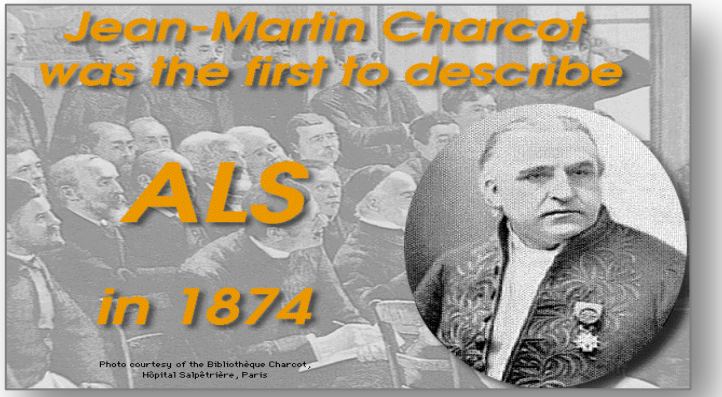
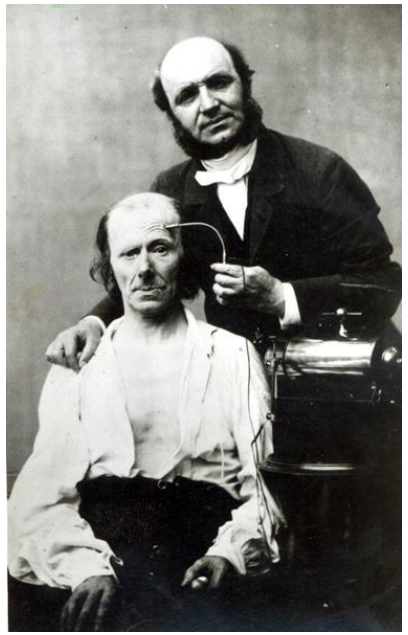
Webinar gratuito

Malattie neuromuscolari: competenze integrate nel percorso assistenziale

webinar ECM
25 marzo 2021



LA STORIA NATURALE DELLE MALATTIE NEUROMUSCOLARI



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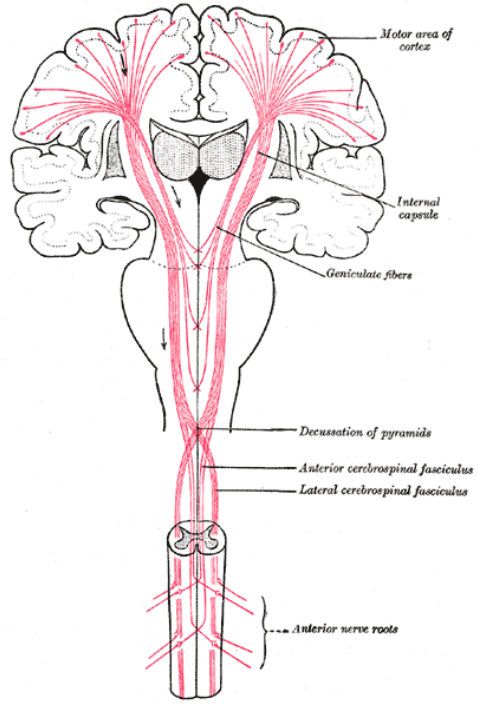
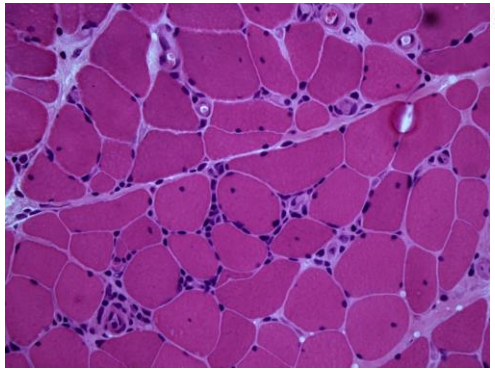
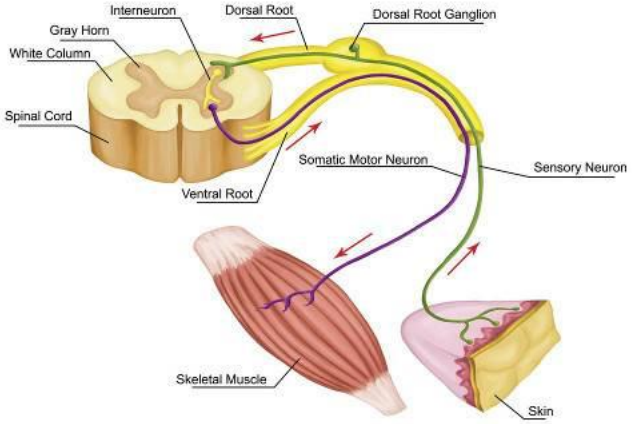
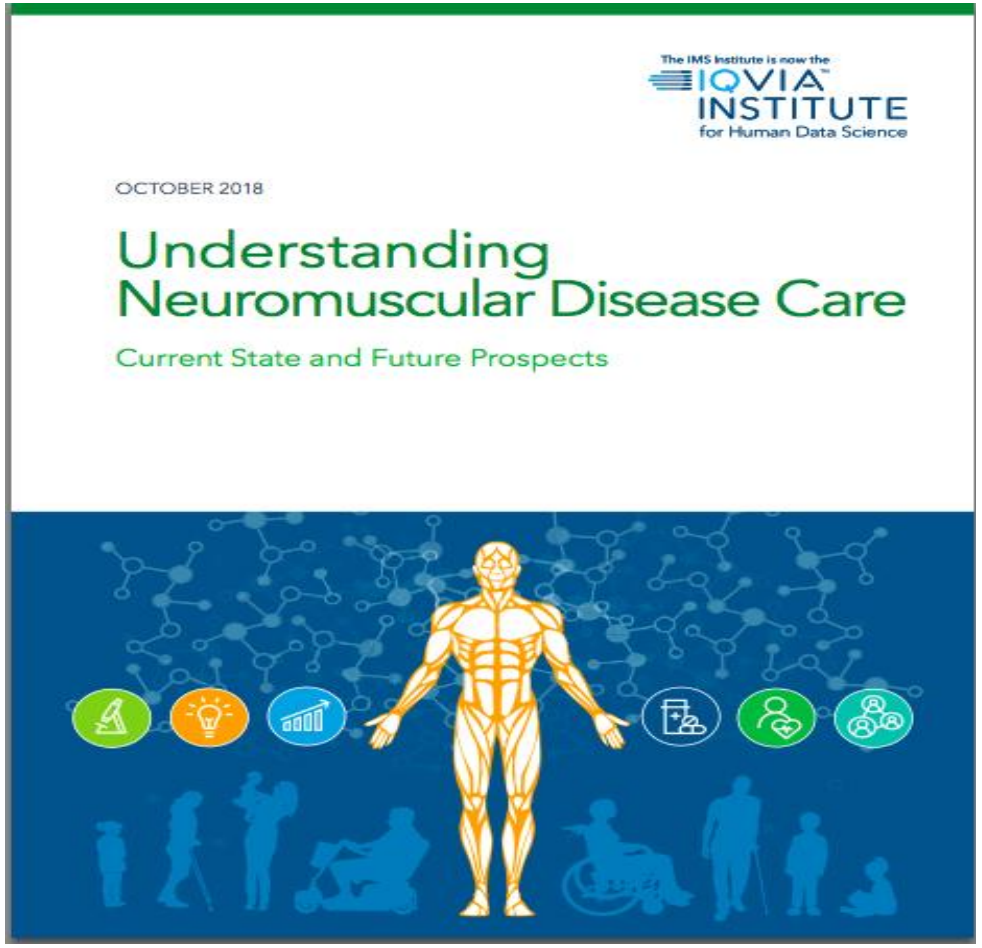
Le malattie neuromuscolari

Sono malattie neurologiche eterogenee dal punto di vista ezio-patogenetico, modalità di esordio, di decorso, caratteristiche cliniche, terapia e prognosi, con impegno diagnostico-assistenziale *necessariamente specifico e diversificato*, anche in relazione ad un possibile interessamento multisistemico.



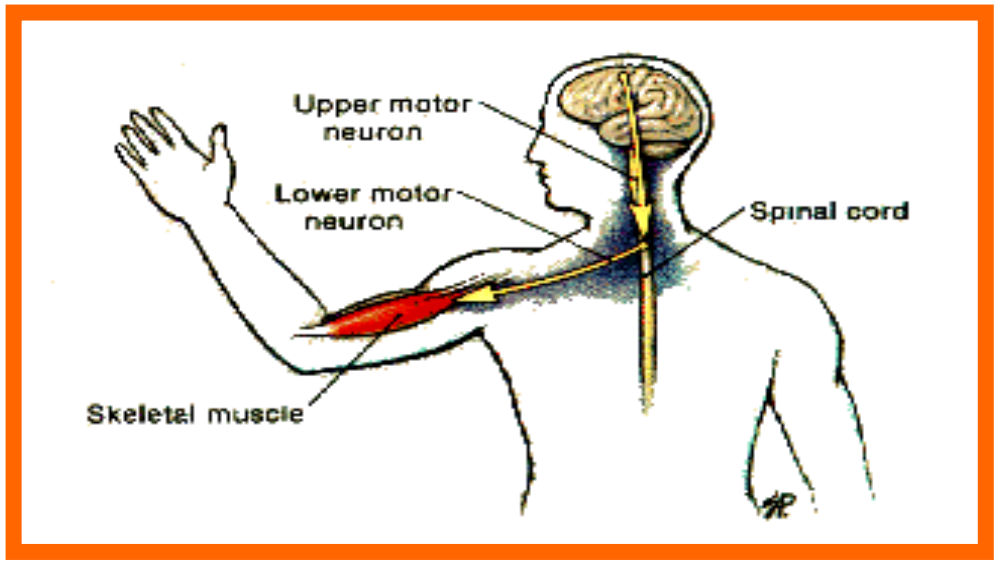


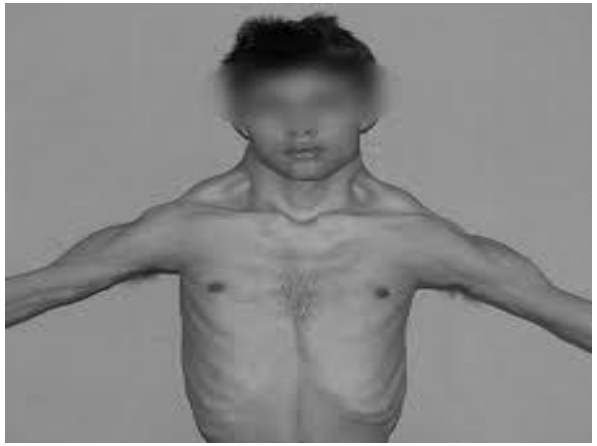


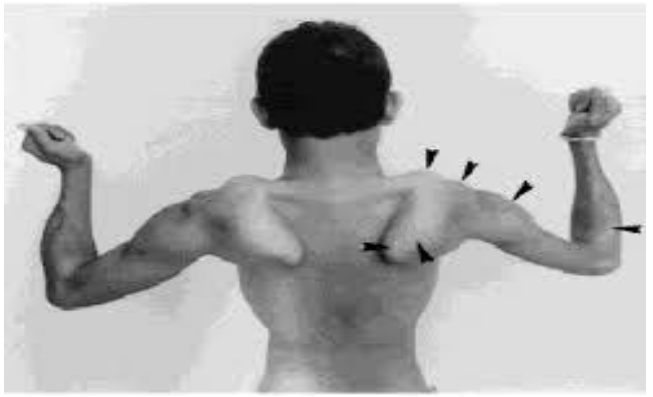


Le malattie neuromuscolari: vasto gruppo di malattie caratterizzate da alterazioni del nervo, muscolo o placca neuro-muscioalre che comportano spesso una progressiva perdita di forza

Prevalenza: difficile da stimare, ma si stima colpiscano fino a 250,000 individui in USA, 500,000 in Europa

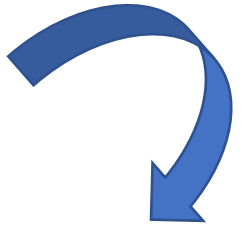






Malattie neuromuscolari

Condizioni patologiche caratterizzate da sintomi e segni attribuibili ad alterazioni biochimiche, elettrofisiologiche o anatomo-patologiche dei costituenti dell'unità motoria:



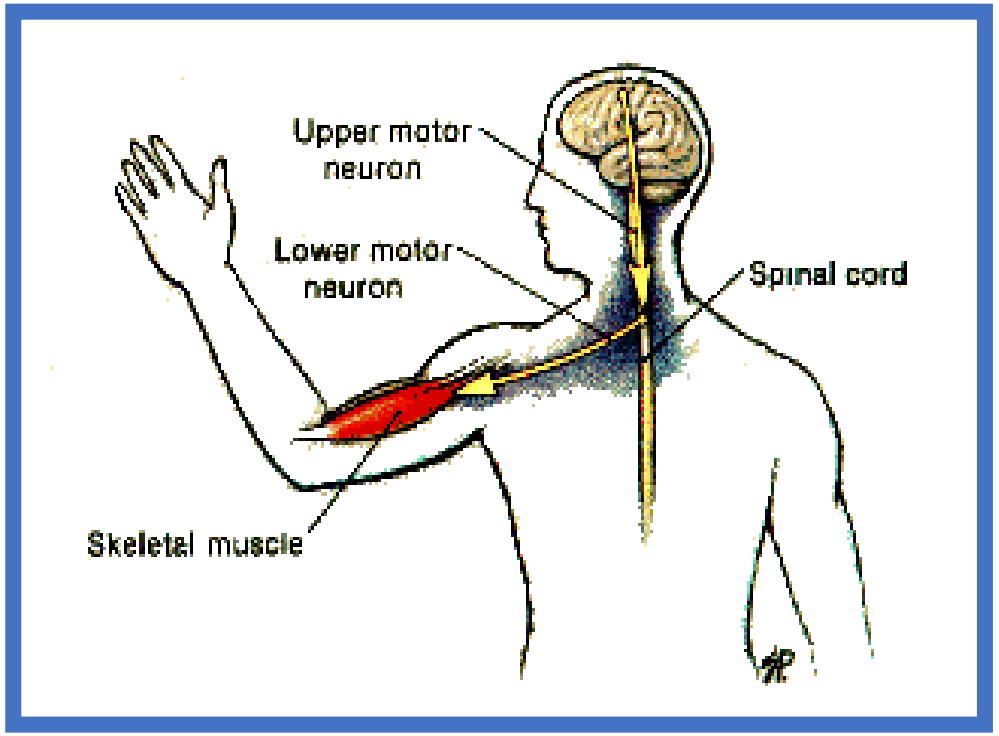
Coinvolgimento multisistemico

Motoneurone
SLA, SMA

Nervo periferico/placca neuromuscolare
CMT, CIDP, MIASTENIA GRAVIS

Muscolo scheletrico
DISTROFIE MUSCOLARI, MIOPATIE METABOLICHE, MALATTIE MITOCONDRIALI

FORME ACQUISITE SPORADICHE/FORME GENETICHE



MALATTIE NEUROMUSCOLARI

Multidisciplinarietà

Un approccio multidisciplinare è fondamentale nella gestione delle malattie muscolari, dal momento che spesso comportano, per le forme sia genetiche sia acquisite, il coinvolgimento di altri sistemi ed apparati.

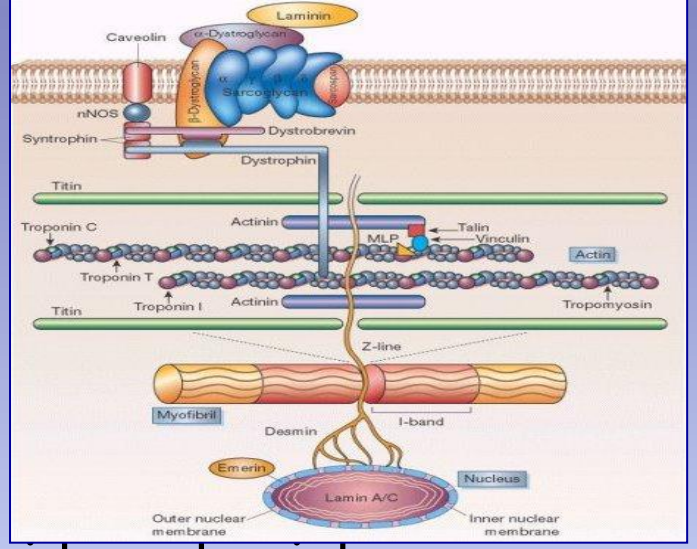
Cronicità

L'andamento cronico della maggior parte delle malattie muscolari, unitamente al carattere disabilitante di esse, ed all' *assenza di cure risolutive*, richiede una presa in carico assistenziale a 360 gradi, che coinvolga, oltre al versante *medico* e *riabilitativo*, anche quello *socio-relazionale*.

La Salute è uno stato di completo Benessere fisico, mentale e sociale, non semplicemente l'assenza di malattia

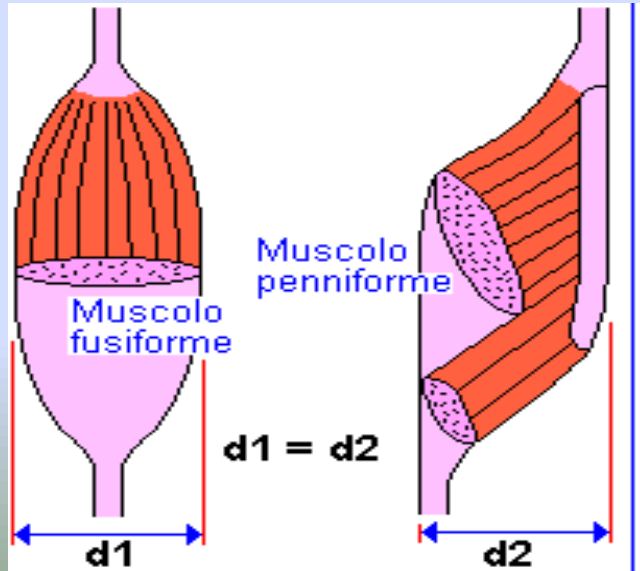
Organizzazione Mondiale della Sanità (OMS) 1946

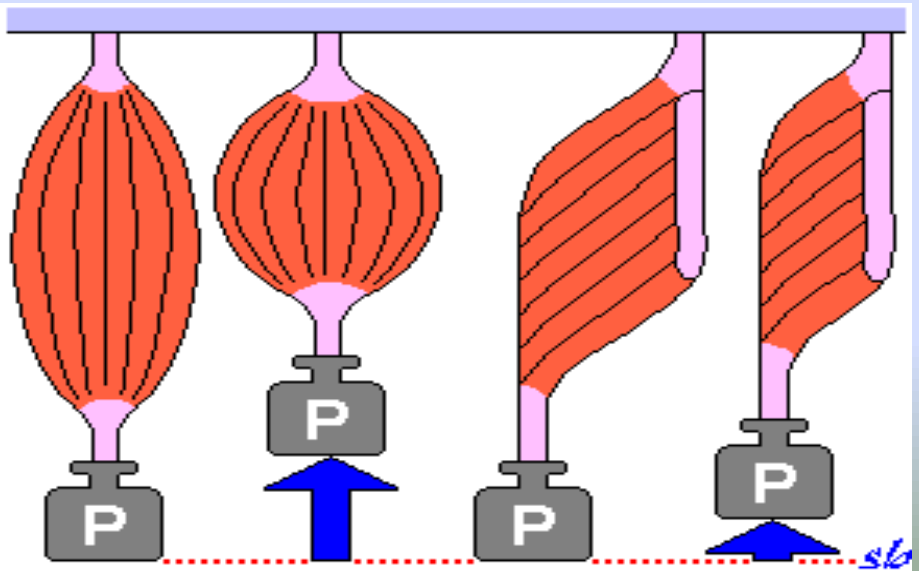
Consequences of myopathic process at contractile level



- less force generation/tissue unit

- muscles with myofibers parallel to tendon longitudinal axis lead to wide and quick displacement
- muscles with myofibers skewed to tendon longitudinal axis lead to great contraction force but slow and limited displacement





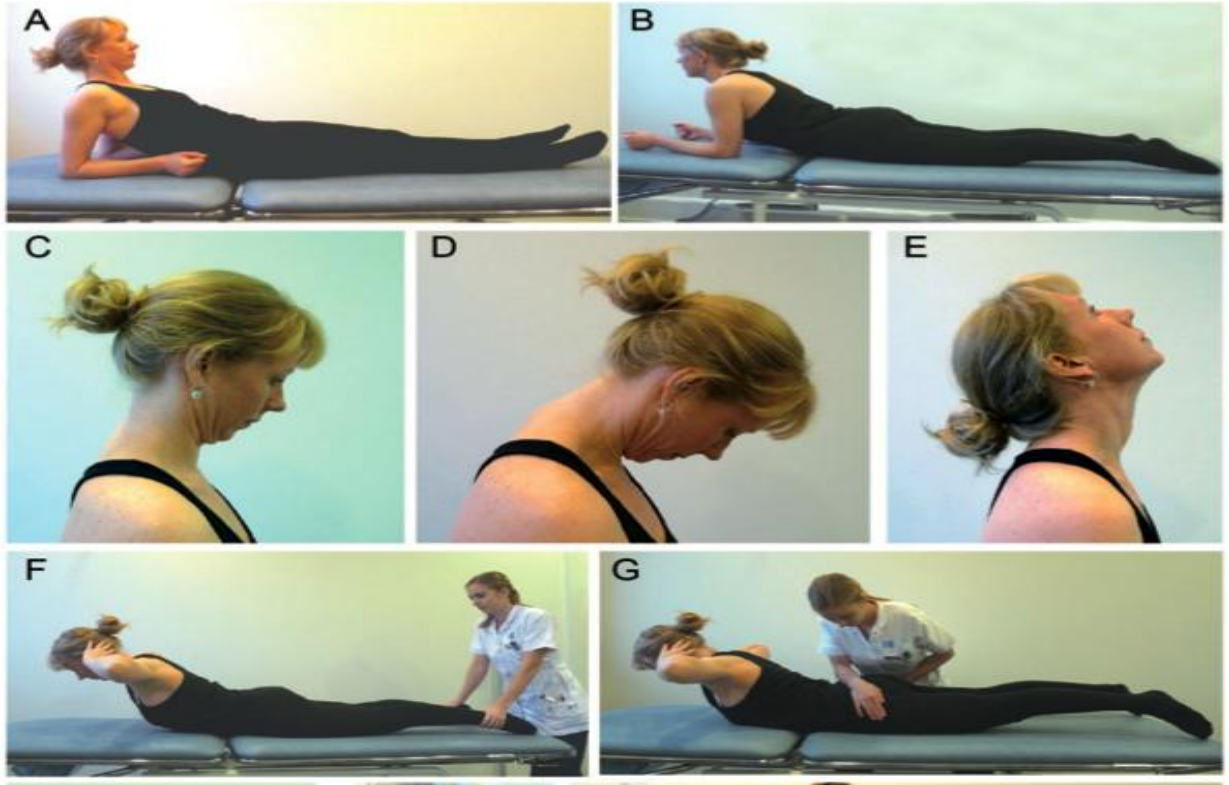
Identification of axial muscle involvement : clinical examination

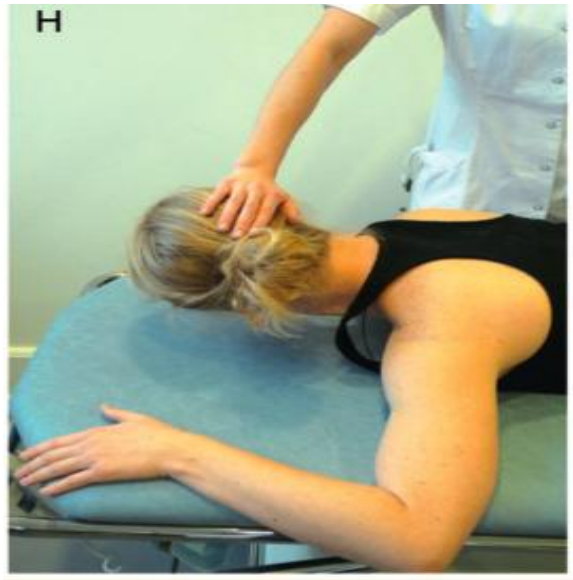
→ **Clinical evaluation**: abnormal posture or severe atrophy of paraspinal muscles . Rarely back pain

→ **Motor function scales** → The Hammersmith Functional Motor Scale (HFMS) : evaluates neck mobility/ strength in 2/32 items and hip/spine mobility in one item. The MFM assesses the ability to roll from side to side, in addition to several other functions. **Thus in the context of paraspinal myopathy, we find these scales too unspecific.**

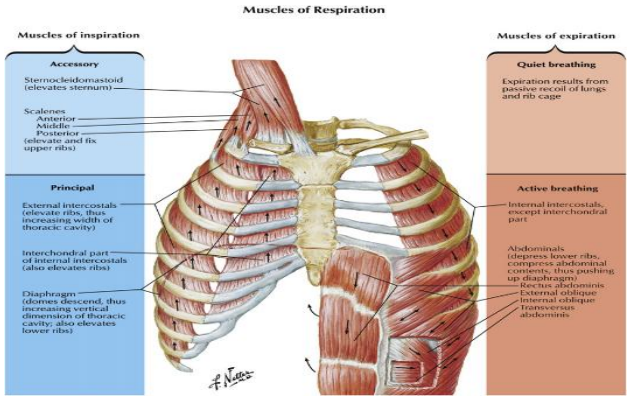
→ **Observation of mobility**

→ **Manual testing of muscle strength and using a dynamometer**

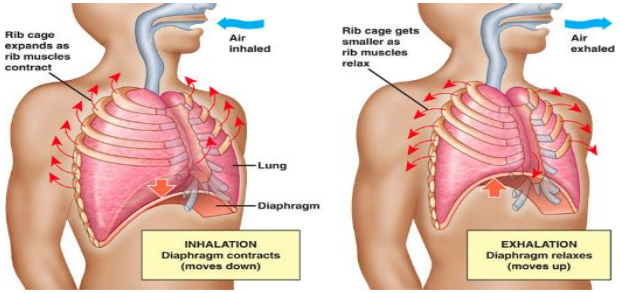




LE COMPLICANZE RESPIRATORIE NELLE MALATTIE NEUROMUSCOLARI



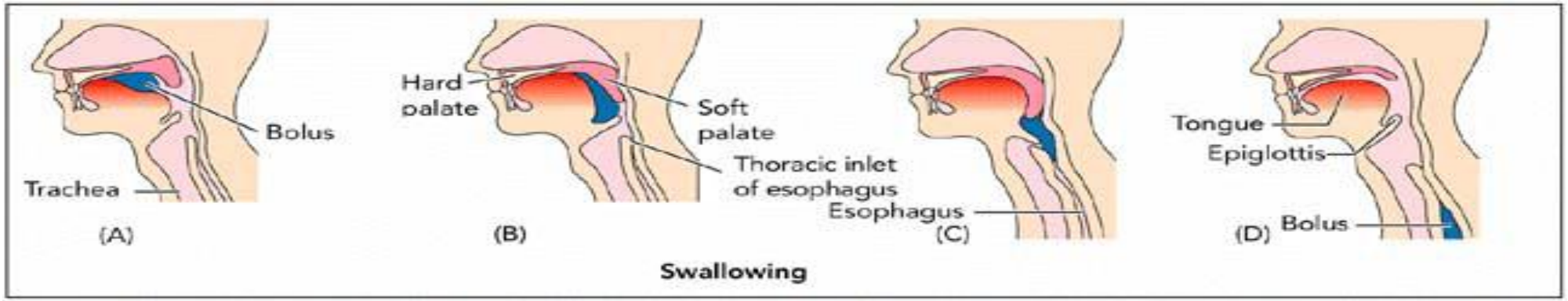
→debolezza dei muscoli respiratori (diaframma e / o muscoli intercostali o muscoli respiratori accessori)
→cifoscoliosi, e deformità della parete toracica
→debolezza dei muscoli faringei e laringei
→fibrosi muscolare
→controllo respiratorio centrale anormale (distrofia miotonica di tipo 1)



- Riduzione forza muscoli respiratori e restrizione da cifoscoliosi → riduzione pompa ventilatoria → alterazione scambi gassosi (incremento pCO2 e riduzione pO2)→ **insufficienza respiratoria**
- Riduzione efficacia della tosse→ riduzione clearance delle secrezioni bronchiali → **incremento infezioni respiratorie**
- Deficit muscolatura bulbare → inalazioni ricorrenti → **polmonite ab ingestis**
- Ridotto tono della muscolatura faringea e alterazioni orofaciali→ **apnee ostruttive**
- Ridotto drive respiratorio → **apnee centrali e ipoventilazione notturna**

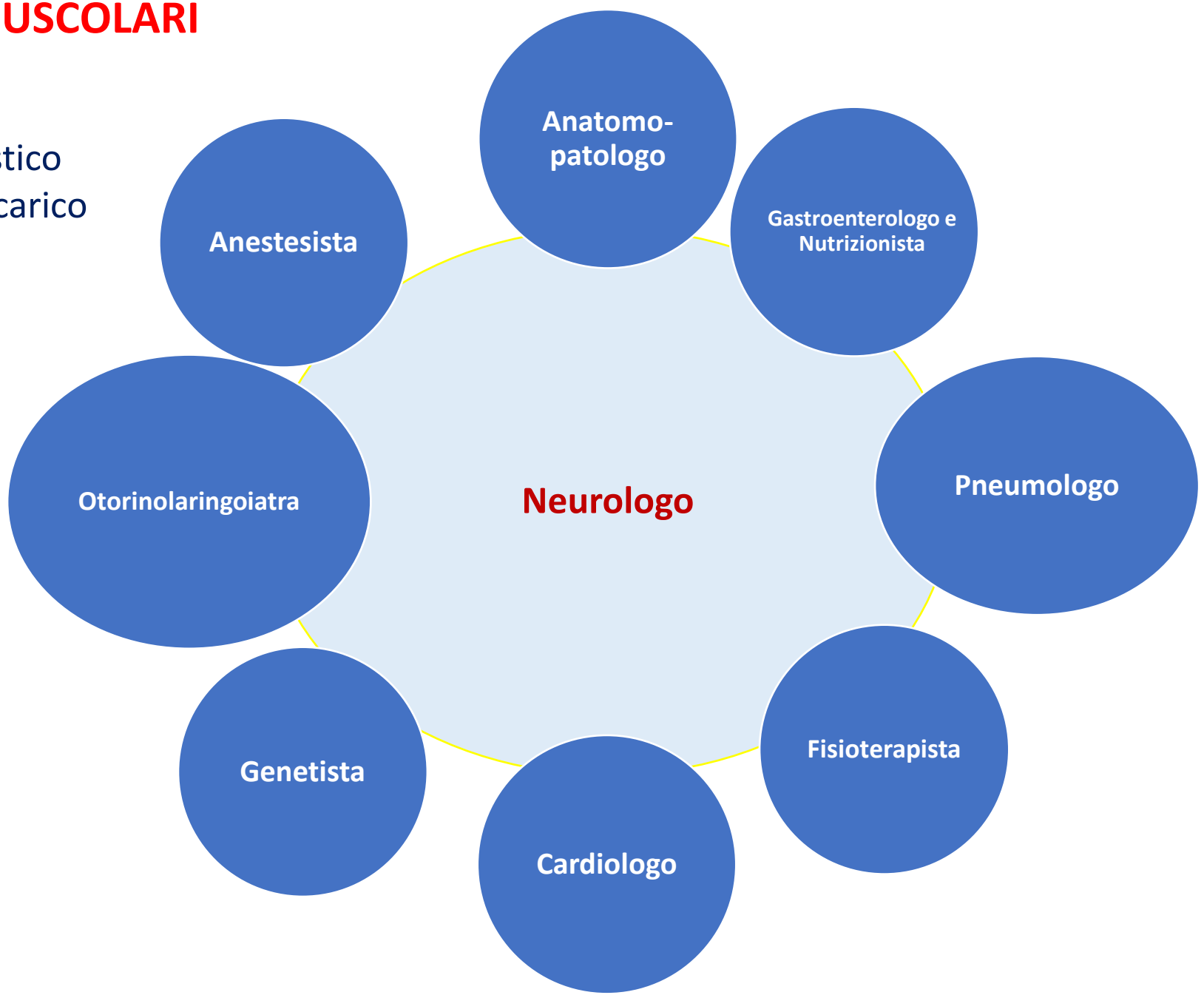
Difficolta’ deglutitorie, disfagia

La disfunzione della deglutizione (disfagia) è comune e frequentemente progressiva nei pazienti con DMD. La valutazione anticipatoria per la disfagia è importante e dovrebbe essere effettuata regolarmente.



MALATTIE NEUROMUSCOLARI

Inquadramento diagnostico
Trattamento e presa in carico
Follow-up



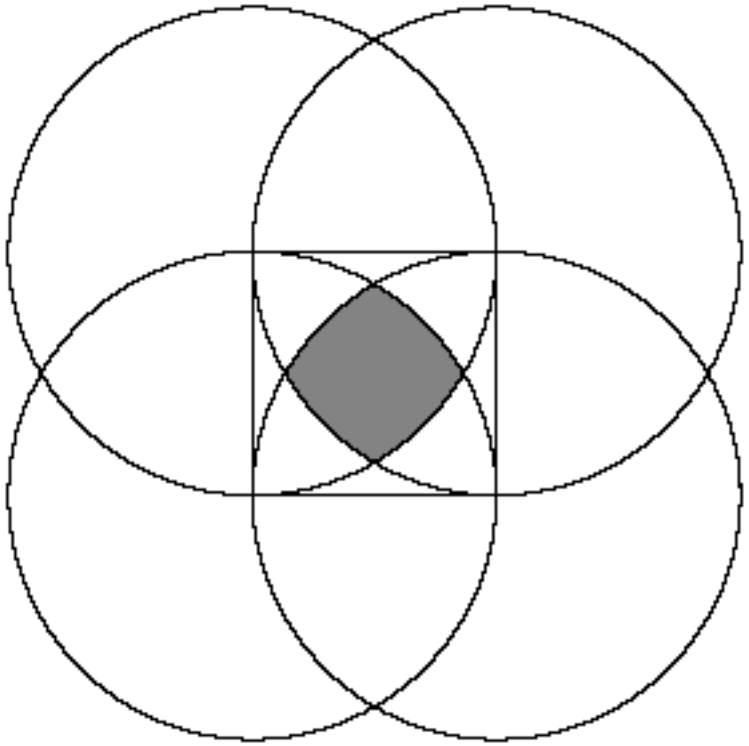
Ampia variabilita' fenotipica ⟷ **Sovrapposizione clinica**

Malattie del motoneurone

Distrofie muscolari

Miopatie miofibrillari

Miopatie secondarie



Miopatie congenite

Miopatie infiammatorie

Miopatie metaboliche

Disturbi funzionali

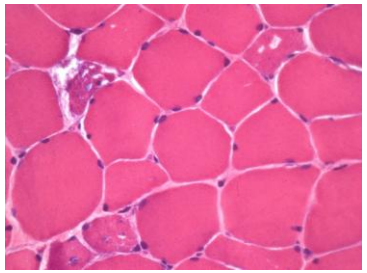
Miopatie mitocondriali

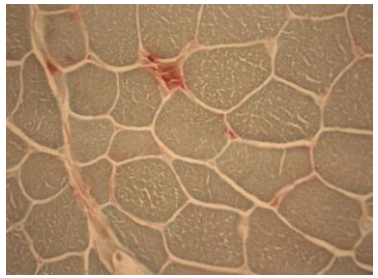
Fibromialgia

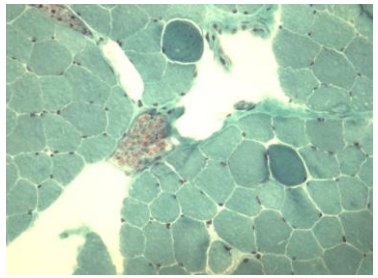
Sarcopenia

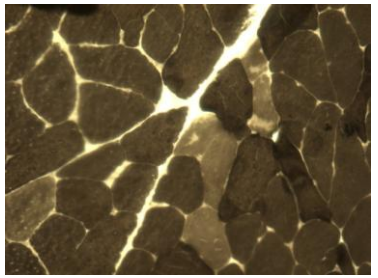
Le malattie muscolari geneticamente determinate

- ✓ Distrofie muscolari
- ✓ Miopatie congenite
- ✓ Miopatie miofibrillari
- ✓ Miopatie metaboliche
- ✓ Canalopatie e miotonie
- ✓ Miopatie mitocondriali









Diagnosi fondamentale per :

→ Scelta terapeutica

→ Prognosi e follow-up

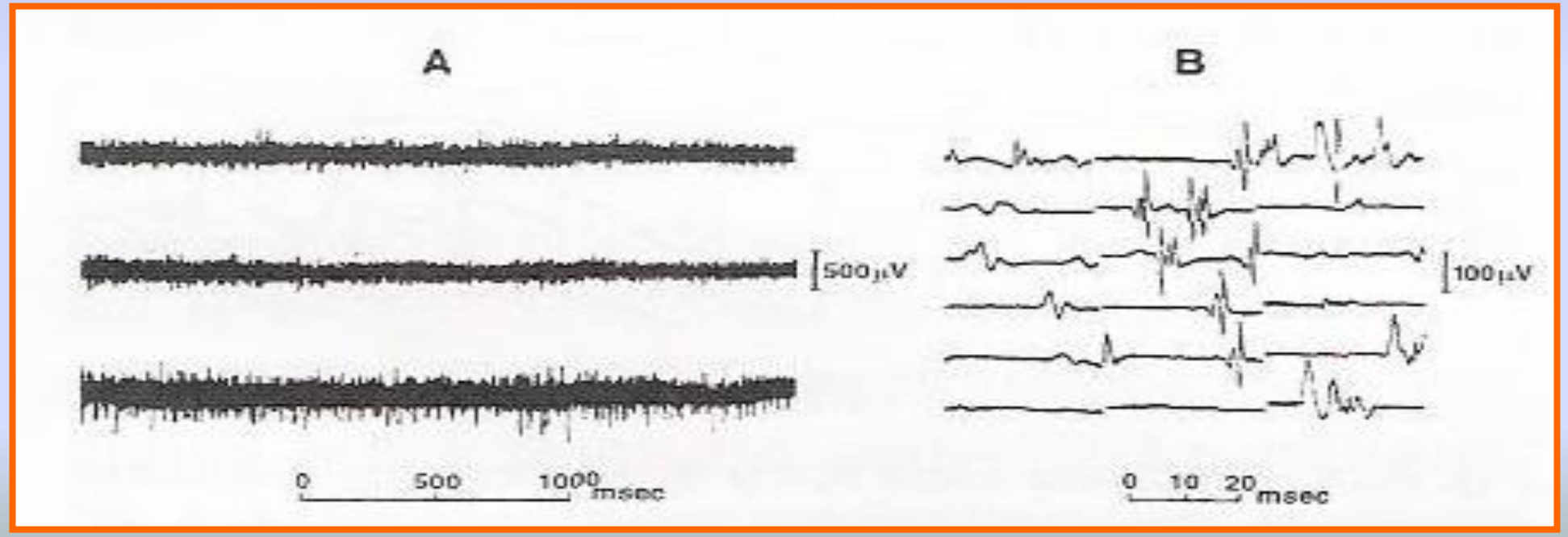
→ Consulenza familiare

→ Studio genetico

Quando indirizzare il paziente verso un ulteriore approfondimento diagnostico

Malattie muscolari: diagnosi

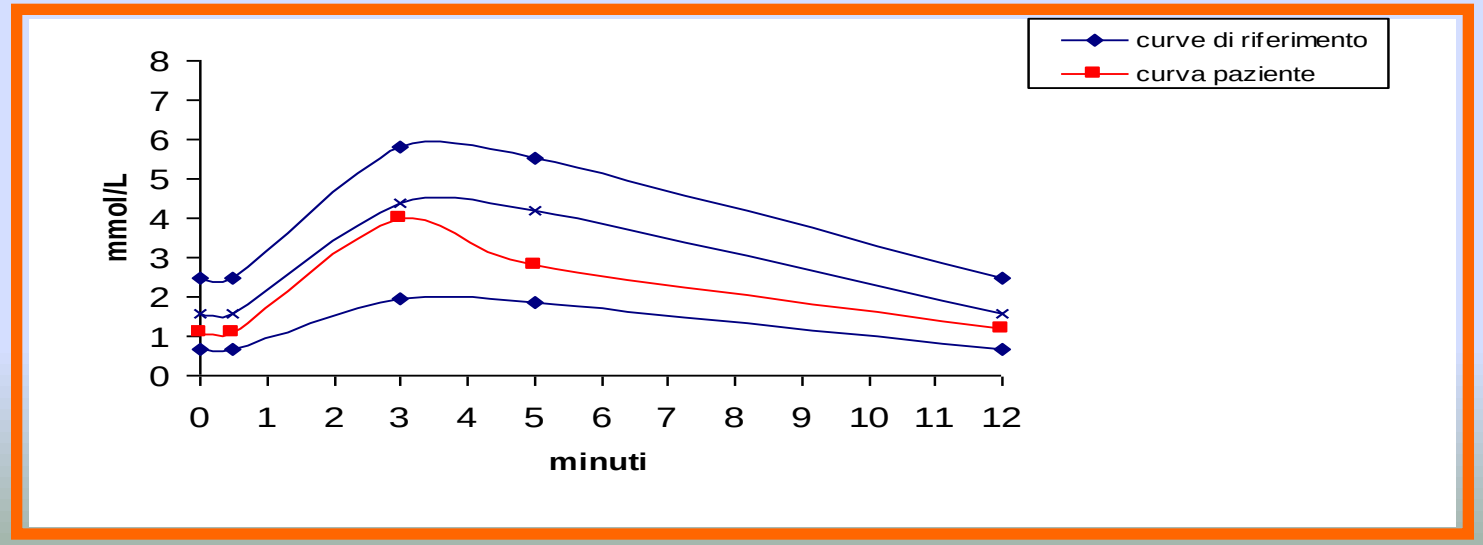
3. Indagini elettrodiagnostiche
   - Elettromiografia
   - Velocità di conduzione



Malattie muscolari: diagnosi

2. Indagini di laboratorio:

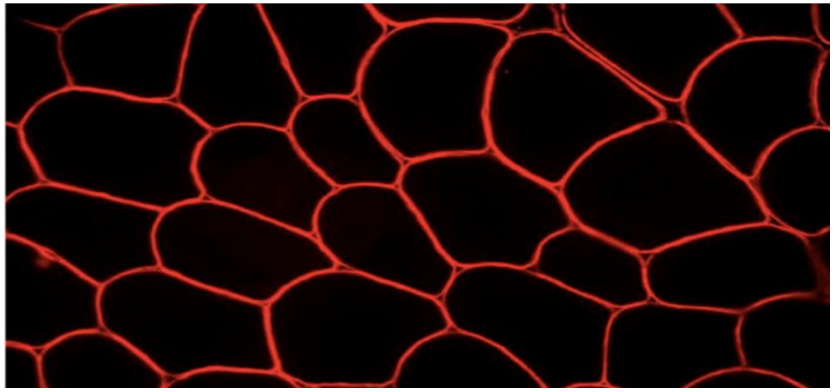
- valutazione enzimatica
  - CPK
  - LDH
  - Aldolasi
- dosaggio dell'acido lattico
  - ischemico
  - aerobico



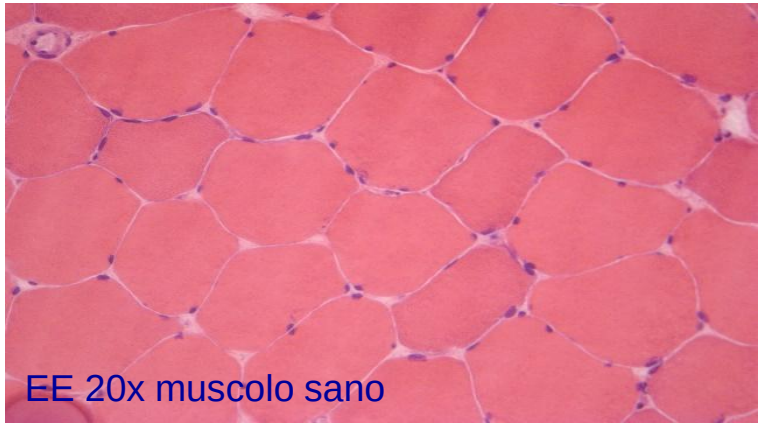
Le distrofie muscolari

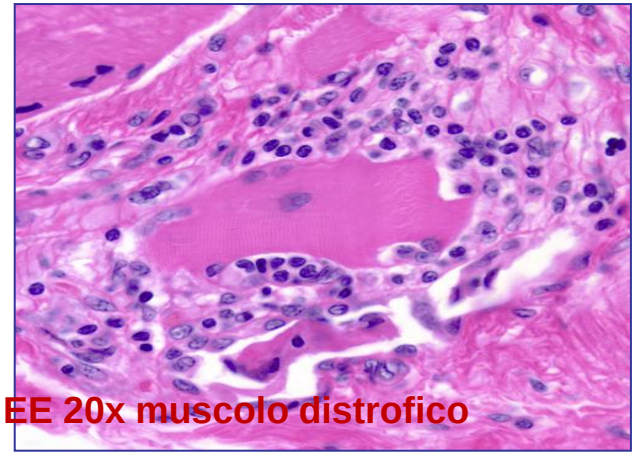
DMD/BMD- Malattia genetica Xp21-linked dovuta a deficit della proteina distrofina

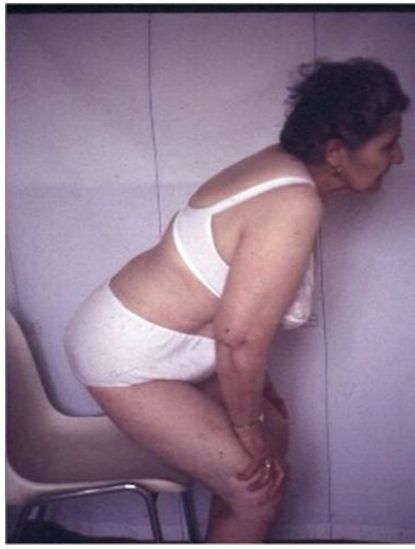
BIOPSIA MUSCOLARE IMMUNOISTOCHIMICA



La progressione della malattia



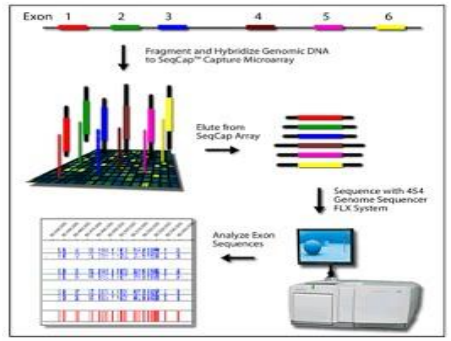




La graduale progressione del quadro clinico

Genetic landscape and novel disease mechanisms from a large LGMD cohort of 4656 patients

Babi Ramesh Reddy Nallamilli[1], Samya Chakravorty[1], Akanchha Kesari[1,2], Alice Tanner[1,2], Arunkanth Ankala[1,2], Thomas Schneider[2], Cristina da Silva[2], Randall Beadling[2], John J. Alexander[1,2], Syed Hussain Askree[1,2], Zachary Whitt[1,3], Lora Bean[1,2], Christin Collins[1], Satish Khadilkar[4,5], Pradnya Gaitonde[6], Rashna Dastur[6], Matthew Wicklund[7], Tahseen Mozaffar[8], Matthew Harms[9], Laura Rufibach[10], Plavi Mittal[11] & Madhuri Hegde[1]



Next generation DNA Sequencing

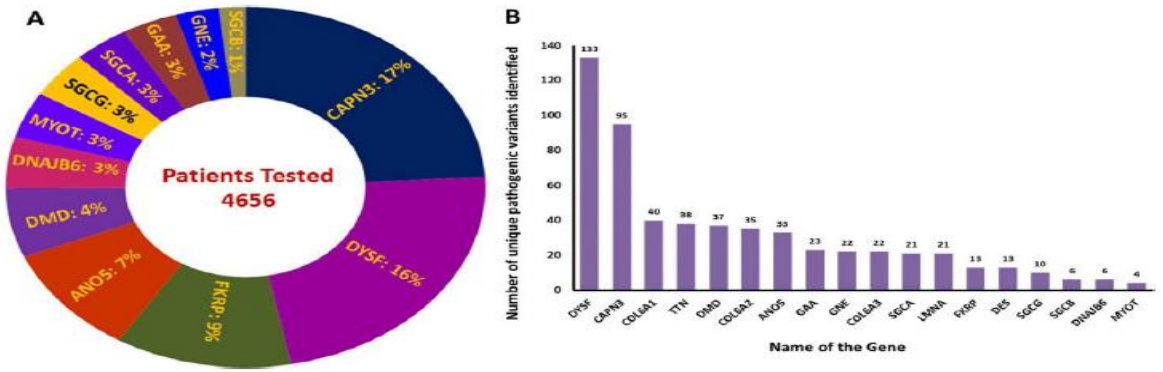


Figure 1. Major contributing LGMD genes. (A) Molecular diagnosis has been established in 27% of the patients. A majority of these patients had a pathogenic variant in one of the following genes *CAPN3* 17%(175/1003), *DYSF* 16%(167/1003), *FKRP* 9%(87/1003), and *ANO5* 7%(72/1003) indicating that these genes are likely the major contributors to LGMD phenotype. (B) Number of unique pathogenic variants identified. Numbers of identified pathogenic variants were compared among the major contributing LGMD genes to understand the allelic heterogeneity of these genes. *DYSF*, *CAPN3*, and *COL6A1* were identified with the most pathogenic variants including 133, 95 and 40, respectively, in each gene, indicating more allelic heterogeneity in these genes.

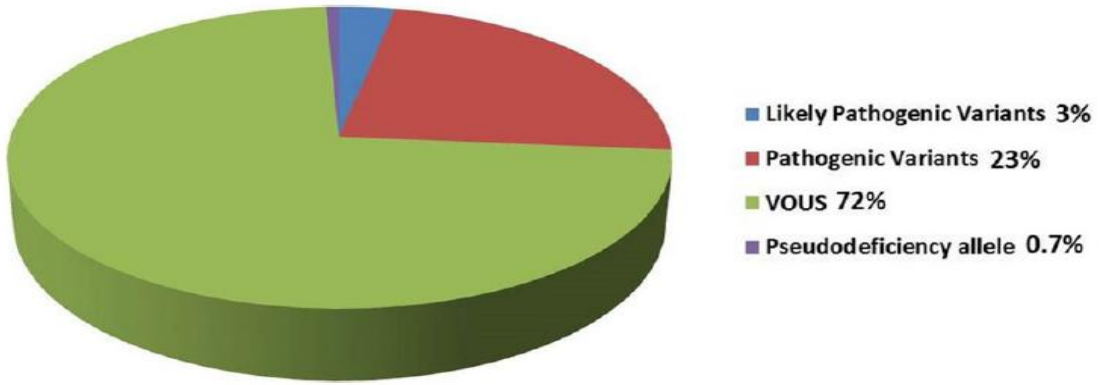


Figure 2. Types of variants identified in the tested LGMD patients. Variants were classified according to standards and guidelines of the American College of Medical Genetics and Genomics. Around 23% of the identified variants are pathogenic. Around 72% of the variants are interpreted as variants of uncertain significance (VUS) because majority of LGMD subtypes are poorly studied and currently limited knowledge available.

MALATTIE NEUROMUSCOLARI: decorso clinico e storia naturale di malattia

Decorso Clinico

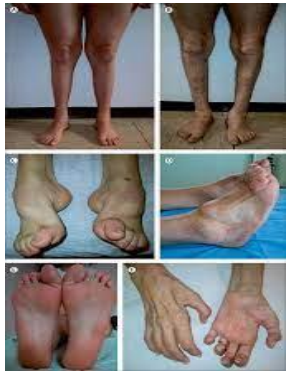
Velocemente progressiva con risoluzione (GBS)

Variabilmente progressiva con relapsing (amiloidosi)

Rapidamente progressiva (SLA)

Relapsing remitting (CIDP)

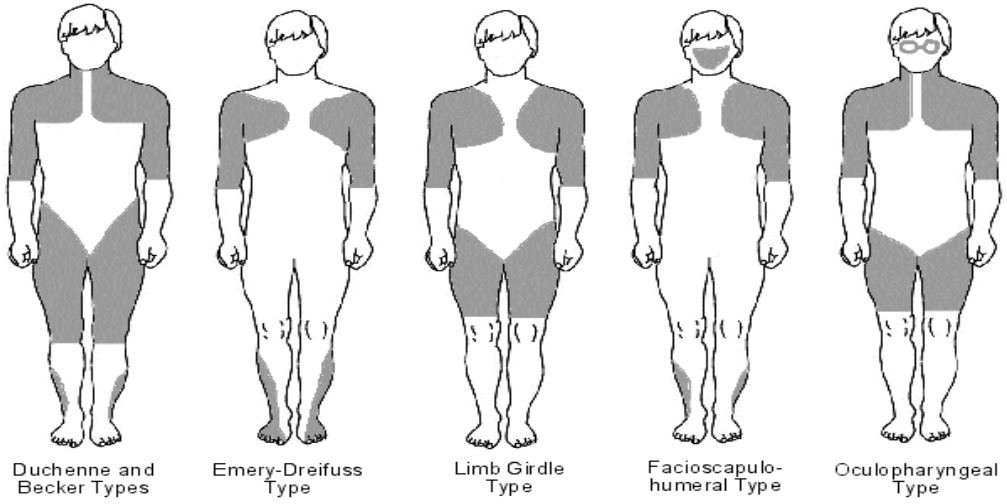
Lentamente progressiva (distrofie muscolari, SMA, CMT)



Tempo: ***anni, mesi o giorni?***

Le distrofie muscolari

- Distrofinopatie (Distrofia di Duchenne, Becker)
- Distrofia miotonica
- Distrofia muscolare facio-scapolo-omerale
- Distrofie muscolari dei cingoli
- Distrofie muscolari congenite



Main areas of muscle weakness in different types of dystrophy

- età d'esordio
- familiarità
- tipo di esordio
- pattern di compromissione muscolare
- trofismo muscolare
  (ipotrofia; pseudoipertrofia)
- sintomatologia muscolare associata
  (intolleranza all'esercizio, mioglobinuria, crampi)
- interessamento di altri organi/apparati
- anamnesi farmacologica

Nuovi geni, nuovi fenotipi

Diagnosi precoce: pre-sintomatici, paucisintomatici

Presa in carico precoce: prevenzione delle complicanze

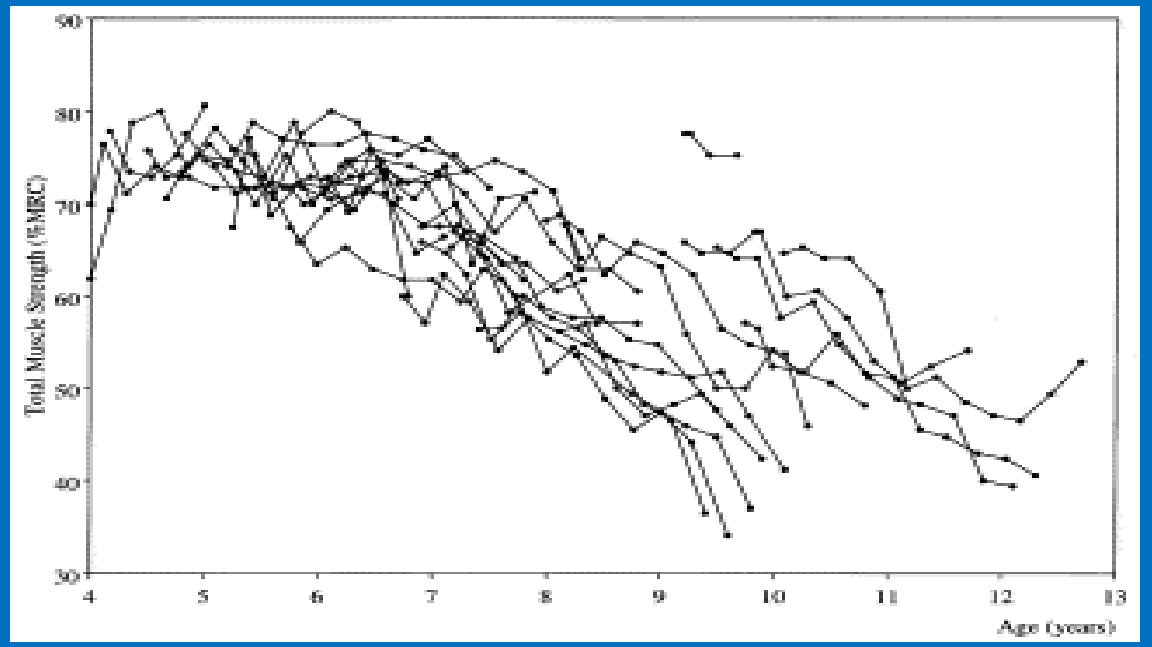
Nuove terapie: come si modifica la storia naturale delle malattie

Giornata
Malattie
Neuromuscolari

sabato 13 marzo 2021

GMN2021
virtuale

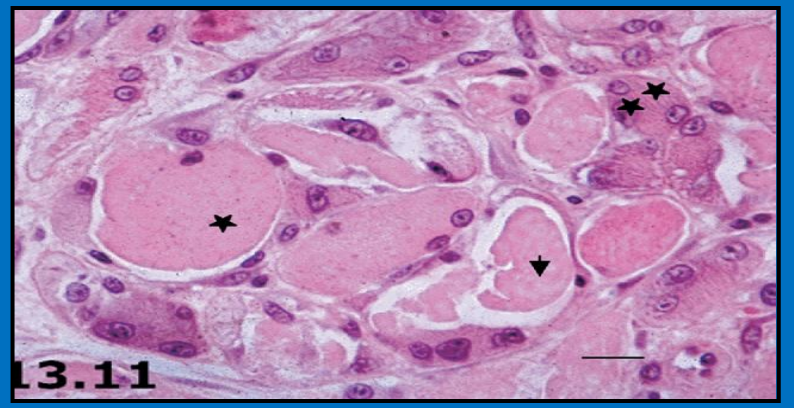
www.giornatamalattieneuromuscolari.it



MRC score in DMD: natural history

Muscle biopsy in muscular dystrophies

- myofiber necrosis/degeneration
- interstitial fibrosis and inflammation
- Regeneration attempt by satellite cells

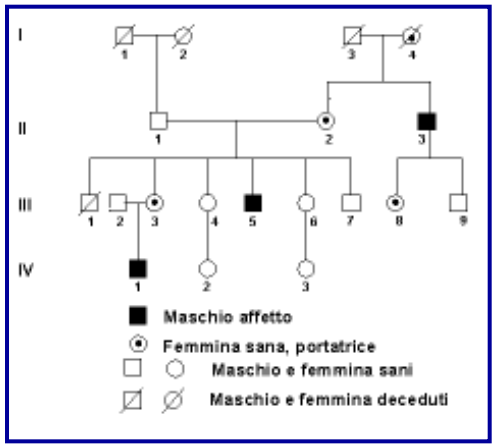


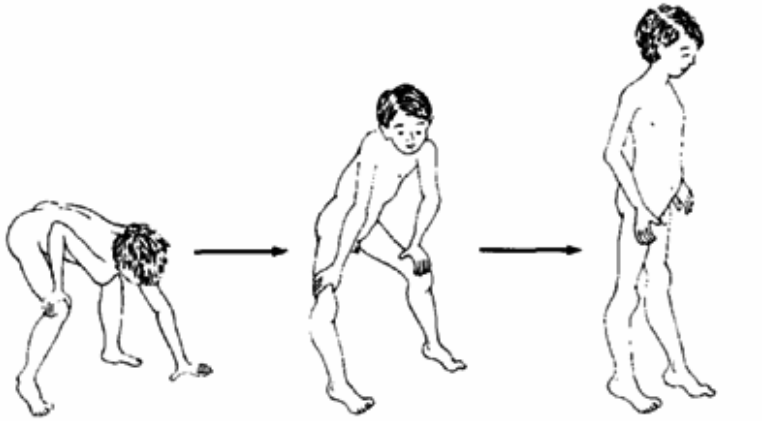
Distrofia Muscolare tipo Duchenne/Becker

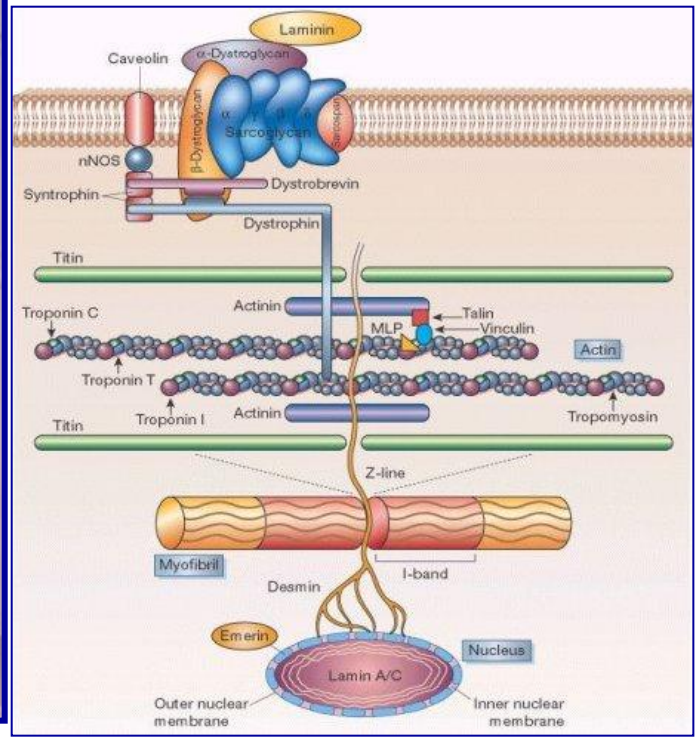
Marcata variabilità nella presentazione clinica e nella progressione di malattia (esordio 2-3 anni/8-10 anni).

Sintomi d'esordio:

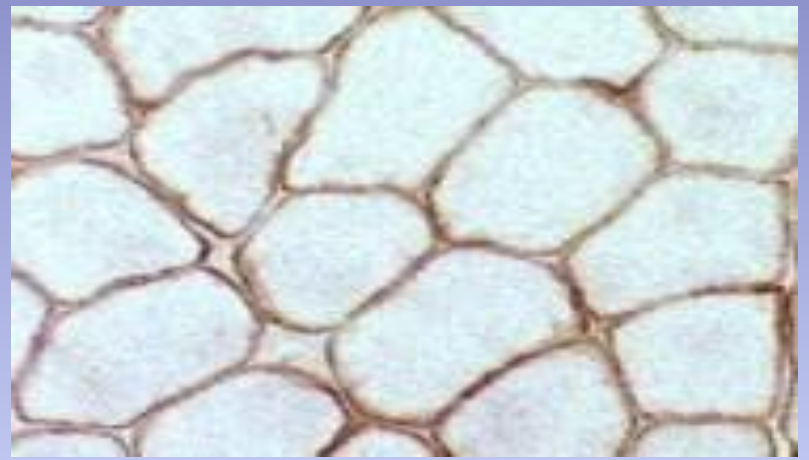
- ✓Debolezza muscolare prossimale
- ✓Crampi muscolari
- ✓Mialgie
- ✓iperCPKmia persistente
- ✓Ipo/atrofia muscolare
- ✓Pseudoipertrofia
- ✓Cardiomiopatia (70%)



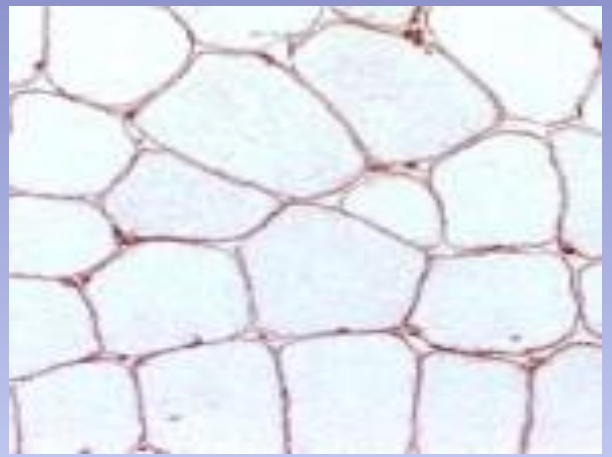




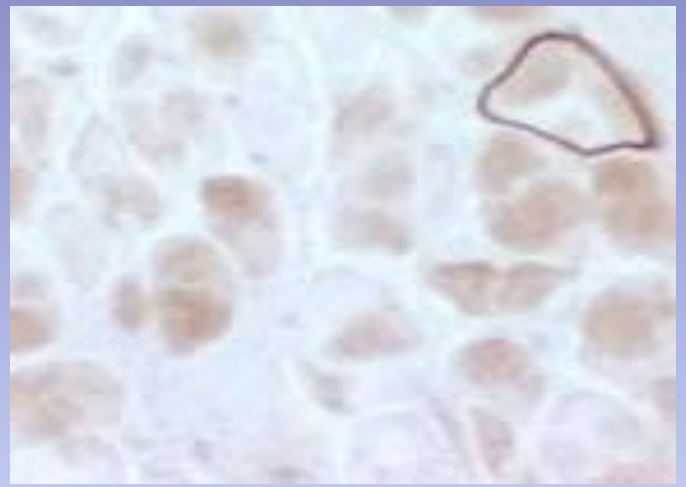
IMMUNOISTOCHIMICA



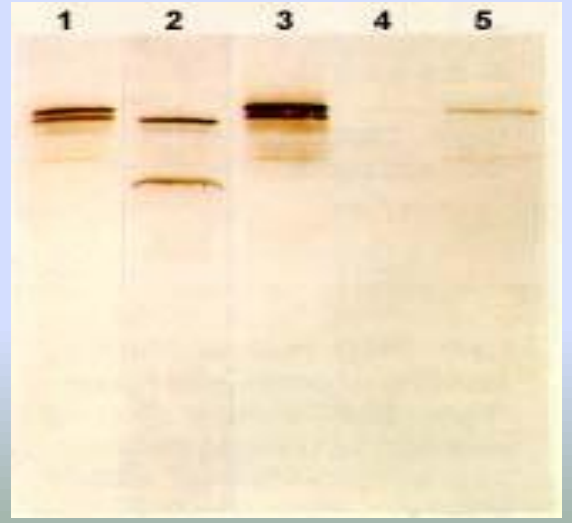
colorazione della distrofina sul contorno delle fibre muscolari di soggetto sano



Distrofia di Becker: ridotta colorazione delle fibre

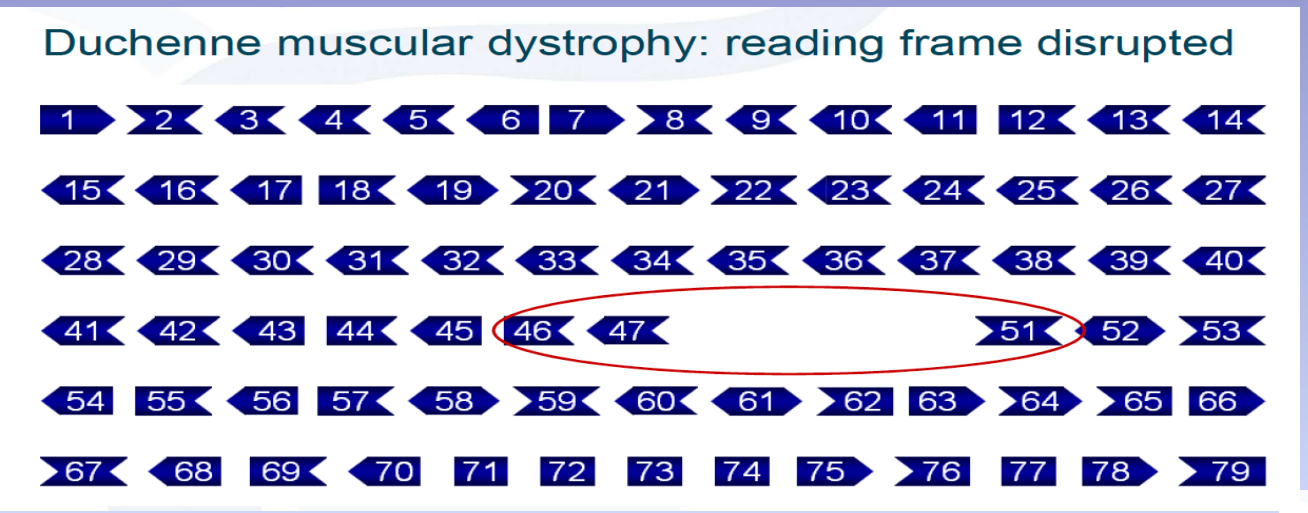


Distrofia di Duchenne: assenza di distrofina

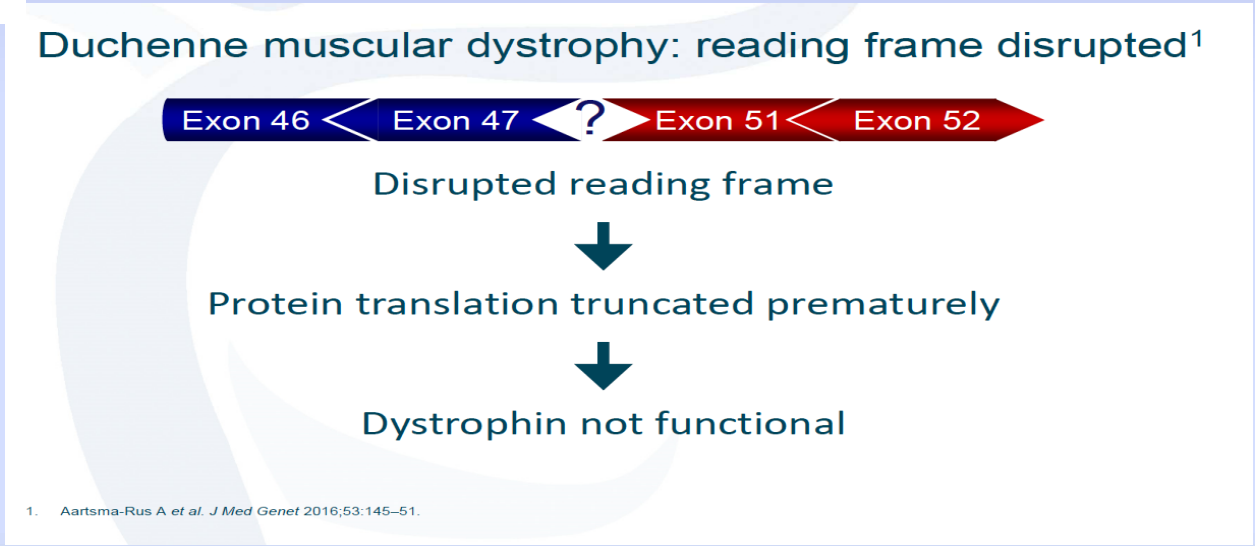


Western blot:
File 1-2: distrofia di Becker
Fila 3: normale espressione di distrofina
File 4-5: distrofia di Duchenne

DNA- next generation sequencing



No sintesi di distrofina



Distrofia Miotonica di Steinert

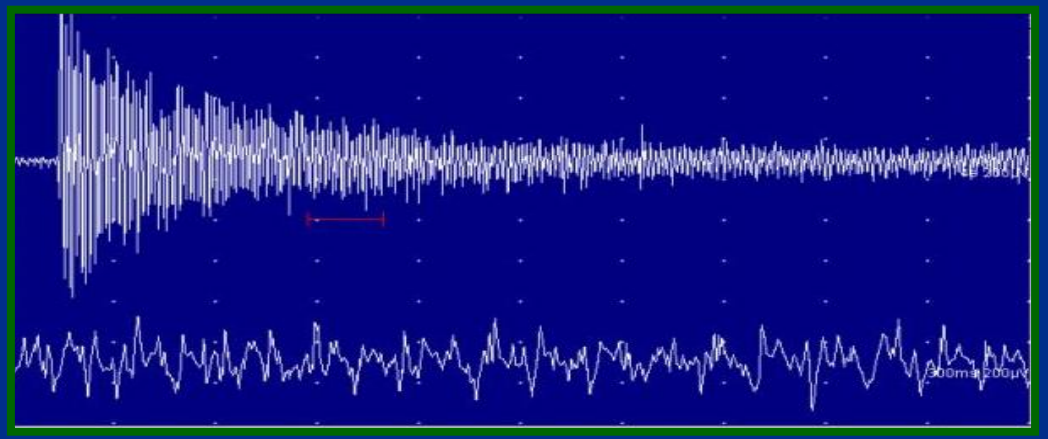
Clinica:

- Debolezza muscolare
- Fenomeno miotonico
- Ipotrofia mm. facciali
- Disturbi di conduzione cardiaca
- Cataratta
- Diabete
- Calvizie frontale

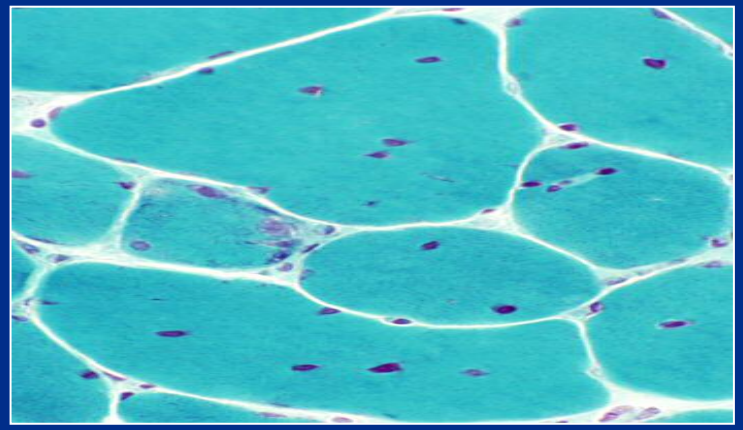
Analisi molecolare:

Trasmissione autosomica dominante
Espansione della tripletta CTG crom. 19q13.2

Fenomeno miotonico



Nuclei interni
(tricromica di Gomori)



Distrofia muscolare facioscapolomerale

Alleli D4Z4 1-3 ripetizioni: forma severa (esordio nell'infanzia)

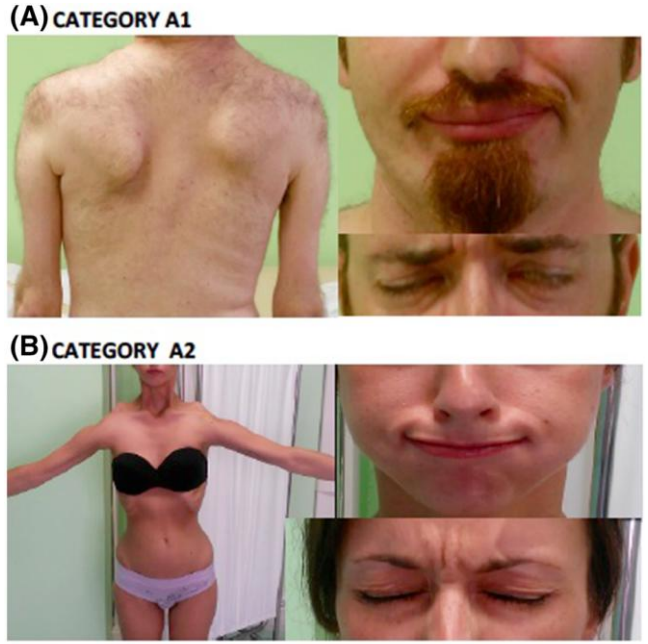
Alleli D4Z4 4-8 ripetizioni: forma classica (esordio entro la seconda decade)

Alleli D4Z4 9-10 ripetizioni: forma lieve (esordio tardivo)

Tipicamente, la malattia si manifesta **nell'infanzia e in età giovanile**.

Deficit della muscolatura facciale.
La **debolezza dei muscoli del cingolo scapolare**, deficit dei muscoli che stabilizzano la scapola rende compromissione dell'elevazione delle braccia
Deficit distale arti inferiori

Nel 20% interessamento severo cingolo pelvico con perdita deambulazione entro la IV decade



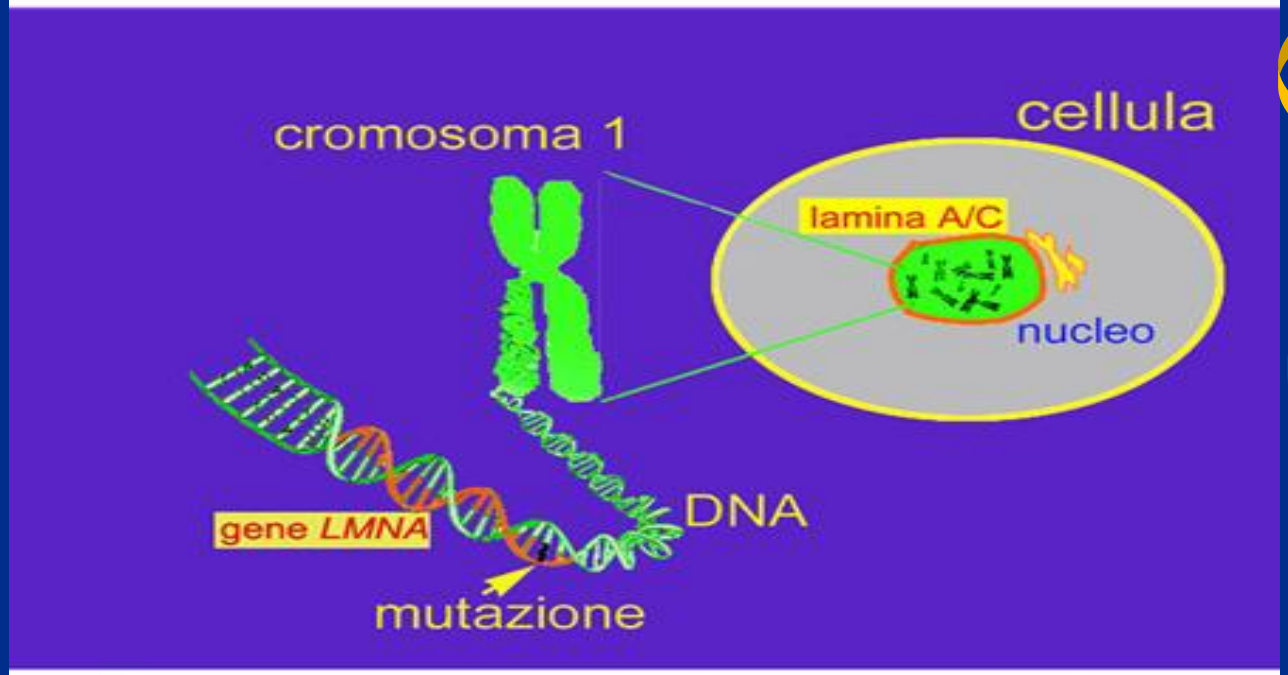
VARIABILITA' FENOTIPICA
INTER e INTRA FAMIGLIE

Le laminopatie

Progetto AIFA:
terapia con corticosteroide nella variante miopatica LGMD e EDMD

Progetto AIFA 2019

qual è la causa delle laminopatie?

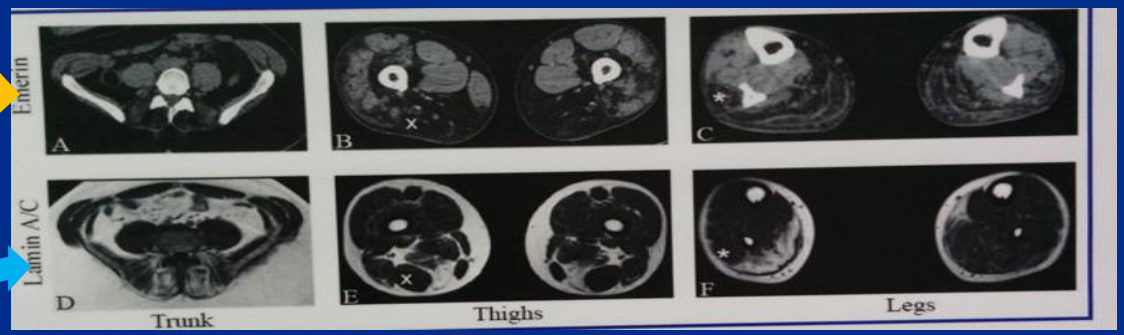


un errore (mutazione) sul gene *LMNA* è la causa di quasi tutte le laminopatie

dal gene *LMNA* verrà prodotta una lamina A/C mutata (non funzionante)

EMERIN

LMNA



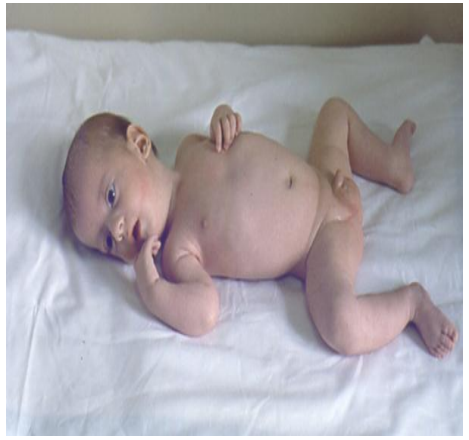
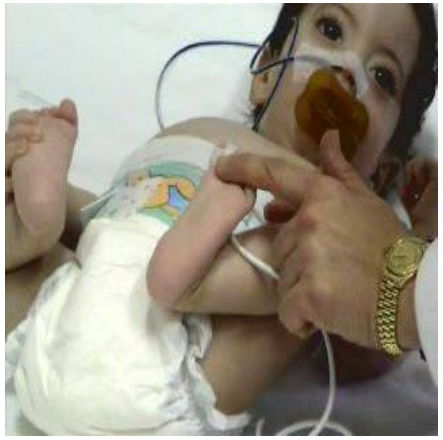
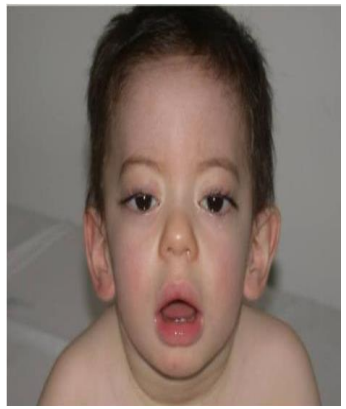
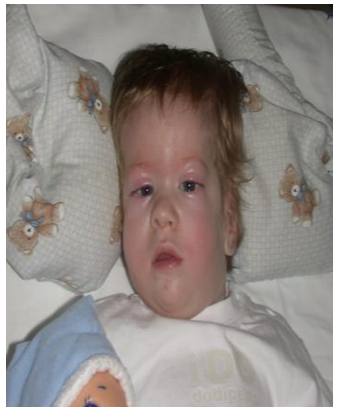
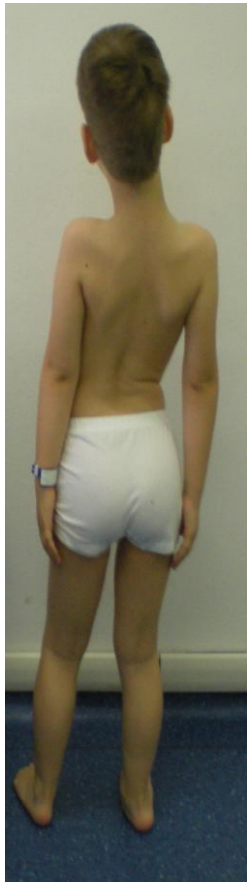
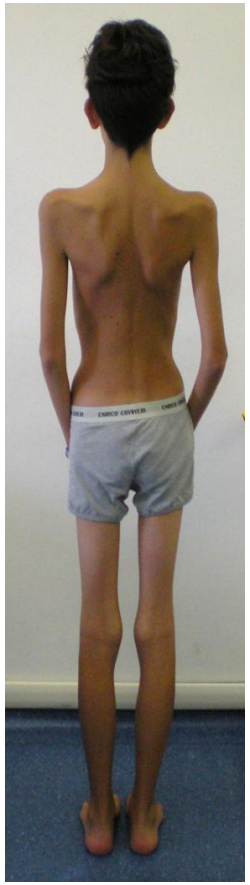
The **congenital myopathies** are a group of genetic muscle disorders characterised by hypotonia and weakness, usually from birth, and a static or slowly progressive clinical course.

<u>Other typical clinical features</u> :
- myopathic facies (ptosis, ophtalmoplegia)
- feeding difficulties
- respiratory distress
- joint laxity or retraction (congenital hip dysplasia)
- delayed motor milestones
- diffuse muscle hypotrophy
- scoliosis

Heart rarely involved. Brain usually spared.

CK normal or mildly elevated.

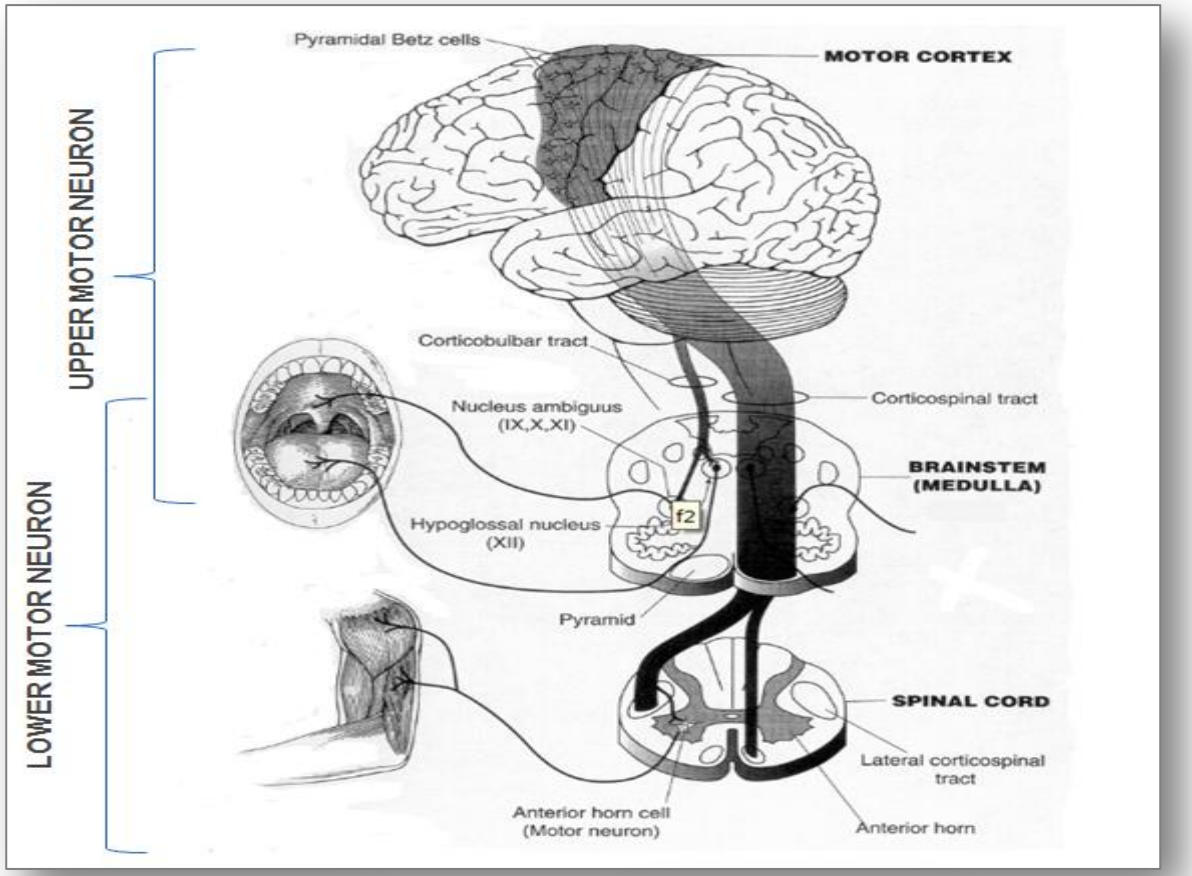
Severity
Fatal forms (X-linked myotubular myopathy)
Later onset milder forms (adult nemaline myopathy)

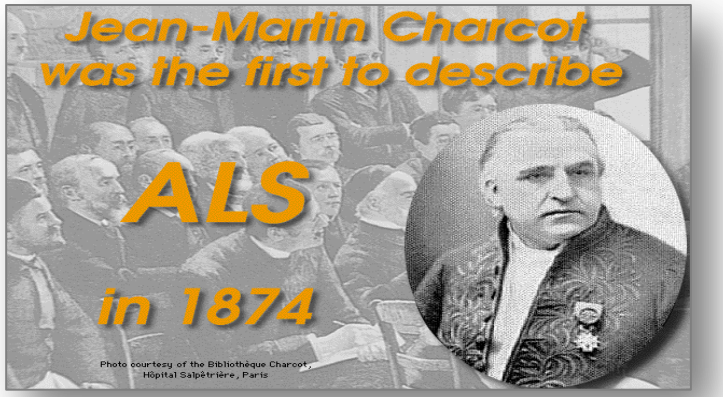







Le altre malattie neuromuscolari

SCLEROSI LATERALE AMIOTROFICA (SLA)

Caratterizzata dalla degenerazione del I e II motoneurone.





Sclerosi → atrofia gliotica

Laterale → cordoni laterali del midollo spinale

Amiotrofica → riduzione della massa muscolare

SLA

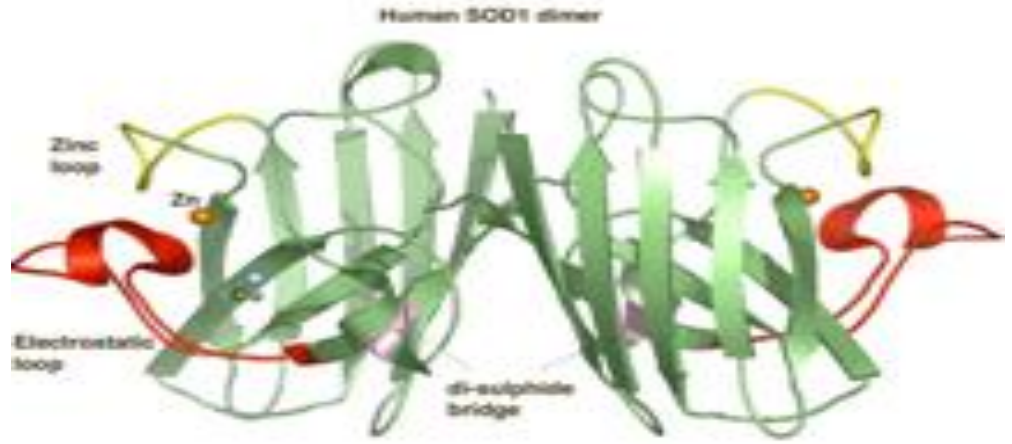
90%
SPORADICA

10%
FAMILIARE

Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis

Daniel R. Rosen*, Teepu Siddique†, David Patterson‡, Denise A. Figlewicz§, Peter Sapp*||, Afif Hentati†, Deirdre Donaldson‡, Jun Goto§, Jeremiah P. O'Regan*||, Han-Xiang Deng†, Zohra Rahmani‡, Aldis Krizus§, Diane McKenna-Yasek*, Annarueber Cayabyab†, Sandra M. Gaston*¶, Ralph Berger‡, Rudolph E. Tanzi¶, John J. Halperin#, Brian Herzfeldt†, Raymond Van den Bergh**, Wu-Yen Hung†, Thomas Bird††, Gang Deng†, Donald W. Mulder‡‡, Celestine Smyth†, Nigel G. Laing§§, Edwin Soriano†, Margaret A. Pericak–Vance|||, Jonathan Haines¶¶, Guy A. Rouleau§, James S. Gusella¶¶, H. Robert Horvitz|| & Robert H. Brown Jr*#

NATURE · VOL 362 · 4 MARCH 1993



(15 %-Mutazione gene Superossido-Dismutasi 1)

Terapia con oligonuclotidi specifici ASOs for FUS-fALS

Jacifusen is a recently developed ASO (Ionis Pharmaceutical and Columbia Medical centre) for patients with mutation in *FUS* gene

Jacifusen is a patient-specific ASO **targeting the *FUS* mutation p.P525 L**, which produces a mutant and toxic protein that accumulate in MN inducing alteration in their functions

In May 2019, the FDA approved the administration of this experimental ASO for a young woman affected by this specific mutation before the completion of toxicological study

FDA further approved the treatment as compassionate use for other three ALS patients with *FUS* mutations.

nature medicine

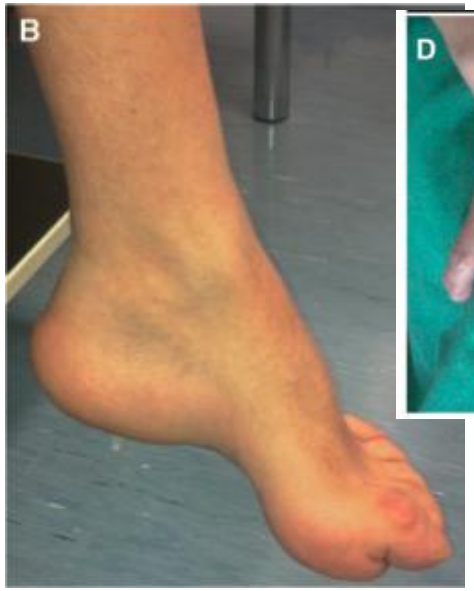
NEWS · 30 MAY 2019

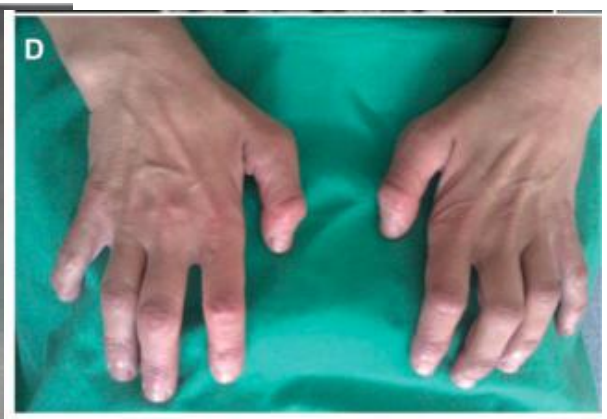
Tailored treatment for ALS poised to move ahead

For a young woman with a rare disease, researchers are pushing the boundaries of personalized medicine

Jaci Hermstad (center) and her parents

Charcot Marie Tooth Type 1 (CMT1)

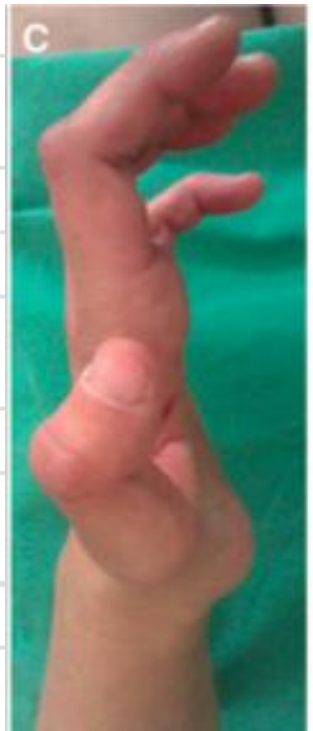




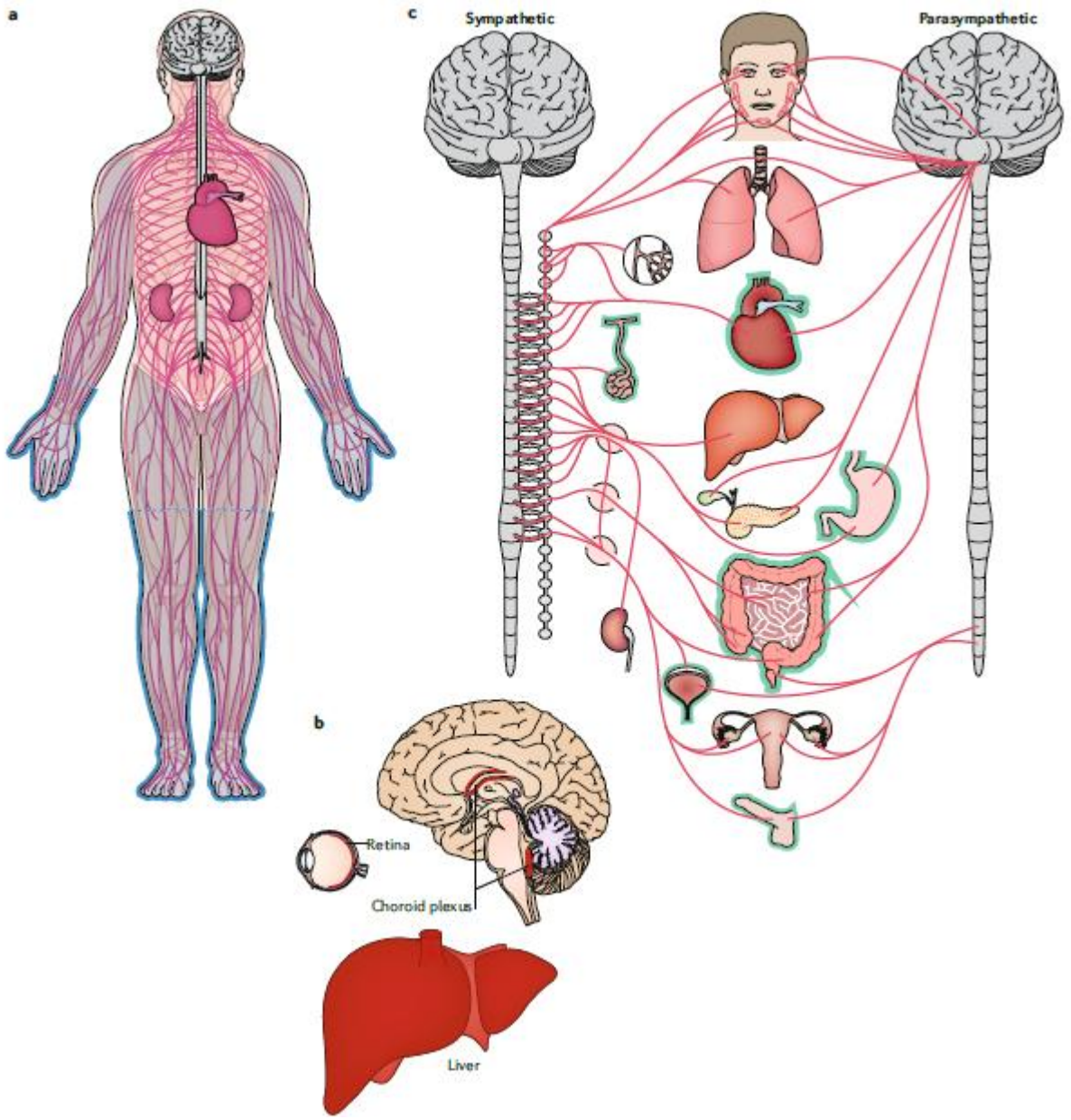
- → Demyelinating
- → Distal muscle weakness and atrophy, sensory loss
- → Slow nerve conduction velocity (typically 5-30 m/sec; normal: >40-45 m/sec).
- → Usually slowly progressive
- → Often associated with pes cavus foot deformity and bilateral foot drop.
- → Affected individuals usually become symptomatic between ages five and 25 years.
- → Fewer than 5% of individuals become wheelchair dependent.
- → Life span is not shortened

Locus Name	Proportion of CMT1 (excluding CMTX) [1]	Gene	Protein Product
CMT1A	70%-80%	*PMP22*	Peripheral myelin protein 22
CMT1B	10%-12%	*MPZ*	Myelin P_0 protein
CMT1C	~1%	*LITAF*	Lipopolysaccharide-induced tumor necrosis factor-alpha factor
CMT1D	Unknown	*EGR2*	Early growth response protein 2
CMT1E	~1%	*PMP22*	Peripheral myelin protein 22 (sequence changes)
CMT1F/2E	Unknown	*NEFL*	Neurofilament light polypeptide

1. Saporta et al [2011]



POLINEUROPATIA AMILOIDOTICA FAMILIARE



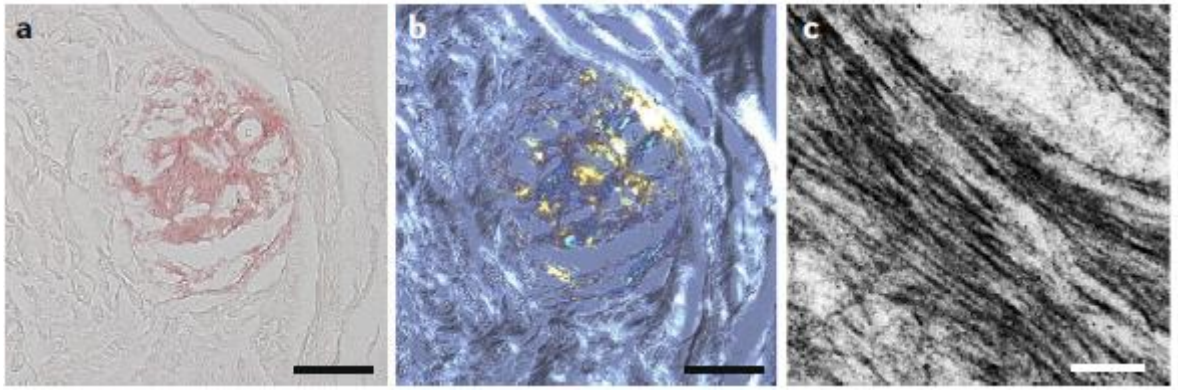
Manifestazioni cliniche

Neuropatia

Polineuropatia delle piccole fibre

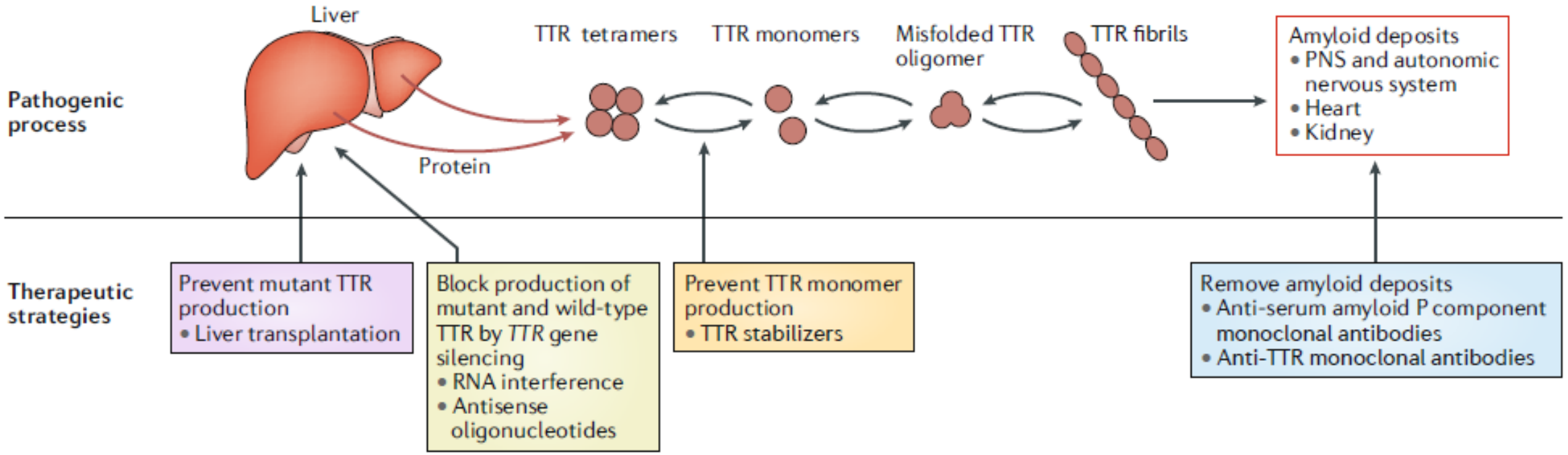
Sintomi sensitivi o sensorimotori: distali, più spesso i piedi

Neuropatia autonomica: disfunzione erettile, sintomi gastrointestinali (costipazione, diarrea, crisi di vomito), dysuria



Microangiopathy – Schwann cell stress

Overview of therapeutic strategies in hereditary transthyretin amyloidosis with polineuropathy



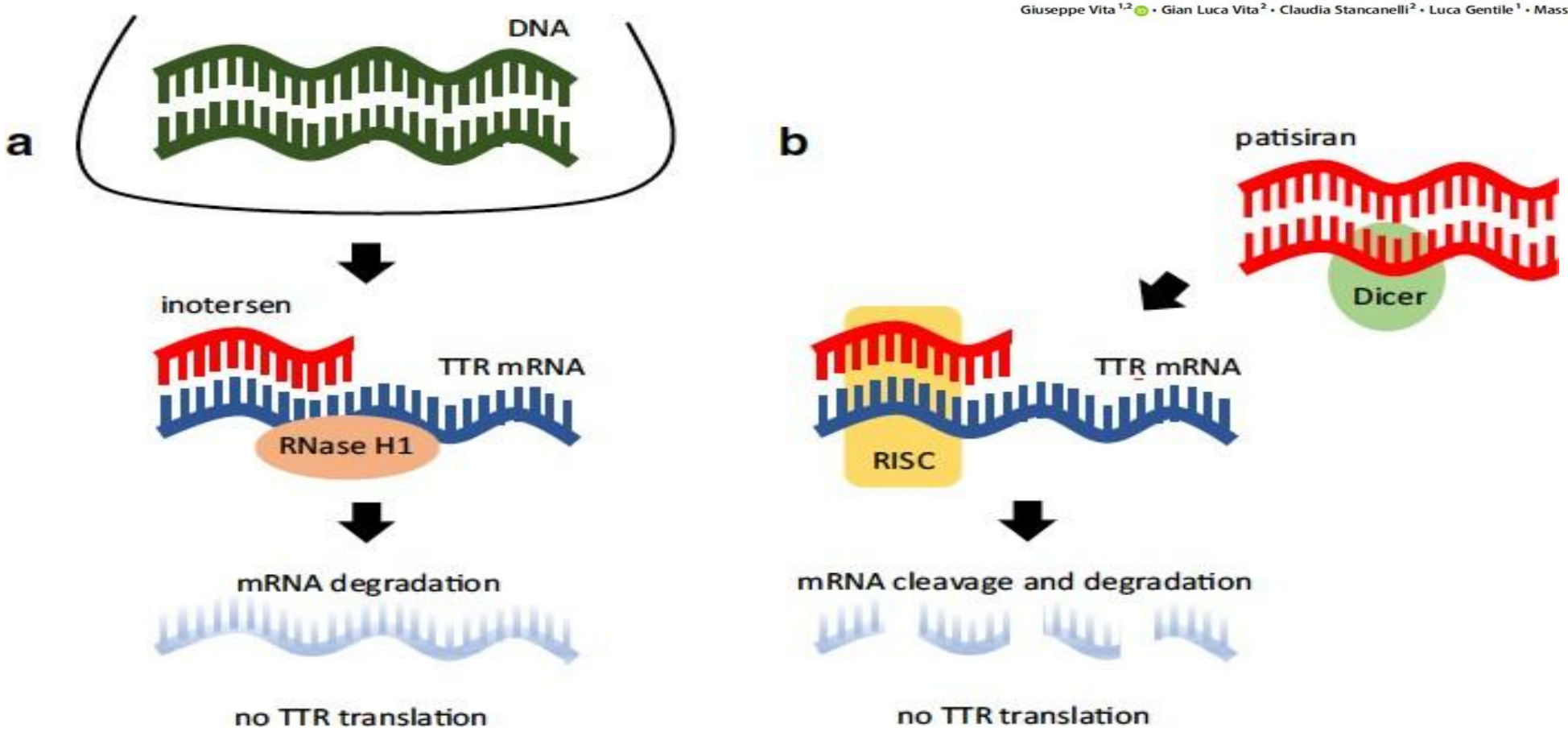
Neurological Sciences (2019) 40:661–669
https://doi.org/10.1007/s10072-019-03778-7

REVIEW ARTICLE

Check for updates

Genetic neuromuscular disorders: living the era of a therapeutic revolution. Part 1: peripheral neuropathies

Giuseppe Vita[1,2] · Gian Luca Vita[2] · Claudia Stancanelli[2] · Luca Gentile[1] · Massimo Russo[2] · Anna Mazzeo[1]

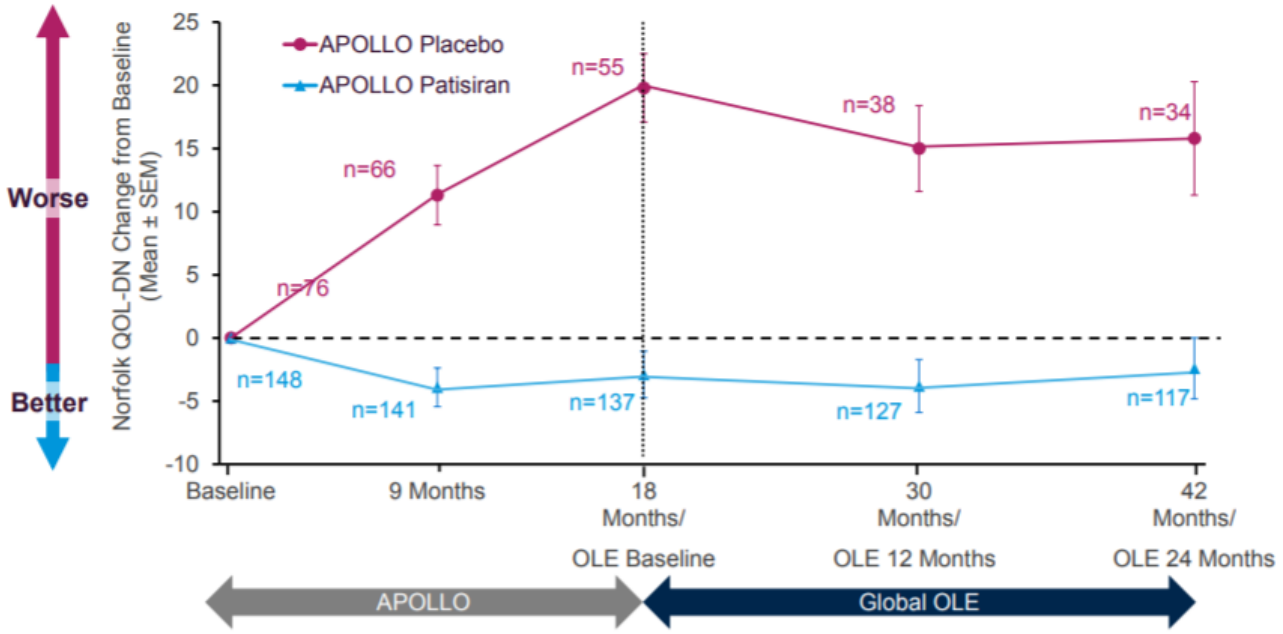


Mechanism of action of inotersen and patisiran. mRNA conveys genetic information from DNA to the ribosome, where the TTR amino acid sequence is translated. **Inotersen** acts binding to mRNA with complimentary base pairing and leading to an RNase H1-mediated degradation of TTR mRNA and no TTR synthesis (a). **Patisiran** is a double-stranded siRNA which selectively targets TTR mRNA and triggers the RNAi pathway. The double-stranded molecule is cut into small double-stranded fragments by an enzyme called Dicer. These small fragments integrate into a multisubunit protein called the RNAinduced silencing complex (RISC), leading to mRNA degradation and suppressing its translation (b)

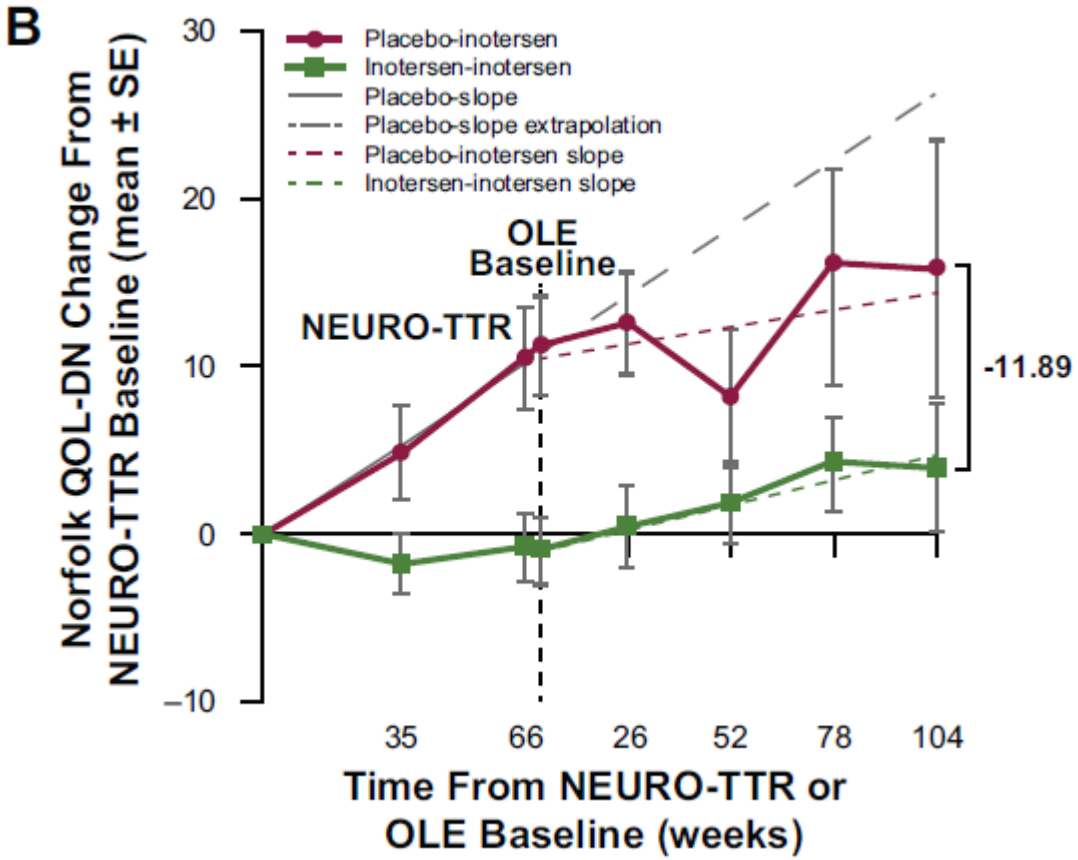
EAN 2020: Norfolk QOL-DN

PATISIRAN

Figure 6. Integrated Change in Norfolk QOL-DN from APOLLO and Global OLE[a]



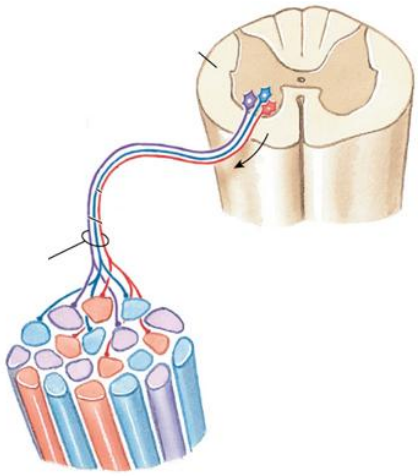
INOTERSEN

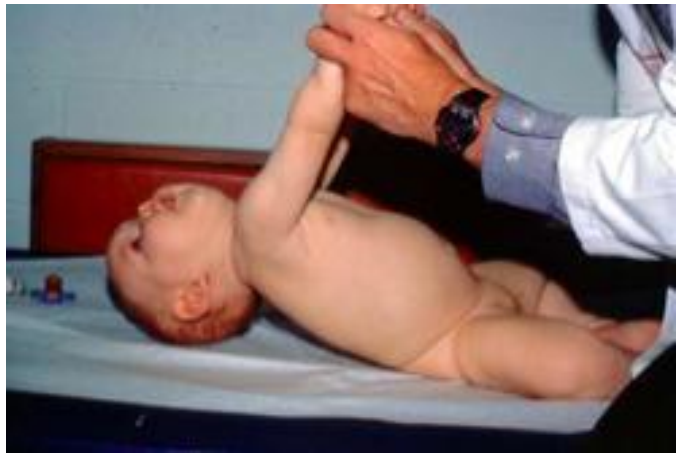


Spinal Muscular Atrophy (SMA)

Progressive neuromuscular disease
diagnosed in infancy
Autosomal recessive disorder

disease incidence is 1:6000 to 1:10000 live births,
the carrier status incidence is 1:40 to 1:60





Patients present muscular **weakness** and **atrophy** resulting from loss and degeneration of **motoneurons (MNs)** of spinal cord ventral horn and of brainstem nuclei.

It is the most common genetic cause of infant death.

Diverse forme di SMA:
Correlazione genotipo-fenotipo in funzione del numero di copie SMN2

SMN2 Copy Number and SMA Clinical Phenotype

SMN2 Copy Number	SMA Clinical Phenotype [1]		
	SMA I	SMA II [2]	SMA III/IV [3]
1	96%	4%	0%
2	79%	16%	5%
3	15%	54%	31%
>=4 [4]	1%	11%	88%

	TYPE 1	TYPE 2	TYPE 3
SMN2 Copy Number	Two	Three or Four	Three or Four
Onset	Before 6 Months	6-18 Months	Early childhood to early adulthood (juvenile)
Incidence per Live Birth	Approximately 60%	Approximately 27%	Approximately 13%
Developmental Milestones	• Will never be able to sit without support • Difficulty breathing & swallowing • Can't crawl/will never walk	• Will never be able to walk or stand without support	• Stand alone and walk but may lose ability to walk in 30s-40s
Survival	• <10% Event free* by two years of age	• 68% alive at age 25	

Modified from IONIS/AVEXIS

NEL DICEMBRE 2016 IL NUSINERSEN E' DIVENTATO IL PRIMO FARMACO APPROVATO DALLA FDA PER LA SMA

AGENZIA ITALIANA DEL FARMACO

DETERMINA 25 settembre 2017

Regime di rimborsabilita' e prezzo del medicinale per uso umano «Spinraza». (Determina n. 1611/2017). (17A06571)

(GU n.226 del 27-9-2017)

Indicazioni terapeutiche: «Spinraza» e' indicato per il trattamento dell'atrofia muscolare spinale 5q.

Ai fini delle prescrizioni a carico del Servizio sanitario nazionale, i centri utilizzatori specificatamente individuati dalle regioni, dovranno compilare la scheda raccolta dati informatizzata di arruolamento che indica i pazienti eleggibili e la scheda di follow-up, applicando le condizioni negoziali secondo le indicazioni

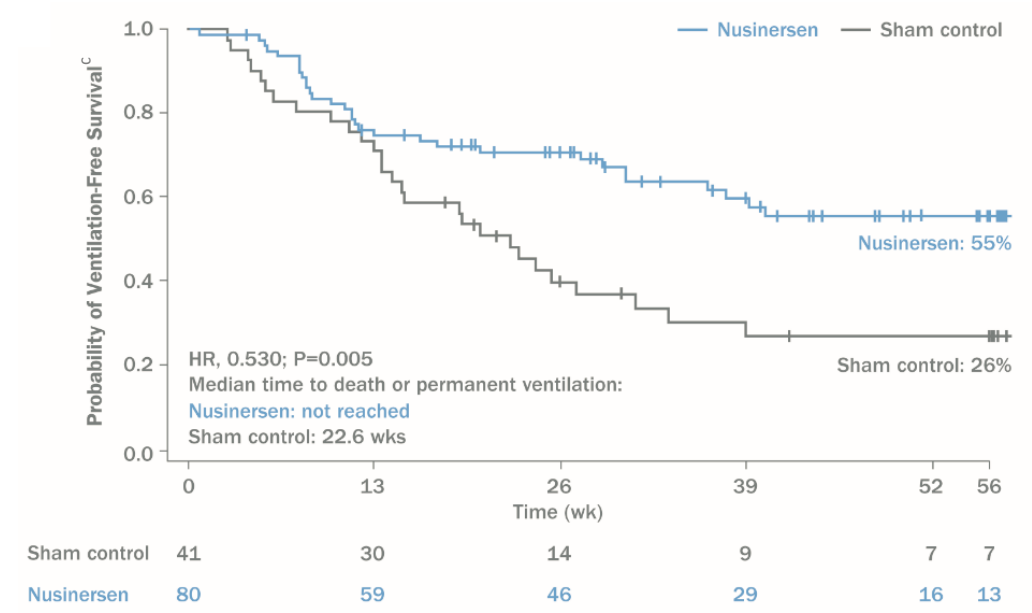
criteri di eleggibilita' e appropriatezza prescrittiva riportati nella documentazione consultabile sul portale istituzionale dell'Agenzia:
http://www.agenziafarmaco.gov.it/it/content/registri-farmaci-sottoposti-monitoraggio

La classificazione ai fini della fornitura del medicinale «Spinraza» e' la seguente: medicinali soggetti a prescrizione medica limitativa, utilizzabili esclusivamente in ambiente ospedaliero o in struttura ad esso assimilabile (OSP).

Tasso di sopravvivenza in assenza di eventi maggiori

- Significantly prolonged event-free survival[a] in nusinersen-treated infants (HR, 0.53; *P*=0.0046[b])

Outcome	Sham control	Nusinersen
Death or permanent ventilation, n (%)	28 (68)	31 (39)
Alive and no permanent ventilation, n (%)	13 (32)	49 (61)



HR = hazard ratio. All infants randomized who received ≥1 dose of nusinersen or sham control were included in the analysis. [a]Event-free survival = time to death or permanent ventilation (permanent ventilation was defined as tracheostomy or ≥16 hours ventilatory support per day for >21 days in the absence of acute reversible event in the determination of an independent endpoint adjudication committee). [b]Log-rank statistical test stratified by disease duration. [c]Estimated from the Kaplan-Meier method.

TERAPIA GENICA per le MALATTIE NEUROMUSCOLARI

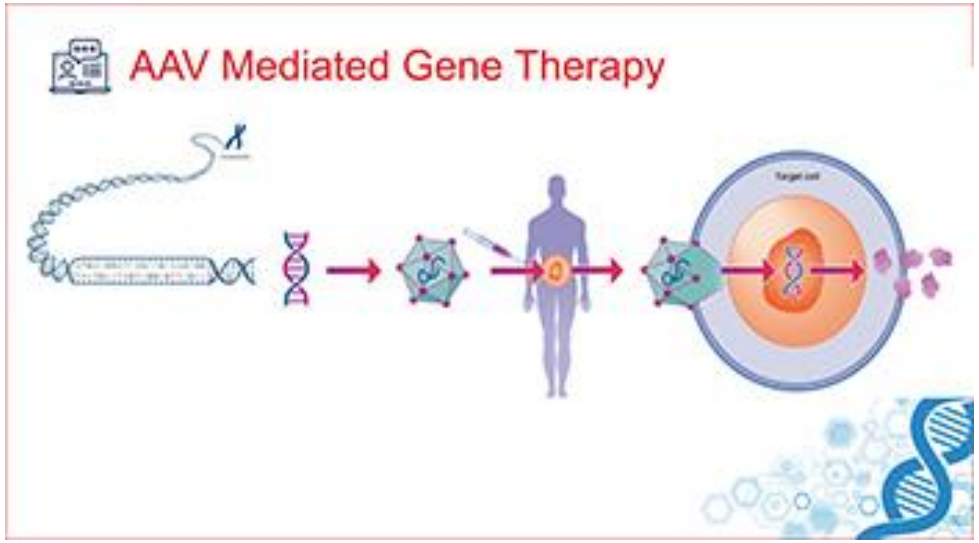
The use of viral vectors and, in particular, of **adenoassociated viral (AAV) vectors** with neural tropism overcomes the need of repeated direct injections with ASOs, enabling persistent and global gene transfer after one single administration. Viral vectors can be used to replace faulty genes in affected tissues or to reduce the expression of toxic proteins.

Several serotypes are investigated for efficient CNS delivery.
In particular, AAV serotype 9 (AAV9) and rh.10 (AAVrh.10), are largely used as preferred vectors for CNS delivery, due to their neuronal tropism and increased ability to cross the BBB

The ongoing effort in testing AAVmediated gene therapy for **SMA** is pivotal for the development and refinement of similar approaches for ALS patients.

Table 1 Viral vector properties and clinical implications on efficacy and safety

	Adeno-associated virus	Adenovirus	Simple retrovirus	Lentivirus	Herpes virus
Transgene carrying capacity	<5 kb	<8 kb	8 kb	9 kb	30–40 kb
Integration into host genome	No	No	Yes	Yes	No
Target cell population	Mitotic and quiescent cells	Mitotic and quiescent cells	Mitotic	Mitotic and quiescent cells	Mitotic and quiescent cells
Transgene expression duration	Long term (in quiescent cells)	Short term	Long term	Long term	Life-long
Immunogenicity	Moderate	High	Low	Low	High
Insertional oncogenesis risk	Low	Low	Very high	Moderate	Low
Oncolytic potential	No	Yes	No	No	Yes
Risk of human pathogenicity*	Negligible	Possible but low risk	High	High	Possible but low risk
Comments on clinical utility	Only vector to be approved and licenced for clinical use in neurological disease†	Reduced utility in patients due to significant immunotoxic effects	Reduced utility in patients due to significant oncogenetic potential	Ex vivo strategies used due to reduced penetrance of BBB in adults	Effective in malignant brain tumours secondary to oncolytic potential



MALATTIA DI POMPE: stessa malattia, diversi fenotipi

Ampio spettro di fenotipi clinici

Forma infantile classica
Forma infantile a fenotipo non classico
Forma giovanile-adulta (late onset)

MYOZYME: ALFA-GLUCOSIDASI ACIDA UMANA RICOMBINANTE

MECCANISMO D'AZIONE

INGRESSO & LEGAME

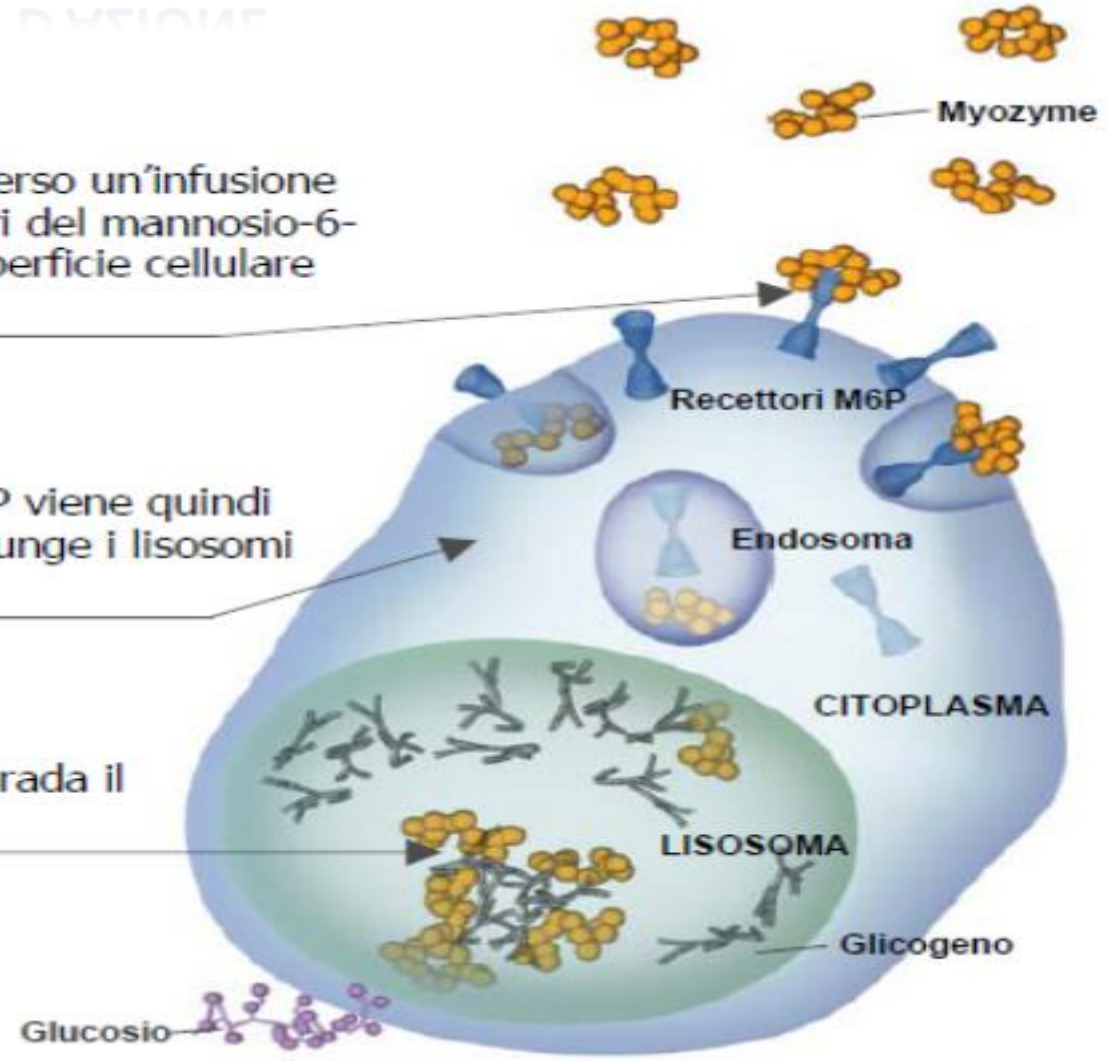
Myozyme entra nell'organismo attraverso un'infusione endovenosa, quindi si lega ai recettori del mannosio-6-fosfato (M6P) che si trovano sulla superficie cellulare formando un complesso.

INTERNALIZZAZIONE E *TRAFFICKING*

Il complesso Myozyme/Recettore M6P viene quindi internalizzato nella cellula dove raggiunge i lisosomi per endocitosi.

DEGRADAZIONE DEL GLICOGENO

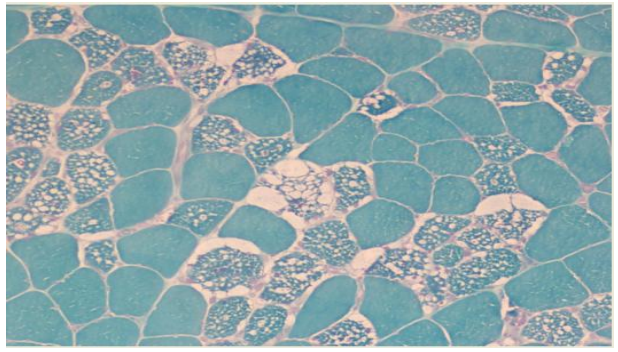
All'interno dei lisosomi, Myozyme degrada il glicogeno accumulato in glucosio.

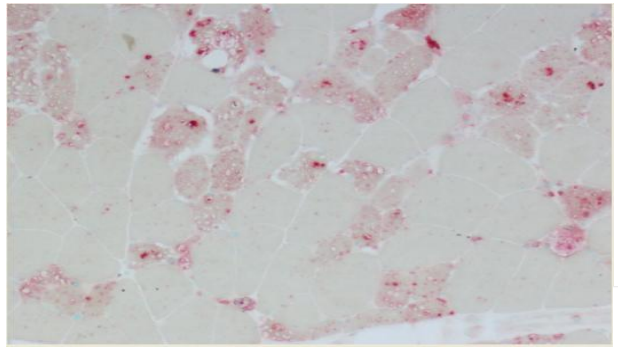


Reuser et al. Exp Cell Res. 1984;155(1):178-189.
van der Ploeg et al. Pediatr Res. 1988 ;24(1):90-94.
van der Ploeg et al. J Clin Invest. 1991;87(2):513-518.
Figura elaborata da Genzyme Srl.

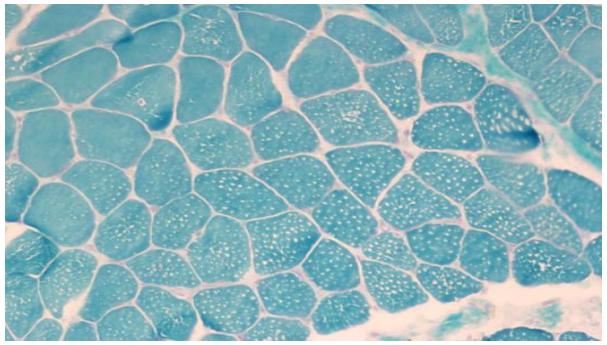
Case 1: A 44 year old man arrived to our attention with one-year history of low back pain and mild hyperCKemia (300 UI/L). In anamnesis, he referred only hearing loss. Neurological examination showed asymmetric winged scapula. DNA testing for FSHD was negative.

Before

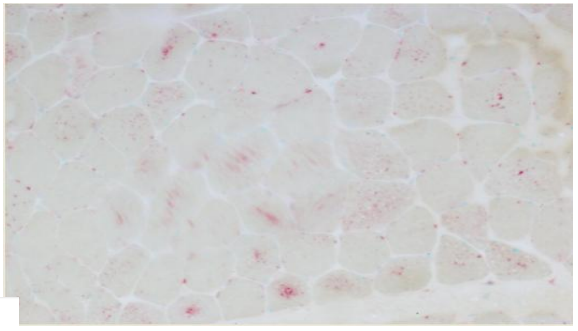




After



Tric (16x)



FA (16x)

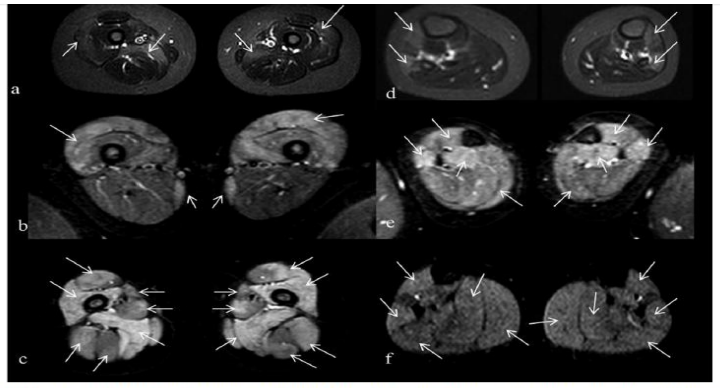


FIGURE 3. Axial STIR images in the thigh (**a–c**) and calf (**d–f**) in patients 6 (age 10 years; **a,d**), 4 (age 6 years; **b,e**), and 8 (age 6 years; **c,f**), show diffuse edema-like hyperintensities at the level of both thigh and calf muscles. Specifically: mild limited changes (mild hyperintensity in less than or equal to one-third of the muscles) are evident in patient 6 (**a,d**), with involvement of both vastus lateralis and adductor magnus muscles bilaterally in the thigh (**a**, arrows) and of the anterior compartment of the calf (**d**, arrows); mild extensive changes (mild hyperintensity in more than one-third of the muscles) are evident in the thigh of patient 4 (**b,e**), predominantly involving the anterior compartment, with the exception of the gracilis muscle in the posterior compartment (**b**, arrows) and more diffuse involvement of the calf with an anteroposterior gradient (**e**, arrows); marked changes (any muscle with marked hyperintensity) are evident in all muscles of the thigh of patient 8 (**c**, arrows) and of the calf of patient 1 (**f**, arrows).

Muscle MRI

UO Neurologia

INSTANT

INtegrated System in Tuscany
For
Approaching Neuromuscular Treatments

3. 671 , 550 (al 30-11-**2020**) abitanti
Fonte ISTAT)

NMD
Are Rare and Take Time to Diagnose

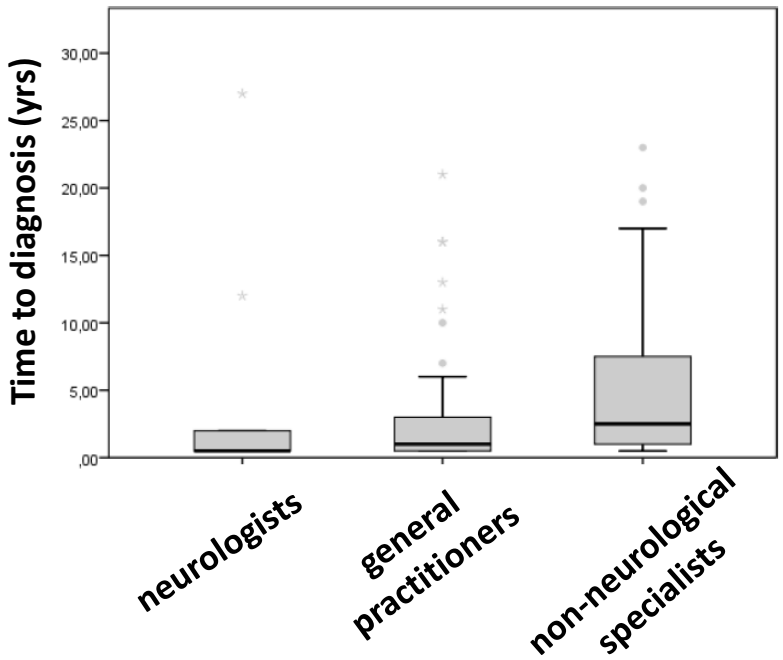
Spuler *et al. BMC Health Services Research* 2011, **11**:91
http://www.biomedcentral.com/1472-6963/11/91

BMC Health Services Research

RESEARCH ARTICLE Open Access

Delay in diagnosis of muscle disorders depends on the subspecialty of the initially consulted physician

Simone Spuler[1], Andrea Stroux[2], Franziska Kuschel[1], Adelheid Kuhlmey[3] and Friederike Kendel[4*]



Simone Spuler et al. BMC Health Services Research 2011

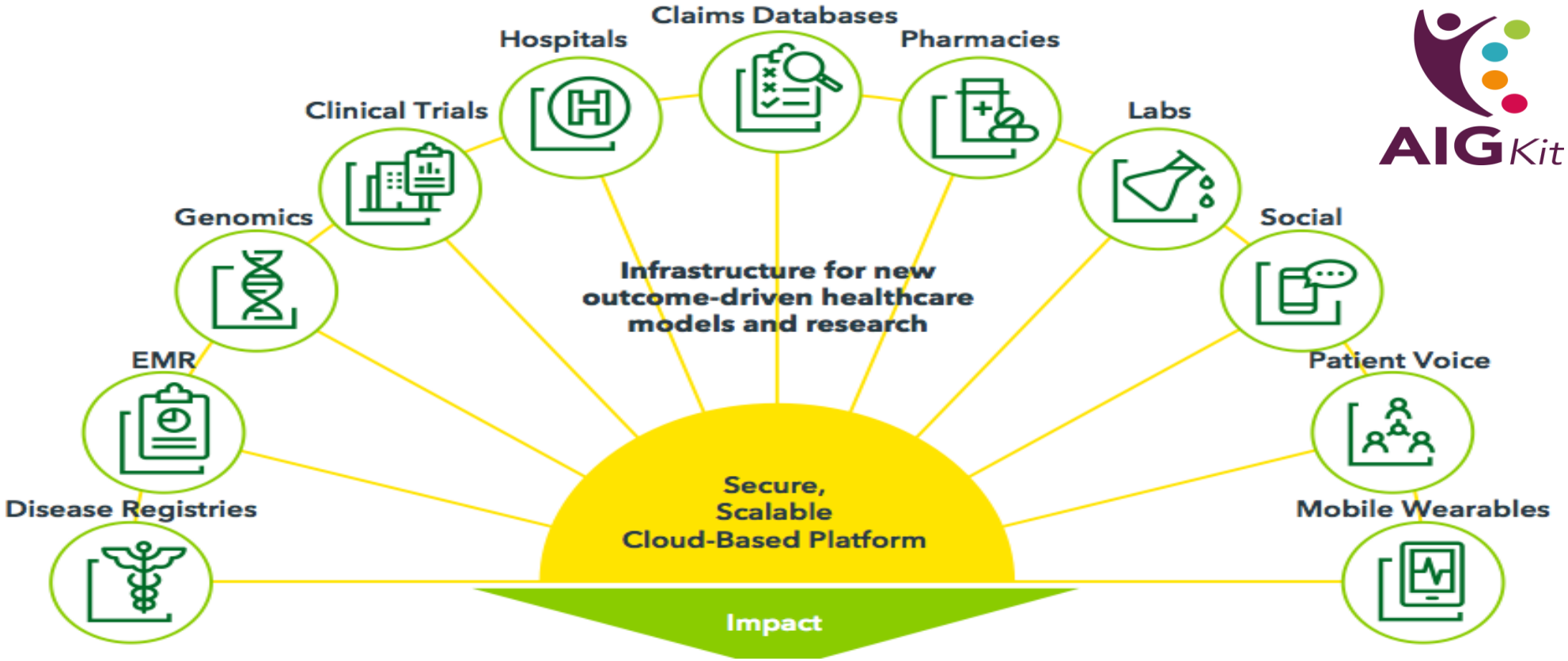
Expert Centers for NMD

Specific European Reference Network for NMD

=> A **wide network** of **healthcare centers** that works to **speed up diagnosis** and **research in NMDs** and **improve the standards of care** for these pathologies

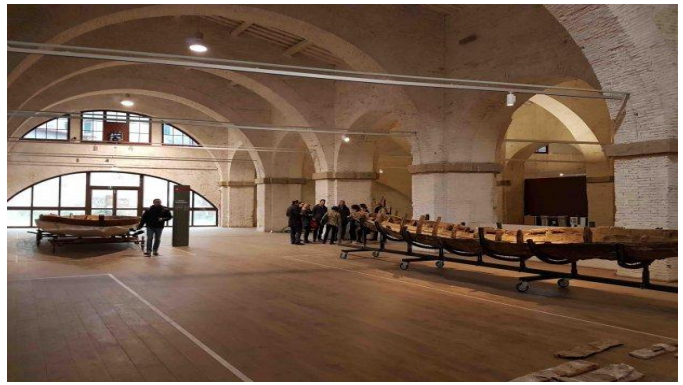
Data Hubs as a Means to Accelerate Advancements in Neuromuscular Disease Care

Progetto AIGKit:
sviluppo di un'applicazione per smartphone
per i pazienti affetti da malattia di Pompe



data hub is a collection of *data* from multiple sources organized for distribution, sharing, and often subsetting and sharing. Generally this *data* distribution is in the form of a *hub* and spoke architecture.

eNMD 2020



E-Health & Innovation
to overcome barriers in Neuromuscular Diseases

DATE: 20-21 March 2020 in Pisa, Italy

Monastero delle Benedettine and Museum of Roman Navy

Topics:

DIGITAL OUTCOMES MEASURES
BIOSENSORS and CONNECTING DEVICES
ROBOTICS
DIGITAL NEUROMUSCLE IMAGING
TELEMEDICINE and mobile-HEALTH
MOLECULAR BIOTECHNOLOGY AND DRUG DEVELOPMENT

Organising Committee: **Gabriele Siciliano (IT), Sabrina Sacconi (FR), John Vissing (DK)**
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