LONG TERM FOLLOW-UP OF CARDIAC INVOLVEMENT OF PROGRESSIVE MUSCULAR DYSTROPHY (DUCHENNE) IN CHILDREN

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Overview

- Muscular Dystrophy
- Pathophysiology
- Diagnosis
- Cardiac involvement
  - ECG
  - Echocardiography
  - Cardiac MR
- Management

Muscular Dystrophy

Duchenne muscular dystrophy (DMD)

- mutations in the dystrophin gene (*DMD; locus Xp21.2)*
- absence of or defect : dystrophin
- progressive muscle degeneration
- loss of independent ambulation : 13 years

Muscular Dystrophy

- Becker muscular dystrophy
  - loss of ambulation over 16 years
  - progression is milder
- X-linked dilated cardiomyopathy (XL-dCMP)
  - isolated cardiac phenotype
- Female carriers
  - 10% : affect cognitive and/or cardiac function
  - skewed X inactivation
  - much milder than in boys
  - few cases : similar severity

Muscular Dystrophy

- Duchenne muscular dystrophy (DMD)
  - X-linked disease
  - 1 in 3600–6000 live male births
  - mildly delayed motor milestones
  - most are unable to run and jump properly
  - classic Gowers’ manoeuvre

Dx Most : 5 years

progressive muscle strength deteriorates

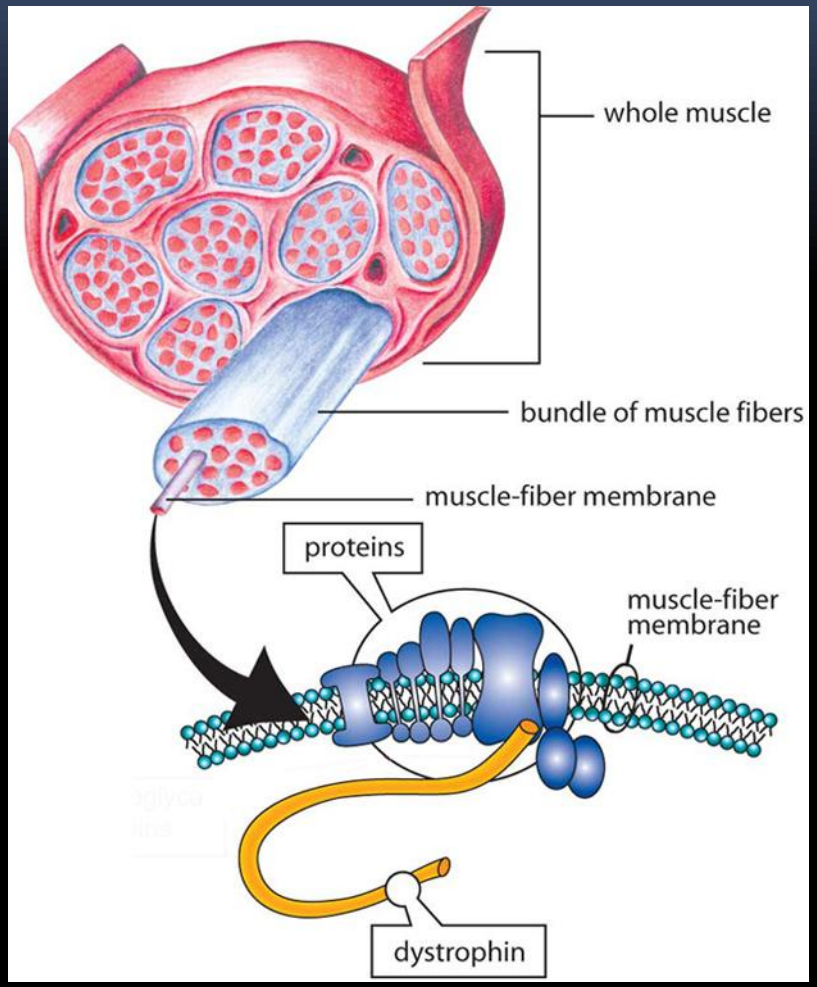
wheelchair use : before teens

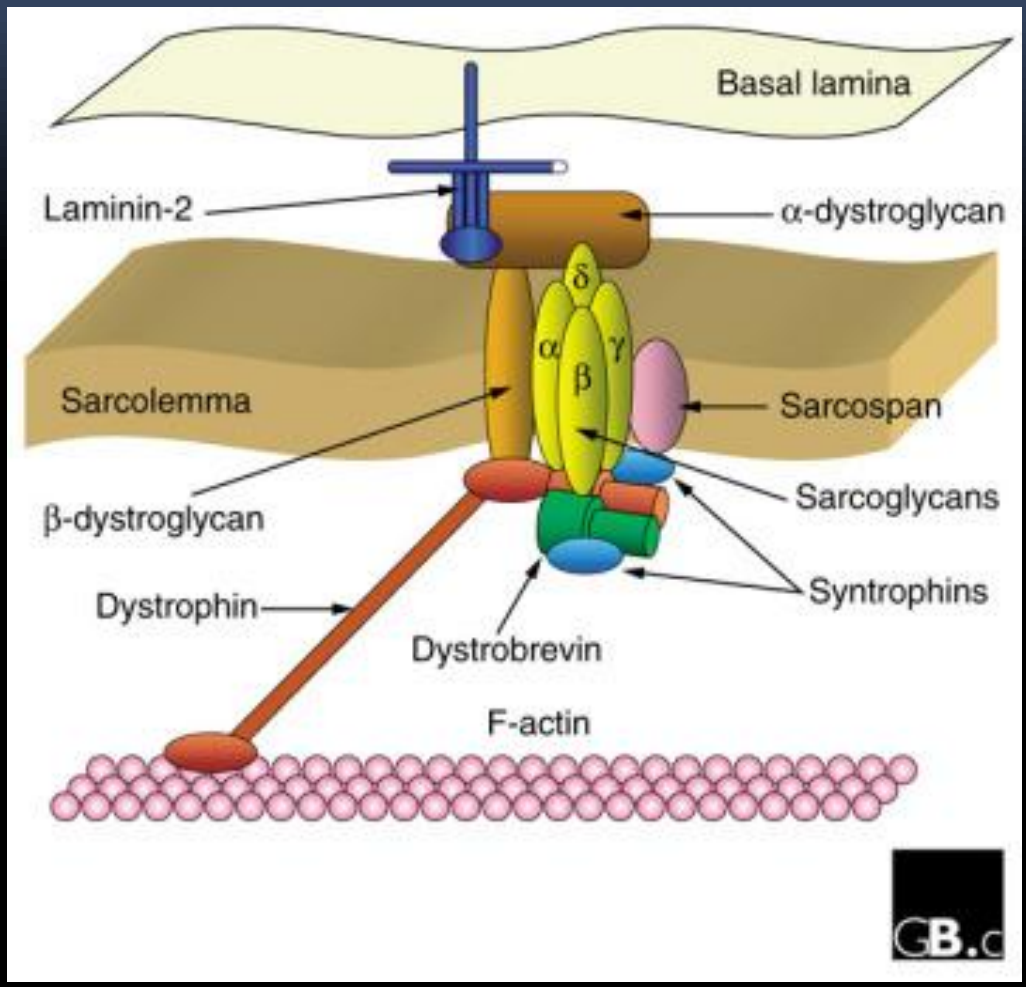
Respiratory, orthopaedic, and cardiac complications

without intervention : death is around 19 years

Non-progressive cognitive dysfunction

Muscular Dystrophy



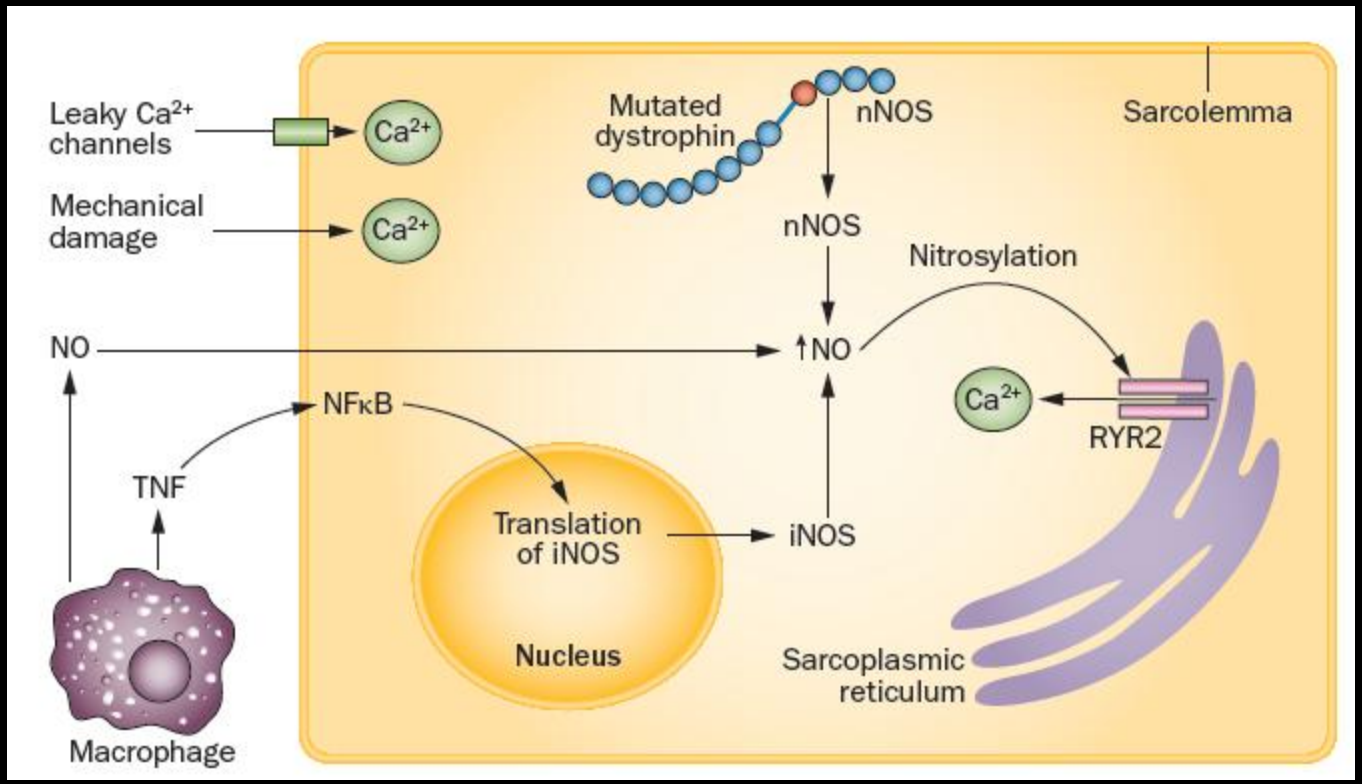


https://www.mda.org/disease/duchenne-muscular-dystrophy/causes-inheritance

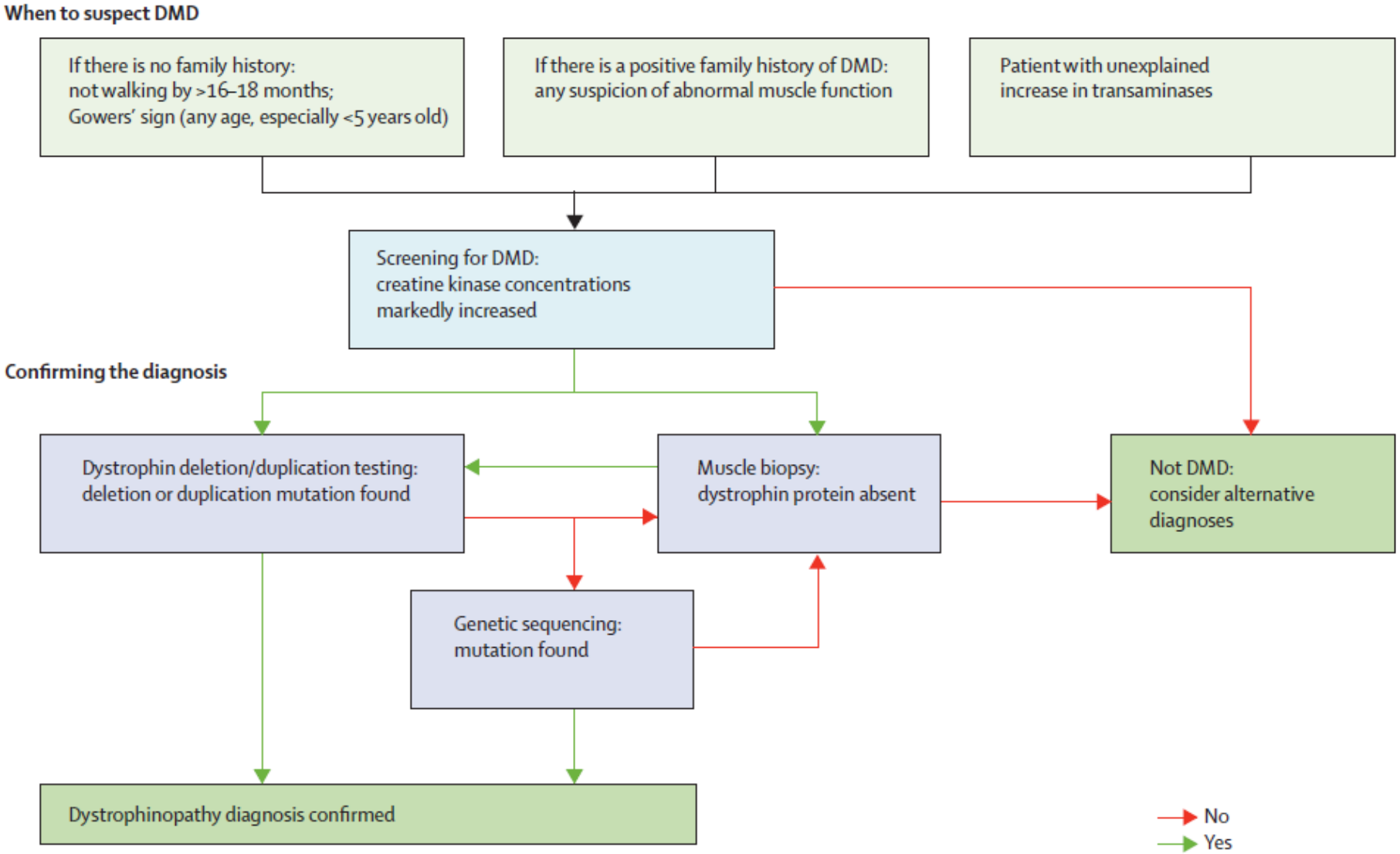
https://mmcneuro.wordpress.com/2014/01/29/duchenne-muscular-dsytrophy/

Pathophysiology

The absence of dystrophin
↑intracellular Ca
overproduction of NO
protein degradation, fibrosis, necrosis,
activation of macrophages



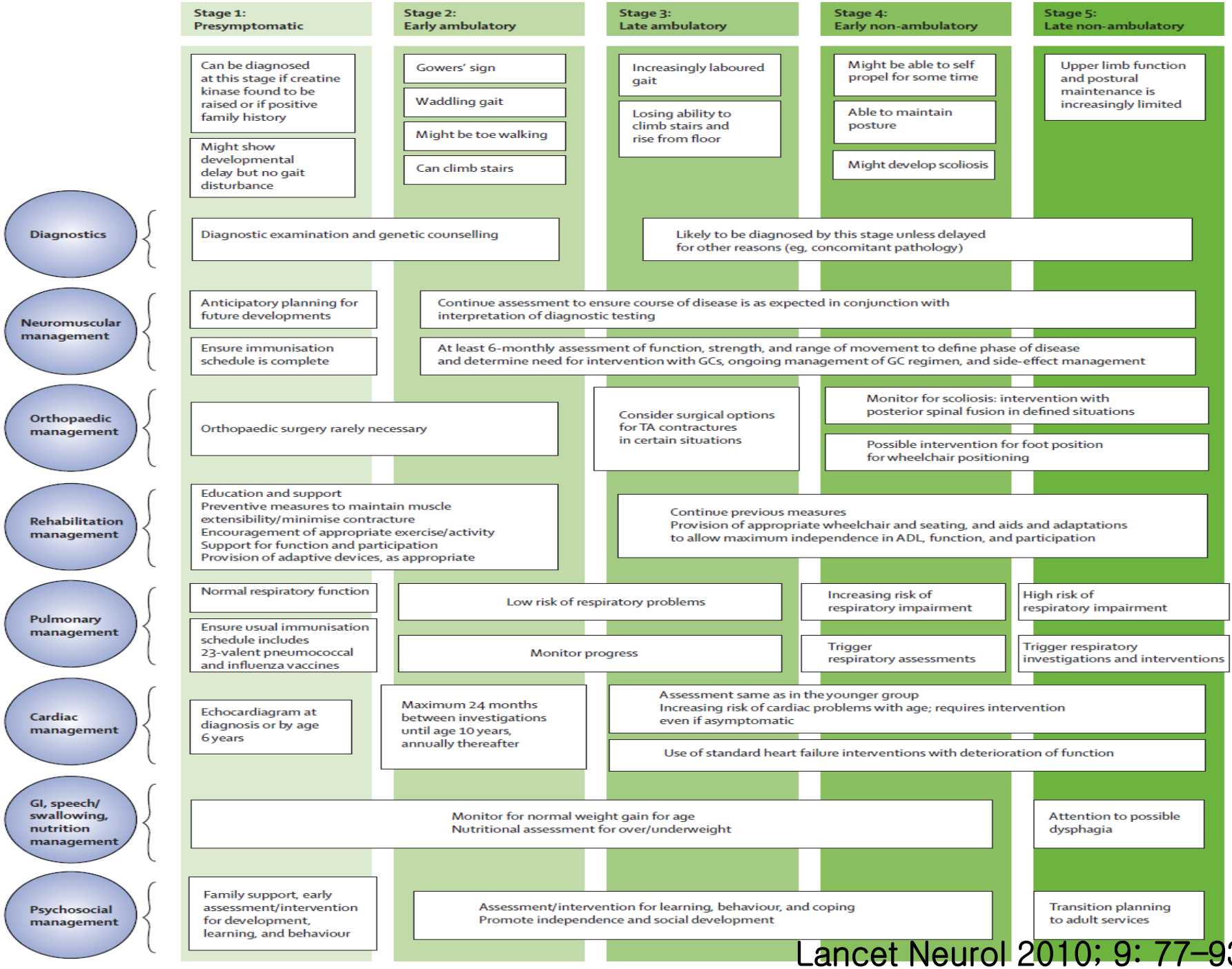
Nat. Rev. Cardiol. 11, 168–179 (2014)



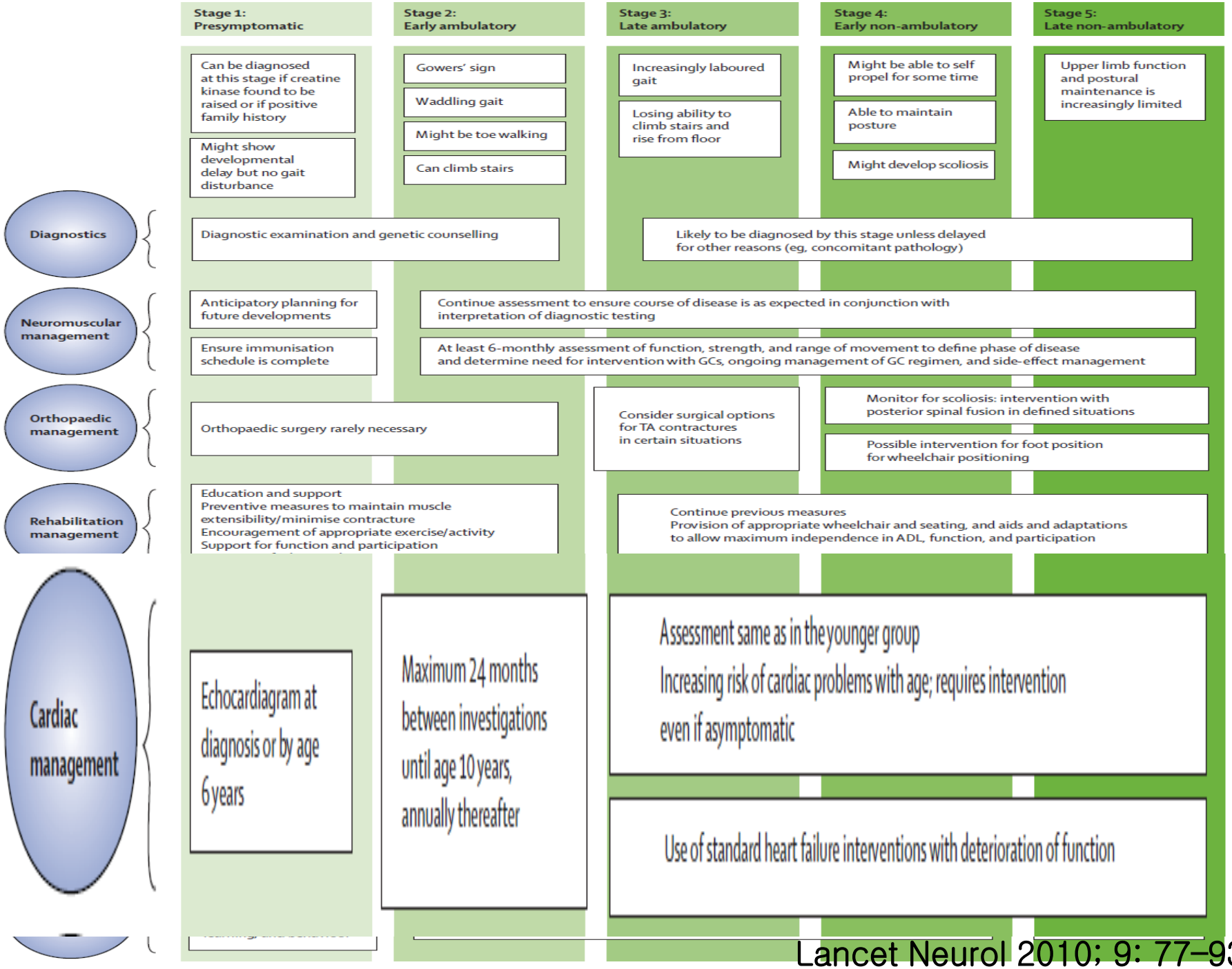
Post-diagnosis

- For patients diagnosed by muscle biopsy, dystrophin genetic testing is also necessary
- For patients diagnosed by genetic testing, muscle biopsy is optional to distinguish DMD from milder phenotypes
- Referral to specialised multidisciplinary follow-up is needed
- Genetic counselling is highly recommended for any at-risk female family members
- Patient and family support and contact with patient organisations should be offered

Lancet Neurol 2010; 9: 77–93

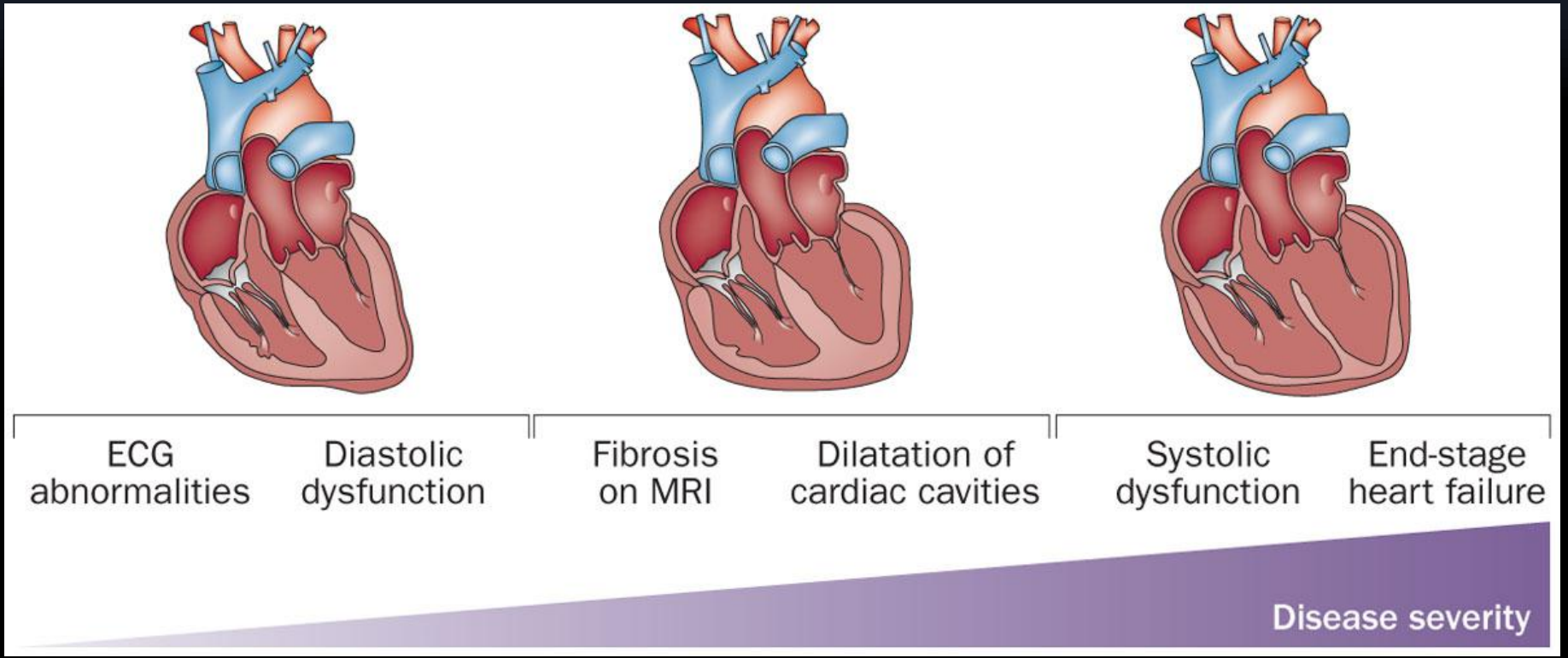


Lancet Neurol 2010; 9: 77–93



Lancet Neurol 2010; 9: 77–93

Progressive cardiac involvement in patients with Duchenne/ Becker muscular dystrophy



Nat. Rev. Cardiol. 11, 168–179 (2014)

Progressive cardiac involvement in patients with Duchenne/ Becker muscular dystrophy

Cardiomyopathy

- asymptomatic in childhood & early teens
- small subset - end-stage heart failure : 18 years

The disease progresses over time

- variable onset of arrhythmias
- ventricular dysfunction

ECG abnormalities : early in the disease & progress with age

- Sinus tachycardia
- frequency - disease duration & systolic dysfunction
- before onset of systolic dysfunction

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Progressive cardiac involvement in patients with Duchenne/ Becker muscular dystrophy

Early cardiomyopathy

hypertrophy of cardiomyocytes→ atrophy and fibrosis

Subendocardial fibrosis & fatty replacement - posterobasal LV & lat. wall

Cardiomyopathy

diastolic dysfunction → eccentric hypertrophy

Progressive dilatation of the ventricles and atria

thinning of the ventricular walls, systolic dysfunction

Ventricular arrhythmias

cardiac and respiratory function : important relationship

adequate respiratory fx → positive effect on cardiac fx

Heart failure : 40% of the deaths of DMD

ECG – cardiac involvement

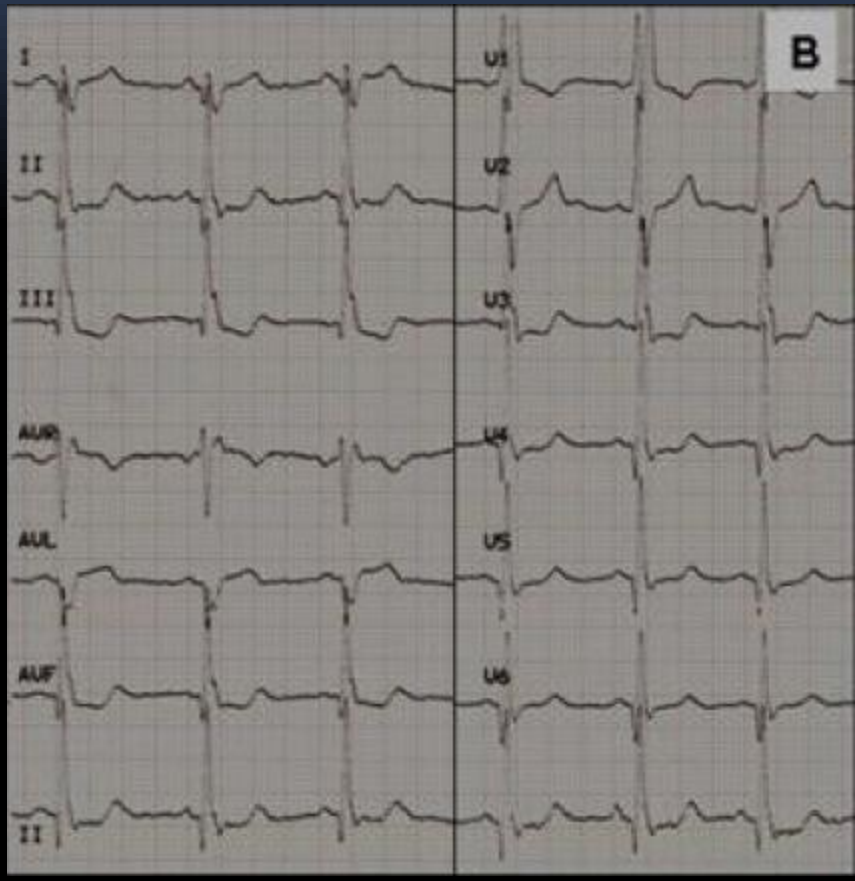
R:S ratio ≥1 in lead V1,

deep Q waves in leads I, aVL, V5–V6,

sinus tachycardia,

right axis deviation

complete right bundle branch block



Heart. 2012;98(5):420-429.

Echocardiography – cardiac involvement

progressive left ventricular (LV) expansion

impaired systolic function

some : rapid and lethal development (< 4 years)

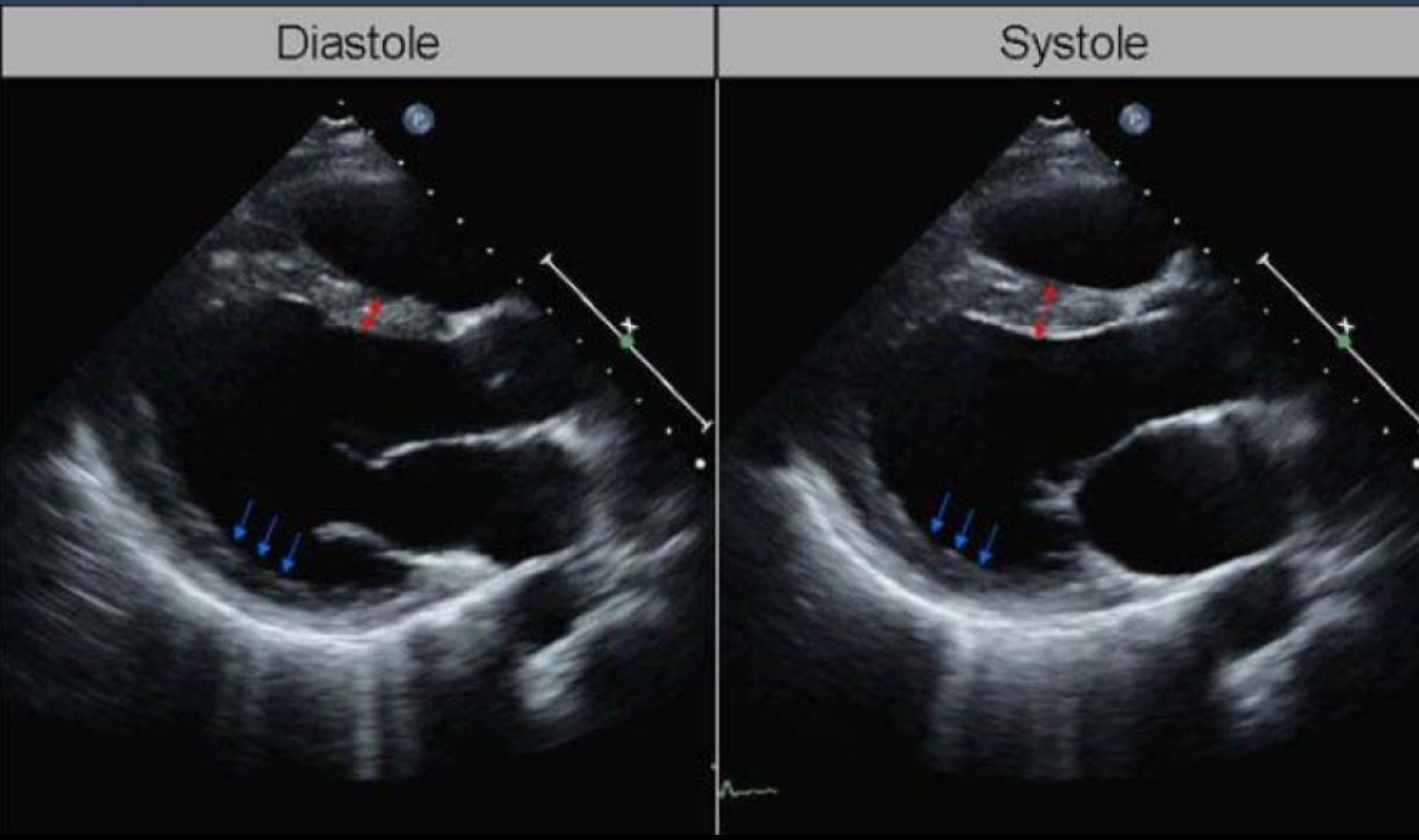
Wall motion abnormalities

posterior and lateral wall segments

Impaired diastolic fx in normal systolic fx

Heart. 2012;98(5):420-429.

Echocardiography – cardiac involvement



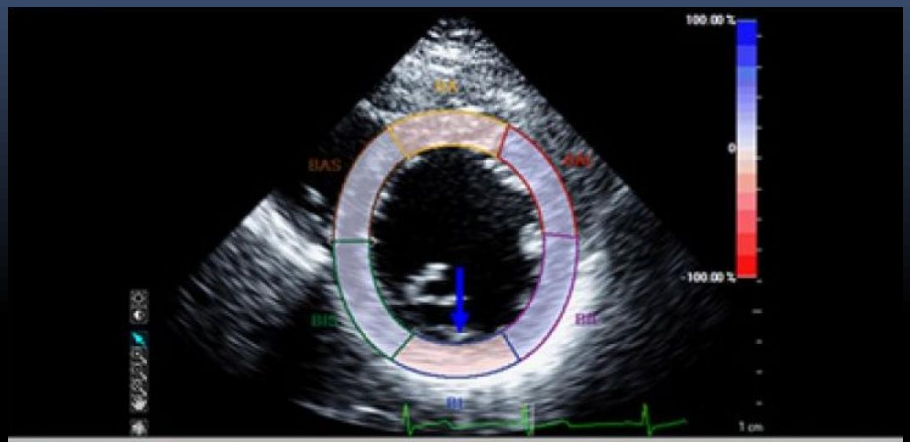
Heart. 2012;98(5):420-429.

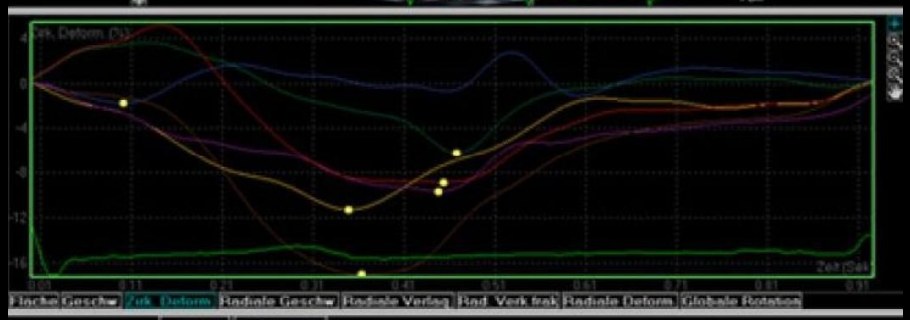
Echocardiography – cardiac involvement

- myocardial velocity and deformation imaging
  - although normal systolic fx
  - significant reductions in radial & longitudinal peak systolic strain
  - ↓ early diastolic myocardial velocities in the lateral LV wall
- LV systolic dysfunction
  - adverse prognostic

Heart. 2012;98(5):420-429.

Echocardiography – cardiac involvement





Global | Regional

Regionaler Bericht (SAX B)

Zirk. Deform. (%)	Max. Verzög. = 366.32 ms		
Segment	Zeit bis Spitze	Spitzenwert	Verzögerung
BAS	363.59 ms	-17.01 %	-84.59 ms
BIL	448.18 ms	-9.63 %	
BA	349.27 ms	-11.25 %	247.62 ms
BI	101.64 ms	-1.75 %	
BAL	453.64 ms	-8.83 %	-14.33 ms
BIS	467.96 ms	-6.18 %	

- Geschw.
- Zirk. Deform.
- Radiale Geschw.
- Radiale Verlag.

Heart. 2012;98(5):420-429.

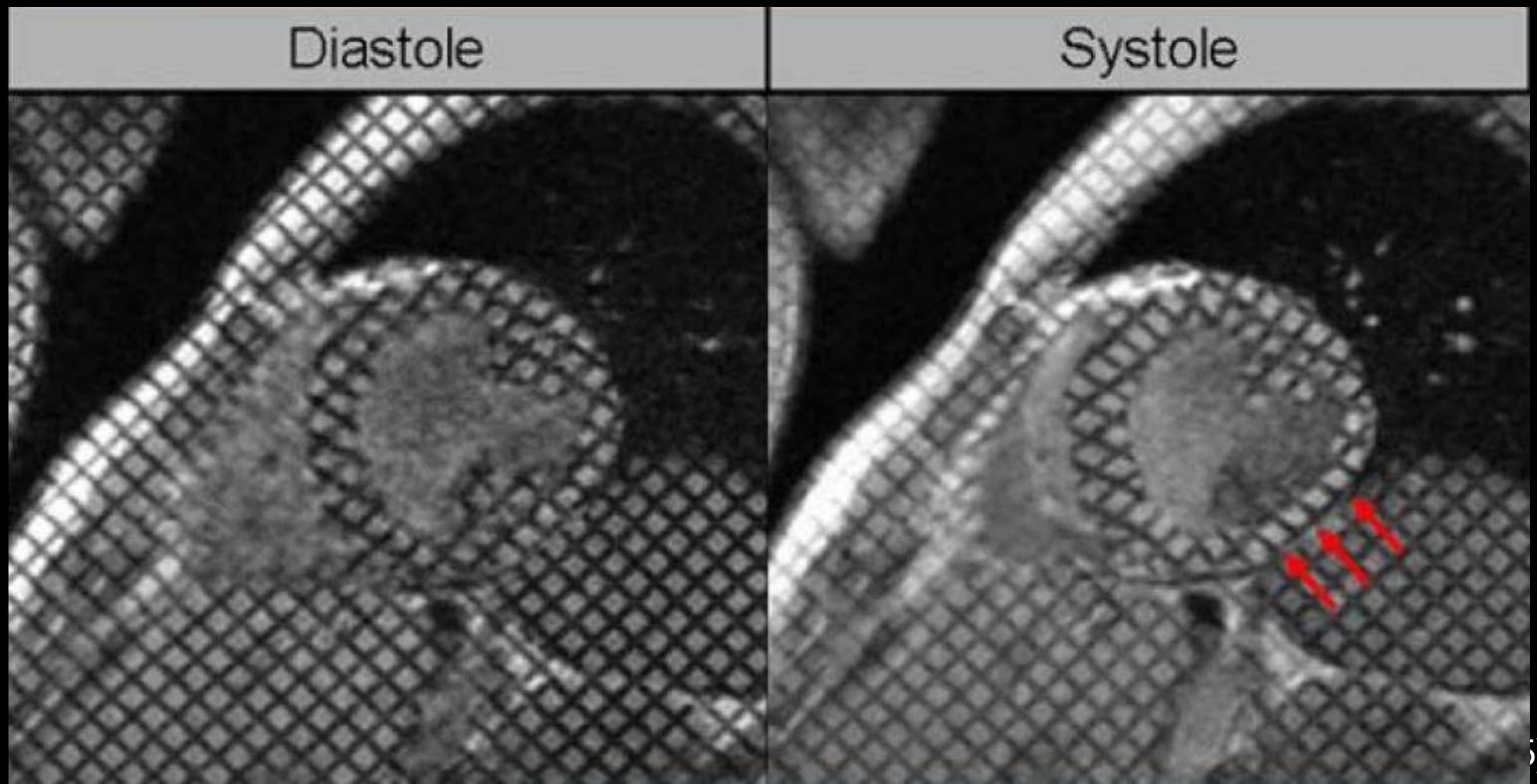
Cardiovascular Magnetic Resonance Imaging

Cine-imaging and CMR tagging

accurate and rapid measurement

of regional transmural myocardial deformation

over the entire cardiac cycle



):420-429.

Contrast enhanced CMR (ceCMR)

Late gadolinium enhancement (LGE)

indicative of myocardial damage

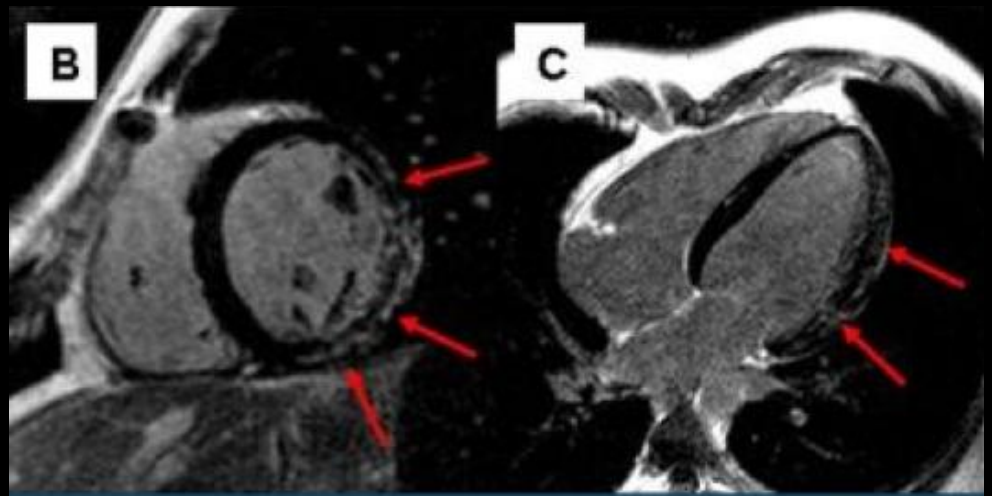
free LV lateral wall : m. c.

BMD subepicardium of the inferolateral wall in the third decade of life

age dependent increase

CMR is more sensitive in detecting pathological findings

>>ECG and conventional echocardiography,



Heart. 2012;98(5):420-429.

Timing of Cardiac Studies

DMD - ECG and echocardiography

at diagnosis, every 2 years to age 10,

and annually after age 10

additional CMR study : > 6Yr, >20 kg

BMD - ECG and echocardiography

at diagnosis, every 5 years in normal

comprehensive CMR study at diagnosis

least every second year

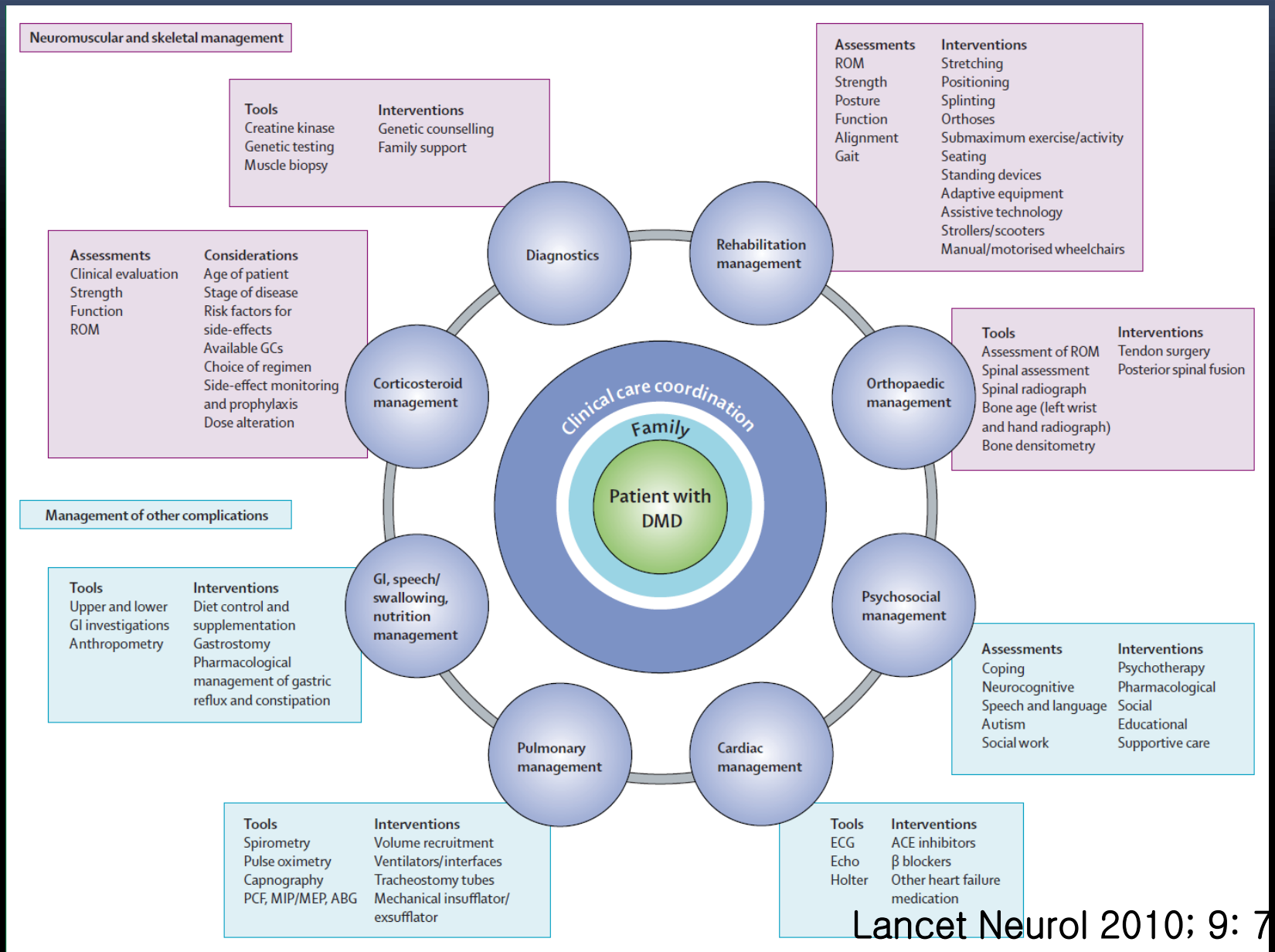
Female carriers of MD

at diagnosis, every 5 years in normal

CMR : tool to diagnose & identify the pattern of cardiomyopathy

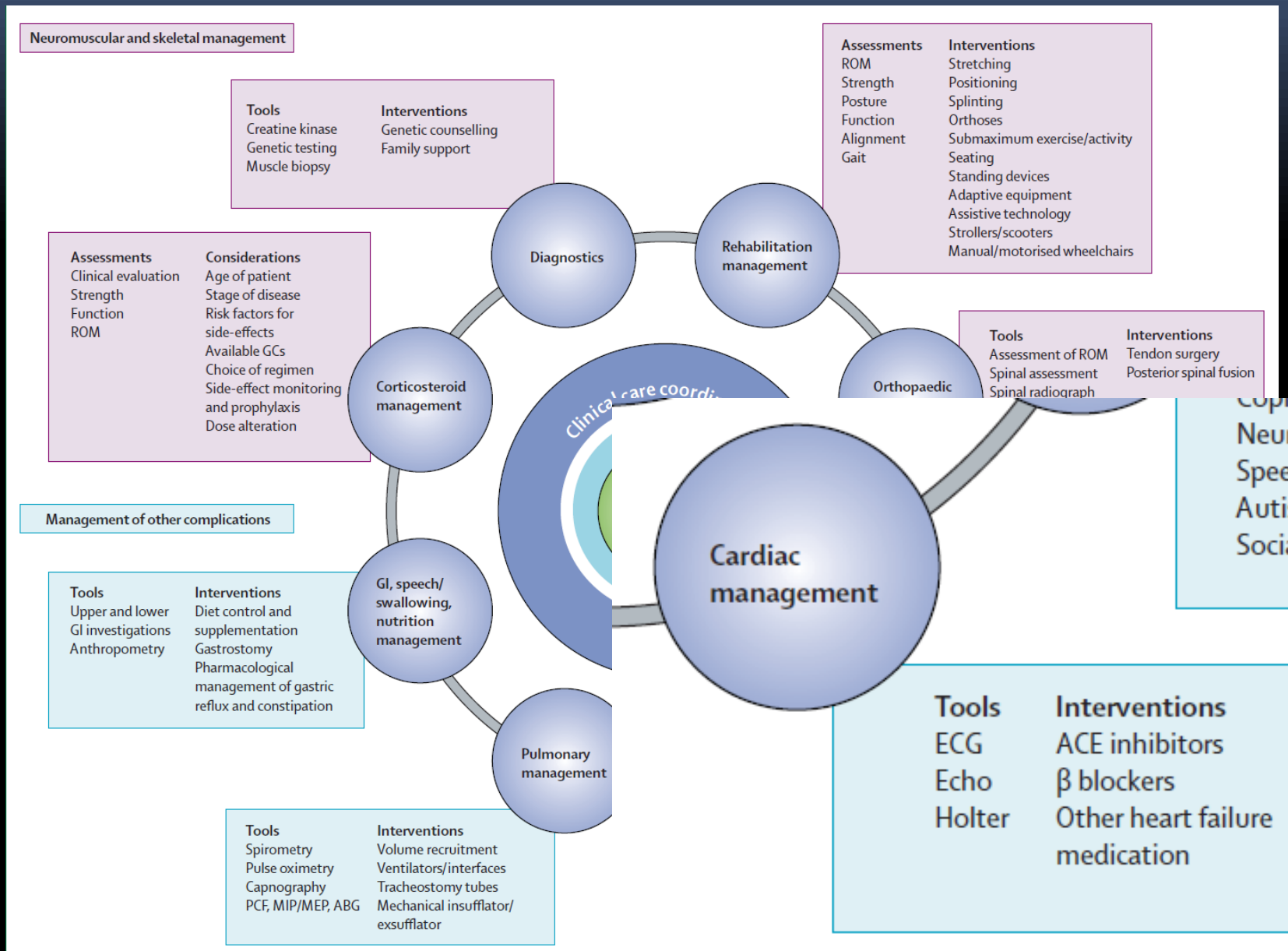
Heart. 2012;98(5):420-429.

Management



Lancet Neurol 2010; 9: 7

Management


Neuromuscular and skeletal management
Tools
Creatine kinase
Genetic testing
Muscle biopsy
Interventions
Genetic counselling
Family support
Assessments
ROM
Strength
Posture
Function
Alignment
Gait
Interventions
Stretching
Positioning
Splinting
Orthoses
Submaximum exercise/activity
Seating
Standing devices
Adaptive equipment
Assistive technology
Strollers/scooters
Manual/motorised wheelchairs
Diagnostics
Rehabilitation management
Assessments
Clinical evaluation
Strength
Function
ROM
Considerations
Age of patient
Stage of disease
Risk factors for side-effects
Available GCs
Choice of regimen
Side-effect monitoring and prophylaxis
Dose alteration
Corticosteroid management
Orthopaedic
Tools
Assessment of ROM
Spinal assessment
Spinal radiograph
Interventions
Tendon surgery
Posterior spinal fusion
Clinical care coordi
Neurocogniti
Speech and la
Autism
Social work
Management of other complications
Cardiac management
Tools
Upper and lower GI investigations
Anthropometry
Interventions
Diet control and supplementation
Gastrostomy
Pharmacological management of gastric reflux and constipation
GI, speech/ swallowing, nutrition management
Tools
ECG
Echo
Holter
Interventions
ACE inhibitors
β blockers
Other heart failure medication
Pulmonary management
Tools
Spirometry
Pulse oximetry
Capnography
PCF, MIP/MEP, ABG
Interventions
Volume recruitment
Ventilators/interfaces
Tracheostomy tubes
Mechanical insufflator/ exsufflator

Steroid treatment

Starting GCs

Prednisone
0·75 mg/kg/day
First line unless pre-existing weight and/or behavioural issues favour deflazacort

Deflazacort
0·9 mg/kg/day
Consider as first line when pre-existing weight and/or behavioural issues

Age <2 years
Improving (typical): GC initiation not recommended
Plateau (uncommon): monitor closely
Decline (atypical): consider alternative diagnoses/concomitant pathology

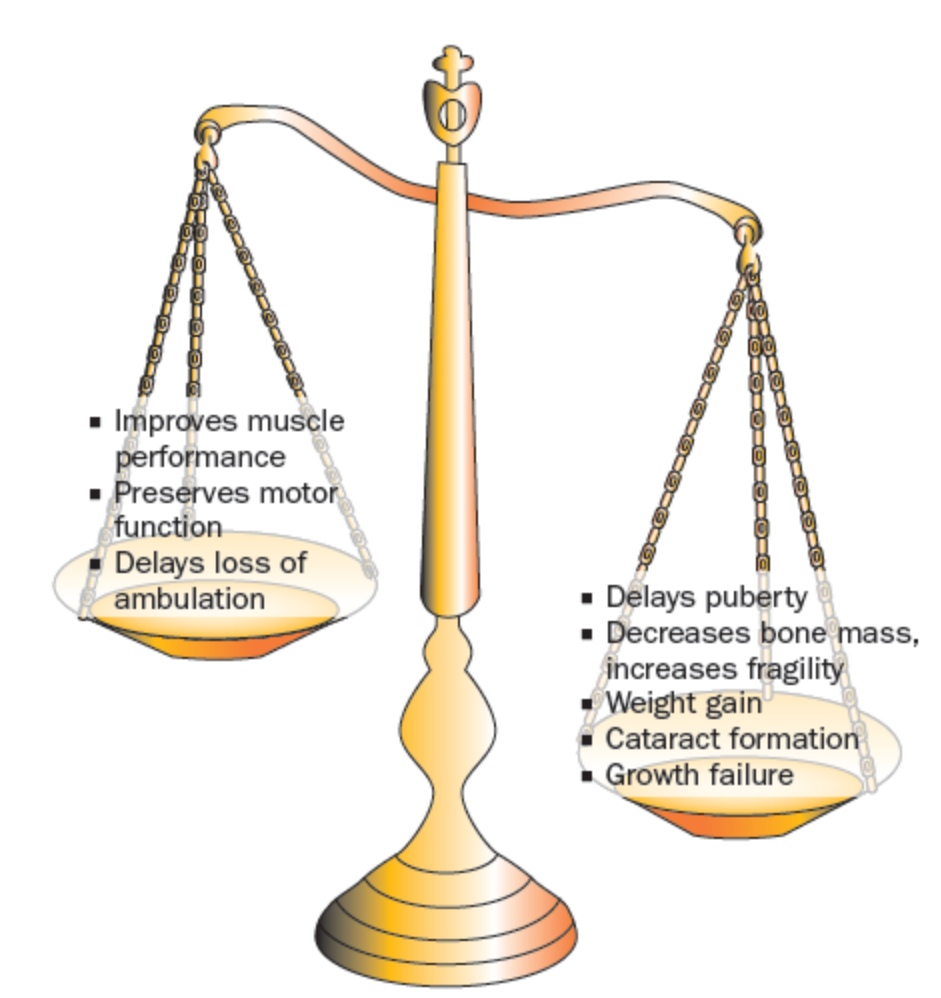
Age 2–5 years
Improving: GC initiation not recommended
Plateau: GC initiation recommended
Decline: GC initiation highly recommended

Age ≥6 years
Improving (uncommon): consider BMD
Plateau: GC initiation highly recommended
Decline: GC initiation highly recommended
Non-ambulatory: refer to text

- Consider age, function (improving, plateau, declining), pre-existing risk factors, physician relationship with family
- Ensure immunisation schedule is complete before initiating GCs

Lancet Neurol 2010; 9: 77–93

Steroid treatment



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Alternative steroid treatment

	Prednisone dose*	Deflazacort dose*	Comments
Alternate day	0·75–1·25 mg/kg every other day	2 mg/kg every other day	Less effective but consider when a daily schedule has side-effects that are not effectively managed or tolerated
High-dose weekend	5 mg/kg given each Friday and Saturday	Not yet tested	Less data on effectiveness as compared to a daily schedule Consider as an alternative to daily treatment, especially if weight gain and behavioural issues are problematic
Intermittent	0·75 mg/kg for 10 days alternating with 10–20 days off medication	0·6 mg/kg on days 1–20 and none for the remainder of the month	Less effective but has fewer side-effects Consider as the least effective but possibly best tolerated regimen before abandoning steroid treatment altogether

GC=glucocorticoid. *No set dose ranges have been clearly accepted as optimum.

Table 3: **Alternative GC dosing strategies**

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Cardiac treatment

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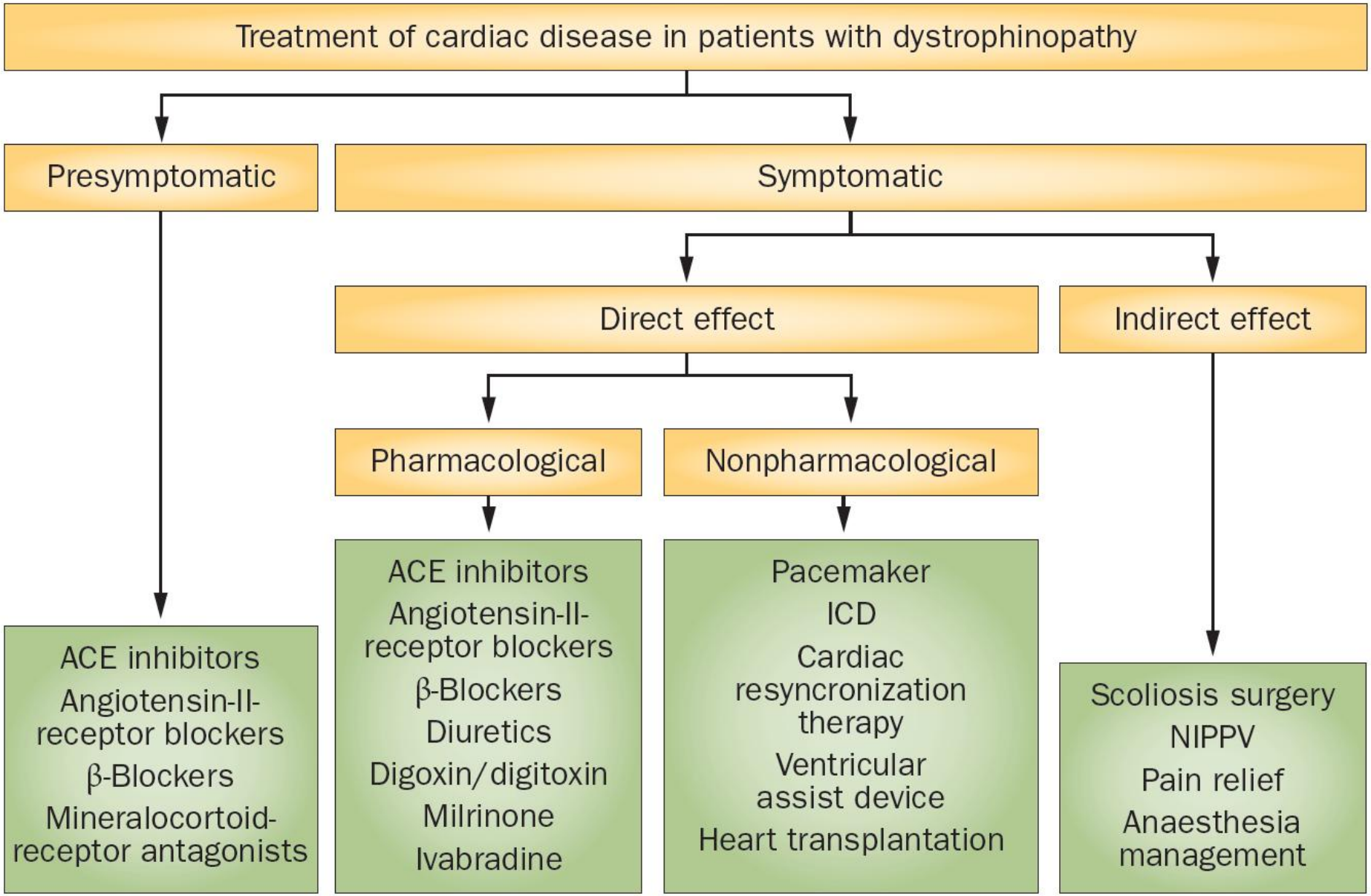

Table 1 | Experimental therapies for cardiac involvement in animal models of dystrophinopathies

Method	Effect	Model	Reference
Pharmacological			
Bradykinin	Restores heart failure	Golden retriever dog model of muscular dystrophy	Su, J. B. *et al.* (2012)[133]
Losartan	Blocks TGF-β signalling	*Dmd*^{mdx} mice	Chamberlain, J. S. (2007)[134]
Osteopontin	Immunomodulation	*Dmd*^{mdx} mice	Dahiya, S. *et al.* (2011)[135]
Polaxomer	Reduction of fibrosis	Golden retriever dog model of muscular dystrophy	Townsend, D. *et al.* (2010)[136]
Resveratrol	p300 protein modulation	*Dmd*^{mdx} mice	Kuno, A. *et al.* (2013)[137] and Hori, Y. S. *et al.* (2011)[138]
Sildenafil	Cardioprotection	*Dmd*^{mdx} mice	Adamo, C. M. *et al.* (2010)[139]
SNT-MC17/idebenone	Corrects diastolic dysfunction	*Dmd*^{mdx} mice	Buyse, G. M. *et al.* (2009)[140]
Suramin	Attenuates cardiomyopathy	*Dmd*^{mdx} mice	de Oliveira Moreira, D. *et al.* (2013)[141]
Molecular			
AAV-mediated transfer of microdystrophin	Gene transfer	*Dmd*^{mdx} mice	Bostick, B. *et al.* (2012)[142] and Kleinschmidt, J. A. *et al.* (2012)[143]
AAV-mediated transfer of microdystrophin	Gene transfer	Hamster	Vitiello, C. *et al.* (2009)[144]
Aminoglycosides	Ribosomal readthrough	*Dmd*^{mdx} mice	Wagner, K. R. *et al.* (2001)[129] and Kimura, S. *et al.* (2005)[145]
Ataluren	Exon skipping	Mice	Beytía Mde, L. *et al.* (2012)[146]
RTC13, RTC14	Ribosomal readthrough	*Dmd*^{mdx} mice	Kayali, R. *et al.* (2012)[128]
Dystrophin surrogates (alternative gene upregulation)			
Arginine butyrate	Utrophin upregulation	*Dmd*^{mdx} mice	Vianello, S. *et al.* (2013)[130]
Recombinant AAV	Expression of claudin-5	Mice	Delfín, D. A. *et al.* (2012)[147]
Other			
Stem cells	Stem-cell transplantation	*Dmd*^{mdx} mice	Chun, J. L. *et al.* (2013)[132]

Abbreviations: AAV, adeno-associated virus; RTC, readthrough compound; TGF-β, transforming growth factor β.

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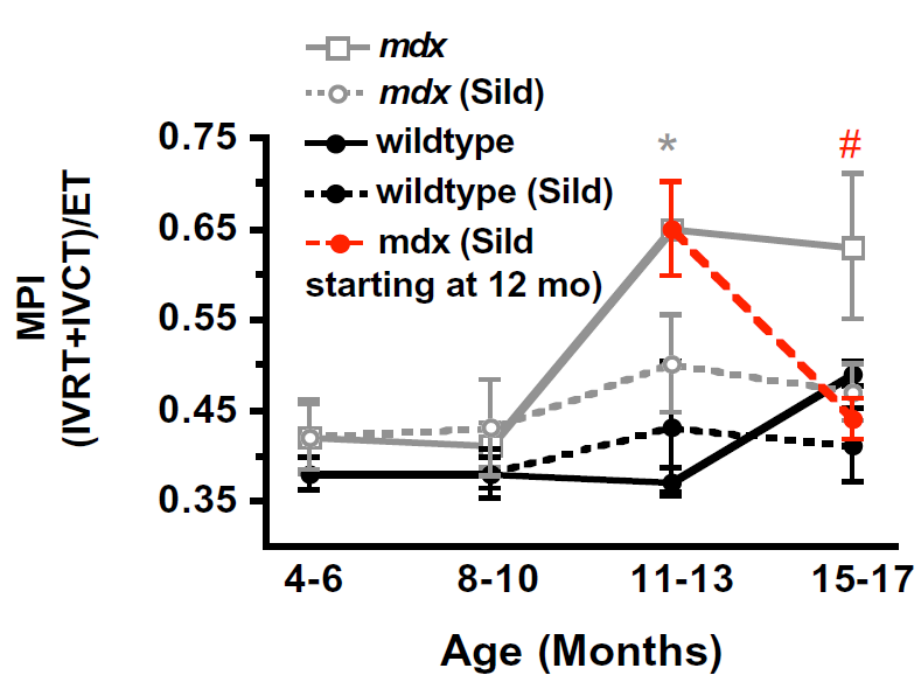
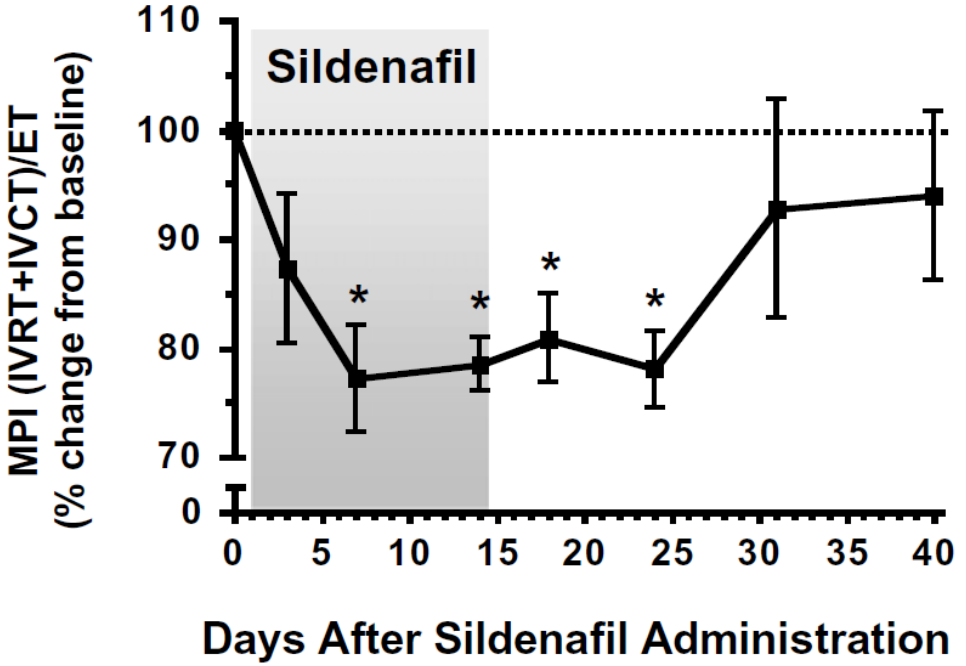
Sidenifil for DMD mouse





Proc Natl Acad Sci U S A. 2010;107(44):19079-83.

해외뉴스

미FDA, 희귀근육병 치료제 개발사에 바우처 지급

신속심사 이용권…타사 판매도 가능해

발행 2015.08.24 12:28:13

혁신적인 RNA표적 치료법의 개발사인 사렙타 테라퓨틱스(Sarepta Therapeutics)는 미국 FDA가 51번 엑손 스키핑으로 치료할 수 있는 듀센형 근이영양증(Duchenne Muscular Dystrophy, DMD) 환자를 위한 약물이 될 가능성이 있는 에테플러센(eteplirsen)을 희귀 소아질환 신속심사 대상으로 지정했다고 발표했다.

희귀 소아질환 약물 지정은 이전에 FDA가 에테플러센을 희귀의약품과 패스트트랙 대상으로 인정한 결정을 보완하게 된다.

사렙타의 최고의료책임자인 에드워드 케이 박사는 "FDA의 희귀의약품 개발부에서 에테플러센을 희귀 소아질환 약물로 지정한 것에 기뻐하고 있다"고 말하며 "FDA가 자사의 핵심 중점 분야인 희귀 소아질환 치료제의 개발을 촉진하기 위해 희귀 소아질환 신속심사 바우처 프로그램을 고안한 것에 감사한다"고 밝혔다.

또 이를 통해 치료제가 절실하게 필요한 소아에게 신속하게 제품을 제공할 수 있길 바라고 있다고 덧붙였다.

에테플러센은 정상적인 디스트로핀 단백질 생성을 가능하게 해 듀센형 근이영양증의 근본적인 원인에 대응하도록 만들어진 시험약이다. 현재까지 임상시험에서는 긍정적인 안전성 및 내약성 프로파일이 입

http://www.newsmp.com/news/articleView.html?idxno=140245

Summary I

- Muscular dystrophy type Duchenne (DMD) and type Becker (BMD)

  X-linked genetic diseases

- Progressive cardiomyopathy

  major cause of morbidity and mortality

- Cardiac involvement

  myocardial damage

  starting from the epicardial third of the inferolateral wall

  → extension in contiguous segments

  → dilated cardiomyopathy or sudden cardiac death

Summary II

- Typical ECG abnormalities : R:S ratio ≥1 in lead V1, deep Q waves in leads I, aVL, V5–V6, sinus tachycardia
  RAD, CRBBB
- Echocardiography : myocardial velocity and deformation imaging
  subtle cardiac abnormalities
  cardiac involvement at early disease stages
  important prognostic information
- Multi-parametric CMR
  both subtle functional & morphological abnormalities
  for cardiac disease progression & therapy monitoring

Summary III

- Heart failure treatment
  - ACE inhibitors, ß-blockers, and diuretics
  - beneficial ventricular remodelling
  - improvement in LV systolic function
- Medical treatment
  - steroids, cardiac resynchronisation, ICD implantation
  - cardiac transplantation
    - consider in rapidly worsening cardiac function