

# Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management



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Duchenne muscular dystrophy (DMD) is a severe, progressive disease that affects 1 in 3600–6000 live male births. Although guidelines are available for various aspects of DMD, comprehensive clinical care recommendations do not exist. The US Centers for Disease Control and Prevention selected 84 clinicians to develop care recommendations using the RAND Corporation–University of California Los Angeles Appropriateness Method. The DMD Care Considerations Working Group evaluated assessments and interventions used in the management of diagnostics, gastroenterology and nutrition, rehabilitation, and neuromuscular, psychosocial, cardiovascular, respiratory, orthopaedic, and surgical aspects of DMD. These recommendations, presented in two parts, are intended for the wide range of practitioners who care for individuals with DMD. They provide a framework for recognising the multisystem primary manifestations and secondary complications of DMD and for providing coordinated multidisciplinary care. In part 1 of this Review, we describe the methods used to generate the recommendations, and the overall perspective on care, pharmacological treatment, and psychosocial management.

## Introduction

Duchenne muscular dystrophy (DMD; Online Mendelian Inheritance in Man [OMIM] reference 310200) is an X-linked disease that affects 1 in 3600–6000 live male births.<sup>1–3</sup> Affected individuals can have mildly delayed motor milestones and most are unable to run and jump properly due to proximal muscle weakness, which also results in the use of the classic Gowers' manoeuvre when arising from the floor. Most patients are diagnosed at approximately 5 years of age, when their physical ability diverges markedly from that of their peers.<sup>4</sup> Untreated, muscle strength deteriorates, and boys require the use of a wheelchair before their teens. Respiratory, orthopaedic, and cardiac complications emerge, and without intervention, the mean age at death is around 19 years. Non-progressive cognitive dysfunction might also be present.<sup>5</sup>

DMD occurs as a result of mutations (mainly deletions) in the dystrophin gene (*DMD*; locus Xp21.2). Mutations lead to an absence of or defect in the protein dystrophin, which results in progressive muscle degeneration leading to loss of independent ambulation by the age of 13 years.<sup>6</sup> Variable phenotypic expression relates mainly to the type of mutation and its effect on the production of dystrophin. Milder allelic forms of the disease also exist, including intermediate muscular dystrophy and Becker muscular dystrophy, which cause loss of ambulation at 13–16 years or over 16 years, respectively. With the use of corticosteroids to prolong ambulation, these boundaries are less distinct. However, that these phenotypes exist is important, and if progression is milder than expected for DMD, assessment for these alternative forms should be done. Some patients with dystrophin mutations also have an isolated cardiac phenotype.<sup>7–12</sup> Approximately 10% of female carriers show some disease manifestations that might include

or even exclusively affect cognitive and/or cardiac function.<sup>13–15</sup> Although the disorder in affected girls is usually much milder than in boys, a few cases do have disease severity similar to that seen in affected boys.<sup>13–15</sup> Apart from a few cases associated with chromosomal rearrangements, most girls are assumed to be affected as a result of skewed X inactivation.

The molecular basis of DMD has been known for over 20 years.<sup>16,17</sup> Many promising therapeutic strategies have since been developed in animal models.<sup>18</sup> Human trials of these strategies have started, leading to the hope of definitive treatments for this currently incurable disease.<sup>18</sup> Although specific treatments for DMD have not yet reached the clinic, the natural history of the disease can be changed by the targeting of interventions to known manifestations and complications. Diagnosis can be swiftly reached; the family and child can be well supported, and individuals who have DMD can reach their full potential in education and employment. Corticosteroid, respiratory, cardiac, orthopaedic, and rehabilitative interventions have led to improvements in function, quality of life, health, and longevity, with children who are diagnosed today having the possibility of a life expectancy into their fourth decade.<sup>19–32</sup>

Advocacy organisations report variable and inconsistent health care for individuals with DMD. Although anticipatory and preventive clinical management of DMD is essential, recommendations exist in only a few areas. Addressing the many complications of DMD in a comprehensive and consistent way is crucial for planning multicentre trials, as well as for improving care worldwide.

The development and implementation of standardised care recommendations were initially emphasised by stakeholders in the DMD community, including government agencies, clinicians, scientists, volunteer

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For OMIM see <http://www.ncbi.nlm.nih.gov/omim/>

For the Muscular Dystrophy  
Association see <http://www.mda.org/>

For Parent Project Muscular  
Dystrophy see <http://www.parentprojectmd.org/>

For TREAT-NMD see <http://www.treat-nmd.eu/>

See Online for webappendix

health agencies, and advocacy organisations such as the Muscular Dystrophy Association and Parent Project Muscular Dystrophy. In the USA, the Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001 directed increased research and public health initiatives towards the muscular dystrophies.<sup>33</sup> Development of these care recommendations are part of these activities. In Europe, a European Union-funded Network of Excellence (EC036825), TREAT-NMD, received funding to advance the treatment and care for neuromuscular diseases, with standardisation of care in DMD as one of their priorities. The US Centers for Disease Control and Prevention (CDC) has facilitated the development of these care recommendations as a collaborative effort among these stakeholders.

The aim of this Review is to present recommendations for DMD management based on analysis of independent expert ratings of assessments and interventions. These recommendations focus attention on the many positive areas promoting efficient diagnosis and effective management in DMD. They are intended for the wide range of health-care providers who work with individuals who have DMD and their families, from primary care to the multidisciplinary team. The purpose of these recommendations is to provide a framework for recognising the primary manifestations and possible complications and for planning optimum treatment across different specialties with a coordinated multidisciplinary team. In the first part of this Review, we describe the methods used, and provide recommendations for diagnosis, pharmacological treatment, and psychosocial management. In the second part,<sup>34</sup> we will discuss the implementation of multidisciplinary care.

## Methods

Very few large-scale randomised controlled trials (RCTs) have been done in DMD. In areas in which such trials exist (eg, for the use of corticosteroids), the evidence that can be derived from these studies has been emphasised. For most of the other recommendations, the CDC chose the RAND Corporation–University of California Los Angeles Appropriateness Method (RAM) to guide their development.<sup>35</sup> RAM combines scientific evidence with the collective judgment of experts to determine the appropriateness and necessity of clinical assessments and interventions. Unlike consensus-driven methods, RAM preserves the integrity of individual expert opinion through anonymous and independent ratings, allowing areas of agreement, as well as areas of disagreement and uncertainty, to be revealed.<sup>35</sup>

An international coalition of 84 experienced practitioners, who represent the specialties involved in the delivery of DMD care, were nominated by their peers, and selected by the CDC and steering committee to serve on one or more panels. Experts independently rated interventions and assessments used in DMD manage-

ment for appropriateness and necessity based on clinical scenarios presented in a matrix format. The matrices were developed from an extensive literature review for articles pertaining to interventions and assessments for DMD, augmented by expert opinion. Of the 1981 articles reviewed, the CDC used 489 articles in its final literature review. On completion of the literature review, the CDC and the expert panellists identified signs and symptoms that trigger the use of an assessment tool or intervention, and any clinical factors that should be taken into account. On the basis of expert input, the CDC organised the clinical factors and signs or symptoms into a matrix format. Each matrix addressed a particular assessment or intervention and included a clinical question, objective, or major presenting symptom (see webappendix for clinical scenarios reviewed).

The experts then rated the matrices in three rounds of ratings: two for appropriateness and one for necessity. In round 1, each expert anonymously rated the appropriateness of using a particular assessment tool or intervention in specific clinical scenarios on an ordinal scale of 1–9. An intervention or assessment tool was designated as “appropriate” if the expected health benefit outweighs the anticipated risk, irrespective of financial implications.<sup>35</sup> The CDC tabulated and analysed median ratings for each scenario according to RAM guidelines. During in-person meetings, the expert panels discussed the results and edited the matrices for round 2 for appropriateness. After round 2, the CDC categorised the assessments and interventions as “appropriate”, “inappropriate”, or “uncertain”, and identified any disagreement among the experts.

In round 3, the experts rated the assessments and interventions deemed appropriate without panel disagreement in round 2 for necessity on a similar 1–9 scale. Experts could rate an intervention or assessment tool as “necessary” if it met the following four criteria: (1) intervention or assessment tool was rated “appropriate” without disagreement; (2) it would be improper not to offer the intervention or assessment tool under the clinical scenario proposed; (3) there is a reasonable chance that the intervention or assessment tool will benefit the patient; and (4) the magnitude of the expected benefit is not small.<sup>35</sup> See webappendix for examples of matrices, analyses, and results. After three rounds of independent ratings, the expert panellists reviewed and interpreted the data to develop the recommendations into a clinically relevant document.

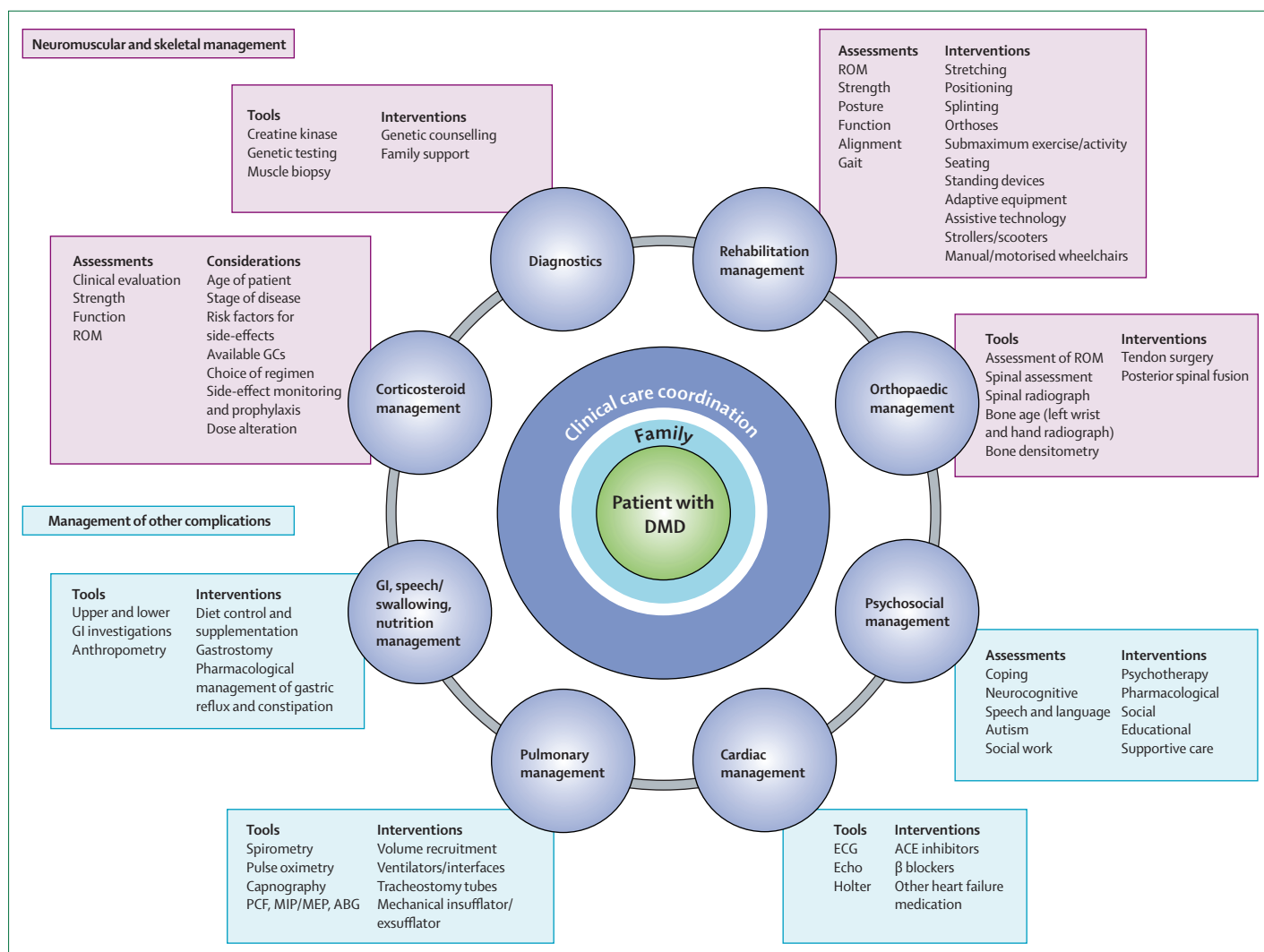
This two-part Review concentrates on those assessments and interventions that were found to be “necessary”, “appropriate”, and “inappropriate”, as defined by RAM. Areas of disagreement or uncertainty are underscored if particularly pertinent to practice. These recommendations are therefore based on the RAM results except in cases in which clinical trial evidence exists, in particular RCT data. We have noted the rare instances in which there is RCT evidence to

support the recommendations. During the development of the recommendations, the expert panels identified clinical questions not covered in the original matrices. If indicated, RAM results were supplemented by literature and expert opinion to provide a comprehensive picture of recommended care for DMD.

### The multidisciplinary team and the toolkit

Each panel defined the toolkit of assessments and interventions applicable to DMD management (figure 1). The multidisciplinary approach to caring for patients with DMD and the range of expertise required are key features of this process. The patient and family should actively engage with the medical professional who

coordinates clinical care. Depending on the patient's circumstances, such as area/country of residence or insurance status, this role might be served by, but is not limited to, a neurologist or paediatric neurologist, rehabilitation specialist, neurogeneticist, paediatric orthopaedist, paediatrician, or primary-care physician. This physician must be aware of the potential issues and be able to access the interventions that are the foundations for proper care in DMD. These include health maintenance and proper monitoring of disease progression and complications to provide anticipatory, preventive care and optimum management. Input from different specialties and the emphasis of interventions will change as the disease progresses (figure 2).



**Figure 1: Interdisciplinary management of DMD**

Coordination of clinical care is a crucial component of the management of DMD. This care is best provided in a multidisciplinary care setting in which the individual and family can access expertise for the required multisystem management of DMD in a collaborative effort. A coordinated clinical care role can be provided by a wide range of health-care professionals depending on local services, including (but not limited to) neurologists or paediatric neurologists, rehabilitation specialists, neurogeneticists, paediatricians, and primary-care physicians. It is crucial that the person responsible for the coordination of clinical care is aware of the available assessments, tools, and interventions to proactively manage all potential issues involving DMD. ABG=arterial blood gas. ACE=angiotensin-converting enzyme. DMD=Duchenne muscular dystrophy. Echo=echocardiogram. ECG=electrocardiogram. GC=glucocorticoids. GI=gastrointestinal. MEP=maximum expiratory pressure. MIP=maximum inspiratory pressure. PCF=peak cough flow. ROM=range of motion.

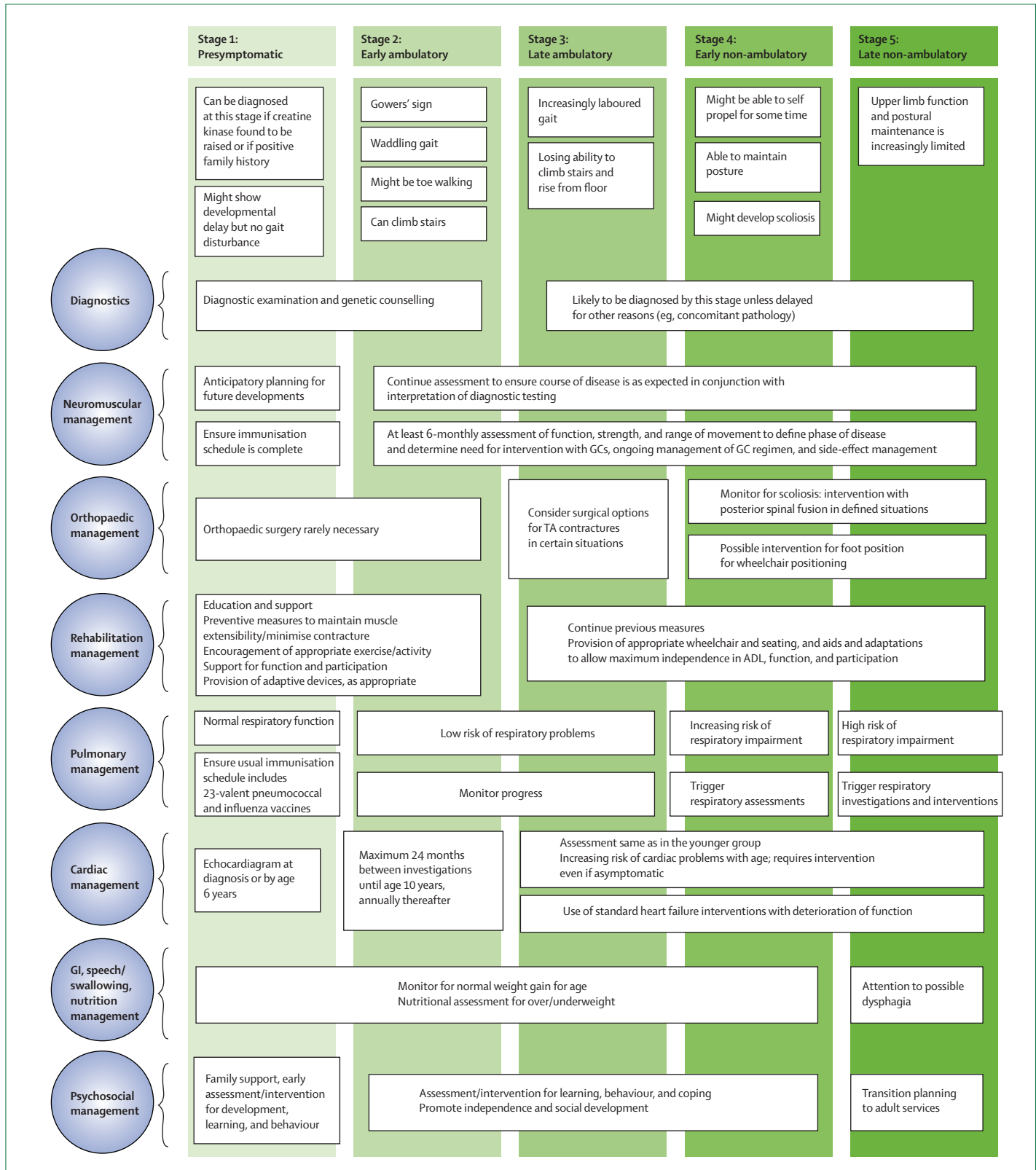


Figure 2: Stages of disease and care considerations  
 ADL=activities of daily living. GCs=glucocorticoids. GI=gastrointestinal. TA=tendo-Achilles.

At a practical level, management of the patient with DMD in the clinic requires a physically accessible environment and parking structure, with proper equipment (eg, mechanical hoist or sliding board) and trained personnel available for the safe transfer of the non-ambulatory patient. The expertise and means to obtain accurate measures of weight, height, and vital signs with appropriately trained staff are essential. Special weight scales that accommodate wheelchairs are available. Height measurements in patients with severe scoliosis are not accurate and can be replaced by arm-span measurements.

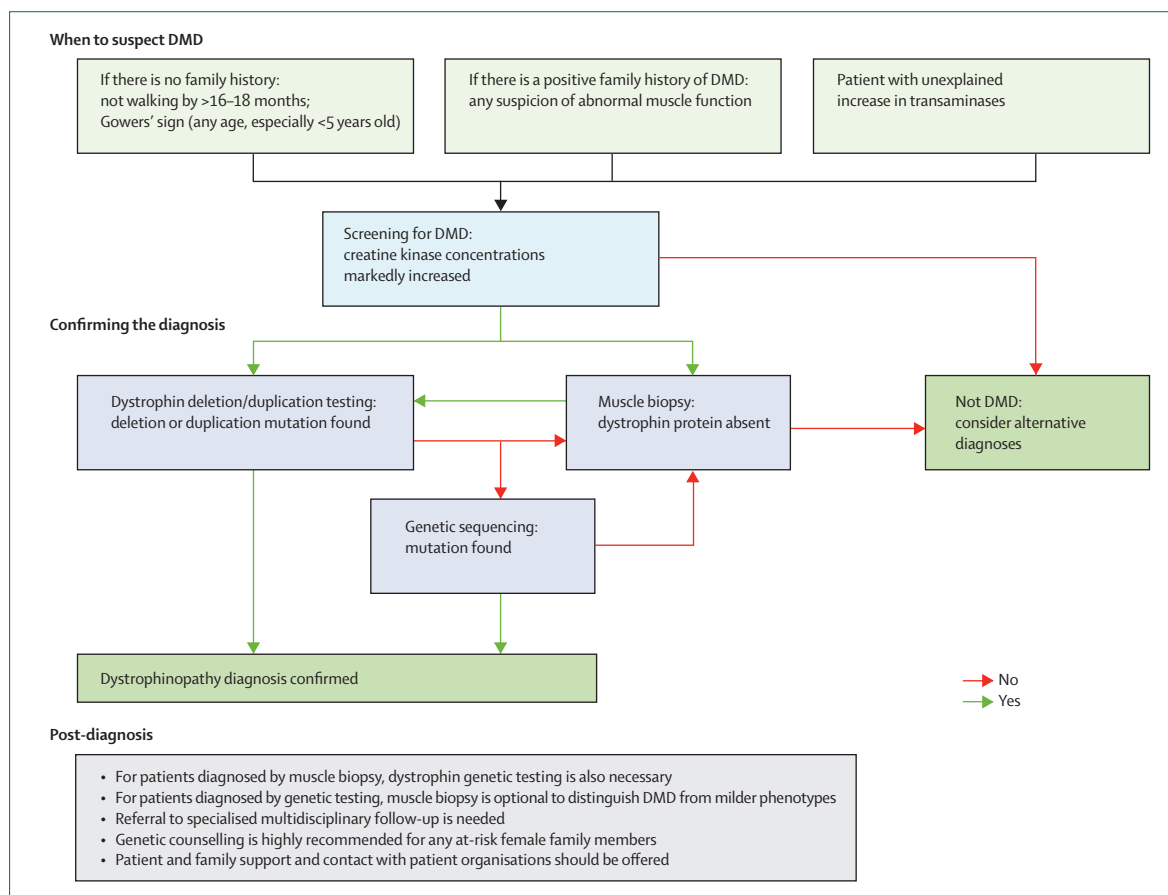
### Diagnosis of DMD

The aim of care around diagnosis is to provide an accurate and prompt diagnosis, allowing initiation of appropriate interventions, continuing support and education, and minimising the length and impact of a potentially protracted diagnostic process. Diagnosis should be done by a neuromuscular specialist who can assess the child clinically and can rapidly access and interpret appropriate investigations in the context of the clinical presentation. Family follow-up and support after diagnosis will often

be augmented by support from geneticists and genetic counsellors.

### When to suspect DMD

Suspicion of the diagnosis of DMD (figure 3) should be considered irrespective of family history and is usually triggered in one of three ways: (1) most commonly, the observation of abnormal muscle function in a male child; (2) the detection of an increase in serum creatine kinase tested for unrelated indications; or (3) after the discovery of increased transaminases (aspartate aminotransferase and alanine aminotransferase, which are produced by muscle as well as liver cells). The diagnosis of DMD should thus be considered before liver biopsy in any male child with increased transaminases. Initial symptoms might include delayed walking, frequent falls, or difficulty with running and climbing stairs. Although DMD is typically diagnosed at around 5 years of age, the diagnosis might be suspected much earlier because of delays in attainment of developmental milestones, such as independent walking or language; such delays have been documented prospectively by following patients with



**Figure 3: Diagnosis of DMD: the pathway from suspicion of the diagnosis to its confirmation**

In cases in which DMD is suspected, the route for further diagnostic testing depends on the increase in CK. In rare cases, a dystrophinopathy diagnosis could be confirmed by absent dystrophin protein on muscle biopsy even if all genetic testing is negative. If a dystrophinopathy diagnosis is not confirmed by either muscle biopsy or genetic testing, the diagnosis of alternative muscular dystrophies is complex and requires specialised input. CK=creatine kinase. DMD=Duchenne muscular dystrophy.



DMD identified by newborn screening.<sup>36</sup> The presence of Gowers' sign in a male child should trigger the diagnostic investigation of DMD, especially if the child also has a waddling gait. Toe walking might be present but is not additionally helpful in deciding whether to suspect DMD. In the presence of a positive family history of DMD, there should be a low threshold for testing creatine kinase, although this will be influenced by the age of the child. In a child less than 5 years of age, suspicion of DMD probably cannot be excluded completely by a normal muscle examination. However, with increasing age, a normal muscle examination renders the chance of a child having DMD progressively less likely. A boy older than 10 years of age with normal muscle function is thus highly unlikely to have DMD.

### Confirmation of the diagnosis

The route to confirming the diagnosis (figure 3) depends on local availability of rapid and reliable testing, which must be interpreted alongside the clinical presentation owing to the range of severity possible with dystrophin mutations. Testing for a *DMD* mutation in a blood sample is always necessary even if DMD is first confirmed by the absence of dystrophin protein expression on muscle biopsy. The results of genetic testing provide the clinical information required for genetic counselling, prenatal diagnosis, and consideration for future mutation-specific therapies. Different types of mutations in *DMD* can be the genetic basis for DMD.<sup>12</sup> The genetic tests commonly used to identify dystrophin mutations are multiplex PCR,<sup>37</sup> multiplex ligation-dependent probe amplification,<sup>38</sup> single-condition amplification/internal primer,<sup>39,40</sup> and multiplex amplifiable probe hybridisation.<sup>40</sup> Multiplex PCR is widely available and the least expensive, but only detects deletions and does not cover the whole gene, so that a deletion might not always be fully characterised. Multiplex ligation-dependent probe amplification and amplifiable probe hybridisation will detect deletions and duplications and cover all exons, and single-condition amplification/internal primer will detect deletions and provide sequence data. None of these techniques is universally available.

If analysis by one or more of these techniques leads to the identification and full characterisation of a dystrophin mutation, then no further testing is required. If deletion/duplication testing is negative, then dystrophin gene sequencing should be done to look for point mutations or small deletions/insertions.<sup>39,40</sup> Full characterisation of the mutation (deletion endpoints or exact position of any point mutation) is required to allow correlation of the predicted effect of the mutation on the reading frame of the gene, which is the major determinant of the phenotypic variability seen in dystrophinopathy,<sup>19,21,22</sup> as well as to determine eligibility for the mutation-specific treatments currently in trials.<sup>41-43</sup>

A muscle biopsy could be done, depending on the clinical situation, availability of genetic testing, and the facilities in

the centre where the patient is seen.<sup>44</sup> An open muscle biopsy is necessary if the differential diagnosis includes DMD among other diagnostic possibilities, such as other types of muscular dystrophy, so that adequate amounts of tissue will be available for further analysis. A needle biopsy might be appropriate if testing is only for DMD or if the clinician is skilled in taking multiple cores of tissue from paediatric patients.<sup>45,46</sup> In those centres where it is done, the conchotome technique has the advantage of providing a larger sample than a single-core needle biopsy, and does not require an open surgical procedure.<sup>47,48</sup>

The key tests done on the muscle biopsy for DMD are immunocytochemistry and immunoblotting for dystrophin, and should be interpreted by an experienced neuromuscular pathologist.<sup>7-9</sup> A muscle biopsy can provide information on the amount and molecular size of dystrophin, as long as the protein is present.<sup>7-9,12,44</sup> Differentiating total and partial absence of dystrophin can help to distinguish DMD from a milder dystrophinopathy phenotype.<sup>7-9,12,44</sup> Electron microscopy is not required to confirm DMD.

Genetic testing after a positive biopsy diagnosis of DMD is mandatory. A muscle biopsy is not necessary if a genetic diagnosis is secured first, particularly as some families might view the procedure as traumatic. However, if genetic testing has been done and no mutation identified, but creatine kinase concentrations are increased and signs or symptoms consistent with DMD are present, then the next necessary diagnostic step is to do a muscle biopsy. This is also the case if there is a family history of DMD and a suspicion of the diagnosis, but no family mutation is known.

Whereas electromyography and nerve-conduction studies have been a traditional part of the assessment of a child with a suspected neuromuscular disorder, these tests are not believed by the expert panels to be now indicated or necessary for the specific assessment of DMD.

### Neuromuscular and skeletal assessments

Clinical assessment in DMD includes taking a standard medical and family history and undertaking a physical examination, with a focus on the musculoskeletal system and related functional impairments. The neuromuscular specialist should be experienced in the expected disease course for DMD to understand the implications of a deviation from this course (eg, the possibility that a milder course might indicate a less severe dystrophinopathy or that more severe disease might suggest concomitant morbidity). This judgment will be informed by the results of regular assessments of disease progression (ie, strength, range of motion, posture, gait, timed testing),<sup>49</sup> monitoring of ability to cope with activities of daily living, and application of motor function scales. These assessments, which are also used to inform decisions about therapeutic interventions and monitor response to therapy, are

	Method	Aim of testing	Ambulatory	Non-ambulatory
Strength testing	Manual muscle testing (MRC scale) <sup>50</sup> Quantitative myometry (beneficial if muscle strength 3–5 on MRC scale)*	Serial assessment: to identify outliers from expected clinical course; to monitor disease progression and predict functional losses; to assess response to treatment; and to monitor muscle imbalance	Test lower extremity strength by manual muscle testing every 6 months	Early stages: test upper and lower extremity strength every 6 months Later stages: value of testing is less certain
Range of motion	Goniometry <sup>51</sup>	Baseline: to identify emerging muscle hypoextensibility and joint contractures that might contribute/lead to functional deterioration or musculoskeletal or integumentary problems To identify need for additional or altered therapeutic/surgical intervention (ie, orthoses, splinting, use of standers, iliotibial band lengthening)	Lower extremities: hip, knee, ankle joints; iliotibial band; hamstrings, gastrocnemius	Lower extremities: hip, knee, ankle joints; iliotibial band; hamstrings, gastrocnemius Upper extremities: elbow, wrist, long finger flexors
Timed testing	Standardised use of timed function tests <sup>50,52</sup>	Easy and relevant measure of daily functional status; responsive to change	Timed 10 m walk, timed Gowers' manoeuvre, time to climb 4 stairs, time to rise from chair, 6-min walk test Time to put on a shirt might be relevant in late ambulatory stage	Time to put on a shirt might be relevant in early non-ambulatory stage, timed testing not applicable in late non-ambulatory stage
Activities of daily living	Assessment of impairment in daily activities in the home, school, and community settings	Highly relevant to targeted input with aids, adaptations, and access to environmental controls	Frequency of falls, step activity monitoring, self-care skills, writing, computer use Functioning in school and community settings	Self-care skills, writing, computer use, control of manual and electric wheelchair Functioning in school and community settings
Motor function scales	Assessment of motor function in specific domains to give a composite score	Allows monitoring of progression and response to therapy	Vignos lower extremity scale, North Star Ambulatory Assessment, motor function measure	Brooke upper extremity scale, Egen Klassifikation functional assessment, Hammersmith motor scales, motor function measure

Routine clinic appointments should be every 6 months, unless otherwise specified. Specialist physical and occupational therapy assessments are recommended every 4 months. MRC=UK Medical Research Council. \*Although the panel found these tests to be appropriate assessment tools, they are used more typically in research than in clinical settings.

**Table 1: Suggested neuromuscular assessments for patients with Duchenne muscular dystrophy**

described in table 1. These tests require training and experience to maintain competence. Choice of tests to use in any particular category will be influenced by local factors; consistency within an individual clinic is important to allow comparison over time.

### Pharmacological interventions for muscle strength and function

Pharmacological intervention has begun to change the natural history of DMD, and further advances and more effective treatment of the underlying pathology of DMD should continue to offer an improved course, potentially including small-molecule and gene therapies. The most devastating and obvious effect of DMD is on the skeletal musculature with resulting loss of strength and function. The progression of muscle degeneration in DMD is well documented both in terms of pathophysiology and pathokinesiology (with a proximal-to-distal progression of muscle weakness, leading to progressive losses in activities of elevation against gravity with eventual loss of ambulation).<sup>53–58</sup> Several panels have addressed treatments aimed at optimising strength and function, which include pharmacological interventions, such as glucocorticoids, and physical therapy interventions (discussed in part 2 of

this Review<sup>34</sup>) involving the use of gentle exercise and activity, and management of the musculoskeletal system to prevent/minimise contracture and deformity.

### Glucocorticoids

Glucocorticoids are the only medication currently available that slows the decline in muscle strength and function in DMD,<sup>19,20,59–63</sup> which in turn reduces the risk of scoliosis and stabilises pulmonary function.<sup>61,62</sup> Cardiac function might also improve, with limited data to date indicating a slower decline in echocardiographic measures of cardiac dysfunction, although these measures are not necessarily predictive of the delay in cardiac symptoms, signs, or cardiac-related mortality.<sup>25,62</sup>

Initial RCTs in patients treated with prednisone for up to 6 months showed an improvement in muscle strength, with 0.75 mg/kg daily having the most favourable profile.<sup>64</sup> Use of a higher dose of 1.5 mg/kg daily was no more effective,<sup>65</sup> and a lower dose of 0.3 mg/kg daily was less beneficial. Daily administration was more effective than treatment on alternate days.<sup>66</sup> Prednisolone is often used in Europe instead of prednisone. Deflazacort, a similar glucocorticoid available in many countries, but not currently approved

for use by the US Food and Drug Administration or the CDC in the USA, has been shown to have a similar efficacy at a daily dose of 0.9 mg/kg and has a slightly different chronic risk profile.<sup>67,68</sup>

Subsequent longer term studies on the use of prednisone/prednisolone and deflazacort have focused more on their effect in prolonging ambulation than on the short-term improvement in strength (ie, decline in motor function still occurs, but more slowly).<sup>69,70</sup> More recently, continued treatment after the patient becomes non-ambulatory has also shown reduction in the risk of progressive scoliosis and stabilisation of pulmonary function test variables.<sup>61,62</sup>

On the basis of this convincing literature, practice parameter guidelines, and personal experience, the panel strongly urges consideration of glucocorticoid therapy in all patients who have DMD.<sup>19,20</sup> The rest of this section provides guidance on what clinical information is necessary to determine when to start glucocorticoid medication and how to monitor and manage side-effects.

The goal of the use of glucocorticoids in the ambulatory child is the preservation of ambulation and the minimisation of later respiratory, cardiac, and orthopaedic complications, taking into account the well-described risks associated with chronic glucocorticoid administration. If such issues are pre-existing, the risk of side-effects might be increased (table 2). Particular care needs to be taken with such patients in deciding which glucocorticoid to choose, when to initiate treatment, and how best to monitor the child for any problems. A high index of suspicion for steroid-related side-effects needs to be maintained at all times. Prevention and management of side-effects needs to be proactive.<sup>59</sup> Families should be provided with a steroid card or similar notification that the child is on steroids, listing emergency-care considerations in the setting of acute medical presentation, fracture, serious infection, need for surgery, or general anaesthesia, to alert any medical professional with whom the child might come into contact.

#### *Initiation of glucocorticoid therapy*

No generally accepted guidelines exist in the literature about the best time to initiate glucocorticoid therapy in an ambulatory boy with DMD. The panel's opinion, derived through the RAM process, is that the timing of initiation of glucocorticoid therapy must be an individual decision, based on functional state and also considering age and pre-existing risk factors for adverse side-effects. Recognition of the three phases of motor function in DMD (making progress, plateau, and decline) helps the clinician to make this decision (figure 4). In all cases, the recommended national immunisation schedule should be complete and varicella immunity should be established before steroids are started.

Initiation of glucocorticoid treatment is not recommended for a child who is still gaining motor skills, especially when he is under 2 years of age. The

typical boy with DMD continues to make progress in motor skills until approximately age 4–6 years, albeit at a slower rate than his peers.<sup>81</sup> The eventual use of glucocorticoids should be discussed with caregivers at this stage, in anticipation of the plateau in motor skills and subsequent decline. The plateau phase, which might last only a few months, can be identified when there is no longer progress in motor skills, but prior to decline, as determined by history and timed testing (table 1). The child who takes longer in timed testing, loses a skill (such as climbing stairs), shows less endurance, or has more falls, is in a decline phase. Once the plateau phase has been clearly identified, usually at age 4–8 years, the clinician should propose initiation of glucocorticoids unless there are substantial reasons (such as major pre-existing risk factors for side-effects) to wait until the decline phase. Starting steroids when in the full decline phase or when ambulation is more marginal is still recommended, but might be of more limited benefit.

These recommendations for when to initiate glucocorticoid treatment should be interpreted as a minimum threshold. Some practitioners favour a more aggressive approach with earlier initiation of treatment when clinical symptoms first appear, although there are no published data to support this, so the panel did not believe it appropriate to endorse earlier glucocorticoid treatment.

Because the decision to initiate glucocorticoids is based on serial assessment as well as parental report, additional care is required in initiating glucocorticoid therapy at an initial visit or at a second-opinion consultation. The assessment of the child's course of motor function (making progress, plateau, and decline) is based purely on the caregiver's history at a first visit, so care should be exercised in making such conclusions in a child aged under 6 years. If glucocorticoids are initiated at a first visit, we suggest that a physician be identified at that time who will be in charge of monitoring the child, particularly if the physician making the recommendation cannot fulfil this role.

Long-term use of glucocorticoids requires much commitment on the part of the family. Essential issues for discussions should include potential side-effects, the obligation to closely monitor and manage any adverse issues that might arise, and the requirement to have the child followed closely by their primary-care physician and specialty health-care team.

#### *Use of glucocorticoids after loss of ambulation*

In patients who have used glucocorticoids while ambulatory, many experts continue medication after loss of ambulation,<sup>62</sup> with the goal of preserving upper limb strength, reducing progression of scoliosis, and delaying decline in respiratory and cardiac function.<sup>19,61,62</sup>

Indications for initiation of glucocorticoids in non-ambulatory patients are more relative than absolute. The effectiveness of glucocorticoid treatment in



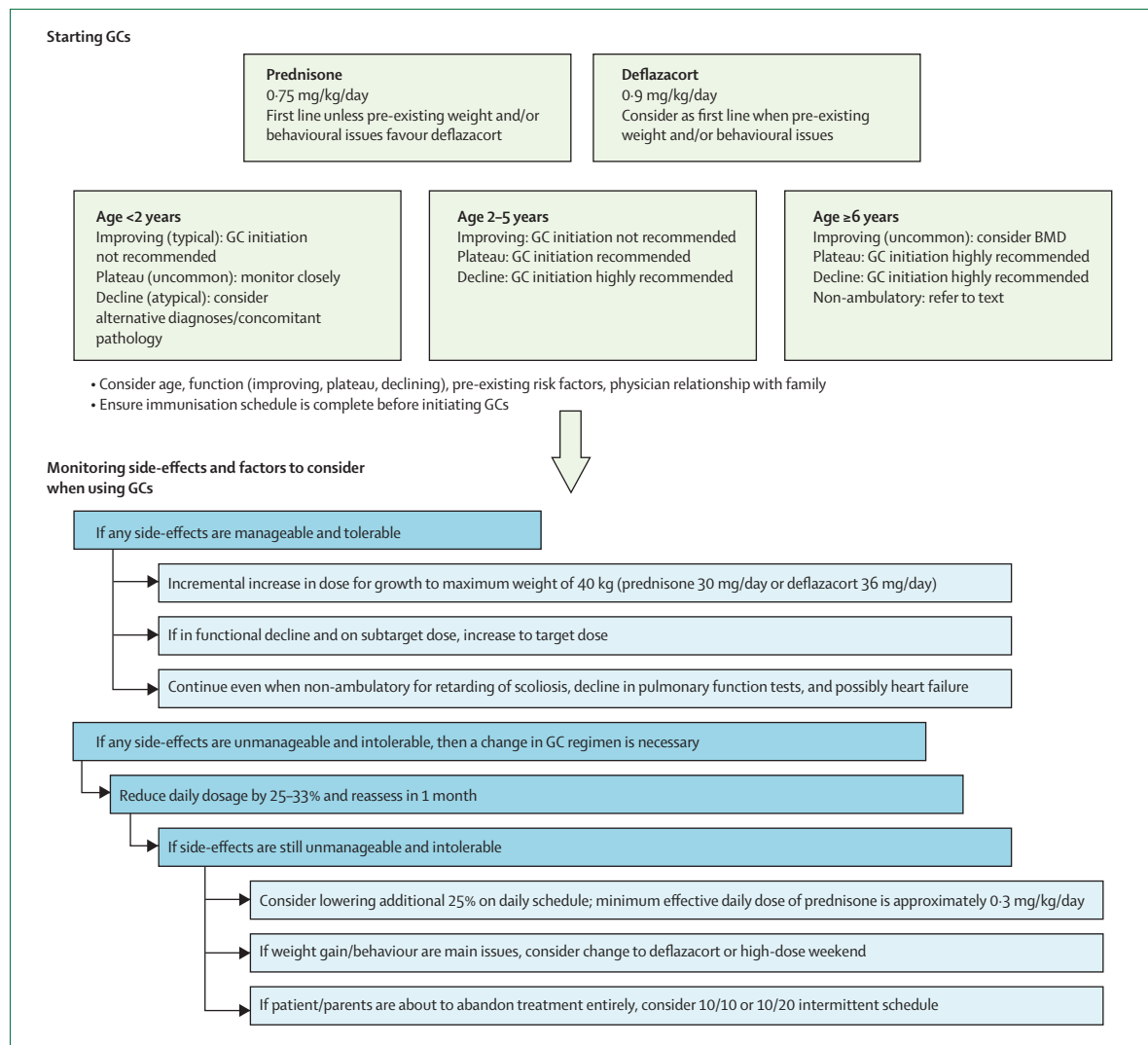
preventing scoliosis or in stabilising cardiac or respiratory function in this setting is not known; this issue thus warrants further study. However, limited data from trials suggest short-term stabilisation of pulmonary function in the early non-ambulatory patient.<sup>65</sup> If the patient and caregiver request the initiation of steroids, daily dosing is indicated if there is a stable functional course. A daily dose is also appropriate in the presence of declining function. However, there is greater need in this group to consider the effect of pre-existing risk factors, such as

behavioural issues, fracture risk, or obesity; side-effects require close monitoring. Whether patients with more limited arm function and advanced pulmonary disease (such as those who already require nocturnal bi-level positive airway pressure assistance) can benefit from glucocorticoid therapy is uncertain. The presence of an abnormal echocardiogram or symptoms of heart failure are not contraindications to glucocorticoid therapy, but use of glucocorticoids if advanced cardiomyopathy is present might carry higher risk of side-effects.

	Recommended monitoring	Intervention
Constitutional and cosmetic		
Cushingoid features, <sup>19</sup> obesity <sup>70,71</sup>	Particular vigilance needed if patient, parents, or siblings are obese Dietary advice to be reinforced before starting steroids; warn about increased appetite	Implement proactive dietary management for the entire family, not just the patient Consider change from prednisone to deflazacort Select an alternative regimen
Hirsutism <sup>19</sup>	Forewarn parents	Does not usually occur to an extent that warrants a change in medication
Acne, tinea, warts	More notable in teenagers	Use ancillary treatment measures (topical prescription) and do not rush to change the GC regimen unless the boy is emotionally distressed
Growth retardation <sup>72,73</sup>	Monitor height at least every 6 months as part of general care (stature tends to be small in DMD even without steroid treatment <sup>61</sup> )	Consider endocrine evaluation if growth plateaus
Delayed puberty	Monitor Tanner stage Identify any family history of delayed sexual maturation	Consider endocrine assessment if notably delayed or patient is upset by the delay
Adverse behavioural changes <sup>19,74-76</sup>	Identify any baseline mood, temperament, ADHD issues, and advise parents that these often transiently worsen in the initial 6 weeks on GC therapy	Decide whether baseline issues should be treated before starting GC therapy (eg, ADHD counselling or prescription) Consider changing timing of GC medication to later in the day Consider behavioural health referral
Immune/adrenal suppression <sup>77</sup>	Advise parents of risk of serious infection and need to promptly address minor infection Advise parents to inform all medical personnel that their child is on steroids and carry steroid alert card Ensure that the GC is not stopped abruptly	Obtain varicella immunisation before starting GC therapy; confirm with protective serum titre Engage in tuberculosis surveillance Obtain infectious diseases consultation if serious infection occurs Substitute prednisone equivalent if deflazacort is temporarily unavailable Implement intravenous stress-dose hydrocortisone or methylprednisolone coverage for surgery or major illness (no accepted treatment strategy; anaesthesia or endocrine consultation recommended) Give intravenous coverage if nothing by mouth
Hypertension <sup>76</sup>	Monitor blood pressure as percentile for height and sex at each clinic visit	If blood pressure >99%, reduce salt intake, weight reduction If ineffective, refer for possible ACE inhibitor or $\beta$ blocker medication
Glucose intolerance	Urine dipstick for glucose at clinic visits Enquire about polyuria, polydipsia	If urine is glucose-positive, then try fasting or post-prandial blood glucose, and if abnormal, then seek an endocrine consultation
GERD	Enquire about GERD symptoms (heartburn) Advise parents to report symptoms	Avoid NSAIDs Prescribe ranitidine or proton-pump inhibitor and antacid if symptomatic
Peptic ulcer disease <sup>78</sup>	Advise parents of risk and to report symptoms History of gastritis, GERD, abdominal pain, or faecal blood Test stool for blood if anaemic or suggestive history	Avoid NSAIDs Prescribe ranitidine or proton-pump inhibitor and antacid if symptomatic Seek gastrointestinal consultation
Cataracts	Annual ophthalmological examination	Consider switching from deflazacort to prednisone if cataracts evolve that affect vision Seek ophthalmology consultation
Bone demineralisation and increased fracture risk <sup>*76,79</sup>	Take careful fracture history Annual DEXA to monitor bone density Annual monitoring of 25-hydroxy vitamin D blood concentration (ideally late winter in seasonal climates) and supplement with vitamin D3 if level is <32 nmol/L Dietitian should assess calcium and vitamin D intake	For 25-hydroxy vitamin D concentration 20–31 nmol/L, give 1000 IU orally twice daily, for <20 nmol/L, give 2000 IU orally twice daily Recheck serum 25-hydroxy vitamin D concentration again after 3 months on therapy Encourage weight-bearing activities Take multivitamin supplements with vitamin D3 Consider bisphosphonates, such as pamidronate
Myoglobinuria <sup>80</sup>	Enquire about abnormal coloration of urine after exercise, urine testing	Advise avoidance of excessive eccentric (eg, descending stairs, squatting down, trampolining) and resistive exercise Commence renal investigations if persistent

Common chronic side-effects of high-dose GC administration in growing children are listed for the ambulatory and non-ambulatory patient who has DMD, assuming typical initiation of prednisone or deflazacort at age 6 years ( $\pm 2$ ) and continued use on a daily schedule.<sup>19,20,59,78,80</sup> Reduction in dose is necessary if side-effects are unmanageable or intolerable. If this is unsuccessful, then further reduction or change to another dosing regimen is necessary before abandoning treatment altogether (figure 5). Close monitoring for side-effects is important, especially within the initial 6 months of treatment. ACE=angiotensin converting enzyme. ADHD=attention-deficit hyperactivity disorder. DEXA=dual-energy x-ray absorptiometry. DMD=Duchenne muscular dystrophy. GC=glucocorticoid. GERD=gastroesophageal reflux disease. NSAID=non-steroidal anti-inflammatory drug. \*See part 2 of this Review (figure 1).

**Table 2: Recommended monitoring and intervention for GC side-effects**



**Figure 4:** Schema for initiation and management of GC medication in Duchenne muscular dystrophy<sup>59,68,80</sup>  
 See table 2 for more on monitoring side-effects. BMD=Becker muscular dystrophy. GC=glucocorticoid.

#### Glucocorticoid regimens and dosing

The conclusion derived through the RAM process was that daily use of a glucocorticoid is preferred to alternative regimens (ie, alternate day, high-dose weekend, or a 10-day “on” cycling with 10 or 20 days “off”; table 3). Newer data from continuing and future studies might lead to modifications in this recommendation.<sup>82</sup>

Prednisone (prednisolone) and deflazacort are believed to work similarly and neither one has a clearly superior effect on altering the decline in motor, respiratory, or cardiac function in DMD.<sup>19,20,59</sup> The choice of which glucocorticoid to use depends on legal availability, cost, formulation, and perceived side-effect profiles (figure 4).<sup>19,20,59</sup> Prednisone is inexpensive and available in a tablet and liquid formulation. Deflazacort, where available, is more expensive and available in fewer tablet sizes, and the liquid formulation is not widely available. Deflazacort

might be preferred to prednisone for some patients because of the likely lower risk of weight gain.<sup>19,20,59,68,70,83</sup>

The recommended starting dose for prednisone in ambulatory boys is 0.75 mg/kg daily and for deflazacort is 0.9 mg/kg daily, given in the morning.<sup>19,20,59</sup> Some patients experience transient behavioural issues (eg, hyperactivity, emotional lability) for a few hours after the medication is given. For these children, administration of the medication in the afternoon following school might be preferred. In general, higher doses of glucocorticoid are no more effective. The minimum effective dose that shows some benefit (albeit not to the maximum extent possible) is believed to be 0.3 mg/kg daily for prednisone.<sup>20,64</sup> On the basis of the usual doses used in those who have continued use of steroids from the ambulatory phase, 0.3–0.6 mg/kg daily might be an option. There are no data or a panel consensus on the

	Prednisone dose*	Deflazacort dose*	Comments	In case of side-effects
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	Must reduce dose if side-effects are not manageable or tolerable
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	Must reduce dose if side-effects are not manageable or tolerable
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	Must reduce dose if side-effects are not manageable or tolerable

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

**Table 3: Alternative GC dosing strategies**

optimum dose of glucocorticoid medication for non-ambulatory steroid-naïve patients.

For ambulatory patients, the dose of glucocorticoid is commonly increased as the child grows, provided side-effects are manageable and tolerable,<sup>82</sup> until he reaches approximately 40 kg in weight, with a prednisone cap of approximately 30–40 mg/day (Clinical Investigators in Duchenne Dystrophy study group dose cap was 40 mg; Pandya S, unpublished) and a deflazacort cap of 36–39 mg/day.<sup>62</sup> Non-ambulatory teenagers maintained on chronic glucocorticoid therapy are usually above 40 kg bodyweight and the dose per kilogram is often allowed to drift down to the 0.3–0.6 mg/kg daily range for prednisone or deflazacort, which still leads to substantial benefit.<sup>61,62</sup> An alternative approach is to not increase the dose of glucocorticoids as the child grows, maintaining the initial dose. How this compares in effectiveness or side-effect profile to the majority view of increasing the dose with growth is not known.

For patients on a relatively low dose of glucocorticoids (less than the starting dose per kg bodyweight) and showing functional decline, the panel felt that it is necessary to consider a functional-rescue adjustment. The dose of glucocorticoids is increased to the target dose and the patient is then re-assessed for benefit and tolerability in 2–3 months. It might also be reasonable to increase the dose in an individual patient beyond the typical target dose in this setting to see whether a boost in strength might prolong ambulation, but there are no data or consensus opinion to support this position at present. However, an increase in glucocorticoid dose might also increase the risk of side-effects and this needs to be taken into consideration.

#### Side-effect management

Attentive management of steroid-related side-effects is crucial once a child has started chronic steroid therapy. Although steroid therapy is currently the mainstay of medication for DMD, it should not be undertaken casually by the health-care provider or family and should be managed in clinics with appropriate expertise. Setting parameters for the management of the growing child

with DMD on chronic glucocorticoid therapy can help to determine the frequency of dosing and dose adjustment (figure 4). Table 2 summarises the main side-effects to be monitored and useful interventions to counteract them.

Maintenance of a daily schedule is appropriate when the child's motor function is stable or in decline and if any glucocorticoid side-effects are manageable and tolerable. If a daily-dosing schedule generates unmanageable and/or intolerable side-effects that are not ameliorated by a reduction in dose at least once, then it is appropriate to change to an alternative regimen (table 3). If, however, any glucocorticoid side-effects are unmanageable and/or not tolerable, then an increase in glucocorticoid dose for growth or declining function is inappropriate, and in fact, a decrease in dose is necessary, whether motor function is stable or in decline. This applies to all dosing regimens. A reduction of approximately 25–33% is suggested, with a reassessment by phone or clinical visit in 1 month to determine whether side-effects have been controlled. If obesity is of concern, then the physician should consider switching treatment from prednisone to deflazacort (table 2). Glucocorticoid therapy should not be abandoned even if side-effects are not manageable and/or tolerable until at least one dose reduction and change to an alternative regimen has been pursued. This recommendation holds for both ambulatory and non-ambulatory patients. However, should adjustments to the glucocorticoid dosing and/or schedule regimens prove ineffective in making any significant side-effects sufficiently manageable and tolerable, then it is necessary to discontinue glucocorticoid therapy, irrespective of the state of motor function. These decisions need to be made individually in partnership with the child and family, because tolerability of side-effects compared to perceived benefit is an individual judgment. Figure 4 and table 2 provide more details on specific issues and management recommendations.

#### Other drugs and dietary supplements

The use of oxandrolone, an anabolic steroid, was not considered necessary or appropriate, either with or without glucocorticoid therapy. The safety of botulinum toxin A has not been studied for the treatment or prevention of

contractures in individuals with DMD and is thought to be inappropriate. No recommendations for the use of creatine were established. An RCT of creatine in DMD failed to show a clear benefit.<sup>84</sup> If a patient is taking creatine and has evidence of renal dysfunction, it is necessary to discontinue this supplement.

Supplements, such as coenzyme Q10, carnitine, aminoacids (glutamine, arginine), anti-inflammatories/anti-oxidants (fish oil, vitamin E, green-tea extract), and others, are being used by some parents and are endorsed by some practitioners. In the absence of supportive data from the literature or expert opinion consensus from these panels, we make no recommendations for the use of supplements. The expert panels also did not rate the value of potential disease-modifying drugs, such as pentoxifylline or various herbal or botanical agents. This was identified as an area for which additional research is needed. Active

involvement of families in activities that help with the advancement of knowledge about DMD, such as patient registries and clinical trials, was encouraged.

### Psychosocial management

The medical care of a patient who has DMD and his family is not complete without support for their psychosocial wellbeing.<sup>85,86</sup> For many parents, the stress caused by the psychosocial problems of their child exceeds the stress associated with the physical aspects of the disease.<sup>87</sup> Needs vary with the age of the patient and stage of disease (figure 2), but several general statements are valid.

DMD is a multilevel/multisystem disease. Biological factors (including the lack of dystrophin and/or its isoforms and the subsequent effect on brain development and functioning),<sup>88</sup> social and emotional factors, and treatment factors (eg, glucocorticoids) can all play a part in psychosocial health.<sup>5</sup> Although most psychosocial issues are not unique to DMD, patients with DMD are at increased risk for problems in these areas. The psychosocial difficulties that are observed in DMD should be treated with the same effective, evidence-based interventions that are used in the general population,<sup>89</sup> with a strong emphasis on prevention and early intervention, because this will maximise potential outcome.

In general, psychosocial adjustment of boys with DMD is similar to that for other chronic medical conditions.<sup>90</sup> However, some specific areas of risk are of particular concern. Difficulties in social functioning might be due to biologically based deficits in specific cognitive skills, such as social reciprocity, social judgment, perspective taking, and affective discrimination, whereas the consequences of DMD (ie, physical limitations) might result in social isolation, social withdrawal, and reduced access to social activities. The pattern of speech and language deficits, including those in language development, short-term verbal memory, and phonological processing, as well as cognitive delays, including impaired intelligence and specific learning disorders, are well documented.<sup>91–94</sup> There is also increased risk for neurobehavioural and neurodevelopmental disorders, including autism spectrum disorders, attention-deficit hyperactivity disorder, and obsessive-compulsive disorder.<sup>95</sup> Problems might be encountered with emotional adjustment and depression.<sup>5</sup> Anxiety might also be an issue and can be exacerbated by cognitive deficits in mental flexibility and adaptability (ie, overly-rigid thought processes). Similarly, deficits in mental flexibility and emotional regulation can result in oppositional/argumentative behaviour and explosive temper problems. Increased rates of depression in parents of children who have DMD underscore the need for assessment and support of the entire family.<sup>96</sup>

### Assessments

Crucial times to consider assessments include the time around diagnosis (for some families, a 6–12-month window will be needed for some assessments to allow for

#### Panel 1: Psychosocial assessments

##### Emotional adjustment/coping

- Brief screening of emotional status is strongly recommended at every clinic visit or on an annual basis at a minimum
- Emotional adjustment screening can be informal in nature and does not require a comprehensive assessment
- Use of short standardised rating scales is appropriate and might be helpful
- Could be completed by a social worker or mental health professional or by other clinical staff with sufficient training in this area (eg, attending physician, nurse)

##### Neurocognitive

- Comprehensive developmental (children  $\leq 4$  years old) or neuropsychological (children  $\geq 5$  years old) assessment is recommended at or near time of diagnosis and prior to entering formal schooling
- Standardised performance-based tests and parent/patient rating scales should be used
- Should be done by a neuropsychologist or other professional with expertise in brain functioning and development within the context of medical conditions

##### Speech and language

Assessment for speech and language therapy services is necessary for:

- Younger children who present with suspected delays in speech and/or language development (as identified by caregiver or because of professional concerns)
- Older patients who present with loss or impairment of functional communication ability

##### Autism spectrum disorders

- Screening is necessary in children with DMD who are suspected of having language delays, restricted or repetitive behaviour patterns, or deficits in social functioning (as identified by caregiver or because of professional concerns)
- Necessary to refer to an experienced professional for comprehensive assessment and management of an autism spectrum disorder following positive screening or if ongoing concerns exist

##### Social work

- Assessment of the caregivers and family by a social-services professional is necessary
- A social services professional is defined as a clinical social worker or other professional who is sufficiently trained and qualified to assess and address emotional adjustment and coping, who has access to financial resources and programmes and social support networks, and who has an understanding/awareness of DMD

DMD=Duchenne muscular dystrophy.

adjustment after diagnosis), before entering school, and after a change in function. Although not every clinic will have direct access to all assessments and interventions listed (panels 1 and 2), we hope that these recommendations can serve as a guide to filling gaps in clinical staff and directing referrals, where appropriate. Assessments are targeted at the areas of emotional adjustment and coping, neurocognitive functioning, speech and language development, the possible presence of autism spectrum disorders, and social support. Routine screening of psychosocial wellbeing in the patient, parents, and siblings is necessary.

### Interventions

Interventions will depend on the individual, but should be available to meet a broad spectrum of needs. Of crucial importance to patient/family psychosocial health is the designation of a care coordinator who can serve as a point of contact for families and who has sufficient knowledge and background in neuromuscular disorders to be able to meet the family's information needs.<sup>86</sup> Proactive intervention to help families and patients avoid the social problems and social isolation that occur in the context of DMD is necessary (panel 2).

Development of an individual education plan for all children with DMD in collaboration with their parents and schools is necessary to address potential learning problems. In addition, this will help with modification of activities that might otherwise prove harmful to the child's muscles (eg, physical education) or might lead to reduced energy/fatigue (eg, walking long distances to and from lunch) or safety (eg, playground activities) and accessibility issues. Promoting patient independence and involvement in decision making (ie, as it relates to their medical care) is also necessary.

Psychopharmacological interventions should be considered for the treatment of moderate to severe psychiatric symptoms as part of a multimodal treatment plan that includes appropriate psychotherapies and educational interventions. Standard prescribing practices and guidelines apply, with additional considerations focused on the patient's cardiac status and drug interactions and side-effects when combined with other medications (eg, weight gain and glucocorticoids), and the patient's general medical condition. Close monitoring with systematic, routine follow-up is highly recommended, including consultation with the appropriate specialist if concerns arise.

Palliative care is appropriate to relieve or prevent suffering and to improve quality of life in patients who have DMD, as needed. In addition to pain management, palliative care teams might also be able to provide emotional and spiritual support, assist families in clarifying treatment goals and making difficult medical decisions, facilitate communication between families and medical teams, and address issues related to grief, loss, and bereavement.

### Panel 2: Psychosocial interventions

#### Psychotherapy

- Parental management training: recommended for externalising behaviours (eg, noncompliance/disruptive behaviour and parent-child conflict)
- Individual therapy: recommended for internalising behaviours (eg, low self-esteem and depression, anxiety, and obsessive-compulsive disorder, adjustment and coping difficulties)
- Group therapy: recommended for social skills deficits
- Family therapy: recommended for adjustment and coping difficulties and parent-child conflict
- Applied behaviour analysis: recommended for specific behaviours related to autism

#### Pharmacological interventions

- Selective serotonin re-uptake inhibitors for depression, anxiety, obsessive-compulsive disorder
- Mood stabilisers for aggression, anger/emotional dysregulation
- Stimulants for attention-deficit hyperactivity disorder

#### Social interaction interventions

- Increasing DMD awareness and knowledge among school personnel
- Peer education about DMD
- Social skills training (as needed to address deficits in this area)
- Modified/adapted sports, summer camps, and youth groups/programmes
- Art groups, equestrian, and aqua therapies, use of service dogs, nature programmes, and internet/chat rooms, among others
- Promoting patient independence and self-advocacy

#### Educational interventions

- Neuropsychological assessment at diagnosis and before entering school
- Individualised education programme on entering school
- Measures to address deficits as they are identified

#### Care/support interventions

- Care coordinator: serves as a point of contact for the family to meet family information needs, schedule and coordinate appointments, and facilitate communication with clinicians, etc; should be a professional with a sufficient level of training regarding clinical care for DMD
- Home health-care services: should be used if a patient's health is at risk because sufficient care cannot be provided in their current setting or circumstances; might also be appropriate in other situations when the current care providers cannot sufficiently meet the patient's care needs
- Transition planning: encouraging self-advocacy in medical care, facilitating transfer to a new medical care team, and developing educational and vocational opportunities
- Palliative care: appropriate for pain management, as needed; emotional and spiritual support; and guidance for treatment and medical decisions
- Hospice care: necessary for end-stage patients

DMD=Duchenne muscular dystrophy.

### Conclusions

The recommendations presented in the two parts of this Review represent the outcome of an international collaboration of clinical experts working to inform optimum care for DMD. Because of a paucity of data from RCTs for DMD (a common situation in rare disorders), a well-established method was chosen to generate statements about the appropriateness or



### Search strategy and selection criteria

Peer-reviewed literature was searched using the key search terms of "Duchenne" or "muscular dystrophy", or both, paired with one of 410 other search terms related to a comprehensive list of assessment tools and interventions used in DMD management. The full list of search terms is available on request. The databases used included Medline, Embase, Web of Science, and the Cochrane Library. Initial inclusion criteria consisted of available abstracts of human studies published in English between 1986 and 2006. Each working group also incorporated major articles from its discipline published before 1986 and from 2007 to mid-2009 in the process of discussions, final assessments, and write-up of recommendations.

inappropriateness and necessity of clinical interventions. RAM offers several benefits compared with other consensus-based methods, including evidence-based generation of the questions to be addressed, independent appraisal of the options followed by group discussion, and several rounds of iteration.<sup>35</sup> A further advantage was the systematic evaluation of distinct clinical scenarios, mimicking as much as possible the clinical decision-making process in all its complexity.

This first part of the care recommendations generated by use of this method emphasises the overall ethos of multidisciplinary care for DMD and goes on to discuss the detail of diagnosis, pharmacological, and psychosocial management. Precise genetic diagnosis is now the gold standard for diagnosis of DMD, and here we recommend that it should be actively sought in all cases. The future possibility of mutation-specific therapies (currently in phase 1 and 2 clinical trials) adds a further urgency to the need for this kind of technology to be universally available.<sup>41</sup> As genetic technologies change, in particular with the development of high-throughput diagnostics, this algorithm should become more straightforward.

The pharmacological mainstay of neuromuscular management in DMD is the use of glucocorticoids. Data from RCTs support their use,<sup>19</sup> although treatment regimens are highly variable across different countries and different clinics. Further trials of glucocorticoids and management of their side-effects are likely to augment our knowledge of their optimum use.<sup>60,82</sup> In the meantime, these guidelines provide a framework for glucocorticoid use that allows greater consistency—a point that is of importance not only for current patient care, but in the context of the planning of multicentre trials of other novel therapies, which are allowing the baseline use of steroids as part of the standard of care.

Despite many studies reporting that both behavioural and learning issues are important for patients with DMD and their families, few publications have provided pragmatic guidelines on psychosocial care in this condition. Providing support for these kinds of issues is

frequently a challenge within a medically orientated care structure, but these recommendations clearly put this element of care at the centre of management, with an emphasis on anticipatory interventions, and suggest that measurement of impact on these areas will be a significant challenge as the field moves towards clinical trials.

In the second part of this Review,<sup>34</sup> the discussion focuses on the role of rehabilitation, cardiovascular, gastroenterology/nutrition, orthopaedic/surgical, and respiratory specialties in DMD, so that together the two Reviews can provide a comprehensive and current guide to management in this condition.

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All authors provided intellectual expertise in the study design, generation and interpretation of data, writing of the Review, and the decision to publish. KB, aided by RF, drafted and edited the Review, and approved the final version. DJB, LEC, LC, SP, and CC were involved in the literature search.

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#### Conflicts of interest

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