What's New in Duchenne Muscular Dystrophy

2022

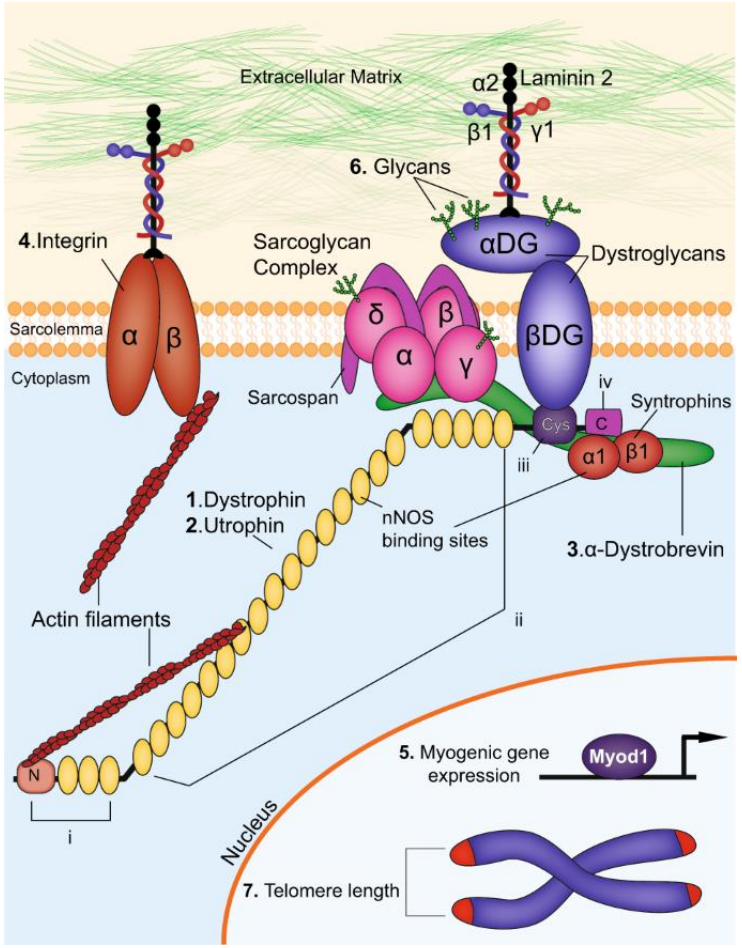
Slide Set Overview

- **Review of Duchenne Muscular Dystrophy (DMD)**
  - Clinical presentation, pathology
  - Diagnostic considerations
- **Clinical management of DMD**
  - Multidisciplinary approach to care
  - Current and emerging therapies
- **DMD resources**

Duchenne muscular dystrophy (DMD)

- DMD is a rare, progressive, X-linked recessive, muscular dystrophy, affecting predominantly males
- DMD occurs in 1 in 5,000 male births and is the most common childhood-onset muscular dystrophy[1,2]
- DMD is caused by mutations in the *DMD* gene that result in absent or decreased dystrophin, a muscle membrane protein[2,3]
- Dystrophin plays a key structural role in muscle fiber function and protects against damage during normal muscle contraction

Dystrophin-associated complex[4]



1. Al-Zaidy S, 2017. 2. Aartsma-Rus A, 2016. 3. Shieh PB, 2018. 4. Yucel N, 2018

Clinical signs and symptoms[1,2]

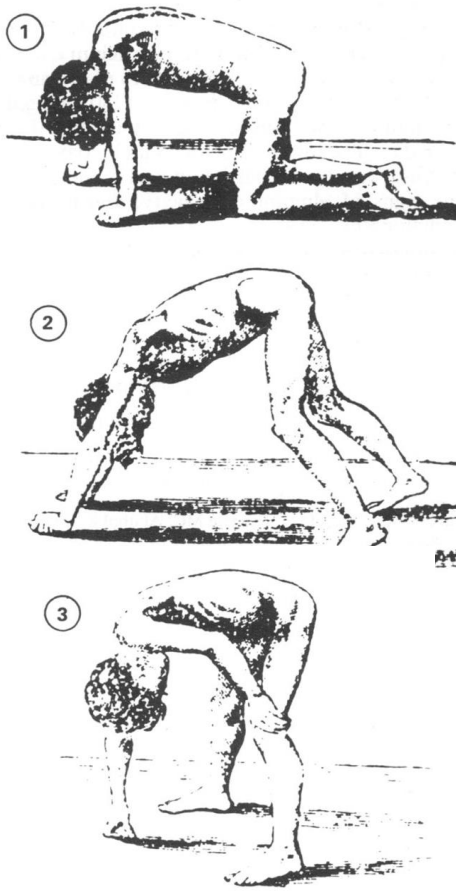
Motor signs[1,2]

- Abnormal gait: waddling
- Frequent falls
- Difficulty climbing steps
- Difficulty getting up from the floor >2”
- Delayed walking
- Toe walking
- Lordosis
- Never able to jump or hop
- Abnormal running
- Enlarged calves

Non-motor signs[1,2]

- Cognitive delay
- Learning deficits
- Attention deficits
- Language delay or difficulty

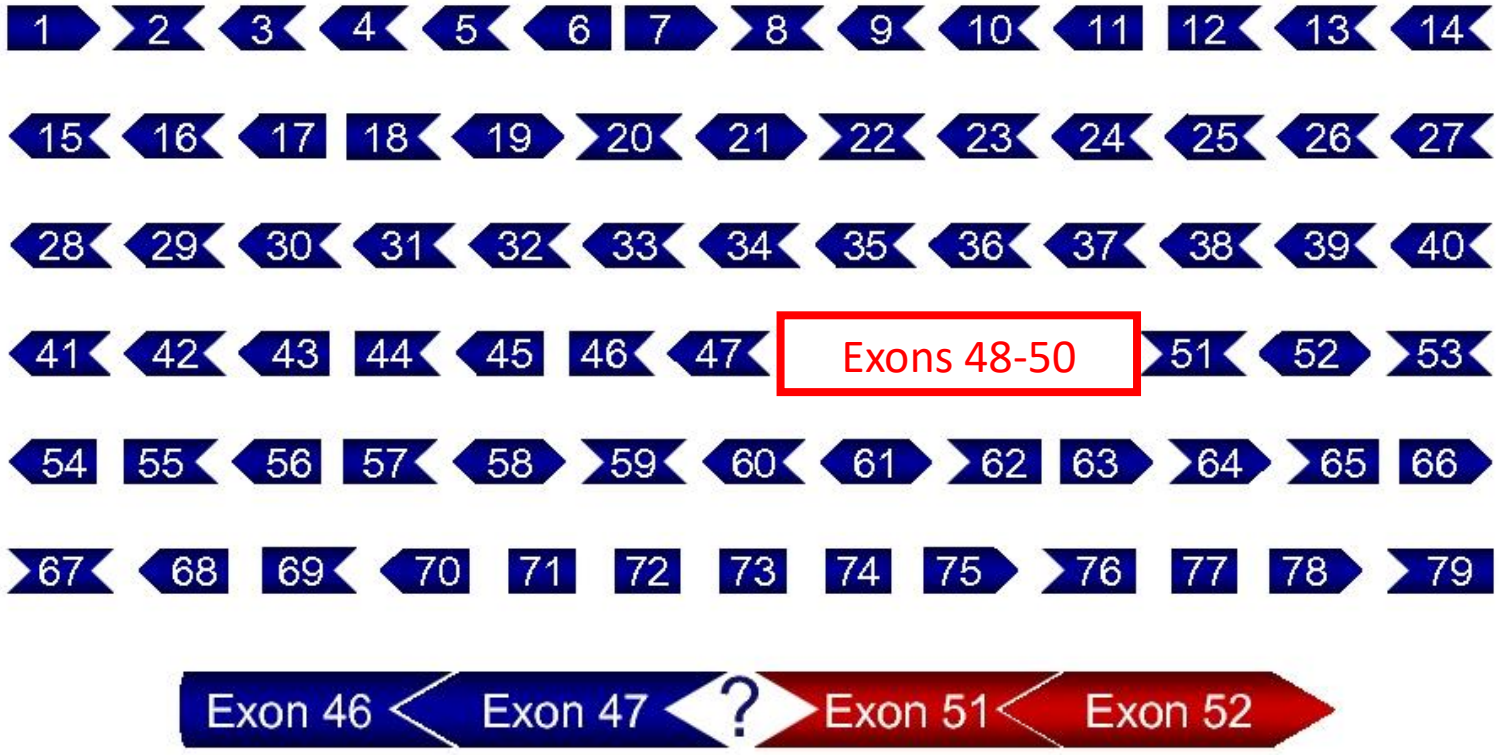
Gower’s Sign[3]



1. Ciafaloni E, 2009 . 2. Birnkrant DJ, 2018. 3. Gowers WR (1845-1915), Public domain, via Wikipedia Commons. Accessed May 23, 2022

DMD pathology: Genetics and reading frame theory

- Mutations that disrupt the reading frame (i.e. “out-of-frame” deletions) such as 48-50, lead to complete loss of dystrophin protein
- Mutations that do not disrupt the reading-frame, allow for production of some dystrophin reduced in size/amount, resulting in a milder phenotype



Duan D, 2021.

DMD vs BMD: Differential diagnosis

- Dystrophinopathies share common pathology and symptoms along a spectrum, but symptoms are most severe among individuals with DMD

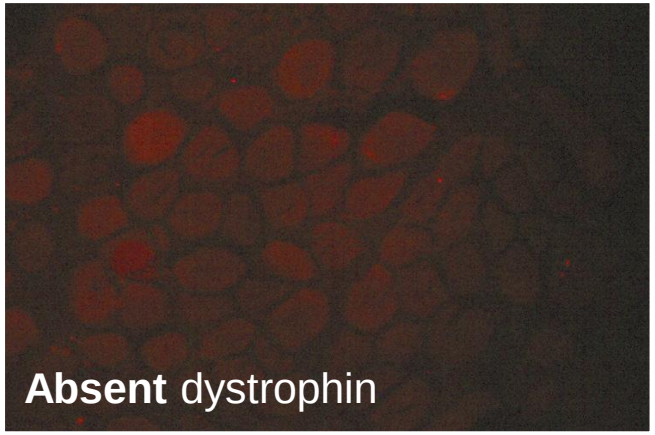
DMD

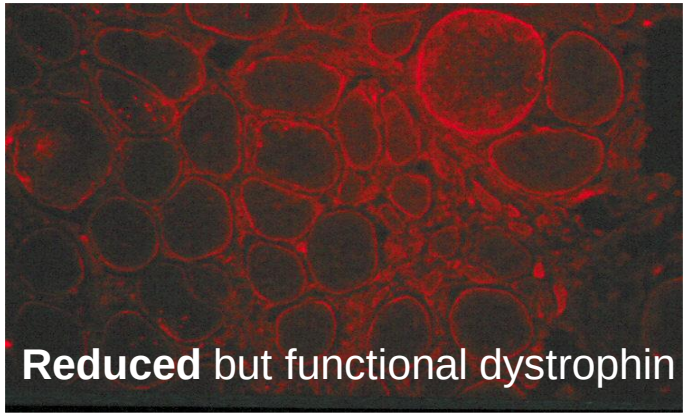
- **More** severe
- **Earlier** onset (always before age 5)
- **Faster** progression
- Reading frame **disrupted**

Intermediate phenotypes

BMD

- **Less** severe
- **Later** onset
- **Slower** progression
- Reading frame **preserved**



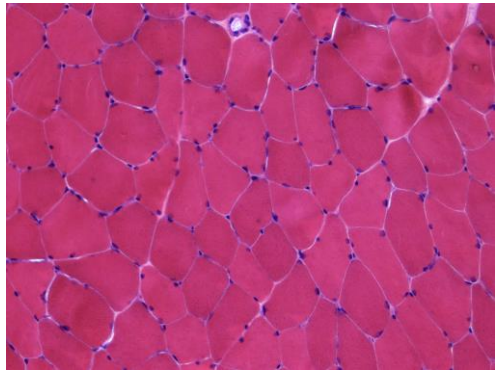


Images courtesy of E Ciafaloni

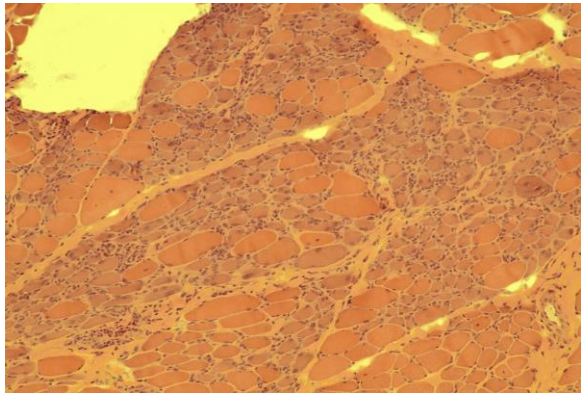
1. Duan D, 2021. 2. Aartsma-Rus A, 2006

Example:
Muscle biopsy and dystrophin staining

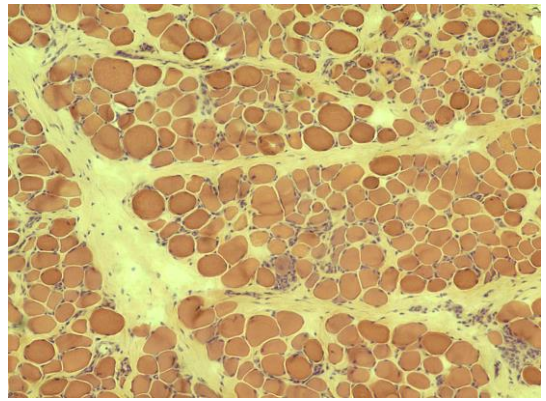
Normal



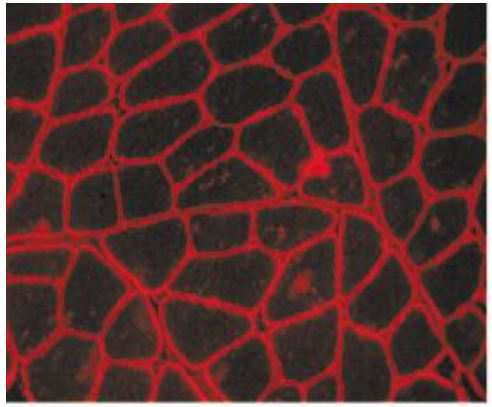
BMD



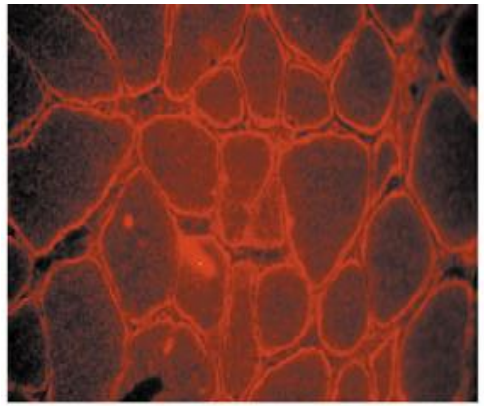
DMD



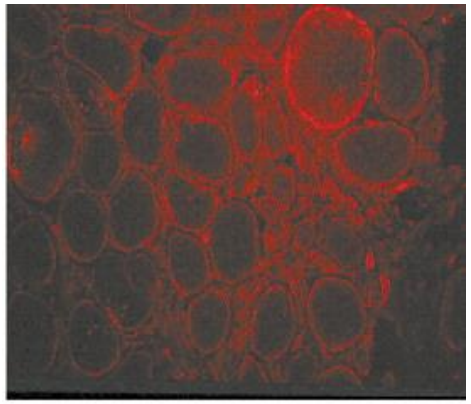
Normal



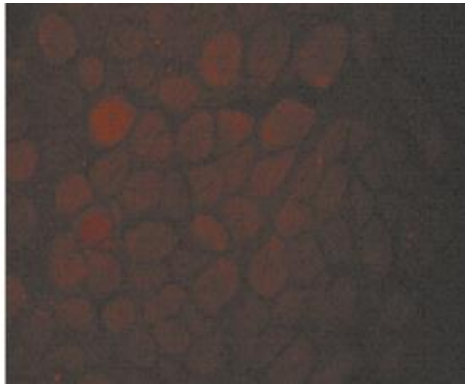
Mild BMD



Severe BMD



DMD



Images courtesy of E Ciafaloni

Stages of DMD Progression

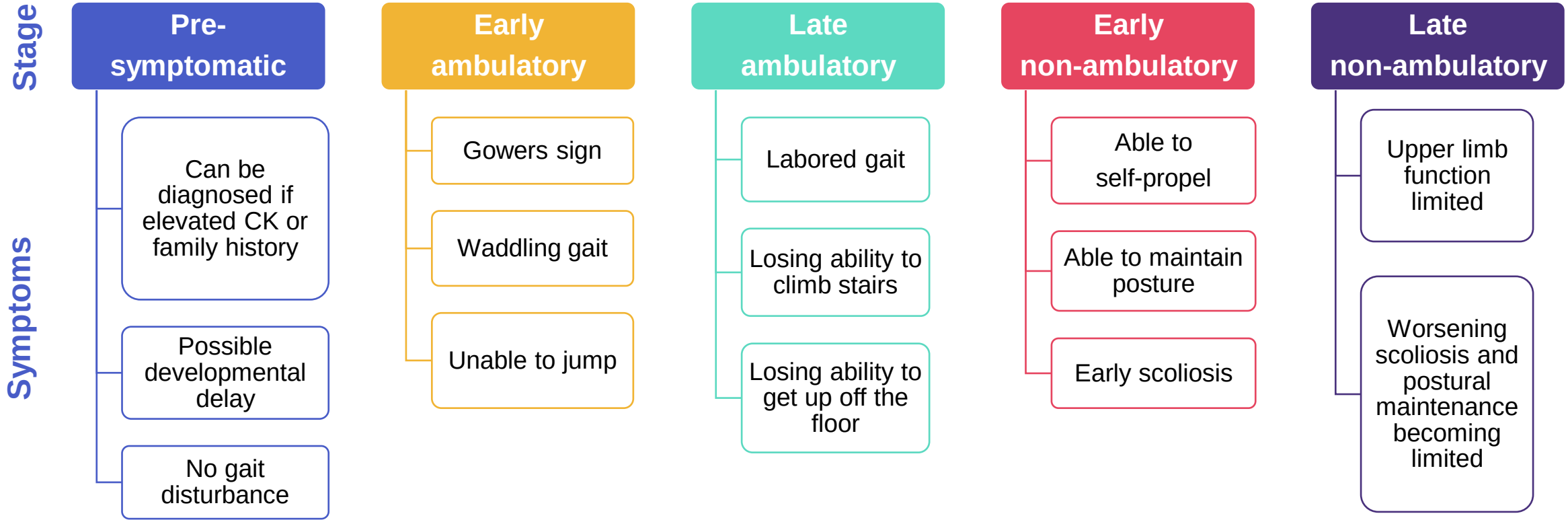


Figure adapted from Birnkrant DJ, 2018

Diagnosis: Recommended tests

- **Elevated CK level** is a hallmark sign of DMD and always elevated from infancy
- **Genetic testing** is confirmatory in **>95%** of DMD cases
  - Muscle biopsy conducted **only** if genetic test is negative and can confirm DMD diagnosis based on absent dystrophin [1]
  - Muscle biopsy rarely needed (<5%)

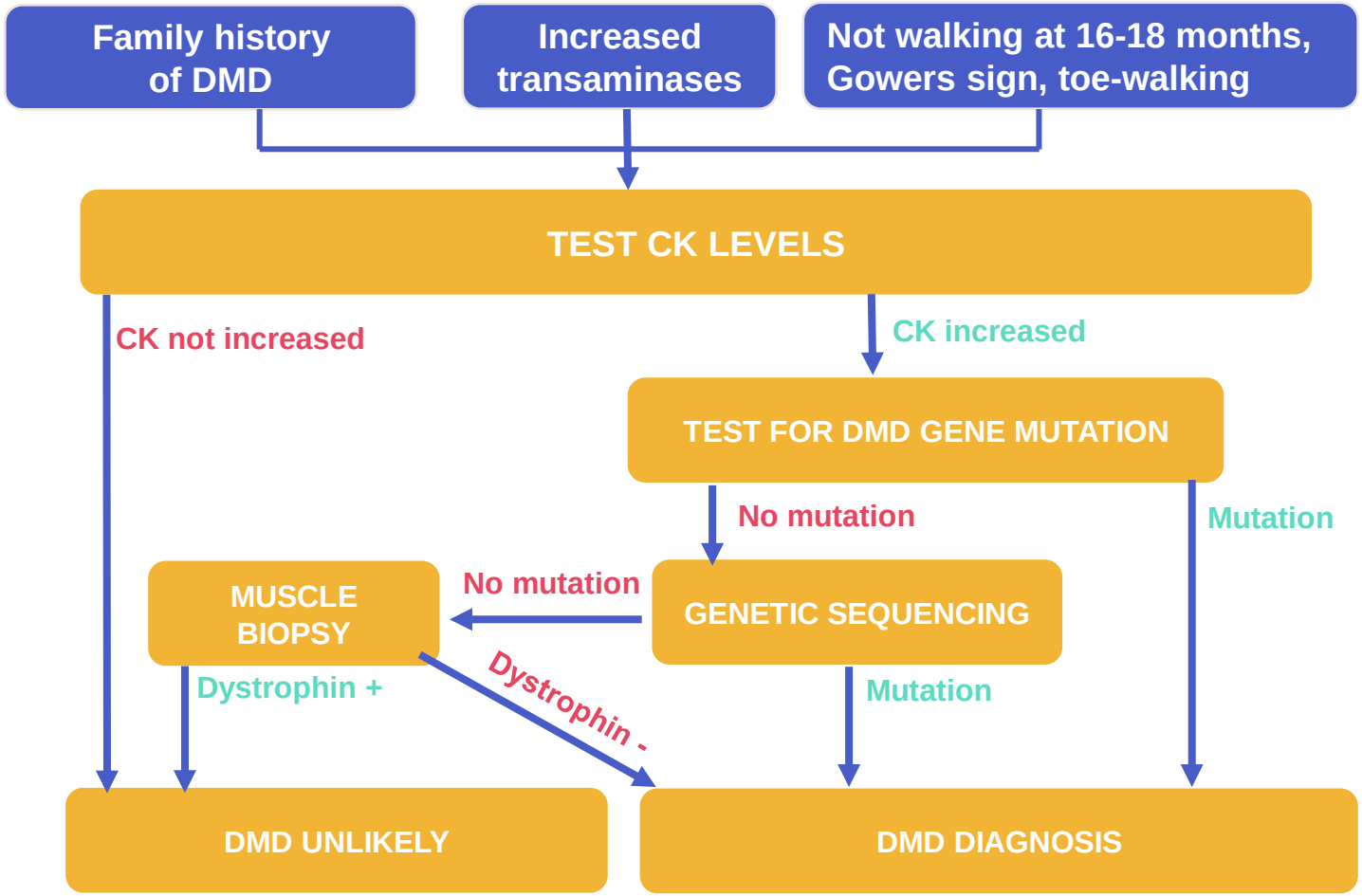


Figure adapted from Birnkrant DJ, 2018

Birnkrant DJ, 2018.

Diagnostic delay in DMD

- An analysis of MD STARnet data indicates a ~2.5-year delay between symptom onset and DMD diagnosis
- Concerns often first noted at ~2 years of age
- First evaluation by a neuromuscular specialist is at ~4.5 years of age
- Definitive diagnosis is at ~5 years of age

Table I. Timeline of diagnostic steps for patients with Duchenne dystrophy without family history of dystrophy (N = 156).

Measure	n	Mean years of age ±SD	Range, years of age
Earliest sign or symptom noted	111	2.5 ± 1.4	0.2-6.1
First evaluation by health specialist	127	3.6 ± 1.7	0.2-8.0
First neurology/neuromuscular visit	131	4.6 ± 1.7	0.3-8.6
First CK test	151	4.7 ± 1.7	0.3-8.6
Age at definitive diagnosis	154	4.9 ± 1.7	0.3-8.8

Delay of ~2.5 years

Early CK testing can reduce delay in diagnosis

Ciafaloni E, 2009

Common causes for diagnostic delay

- Non-universal screening of lab abnormalities at birth
  - Screening for CK/transaminase levels is not a universal standard
  - CK should be tested in any boy with early motor/ developmental delay
- Subtle signs of early disease missed
  - Earliest signs are noted by parents and not trained professionals who may be more adept at recognizing subtle delays
- Cognitive delay/“autism” and DMD can be a comorbidity and may delay DMD diagnosis

Ciafaloni E, 2009

Improving diagnosis

- **Early CK testing** in boys with developmental delay may help speed definitive diagnosis and enable earlier treatment
- DMD is not currently included on the Recommended Uniform Screening Panel for genetic testing[1,2]
  - Treatments may be most effective if initiated early in disease onset/prior to symptom onset
- Efforts are underway by advocacy and government groups to implement newborn screening for DMD nationwide[3]

1. Baby's First Test, Accessed Oct 2021. 2. Duan D, 2021. 3. Al-Zaidy S, 2017

Progress in DMD newborn screening

2007-2011

Ohio Duchenne Newborn Screening (DNBS) pilot study establishes success of a 2-tier approach to identify infants with DMD[1]

- Dried blood spot first tested for elevated CK, then genetic testing

Sep 2018

Pilot program initiated in NY state (a high birth-rate state)[2]

- First baby tested in Oct 2019
- Projected to screen up to 100K infants

Dec 2019

FDA authorizes GSP Neonatal Creatinine Kinase-MM kit[3]

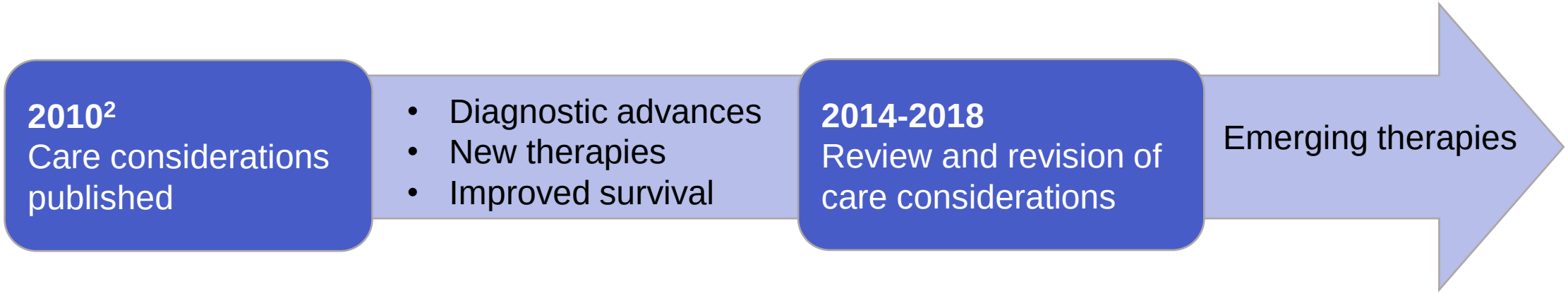
With ongoing success of pilot programs, DMD screening is likely to be adopted into state-based programs nationwide

1. Al-Zaidy S, 2017. 2. Muscular Dystrophy News, 2019. 3. FDA, 2019

Clinical Management of DMD

DMD care guidelines continue to evolve

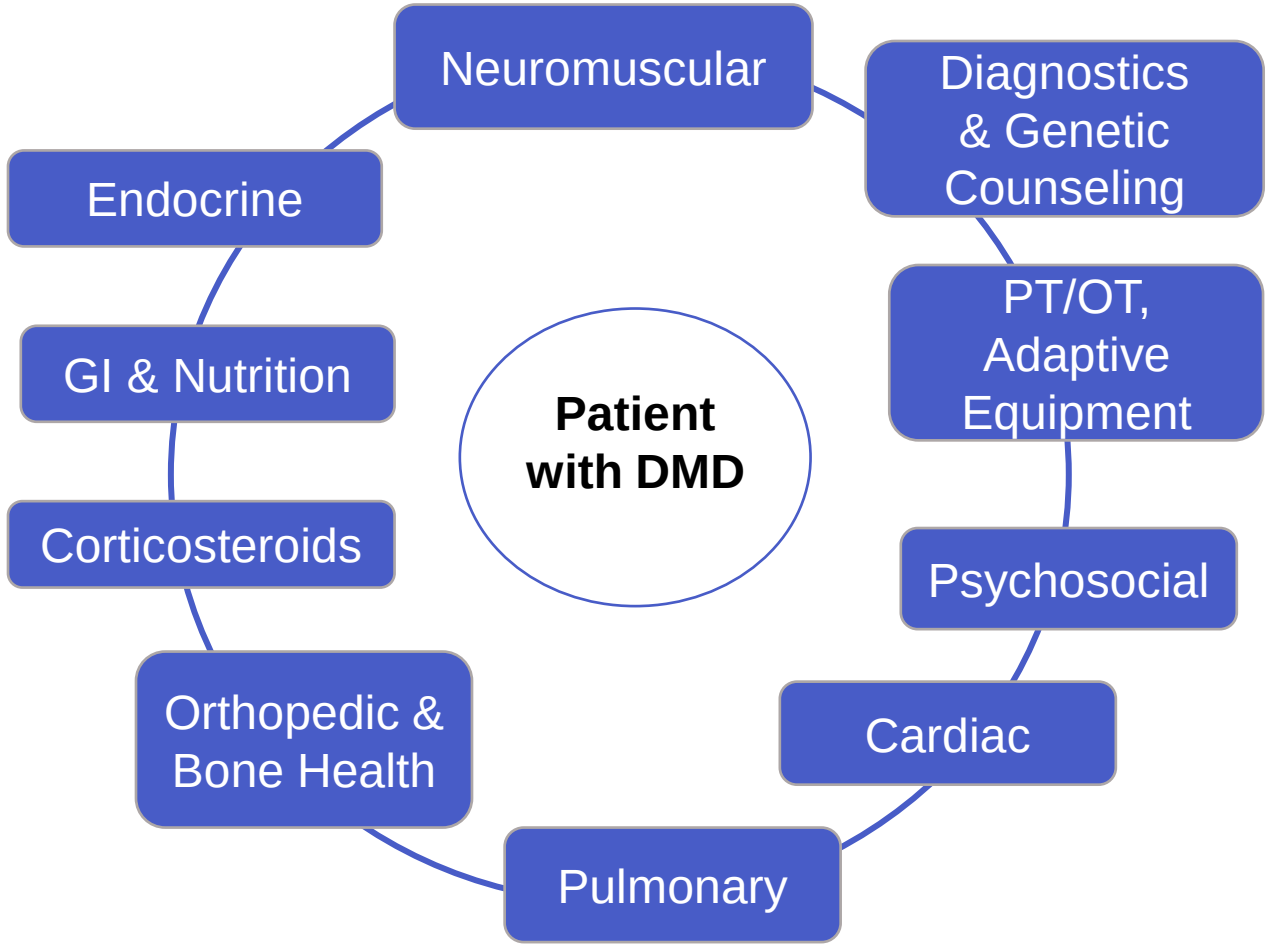
- Care guidelines were updated in 2018 to align with the evolving DMD landscape[1,2]
  - Prolonged survival associated with optimized multidisciplinary care has shifted care goals towards prevention, earlier identification, and treatment of predictable and modifiable complications
  - With patients surviving longer, more emphasis can be placed on quality of life, psychosocial management, and ensuring smooth care transitions across the lifespan
  - Therapeutic options continue to emerge



1. Birnkrant DJ., 2018. 2. Bushby K., 2010

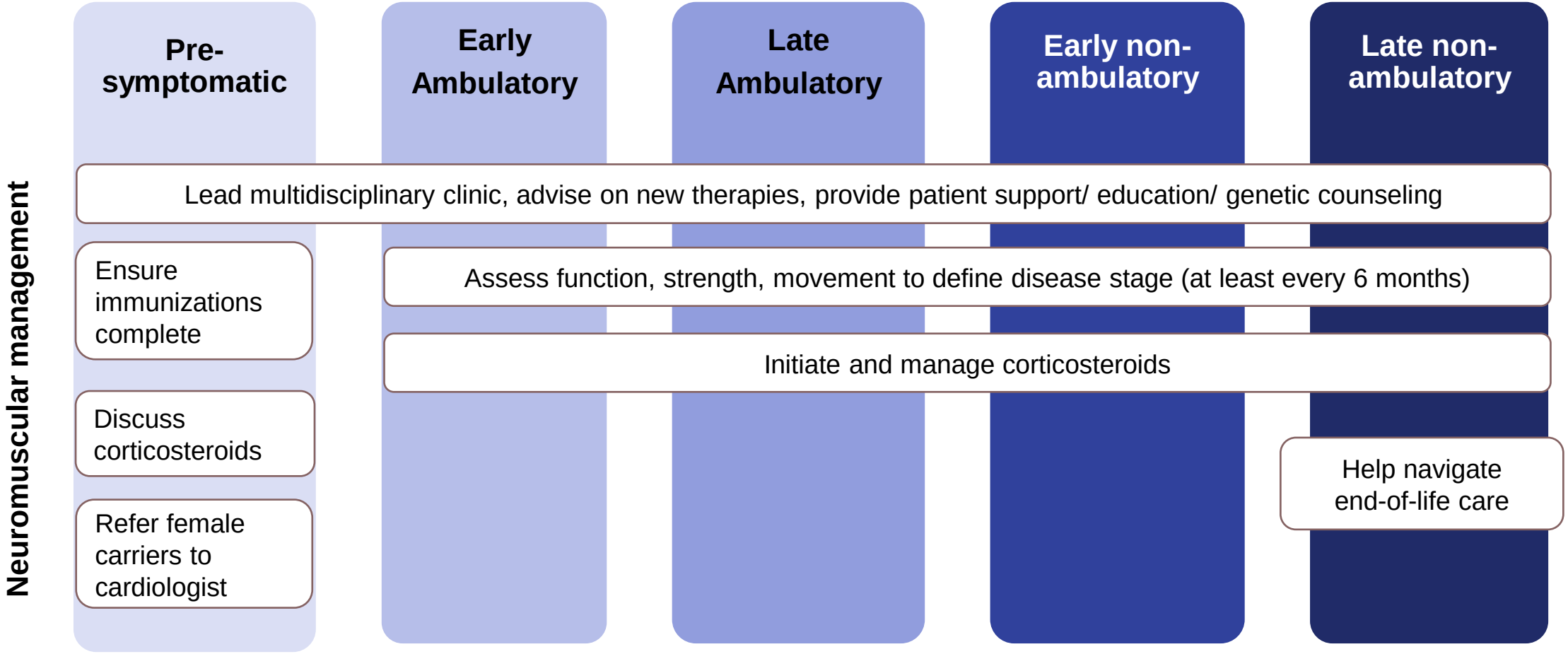
Multidisciplinary care has improved DMD outcomes

- A proactive and multidisciplinary approach has prolonged survival and improved outcomes in DMD[1-3]
  - Prior to 1970, a patient with DMD could expect to live until their 20s[3]
  - Those diagnosed after 1970 can expect to live into their 40s[3]
- Requires coordination of specialists throughout the different stages of the disease[1,2]



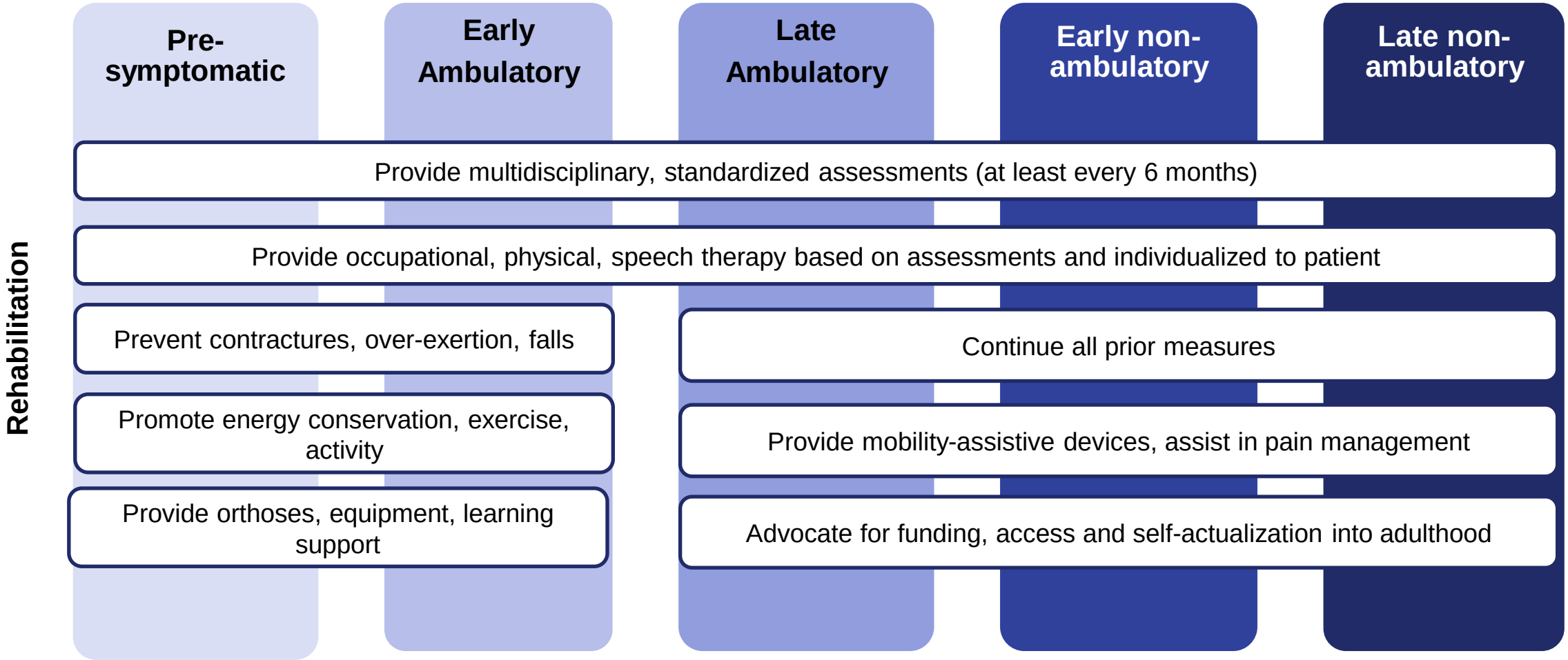
1. Bushby K, 2010. 2.. Birnkrant DJ, 2018. 3. Duan D, 2021

Care recommendations (2018 update):



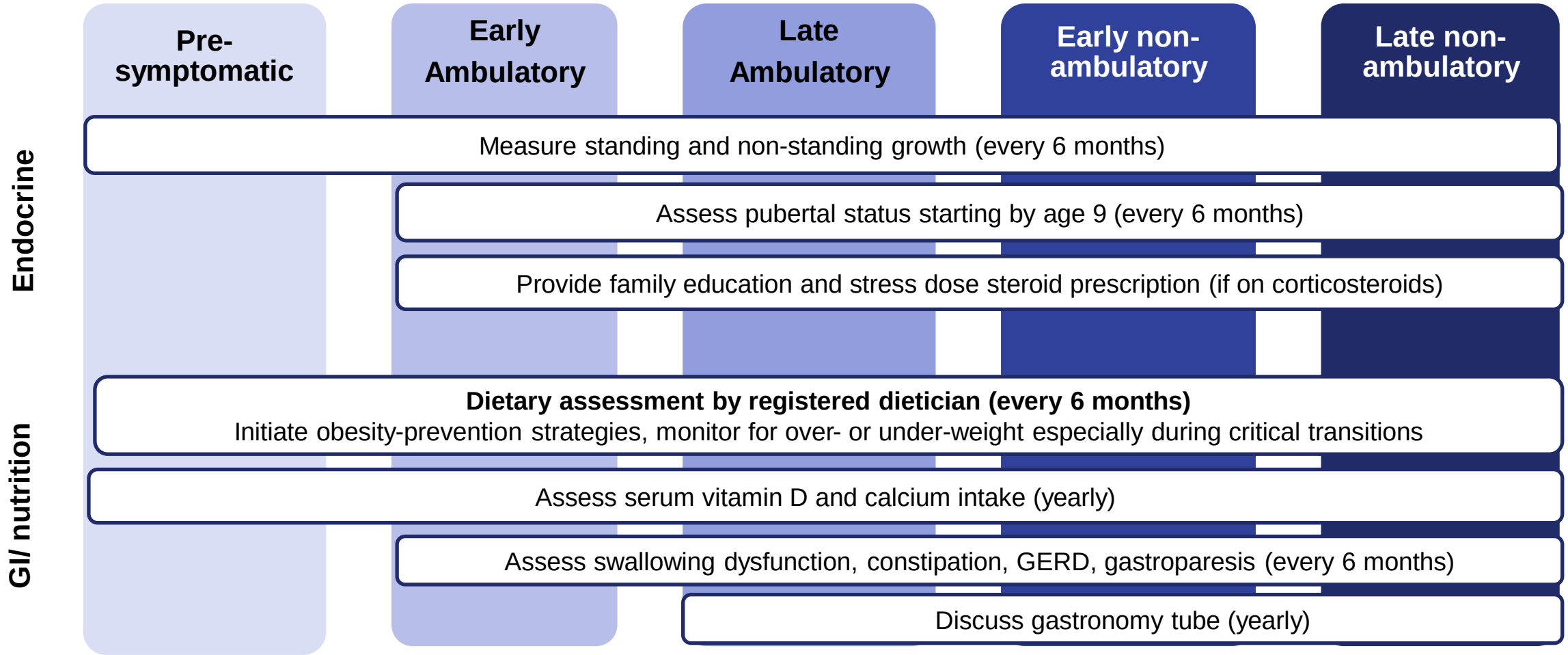
Birnkrant DJ, 2018

Care recommendations (2018 update):



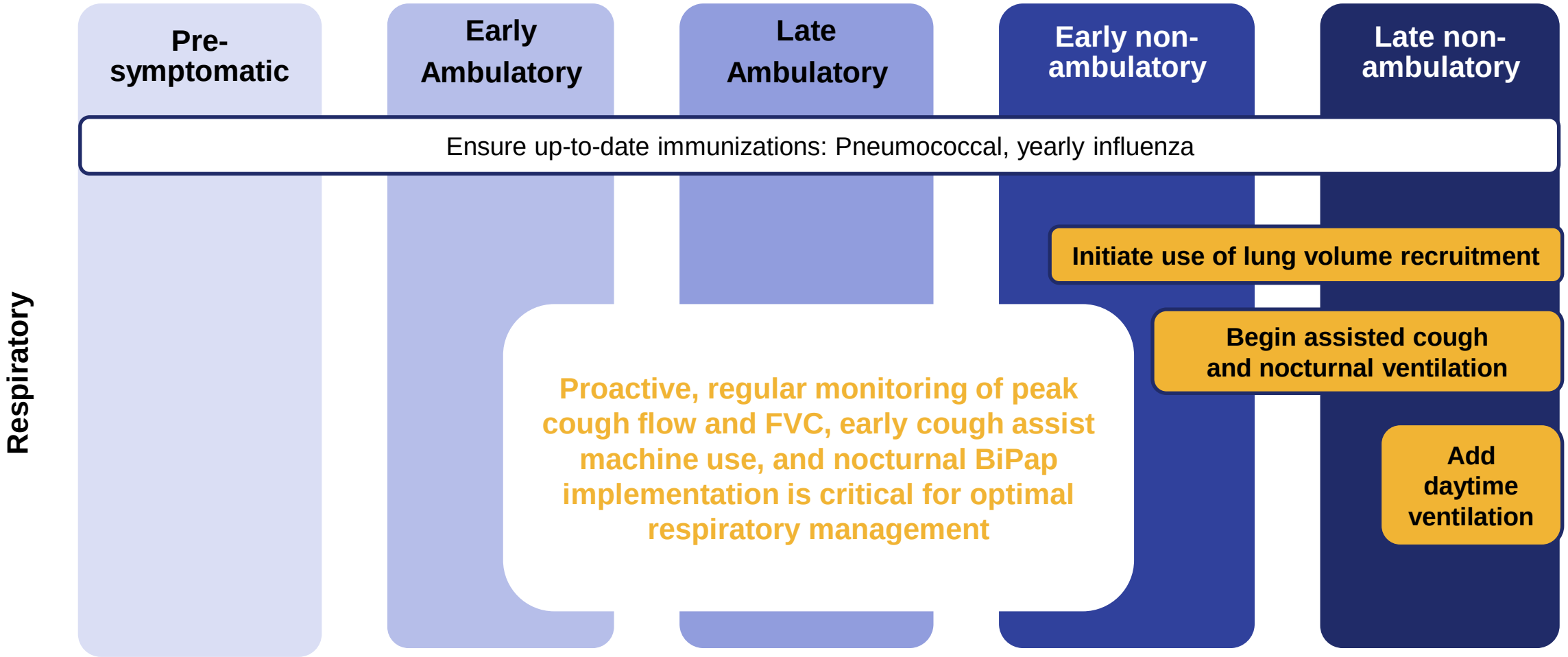
Birnkrant DJ, 2018

Care recommendations (2018 update):



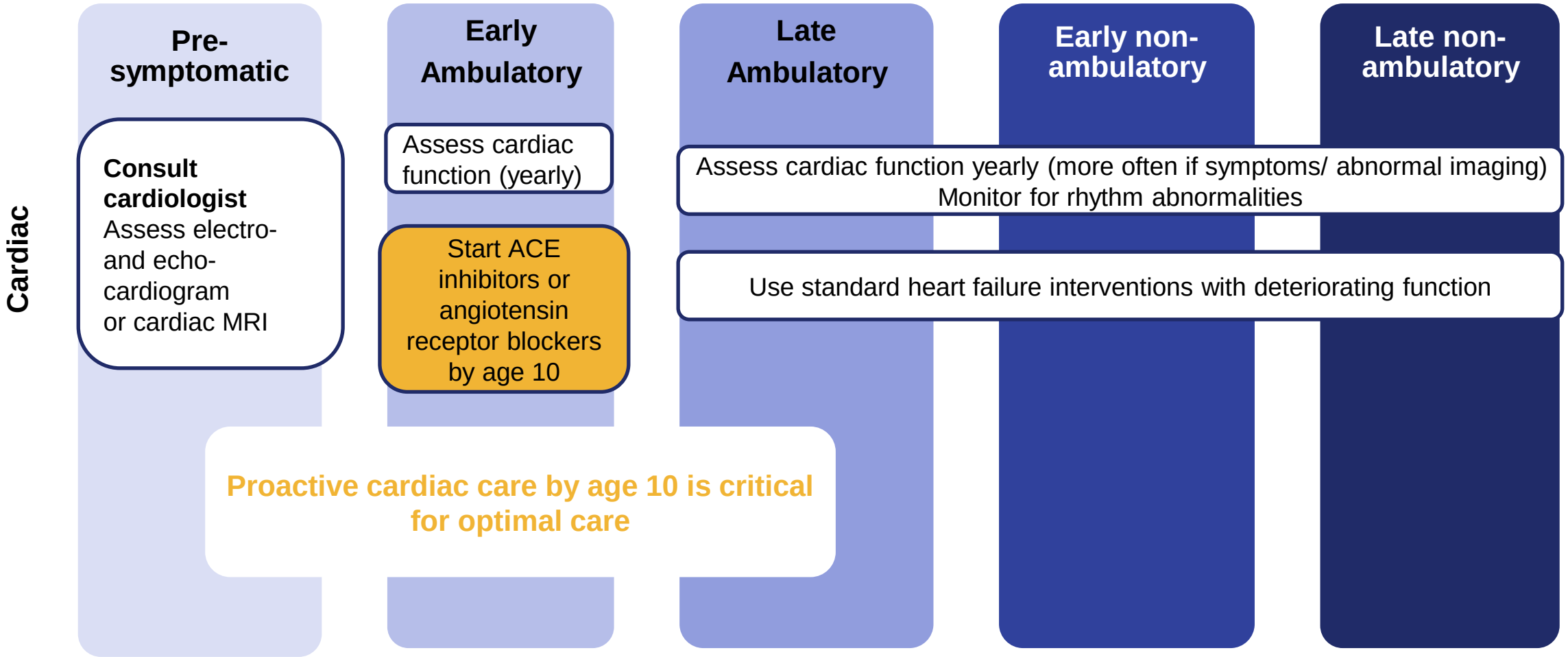
Birnkrant DJ, 2018

Care recommendations (2018 update):



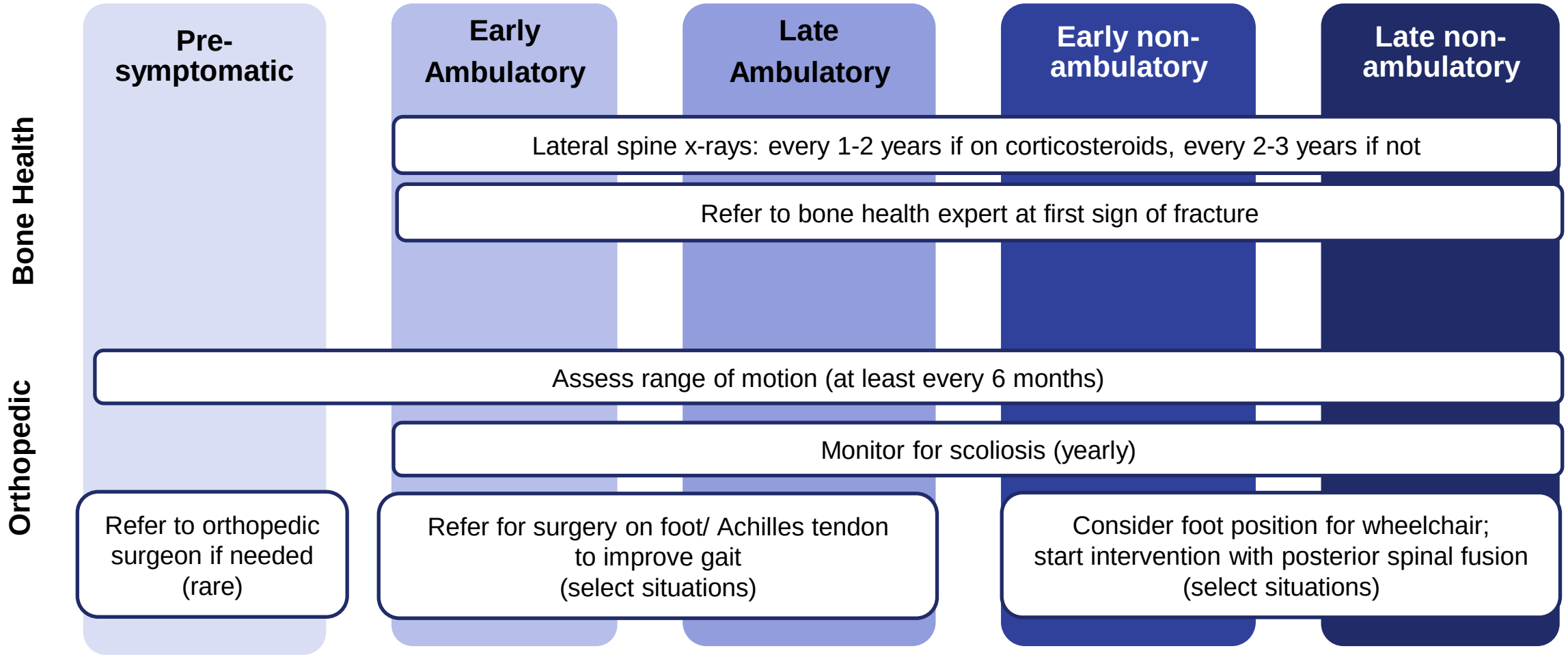
Birnkrant DJ, 2018

Care recommendations (2018 update):



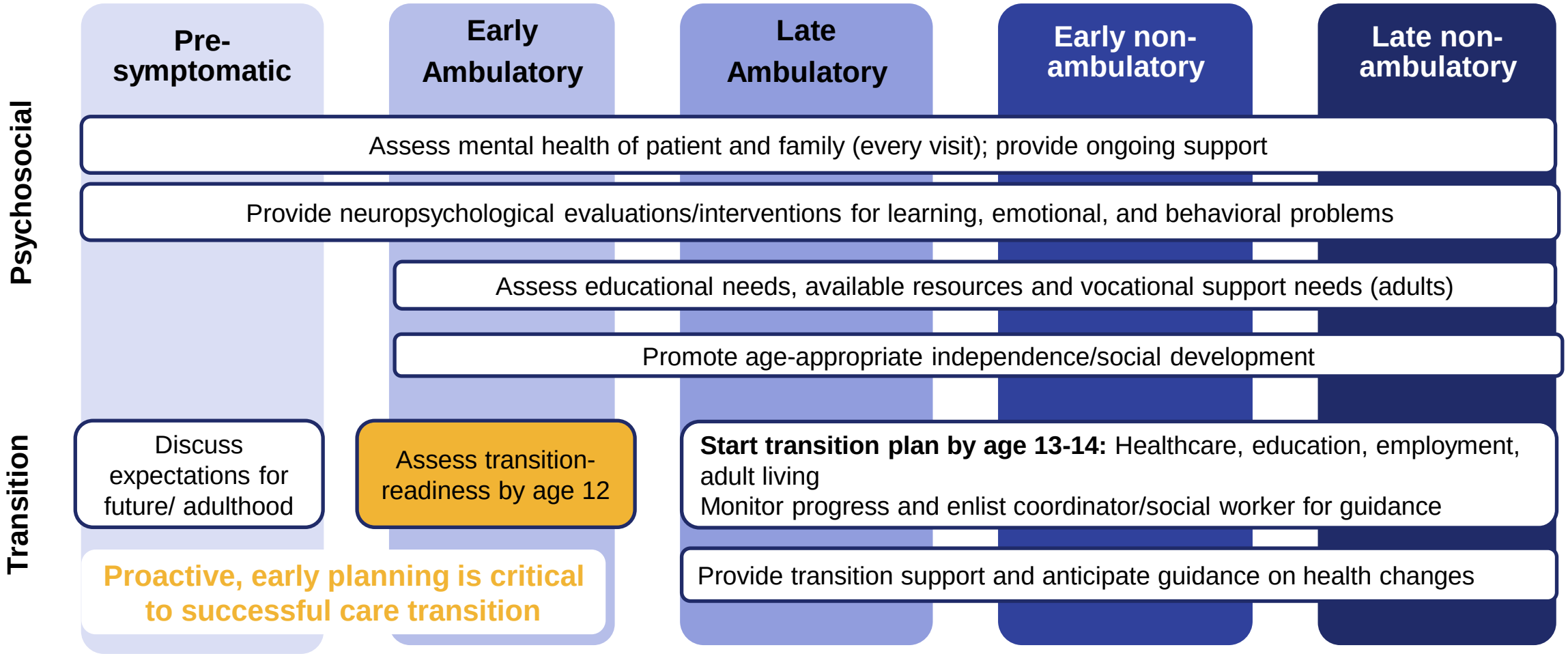
Birnkrant DJ, 2018

Care recommendations (2018 update):



Birnkrant DJ, 2018

Care recommendations (2018 update):



Birnkrant DJ, 2018

Key treatment strategies in DMD

Corticosteroid therapy (standard of care)[1,2]

Goal: Reduce inflammation to increase muscle mass/ strength

- Exact mechanism of action unknown, but likely acts on several targets

Dystrophin-restoration strategies[3]

Goal: Restore dystrophin by manipulating transcription/ translation activity or gene replacement[3]

- Exon-skipping (anti-sense oligonucleotides)
- Nonsense mutation read-through
- Gene transfer (AAV-mediated delivery of micro/mini dystrophin)

1. Duan D, 2021. 2. Birnkrant DJ, 2018. 3. Shieh PB, 2018

Corticosteroid therapy

- Corticosteroids are recognized as the **standard of care** in DMD[1-3]
  - Steroids are effective and associated with several benefits[2]
- Guidelines recommend the use of **prednisone** or **deflazacort**
  - No consensus on **which agent** or **regimen is best**, but studies are ongoing

Benefits

- Prolong ambulation (mean ~10 years)[1,3]
- Preserve upper limb and respiratory function[1]
- Reduce the need for scoliosis surgery[1,3]
- Delay onset of cardiomyopathy[2]

Adverse events[2,4,5]

- Weight gain
- Short stature
- Skin marks
- Bone fragility

1. Duan D, 2021. 2. Birnkrant DJ, 2018. 3. Shieh PB, 2018. 4. Connelly AM, 2019. 5. Griggs RC, 2016

Corticosteroid therapy: Clinical trials

- Research is underway to help identify which corticosteroid regimens are most effective and may offer patients a more tolerable regimen/ agent[1-6]
- **Vamorolone** is being evaluated as a potentially safer alternative to currently available options[2]

Topic	Select Trials[6]
Optimal regimens	• FOR-DMD: Finding the optimum regimen for DMD (NCT01603407) • Weekend steroids and exercise (NCT04322357)
Vamorolone	• Vamorolone in boys with DMD (NCT03439670)
Combination therapy	• Pamrevlumab in combination with steroids (NCT04632940) • Spironolactone vs prednisolone (NCT03777319)

For details, visit **clinicaltrials.gov**

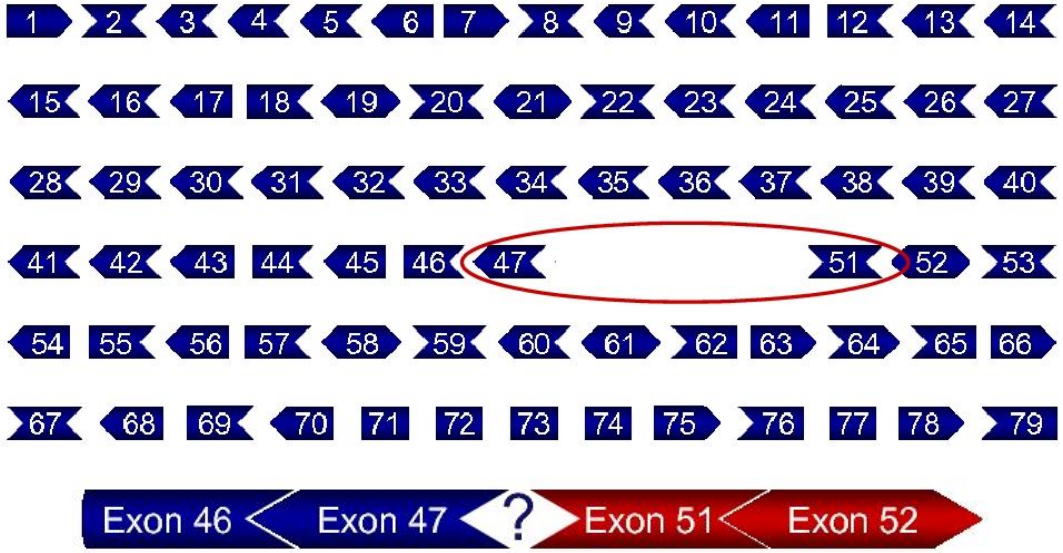
1. Duan D, 2021. 2. Birnkrant DJ, 2018. 3. Shieh PB, 2018. 4. Connelly AM, 2019/ 5. Griggs RC, 2016. 6. ClinicalTrials.gov, Accessed Oct 2021

Dystrophin restoration: Exon-skipping

Strategy: Restore the reading frame of out-of-frame (ie, DMD) dystrophin transcripts to produce partially functional dystrophins (akin to BMD)

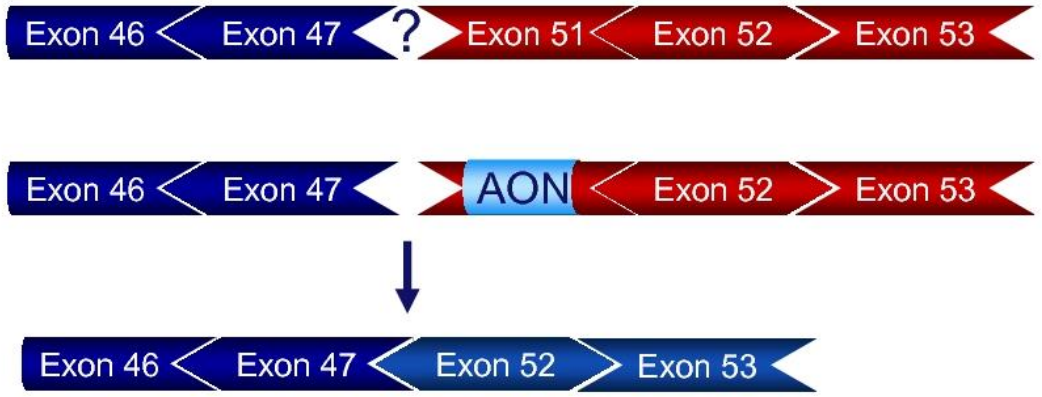
- Different exons are skipped based on mutation size and location (mutation-specific)

Patient with DMD: Exon 48-50 out-of-frame



Out- of- frame mRNA → DMD: No dystrophin

Exon 51 skipping therapy



In-frame mRNA → BMD-like dystrophin

Image courtesy of E Ciafoloni

Duan D, 2021

Dystrophin restoration: Exon-skipping

- Administered via **systemic IV** as an add-on to ongoing **oral** corticosteroid therapy
- **Four** exon-skipping therapies have been **FDA-approved**[1,2]

Exon	Population addressed[3]	Agent	Status[1,4]
45	8-9%	Casimersen (Amondys 45)	Approved
51	13-14%	Eteplirsen (Exondys 51)	Approved
		SRP-5051	Phase 2 ongoing
		Suvodiresen (WVE-210201)	Phase 3 terminated (DYSTANCE 51)
53	7-10%	Golodirsen (Vyondys 53)	Approved
		Viltolarsen (Viltepso)	Approved
		NS-065	Phase 2 ongoing

1. Duan D, 2021. 2. Shirley M, 2021. 3. Shieh PB, 2018. 4. ClinicalTrials.gov, Accessed Sept 2021

Dystrophin restoration: Nonsense mutation-read through

Strategy: Force read-through of nonsense mutations to restore dystrophin[1]

- A subset of individuals with DMD harbor *nonsense mutations* (vs *frameshifting* ones that are amenable to exon-skipping therapies)
  - In these mutations, a codon is substituted with a *stop* codon, which interrupts RNA translation and leads to a truncated, non-functional dystrophin
- Therapies that promote read-through may help the population of 11% of boys with DMD caused by nonsense mutations[2,3]
- **No read-through therapies are approved in the US** for nonsense mutation-based DMD
  - Ataluren is approved for use in the EU

1. Duan D, 2021. 2. Birnkrant DJ, 2018. 3. Shieh PB, 2018

Dystrophin restoration: Gene transfer therapy

Strategy: Deliver a functional cDNA copy of dystrophin gene to muscle tissue

- Packaged and delivered to muscle tissue via an adeno-associated virus (administered as a one-time IV infusion)[1]
- Delivering the dystrophin gene presents challenges due to its size[1]
  - Dystrophin is one of the largest genes in the human genome (~11.4kb)
  - AAVs have a limited carrying capacity (~4.7kb)
  - Micro- or mini- dystrophin constructs have been developed to enable packaging and delivery

The dystrophin gene (Dp427)[2]

Image from Shieh 2018

1. Duan D, 2021. 2. Shieh PB, 2018

Gene transfer therapy: Micro- and mini-dystrophin agents in clinical trials

Dystrophin gene (Dp427)

AAVrh74 (SRP-9001; Nationwide/Sarepta)

AAV9 (SGT-001; Solid Biosciences)

AAV9 (PF-06939926; Pfizer)

Images from Shieh 2018

Shieh PB, 2018

Clinical trial status: SRP-9001 (Sarepta)

- Phase 1 **ENDEAVOR** trial (NCT04626674) ongoing in boys with DMD (>4 years); enrolling via invitation only[1,2]
- **Positive results in first 11 participants[2]**
  - Treatment generally well-tolerated; 2 participants with SAEs (nausea/vomiting, elevated liver enzymes, resolved)
  - Robust micro-dystrophin expression at 3 months (~70% vs ~12% at baseline)
- Pivotal **EMBARK trial** will recruit up to 120 boys with DMD at 40 sites[3]

EMBARK Trial: Phase 3 trial enrolling in US

1. Shieh PB, 2018. 2. ClinicalTrials.gov, Accessed Oct 2021. 3. Muscular Dystrophy News, 2021

Clinical trial status: SGT-001(Solid Biosciences)

- Phase 1/2 trial is ongoing and recruiting[1]
- **Positive results in first 6 participants[2]**
  - Treatment generally well-tolerated; inflammatory SAE reported in 1 patient (resolved)
  - Increased micro-dystrophin at 3 months (up to ~17% of normal dystrophin); levels sustained or increased at 1-2 years
  - Decreased CK levels at 1-year post-treatment
  - Two additional patients have been dosed since data readout

Phase 1/2 IGNITE DMD Trial (NCT03368742): Recruiting

N=16

Key eligibility criteria
- Boys with DMD, 4-17 yo
- ≥ 3 mo corticosteroid therapy
- AAV seronegative

SGT-001 (Dose 1 or 2)

Placebo

12 months

Primary endpoint:
- Micro-dystrophin protein change from baseline

Primary completion: Dec 2023

1. Scott E, 2012. 2. ClinicalTrials.gov, Accessed Oct 2021. 3. Muscular Dystrophy News, 2021

Clinical trial status: PF-06939926 (Pfizer)

- Designated **Orphan Drug** status by FDA (May 2017)
- Phase 1 trial (NCT03362502) ongoing in boys with DMD (ambulatory, 5-10 years old)
- **Positive results in first 9 participants (1 year)[2]**
  - Treatment generally well-tolerated
  - Sustained production of mini-dystrophin protein
  - Improved motor function based on NSAA score change (+3.5 points vs -4 points with placebo)
- Global CIFFREO **Phase 3 trial** is recruiting up to 99 boys with DMD

Phase 3 CIFFREO Trial (NCT04281485): Recruiting

N=99

Key eligibility criteria
- Boys with DMD, 4-8 yo
- ≥ 3 mo corticosteroid therapy
- AAV seronegative

PF-0693992

Placebo

52 weeks

Primary endpoint:
- NSAA change from baseline

Primary completion: Jan 2023

1. ClinicalTrials.gov, Accessed Oct 2021. 2. Muscular Dystrophy News, 2021

Additional strategies under investigation

Strategy[1,2]	Agents[1]	Status[1]
Inhibit myostatin (a muscle growth inhibitor)	• Domogrozumab • Talditercept alfa	Clinical trials failed to demonstrate therapeutic effect[2]
Improve mitochondrial function/ metabolism	Idebenone	Studies terminated due to lack of therapeutic effect[2]
Reduce inflammation/ fibrosis and improve regeneration	Givinostat (HDAC inhibitor)	Phase 2/ 3 study ongoing[3] (NCT03373968)
Reduce fibrosis	Pamrevlumab (anti-CTGF monclonal antibody)	Phase 3 trial ongoing (NCT04371666)[2,3]
Allogenic cardiosphere-derived cells	CAP-1002	Phase 2 extension ongoing (NCT02485938)[3]
Modulate utrophin expression	AAV-based gene delivery (GALG2)	Phase 1/2 trial ongoing (NCT03333590)[3]

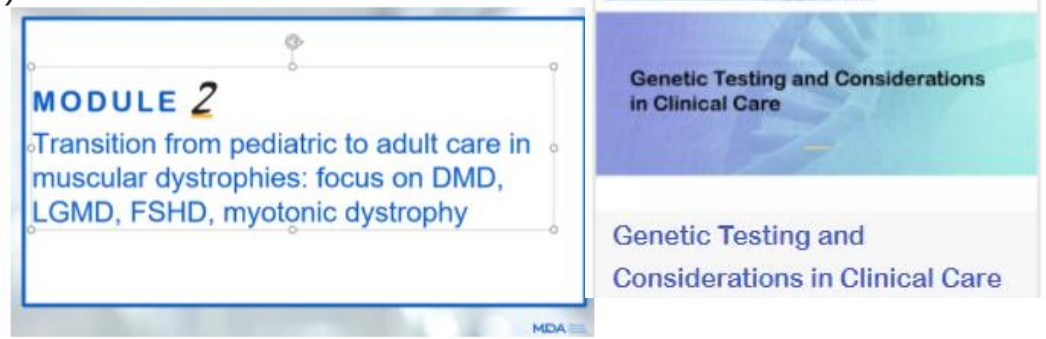
CTGF, connective tissue growth factor

1. Shieh PB, 2018. 2. Duan D, 2021. 3. ClinicalTrials.gov, Accessed Oct 2021

DMD resources: Clinicians

- **DMD care recommendations**
  - Birnkrant et al, 2018. Diagnosis and management of Duchenne muscular dystrophy. *Lancet Neurology* (published as 3-part series)
- **NIH clinical trials database**
  - https://clinicaltrials.gov/
- **MDA Grand Round webinars:**
  - https://www.mda.org/meded/grand-rounds-webinars
- **MDA Clinical Case studies (downloadable pdfs):**
  - https://www.mda.org/meded/considerations-in-care-case-studies

NIH U.S. National Library of Medicine
ClinicalTrials.gov



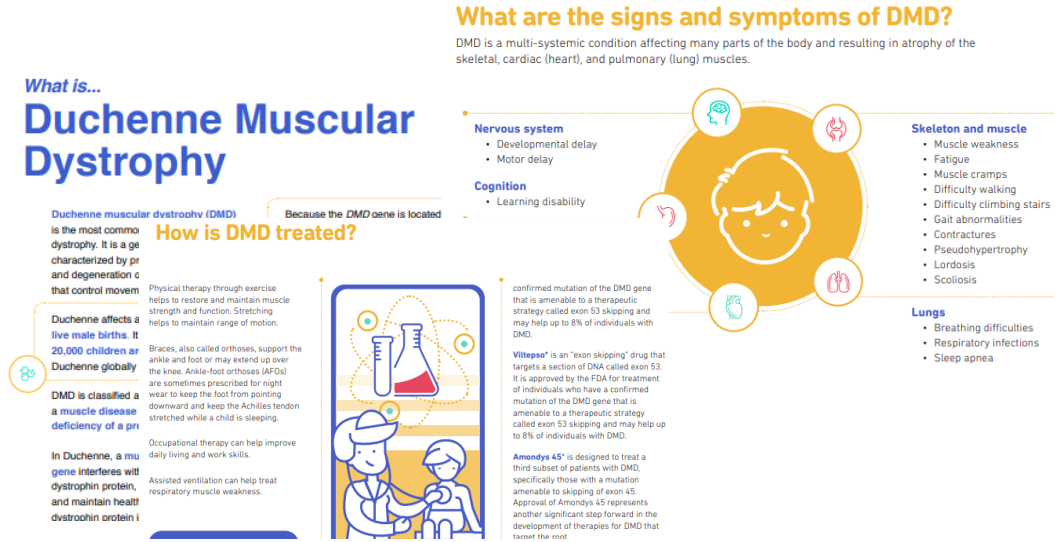
DMD resources: Free genetic testing

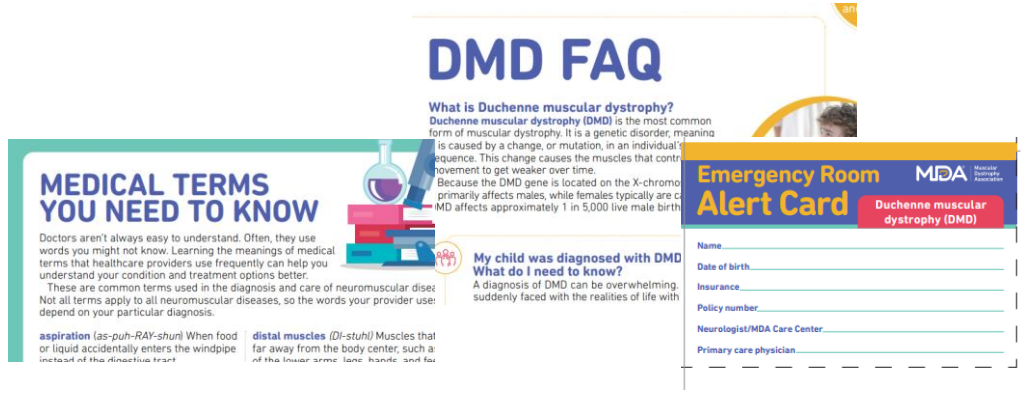
- **MDA/ Invitae *Detect Muscular Dystrophy***
  - Free genetic testing for DMD
  - Remote saliva collection option (ship-to-home) option included
  - https://www.invitae.com/en/detect-muscular-dystrophy/
  - MDA-sponsored program: Visit MDA.org or call 1-833-ASK-MDA1

- ***Decode Duchenne***
  - Free genetic testing (diagnostic and carrier) and counseling– US and CA only
  - https://www.parentprojectmd.org/about-duchenne/decode-duchenne/

DMD resources: Individuals and families

- **MDA clinical trial finder tool:** https://www.mda.org/research/clinical-trials
- **MDA educational materials (downloadable pdfs):**
  - Fact sheet, DMD emergency room card alert, DMD FAQ
  - https://www.mda.org/services/education-materials
- **MDA Engage webinars (various topics)**
  - https://www.mda.org/care/mda-engage/disease-symposia





Enrolling observational studies

- Patients with DMD may be eligible to participate in ongoing registries or observational studies aimed at improving understanding of DMD

Areas of observational research in DMD

Research area	Select studies (US-based)
Patient registries	• The Duchenne Registry [https://www.duchenneregistry.org/] • CureDuchenne Link™ [https://www.cureduchenne.org/cureduchenne-link/]
Wearable technology	Wearable technology to assess gait function [NCT04193085]
Biomarkers	• Extracellular RNA biomarkers [NCT05016908] • MRI and biomarkers [NCT01484678] • Biomarker development for MDs [NCT05019625]
Newborn screening	Early check: Expanded screening for newborns [https://earlycheck.org/]

Additional information on clinical studies is available at **clinicaltrials.gov**