KEY TAKEAWAYS

- DMD is a rare genetic disorder that causes progressive muscular damage and degeneration[1,2]
- Once muscle is lost, it cannot be restored[2,4,14]
- Early intervention is critical to delay disease progression and treat potentially life-threatening complications[1,2,13,14]
- Slowing the decline in physical function during the ambulatory phase of the disease could delay disease progression[1,18]
- Developmental delay should trigger a CK test[2,25]
- Patients with elevated CK levels or missed developmental milestones should be referred to a neuromuscular specialist[2,25]
- Genetic testing is the only method for determining a patient's specific mutation type, which may help identify medical management options and potential to enrol into clinical trials[2,6]

BMD, Becker muscular dystrophy; CGH, comparative genome hybridisation; CK, creatine kinase; DMD, Duchenne muscular dystrophy; FVC, forced vital capacity; L, litres; MPLA, multiplex ligation-dependent probe amplification; NGS, next generation sequencing.

REFERENCES

1. van Ruiten HJ, *et al. Arch Dis Child.* 2014;99:1074–1077. **2.** Birnkrant DJ, *et al. Lancet Neurol.* 2018;17:251–267. **3.** Grounds MD, *et al. Dis Model Mech.* 2020;13(2):dmm043638. **4.** Blake DJ, *et al. Physiol Rev.* 2002;82:291–329. **5.** MDA. DMD muscular dystrophy (DMD): causes/inheritance. Available at: https://www.mda.org/disease/DMD-muscular-dystrophy/causes-inheritance [Accessed July 2020]. **6.** Aartsma-Rus A, *et al. J Med Genet.* 2016;53:145–151. **7.** Crisafulli S, *et al. Orphanet J Rare Dis.* 2020;15:141. **8.** Bushby K, *et al. Lancet.* 2010;9:77-93. **9.** DFSG. Carriers of Duchenne. Available at: https://www.dfsg.org.uk/understand-dmd/carriers-of-duchennebecker-muscular-dystrophy/ [Accessed July 2020]. **10.** National Institutes of Health. Muscular dystrophy. Available at: https://www. nichd.nih.gov/health/topics/factsheets/540 [Accessed July 2020]. **11.** Ciafaloni E, *et al. J Pediatr.* 2009;155:380–385. **12.** Dent KM, *et al. Am J Med Genet.* 2005;134:295–298. **13.** Lurio JG, *et al. Am Fam Physician.* 2015;91:38–44. **14.** Laing NG, *et al. Clin Biochem Rev.* 2011;32:129–134. **15.** Noritz GH, *et al. Pediatrics.* 2013;131:e2016–e2027. **16.** Mendell JR, Lloyd-Puryear M. *Muscle Nerve.* 2013;48:21–26. **17.** van Dommelen P, *et al. Dev med Child Neurol.* 2020; doi: 10.1111/dmcn. **18.** Humbertclaude V, *et al. Eur J Paediatr Neurol.* 2012;16:149–160. **19.** Centers for Disease Control and Prevention. Developmental milestones. Available at: https://www.cdc.gov/ncbddd/actearly/pdf/checklists/all_checklists.pdf [Accessed July 2020]. **20.** National Task Force for Early Identification of Childhood Neuromuscular Disorders. Child Muscle Weakness. 2019. Available at: childmuscleweakness.org [Accessed July 2020]. **21.** Parsons EP, *et al. Eur J Paediatr Neurol.* 2004;8:145-153. **22.** Ardıçlı D, *et al. Neuropediatrics.* 2019;50:41-45. **23.** Counterman KJ, *et al. Muscle Nerve.* 2020;61:36-34. **24.** Aartsma-Rus A, *et al. J Pediatr.* 2019;204:305–313.e14. **25.** National Task Force for Early Identification of Childhood Neuromuscular Disorders. Guide for primary care providers. Available at: https://childmuscleweakness.org/wp-content/uploads/2019/05/PrimaryCareProviderPacket.pdf [Accessed July 2020]. **26.** McDonald CM. *Phys Med Rehabil Clin N Am.* 2012;23:495–563. **27.** Chakrabarty T, *et al. Arch Dis Child Educ Pract Ed.* 2020;105:157–163. **28.** Essex C, *et al. BMJ.* 2001;323:37–38. **29.** Dubrovsky AL. *EMJ Neurol.* 2018;6:64–67.

PTC THERAPEUTICS™

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TAKE ON DUCHENNE

*A creatine kinase (CK) test could help answer some **BIG** questions*

Think CK Test

Developmental delay? Order a CK test today

PTC THERAPEUTICS™

This material is intended for healthcare professionals only.

This document is developed and funded by PTC Therapeutics.

DMD CAUSES PROGRESSIVE MUSCULAR DAMAGE AND DEGENERATION[1,2]

- DMD is a rare genetic disorder, caused by mutations in the dystrophin gene.[2] This results in absent or insufficient functional dystrophin, leading to muscle degeneration and fibrosis[2-4]
- DMD is an X-linked recessive disorder that primarily, but not exclusively, affects males[2,5]

Affects **~1 in every 3,600 – 6,000 live male births**[1,2,6–8]

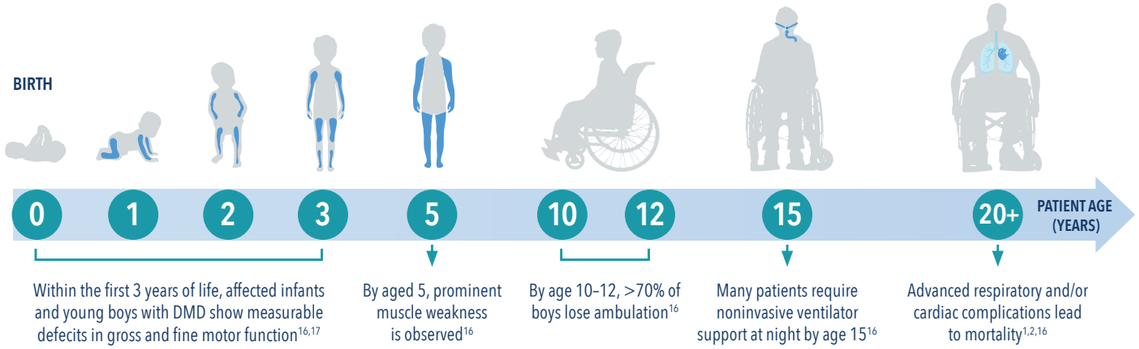
Approximately **10% of heterozygous females** will show disease symptoms[9]

One of the most **common and severe** forms of **muscular dystrophy**[1,10]

Approximately 1/3 of cases are caused by a **spontaneous mutation** with **no family history**[11,12]

EARLY INTERVENTION IS CRITICAL TO HELP DELAY DISEASE PROGRESSION AND TREAT POTENTIALLY LIFE-THREATENING COMPLICATIONS[1,2,13,14]

- Once muscle is lost, it cannot be restored[2,4,14]
- The role of GPs is vital as they are in an ideal position to spot early signs of neuromuscular disease[1,2,15]

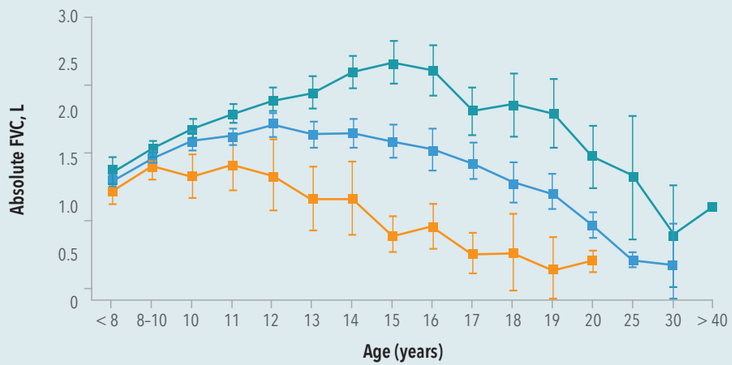


Interventions that potentially modify the natural history of DMD may be of greater benefit in the less damaged muscles of younger children[1]

LOSS OF AMBULATION IS A KEY PREDICTOR OF DISEASE PROGRESSION[18]

- Loss of ambulation is a key predictor of natural disease progression, including severe respiratory insufficiency and death due to respiratory failure[18]

EARLIER AGE AT LOSS OF AMBULATION IS ASSOCIATED WITH EARLIER AND MORE SEVERE RESPIRATORY FAILURE[18]



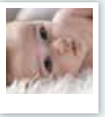
Comparison between the three groups significantly different maximum FVC, age of maximum FVC, minimum FVC and age at minimum FVC ($p<0.001$)

Adapted from Humbertcalude, *et al.* 2012[18]

Slowing the decline in physical function during the ambulatory phase of the disease could delay disease progression[1,18]

*Maximum number of patients per group during the study.[18]

RECOGNISING RED FLAG SIGNS AND SYMPTOMS



0–6 months

- No head control at 2 months[15,19]
- Not making sounds at 4 months[19]
- Not reaching or grasping by 6 months[15,19]
- Not rolling over by 6 months[15,19]

6–18 months

- Not sitting independently at 9 months[13,19]
- Not crawling by 9–15 months[15,17]
- Not speaking first words by 12 months[19]
- Difficulty Not rising to stand by 18 months[11,20]
- Not walking well by 16–18 months[2,13,19,20]

2–3 years

- Gowers' sign from 2 years old[21]
- Not walking smoothly at 2 years old (tip-toe walking)[21]
- Not jumping at 2 years old[15]
- Difficulty running or climbing at 3 years old[15,19]
- Not speaking sentences at 3 years old[19]

Other signs and symptoms

- Elevated serum CK or transaminases[22,23]
- Cognitive delay[2]
- Calf hypertrophy[2,11]
- Abnormal gait[2]
- Frequent falls[2,24]

Scheduled health checks are a good opportunity to check neuromuscular development[1,15]

DEVELOPMENTAL DELAY SHOULD TRIGGER A CK TEST[2,25]

- Elevated CK levels reflect muscle damage, and are a sign of certain neuromuscular disorders[1,2,25–27]
- A CK test is quick, simple and inexpensive[1,25,28]

POSITIVE FAMILY HISTORY WITH SUSPICION OF ABNORMAL MUSCLE FUNCTION[2]

DEVELOPMENTAL DELAY, SUCH AS DIFFICULTY RISING TO STAND OR NOT WALKING WELL BY 18 MONTHS[2,13,19,25]

UNEXPLAINED INCREASES IN TRANSAMINASES[2]

PERFORM A CK TEST

ELEVATED CK* (>250 U/L)

NORMAL CK*

PROMPTLY REFER TO A NEUROMUSCULAR SPECIALIST OR GENETICIST[2,24,25]

PATIENTS WITH MISSED MOTOR MILESTONES SHOULD BE REFERRED TO A NEUROMUSCULAR SPECIALIST[25]

Normal or mildly elevated CK levels do not rule out neuromuscular disease[25]

Prompt CK testing can help to achieve the correct diagnosis and bring reassurance to families[25,29]

*The normal CK range is generally up to 250 U/L. Absolute values may differ between laboratories.[25]

GENETIC TESTING CAN CONFIRM DMD[2,6]

- A prompt referral for diagnosis is vital to give your patients the best chance of better clinical outcomes[1,2]
- A genetic diagnosis is required to confirm DMD and to identify the specific mutation causing the disease[2]
- An understanding of the specific DMD-causing mutation is important because it may help identify medical management options and potential to enrol into clinical trials[6]

Early diagnosis is critical to gain access to the right treatments and services[1,2,13]

PATIENT WITH ELEVATED CK LEVELS (>250 U/L)*

TEST FOR *DMD* GENE DELETION OR DUPLICATION USING MLPA OR CGH

✓ **MUTATION FOUND:†** DMD DIAGNOSIS — ~70-80% of DMD patients

✗ **NO MUTATION FOUND:** PERFORM SANGER OR NGS TO TEST FOR SMALL SCALE MUTATIONS IN THE *DMD* GENE

✓ **MUTATION FOUND:†** DMD DIAGNOSIS — ~20-30% of DMD patients

✗ **NO MUTATION FOUND:** PERFORM MUSCLE BIOPSY

✓ **DYSTROPHIN ABSENT:** DMD DIAGNOSIS; TEST FOR DEEP INTRONIC MUTATIONS IN THE *DMD* GENE WITH mRNA ANALYSIS — ~0.3% of DMD patients have a deep intronic mutation

✗ **DYSTROPHIN PRESENT:** DMD UNLIKELY; CONSIDER ALTERNATIVE DIAGNOSES

Adapted from references 2, 24 and 25.

*The normal CK range is generally up to 250 U/L. Absolute values may differ between laboratories.[25] †Reading frame rule: in general, out-of-frame mutations confirm DMD and in-frame mutations confirm BMD, a less severe form of the disease. ~4-9% of DMD gene mutations do not follow the reading frame rule.[24]