One disease, multiple symptoms

Click on the button below to explore the organ systems affected by DM1 and learn about the resulting clinical manifestations.

START HERE

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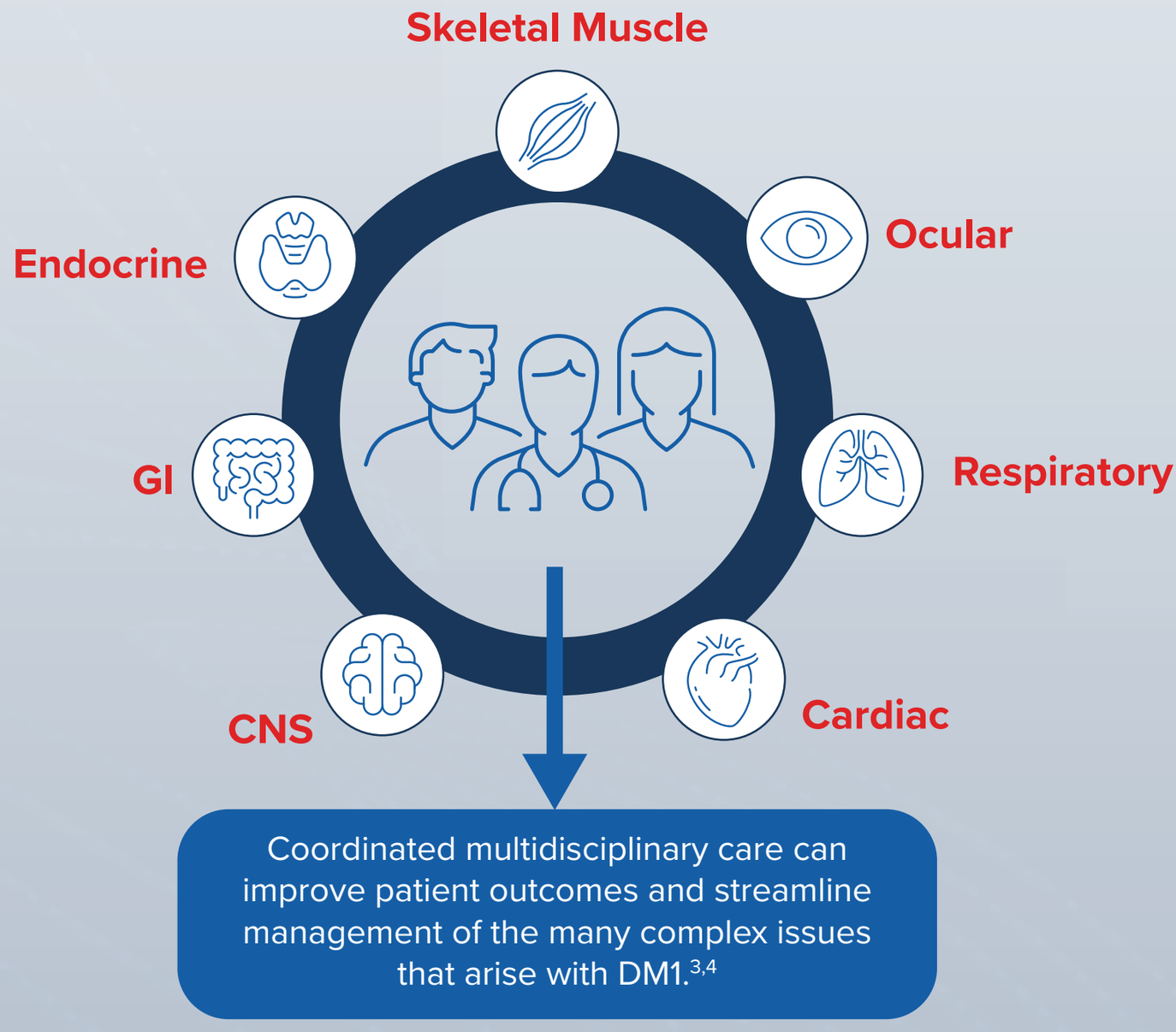
Spliceopathy drives the multisystem clinical manifestations of DM1[1]

Mutant *DMPK* mRNA sequesters members of the MBNL family of proteins (critical regulators of alternative splicing), leading to splicing dysregulation known as spliceopathy.[1]

Dysregulated alternative splicing of pre-mRNA due to mutation of the *DMPK* gene is a molecular hallmark of DM1.[1]

As MBNL proteins control the alternative splicing of genes contributing to regulation of multiple cellular pathways, individuals with DM1 experience a spectrum of clinical manifestations in various organ systems.[1]

Organ systems affected by DM1[2]



Coordinated multidisciplinary care can improve patient outcomes and streamline management of the many complex issues that arise with DM1.[3,4]

DM1, myotonic dystrophy type 1; ***DMPK*,** dystrophia myotonica protein kinase; **mRNA,** messenger ribonucleic acid; **MBNL,** muscleblind-like.

References: 1. López-Martínez A, et al. *Genes (Basel)* 2020;11:1109; 2. LoRusso S, et al. *Neurotherapeutics* 2018;15:872–884; 3. Ashizawa T, et al. *Neurol Clin Pract* 2018;8:507–520; 4. Gutiérrez Gutiérrez G, et al. *Neurolgía* 2020;35:185–206.

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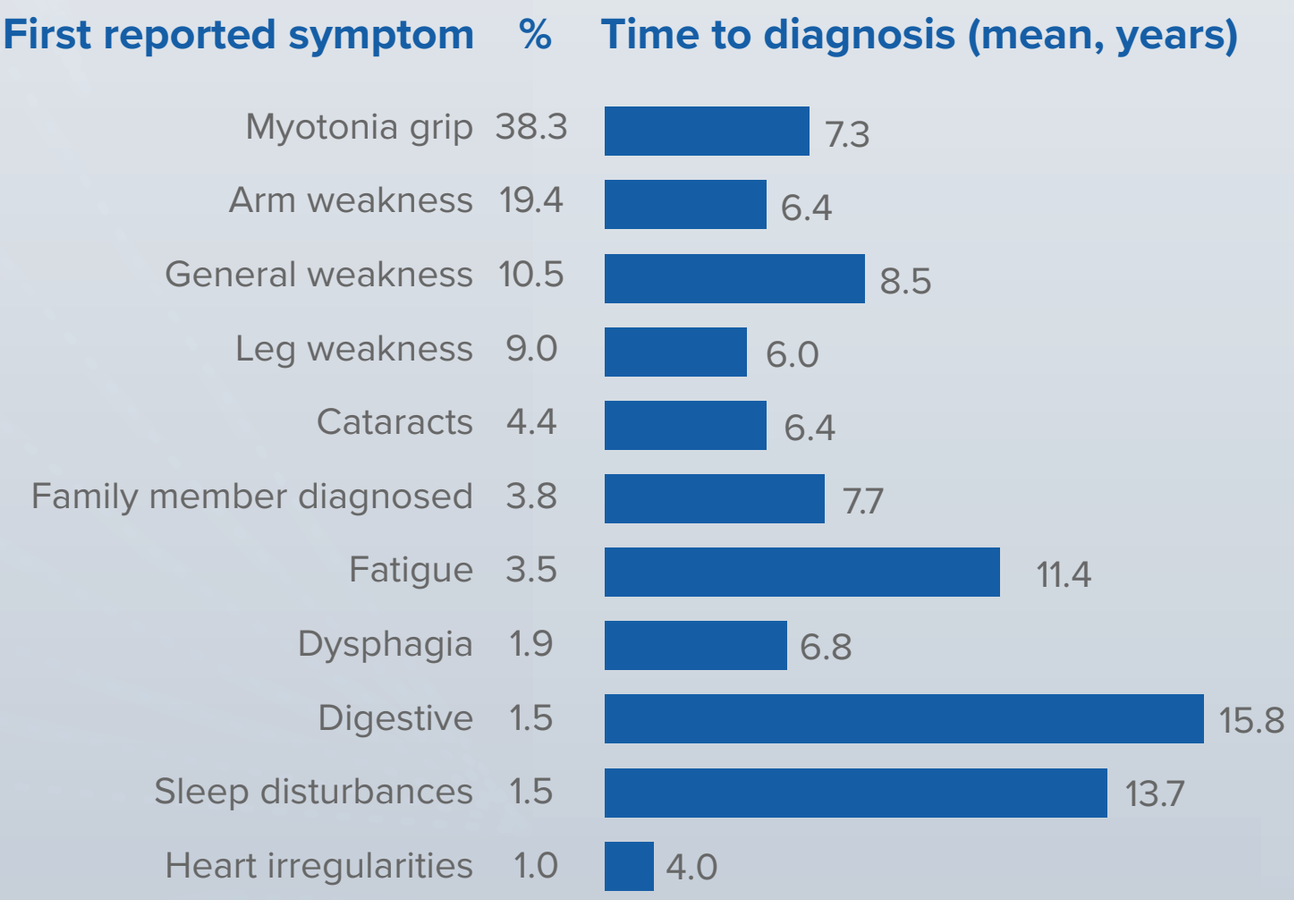
The average diagnostic delay for adult patients with DM1 is 6–7 YEARS[1–3]

DM1 shows a remarkably diverse set of symptoms and wide variability of disease onset. Together, this often results in a delay in diagnosis or misdiagnosis.[1,4]

Most common first-reported symptoms in DM1[1]



The skeletal muscle and extra-skeletal muscle manifestations of DM1 have a high inter- and intra-individual variability.[4]

References:
1. Hilbert JE, et al. *J Neurol* 2013;260:2497–2504; 2. Hamel JI, et al. *Muscle Nerve* 2022;66:508–512;
3. Hagerman KA, et al. *Muscle Nerve* 2019;59:457–464; 4. Wenninger S, et al. *Front Neurol* 2018;9:303.

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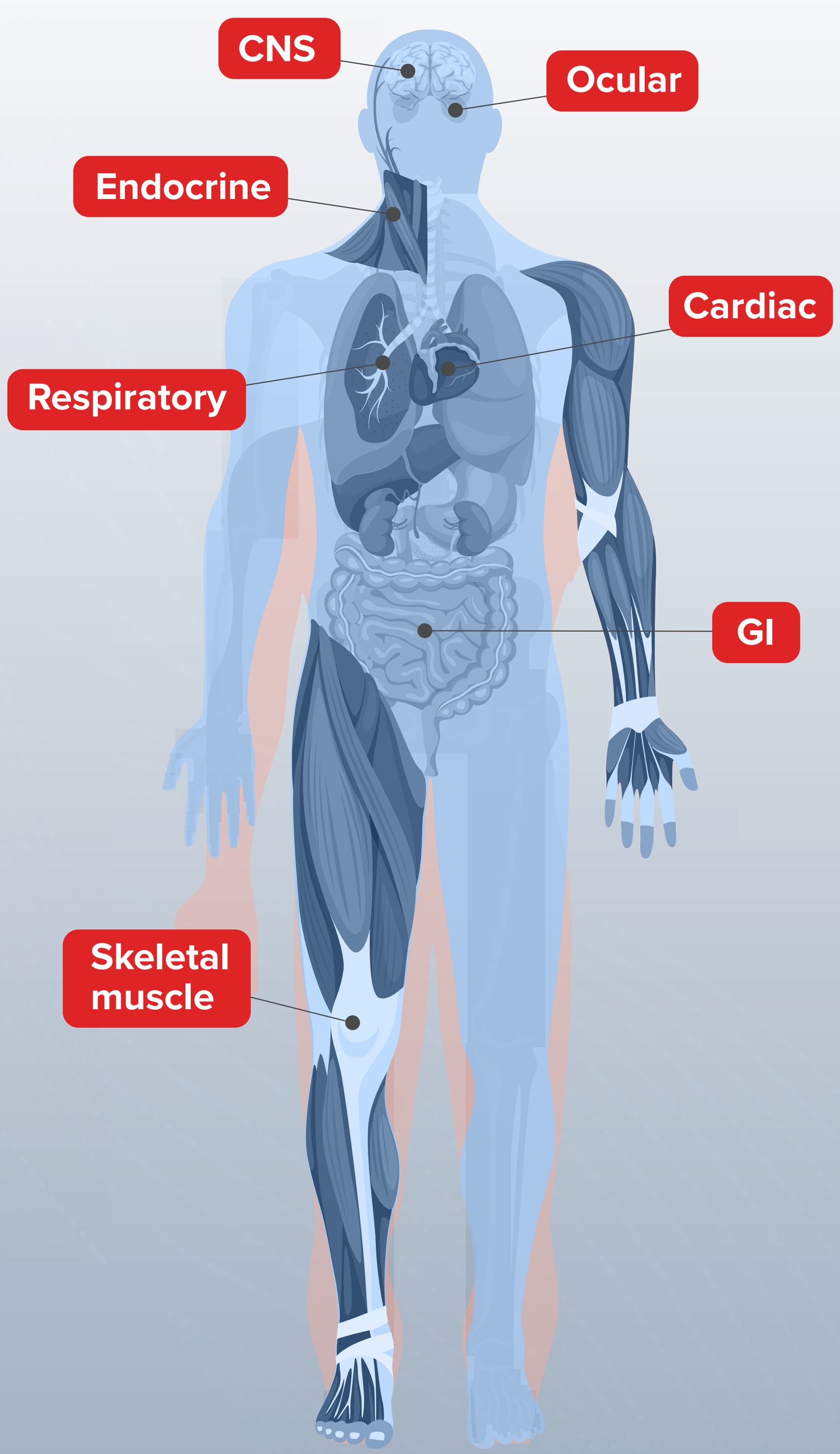
Tap each area to learn more about the clinical manifestations observed in DM1



CNS, central nervous system; **GI,** gastrointestinal.

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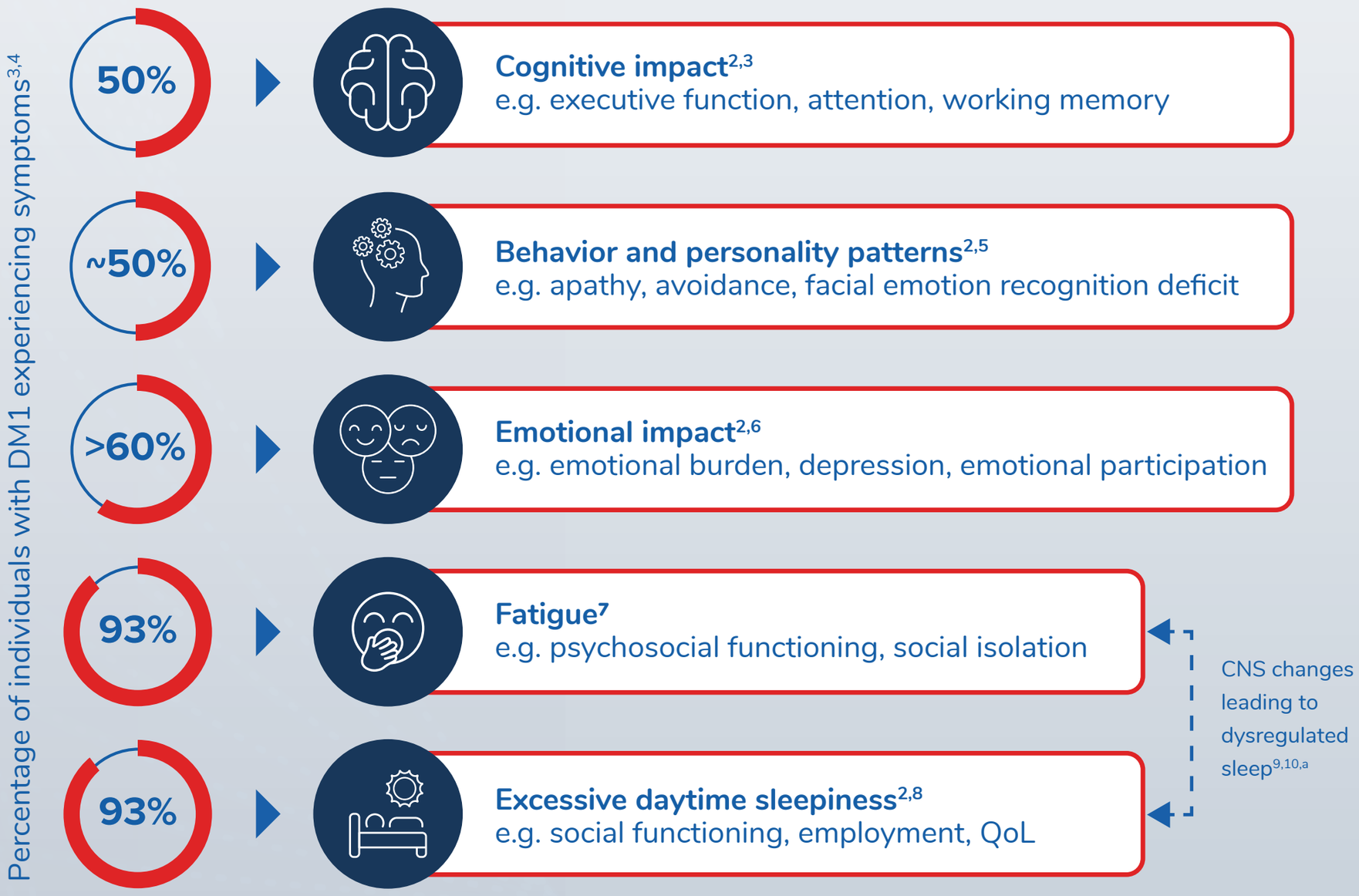
CNS features

Almost every individual with DM1 experiences some form of CNS involvement, yet symptoms are heterogeneous, spanning a range of neuropsychological aspects[1,2]



DM1 symptoms with a CNS component negatively impact relationships, social interactions, employment and other aspects of the lives of individuals living with DM1[1,2,4,11]

[a]**Sleep-related symptoms in DM1 are driven by complex interactions between many factors, with sleep disordered breathing, primary CNS dysfunction, and muscle weakness all playing a role.**

CNS, central nervous system; **DM1,** myotonic dystrophy type 1; **QoL,** quality of life.

References: 1. Wenninger S, *et al. Front Neurol.* 2018;9:303; 2. Meola G & Sansone V. *Muscle Nerve.* 2007;36:294–306; 3. Fujino H, *et al. Muscle Nerve.* 2018;57(5):742–748; 4. Hagerman KA, *et al. Muscle Nerve.* 2019;59:457–464; 5. Winblad S, *et al. J Neurol Neurosurg Psychiatry*. 2006;77(2):219–223; 6. Minier L, *et al. J Neuromuscul Dis.* 2018;5(3):279–294; 7. Winblad S & Lindberg C. *BMC Neurol.* 2019;19(1):45; 8. Laberge L, *et al. Curr Neurol Neurosci Rep.* 2013;13(4):340; 9. Subramony SH, *et al. Muscle Nerve.* 2020;62(3):309–320; 10. Hamilton MJ, *et al. Neuromuscul Disord.* 2022;32(5):377–389; 11. Heatwole C, *et al. Neurology.* 2012;79(4):348–357.

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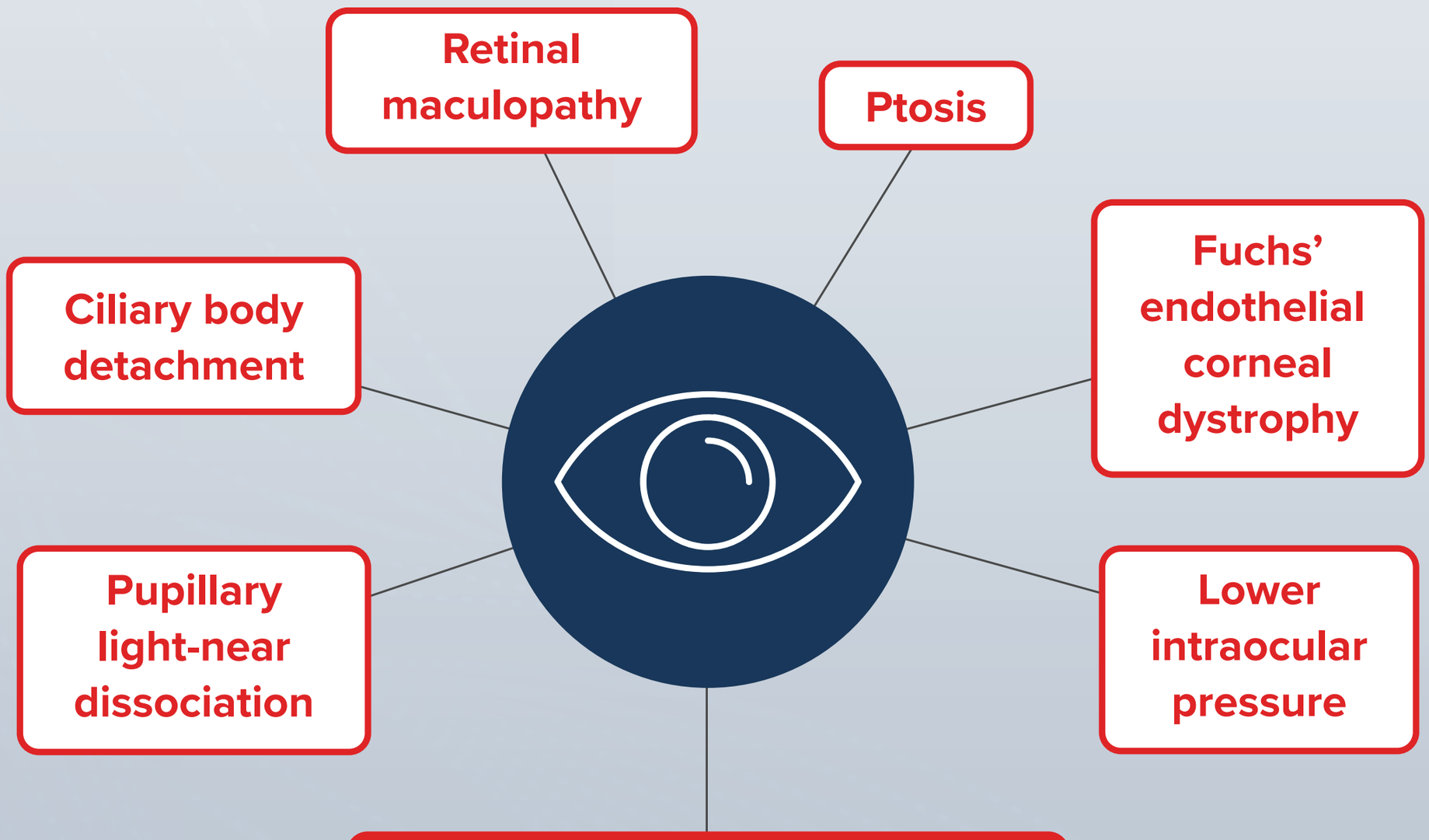
Ocular features

Cataract formation is the most common ocular feature in DM1.[1]

Cataracts in DM1 may progress faster than other cataracts leading to early-onset cataracts.[2]

Other ocular symptoms in adult patients with DM1[1]



Reference: 1. Moshirfar M, et al. *Clin Ophthalmol* 2022;16:2837–2842;
2. MDF. Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type 1. https://www.myotonic.org/sites/default/files/pages/files/MDF_Consensus-basedCareRecsAdultsDM1_1_21.pdf (accessed August 2024).

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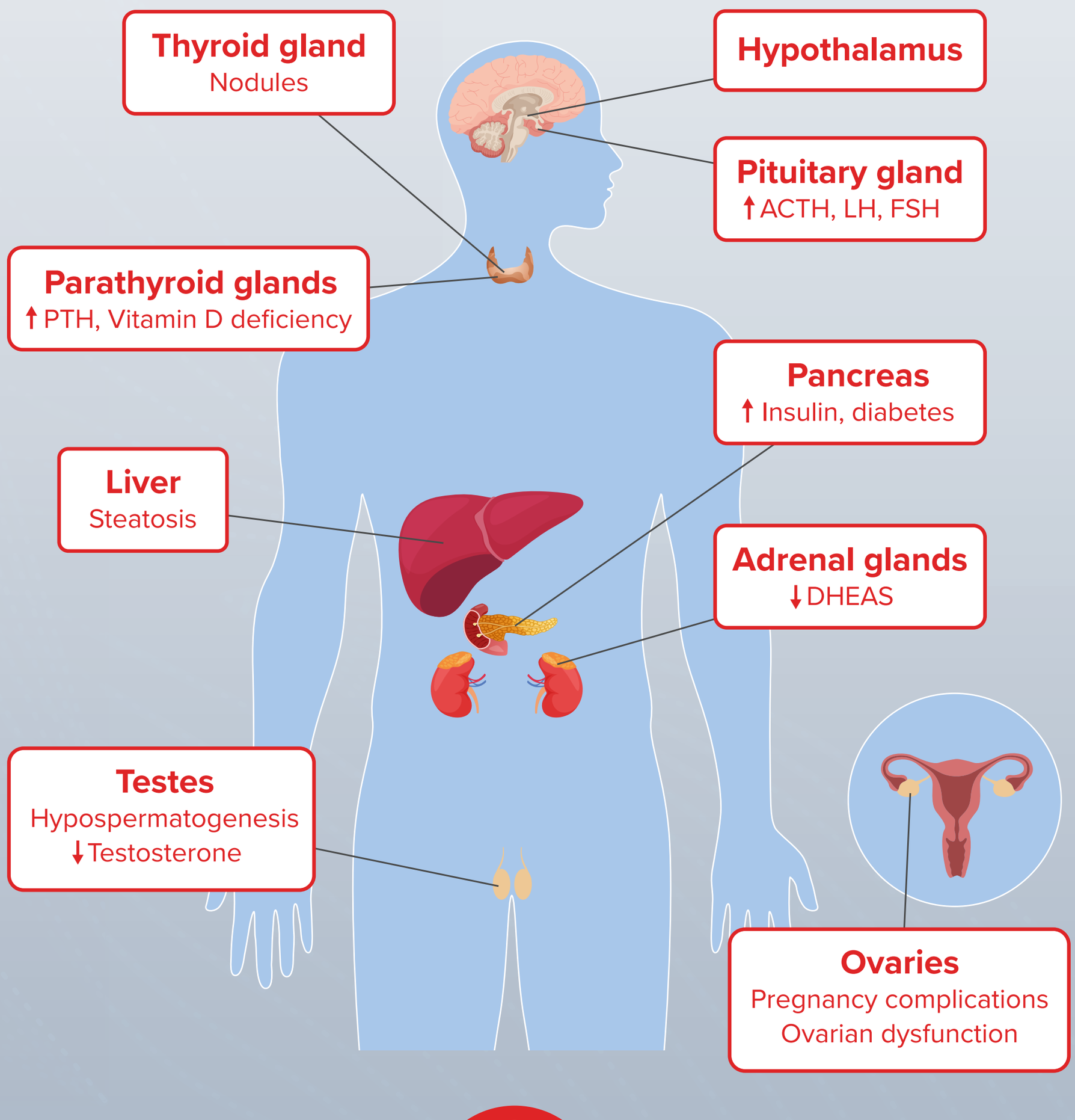
Endocrine features

The risk for type 2 diabetes is approximately three times higher in patients with DM1 compared with individuals without DM1.[1]

Mutant *DMPK* mRNA is expressed in the testes, pituitary gland, thyroid, pancreas, and liver, and results in loss of function and abnormal processing of gene products, eg the insulin receptor.[2]

Endocrine abnormalities in patients with DM1[2]



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ACTH, adrenocorticotropic hormone; **DHEAS,** dehydroepiandrosterone sulfate; **FSH,** follicle-stimulating hormone; **LH,** luteinizing hormone; **mRNA,** messenger ribonucleic acid; **PTH,** parathyroid hormone.

Reference: 1. Alsaggaf R, et al. *Int J Cancer* 2020;147:785–792; 2. Winters SJ. *J Clin Endocrinol Metab* 2021;106;2819–2827.

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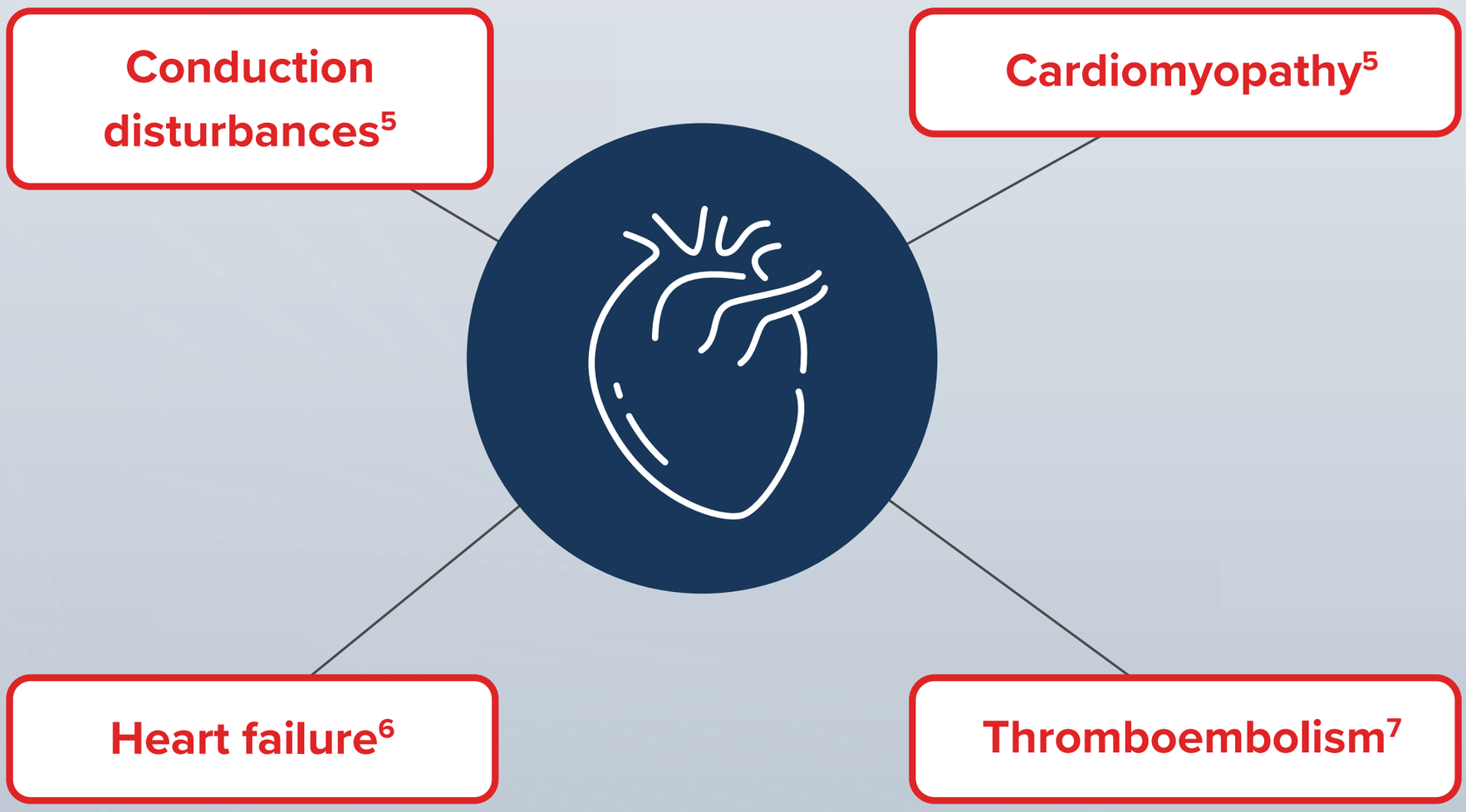
Cardiac features

Cardiac abnormalities are the second leading cause of mortality in DM1, accounting for 20–35% of deaths.[1–3]

Cardiac conduction disorders in DM1 are likely caused by myocyte hypertrophy, interstitial fibrosis, and fatty infiltration.[4]

Cardiac abnormalities are detected in >50% of individuals with DM1[4]



Patients with DM1 have a three-fold higher risk of sudden cardiac death than age-matched controls.[8]

References: 1. Mathieu J, et al. *Neurology* 1999;52:1658–1662; 2. de Die-Smulders CE, et al. *Brain* 1998;121:1557–1563; 3. Groh WJ, et al. *Muscle Nerve* 2011;43:648–651; 4. Petri H, et al. *Int J Cardiol* 2014;174:31–36; 5. McNally EM, Sparano D. *Heart* 2011;97:1094–1100; 6: McNally EM, et al. *J Am Heart Assoc* 2020;9:e014006; 7. Sochala M, et al. *Circulation* 2018;138:1169–1171; 8. Russo V, et al. *J Clin Med* 2023;12:1947.

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Respiratory failure

Respiratory failure is the primary cause of death, accounting for mortality in 31–51% of individuals with DM1.[1–3]

Reduced cough efficiency in DM1 is due to weakness of the inspiratory and expiratory muscles. This leads to impaired airway clearance and an increased risk of aspiration and pulmonary infections.[4]

Respiratory features of DM1

Respiratory failure typically occurs in adults between 50–60 years of age[2,3]

Restrictive ventilatory pattern is the predominant ventilatory function abnormality in DM1[5]

Most commonly impaired respiratory parameters:[5,6]
Forced vital capacity (FVC)
Vital capacity (VC)

References: 1. Mathieu J, et al. *Neurology* 1999;52:1658–1662; 2. de Die-Smulders CE, et al. *Brain* 1998;121:1557–1563; 3. Groh WJ, et al. *Muscle Nerve* 2011;43:648–651; 4. Boentert M, et al. *Respiration* 2020;99:360–368; 5. Hawkins AM, et al. *Neuromuscul Disord* 2019;29:198–212; 6. Hartog L, et al. *Front Neurol* 2021;12:658532.

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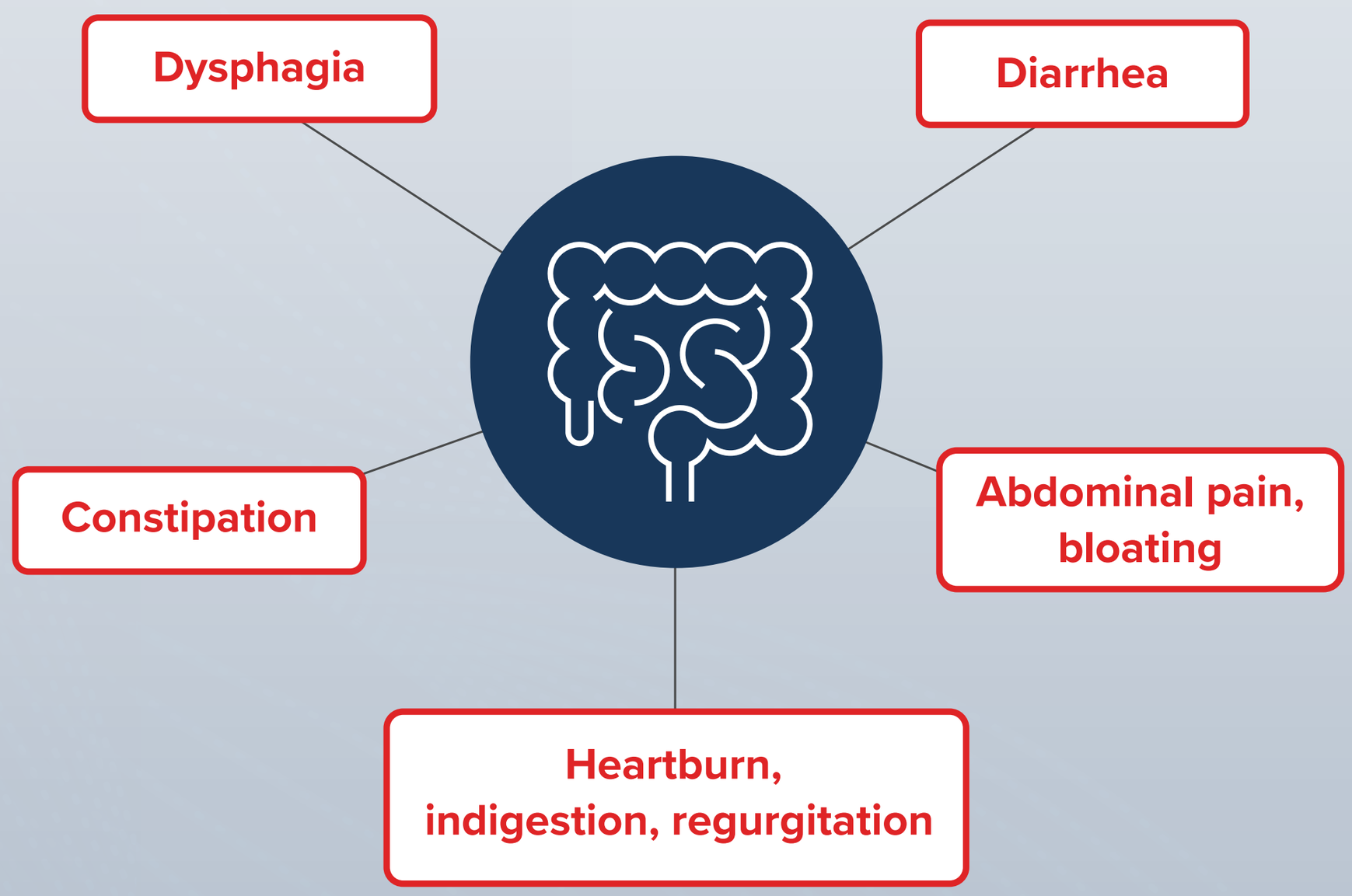
GI features

Gastrointestinal (GI) manifestations are reported by ~80% of patients[1] with DM1 and occur along the entire digestive tract.[2,3]

GI symptoms in DM1 are generally attributed to motility disorders caused by striated and smooth muscle dysfunction. Neurologic alterations may also play a role.[3,4]

GI symptoms observed in DM1[2,3]



References: 1. Heatwole C, et al. *Neurology* 2012;79:348–357; 2. Hilbert JE, et al. *Neurology* 2017;89:1348–1354; 3. Bellini M, et al. *World J Gastroenterol* 2006;12:1821–1828; 4. Peterson JAM, Cooper A. *Int J Mol Sci* 2022;23:14479.

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Skeletal muscle

Please select from the options below to learn more

Myotonia

Myopathic face

Muscle weakness

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One disease,
multiple symptoms

Skeletal muscle

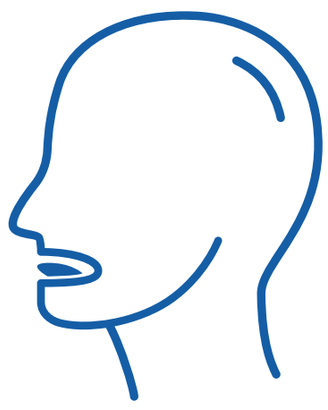
Please select from the options below to learn more

Myotonia | **Myopathic face** | **Muscle weakness**

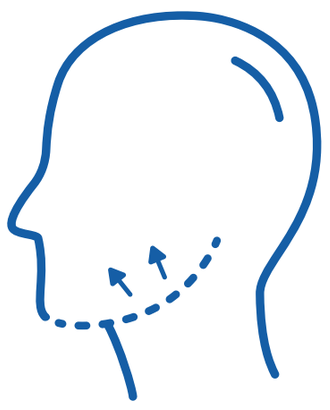
88%[a] of patients with DM1 experience myotonia (difficulty relaxing muscles)[1]

Parts of the body affected by myotonia[2]

Fingers



Tongue



Jaw

Myotonia in DM1 is thought to arise due to increased excitability of muscle fibers, leading to continuous discharges of repetitive action potentials after mechanical stimulation or voluntary contraction.[2]

[a] Significantly higher prevalence or impact of symptoms in females ($p<0.05$).

References: 1. Hagerman KA, et al. *Muscle Nerve* 2019;59:457–464; 2. Wenninger S, et al. *Front Neurol* 2018;9:303; 3. Turner C, Hilton-Jones D. *J Neurol Neurosurg Psychiatry* 2010;81:358–367.

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Skeletal muscle

Please select from the options below to learn more

Myotonia | **Myopathic face** | **Muscle weakness**

‘Myopathic face’ is a prominent early feature of DM1[2]

Facial features in adults with DM1[2]

Weakness and atrophy of facial muscles may falsely indicate a tired, sad, or emotionless patient.[2]

Image from Wenninger S, et al. *Front Neurol.* 2018;9:303, licensed under a CC-BY 4.0 Creative Commons license; doi: 10.3389/fneur.2018.00303.

References: 1. Hagerman KA, et al. *Muscle Nerve* 2019;59:457–464; 2. Wenninger S, et al. *Front Neurol* 2018;9:303; 3. Turner C, Hilton-Jones D. *J Neurol Neurosurg Psychiatry* 2010;81:358–367.

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Skeletal muscle

Please select from the options below to learn more

Myotonia | **Myopathic face** | **Muscle weakness**

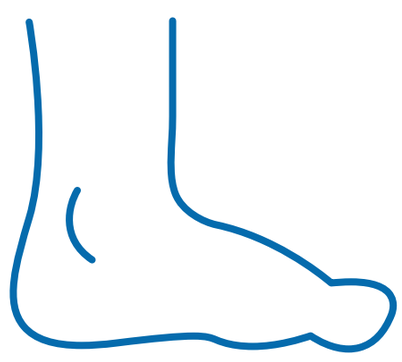
Muscle weakness is reported in 94% of adults with DM1 and is considered the symptom with the highest impact[1]

In patients with DM1, muscle biopsy demonstrates variability in muscle fiber size, rows of internal nuclei, fibrosis, aberrant myofibril orientation, and type I fiber atrophy.[3]

Distally predominant muscle weakness and atrophy are characteristic of DM1 and mainly involve:[2]

Finger flexors

Wrist flexors



Foot extensors

References: 1. Hagerman KA, et al. *Muscle Nerve* 2019;59:457–464; 2. Wenninger S, et al. *Front Neurol* 2018;9:303; 3. Turner C, Hilton-Jones D. *J Neurol Neurosurg Psychiatry* 2010;81:358–367.

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