Clinical Management of DMD-Associated Cardiomyopathy: Insights from the Wellstone Study

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This is to acknowledge that Pradeep Mammen, MD has disclosed that he does have financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Mammen will not be discussing off-label use of FDA-approved drugs.

Mammen Biosketch:

Clinical Expertise: Dr. Mammen is a clinician-scientist with clinical expertise in advanced heart failure, ventricular assist devices (VAD) and heart transplantation. He is an Associate Professor of Medicine at UT Southwestern Medical Center and holds the Alfred W. Harris, M.D. Professorship in Cardiology. Dr. Mammen serves as the Co-Director of the UT Southwestern Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center and the Director for Translational Research for the Advanced Heart Failure and Transplant Cardiology Program at UT Southwestern. Due to additional training he received in molecular cardiology, Dr. Mammen has also developed a unique interest as well as expertise in the care of patients who develop a familial or genetic form of cardiomyopathy (esp. neuromuscular-associated cardiomyopathies). In July of 2010, Dr. Mammen became the founding Medical Director of the UT Southwestern Neuromuscular Cardiomyopathy Clinic. Referrals to this clinic have exploded (700 patients to date), demonstrating the great clinical need for such a clinic in the community. Finally, he is utilizing this clinic as a platform for translational studies focused on novel therapies directed towards muscular dystrophy patients. These studies are aimed at improving both the overall care as well as the cardiovascular care provided to this unique patient population.

Scientific Expertise: In keeping with Dr. Mammen's clinical expertise, he has developed significant scientific interest in investigating the molecular mechanisms and signaling pathways that contribute to heart failure and skeletal muscle myopathies. He runs a molecular cardiology laboratory that has been continuously funded by various federal (NIH), private (AHA) and industry (Catabasis Inc., GlaxoSmithKline Research Foundation, and PhaseBio Inc.) granting agencies. In particular, his research team is investigating the role of redox signaling to enhance our understanding of myogenesis, muscle regeneration, and cardiac/muscle remodeling.

Purpose & Overview

Duchenne muscular dystrophy (DMD) is an X-linked recessive dystrophinopathy that affects males at a rate of 1 in 3,500 to 5,000. The lack of dystrophin results in progressive muscle degeneration leading to necrosis and atrophy within cardiac and skeletal muscle of DMD patients. Multiple studies highlight early cardiac involvement, with a majority of patients developing a cardiomyopathy by 18 years of age. Due to an enhanced understanding of the overall underlying pathogenesis of DMD and advances in neurological and pulmonary care, the primary mode of death in 2020 in the vast majority of DMD patients is cardiovascular in nature. Despite the high incidence of cardiomyopathy in DMD patients, there is limited knowledge regarding the exact mode of cardiac remodeling in DMD and the optimal management of this type of cardiomyopathy. Therefore, the objective of this Medicine Grand Rounds is to enhance ones understanding of the pathogenesis of DMD-associated cardiomyopathy and how current management of DMD-associated cardiomyopathy may be affected by emerging innovative therapies targeting DMD.

Educational Objectives

1. Recognize the high prevalence and mortality of DMD-associated cardiomyopathy.
2. Recognize objective clinical data supporting the current management of DMD-associated cardiomyopathy.
3. Recognize the unique characteristics of DMD-associated cardiomyopathy and the potential novel mode of cardiac remodeling in DMD.
4. Recognize the potential impact of genome editing on the clinical management of DMD-associated cardiomyopathy.

Introduction

The neuromuscular disorders represent an array of inherited myogenic disorders involving mutations and dysregulations of a variety of cytoskeleton, mitochondrial or nuclear proteins. Skeletal muscle is particularly susceptible to injury due to genetic mutations in one of these proteins[1, 2]. These mutations result in progressive muscle degeneration/regeneration which ultimately leads to loss of muscle fibers and subsequent replacement with fatty tissue and fibrosis. Similarly, many of these inherited myogenic disorders also effect the respiratory as well cardiac muscles resulting in restrictive lung disease as well as cardiomyopathy. Unfortunately to date, there is no definitive therapy to reverse or cure neuromuscular disorders. Thus, the associated morbidity and mortality in patients with neuromuscular disorders is very high.

Due to an enhanced understanding of the underlying pathogenesis of many of the neuromuscular disorders and advances in neurological and pulmonary care over the past 2 decades, the primary mode of death today in many of these patients is cardiovascular in nature. However, despite the high incidence of cardiomyopathy in many neuromuscular patients there is limited data regarding optimal management of the underlying cardiomyopathy.

Although neuromuscular disorders represent a heterogeneous group of genetic diseases, advances in molecular genetics have enabled the medical community to make definitive diagnoses, which has enhanced our understanding of the underlying pathophysiology of these disorders. The particular genetic mutation drives the clinical phenotype of patients with neuromuscular disorders. Listed below are examples of various neuromuscular disorders grouped by the location of the genetic defect:

1. Mutations within the dystrophin–glycoprotein complex: Duchenne/Becker muscular dystrophy (DMD & BMD), limb-girdle muscular dystrophy, and X-linked dilated cardiomyopathy.
2. Mutations within the nuclear lamina: Emery Dreifuss muscular dystrophy.
3. Unstable repeat expansion within introns: myotonic dystrophy and Friedreich ataxia.
4. Mutations within mitochondrial proteins: mitochondrial myopathies.
5. Glycogen storage disorders: Pompe disease.
6. Mutations within the extracellular matrix: Bethlem myopathy, collagen VI-associated myopathies, congenital muscular dystrophy, and Ullrich congenital muscular dystrophy.
7. Miscellaneous mutations: Facioscapulohumeral muscular dystrophy.

The frequency of cardiac involvement in patients with neuromuscular disorders is variable but it is not insignificant. The development of cardiomyopathy and/or conduction disease (AV block or atrial/ventricular arrhythmias) are the most common cardiovascular abnormalities that occur in patients with neuromuscular disorders[3-5]. The true incidence and prevalence of cardiovascular complications amongst this patient population is often difficult to accurately determine and the assessment is hampered by a number of factors including the following:

1. Low prevalence of inherited myogenic disorders amongst the general population.
2. Lack of obvious clinical signs and symptoms of cardiovascular disease due to the limited mobility amongst patients with neuromuscular disorders.
3. Lack of awareness amongst a board range of physicians (including internists and adult cardiologists) of the extent of associated cardiovascular disease in neuromuscular patients.

Of the known 519 genetic causative mutations resulting in neuromuscular disorders, the dystrophinopathies have the highest mortality rate due to complications related to the development of cardiomyopathy[6]. Although there is a growing body of clinical data supporting the management of cardiovascular disorders stemming from a variety of neuromuscular disorders, the strongest objective data providing clinical guidance is in regards to the clinical management of DMD-induced cardiomyopathy[7]. Therefore, the remainder of this manuscript will focus on the epidemiology of DMD, the clinical evidence supporting the current guidelines of managing DMD-associated cardiomyopathy, and data supporting the unique features of DMD-associated cardiomyopathy. Finally, there will be a discussion of emerging therapeutics in the overall management of DMD with particular attention given to the potential impact of genome editing and CRISPR-Cas9 technology on the clinical management of DMD-associated cardiomyopathy.

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is one of the most common and deadly forms of muscular dystrophies (Figure1)[8]. DMD is an X-linked recessive dystrophinopathy resulting from a mutation in the dystrophin gene and it affects approximately 1 in 3,500 to 5,000 live male births[9, 10]. The complete absence of dystrophin expression within the myocyte results in progressive muscle degeneration leading to necrosis and atrophy within cardiac and skeletal muscle of DMD patients. Multiple studies highlight early cardiac involvement, with a vast majority of DMD patients manifesting a cardiomyopathy by 18 years of age (Figure 2)[11, 12].

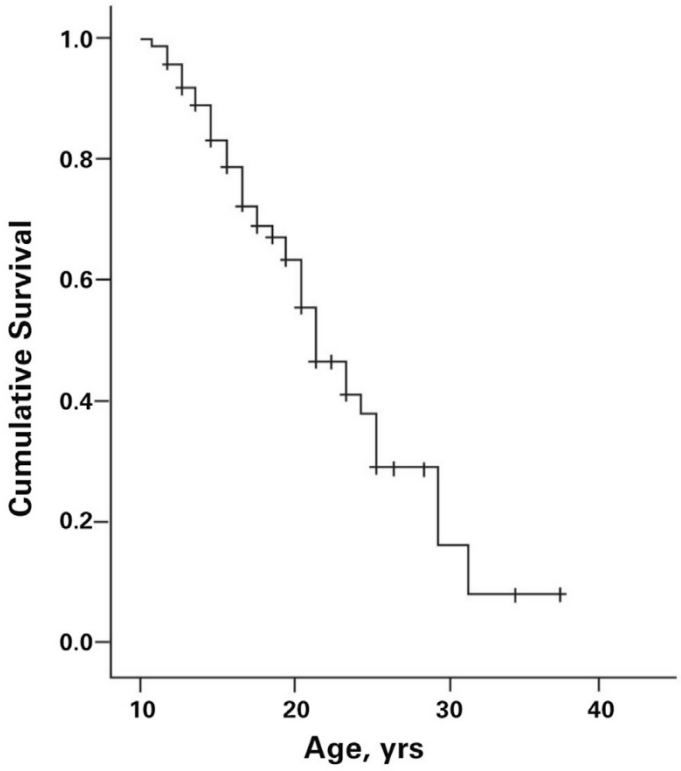


Figure 1: Cumulative survival rate among DMD patients as a function of age.

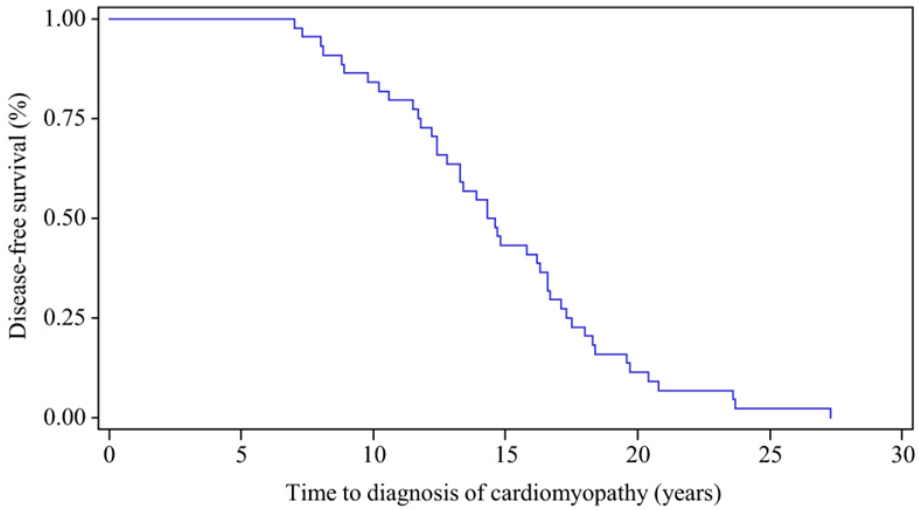


Figure 2: Age of onset of cardiomyopathy in DMD patients.

There are over 3,000 known mutations within the dystrophin gene that can cause DMD and these mutations are divided primarily into deletions (70%), duplications (5%), and point mutations (25%). Although the mutations are distributed throughout the DMD gene, there are certain hot spots (red) that make up 50-60% of the known causative DMD mutations (Figure 3).

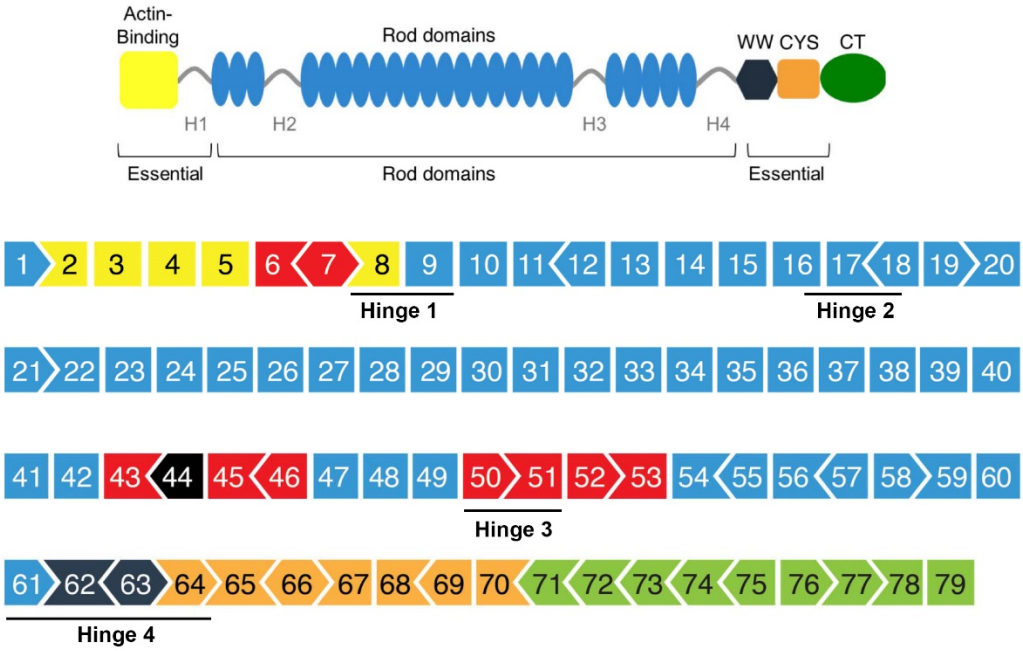


Figure 3: Exon structure of the DMD gene with 50-60% of mutations located with the "hot spots" identified in red.

Regardless of the specific site of the mutation, the subsequent loss of dystrophin expression within skeletal muscle leads to a cycle of muscle degeneration and regeneration[2, 13]. Over time there is a decreased capacity to regenerate muscle in response to degeneration due to a decrease in the number of myogenic progenitor cells and the life-span of skeletal myoblasts[14-17]. The continual cycle of muscle degeneration and regeneration results in the development of progressive muscle wasting and atrophy[2, 13, 18-21]. The clinical manifestation of the disease results in loss of ambulation by the early teenage years and development of restrictive lung disease due to diaphragmatic weakness and scoliosis. In addition, DMD patients develop progressive cardiomyopathy, as loss of dystrophin within cardiomyocytes results in cell death

leading to cardiac fibrosis and a decrease in cardiac function. Finally, there is limited data that suggests the genotype of the DMD patient may predict the severity of the cardiomyopathy[22].

The molecular basis of DMD and the natural history of a DMD patient have been well investigated over the past two decades. Advances in pulmonary care, orthopedic and rehabilitative interventions, and the beneficial effects of certain medications (i.e. corticosteroids, angiotensin-converting enzyme inhibitors, and mineralocorticoid receptor antagonists) have collectively improved the morbidity and mortality of DMD patients with life expectancy reaching into the third and even fourth decades of life[23-28]. In particular, the wide spread use of the home ventilator [non-invasive positive pressure ventilators (NIPPV)] has dramatically decreased respiratory failure as a cause of death in many DMD patients (Figure 4). Therefore, in the current era the mortality of DMD patients is predominately related to cardiovascular complications related to advanced cardiomyopathy[24, 29-31].

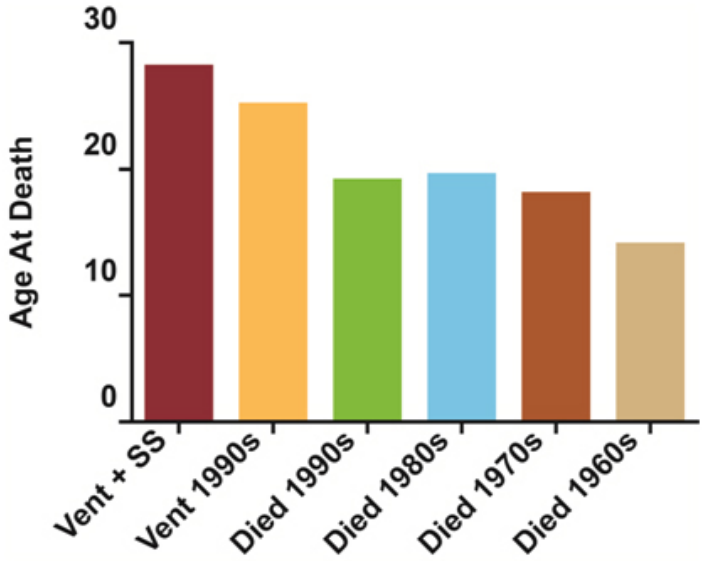


Figure 4: Non-cardiac interventions prolong survival in DMD. Innovative ventilatory strategies and spinal stabilization surgeries have markedly improved the survival rate amongst DMD patients since the 1960s.

In 2020, the primary mode of death in the vast majority of DMD patients is secondary to complications from advanced cardiomyopathy[31]. Although there is increasing evidence-based medicine outlining the clinical approach to the management of DMD-associated cardiomyopathy, the number of well-designed randomized clinical trials demonstrating the proven beneficial effects of guideline directed heart failure medications is limited. Thus, the approach to managing DMD-associated cardiomyopathy adopted by many of the heart failure cardiologists across the country is based on guideline directed management of non-ischemic cardiomyopathy patients.

DMD-Associated Cardiomyopathy

The reduction of respiratory related deaths due to nocturnal ventilation and spinal stenosis has resulted in DMD patients living longer but ultimately succumbing to complications related to DMD-associated cardiomyopathy[24, 31-33]. Cardiac involvement is nearly ubiquitous in older DMD patients as more than 90% of young men over the age of 18 demonstrate evidence of cardiac dysfunction[11]. A cardiomyopathy typically has an onset in the mid-teen years and there is progressive maladaptive cardiac remodeling that eventually contributes to the demise of the DMD patient[11, 34]. Distinct dystrophin mutations have been correlated to an increased incidence of cardiomyopathy and possible response to treatment[22]. Recognition of the presence of a cardiomyopathy in a DMD patient can be challenging due to physical inactivity and other respiratory complaints that can obscure the diagnosis[35]. Currently, clinical guidelines

recommend an initial cardiac screening at the time of diagnosis of DMD and then every 2 years until age 10 and then yearly[7, 26, 36].

DMD-Associated Cardiomyopathy: Cardiac Imaging

Cardiac imaging can be challenging in patients with end-stage DMD due to scoliosis, ventilation, and contractures. Current imaging modalities that are commonly used include echocardiography cardiac CT scanning, and cardiac magnetic resonance imaging (cMRI). Echocardiography in DMD-associated cardiomyopathy has demonstrated regional wall motion abnormalities in the posterior basal wall, left ventricular dilation, and overall reduced systolic function[37]. Current guidelines recommend obtaining an echocardiogram at the time of diagnosis or by age 6 with repeat echocardiograms every 1-2 years until the age of 10. After the age of 10, it is currently recommended that patients undergo a cardiac MRI every 1-2 years to better assess the presence of a cardiomyopathy[26]. While echocardiography is easily accessible, relatively quick, and a cost-effective imaging modality, it is often technically challenging in DMD patients due to chest wall deformities, scoliosis, and respiratory dysfunction, thus limiting the diagnostic yield [38]. Therefore, cMRI is rapidly becoming the gold standard imaging modality to assess the cardiac structure and function in DMD patients. cMRI has been demonstrated to be more sensitive in assessing overall left ventricular size and function[39-42]. Silva et al. performed gadolinium contrast enhanced cMRI on 10 patients with dystrophinopathies (8 DMD and 2 BMD patients) and were the first to demonstrate late gadolinium enhancement (LGE) by cMRI in the dystrophic heart. They further reported that LGE was present even with normal left ventricular function by echocardiography[40]. Pulchalski et al. subsequently performed a study of 74 patients with DMD where the majority of patients had LGE in the posterobasal region of the left ventricle in a subepicardial distribution pattern[43]. This pattern of LGE in the basal inferior and inferolateral walls is consistent with the pathological findings of fibrosis in the inferior basal wall[44, 45]. A large single center retrospective study by Hor et al. evaluated LGE in 314 DMD patients, and demonstrated that LGE increased with age and with decreasing LVEF[46]. Finally, in a recent study Silva et al demonstrated the presence of LGE on a cMRI had prognostic implications to patient survival. DMD patients with LGE demonstrated on the cMRI imaging had a greater risk of death over the next 2-3 years (Figure 5)[47]. Thus cMRI, provides an earlier and more sensitive detection of cardiovascular involvement in DMD patients and allows for accurate and reproducible quantification of left ventricular function and size, which will promote initiation of cardioprotective therapies at an earlier age. Although cMRI has many imaging benefits for patients with DMD, it can also be challenging, especially in the pediatric population due to the need for sedation, cost, and lack of accessibility.

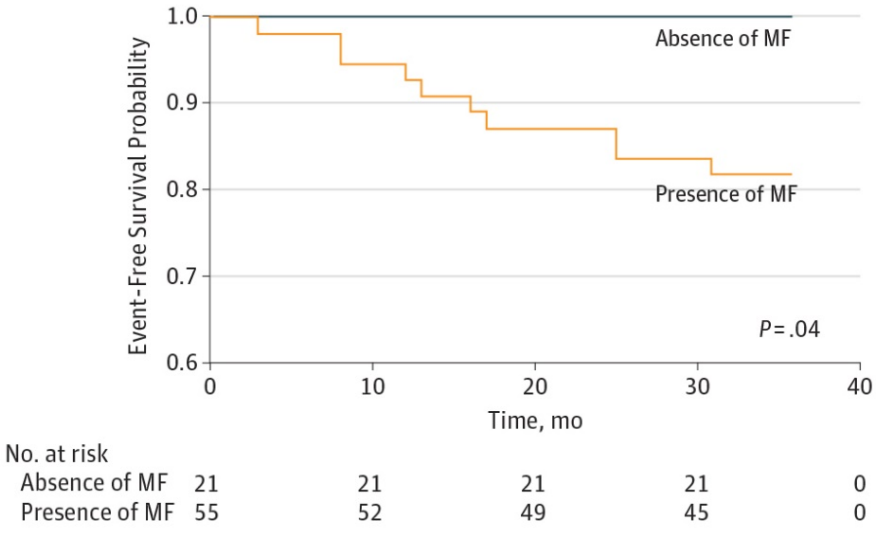


Figure 5: Myocardial fibrosis as assessed by the presence of late gadolinium enhancement on cMRI is predictive of survival in DMD patients.

DMD-Associated Cardiomyopathy: Medical Therapy

In 2020, there are a multitude of large randomized double-blind clinical studies supporting beneficial effects of various heart failure medications, devices [AICD and biventricular pacemaker(BiV)/AICD], and advanced heart failure therapies [left ventricular assist devices (LVAD) and heart transplantation] that have been demonstrated to improve the mortality and morbidity of patients with ischemic and non-ischemic cardiomyopathy[48]. Initiation of optimal medical therapy can induce significant reverse cardiac remodeling and markedly improved survival and morbidity in patients with both ischemic and non-ischemic cardiomyopathy. In non-ischemic cardiomyopathy, there exists the 33% rule. With optimal medical therapy 33% of patients achieve complete reverse cardiac remodeling, 33% of patients achieve only partial reverse cardiac remodeling, and finally the remaining 33% of patients develop only minimal reverse cardiac remodeling and often will progress to end-stage cardiomyopathy requiring either implantation of a LVAD, a heart transplant, or death[49, 50].

Over the past 15 years small, but well-designed randomized studies have been undertaken in the DMD population regarding the potential benefits of beta-blockers, angiotensin-converting enzyme inhibitors (ACE inhibitors), and mineralocorticoid receptor antagonists (MRA). In 2005, Duboc et al. evaluated the impact of perindopril, an ACE inhibitor, in patients with DMD with preserved left ventricular function[23]. The investigators randomized 57 children with DMD (mean age of 10.7 years) to perindopril (2-4mg/day) or placebo. At three years of follow up there was no significant difference in LV function between the children treated with perindopril or placebo. However, at the three year mark all patients were switched to perindopril treatment and followed for an additional two years. After crossing over to perindopril at two years, there was no difference in mean LV function between those patients treated with initially perindopril versus those initially treated with placebo. However, in the initial placebo group there were 8 of 29 patients with LVEF < 45% and only 1 of 27 patients in the perindopril group (p = 0.02), which was suggestive that early treatment with perindopril was effective in preventing progression to left ventricular dysfunction in DMD (Figure 6). Subsequently these patients were followed for 10 years, and in the initial placebo group only 65% of patients were alive versus 92.9% in the initial perindopril group (p = 0.013) , which emphasized that early initiation of an ACE inhibitor reduced mortality in patients with DMD [51].

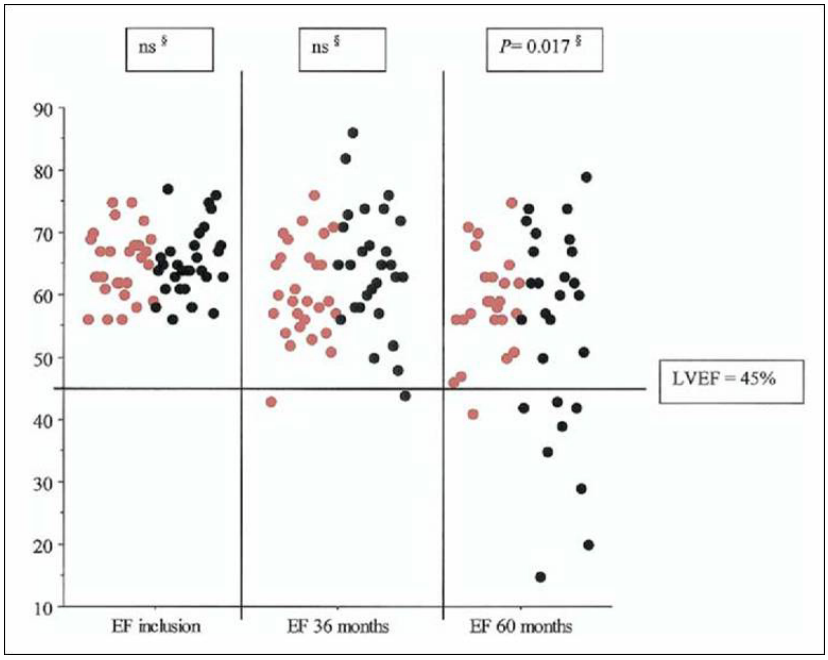


Figure 6: Perindopril prevents or delays the onset of DMD-associated cardiomyopathy. The red dots represents DMD patients initially treated with an ACE inhibitor, while the black dots represents the DMD patients randomized to placebo.

Based on the studies by Duboc et al. the current cardiac specific guidelines for DMD patients recommends initiation of an ACE inhibitor before the development of left ventricular dysfunction in DMD patients, as they are at high risk for developing left ventricular dysfunction (ACC/AHA Heart Failure Stage A)[7, 26, 36]. Additionally, for those patients who are intolerant to ACE inhibitors, angiotensin receptor blockers (ARBs) can also be used as ARBs have been demonstrated to be as effective as ACE inhibitors in DMD[52].

While the benefit of ACE inhibitors in DMD-associated cardiomyopathy has been definitive, the timing as to when to start a beta-blocker in DMD patients has been less clear, especially in the pediatric DMD patients with normal cardiac function[12, 53-56]. The use of carvedilol has been assessed in pediatric DMD patients with elevated atrial natriuretic peptide (ANP) or brain natriuretic peptide (BNP) and a low ejection fraction (EF < 40%) by echocardiography with no significant difference in carvedilol treated patients with reference to symptoms or left ventricular dysfunction[57]. However, in a study by Rhodes et al., carvedilol was shown to be efficacious in patients with DMD-associated cardiomyopathy[54]. When superimposed on background therapy of ACE inhibitors, the use of carvedilol in this patient population remains unclear. An analysis of 13 patients with DMD who were treated with an ACE inhibitor vs. ACE inhibitor and carvedilol revealed a beneficial effect of beta blocker therapy in increasing left ventricular shortening and decreasing left ventricular end diastolic dimensions using echocardiography[53]. In contrast, a study by Viollet et al. tested an ACE inhibitor alone vs. ACE inhibitor and metoprolol; however, in this study low dose beta blocker was added only for heart rates above 100 bpm or if arrhythmias occurred[12]. The results of this study showed an improvement from pretreatment LVEF in both groups, but no difference between the treatment groups. Further studies with larger groups of patients and more robust trial designs are required to definitively address the use of beta-blockers in pediatric DMD patients with normal cardiac function; however, based on current ACC/AHA/HFSA guidelines it is still recommended that beta-blockers (carvedilol or Toprol XL) be initiated in all DMD patients with left ventricular dysfunction, irrespective of age[48, 58].

The initiation of a mineralocorticoid receptor antagonist (MRA) along with an ACE inhibitor is now considered standard heart failure therapy in all DMD patients irrespective of left ventricular (LV) systolic function. The beneficial effects of a MRA has been demonstrated in both a DMD murine model as well as in teenage DMD boys, irrespective of cardiac function[59, 60]. In a recently completed randomized double-blinded clinical trial, DMD patients were treated with either eplerenone (a MRA) or placebo with a background therapy of ACE inhibitors or ARBs to assess the efficacy of eplerenone in preventing a cardiomyopathy in DMD. Twenty patients were randomized to eplerenone and 20 to placebo and were followed for 6 and 12 months with cardiac MRI. The primary endpoint was change in LV circumferential strain, which is a marker of myocardial stress, at 12 months[60]. At 12 months, the decline in LV circumferential strain was statistically lower in the group treated with eplerenone as compared to the placebo group ($p<0.02$) (Figure 7A). Likewise, there was a statistically slower decline in the LV ejection fraction in DMD patients receiving eplerenone as compared to placebo ($p<0.03$) (Figure 7B). This small study demonstrated the added benefit of a MRA combined with an ACE inhibitor in attenuating progression of LV dysfunction in DMD patients. Although this study is considered positive, further studies to assess the impact of MRA in DMD survival are warranted.

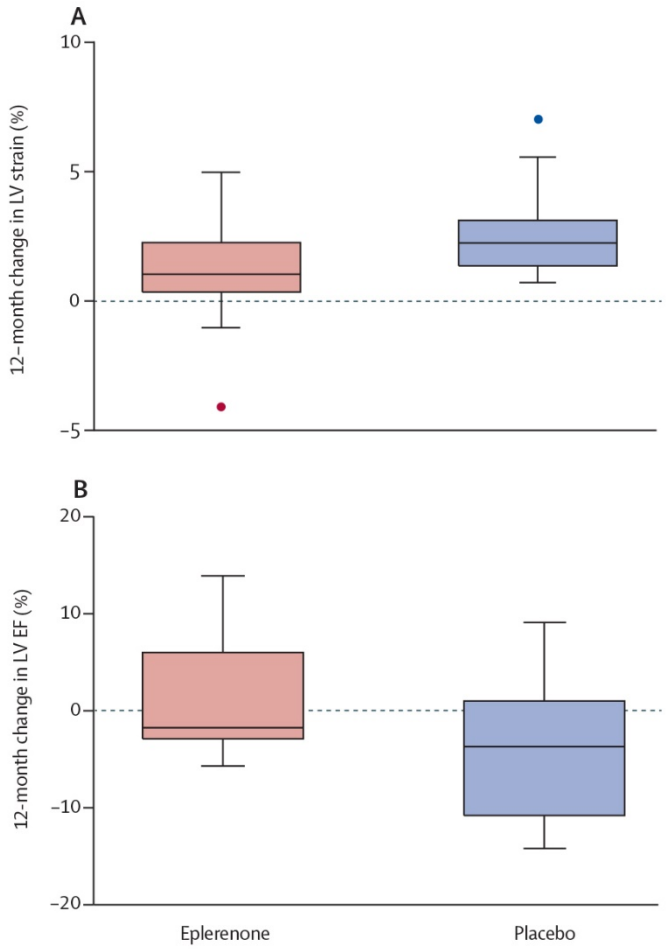
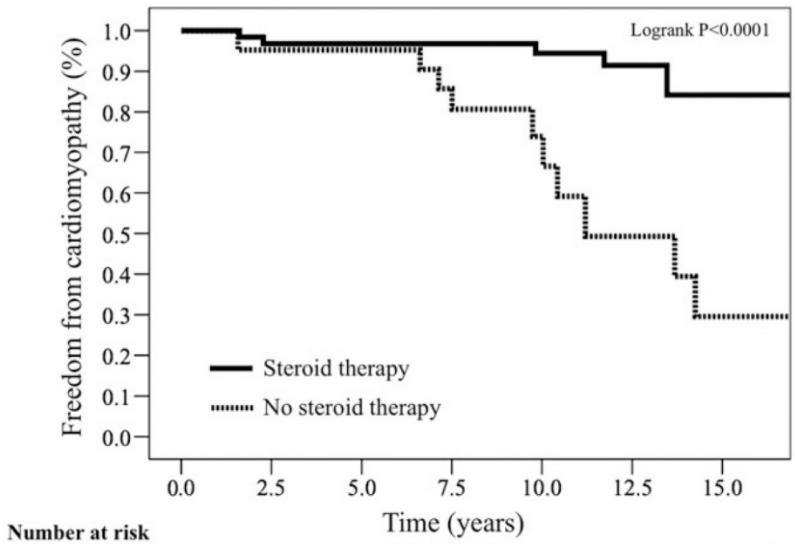


Figure 7: Effect of eplerenone on ventricular systolic function in teenage DMD patients as measured by **(A)** strain or **(B)** ejection fraction over a 12 month period.

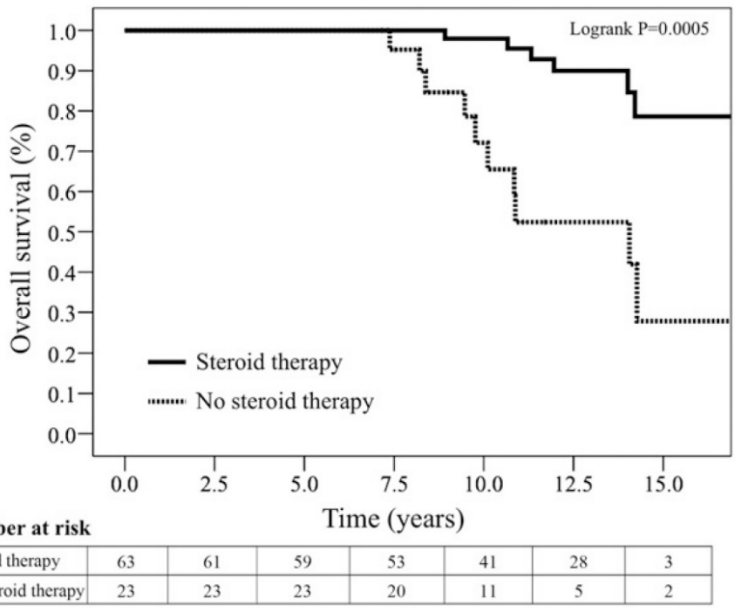
Finally, previous studies have demonstrated the benefits of corticosteroid therapy in prolonging ambulation and improving lung capacity[61, 62]. Although there is retrospective data supporting the notion that steroid treatment delays the development of LV systolic dysfunction and prolongs survival in DMD patients, to date there is no prospective, randomized data supporting the continued use of steroids in adult DMD patients (Figures 8 and 9)[25, 34].



Number at risk

Steroid therapy	63	59	57	51	39	26	3
No steroid therapy	21	20	20	17	10	5	2

Figure 8: Retrospective study demonstrating the role of steroids in preventing DMD-associated cardiomyopathy.



Number at risk

Steroid therapy	63	61	59	53	41	28	3
No steroid therapy	23	23	23	20	11	5	2

Figure 9: Retrospective study demonstrating the role of steroids in improving overall survival in DMD patients.

DMD-Associated Cardiomyopathy: Advanced Medical Therapies

The gold-standard for end-stage or advanced cardiomyopathy remains heart transplantation. Heart failure with multisystem organ involvement and inability to rehabilitate after cardiac transplantation have been relative contraindications to heart transplant and thus this therapy is believed to have limited applicability to patients with dystrophinopathies (DMD and BMD). With that stated, there are 4 retrospective studies analyzing the clinical outcomes of dystrophinopathy patients who underwent heart transplantation and the studies are as follows:

1. Rees et al. were the first to describe heart transplantation in patients with muscular dystrophies in a single German center[63]. Of 582 transplants performed, they had 3 patients with DMD and 1 patient with BMD who underwent heart transplantation with a mean duration of follow up of 40 months. They described that these patients tolerated immunosuppression, had no difference in postoperative intubation, and were able to be rehabilitated.
2. Ruiz-Cano et al. described a Spanish single center experience with heart transplantation in 3 patients with BMD who underwent heart transplantation with a mean follow up duration of 57 months[64]. These investigators also demonstrated that BMD patients had an intraoperative and postoperative course comparable to non-muscular dystrophy patients undergoing heart transplantation.
3. Patane et al. described a single case of successful transplantation in a patient with BMD-associated cardiomyopathy secondary to BMD with no significant immediate complications[65].
4. Finally, the UT Southwestern Heart Transplant Program performed the largest multicenter registry analysis of muscular dystrophy patients who underwent heart transplantation between 1995 and 2005 and the outcomes were compared to 275 non-muscular dystrophy non-ischemic patients who were matched for age, body mass index, gender and race[66]. Utilizing the Cardiac Transplant Research Database, 29 patients with muscular dystrophies were identified, out of which 15 patients had BMD and 3 patients had DMD. The study demonstrated that there was no significant difference in survival at 1 or 5 years, transplant rejection, infection, or allograft vasculopathy between the muscular dystrophy and non-muscular dystrophy patients.

These studies have all described comparable outcomes of heart transplantation in a small but highly selected group of patients with DMD and BMD with end-stage cardiomyopathy; however, the functional status of these patients prior to transplantation were not known and these studies may have a selection bias. Further studies investigating the role of heart transplantation in patients with DMD- and BMD-associated cardiomyopathy are warranted.

Given the scarcity of organs for heart transplantation, left ventricular assist devices (LVADs) have been demonstrated to be effective in treating patients with end-stage cardiomyopathies[67-69]. In addition, this therapy is applicable to a larger population including those with muscular dystrophies as it can be used as destination therapy without the need for transplantation. Three groups have reported cases of successful implantation of LVADs as destination therapy in DMD patients[70-72]. Amedeo et al. were the first to describe LVAD implantation in two pediatric DMD patients[70]. These investigators implanted the Jarvik 2000 LVAD in a 15 year-old boy with DMD who had inotrope refractory heart failure and in a 14 year-old boy with DMD who was bridged from extracorporeal membrane oxygenation to a Jarvik 2000 LVAD. The first patient was discharged 3 months after LVAD implantation and the second patient 6 months after LVAD implantation. Ryan et al. subsequently described a HeartMate II LVAD implantation in a 29 year-old male patient with DMD and end-stage heart failure and a HeartWare LVAD implantation in a 23 year-old female symptomatic DMD carrier with end-stage heart failure[71]. Finally, Stoller et al. described implantation of a HeartWare LVAD into a DMD patient who presented in cardiogenic shock[72]. This case represents the longest living DMD patient with a LVAD and the patient is currently 7 years post-LVAD implantation with no LVAD complications. One key factor to this patient's success is the choice of the LVAD, which did not disrupt the diaphragm. There is much that can be learned from the success of this particular case and in setting future guidelines for the implantation of LVADs into DMD patients with end-stage cardiomyopathy that is refractory to conventional medical therapies.

Implantation of a LVAD is potentially a promising therapy to address the end-stage cardiomyopathy in patients with dystrophin-deficient heart failure; however, the risk of developing post-operative complications including respiratory failure, rehabilitation, bleeding, stroke, and arrhythmias will need to be evaluated further in this population. Extensive preoperative and post-operative management in an experienced center will be necessary for successful LVAD implantation in very select DMD patients and larger studies will be needed to evaluate the efficacy and outcomes in this population.

Unique Characteristics of DMD-Associated Cardiomyopathy

To date the UT Southwestern Neuromuscular Cardiomyopathy Clinic has been following approximately 200 patients with dystrophinopathies, of which 70 patients have DMD. Despite aggressive medical management of their cardiomyopathy, 15 patient have died to date and 12 of these patients have died in their sleep. This data suggests that perhaps the current standard of care heart failure medications used to treat DMD-associated cardiomyopathy are not fully adequate to induce significant reverse cardiac remodeling (Figure 10).

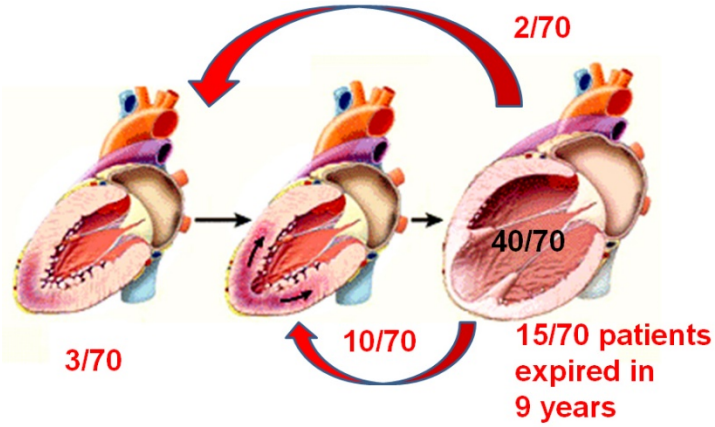


Figure 10: Effect of optimal medical management of DMD-associated cardiomyopathy.

Recently, we have undertaken a cardiac MRI study demonstrating that adult DMD patients have very low LV mass and low LV concentricity as compared to age-, sex-, and weight-matched patients with non-ischemic cardiomyopathy as well as normal, healthy patients enrolled in the Dallas Heart Study (Table 1).

Table 1: Cardiac MRI Parameters

	DMD (n=18)	NICM (n=18)	DHS (n=36)	p-value		
	mean ± SD	mean ± SD	mean ± SD	DMD vs NICM	DMD vs DHS	NICM vs DHS
LVEDV (ml)	120 ± 34	254 ± 91	140 ± 18	<0.0001	0.03	<0.0001
LVESV (ml)	60 ± 28	171 ± 93	55 ± 12	<0.0001	0.51	<0.0001
LVSV (ml)	60 ± 13	83 ± 18	85 ± 12	<0.0001	<0.0001	0.66
LVEDV index (ml/m^2)	69 ± 21	117 ± 39	75 ± 8	<0.0001	0.19	0.0003
LVESV index (ml/m^2)	34 ± 16	78 ± 41	29 ± 6	0.0003	0.26	<0.0001
LVSV index (ml/m^2)	35 ± 8	39 ± 9	46 ± 6	0.15	<0.0001	0.001
LVEF (%)	53 ± 12	37 ± 14	61 ± 6	0.001	0.001	<0.0001
LV Mass (g)	92 ± 26	182 ± 64	114 ± 26	<0.0001	0.005	0.0003
LV mass index (g/m^2)	**52 ± 13**	**83 ± 23**	**61 ± 11**	**<0.0001**	**0.02**	**0.001**
LV concentricity (g/mL)	**3.8 ± 0.9**	**4.5 ± 1.0**	**4.0 ± 0.8**	**0.04**	0.18	0.22

This observation is novel and raises the question as to whether the development of pathological cardiac hypertrophy is the primary mechanism underlying DMD-associated cardiomyopathy. In fact, data from the Mammen laboratory indicates that *mdx* mice, a murine model of DMD, also have low cardiac mass due to a decrease in nuclear Yap in neonatal cardiomyocytes resulting in defects in cardiac proliferation during the first week of life. These observations may provide an explanation for the high mortality rate in DMD patients despite aggressive medical management of their cardiomyopathy. Therefore, we propose that DMD patients are actually born with small hearts due to proliferative defects during the first years of life resulting from the lack of dystrophin expression. Eventually, these DMD hearts will dilate and the DMD patients will develop advanced end-stage cardiomyopathy and succumb to complications related to cardiomyopathy (Figure 11).

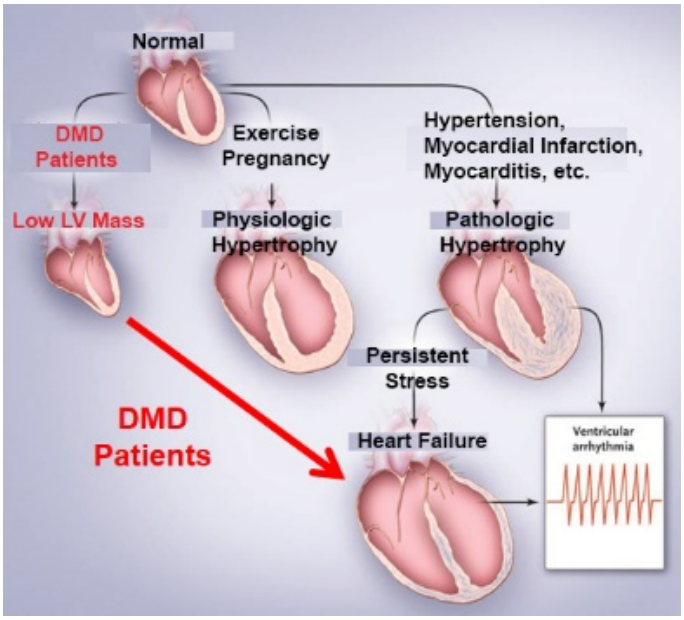


Figure 11: Initially, DMD patients develop small hearts with decrease in LV systolic function, but eventually they will progress to a dilated cardiomyopathy leading to death in the vast majority of these patients. (Modified from Hill & Olson *NEJM* 2008 358(13):1370-1380)[73]

Summary of the Current Management of DMD-Associated Cardiomyopathy

The table below summarizes the current clinical treatment of DMD-associated cardiomyopathy:

Table 2: Management Approach to DMD-Associated Cardiomyopathy in 2020

Medications	Devices	Advanced Heart Failure Therapies
Beta-Blockers (Carvedilol, Toprol XL, Bisoprolol)	AICD (LVEF<35% despite optimal medical therapy)	Left Ventricular Assist Devices (LVAD) (beneficial in selected DMD patients)
ACEI or ARB	BiV/AICD (QRS>120msec and/or cardiac dyssynchrony noted by ECHO along with a LVEF<35%)	Heart Transplantation (rarely used in the DMD population)
Aldosterone Inhibitors (Spironolactone or Eplerenone)		
ARNI (ARB + inhibitor of neprilysin; Entresto)		
BiDil (or Isordil/Hydralazine)		
Ivabradine (Corlanor)		
Diuretics (only if volume overloaded)		
Digoxin		
Steroids (prednisone or deflazacort)		

Therapies marked in red are supported by either retrospective or prospective randomized clinical studies.

UT Southwestern Neuromuscular Cardiomyopathy: Platform for Translation

The UT Southwestern Neuromuscular Cardiomyopathy Clinic serves as a platform for translational studies focused on novel therapies directed specifically towards patients with neuromuscular disorders (Figure 12). These studies are aimed at improving both the overall care as well as the cardiovascular care we provide to this unique patient population.

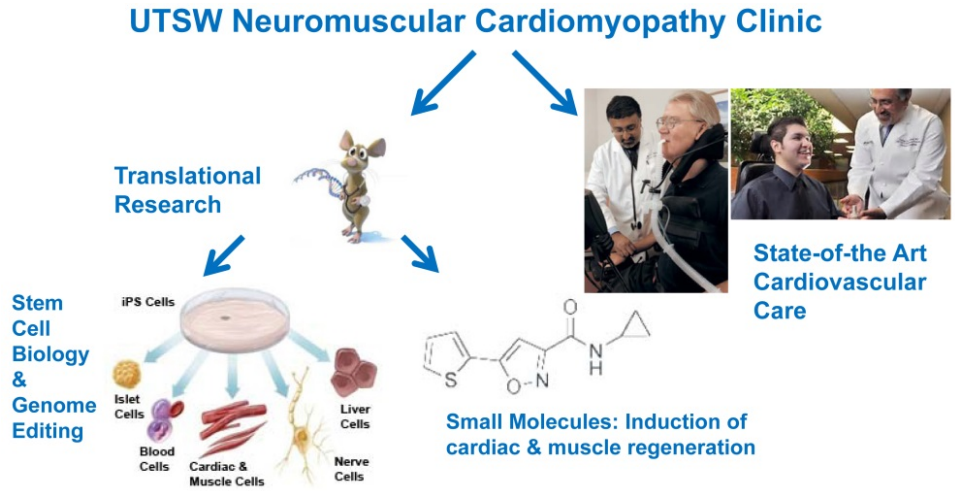


Figure 12: The UT Southwestern Neuromuscular Cardiomyopathy Clinic services as a platform for translational studies.

In the Fall of 2015, the National Institute of Health awarded UT Southwestern one of six coveted Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (MDCRC). Dr. Eric Olson and I serve as Co-Directors of the UTSW Wellstone Center. The overall mission of the UTSW Wellstone Center is to rapidly translate the discoveries by Dr. Olson's research team on genome editing into an innovative therapy for the treatment of DMD patients (Figure 13)[74, 75].

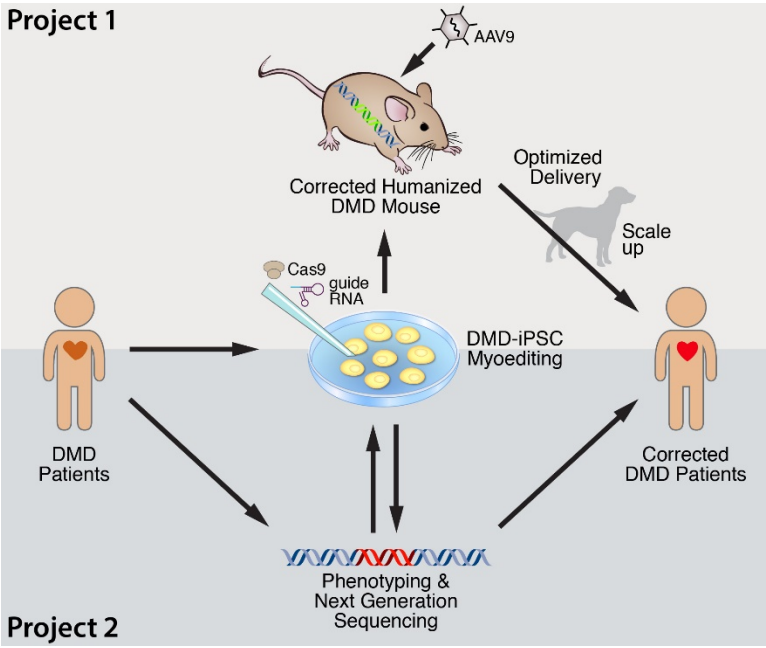


Figure 13: Schematic overview emphasizing synergistic interactions and seamless integration of projects, patients, cores, and resources. Project 1 seeks to optimize and adapt CRISPR/Cas9-mediated genome editing to postnatal muscle in genetically engineered humanized DMD mice. Project 2 will feed into Project 1 by identifying, phenotyping, and sequencing new DMD patients. The Myoediting Core will serve as a bridge between the 2 Projects as well as the scientific research community at large.

Over the past 5 years, the UTSW Wellstone Center, under the leadership of Dr. Olson, has made significant progress to demonstrate the potential benefits of CRISPR/Cas9-mediated genome editing as a viable therapeutic modality for the treatment of DMD[74-79]. Since there are over 3,000 different mutations that can cause DMD, our Center has proposed to use a single cut approach to develop different CRISPR-Cas9 "drugs" to target the key "hot spots" within the DMD gene.

Thus, this approach will essentially convert a DMD patient into a BMD patient. Clearly, this innovative therapy will be a major advance in the treatment of DMD. With that stated, we still need to be mindful of the development of a cardiomyopathy in genome edited DMD patients. Although BMD patients produce a truncated version of the dystrophin protein, they also have symptoms related to muscular dystrophy. In particular, 70-80% of BMD patients will develop a progressive cardiomyopathy, which oftens results in their demise in the 5th to 6th decade of life. More details regarding this issue will be discussed at the time of the lecture.

Summary

In conclusion, there has been significant progress in the treatment of DMD. This disease entity is no longer a pediatric disease as the majority of these patients will live into early adulthood. In fact in 2020, the majority of DMD patients will succumb to complications related to DMD-associated cardiomyopathy in the late-20s to mid-30s. Therefore, primary care physicians and cardiologists need to be aware of complications related to DMD. All adult DMD patients should undergo extensive cardiac assessments, which should include a thorough history and physical, clinical phenotyping (including a cardiac MRI) and genetic phenotyping. Today, there is emerging data supporting the use of beta-blockers, ACE inhibitors (or ARBs), and MRAs to decrease the morbidity faced by adult DMD patients. Unfortunately, despite aggressive management of DMD-associated cardiomyopathy, the mortality rate remains very high, with 100% of DMD patients expiring before the age of 45 years old. However, there is much hope across the horizon as CRISPR/Cas9-mediated genome editing will become a therapeutic modality for many DMD patients. However, we need to be aware that this innovative approach as it is currently designed will not “cure” DMD but rather convert the DMD patients into BMD patients. Thus, the risk of developing advanced end-stage cardiomyopathy will remain a critical problem in many of these patients.

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