Think you know DM1?

Click the button below to explore key facts about DM1 – did you know them all?

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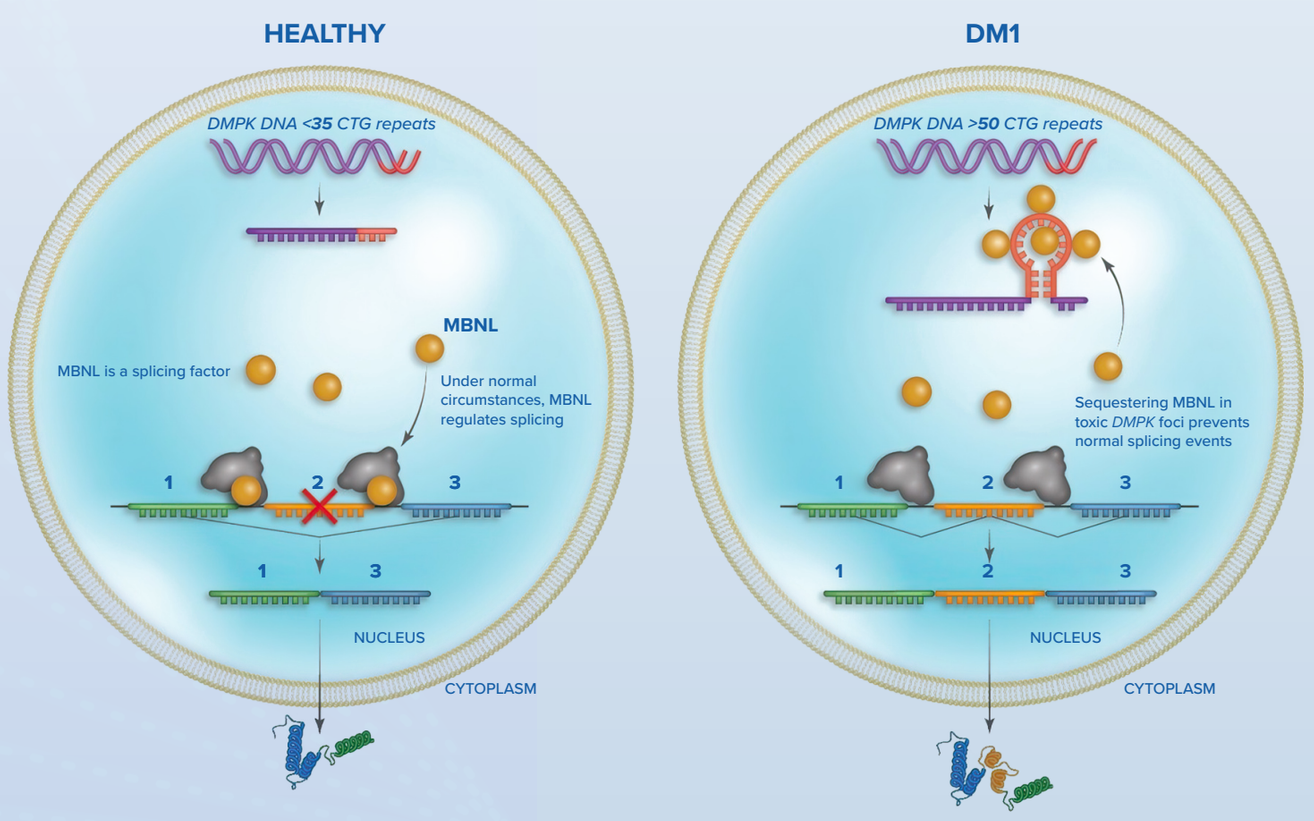
Think you know **DM1?**

DM1 is an example of a spliceopathy

Abnormal regulation of pre-mRNA alternative splicing, due to expansion of a CTG trinucleotide repeat in the 3’ untranslated region of the *DMPK* gene, is a molecular hallmark of DM1 across phenotypes. Expanded CUG repeats in the RNA transcribed from the mutated gene form hairpin loops which sequester members of the muscleblind-like (MBNL) family of proteins into nuclear foci. Under normal circumstances, MBNL is a splicing regulator.[1–3]

The resulting aberrant splicing pattern, known as a spliceopathy, drives the clinical manifestations of DM1. Hundreds of splicing events are misregulated in multiple tissues, explaining why DM1 is a multisystemic disorder characterized by a diverse array of signs and symptoms affecting most organ systems.[3]

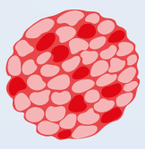
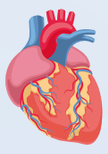
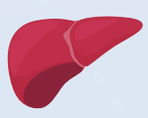


Normal splicing leads to **appropriate protein synthesis**

Disrupted splicing **impairs normal protein synthesis**

This representation of mis-splicing has been simplified.

Examples of genes that are mis-spliced in DM1

Myotonia and muscle weakness[3] 	*CLCN1*, *BIN1*, *TNNT3*, *MTMR1*, *NFIX*, *DTNA*, *CACNA1S*, *DMD*, *ATP5MC2*, *NEB*, *PKM2*, *RyR1*, *CAPN3*, *NCOR2*, *SOS1*, *MBNL1*, *ATP2A1*
Cardiac conduction complications[3] 	*ATP2A2*, *LDB3*, *SCN5A*, *TNNT2*, *TTN*, *MYOM1*, *ALPK3*, *RBFOX2*, *ZASP/LDB*
Cognitive impairment[3,4] 	*MAPT*, *NMDAR1*, *MBNL1*, *MBNL2*, *APP*, *GRIP1*
Metabolic complications[3] 	*INSR*, *PKM2*

See the Module 2 digital handout to explore the molecular pathology of DM1

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

References 1. Davis BM, et al. *Proc Natl Acad Sci USA* 1997;94:7388–7393; 2. Chau A & Kalsotra A. *Dev Dyn* 2015;244:377–390; 3. López-Martínez A, et al. *Genes (Basel)* 2020;11:1109; 4. Otero BA, et al. *Cell Rep* 2021;34:108634.

Think you know **DM1?**

DM1 is the most common form of myotonic dystrophy in adults

DM1 is estimated to have a global prevalence of 9.27 cases per 100,000.[1]

It is estimated to affect ~40,000 individuals in the United States and ~55,000 individuals in the EU.[1] The genetic prevalence of DM1 among infants born in New York state between 2013 and 2014, defined by an expansion of ≥50 CTG repeats, was 1 in 2,100.[2]

References
1. Liao Q, et al. *Neuroepidemiology* 2022;56:163–173; 2. Johnson NE, et al. *Neurology* 2021;96:e1045–e1253.

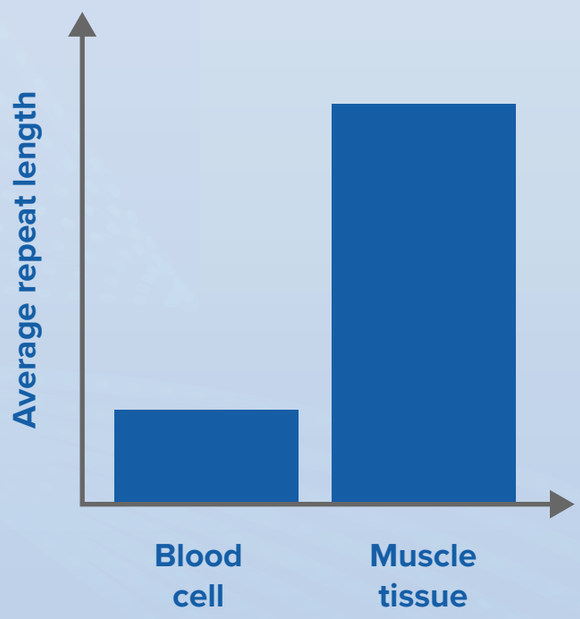
Think you know **DM1?**

The expanded *DMPK* CTG region is highly unstable and increases in length both during intergenerational transmission and as an individual with DM1 ages

Individuals with DM1 have at least 50 and can have as many as several thousand repeats in the expanded *DMPK* CTG region. The unstable nature of the expanded region during transmission results in increasing disease severity and decreasing age of onset in successive generations, a phenomenon known as anticipation.[1]

The expansion is also highly unstable within the somatic cells of individuals with DM1, leading to variability of repeat length in different tissues, a concept known as somatic mosaicism.[1,2] Somatic mosaicism in DM1 is tissue-specific and biased toward further expansion during aging, contributing to the progressive and heterogeneous nature of the disease.[1]

CTG repeat length is more unstable in non-dividing skeletal muscle than proliferating blood cells[1,2]



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1. Thornton CA. *Neurol Clin* 2014;32:705–719;
2. López-Martínez A, et al. *Genes (Basel)* 2020;11:1109.

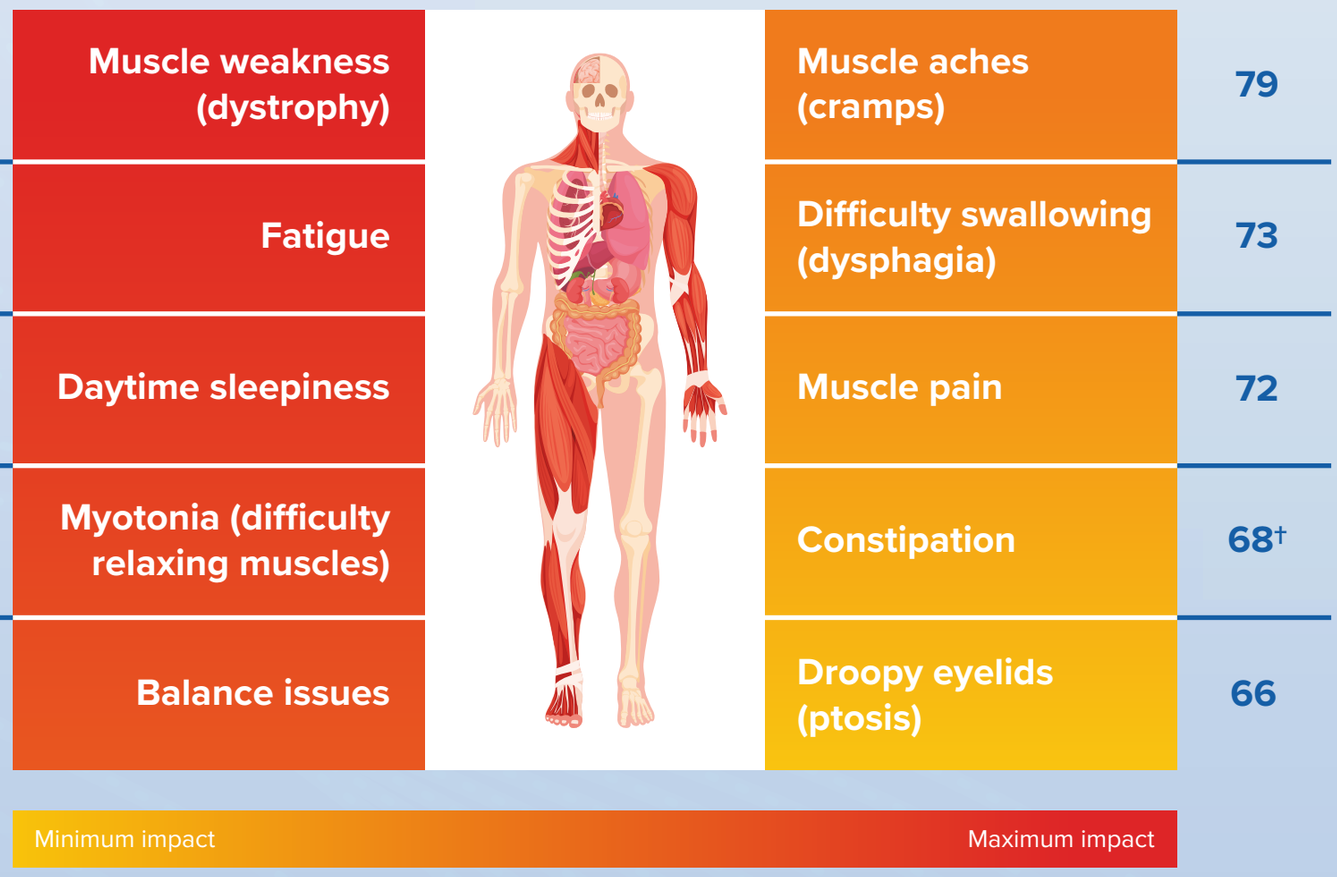
Think you know **DM1?**

DM1 is a multisystemic disorder that presents with a wide range of symptoms

DM1 affects a wide array of cells in multiple tissue types leading to diversity in the symptoms that patients can present with.[1,2]

The most prominent musculoskeletal symptoms include myotonia, muscular weakness, and atrophy.[3,4] DM1 can also lead to CNS symptoms, such as fatigue, cognitive decline, and excessive daytime sleepiness,[5] gastrointestinal manifestations, such as dysphagia and constipation, and cardiac conduction abnormalities.[3]

Top 10 most commonly reported DM1 symptoms and their impact[6]



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

See the Module 3 digital handout to explore the multisystemic clinical manifestations of DM1

CNS, central nervous system

References
1. Hilbert JE, et al. *J Neurol* 2013;260:2497–2504; 2. López-Martínez A, et al. *Genes (Basel)* 2020;11:1109;
3. LoRusso S, et al. *Neurotherapeutics* 2018;15:872–884; 4. Wenninger S, et al. *Front Neurol* 2018;9:303;
5. White M. *Ther Innov Regul Sci* 2020;54:1010–1017; 6. Hagerman KA, et al. *Muscle Nerve* 2019;59:457–464.

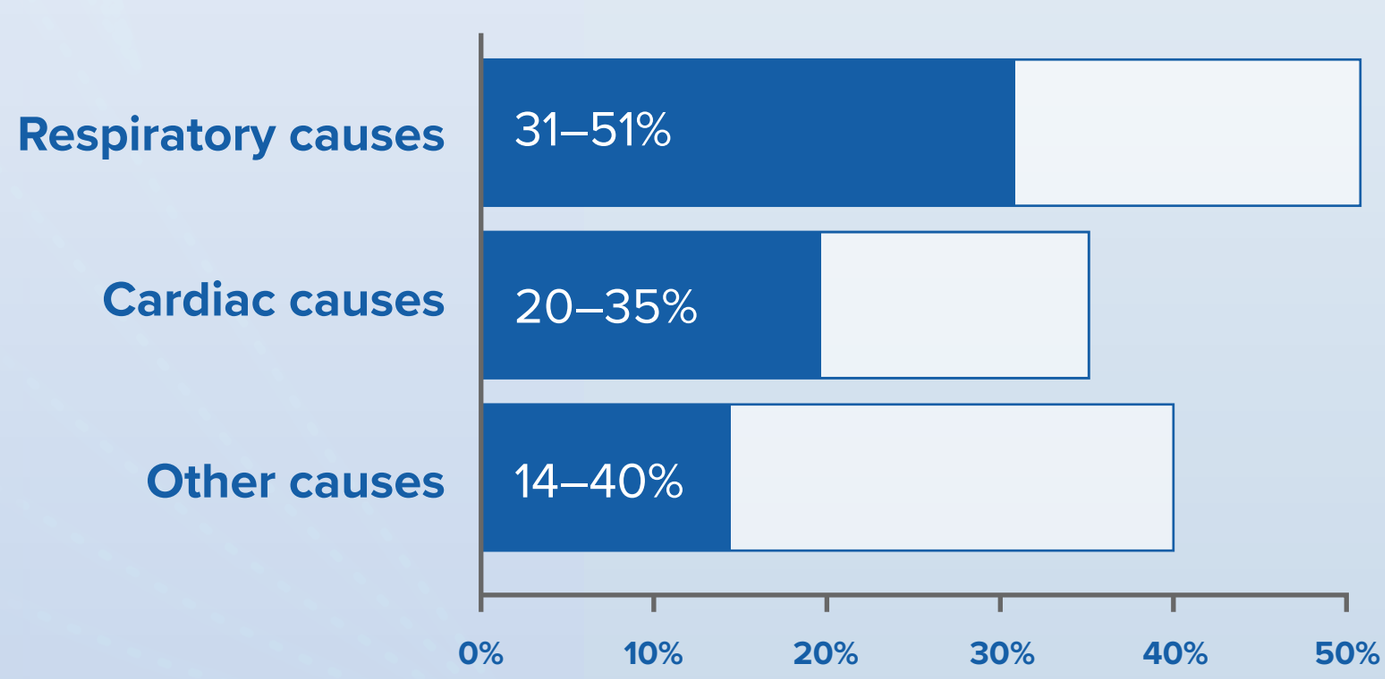
Think you know **DM1?**

Cardiac and pulmonary abnormalities are the leading cause of mortality in DM1

Individuals with DM1 have a greatly reduced life expectancy, with cardiac and pulmonary abnormalities being the leading causes of mortality.[1–3]

Longitudinal studies of individuals with myotonic dystrophy suggest the average age at death to be 53–56 years,[1–3] with one study finding mortality to be 7.3 times higher compared with an age-matched reference population.[1]

Causes of death in patients with myotonic dystrophy[1–3]



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.

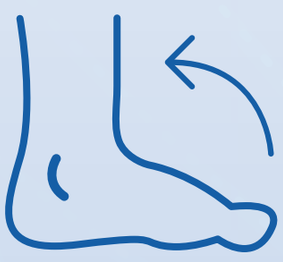
Think you know **DM1?**

CASI has shown correlation with functional outcomes in patients with DM1

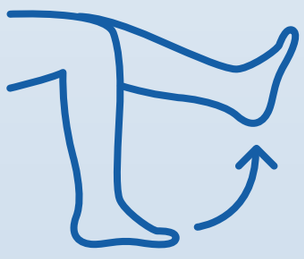
Mis-splicing has been shown to correlate with functional outcomes in several natural history studies of DM1 cohorts.[1–4]

The composite alternative splicing index (CASI) measures RNA mis-splicing across a panel of 22 genes implicated in DM1 pathology.[3,5] A score of 0 represents the median score of healthy subjects, while a score of 1 represents the 95th percentile severity of DM1 patients.[3]

In a study of 95 muscle biopsies taken from adults with DM1, composite splice index score was shown to correlate with common clinical outcome measures for DM1:[3]



Ankle dorsiflexion (n = 85)
R = -0.719
P<0.0001



Knee extension (n = 87)
R = -0.392
P<0.001

Hand grip strength (n = 87)
R = -0.716
P<0.0001

vHOT (middle finger, n = 50)
R = 0.454
P<0.001

10MRW (n = 82)
R = -0.680
P<0.0001

vHOT (thumb, n = 49)
R = 0.378
P<0.01

All correlations are reported as Pearson or Spearman r [95% CI] with two-tailed p-value.

10MRW, 10-metre run/walk; **CASI,** composite alternative splicing index; **DM1,** myotonic dystrophy type 1; **RNA,** ribonucleic acid; **vHOT,** visual hand opening time.

References
1. Nakamori M, et al. *Ann Neurol.* 2013;74:862–872; 2. Wang ET, et al. *Hum Mol Genet.* 2019;28:1312–1321;
3. Provenzano M, et al. *J Clin Invest.* 2025;135:e185426; 4. Hartman JM, et al. *Ann Clin Transl Neurol.* 2024;11:3175–3191; 5. Wang W. 2017. University of Rochester School of Medicine and Dentistry PhD thesis. Available at http://hdl.handle.net/1802/32572. Accessed September 2025.

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Think you know **DM1?**

DM1 presents with varying disease phenotypes across the age continuum.[1–3]

Phenotype*	Age of onset	Clinical manifestations[1,2]	Life expectancy
Congenital[1,2]	<1 month[1]	Hypotonia Respiratory distress Cognitive defects Motor and developmental delays Feeding difficulties	45 years† (30–40% mortality rate within neonatal period)[2]
Childhood[1]	1 month – 20 years[1]	Facial weakness Cognitive defects Psychosocial issues Incontinence	~60 years[2†]
Adult[1–3]	20–40 years[1]	Myotonia Muscle weakness Cognitive defects Cataracts Conduction defects Insulin resistance Respiratory failure	Up to 55 years[3]
Late-onset adult[1–3]	>40 years[1]	Mild myotonia Cataracts	60 years to normal[3]

*There is currently no standard on the classifications of DM1. †Mean.

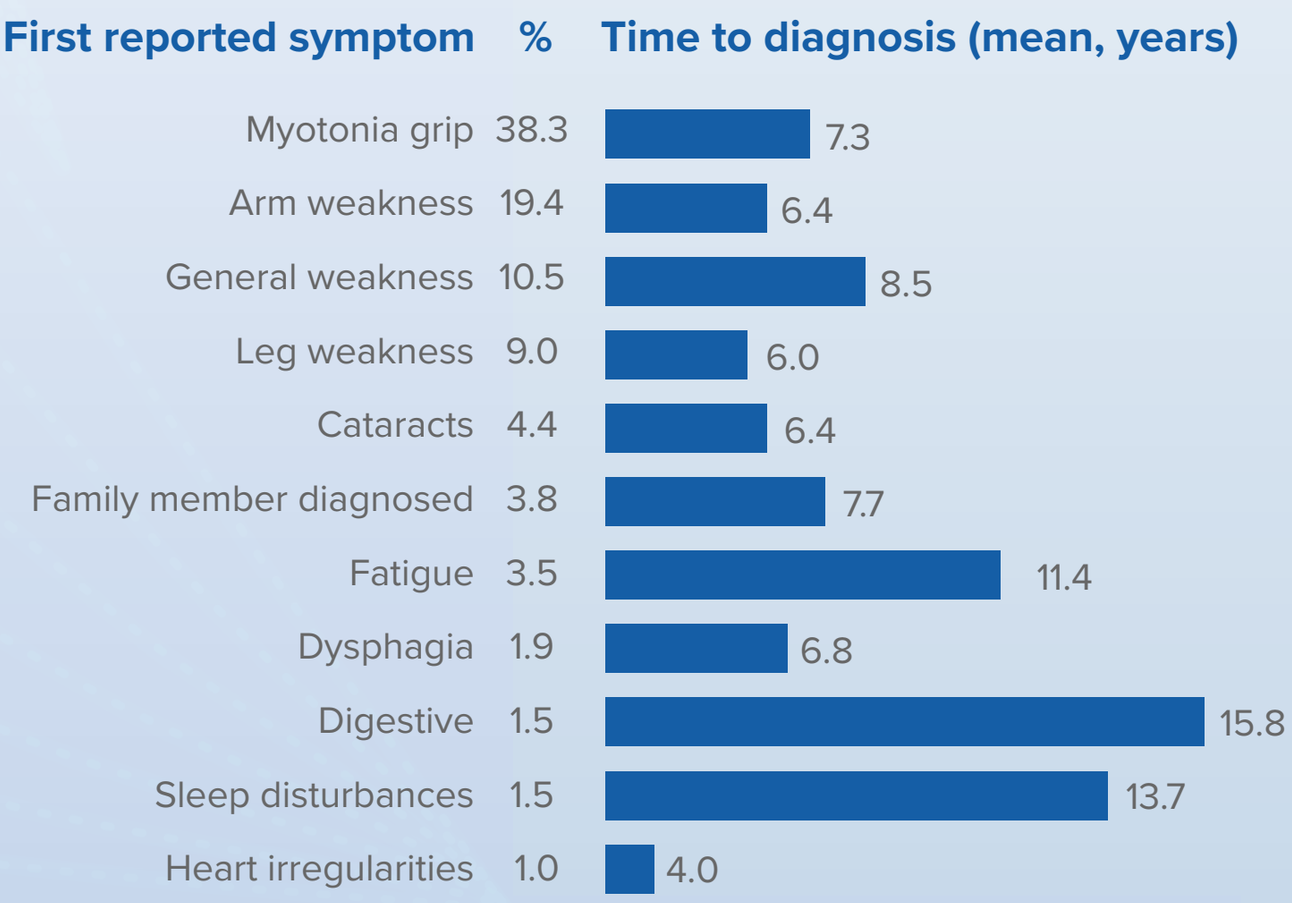
Referenes
1. De Antonio M, et al. *Rev Neurol (Paris)* 2016;172:572–580;
2. Ho G, et al. *World J Clin Pediatr.* 2015;4:66–80;
3. Bird TD. Myotonic Dystrophy Type 1. 1999 Sep 17 [Updated 2021 Mar 25]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022.

Think you know **DM1?**

Individuals with DM1 frequently wait many years for a diagnosis

DM1 is associated with a diagnostic delay of 6–7 years.[1–3] This delay is influenced by which symptom presents first and is therefore driven in part by the multisystemic nature of DM1.[1] The variability in age of onset and low level of awareness among neurologists, other healthcare professionals, and the general public may also delay DM1 diagnosis.[1]

Most common first-reported symptoms[1]



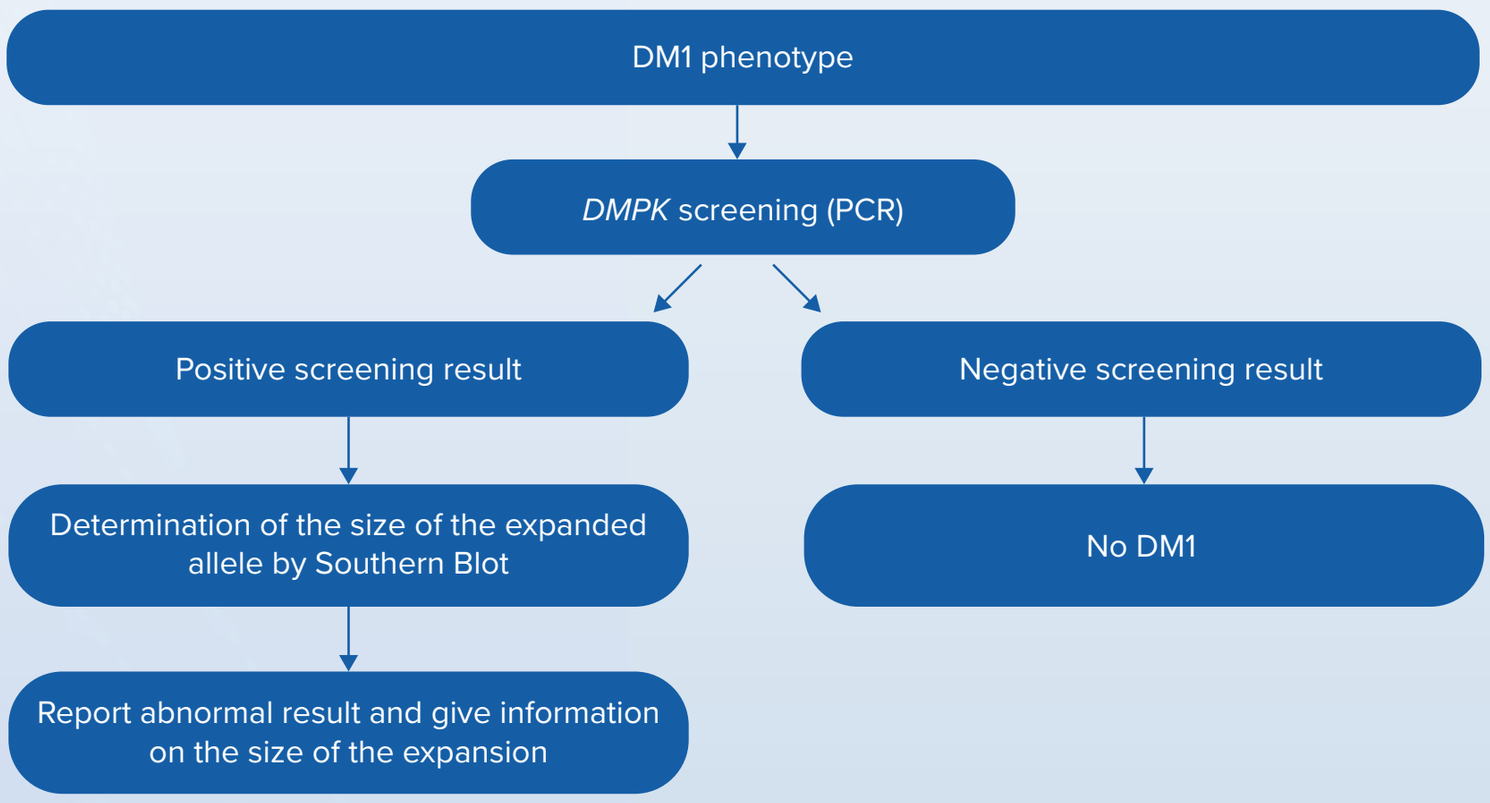
References
1. Hilbert JE, et al. *J Neurol* 2013;260:2497–2504;
2. Hagerman KA, et al. *Muscle Nerve* 2019;59:457–464;
3. Hamel JI, et al. *Muscle Nerve* 2022;66:508–512.

Think you know **DM1?**

A DM1 diagnosis is confirmed through genetic testing

Once DM1 is suspected based on family history and/or clinical presentation, molecular testing using a blood sample is used to confirm the diagnosis.[1,2] A muscle biopsy is not required.

Genetic testing strategy for DM1[3]



Asymptomatic individuals found to have CTG repeat expansion should be considered at risk for developing DM1, however, they may never develop symptoms.[4]

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PCR, polymerase chain reaction

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1. Johnson NE, et al. *Neurol Clin Pract* 2019;9:443–454;
2. Gutierrez Gutierrez G, et al. *Neurologia (Engl Ed)* 2020;35:185–206;
3. Chakraborty S, et al. *Curr Protoc Hum Genet* 2016;91:9.29.1–19;
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