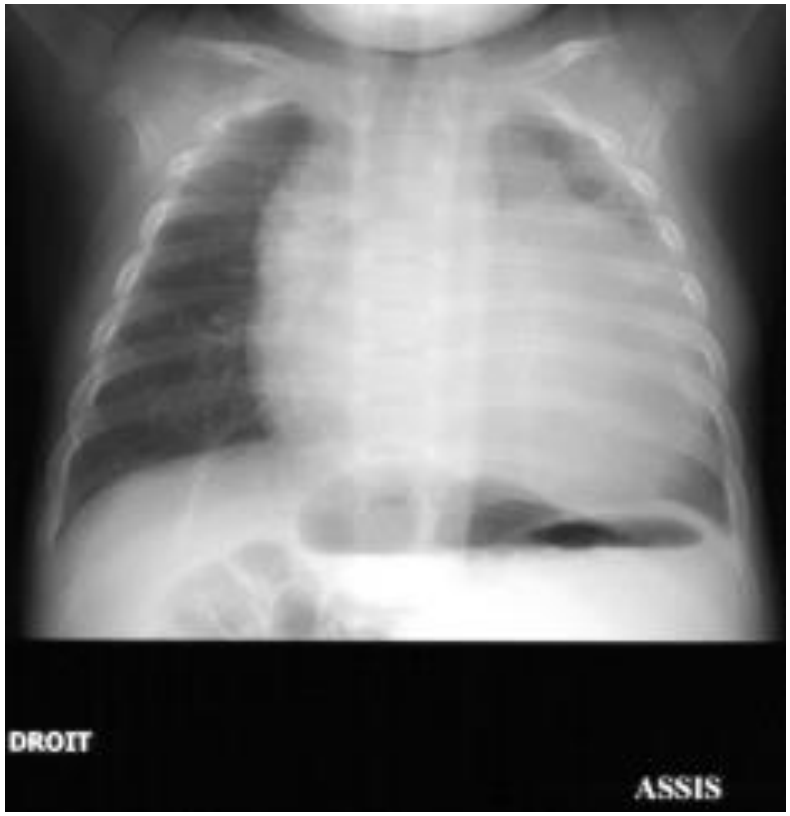
Improvement of muscle histology



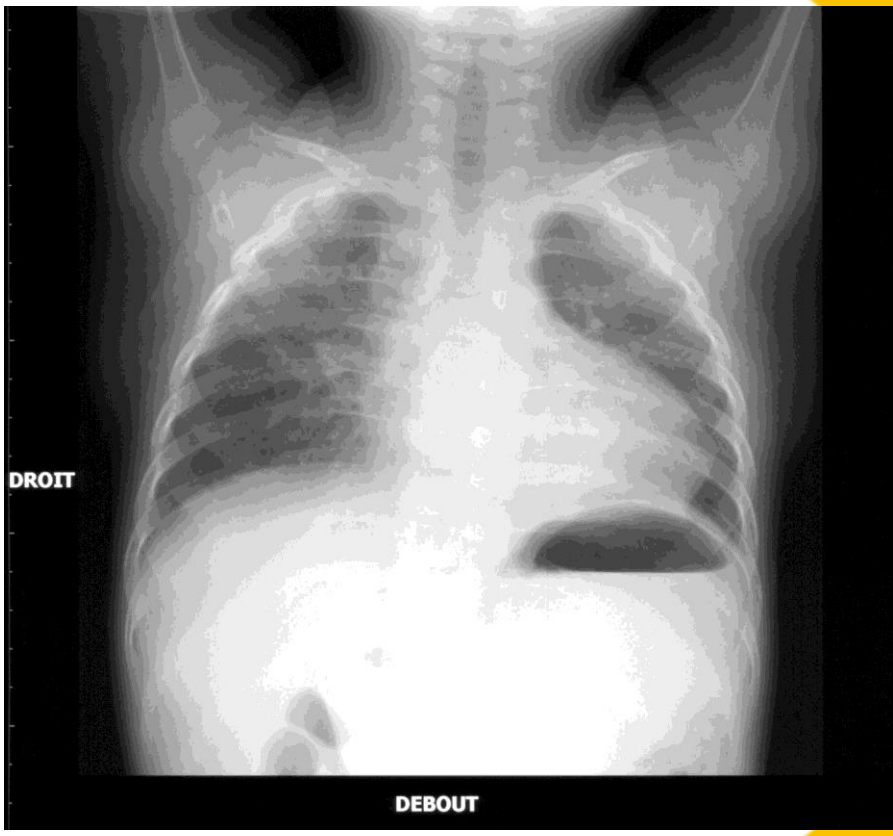
- Pilot studies showed a somewhat dramatic reduction
- In glycogen content
- Cannot be used routinely as an outcome measure

Response in cardiac muscle

Patient N-J



baseline



Week 52

Natural history and ERT in infantile-onset Pompe disease

Immune mediated myopathies

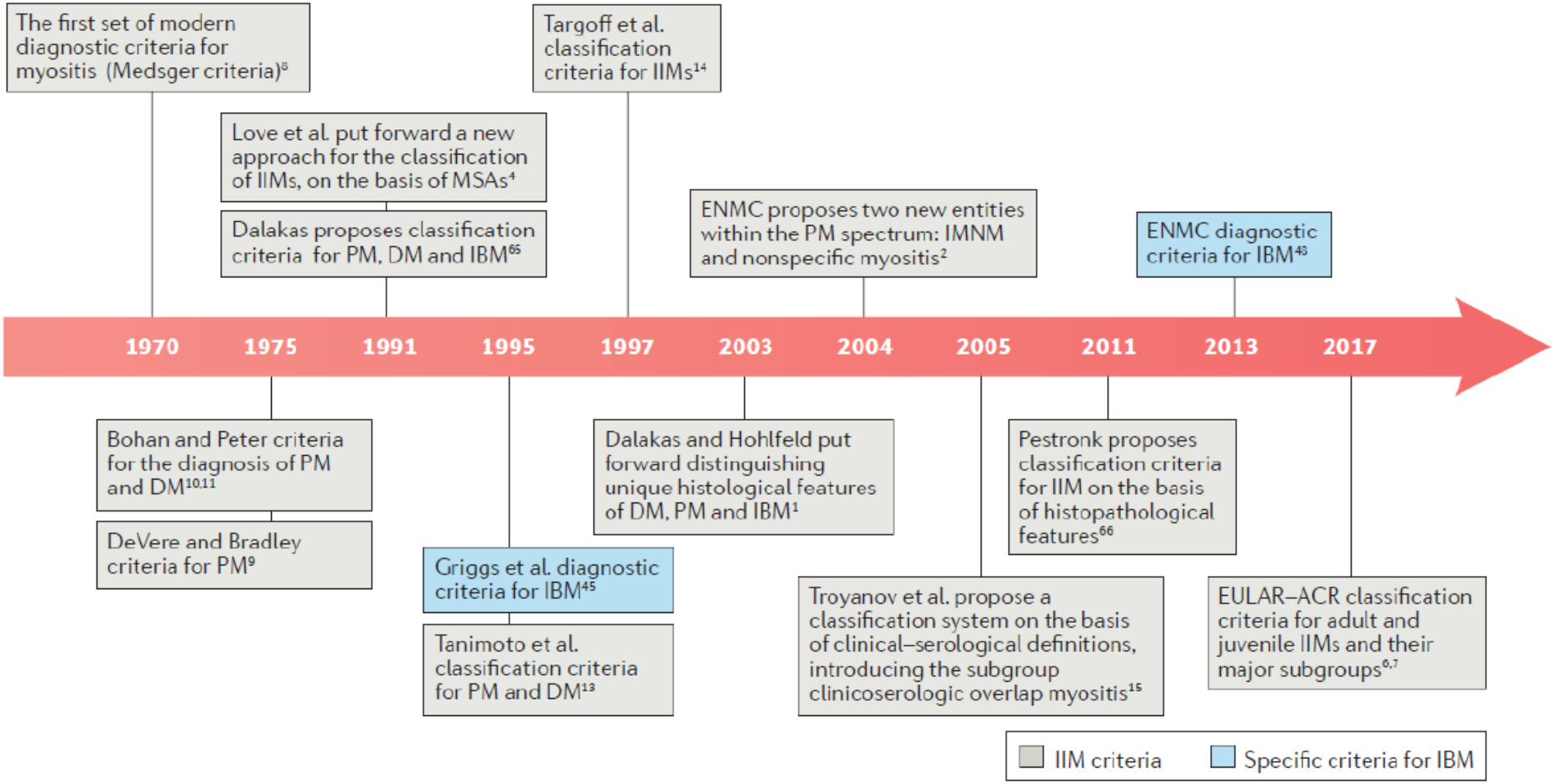


Figure 1 | **Development of classification and diagnostic criteria for idiopathic inflammatory myopathies over time.** Since the 1970s, multiple sets of criteria have been published for the classification and/or diagnosis of idiopathic inflammatory myopathies (IIMs), including specific criteria for inclusion body myositis (IBM; indicated in blue). DM, dermatomyositis; ENMC, European Neuromuscular Centre; IMNM, immune-mediated necrotizing myopathy; MSAs, myositis-specific autoantibodies; PM, polymyositis.

Lundberg, Curr Op, 2018

To take home message

- **NMD are not that rare (1:3 000)**
- **You better fight your enemy once you named it!**
- **To differentiate the curable forms**
- **Revolutions – fast moving field**
- **More than 800 entities**

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