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Contemporary Cardiac Issues in Duchenne Muscular Dystrophy

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Duchenne muscular dystrophy (DMD) is an X-linked genetic disorder diagnosed in childhood. It affects ≈1 in every 5000 live male births (≈20 000 new cases worldwide each year).[1,2] This results in a US prevalence of 1.3 to 1.8 per 10 000 males 5 to 24 years of age. DMD is caused by mutations in the gene encoding the dystrophin protein. The loss of dystrophin results in a cascade of events leading to progressive loss of muscle function. Without supportive care, young men with DMD typically die in their late teens and early 20s. Historically, the most common cause of death has been respiratory failure. However, with improved respiratory support, an increasingly important source of morbidity and mortality is cardiomyopathy leading to heart failure and arrhythmias.[3,4] There are important differences in DMD cardiomyopathy compared with other types of pediatric dilated cardiomyopathy.[5] DMD cardiomyopathy is similar to the cardiomyopathy seen in some forms of limb girdle muscular dystrophy and congenital muscular dystrophy. In particular, a shared cardiomyopathic process is seen in those disorders in which the primary mutation alters components that directly or indirectly interact with dystrophin. There is less left ventricular (LV) enlargement at diagnosis in DMD. Only 30% of boys with DMD have cardiac symptoms at diagnosis (far fewer than other dilated cardiomyopathy). DMD cardiomyopathy is less often treated at the time of diagnosis. However, treatment rates have increased over time. Finally, there is a higher mortality for DMD cardiomyopathy than for other dilated cardiomyopathies.

The DMD Care Considerations published in 2010 addressed cardiac care recommendations based on minimal surveillance standards with echocardiography.[6,7] However, echocardiography has known limitations in DMD patients.[8] Since the 2010 publication of the DMD Care Considerations,[6,7] there have been significant advances in the understanding and management of DMD cardiomyopathy. These include the expanded use of cardiac magnetic resonance imaging (CMR) for surveillance of myocardial damage and function, expanded consideration of existing traditional and novel heart failure therapies, and the exploratory use of nonpharmacological therapies, including heart transplantation, mechanical circulatory support, and implantable cardioverter-defibrillators (ICDs). It is unclear at this time how to best use these technologies to optimize clinical outcomes in DMD cardiomyopathy, but it seems clear that treatment should be more aggressive. Despite a broader appreciation of the impact of DMD cardiomyopathy, cardiac management remains highly variable and generally underused. In a recent natural history study of DMD patients, cardiomyopathy was still underdiagnosed and undertreated.[9] Thus, there is a need to develop improved and more consistent diagnosis and treatment of DMD cardiomyopathy.

In response to these concerns, the National Heart, Lung, and Blood Institute, in collaboration with Parent Project Muscular Dystrophy, convened a Working Group meeting on July 2014,

in Bethesda, MD, to explore clinical and research questions related to cardiac disease in patients with DMD. As a result of respiratory support and glucocorticoid use, patients with DMD are living longer, bringing the associated cardiomyopathy to the forefront of management concern for Duchenne patients as they age. A number of experimental agents targeted to the skeletal muscle phenotype are in clinical trials for DMD, and the effect of these compounds on cardiac function has not been well characterized. The Working Group consisted of experts in cardiology, pulmonology, neurology, product regulation, and patient advocacy. The Working Group made clinical and research recommendations that are based on the current literature and expert opinion. Furthermore, the Working Group identified gaps in knowledge to be filled through ongoing efforts of the research and clinical communities. These recommendations to improve the diagnosis and management of cardiomyopathy in DMD included the use of CMR in clinical care and research, particularly clinical trials; the need for updated protocols to evaluate the cardiac condition in preclinical models; and the development of coordinated international biorepositories to advance treatment and research for this rare genetic disease (Table).

Cardiac Care Guidelines

The 2010 DMD Care Considerations provided a comprehensive set of multidisciplinary guidelines focused on the diagnosis and management of children diagnosed with DMD.[6,7] Areas of emphasis in the Care Considerations included diagnosis, corticosteroid use, rehabilitation, and orthopedic, psychosocial, cardiac, pulmonary, and gastrointestinal (including nutritional) management. The methods used to develop these guidelines relied on published literature, especially that supported by clinical trials, and expert opinion using the RAND/UCLA Appropriateness Methods criteria.

Given that DMD is a rare disease, there are limited clinical trial data on which to base guideline recommendations. Natural history studies on the cardiac disease associated with DMD have often reported relatively small DMD cohorts, usually restricted to a geographic region or a single center. Accordingly, larger natural history studies on DMD in the United States have been undertaken, including the Center for Disease Control and Prevention MD STARnet project (Muscular Dystrophy Surveillance, Tracking and Research Network)[1] and a survey of DMD patients from Arizona, Georgia, Hawaii, Iowa, and western New York, to update data on prevalence, incidence and variation in practice patterns and outcome.[10,11] These studies found differing outcomes in DMD on the basis of race and ethnicity and suggested that health-care disparities were associated with later diagnosis, less steroid use, and increased cardiac and respiratory complications.

Existing cardiac management guidelines emphasize monitoring and treatment. Two overlapping sets of recommendations were used to form the 2010 Care Considerations guidance for surveillance and medical treatment.[12,13] Specific imaging recommendations included an echocardiogram beginning at 6 years of age and then subsequent studies every 1 to 2 years, depending on age. After 10 years of age, it was recommended that DMD subjects undergo annual echocardiograms. However, the technical quality of echocardiography and the resulting interpretability may be limited in DMD because of the development of chest wall deformities, scoliosis, and respiratory disease. Even simple measures of systolic

function can be quite limited in teenage boys with DMD. New echocardiographic imaging techniques, including myocardial strain analysis, are promising possibilities, but many of the same challenges remain. Therefore, valid longitudinal echocardiographic measures during clinical trials can be difficult to obtain across the age spectrum as cardiomyopathy progresses.

Imaging

The Care Considerations, published in 2010, did not specifically address the use of CMR but rather cardiac imaging in general. Since that time, CMR has been more widely applied to DMD cardiomyopathy for its ability to characterize myocardial abnormalities.[14,15] CMR is well suited not only to image myocardial damage but also to provide more reliable measurement of ventricular structure and function. CMR with gadolinium is an additional emerging tool that is rapidly becoming a preferred method for cardiac monitoring in boys with DMD. Evidence for increased gadolinium enhancement on CMR is thought to reflect myocardial damage and fibrosis in the DMD heart. Because this enhancement is one of the earliest findings of cardiac involvement in DMD, its presence has been used to support early institution of cardioprotective medications for DMD cardiomyopathy. However, the need for sedation in children <6 years of age may limit the utility of CMR in this subset of boys with DMD. On the basis of emerging data, the Working Group concluded that updated and expanded cardiac care considerations were needed and that these guidelines should extend to the adult DMD population. It should be noted that the Care Considerations are currently under revision by the Centers for Disease Control and Prevention. Newer cardiac guidelines should take into account CMR and advanced echocardiography approaches that provide additional measures of myocardial disease and function, serving as early indicators of cardiac pathology before an abnormal ejection fraction. These updated recommendations are also essential for appropriate patient management because many insurance providers use them as guidelines when making payment decisions about advanced imaging procedures.

Medical Management

Medical management recommendations from the Care Considerations document discuss the use of angiotensin-converting enzyme (ACE) inhibitors as first-line therapy once LV dysfunction has developed.[6] However, initiation of therapy is often considered before ventricular dysfunction is detected in hopes of delaying its onset. A randomized, clinical trial examined initiation of therapy with an ACE inhibitor in DMD before the second decade and before a measured reduction in LV systolic function.[16] This study reported that early institution of ACE inhibition delayed the onset of LV dysfunction and improved mortality.[16,17] Angiotensin receptor blockers (ARBs) can readily be substituted for an ACE inhibitor in those who are intolerant of ACE inhibitors.[18] The use of β-adrenergic blockade in pediatric cardiomyopathy has been controversial because a multi-institutional, randomized, double-blind, placebo-controlled, 8-month study of carvedilol in pediatric heart failure failed to show clear benefit.[19] Because this study included primarily patients with congenital heart disease, it is difficult to know how the results might apply to DMD cardiomyopathy. Over the last decade, a number of retrospective[20,21] and prospective open, nonrandomized[22,23] studies have suggested a benefit of β-blockade in DMD cardiomyopathy. In a prospective open study of DMD, an ACE inhibitor alone or in

combination with a β-blocker showed improvement in LV ejection fraction.[24] Although the combination of ACE inhibitor plus β-blocker did not fare better than ACE inhibitor alone, the group who received β-blockers was older (age, 15.7 versus 14.1 years). Notably, both groups showed improvement in <12 months of treatment. On the basis of this evidence, it is not likely that patients and families would participate in a placebo-controlled trial of β-blockade in DMD cardiomyopathy. Research in this area is still needed to develop clear recommendations for the age or clinical status at which such agents should be instituted and optimal dosing. Nonetheless, it is recommended that published guidelines for adults with chronic heart failure be used in patients with DMD despite differences in the patient populations and disease characteristics.[25]

The Care Considerations urged use of glucocorticoid therapy in DMD, although such agents are not labeled for this use. The use of glucocorticoids in ambulatory DMD patients is known to prolong ambulation.[26] Data from animal studies have suggested that the use of prednisone, alone or in combination with ACE inhibitors, may be deleterious to myocardial function,[27–29] but human DMD data have suggested that steroid use has a protective effect on the heart.[8,30] A population-based surveillance program suggested that a longer duration of steroid use correlates with a greater improvement in measures of LV function.[31] A recent retrospective cohort study examined the long-term use of glucocorticoids in DMD, beyond loss of ambulation, and reported that glucocorticoid use led to improvement in all-cause mortality, almost entirely because of improved cardiac outcome.[32] Because this retrospective study examined a single population and included only those subjects who could remain on glucocorticoid long term without significant additional adverse side effects, it is not clear whether these study results could be reproduced in a prospective study or in a different population.[33] The divergence between observations in animal studies and the human DMD population, showing opposite effects of glucocorticoids on the DMD cardiomyopathy, warrants additional investigation.

The Working Group concluded that medical management guidelines should extrapolate from newer animal model data and data from adult heart failure trials, including those that include the use of mineralocorticoid receptor antagonism.[34] The use of ACE inhibitors or ARBs has now become more mainstream in the DMD population, although the age at which such therapy should begin remains an important question. It was the opinion of the Working Group that ACE inhibitor/ARB use in DMD should begin by 10 years of age (barring contraindications), but the relatively low risk of ACE inhibitors and ARBs should not discourage the consideration of earlier therapy. The recommendations for β-adrenergic blockade remain variable, with common practice to begin after the onset of ACE inhibitor/ARB use, usually on the basis of ventricular dysfunction or elevated heart rate. The timing of mineralocorticoid receptor antagonism use has not been adequately addressed, and clinical practice varies widely. The recent randomized, prospective study of mineralocorticoid receptor antagonism with eplerenone demonstrated an attenuation of the decline in LV function, measured by circumferential strain.[35] The Working Group acknowledges that there is a great deal of anxiety among families about the delay of initiation of cardiac medications. The relatively low risk of these drugs and the lack of DMD cardiomyopathy clinical trials for boys <10 years of age often lead families to desire a more

proactive strategy, which can put them at odds with physicians following a more conservative approach.

Arrhythmias

Screening and therapy for cardiac arrhythmias in DMD were identified as understudied areas. The natural history of the rhythm abnormalities in this disease has not been well documented in the literature. There is a perceived increase in sudden cardiac death in DMD, but this has never been well established. In advanced DMD cardiomyopathy, cardiac arrhythmias have been observed that are similar to those seen in other cardiomyopathies, including atrial fibrillation/flutter, ventricular tachycardia, and ventricular fibrillation. A greater burden of late gadolinium enhancement on CMR was associated with increased arrhythmia risk in DMD.[36] The adult Duchenne population may benefit from following adult heart failure guidelines for primary arrhythmia prevention. In the general adult heart failure population, benefit outweighs risk for ICDs for patients with an LV ejection fraction <35%. However, the risk of intervention may be greater in the DMD population. Severe kyphoscoliosis and respiratory muscle weakness, which are common in the advanced DMD patient, may increase risks associated with ICD placement. Use of antiarrhythmic agents for managing atrial fibrillation and ventricular arrhythmias currently follows adult heart failure and arrhythmia management, although there has been no surveillance of this practice in the advanced DMD population. Understanding practice variability in the management of arrhythmias in advanced DMD cardiomyopathy would be valuable. The use of biventricular pacing in DMD has not been assessed. However, the pattern of inferolateral involvement seen in the early-phase cardiomyopathic DMD heart is similar to the pattern that correlates with a lack of response to resynchronization therapy in the general adult heart failure population.[37]

Mechanical Circulatory Support

The use of mechanical circulatory support in DMD has been described in case reports and small series.[38] Considerations for ventricular assist devices extend beyond immediate recovery or rescue from cardiac failure or dysfunction. Currently indicated as a bridge to transplantation, long-term ventricular assist device use has increasing potential as destination therapy. As with all technologies, in all patients, the burdens of chronic technology dependence should be explored before, during, and after device implementation. Risk of device placement may be higher in the presence of kyphoscoliosis and respiratory muscle weakness, and recovery and rehabilitation after surgery may take longer. Additionally, end-of-life management preferences in neuromuscular diseases, including DMD, are a challenging area.[39] It was agreed that the cardiologist has a role in these discussions, and the Working Group acknowledged the value of a long-term patient/family/physician relationship before the urgent need for device placement. Longitudinal discussion better allows careful deliberation and understanding of long-term outcomes and goals of therapy.[40]

Cardiac Monitoring in Clinical Trials

Clinical trials are ongoing to study interventions such as exon skipping, stop codon suppression, antifibrotics, and phosphodiesterase inhibition in DMD, targeting primarily skeletal muscle disease. The effect of these interventions on DMD cardiomyopathy requires careful evaluation. Clinical trials in DMD, even those aimed at younger ambulatory DMD patients, should improve their monitoring of cardiac function to detect concomitant benefits or toxicity and to better characterize the natural history of cardiac function. It might be possible to test cardiac interventions in a separate randomization (factorial study). CMR is preferred to echocardiography for the purpose of assessing cardiac status because of superior information on tissue characteristics, chamber dimensions, and function, although the need for sedation may necessitate the use of echocardiography in younger children. Specific CMR measurements that could be monitored in clinical trials include degree and pattern of late gadolinium enhancement, myocardial strain, and extracellular volume. Additional cardiac measurements to be considered include heart rate and strain measurements (from echocardiography). Sinus tachycardia may also be useful as a biomarker because it is frequent in the DMD patient, often precedes cardiac dysfunction,[41] and may reflect a component of early respiratory involvement.

Functional measurements and quality-of-life assessment in DMD cardiomyopathy are confounded by already impaired skeletal muscle function. The “typical” heart failure symptoms such as exercise limitation or dyspnea are often absent in DMD and require unique assessments. In addition, systolic blood pressure is typically lower in the DMD population, especially in the advanced DMD population.[42] Relative hypotension complicates the use and titration of many standard heart failure medications.

Clinical Research Questions in DMD Cardiomyopathy

The Working Group discussed a number of clinical research questions in DMD cardiomyopathy that need to be addressed. The following were those prioritized as most important.

Prevention of DMD Cardiomyopathy

The Working Group acknowledged the importance of studying DMD cardiomyopathy because it represents an important cause of DMD disability and is an example of a genetically mediated cardiomyopathy that typically develops over a short and predictable window compared with other forms of cardiomyopathy. Importantly, the presence of disease can be identified long before symptoms appear. In the perindopril prevention study, 20% of the DMD subjects at 10 years of age were excluded for abnormal LV ejection fraction.[16] Using CMR, 59% of DMD patients had evident myocardial damage, seen as late gadolinium enhancement, by 16 years of age.[43] The relatively early onset of cardiomyopathy, usually by the second decade of life, clearly invites assessment of strategies to prevent cardiomyopathy. As mentioned, ACE inhibitors, ARBs, and β-blockers are commonly used in practice and are relatively well tolerated. Whether these agents should be started earlier such as at the time of diagnosis of DMD or before the onset of decreased cardiac function or used together is not known and should be investigated. During studies of other interventions, it might be possible

to address the question of β-blocker outcome benefit with other study designs such as a factorial design, comparing β-blocker monotherapy, ACE inhibitor monotherapy, and a β-blocker/ACE-inhibitor combination. A recent study on mineralocorticoid receptor antagonism indicates that early use of these agents is helpful for DMD cardiomyopathy,[35] but the combinatorial use of these medications and timing of institution are questions that remain unanswered. The use of additional therapies such as phosphodiesterase inhibitors requires additional evaluation. Phosphodiesterase inhibition is being tested for its effect on skeletal muscle function and, on the basis of animal studies, may also be considered for its cardiovascular benefit.[44,45] Early-phase studies in DMD and Becker muscular dystrophy using phosphodiesterase inhibition suggest skeletal muscle benefit.[46,47] However, the effect of these agents on the heart may be different because sildenafil showed no effect on exercise-induced cardiac output,[48] and a separate study of sildenafil for heart function in adult Becker muscular dystrophy and DMD was not completed because there was no clear benefit.[49]

Arrhythmia Complications in DMD

Arrhythmias were identified as an important potential contributor to mortality in DMD, but surprisingly little is known of this possibility. It was recommended that surveillance studies be undertaken to estimate the frequency of such events and to monitor current practices. Longitudinal studies will also be critical for identifying risk factors for arrhythmias and sudden cardiac death. In the general adult heart failure population, ICDs have favorable outcomes compared with medical therapy alone. It is unknown whether the Duchenne population would have a similar benefit, especially given that the placement of an ICD in patients with DMD may confer higher risk because of accompanying skeletal muscle and respiratory compromise. The incidence and management of atrial arrhythmias, including the need for anticoagulation, were also viewed as areas that required more information. Currently, there are no guidelines for the surveillance and management of arrhythmias in DMD cardiomyopathy except for other published general adult heart failure recommendations for managing arrhythmias in the setting of abnormal systolic function. The majority of advanced DMD cardiomyopathy occurs in the late second decade and third decade. Thus, guidelines that are based on a significantly older population may or may not be appropriate.

Cardiopulmonary Interactions

The concurrent decline in respiratory function and cardiac function in DMD may arise from independent or interdependent pathologies.[50–52] The use of noninvasive nocturnal ventilation has increased survival in DMD.[3] As prevention strategies have gained hold in clinical practice for the medical prevention of cardiomyopathy in DMD, the Working Group suggested that earlier institution of nocturnal noninvasive ventilation may have cardiac benefit in DMD and thus should be a target for clinical investigation.

Genotype–Phenotype Correlations in DMD Cardiomyopathy

Early studies correlating genotype with phenotype included only patients with deletions or duplications of DNA, which represents only two thirds of DMD patients. The remaining patients have smaller point mutations that can be detected only by DNA sequencing. It is

unknown whether these mutations result in the same cardiac phenotype. DMD is now most commonly diagnosed by DNA mutation analysis rather than invasive muscle biopsies. Moreover, with mutation-specific therapies on the horizon, it is unknown whether cardiac therapy should be identical for all DMD mutation classes. With the availability of larger databases of genotypically defined DMD populations, this information should be better correlated with sensitive cardiac imaging modalities like CMR to improve genotype–phenotype correlations for the heart.

Female Carrier Cardiomyopathy Risk

The degree to which female carriers of DMD mutations have cardiac complications has been debated.[53] Improved molecular diagnosis, coupled with clear recommendations for cardiac screening in the carrier population, provides an opportunity to better correlate genetic data with clinical outcomes in women.

Clinical Research Infrastructure

As mentioned, a significant number of previous studies of DMD cardiomyopathy have been limited to relatively small DMD cohorts, often restricted to a single center. Given the broad age range, varying disease state, and limited sample size at any one institution or program, the Working Group strongly supported collaborative multi-institutional research. More recent collaborative efforts are beginning to make progress in addressing these limitations. The EuroBioBank Network has promoted international efforts that include DMD.[54] US efforts include the United Dystrophinopathy Project.[55] The Working Group encouraged alignment of these programs to establish larger clinical databases and biomaterial collections to promote DMD-related efforts, including focus on cardiomyopathy in DMD. The Working Group identified this as a critically important infrastructure needed to advance clinical research focused on DMD cardiomyopathy, including coordinated and accessible clinical registries linked to biospecimen repositories.

A Registry to Assist With Standardized Data Collection, Evaluation, and Patient Follow-Up

A better understanding of the natural history of all aspects of DMD, including the cardiac manifestations, would greatly help in the design of trials (eg, choice of end points, age strata). Coordinated efforts to design and implement patient registries are mature in some countries, particularly those with nationalized or centralized health delivery systems. Registries in the United States are supported mostly by patient advocacy groups or individual academic institutions, and many have no mechanism for linking data among registries and to other data sets, including electronic medical records. Having such data sets, especially for a rare disease like DMD, would facilitate clinical trials. It is noteworthy that counterpart DMD registries in Europe take advantage of government-provided health care and often encompass all DMD patients. In the United States, the DuchenneConnect registry was created in 2007 to allow patients and families to provide data directly.[56,57] Patient-entered databases, although valuable, may be limited in depth and completeness of data to adequately support clinical research. The ability of the United States to collaborate on the scale that is being pursued in Europe would certainly increase the value of the data collected. The first set of common data elements for neuromuscular diseases was developed

in 2011 by the National Institutes of Health. The data elements for the Neuromuscular Diseases were formed by unique Working Groups, including a cardiac group (http://www.commonda-taelements.ninds.nih.gov/NMD.aspx#tab=Data_Standards; the forms under Assessments and Examinations include cardiac data elements). The use of these tools or similar data collection tools would facilitate research.

A Biorepository to Centrally Store DNA, Blood Samples, and Tissue Specimens

The Working Group noted the importance of studying human tissue to improve the pathophysiological understanding of human disease. The need for such study is highlighted by the differences in cardiac effects of glucocorticoids between the *mdx* mouse and humans. In the DMD population, access to human cardiac tissue is rare. Tissue acquired during a cardiac catheterization endomyocardial biopsy, tissue cores (obtained at the time of ventricular assist device placement), explanted hearts, or autopsy materials should be stored and made available to the scientific community. There is an additional need for less invasive, large-scale and multi-institutional acquisition of materials such as human DNA and fibroblasts to be made available. Cell lines from DMD patients are useful for establishing induced pluripotent stem cell lines and other cell-based models of disease valuable for preclinical testing. Biomarker studies in both blood and urine are rapidly expanding in DMD.[58–60] Biomarkers hold promise for expediting drug development as pharmacodynamic biomarkers (objective monitoring of drug response) and perhaps as surrogate outcome measures (predicting later clinical benefit). It will be important to define the subset of blood or urine biomarkers that are heart derived and thus potentially useful in cardiac interventional studies.

Animal Models for DMD

The *mdx* mouse model has served as an important, if imperfect, model for DMD. A de novo premature stop codon in exon 23 of the dystrophin gene leads to the histopathological features seen in DMD muscle.[61,62] The *mdx* mouse has a significant 20% reduction in life span and displays progressive fibrosis and fatty infiltration in most skeletal muscles.[63,64] The respiratory muscles, especially the diaphragm muscle, are significantly affected by DMD pathology and very closely mimic what occurs in the human muscle. At the equivalent age for human cardiomyopathy, the *mdx* mouse displays only mild features of cardiomyopathy. Markedly decreased baseline cardiac function, measured by conventional echocardiography, is evident only in the aged *mdx* mouse.[64–66] The reason for this relatively preserved function in younger *mdx* mice under baseline conditions is not known. The shorter life span of mice, an improved regenerative capacity, smaller muscles and heart, and limited physical exertion of caged mice have all been suggested as reasons for the milder baseline cardiac phenotype in *mdx* mice. Importantly, cardiomyopathy and acute heart pump failure can be readily unmasked in *mdx* mice by pharmacological or mechanical cardiac stress testing.[67,68] Other genetic murine models with notable cardiomyopathy at baseline also are useful for preclinical studies focused on the rescue of the cardiac phenotype. These models include (but are not limited to) the *mdx/utrn* (utrophin) double-null model and the *mdx/utrn* heterozygous mouse model.[69] The *mdx/utrn* double-null mouse has profound kyphoscoliosis, respiratory compromise, and cardiomyopathy.[70] The short life span of *mdx/*

utrn double-null mice is useful when survival is an end point. The *mdx/utrn* heterozygous model is easier to breed and therefore more available for study. The cardiomyopathy in this model can be more readily detected by imaging approaches and therefore may be more useful experimentally. However, the *mdx/utrn* model is not a genetic match to the DMD human heart.

Mice lacking dystrophin-associated proteins, including β-, γ-, and δ-sarcoglycan, have also been used for preclinical studies of muscular dystrophy.[71] These models display a more advanced cardiac phenotype at baseline conditions than age-matched *mdx* mice and are useful for testing drugs and genetic pathways that alter the cardiac outcome. These models share a pathological pathway in that they also have a disrupted dystrophin complex in striated muscle. However, like the *mdx/utrn* models, they are not genetically identical to DMD. As noted, studies using glucocorticoid steroids in these murine models showed adverse cardiac consequences of steroids. It is not known what accounts for the discrepancy between human and murine hearts in this regard, but secondary effects of glucocorticoids on systemic blood pressure and other pathways could account for these differences.

Large animal models of DMD have been used to study gene-, cell-, and chemical-based experimental therapies on cardiac and respiratory outcomes.[72–74] The Golden Retriever Muscular Dystrophy model has been studied extensively for gene therapy, including cardiac gene therapy for DMD. The canine model may more faithfully replicate key aspects of the cardiac phenotype in DMD. However, its scarce supply, the need for canine-specific reagents, and the high cost of conducting trials argue for judicious and collaborative use of the Golden Retriever Muscular Dystrophy model. Additionally, the canine heart has a more developed collateral coronary circulation that differs from what is seen in the human heart, and this difference in anatomy may alter the manifestation of cardiomyopathy.[75] Recent de novo and engineered mutations in dystrophin in the porcine model could emerge as a new large animal model of dystrophic cardiomyopathy.[76,77] The pig model, for example, could be highly valuable to help advance screening for cardiac arrhythmias in DMD.

For all animal models, it was recommended that the assessment of cardiac phenotype be updated and, in some cases, established. Monitoring cardiac outcomes in mice, dogs, and pigs, as in humans, can be achieved with improved imaging. Such cardiac imaging may rely on CMR or echocardiography with strain measurements. It was noted that protocols for analysis are available on the TREAT-NMD repository, but it was also noted that newer imaging modalities had not yet been incorporated into the repository. Effort is needed to update cardiac assessment protocols for preclinical animal models with focus on imaging, telemetry monitoring, and histopathological assessment, as well as expert opinion as to what models maximize the opportunity to answer specific research questions.

Although there are large animal models of DMD, few natural history data are available for these models. However, this deficit must be balanced against the limited availability of these large animal resources. Several additional canine models of DMD have been described, and in many cases, these models have distinct mutations in the DMD gene compared with the Golden Retriever Muscular Dystrophy model. Hence, they offer excellent opportunities to test gene-specific therapies. It is not known whether these unique mutations will confer

distinct phenotypes. The degree of genetic identity among canine breeds vastly exceeds the genetic identity among mouse strains.

Animal models of DMD remain necessary for preclinical testing and can be useful for developing biomarkers for DMD. With the ongoing clinical trials in DMD, there has been a need for biomarkers that reflect DMD progression and mirror clinical improvements when present. The ability to readily assess multiple tissues and to have ready access to serum, blood, urine, and cells from preclinical models supports the continued development of these models as adjuncts for biomarker development.

Conclusion

Improved understanding of the pathogenesis and management of cardiac disease in DMD through the use of appropriate animal models and clinical research supported by a collaborative research infrastructure will, we hope, bring increased survival and better quality of life to patients.

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Table

Recommendations of the Working Group

- Refine and update guidelines for cardiac care after reviewing currently available data and expert consensus opinion
  - Include appropriate expertise from the pediatric and adult cardiology, neuromuscular, rehabilitation, and pulmonary communities
  - Address:
    - Medical management, including the use of steroids and angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists
    - Cardiac surveillance, particularly imaging with CMR
    - Early intervention and management of the advanced DMD patient
- Include sufficient cardiac monitoring with CMR in all phase II or III trials of muscle therapies; when appropriate, incorporate cardiac end points into trial design
- Refine and update standard operating procedures for the use of various DMD animal models
  - Use state-of-the-art imaging protocols to assess cardiac function
  - Create a repository of detailed, consensus-based working protocols
- Address the following research questions related to cardiac care in DMD:
  - What early evaluation and therapeutic strategies can slow, reverse, or prevent cardiac disease progression?
  - What is the best method to risk stratify patients for arrhythmia complications and sudden cardiac death?
  - Does early pulmonary intervention prevent cardiac disease progression?
  - With the use of state-of-the-art genotyping/sequencing techniques combined with better cardiac phenotyping, can genotype be associated with cardiac phenotype?
  - How should female carriers be monitored for cardiac disease?
- Develop needed research infrastructure
  - Develop a registry to assist with standardized data collection and follow-up
  - Develop a biorepository to centrally store DNA, cell, and tissue specimens

CMR indicates cardiac magnetic resonance imaging; and DMD, Duchenne muscular dystrophy.