XII CONGRESSO NAZIONALE FIMP 2018

fimp Federazione Italiana Medici Pediatri

AIM GROUP INTERNATIONAL

Diagnosi precoce e clinica delle malattie neuromuscolari: implicazioni per la Distrofia Muscolare di Duchenne

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Distrofia Muscolare di Duchenne (DMD)

- Distrofia muscolare più comune in età pediatrica
- Circa 1 ogni 5.000 nati maschi
- Malattia X-linked
- Assenza di distrofina a livello muscolare
- Esordio di debolezza muscolare in età infantile
- Possibile ritardo di sviluppo globale, difficoltà di linguaggio, disturbi comportamentali
- In assenza di trattamento, perdita della deambulazione entro i 13 anni di età e decesso entro inizio della 3^ decade di vita per insufficienza cardiaca o respiratoria

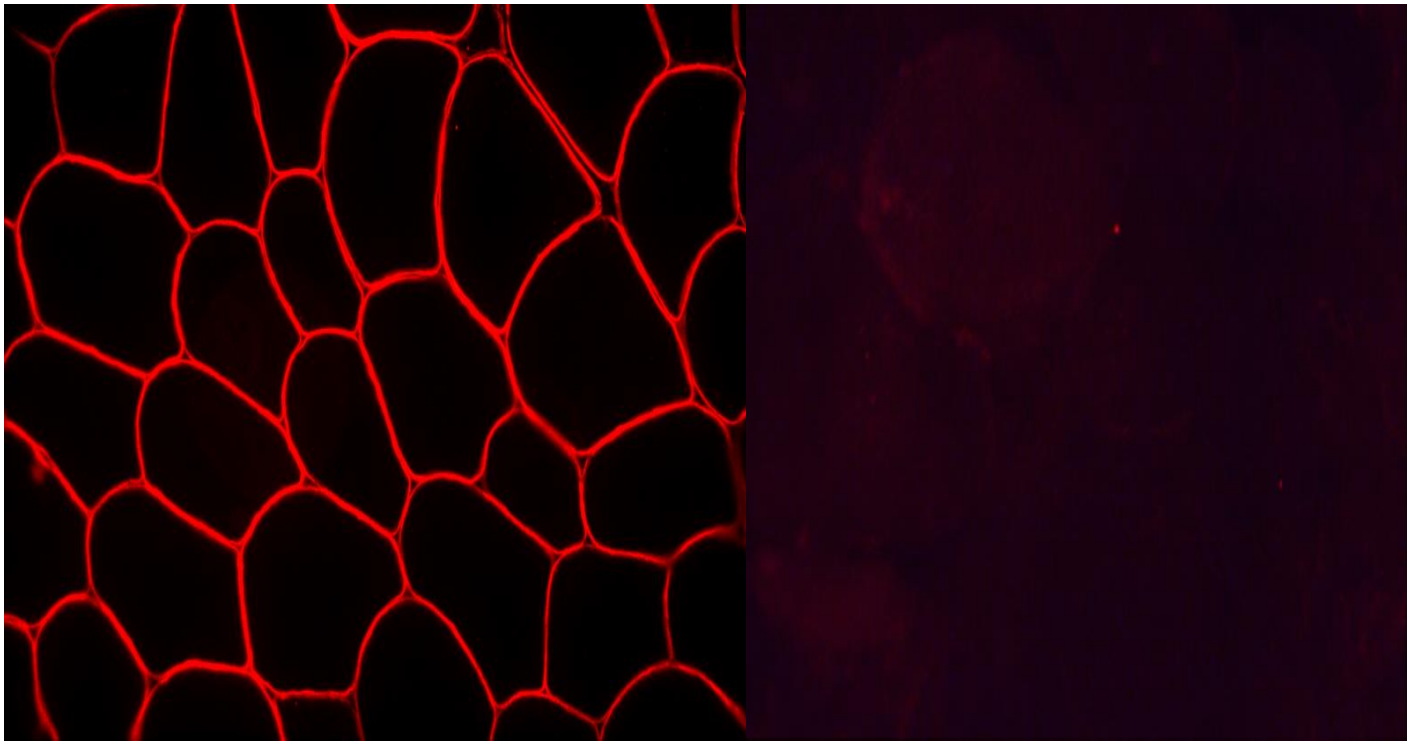
[1] Mendell J et al. Ann Neurol 2012;

[2] Pane M et al. J Pediatr. 2012; [3] Chieffo D PLoS One. 2015; [4] Hinton VJ et al. Dev Med Child Neurol. 2007.

Dystrophin: The protein product of the duchenne muscular dystrophy locus
Eric P. Hoffman,Robert H. Brown Jr., Louis M. Kunkel 51:919–928,1987

Duchenne muscular dystrophy: Deficiency of dystrophin at the muscle cell surface Eduardo Bonilla, Craig E. Samitt, Armand F. Miranda, Arthur P. Hays, Giovanni Salviati, Salvatore DiMauro, Louis M. Kunkel, Eric P. Hoffman Lewis P. Rowland 54: 447-452, 1988

Distrofia Muscolare di Duchenne



Presentazione clinica

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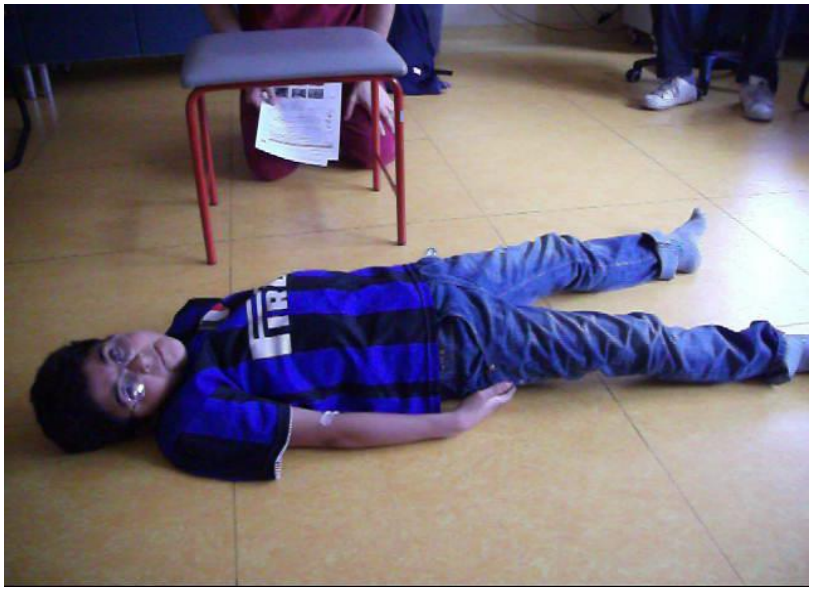
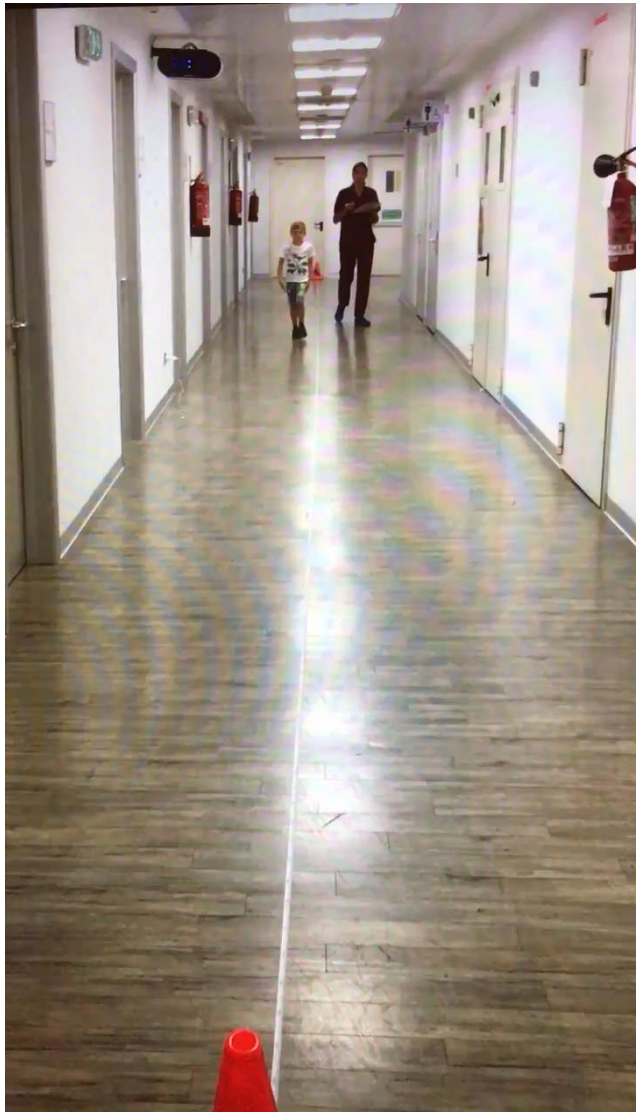


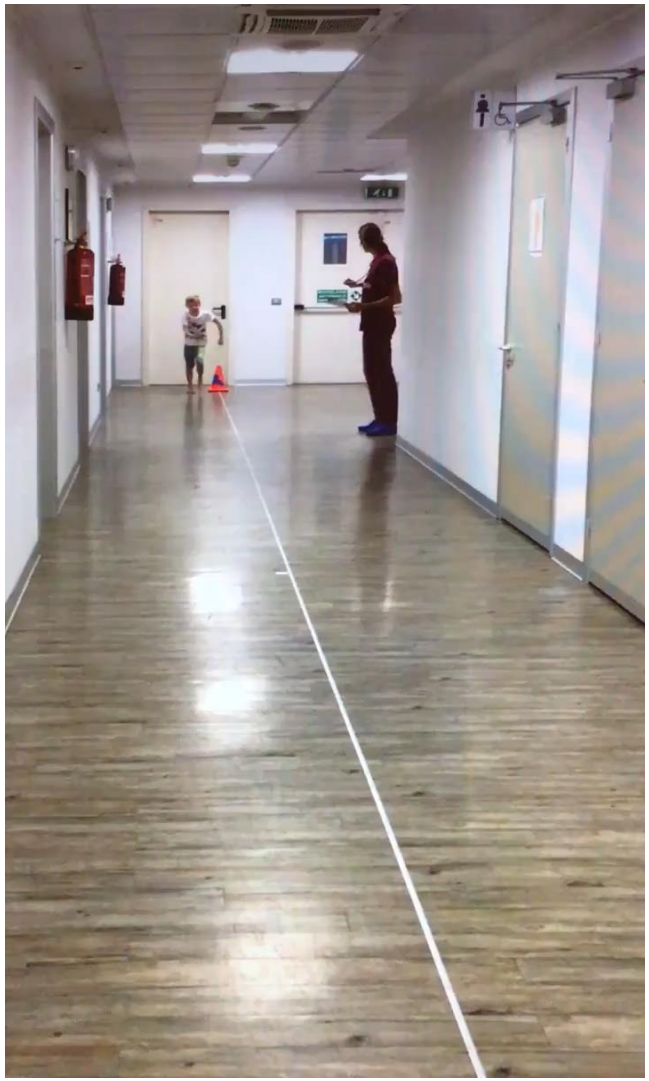
Presentazione clinica

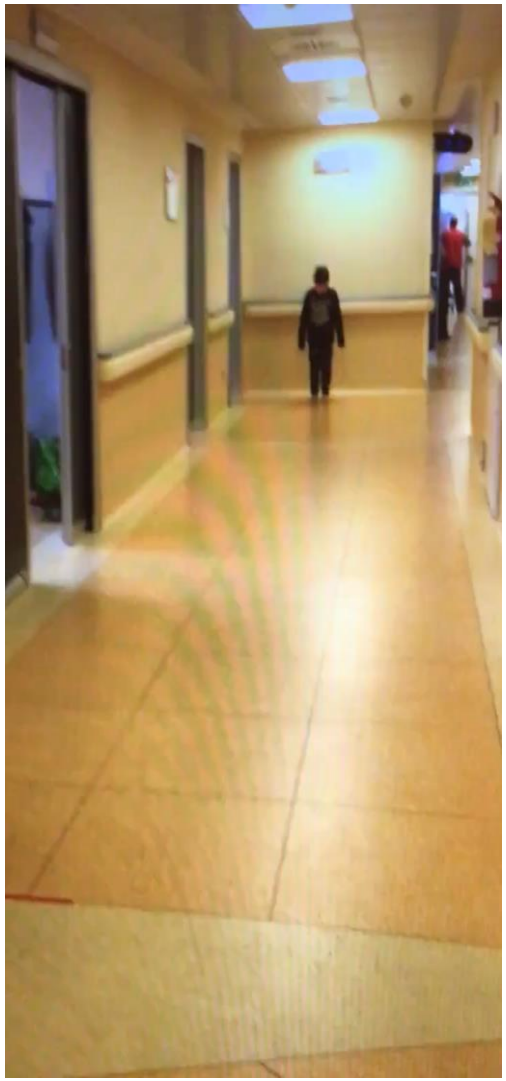
Quadro clinico precoce - cammino

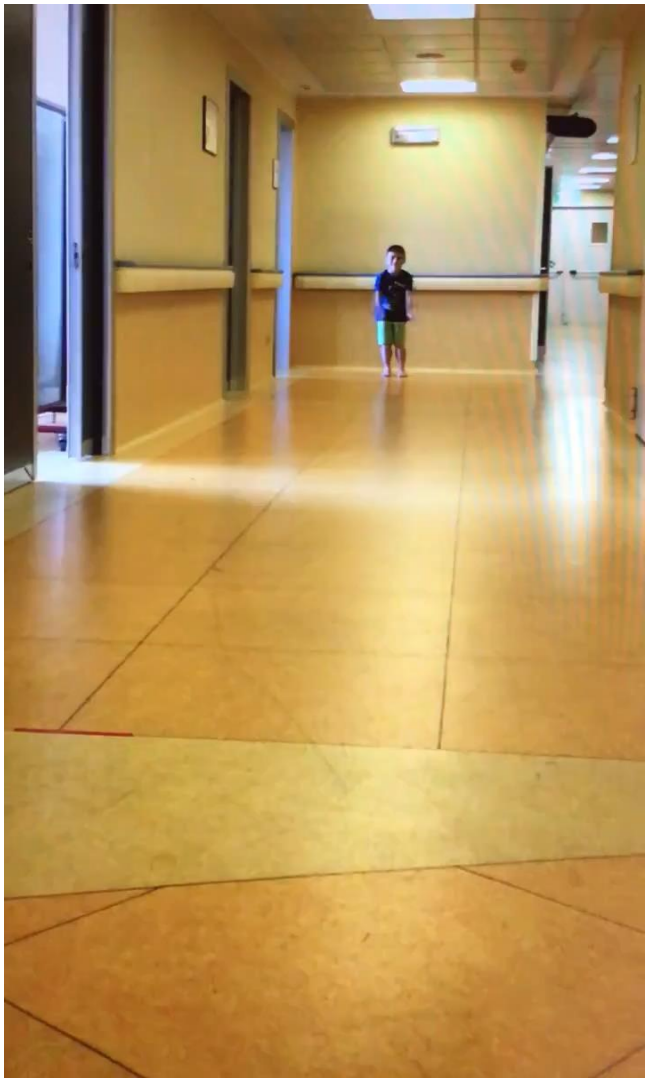


Quadro clinico precoce - cammino

Quadro clinico precoce – corsa

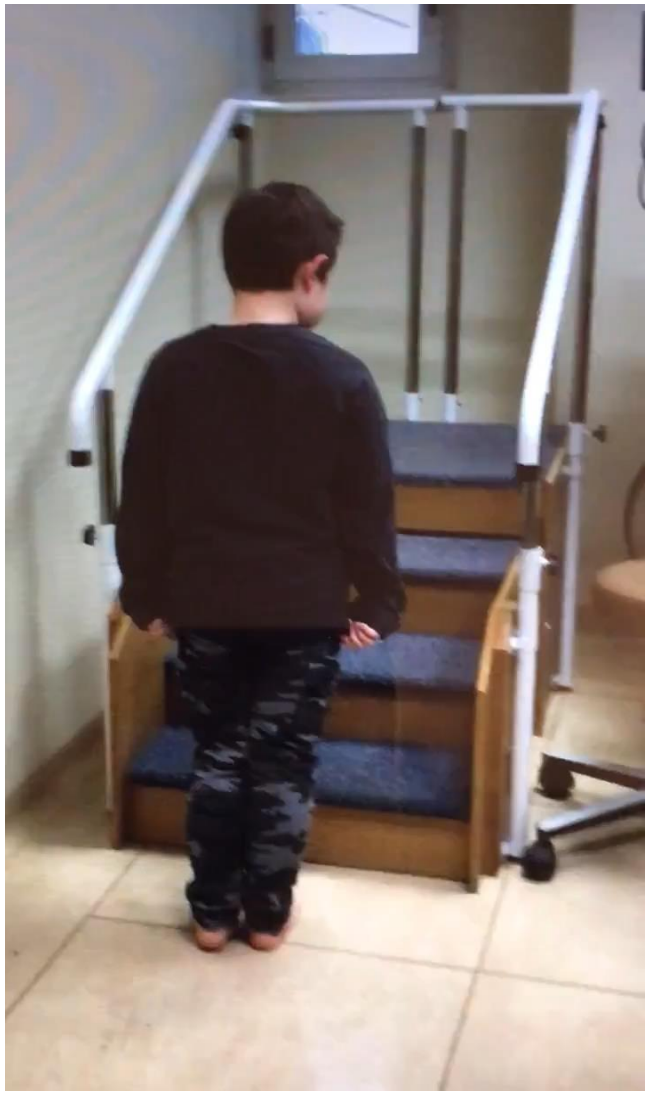




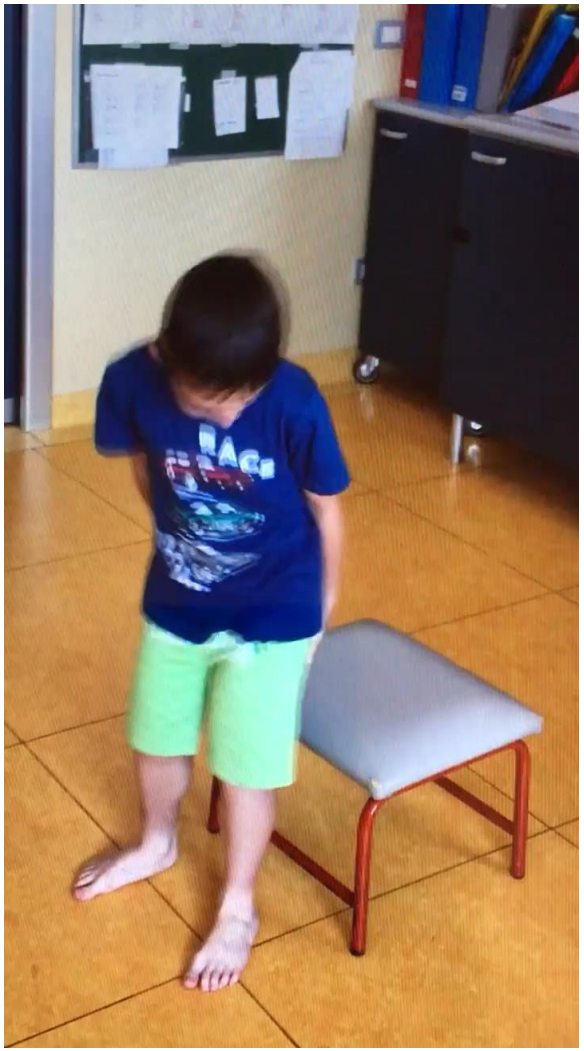


Quadro clinico precoce – Gowers

Quadro clinico precoce – salire le scale



Quadro clinico precoce – alzarsi da una sedia



Quadro clinico precoce - salto

Diagnosi DMD in Italia

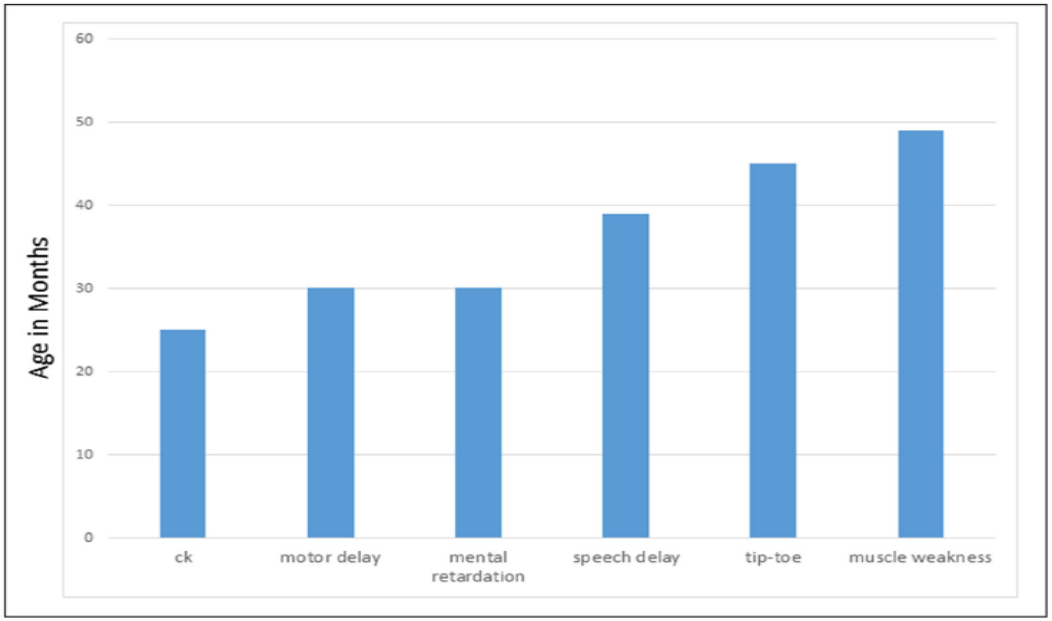
Studio multicentrico retrospettivo

384 ragazzi italiani con diagnosi di DMD dal 2005 al 2014

Età media al primo sospetto: **31 mesi**
Età media alla diagnosi: **41 mesi**

Principali reperti che hanno portato al sospetto di DMD:

- riscontro di iperCKemia (44%)
- ritardo motorio (16%)
- debolezza muscolare (14%)
- aumento transaminasi (9%)
- familiarità (8%)
- cammino sulle punte (5%)
- disabilità intellettiva (2.6 %)
- ritardo nel linguaggio (1%)
- altri sintomi (0.4%)



Neuromuscular Disorders 27 (2017) 447–451

Diagnosi di Distrofia Muscolare di Duchenne in Italia nell'ultima decade: problemi critici

Sospetto iniziale da parte di:

- Specialista di ospedale di I livello (38%)
- Pediatra di base (30%)
- Specialista di centro di III livello (22%)
- Altro (20%)

Diagnosis of Duchenne Muscular Dystrophy in Italy in the last decade: Critical issues and areas for improvements

Adele D'Amico [a,*], Michela Catteruccia [a], Giovanni Baranello [b], Luisa Politano [c], Alessandra Govoni [d], Stefano Carlo Previtali [e], Marika Pane [f], Maria Grazia D'Angelo [g], Claudio Bruno [h], Sonia Messina [i], Federica Ricci [j], Elena Pegoraro [k], Antonella Pini [l], Angela Berardinelli [m], Ksenjia Gorni [n], Roberta Battini [o], Gianluca Vita [i], Federica Trucco [h], Marianna Scutifero [c], Roberta Petillo [c], Paola D'Ambrosio [c], Anna Ardissone [b], Barbara Pasanisi [b], Giuseppe Vita [i], Tiziana Mongini [j], Maurizio Moggio [d], Giacomo Pietro Comi [d], Eugenio Mercuri [f], Enrico Bertini [a]

Ritardo diagnostico

Data analysis of ages at suspicion and diagnosis and the interval between presenting symptoms and diagnosis in the different groups of patients.

Regions of origin	Age at first suspect	Age at diagnosis	Time for diagnosis
Northern n = 134	30 mo (0.2–84)	42 mo (1.1–101)	12 mo
Central n = 115	32 mo (2–86)	39 mo (2–102)	7 mo
Southern n = 135	36 mo (0.2–92)	45 mo (0.3–135)	9 mo
Presenting sign or symptom			
Whole cohort	31 mo (0.2–95 mo)	41 mo (0.3–135 mo)	10 mo
High CK/transaminases	25 mo (0–60 mo)	28.7 mo (1–81 mo)	3.7 mo
Motor delay	30 mo (10–84 mo)	48 mo (11–107 mo)	18 mo
Intellectual disability	30 mo (12–72 mo)	52 mo (13–102 mo)	22 mo
Muscle weakness	45 mo (18–92 mo)	62 mo (25–103 mo)	17 mo
Tip-toe walking	49 mo (12–95 mo)	70 mo (26–135 mo)	21 mo
Family history	27 mo (0–52 mo)	33 mo (1–69 mo)	6 mo

Diagnosi di Distrofia Muscolare di Duchenne in Italia nell'ultima decade: problemi critici

Esami effettuati prima della diagnosi:

- Valori di creatin-kinasi (CK) in tutti i pazienti
- EMG in 34 pazienti (9%)
- Ecografia muscolare in 5 pazienti (1.3%)
- Ecografia epatica e sierologia per epatite dopo riscontro di ipertransaminasemia in 17 su 36 pazienti (9.3%) e biopsia epatica in 2 casi
- Valutazione fisiatrica e ortopedica in 10 su 61 pazienti (2.6%) con ritardo motorio come unico sintomo di esordio
- RMN encefalo e EEG in 4 su 10 pazienti con disabilità intellettiva

Genotype and phenotype characterization in a large dystrophinopathic cohort with extended follow-up

Francesca Magri · Alessandra Govoni · Maria Grazia D'Angelo · Roberto Del Bo · Serena Ghezzi · Gandossini Sandra · Anna Carla Turconi · Monica Sciacco · Patrizia Ciscato · Andreina Bordoni · Silvana Tedeschi · Francesco Fortunato · Valeria Lucchini · Sara Bonato · Costanza Lamperti · Domenico Coviello · Yvan Torrente · Stefania Corti · Maurizio Moggio · Nereo Bresolin · Giacomo Pietro Comi

J Neurol (2011) 258:1610–1623

- 320 pazienti (286 famiglie)
- 205 DMD (184 famiglie)
- 115 BMD (102 famiglie)

Criteri di inclusione

- Fenotipo clinico suggestivo di distrofinopatia
- Pattern distrofico alla biopsia muscolare

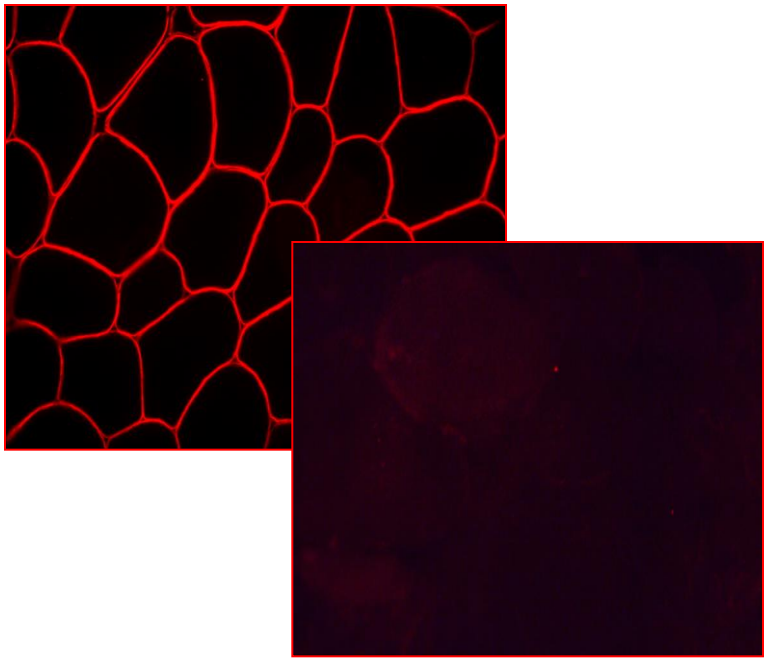
e

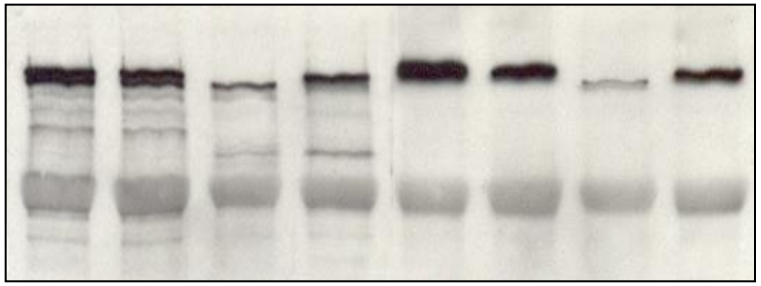
- Assenza o diminuzione di distrofina all'analisi immunoistochimica

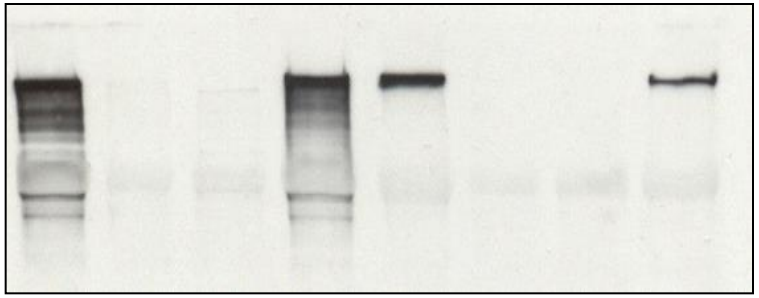
e/o

- Assenza o diminuzione di distrofina al Western Blot

Esami diagnostici

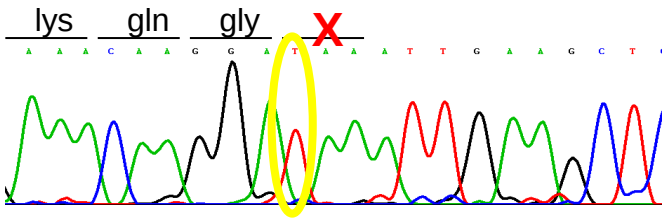


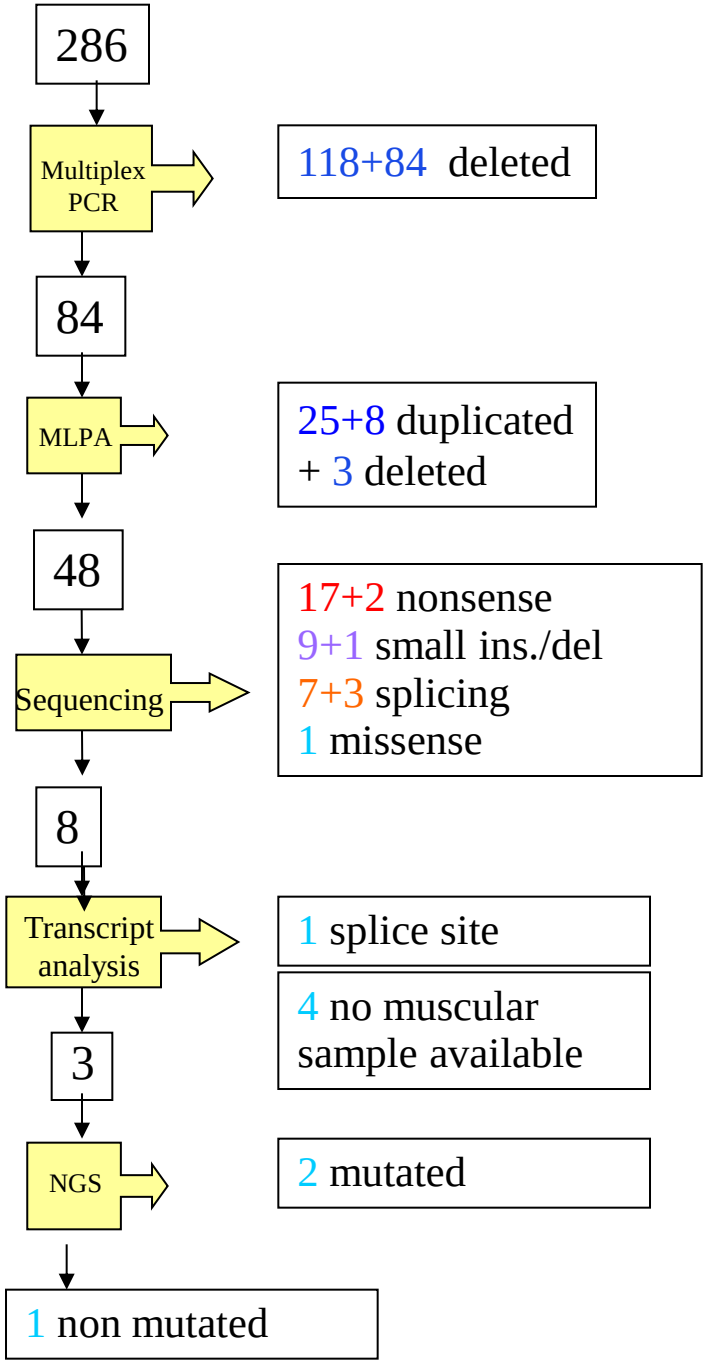




- Biopsia muscolare
- Immunoistochimica
- Western Blot
- Multiplex – PCR

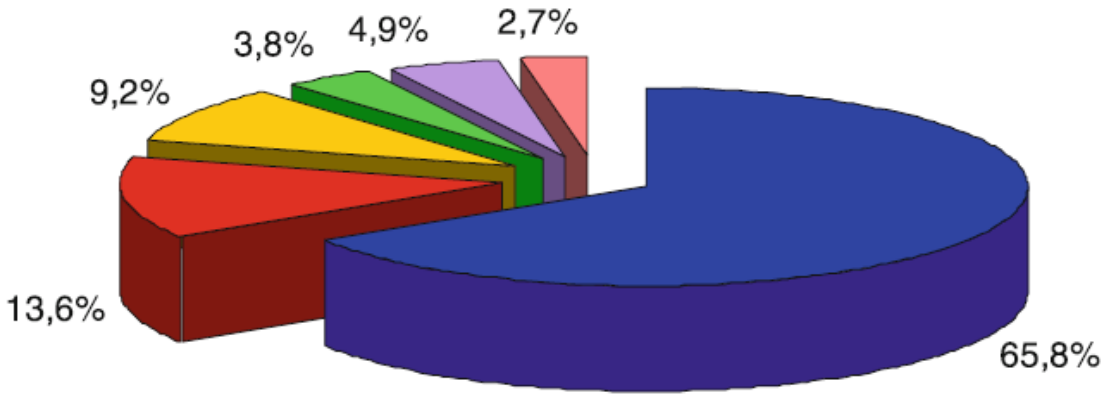
  (Sensibilità per delezioni: 97.5%)
- MLPA
- Sanger Sequencing
- Analisi del trascritto
- Targeted NGS



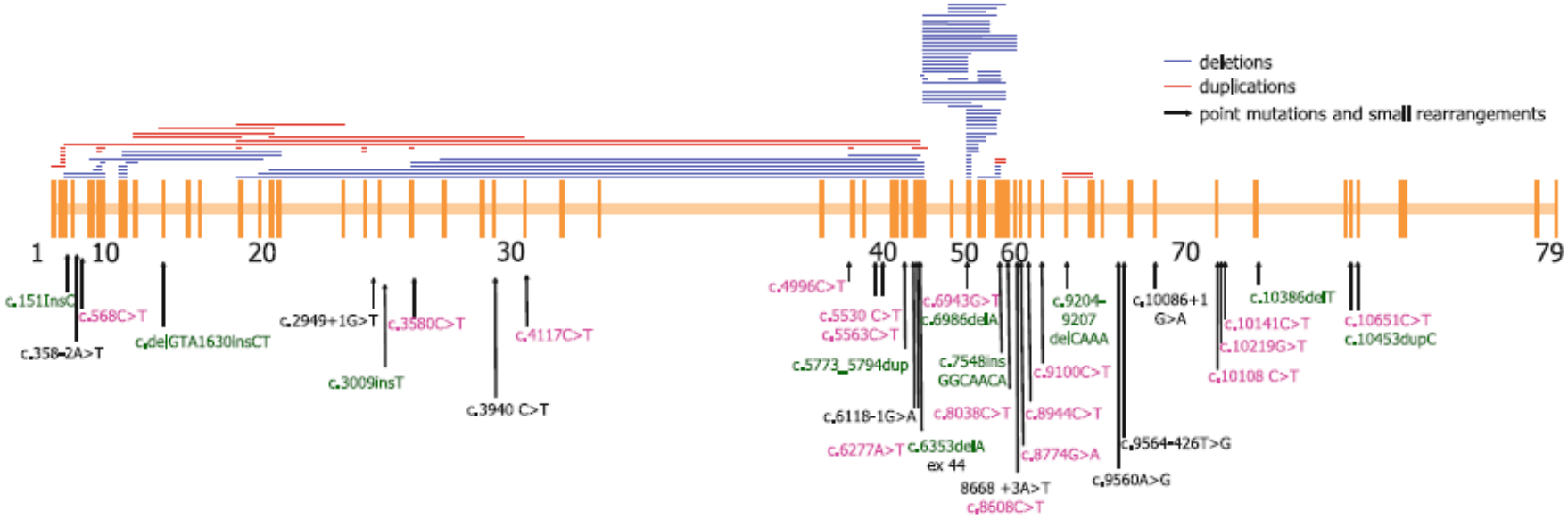


Tasso complessivo di identificazione delle mutazioni: **99.6%**

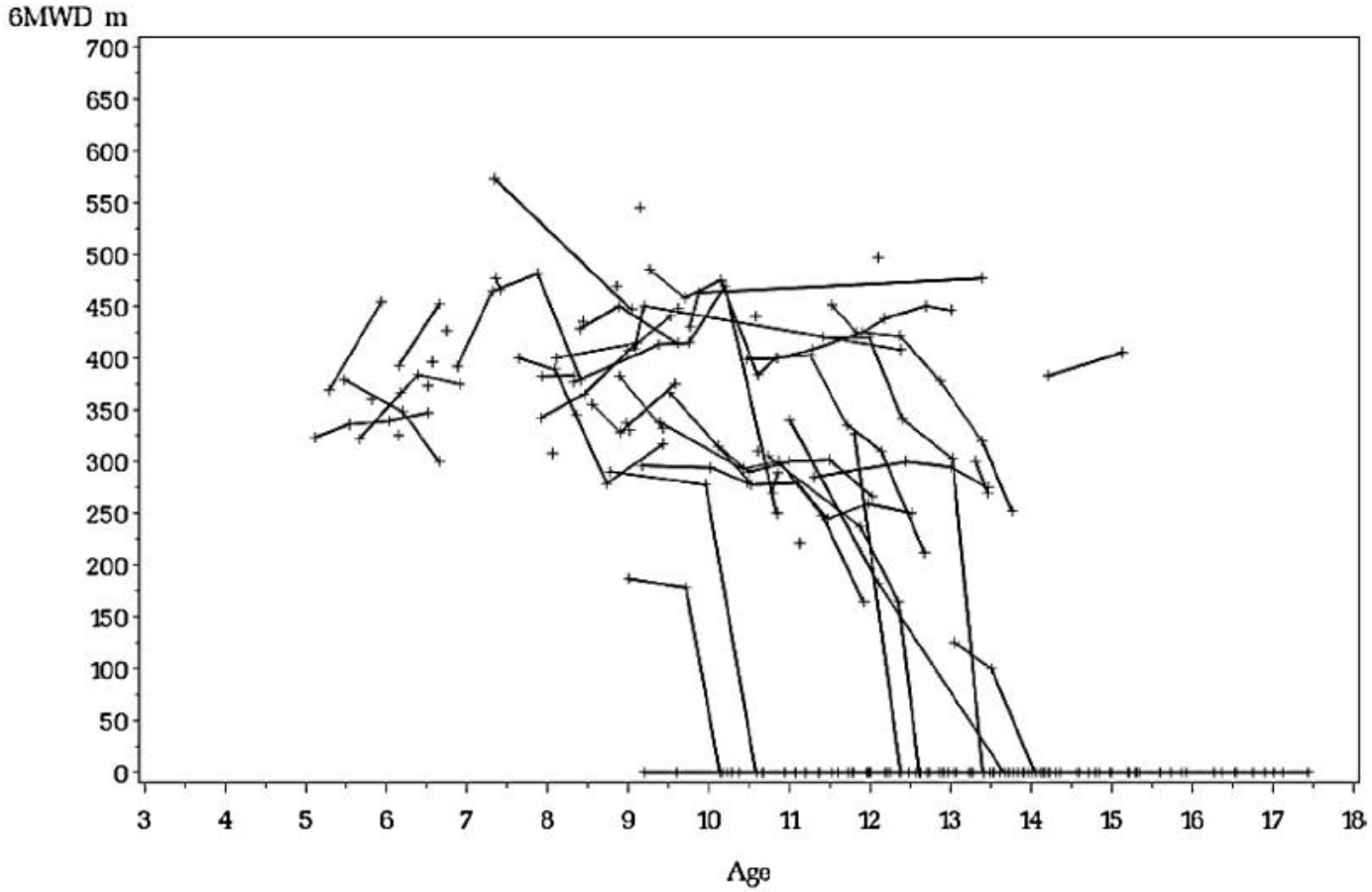
Mutazioni in DMD



Deletion
Spice-Site
Duplication
Del/Ins
Nonsense
Un-mutated

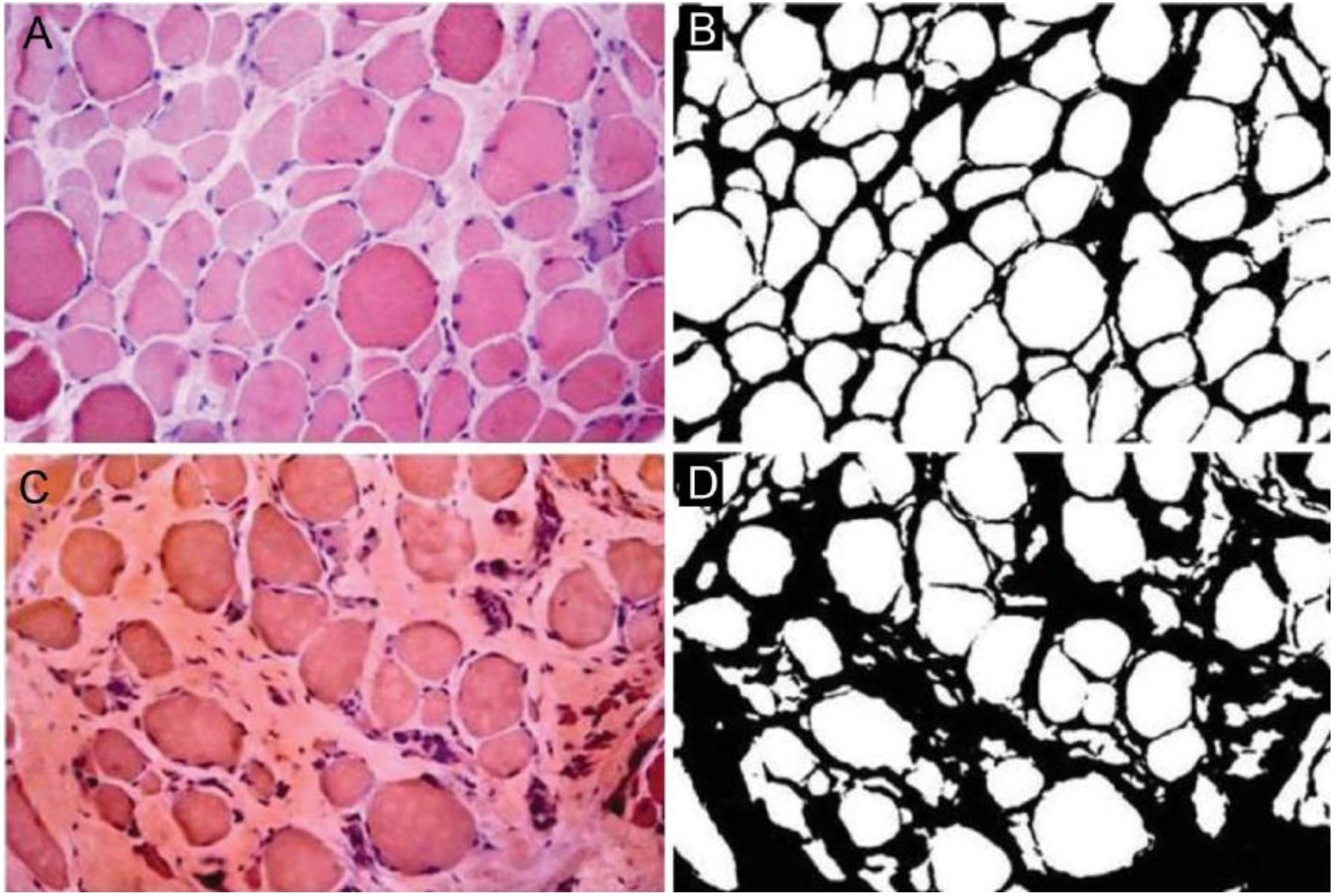


Storia naturale

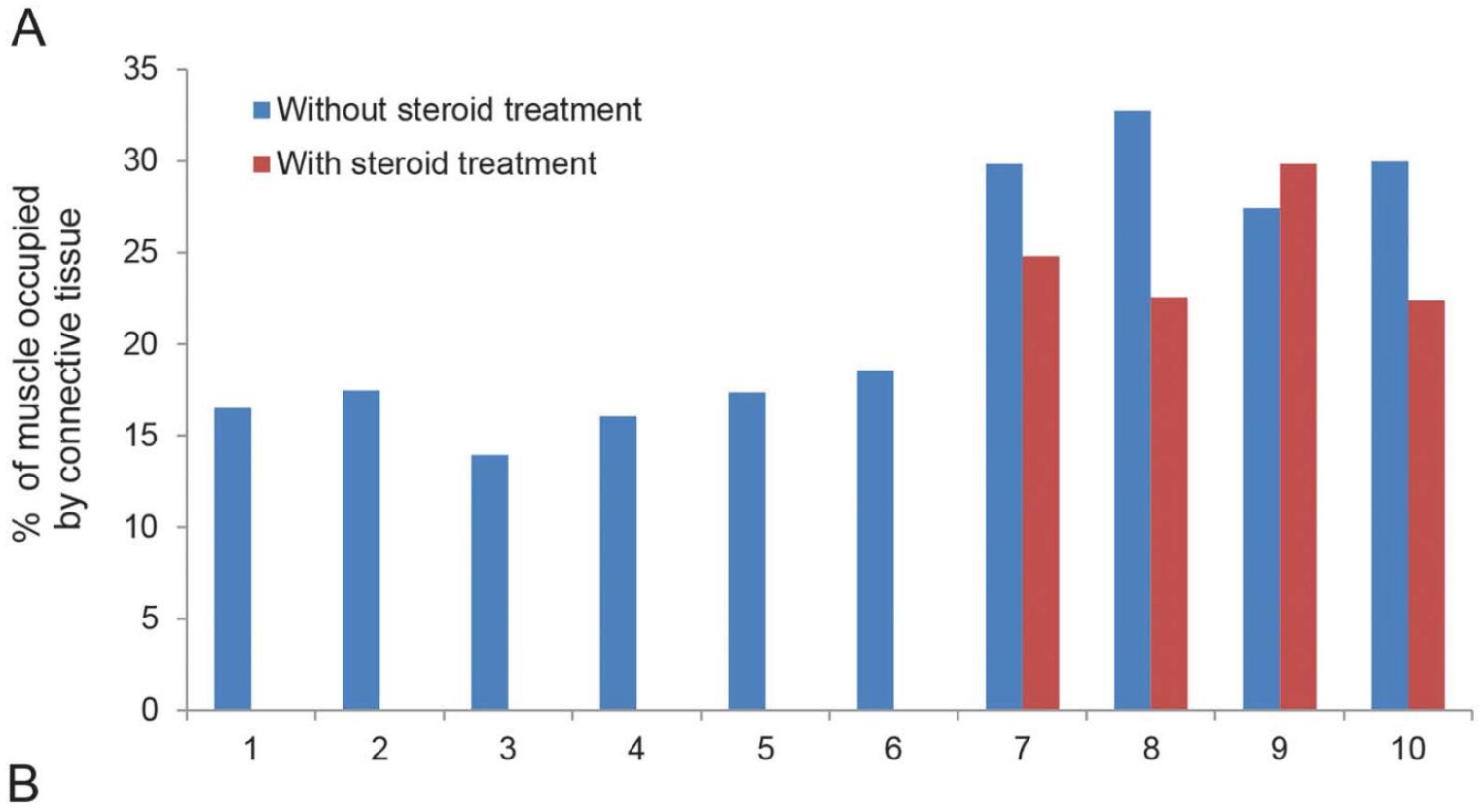


Deambulazione e progressione di malattia valutata tramite 6-minute-walk-distance (6MWT/6MWD) in pazienti con **Distrofia Muscolare di Duchenne** in trattamento corticosteroideo giornaliero

Goemans et al. Neuromuscular Disorders 2013

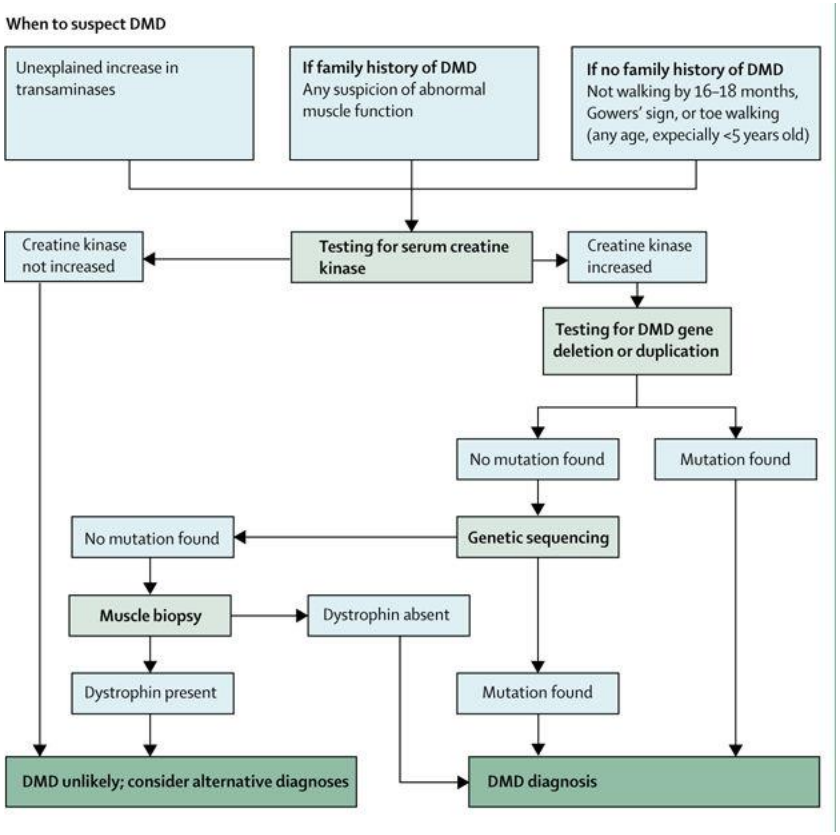

A
B
C
D

Storia naturale



Peverelli et al. Histologic muscular history in steroid-treated and untreated patients with Duchenne dystrophy. Neurology. 2015; 85:1886-93

Standard of care - diagnosi



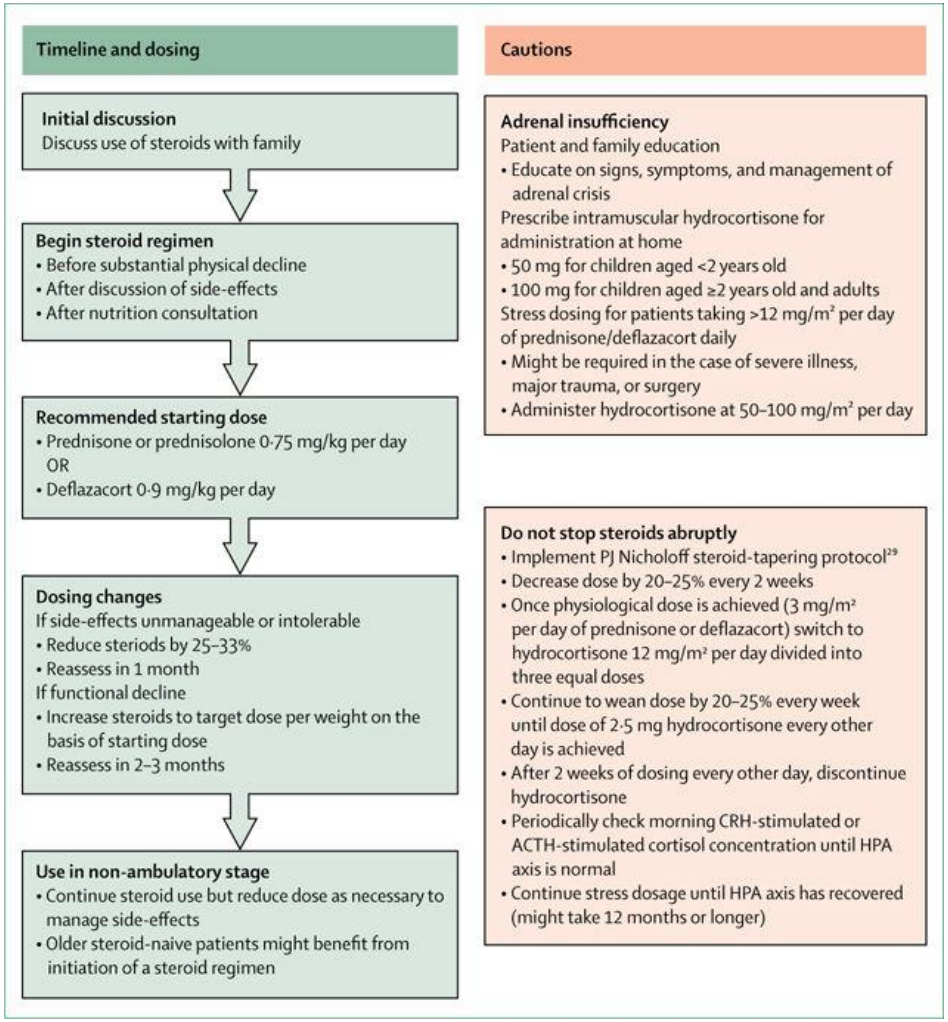
Most commonly observed early signs and symptoms in patients with DMD

Motor
- Abnormal gait
- Calf pseudohypertrophy
- Inability to jump
- Decreased endurance
- Decreased head control when pulled to sit
- Difficulty climbing stairs
- Flat feet
- Frequent falling or clumsiness
- Gowers' sign on rising from floor
- Gross motor delay
- Hypotonia
- Inability to keep up with peers
- Loss of motor skills
- Muscle pain or cramping
- Toe walking
- Difficulty running or climbing

Non-motor
- Behavioural issues
- Cognitive delay
- Failure to thrive or poor weight gain
- Learning and attentional issues
- Speech delay or articulation difficulties

Birnkrant DJ et al. *Diagnosis and management of Duchenne muscular dystrophy.* Lancet Neurol. 2018 May;17(5)

Standard of care – trattamento

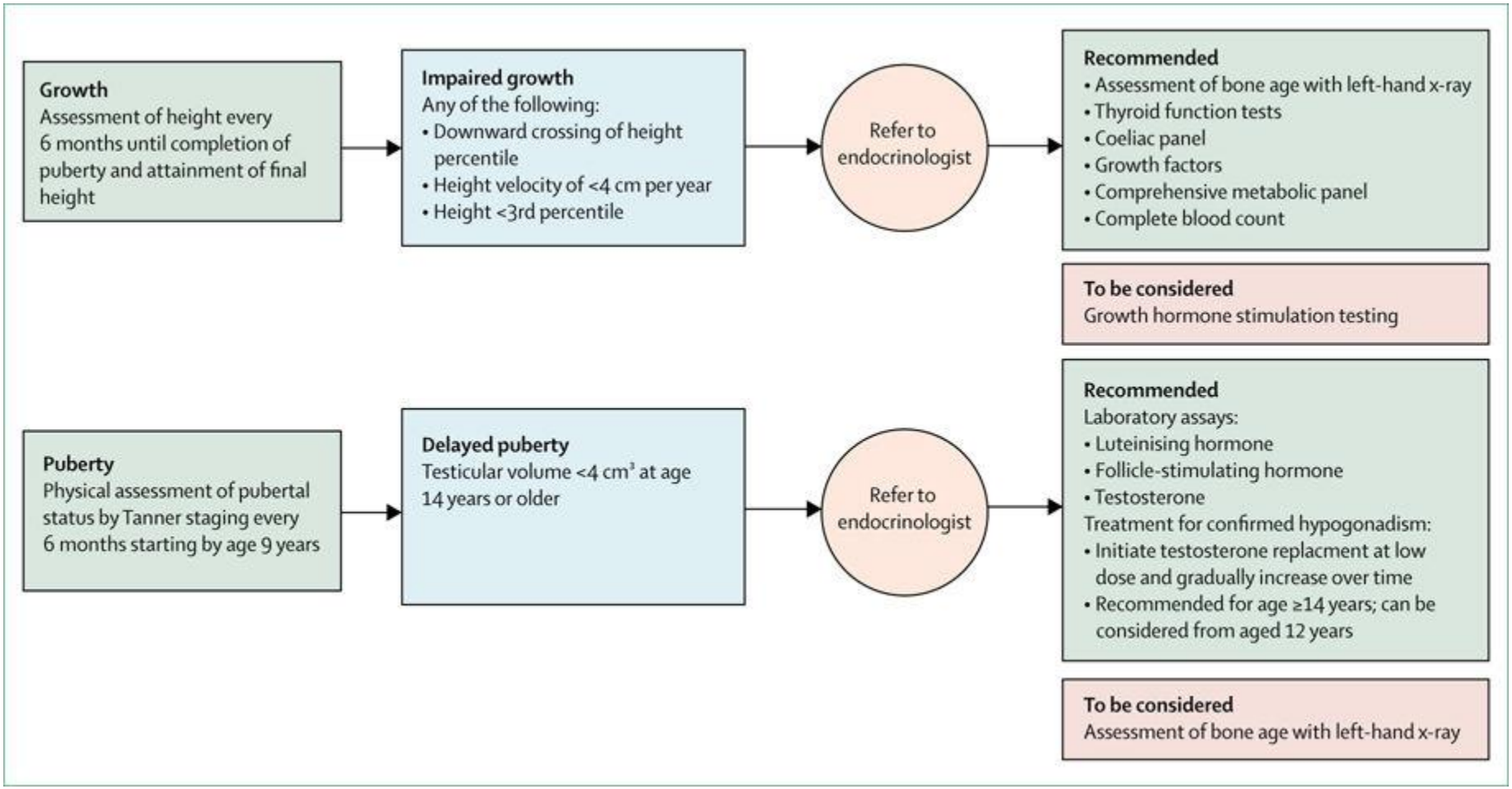


Prednisone 0.75 mg/kg al giorno

Deflazacort 0.9 mg/kg al giorno

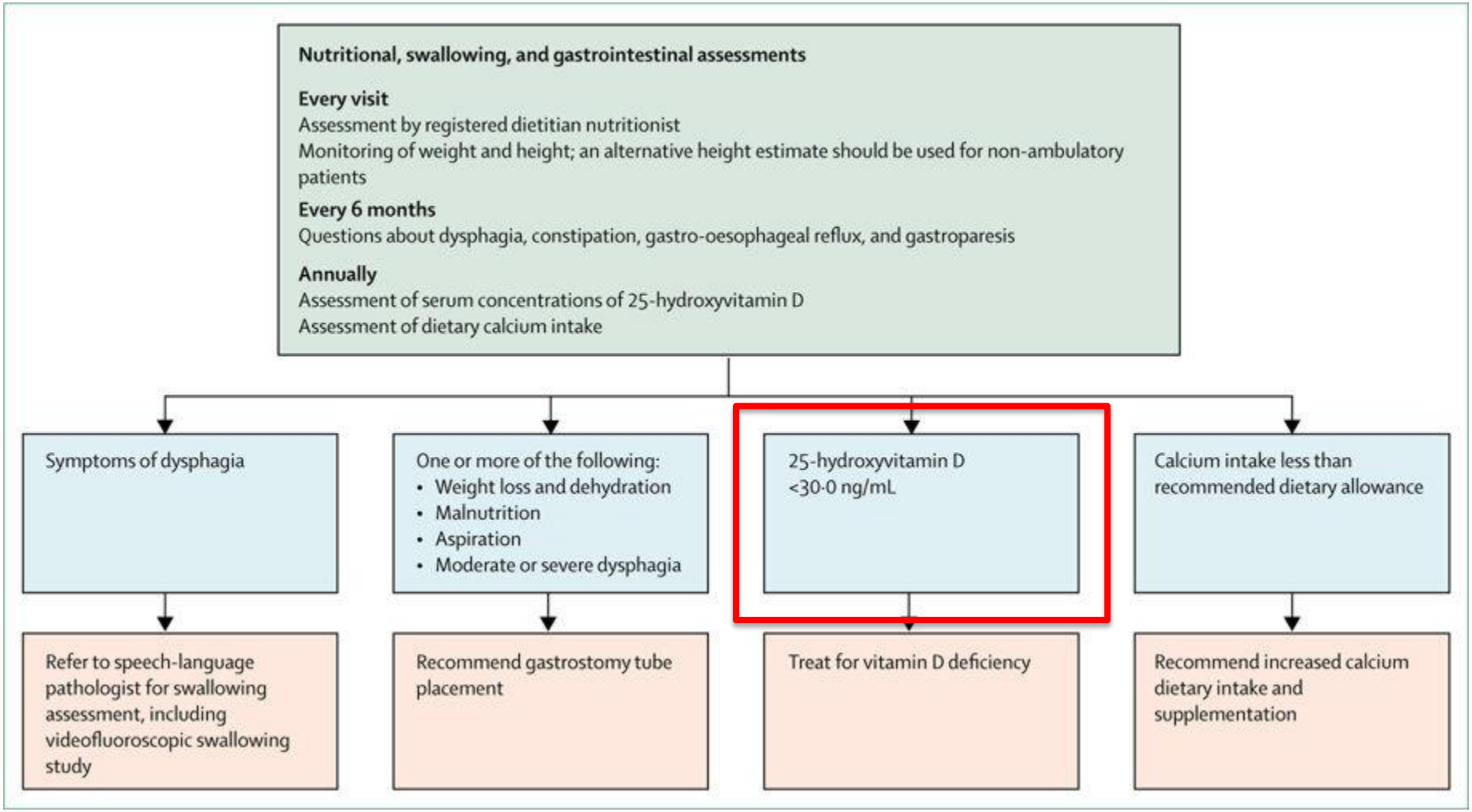
Birnkrant DJ et al. *Diagnosis and management of Duchenne muscular dystrophy.* Lancet Neurol. 2018 May;17(5)

Standard of care – crescita



Birnkrant DJ et al. *Diagnosis and management of Duchenne muscular dystrophy.* Lancet Neurol. 2018 May;17(5)

Standard of care - nutrizione



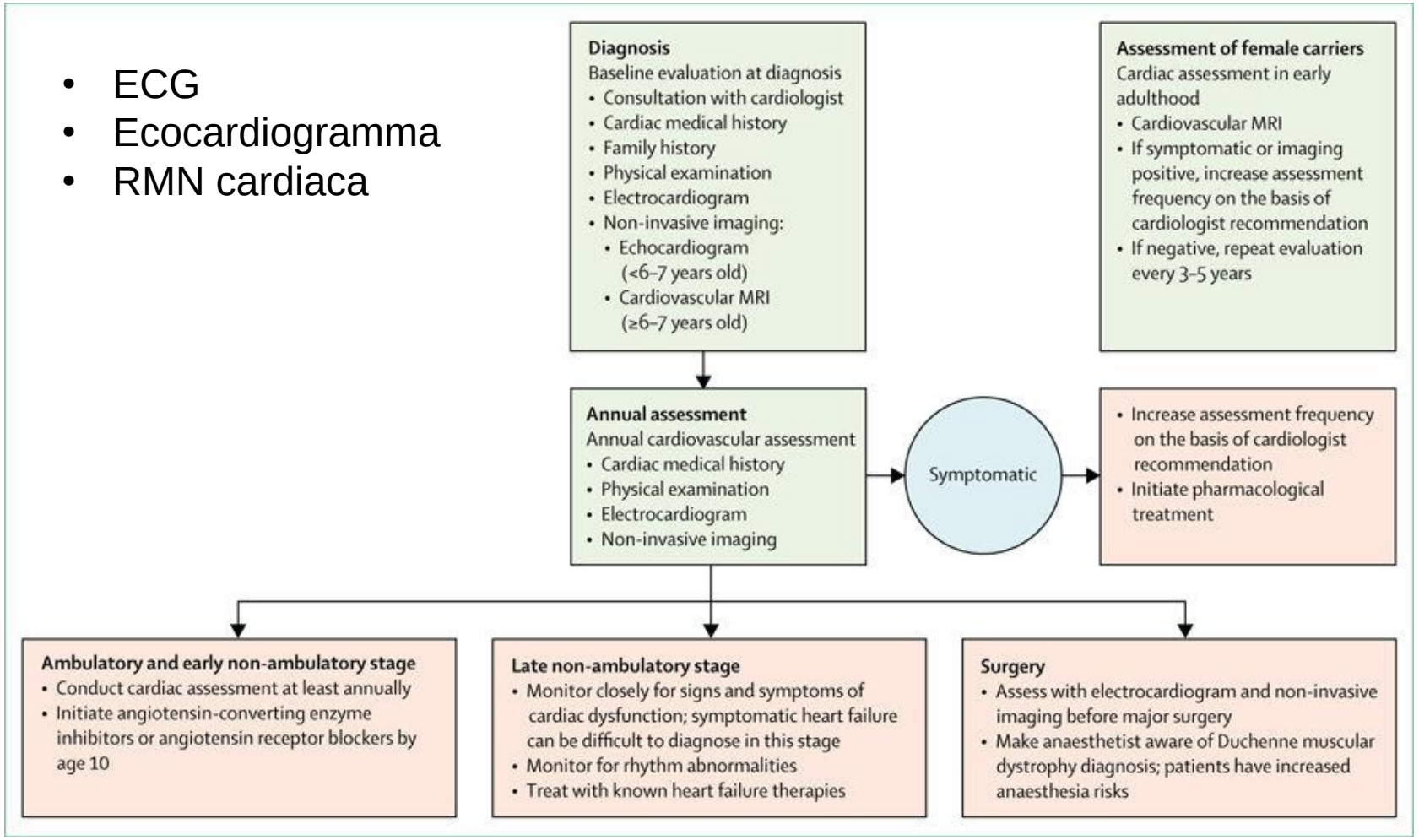
Birnkrant DJ et al. *Diagnosis and management of Duchenne muscular dystrophy.* Lancet Neurol. 2018 May;17(5)

Standard of care – quadro respiratorio

Birnkrant DJ et al. *Diagnosis and management of Duchenne muscular dystrophy.* Lancet Neurol. 2018 May;17(5)

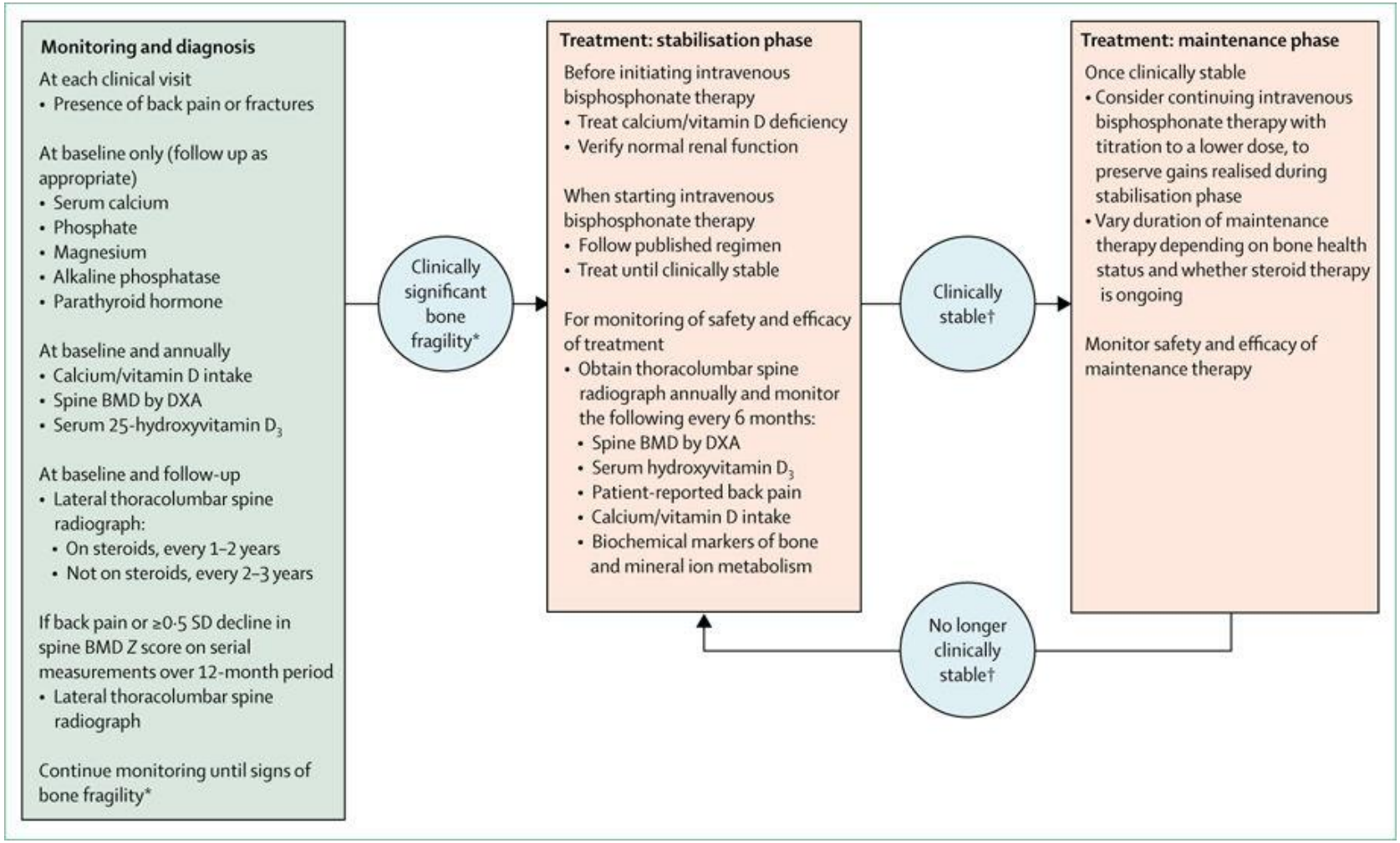
Standard of care – cardiopatia

- ECG
- Ecocardiogramma
- RMN cardiaca



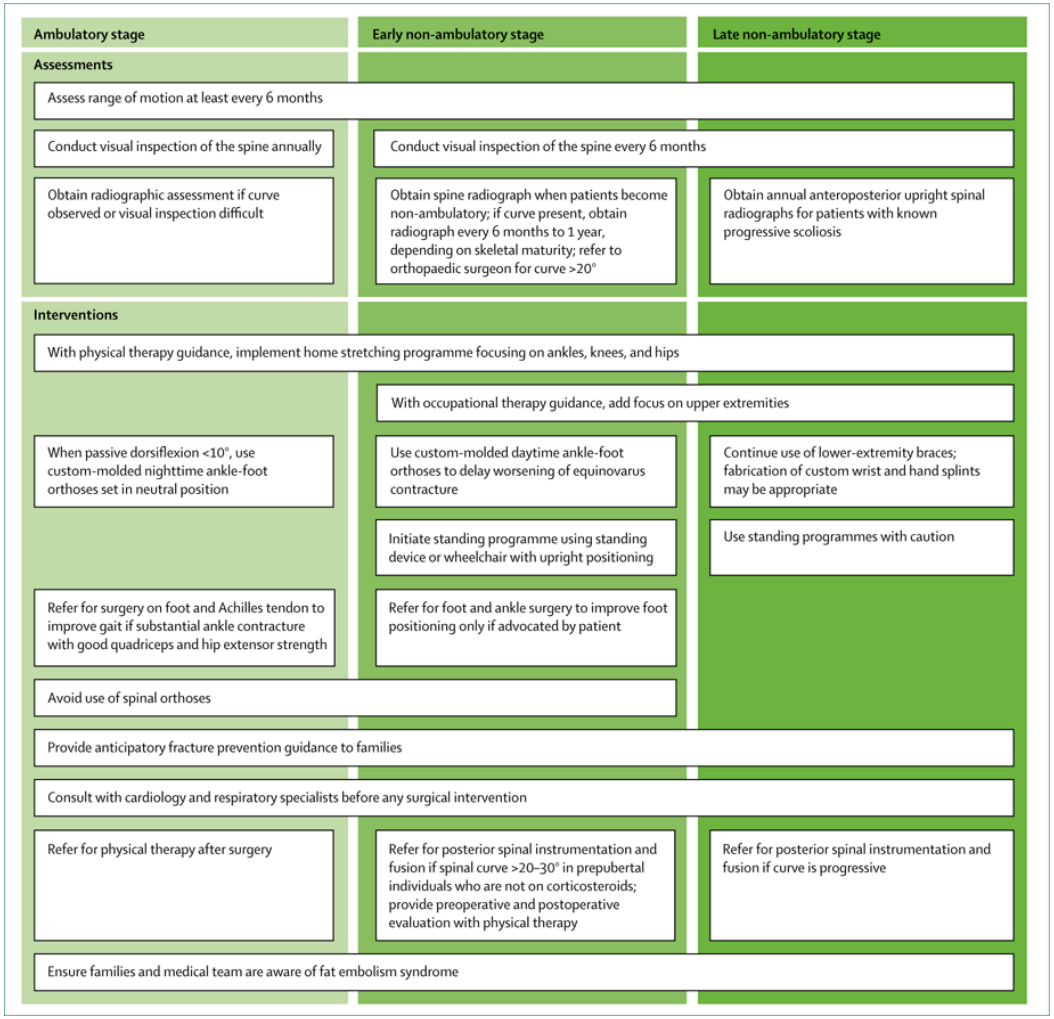
Birnkrant DJ et al. *Diagnosis and management of Duchenne muscular dystrophy.* Lancet Neurol. 2018 May;17(5)

Standard of care - osteoporosi



Birnkrant DJ et al. *Diagnosis and management of Duchenne muscular dystrophy.* Lancet Neurol. 2018 May;17(5)

Standard of care – quadro ortopedico



Ambulatory stage	Early non-ambulatory stage	Late non-ambulatory stage
Assessments		
Assess range of motion at least every 6 months		
Conduct visual inspection of the spine annually	Conduct visual inspection of the spine every 6 months	
Obtain radiographic assessment if curve observed or visual inspection difficult	Obtain spine radiograph when patients become non-ambulatory; if curve present, obtain radiograph every 6 months to 1 year, depending on skeletal maturity; refer to orthopaedic surgeon for curve >20°	Obtain annual anteroposterior upright spinal radiographs for patients with known progressive scoliosis
Interventions		
With physical therapy guidance, implement home stretching programme focusing on ankles, knees, and hips		
	With occupational therapy guidance, add focus on upper extremities	
When passive dorsiflexion <10°, use custom-molded nighttime ankle-foot orthoses set in neutral position	Use custom-molded daytime ankle-foot orthoses to delay worsening of equinovarus contracture	Continue use of lower-extremity braces; fabrication of custom wrist and hand splints may be appropriate
	Initiate standing programme using standing device or wheelchair with upright positioning	Use standing programmes with caution
Refer for surgery on foot and Achilles tendon to improve gait if substantial ankle contracture with good quadriceps and hip extensor strength	Refer for foot and ankle surgery to improve foot positioning only if advocated by patient	
Avoid use of spinal orthoses		
Provide anticipatory fracture prevention guidance to families		
Consult with cardiology and respiratory specialists before any surgical intervention		
Refer for physical therapy after surgery	Refer for posterior spinal instrumentation and fusion if spinal curve >20–30° in prepubertal individuals who are not on corticosteroids; provide preoperative and postoperative evaluation with physical therapy	Refer for posterior spinal instrumentation and fusion if curve is progressive
Ensure families and medical team are aware of fat embolism syndrome		

- Fisioterapia
- Tutori e ortesi
- Allungamento tendine di Achille
- Prevenzione fratture
- Scoliosi

Birnkrant DJ et al. *Diagnosis and management of Duchenne muscular dystrophy.* Lancet Neurol. 2018 May;17(5)

Standard of care – intervento chirurgico

Cardiac care

A cardiologist should be consulted before all surgical procedures
Anaesthetists should be aware that patients with DMD are at risk of cardiac decompensation during surgery

Major surgical procedures
- Patients with DMD are at particular risk of cardiac compromise during major procedures
- Echocardiogram and electrocardiogram should be done in close proximity to any planned surgery

Minor surgical procedures
- In patients with normal cardiac function, a cardiac assessment is suggested if last investigation was >1 year before

Respiratory care

Preoperative training in and postoperative use of assisted cough techniques
- Cough techniques are necessary for patients with baseline peak cough flow <270 L/min or baseline maximum expiratory pressure <60 cm H_2O*

Preoperative training in and postoperative use of non-invasive ventilation
- Non-invasive ventilation is necessary for patients with baseline FVC <30% predicted
- Non-invasive ventilation is strongly recommended for patients with FVC <50% predicted

Extubation to supplemental oxygen alone without concomitant use of non-invasive ventilation should be avoided

Incentive spirometry is not indicated because it is potentially ineffective in patients with respiratory muscle weakness, and preferred alternatives are available

Anaesthesia

Total intravenous anaesthesia is strongly recommended
Depolarising muscle relaxants, such as suxamethonium chloride, are absolutely contraindicated because of risk of fatal reactions

Risk of rhabdomyolysis and hyperkalaemia
- Patients with DMD are at risk of developing rhabdomyolysis with inhalational anaesthetics or when given suxamethonium chloride
- Rhabdomyolysis complications are frequently confused with malignant hyperthermia

Blood loss

Hypotensive anaesthetics to minimise blood loss are not recommended because of haemodynamic risk with cardiomyopathy in patients with DMD

Cell-saver technology, along with use of aminocarpoic acid or tanexamic acid, can be considered to help manage intraoperative blood loss

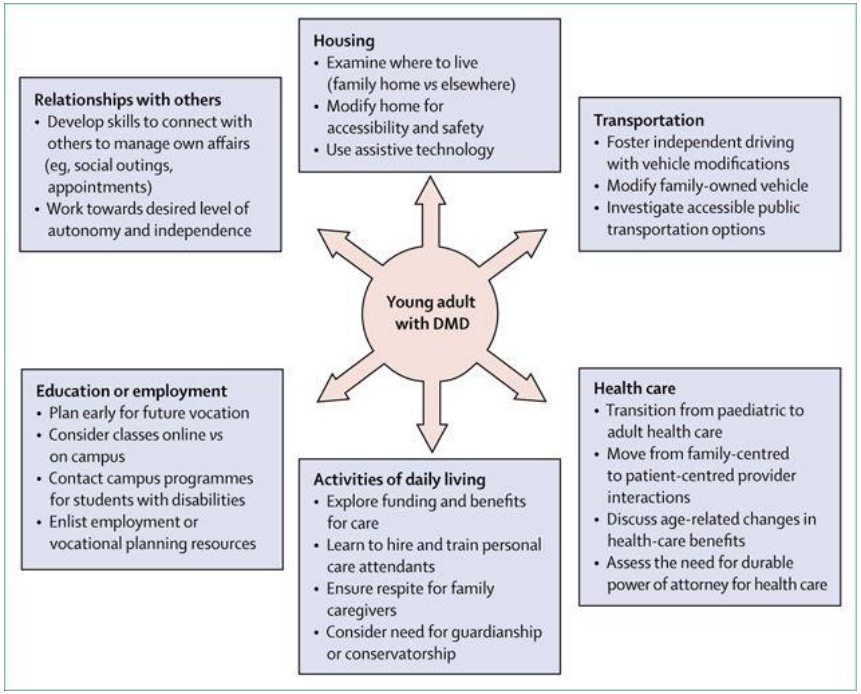
Postoperative anticoagulation with heparin or aspirin is not appropriate for patients with DMD

Compression stockings of sequential compression might be indicated for prevention of deep-vein thrombosis

Birnkrant DJ et al. *Diagnosis and management of Duchenne muscular dystrophy.* Lancet Neurol. 2018 May;17(5)

Standard of care – quadro psicosociale

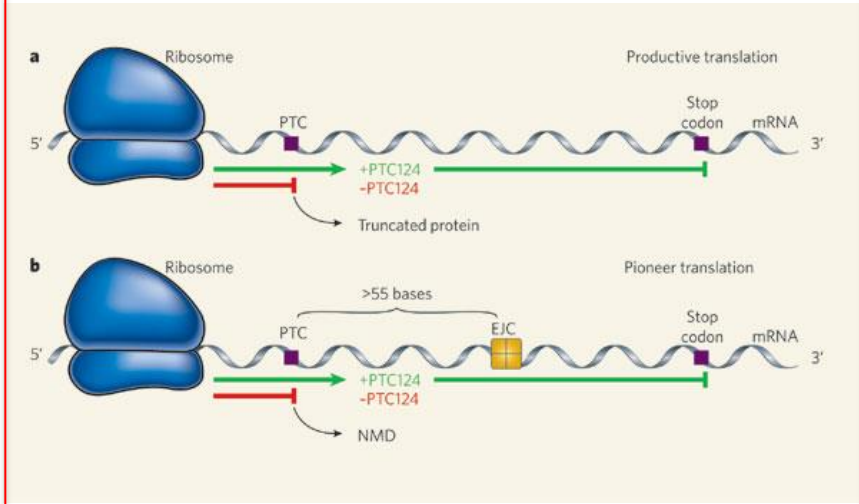
- Valutazione neuropsicologica
- Ritardo nel linguaggio
- Supporto psicologico



Birnkrant DJ et al. *Diagnosis and management of Duchenne muscular dystrophy.* Lancet Neurol. 2018 May;17(5)

Attuali terapie

Approvato da EMA-AIFA

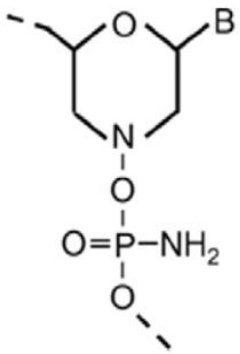


Ataluren

Stop codon read through

Approvato da FDA

Phosphorodiamidate morpholino oligonucleotides

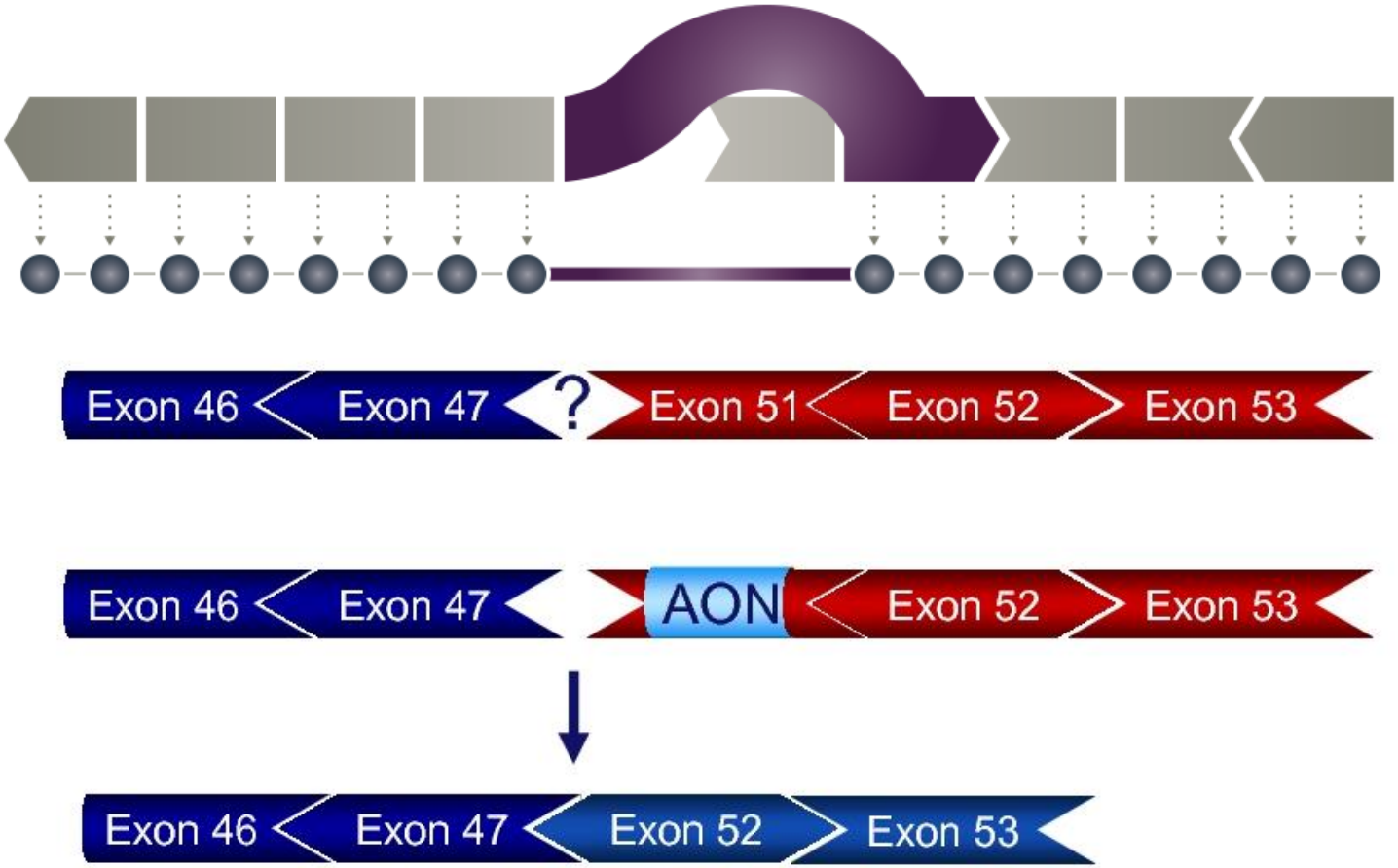


Eteplirsen

Exon 51 skipping

Eteplirsen

Oligonucleotidi antisenso - Exon skipping

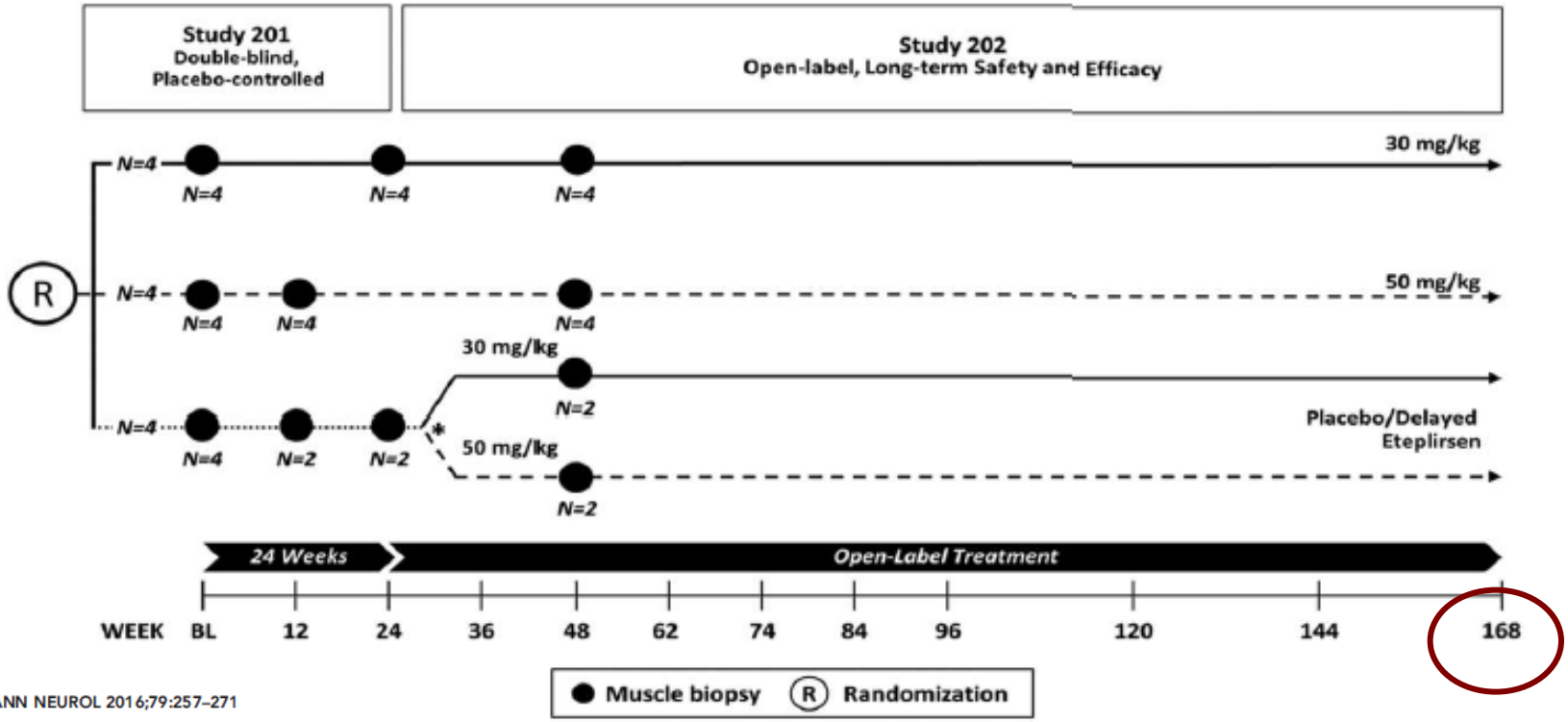


Eteplirsen

Criteri di inclusione:

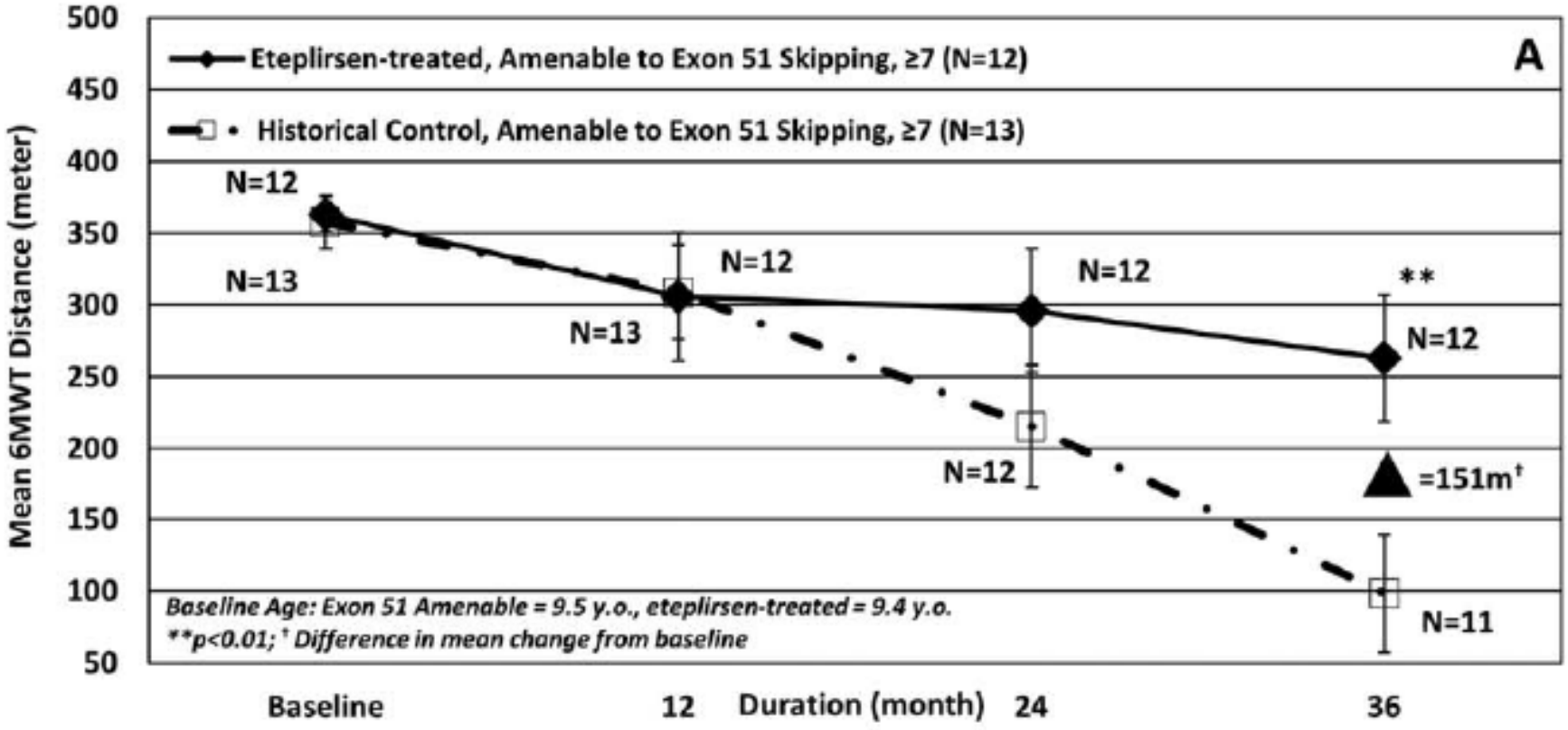
- Età 7-13 anni
- 6MWD compreso tra 180 e 440 metri
- Delezione compatibile con skipping **esone 51**
- Corticosteroidi ≥ 24 settimane

- **Infusione endovenosa settimanale**
- 30 o 50 mg/kg/settimana
- Nationwide Children Hospital
- Gruppo storico di controllo



ANN NEUROL 2016;79:257–271

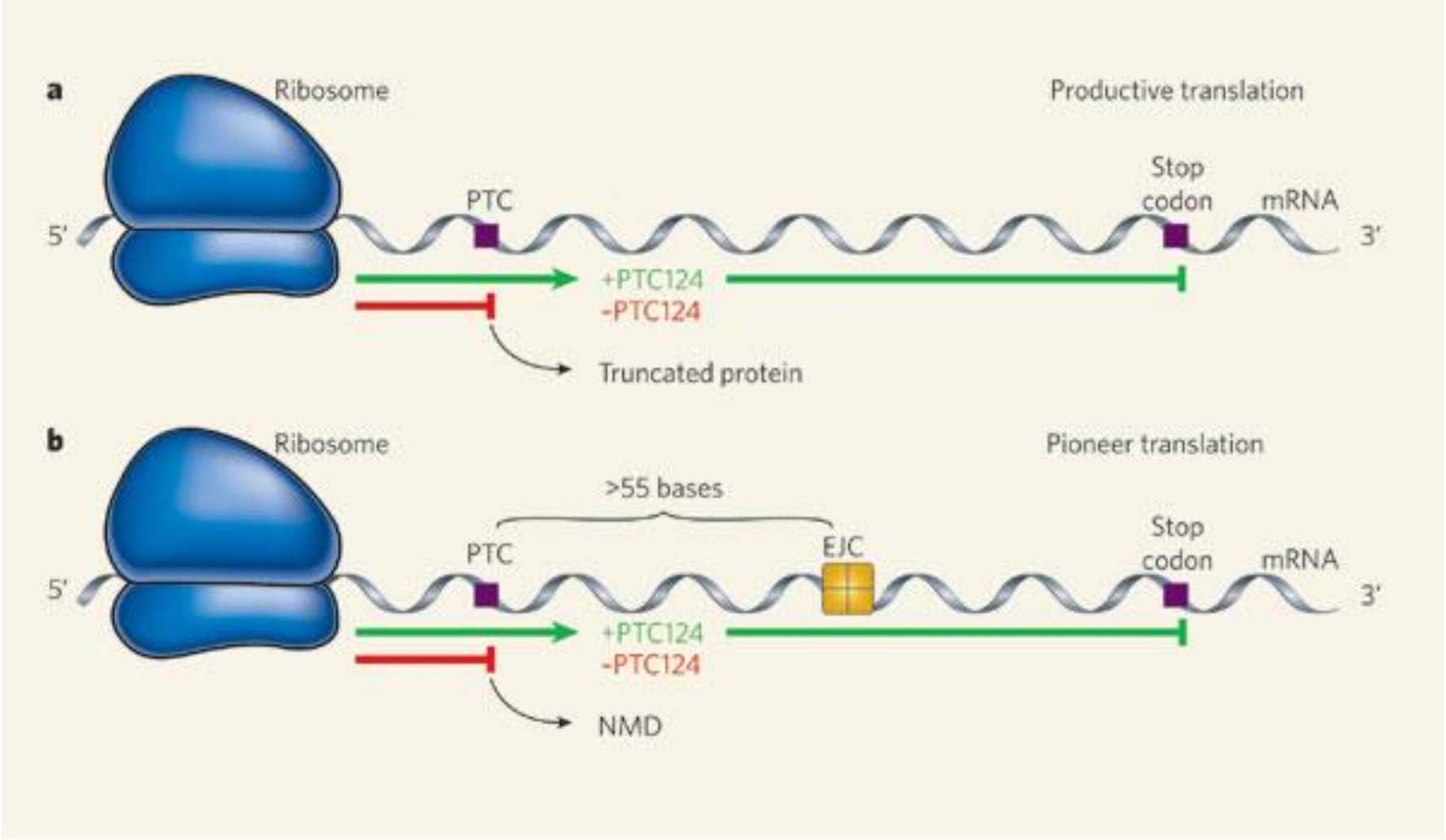
Eteplirsen



ANN NEUROL 2016;79:257–271

Ataluren (PTC124)

Stop codon reading through Mutazione nonsenso (nmDMD)



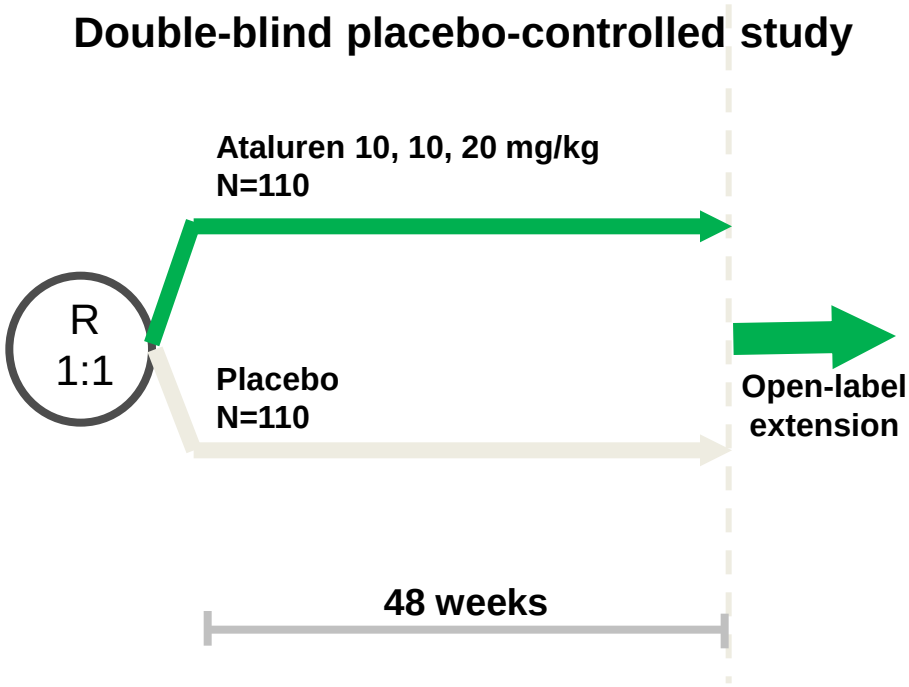
Ataluren – ACT DMD

Valutazione dell'efficacia di Ataluren dopo 48 settimane in pazienti con nmDMD

Endpoint primario
- Variazione 6MWD

Endpoint secondari
- Peggioramento 10% 6MWD
- Variazione 10-m walk/run
- Variazione 4-stair climb
- Variazione 4-stair descend

Endpoint esplorativi
- Variazione NSAA
- Variazione PODCI

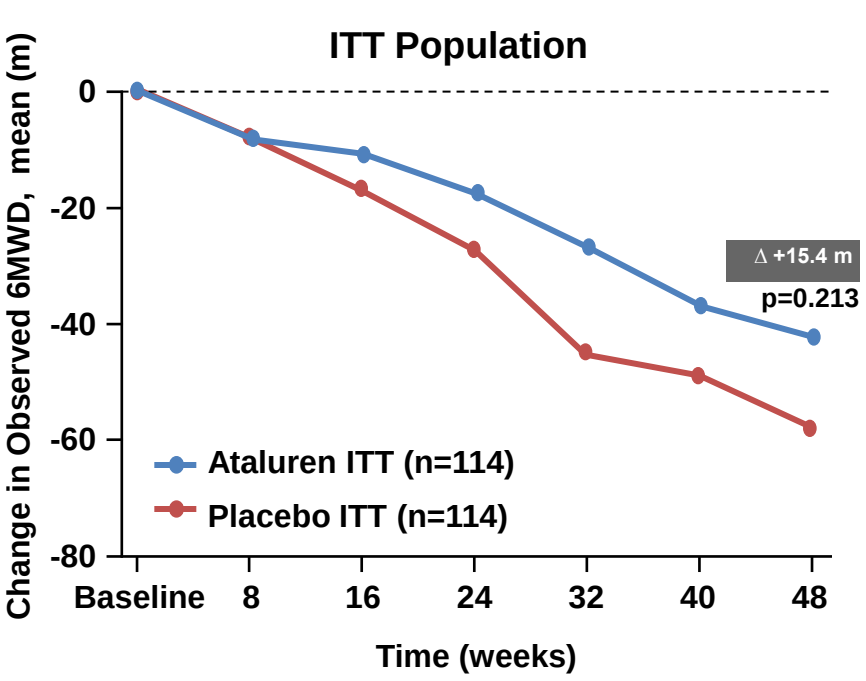


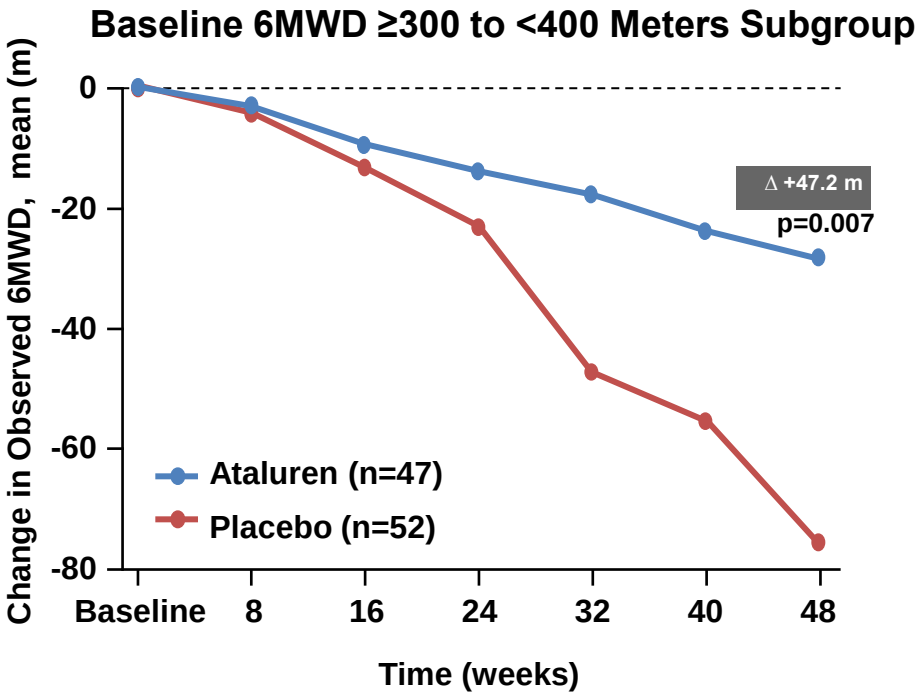
Criteri di inclusione:
- Età ≥7 e ≤16 anni
- Utilizzo di corticosteroidi ≥6 mesi
- 6MWD ≥150 m e ≤80% del predetto

- **Somministrazione per via orale**
- 10 + 10 + 20 mg/kg al giorno

Ataluren – ACT DMD

- Variazione media del 6MWD dal baseline a settimana 48 a favore di Ataluren rispetto al gruppo in placebo. Differenza significativa nel sottogruppo di pazienti con 6MWD compreso tra 300 e 400 metri al baseline.
- Variazione media dei punteggi dei test temporizzati a favore di Ataluren rispetto a placebo con differenze statisticamente significative per 4-stair descend (p=0.012) e 4-stair climb (p=0.058).





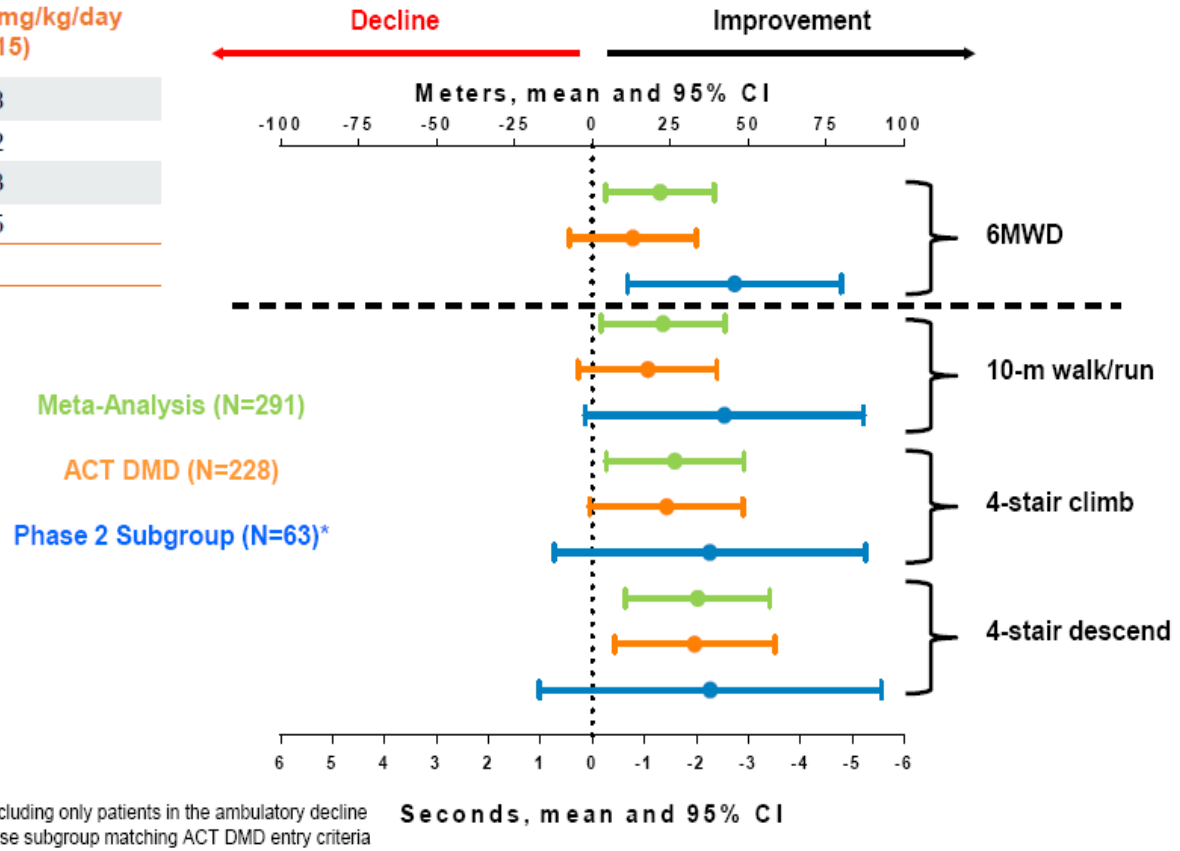
Ataluren – ACT DMD

- Eventi avversi simili nei pazienti trattati con Ataluren o placebo

Table 3. Treatment-related AEs With a >2.5% Higher Incidence in the Ataluren Group vs the Placebo Group

TEAE, %	Placebo (n=115)	Ataluren 40 mg/kg/day (n=115)
Vomiting	0.9	7.8
Headache	2.6	5.2
Diarrhea	0.9	4.3
Nausea	0	3.5

TEAEs, treatment-emergent adverse events.



* Including only patients in the ambulatory decline phase subgroup matching ACT DMD entry criteria

Ataluren – Study 030

Sicurezza di Ataluren su 52 settimane in pazienti con nmDMD di età **2-4 years**

Primary endpoint
- Long term Safety

Secondary endpoints
- Plasma pharmacokinetics

Exploratory endpoints
- Change in TFTs
- Change in NSAA

Open label Phase 2 study

Ataluren 10, 10, 20 mg/kg
N=14

52 weeks

Criteri di inclusione:

- Età ≥ 2 e <5 anni
- Peso ≥ 12 kg

Criteri di esclusione:
- Altro farmaco sperimentale ≤3 mesi
- Intervento chirurgico maggiore programmato
- Comorbidità significativa
- Precedente trattamento con Ataluren
- Somministrazione di aminoglicosidi ≤3 mesi

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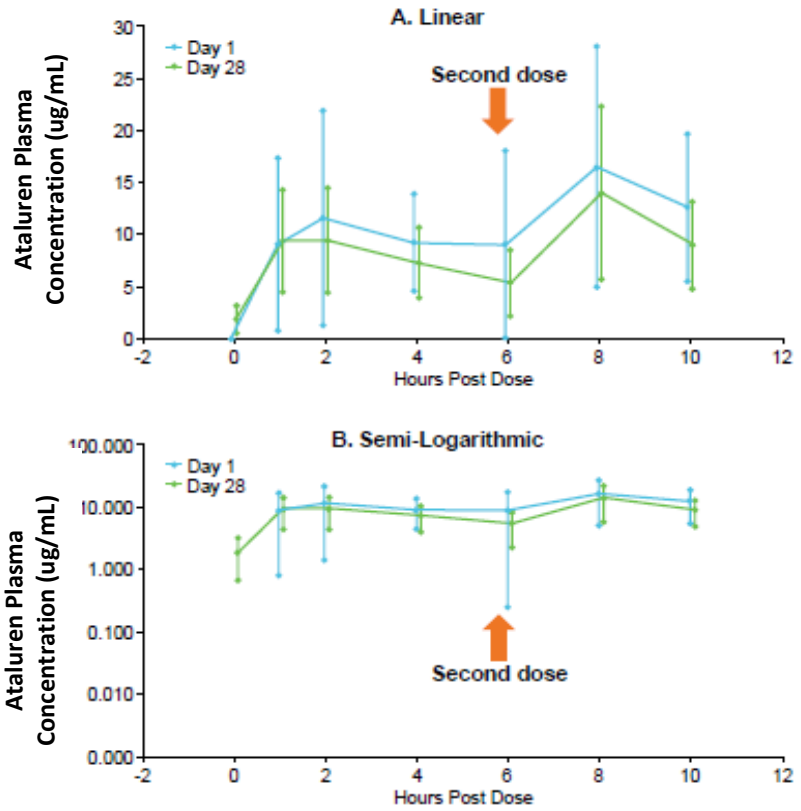
Ataluren – Study 030

- **Eventi avversi**: rash, flatulenza, nausea, vomito
- Nessun evento avverso di grado severo
- **Farmacocinetica**: concentrazione plasmatica media simile tra giorno 1 e 28

TEAE	PK Phase (N=14)	Extension Phase (N=14)	Overall (N=14)
Any TEAE	13 (92.9%)	10 (71.4%)	14 (100%)
Pyrexia	5 (35.7%)	3 (21.4%)	6 (42.9%)
Ear Infection	1 (7.1%)	3 (21.4%)	4 (28.6%)
Nasopharyngitis	1 (7.1%)	3 (21.4%)	4 (28.6%)
Rash	3 (21.4%)	0 (0.0%)	3 (21.4%)
Cough	2 (14.3%)	1 (7.1%)	3 (21.4%)
Vomiting	1 (7.1%)	2 (14.3%)	3 (21.4%)
Flatulence	2 (14.3%)	0 (0.0%)	2 (14.3%)
Upper Respiratory Tract Infection	1 (7.1%)	1 (7.1%)	2 (14.3%)
Arthropod Bite	0 (0.0%)	2 (14.3%)	2 (14.3%)
Influenza	0 (0.0%)	2 (14.3%)	2 (14.3%)



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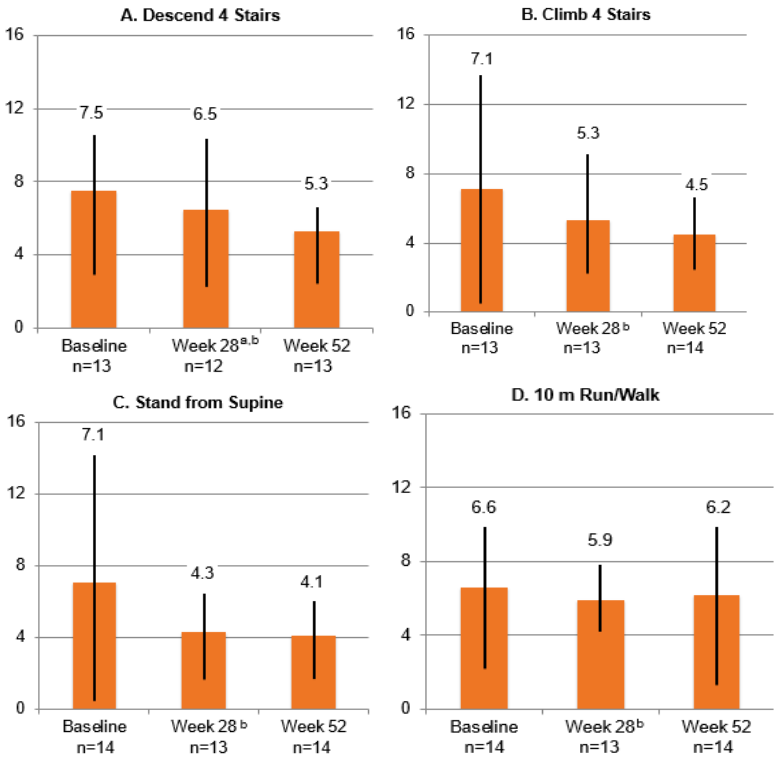
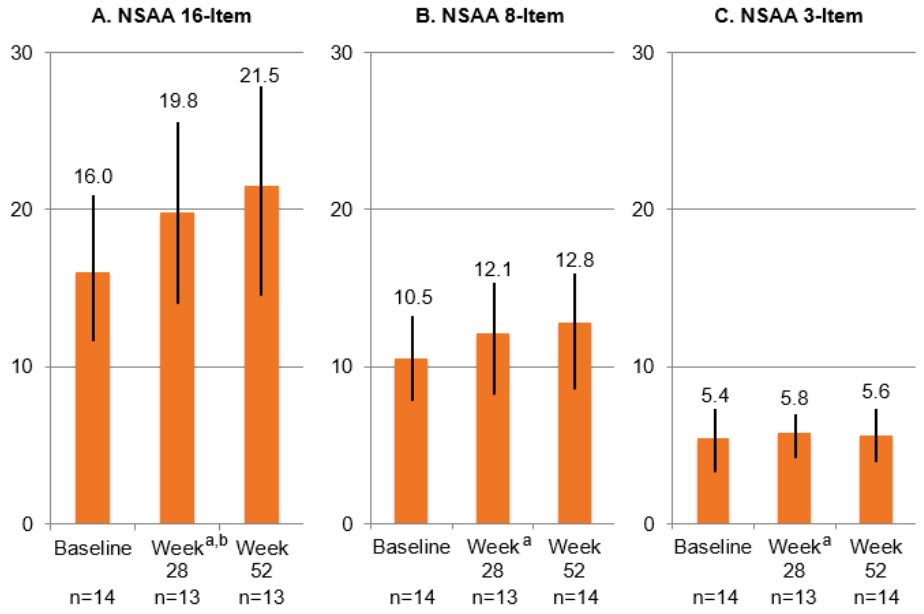
Ataluren – Study 030

Indicatori di efficacia:

- Diminuzione del punteggio ai test temporizzati e aumento del punteggio NSAA rispetto al baseline dopo trattamento con Ataluren in paziente con nmDMD di età compresa tra 2 e 5 anni. In questa fascia di età è generalmente previsto un miglioramento legato alla normale crescita.





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Grazie

Ai bambini e alle loro famiglie

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