Parent Project Muscular Dystrophy

JOIN THE FIGHT. END DUCHENNE.

2022 CARDIAC CARE AND DUCHENNE WORKSHOP REPORT

ENDDUCHENNE.ORG

2022 CARDIAC CARE AND DUCHENNE WORKSHOP REPORT

The monitoring, care, and management of the cardiac manifestations of the cardiomyopathy associated with Duchenne muscular dystrophy (Duchenne) has come to greater attention with the recognition that heart disease has now become a leading cause of death in Duchenne and related dystrophinopathies. On March 17 and 18, 2022, Parent Project Muscular Dystrophy (PPMD) convened a workshop in Charleston, South Carolina to drive consensus in four key areas of cardiac care for individuals with dystrophic cardiomyopathy:

– What are appropriate **cardiac endpoints** to monitor progression in clinical practice and clinical trials?

– How can researchers **assess heart disease progression risk** and compare individuals with Duchenne and Becker muscular dystrophy (Becker) across their heterogeneous phenotypes?

– What **traditional and advanced heart failure therapies** should individuals be offered at different stages of disease, and, particularly, what should be standardized across the different sites in clinical trials? What **new treatments** should first be evaluated in clinical trials?

– What will **the impact of emerging gene therapies be on the heart,** and what standards of cardiac care and monitoring should be incorporated into gene therapy studies?

Outcome measures in clinical trials and the regulatory environment

One of the key challenges confronting the field is the identification of suitable measures to use in clinical trials of dystrophic cardiomyopathy. This is common in rare diseases because natural history data and disease-specific assessment tools are limited, according to Dr. Kim McBride, Division Director of Genetics at Nationwide Children's Hospital. He described how new tools either have to be created, or existing tools adapted to be fit-for-purpose, and then tested clinically. This is especially true for dystrophic cardiomyopathy where the pathology, clinical presentation, and symptoms of heart failure (HF) are unique and vary from that of other cardiomyopathies.

This has not led to great flexibility on the part of regulators, however, as evidenced by the presentation from Dr. Fortunato Senatore of the United States (US) Food and Drug Administration (FDA) who said that cardiac endpoints in Duchenne trials should be based on the same "feel-function-survive" paradigm used in adult HF trials. He suggested acceptable endpoints would include major adverse cardiac events (MACE) composite endpoints (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke), or MACE+4 or 5, which add events such as hospitalizations and surgical procedures to reduce the sample size needed.

However, MACE+4 or 5 would be challenging to use in dystrophic cardiomyopathy trials, according to Dr. Gabriel Brooks, an adult cardiologist working with Pfizer. As for the "feel", HF is typically measured by dyspnea and symptoms that, in Duchenne, can be conflated with respiratory distress and skeletal muscle-related issues. In Duchenne, HF symptoms can be very subtle: only 30% of boys express cardiac symptoms when diagnosed with cardiomyopathy.[1] In addition, there are no validated patient-reported outcomes (PROs) or quality of life measures. With regards to "function", pharmaceutical companies have used cardiac pulmonary exercise tests, 6-minute walk test, 10-meter walk, and stair climb in ambulatory individuals, but loss of ambulation confounds exertional measures of cardiac functional capacity.

Moreover, the disease's rarity and slow progression to mortality make survival and MACE+5 endpoint studies difficult, if not unfeasible. According to a model Brooks presented, even with highly effective treatment, it could take a decade to collect enough endpoints—and the trial could be unsuccessful if either the benefit or event rate is less than expected. Professor Robert E. Shaddy of the University of Southern California added that some MACE+4 or 5 events are subjective—and events/deaths in the hospital are difficult to adjudicate given patients may pass outside of tertiary neuromuscular centers. Furthermore, in later-stage disease both cardiac and pulmonary disease may contribute to hospitalization and mortality. Separating out these components can be challenging.

However, alternatives such as intermediate endpoints or surrogate markers (like circulating or imaging biomarkers) "are risky," according to Senatore, and could lead to approval of an ineffective drug if the change in a biomarker is not on the causal pathway of the disease process. The bar for a surrogate marker is high: It must predict risk of the outcome in patients without a given medical intervention; continue to correlate with risk of the outcome after modulation by treatment, and, when therapeutically modulated, the measure must predict the net effect (clinical benefit) of the treatment.[2]

Nevertheless, Brooks said, developing 'on-target' biomarkers that affect the disease process is the only way to learn whether a drug is worth taking into phase III development in the first place.[3] Several biomarkers are under evaluation, including exploratory circulating biomarkers that could yield information on different stages of progression. One, NTproBNP, was recently used as a surrogate to expand the indication of an already approved drug in pediatric heart failure for children,[4,5] and may be associated with mortality risk in Duchenne patients.

There was also wide agreement that imaging biomarkers of cardiac structure, function (ventricular volumes, ejection fractions [EFs], and hypokinesia) and tissue characteristics (inflammation, focal and diffuse myocardial fibrosis/fibrofatty replacement) need to be included as outcome measures in Duchenne clinical trials.

Left ventricular EF (LVEF) is commonly used in clinical practice but has limited utility as an outcome measure. According to Dr. Jonathan Soslow of Vanderbilt University, while echocardiography (echo) can easily obtain LVEF, in trials, it is most useful for monitoring safety in children aged 10 years or younger. Cardiac MRI is the gold standard for LVEF, as it is more reproducible and has better precision.[6-8] However, although very low LVEF is associated with greater mortality in late-stage

disease,[9] Dr. Chris Spurney of Children's National Hospital noted that even patients with less than normal LVEF usually display a very slow decline[10,11] of around 1%-2% per year.[12] With a standard deviation of plus or minus 5% to 10%, teasing out such a change presents challenges in clinical trials.

Cardiac MRI measures of strain abnormalities and late gadolinium enhancement (LGE) in the myocardium that measures fibrofatty infiltration/replacement may better identify the potential therapeutic window for cardiomyopathy, years before MACE endpoints can be measured. Global circumferential strain decreases significantly over time[13] and patients have decreased two-and three-dimensional strain before they develop cardiomyopathy.[14] In terms of tissue characterization, LGE provides evidence of pathological changes in the myocardium that precede depressed LVEF (which does not decline significantly in absence of LGE).[15-19]

Regulators still see these measures as being in a developmental stage and not ready for use as surrogate endpoints; however, Senatore suggested that the FDA might consider a composite endpoint combining cardiac imaging data from measures such as LGE and strain with outcome measures such as performance of upper limb function (PUL) that can be used in both late ambulatory and nonambulatory patients. But while composite endpoints can increase statistical power, there is no guarantee that a treatment will have a uniform effect on all components. Also, treatments that only improve skeletal muscle performance—increasing physical activity—could place more burden on a heart with little contractile tissue left.

Insights into the natural history of cardiac dystrophinopathy revealed

By late-stage disease, LGE may mostly represent fatty infiltration. Dr. Jennifer Kasten of Cincinnati Children's Hospital (CCH) described a retrospective histological case series of 10 mostly steroid pretreated long-term survivor patients with dystrophic cardiomyopathy for whom pathology specimens were available. In one patient who reported no symptoms of HF before his unexpected death at age 36, subepicardial fat infiltration was so pronounced that portions of his heart were translucent—his myocardium was completely replaced by fat with very few myocytes (<5%) remaining. The same patchy pattern was observed in most participants in the series. In another autopsied heart, resectioned using a recent MRI as a guide, histology revealed the subepicardial fat corresponded to areas of LGE on MRI.

The therapeutic implications are stark. Once fatty replacement of the myocardium becomes extensive, antifibrotic agents would not be expected to have any effect. Once the myocardium is lost, restoration cannot occur and the benefit of muscle preserving therapy is likely to be minimal. The disease process must be seen as starting early—and interventions need to be initiated before irreversible damage occurs. However, in late-stage cardiomyopathy, once extensive fibrofatty replacement has occurred, LGE may be less effective at predicting outcomes and markers including EF and cardiac volumes may be more predictive of outcomes (though analyses may be confounded by noncardiac mortality).[9]

Learning from skeletal muscle MRI

MRI images provide more granular evidence of the pathological changes in dystrophic cardiomyopathy. Soslow described work with parametric mapping (native T_1, T_2, and extracellular volume mapping) suggesting that edema and inflammation play a role in the early progression of myocardial disease, and that most early LGE is fibrosis, with increased fatty infiltration in older patients and those with worse disease progression.

Skeletal muscle MRI reveal similar patterns. Dr. Glenn Walter of the University of Florida and the ImagingDMD Initiative explained how T_1-weighted images and T_2-weighted images could distinguish between normal and dystrophic skeletal muscle and observe changes over time. With the addition of MR spectroscopy, it is possible to quantify the types of fluid and fat, fat fraction and even muscle metabolites. With further study, it has become clear the predominant feature in skeletal muscle dystrophinopathy was the replacement of muscle by fat, and that the replacement of contractile tissue by noncontractile tissue is associated with clinical progression and changes in clinical function.

However, when used as endpoint measurements, variability in the acquisition, display, and interpretation methods of imaging could result in increased variability and compromise the ability of a trial to achieve its objectives.[20] To meet FDA standards, ImagingDMD chose to implement simple, standardized MRI sequences that would result in quantitative results that could be used for longitudinal measurements at multiple sites on different systems. The project now has 15 years of MR and natural history data in approximately 200 patients, with over 1500 visits at the sites, with years of longitudinal functional data. ImagingDMD's skeletal muscle MRI approaches now meet the requirements for use as a biomarker in trials.[21-25] This achievement required training, standardization, and complete oversight in terms of rigor and quality control to obtain these images, with centralized data analysis and processing. A large team is also needed for MR imaging work, including basic scientists, Duchenne experts, MR experts, clinicians, physical therapists, and support staff to make the patients feel comfortable, create an inviting environment, so that the patients are willing to come back for longitudinal scans.

Brooks stressed that industry would need the support of academia and clinicians to provide further evidence of predictive effects of cardiac MRI. By working together to apply lessons learned in skeletal muscle, using simplified techniques, standardization, and training across sites to develop quantitative cardiac imaging, centers could systematically provide support for the use of cardiac MRI measures as biomarkers of the pathology in dystrophic cardiomyopathy.

Harmonization of clinical care and medical therapy

Treatment standards need to be implemented, otherwise, heterogeneity in practice will make clinical development of new agents difficult—but current guidance regarding issues such as when to start prophylaxis with angiotensin-converting enzyme inhibitors (ACEi), or angiotensin receptor blockers (ARB) therapy in normal LVEF is dated, inconsistent, and not granular. Furthermore, the

data continue to grow stronger that early initiation of ace inhibitors slows the progression to heart failure. Evidence also suggest that beta blockers (BB) and mineralocorticoid receptor antagonists (MRAs)/aldosterone inhibitors (AIs), such as eplenerone, may be useful when there is LGE, although the data are less robust for these classes at this time.[26,27]

There is currently diversity of practice. In a survey of 31 providers working at 23 centers in the Advanced Cardiac Therapies Improving Outcomes Network (ACTION),[28] about half see their patients under the age of 10 years annually. Most centers were using cardiac MRI, with more than half starting by the age of 10 years, and many using serial MRIs. In terms of prophylaxis, 68% were prescribing ACEis, and 10% MRAs by age 10 years—though 58% were prescribing MRAs in those with LGE.

Dr. Ashwin Lal of Intermountain Primary Children's Hospital focused on the limitations of existing guidance in dystrophic cardiomyopathy[29-33,] and reviewed the guidance regarding the timing, method and frequency of noninvasive imaging, which is more aggressive in the Duchenne Care Considerations (DCC) than the American Heart Association (AHA) guidance.[27,31] Lal believes the lack of data about when to start prophylaxis with ACEI and/or MRA, particularly in those with more preserved heart function, and what doses to use should be explained to patients and caregivers. However, as Spurney noted, even those without any obvious identified structural abnormalities should be treated as having a predisposition to develop cardiomyopathy. Dr. Pradeep Mammen, an adult cardiologist at the University of Texas Southwestern Medical Center, said that in the absence of data to guide management clinicians must extrapolate how to use these drugs as best they can. Others agreed that while centers need to expand the evidence base for practice in dystrophic cardiomyopathy, failure to use what works in other dilated cardiomyopathies could amount to a generation of patients with missed opportunities.

Mammen starts ACEis early in his Duchenne patients irrespective of LV function, and beta-blockers are a mainstay that he tries to maximize, though blood pressure can be an issue. He also adds an MRA/AI such as spironolactone but at a reduced dose due to the risk of hyperkalemia. Notably, Professor Jill Rafael-Fortney of Ohio State University presented basic science research showing MRAs may improve membrane stabilization and have anti-inflammatory and antifibrotic properties in dystrophic muscles and the heart that merit further study, particularly third-generation MRAs with fewer side effects.

Whether early or late, acute decompensated symptomatic HF can develop rapidly, particularly in patients who develop concurrent illnesses. Spurney said that, at this point, the HF team employs the standard HF treatment and may add more novel therapies, such as angiotensin receptor neprilysin inhibitors (sacubitril/valsartan),[34] ivabradine, a voltage gated ion current inhibitor[35] and the sodium glucose co-transporter 2 (SGLT2) inhibitors, each used for adult HF, that have potential in Duchenne cardiomyopathy.[36] Mammen described dystrophic HF management as a 3- to 7-drug treatment including these novel therapies (and emphasized the positive experience using SGLT2 inhibitors at his center). However, he advised clinicians to be aware the novel agents have drug-drug interactions with existing therapy and contraindications, and that starting doses in dystrophic cardiomyopathy populations may need to be lower than doses demonstrated effective in the large adult HF studies.

In chronic decompensated HF, Spurney said his team considers options such as implantable cardioverter-defibrillators (ICDs) in those with very low EFs, and ventricular assist devices (VADs) in carefully selected patients. He considers cardiac transplantation in younger patients with minimal comorbidities and acute cardiac decline. Mammen stated that Becker patients with more minimal skeletal muscle disease are more frequently transplanted at his institution.

Advanced therapies: monitoring and implantable devices

Determining whether such interventions are appropriate requires advanced monitoring approaches as well as more data on the use of advanced therapies such as ICD's in arrythmia and VADs in those with pump failure.

Dr. Andreas Barth of Johns Hopkins University described how fibrosis on LGE can be associated with increased risk of ventricular tachycardia and ventricular fibrillation[37] but said standard monitoring approaches, such as electrocardiograms (EKGs) may not be as useful as in other diseases. Other options for rhythm monitoring include wearable measures, such as 24- or 48-hour Holter monitors that have been used in a number of Duchenne studies. However, Holter monitors are uncomfortable to wear and have limited ability to detect the risk of sudden cardiac death (SCD) when EF is normal.

Most cardiologists have switched to event monitors (there are several brands including the Ziopatch), 12-30-hour monitors that can be applied by the patients themselves. Another option is an implantable loop recorder (ILR) that can detect arrhythmias an event monitor might miss. These are small, easy to implant, and the newest models provide continuous monitoring for up to 5 years and send data via Bluetooth to cellphone apps.

Barth performed a study in patients with abnormal EFs using ILRs or Ziopatches. Atrial fibrillation was rare, but non-sustained VT was observed in about 25% of the patients. This risk of tachyarrhythmias increased with the severity of LV dysfunction and extent of LGE by cMRI. He believes prolonged monitoring when LVEF is ≤50% is necessary to detect subclinical atrial fibrillation and NSV. Currently, Barth is working on a virtual electrophysiology study, combining patient's rhythm monitoring data with ancillary MRI data to generate personalized 3-D heart models.

Dr. Carol Wittlieb-Weber of the Children's Hospital of Philadelphia also described studies on arrhythmia burden and the risk factors for death in Duchenne—with some suggesting ICDs are underutilized. Expanded use of ILRs is needed to gather longer-term data on the overall burden of clinically significant arrhythmias and severe dysfunction and how arrhythmia is contributing to cause of death in patients with Duchenne—with other factors, such as obstructive sleep apnea, potentially triggering SCDs.[38] There are also data suggesting ICD use may be associated with improved survival and minimal complications in Duchenne cardiomyopathy with systolic left ventricular diameter ± nonsustained ventricular tachycardia—though inadequate background cardiac therapy in many patients may have confounded interpretation.[39]

According to the survey of ACTION sites, ICD use is not common—about half the sites had a patient or two with an ICD.[28] Dystrophic cardiomyopathy-specific guidance on ICDs are needed because of safety and risks in patients with Duchenne, with difficulties brought about by body habitus.[40] The unknown risks and benefits of ICDs (and other options) need to be discussed with candidate patients—prioritizing the patient/family therapy goals of care. However, in one small preference study, some respondents expressed willingness to participate in studies using ICDs to gather more information.[41] Centers should start building a database across sites on procedural management of complications in all dystrophic cardiomyopathy patients with ICD use.

Advanced home monitoring (or remote patient monitoring [RPM]) can gather other vital patient data. RPMs are systems that use one or more home-based or mobile monitoring devices that transmit vital sign data or information on activities of daily living that are subsequently reviewed by healthcare professionals. Dr. David M. Peng of C.S. Mott Children's Hospital said RPM could improve access and quality of care for those who do not see a cardiologist often, have not had cardiac imaging or received ambulatory cardiac monitoring. RPM could provide real-time data for earlier detection and response to deterioration, preventing severe decompensation and events. RPM can more closely monitor adherence to treatment, responses to medications and interventions, and side effects. Some RPM measures may eventually prove useful as endpoints in future clinical trials.

For instance, in ambulatory Duchenne patients, the European Medical Agency recently accepted the measurement of stride velocity 95th percentile (the minimal velocity of the 5% most rapid strides taken by a patient in a real-world setting) by a wearable accelerometer as a secondary endpoint for use in clinical trials.[42] Wearables that measure arm accelerometry and appear to correlate with PUL assessments are in development.[43] The ACTION network is also conducting a study in pediatric patients with acute HF to evaluate whether biometric data gathered by a smart watch application correlate with clinical markers and assessments of pediatric HF severity and functional status and can be used to reduce events including hospitalizations, cardiac arrest, and death.

There are also data showing that the CardioMEMS HF system, an implantable pulmonary artery (PA) pressure monitor, can reduce hospitalizations in symptomatic patients with previous HF hospitalization.[44] In one case study presented at the meeting, implantation in a patient with dystrophic cardiomyopathy resulted in lower PA pressures and improved symptoms and quality of life.

Finally, the majority of deaths in dystrophic cardiomyopathy are due to pump failure—but sometimes this occurs acutely in an individual with an acceptable quality of life. Dr. Deipanjan Nandi of Nationwide Children's Hospital described data on the use of VADS, including the experience across 12 sites in mostly dystrophic patients, that showed positive outcomes for VAD as a bridge to a heart transplant in 4 out of 5 individuals, and as a permanent treatment that extended survival out to one or two years of follow-up in the majority of the participants.[45] But the procedure can be associated with adverse events and potential VAD recipients should be counseled of the potential complications. This is another area where there is a lack of consensus and guidance should be developed.

Gene therapy and the heart

There may be a much greater need for interventions such as VAD and heart transplants in the future if the gene therapies (GTs) in development benefit skeletal muscle more than the heart. As Dr. Tim Cripe of Nationwide Children's Hospital and Dr. Lee Sweeney, of the University of Florida described, there are also questions whether GT products will be safe in patients with dystrophic cardiomyopathy—and whether industry is adequately monitoring for effects, beneficial or harmful, in the heart.

Duchenne GT approaches that attempt to remedy dystrophin deficiency in muscle include a CRISPR-Cas9 gene editing approach, use of modified U7 constructs to promote exon-skipping, and recombinant adeno-associated virus (rAAV) vectors to deliver mini- or microdystrophin transgenes into striated muscle and other cells—the GT products furthest along in development. While AAVs serotypes have different cell tropisms, they all reach more than one type of cell, including in most cases, lung tissue, the liver, the CNS, as well as the heart—and thus also deliver promoters for selectively expressing proteins in different cells lines.

AAVs can deliver only a limited amount of genetic material into a cell,[46] and not the full-length dystrophin gene[47] or even the truncated genes that produce mini-dystrophins associated with Becker. The three rAAV GT programs that are furthest along in Duchenne, led by Sarepta, Pfizer, and Solid Biosciences, each deliver a different transgene that has had sequences removed that were deemed nonessential for functionality in the skeletal muscle. With substantial evidence showing prolonged skeletal muscle function in animal models, these are now in phase I-III trials, enrolling patients from different age groups. There are encouraging preliminary clinical data, such as open-label study in four children with improvements in various measures.[48]

But there are various challenges for rAAV GTs. One is that skeletal muscle cells turn over, so there are questions about the durability of rAAV GT. Consequently, high doses are used to achieve concentrations to saturate the muscle satellite (precursor) cells. Note, that this is not an issue in cardiomyocytes—if they are treated, they remain treated.

Another issue is that although AAV is a nonpathogenic virus, many individuals have been exposed to it, and pre-existing antibodies may limit delivery and effectiveness of the GT product. Consequently, companies are testing for antibodies and limiting eligibility to those with low titers. For this same reason, redosing is not yet possible and could pose a risk of a life-threatening immune reaction. There can be both humoral and cellular immune response to components of GT, including cases of complement system activation causing severe clinical problems and cytotoxic reactions to regions of the dystrophin protein that the patient does not normally express—though studies of GT in other diseases are exploring whether these different immunological risks can be mitigated. There are also other questions clinical trials need to answer, such as, at what age or disease stage should treatment start; if and how well will it work; and will it offer durable benefit in all types of muscle including the diaphragm and heart?

Cripe shared findings from murine models showing cardiac transduction following intravenous administration—suggesting systemic GT can affect the heart. Sweeney, however, shared findings from a murine model suggesting that while current microdystophin constructs improve skeletal function, they may not provide adequate cardiac benefit (and in some cases, with overexpression, may even be harmful). This could lead to a situation where GT restores physical activity that puts more load on the heart, leading to earlier cardiomyopathy. There was, however, some discussion regarding the model's methodology; and Rafael-Fortney noted that other researchers had reached contradictory conclusions.

In clinic, there has been one unexplained death in an older Duchenne GT trial participant due to cardiac failure or systemic organ failure five days after dosing. Sweeney theorized the event could be related to a rapid transient cardiac inflammation with the high doses of rAAV, which his team has observed in the dog model, with inflammation in the tissue which usually resolves within a week in most animals. This could be a common response in humans as well—but one that goes unnoticed in younger trial participants. However, in older patients, with fragile hearts, there is a concern the inflammatory response may cause injury or even be life-threatening to more vulnerable hearts. Either way, Sweeney said, industry needs to monitor for such events; and the sentiment was echoed by Dr. Linda Cripe of Nationwide Children's Hospital, who warned that with close to 300 participants with Duchenne enrolling in GT trials, "a storm might be coming," so clinicians treating these children should be monitoring their hearts closely.

Other approaches entering trials

An orthogonal approach to GT for dystrophic cardiomyopathy was described by Dr. Roger Hajjar of Mt. Sinai Hospital and SARDOCOR. Rather than addressing dystrophin deficiency, this GT aims to increase the expression of the cardiac isoform of sarcoplasmic reticulum calcium ATPase (SERCA2a), an intracellular Ca2+ transport pump that is critical for contraction and relaxation of cardiac muscle cells. In animal models, restoration of SERCA2a protein levels and activity decreases fibrosis, recovers LV function and improves other cardiac parameters.[49] Low doses of GT AAV1.SERCA2a have been safely administered in adults with HF.[50] With positive findings in Duchenne animal models, the company plans higher dose studies in young men with Duchenne (with LVEF<45% and LGE).

Dr. Andrew Marks of Columbia University described a (non-GT) approach targeting dystrophic cardiomyopathy, ARM210, a compound to stabilize ryanodine receptors (RyR1)—sarcoplasmic reticulum Ca2+ release channels that are chronically remodeled in dystrophinopathies leading to intracellular Ca2+ leakage that causes damage and weakness in skeletal muscle, and a weakening of muscle contraction and electrical arrythmias in the heart.[51] Another experimental mitochondrial treatment studied for Barth Syndrome, elamipretide, is also under evaluation in Duchenne.

In addition, Dr. Dominic Fullenkamp of Northwestern University Feinberg School of Medicine described preclinical models of dystrophic cardiomyopathy that could explore the effects of other existing and experimental treatments and that could help identify microdystrophin constructs that provide greater benefit to the heart.

Roadmap to clinical trials

Dr. Jim Carr of Stealth Bio Therapeutics and Dr. Joanne Donovan of Edgewise Pharmaceuticals reiterated that more natural history data is needed for industry to move forward with clinical trials of drugs specifically targeting dystrophic cardiomyopathy. They emphasized that standardizing cardiac treatment of Duchenne cardiomyopathy is a critical first step across centers to reduce variability in clinical trials.

Carr described the collection of natural history data as critical for accelerated approval for drugs in rare diseases. Data are needed to characterize the relationship between intermediate outcome measures, including imaging and circulating biomarkers, and to develop endpoints that are measurable, clinically meaningful and acceptable for regulators. In dystrophic cardiomyopathy, Carr said this will require collaborative efforts to create predictive models quantifying the relationship between changes in LV structure and/or function to later outcomes. A rigorously conducted cardiovascular registry could gather this natural history data that could also potentially serve as the control for confirmatory outcome trials.

ACTION is a potential framework for such collaboration. Professor Angie Lorts of Cincinnati Children's Hospital said the network was established as there was no standard of care for the diverse pediatric populations with HF. A small group of providers initiated the network in 2017 to improve outcomes in pediatric HF patients. The network quickly grew to over 50 institutions (there are 58 today). Although there are numerous drugs and devices currently been employed in adult HF treatment, few of these devices and drugs had been studied in pediatric populations. To address this need, ACTION standardized care in three areas: treatment, monitoring, and how centers/clinicians communicated as teams.

ACTION recognized there was a great inequity in the care of advanced HF—not every child can attend a center of excellence. Clinicians at other centers were uncomfortable using treatments and devices when there was a lack of clear guidance and products were not labeled for pediatric use. ACTION met with the FDA; explained these challenges; and together they developed a plan for the network to collect real world data that industry could submit to FDA as the labeling application. In addition to setting up a real-world data structure to collect the data, ACTION set up a team of physicians and nurses to adjudicate events so that the FDA can use the data for real world evidence. Within 18 months of conceiving the idea, ACTION was able obtain a pediatric labeling for the Berlin Heart. This success led to FDA asking ACTION to set up a template for prospective trials for pediatric cardiac devices (Trials in ACTION, or TRACTION).

For institutions to collaborate safely, without conflicts of interest, ACTION established a single institutional review board (IRB) that was now handling 60 separate projects. With this single IRB, it was possible to set up many registries including the Cardiomyopathy in Duchenne Registry. A data use agreement was also established with an honest broker: Cincinnati Children's Hospital, which keeps the patient identifiers but does not send them out unless patients are consented. This allows efficient linkage with other registries. The collaborative agreements/contracts with industry, which involve funding to support the registry, are set up as research agreements—and ACTION is able to share the data with industry for regulatory purposes.

Lorts believes the Duchenne cardiomyopathy registry could use this model, and collect data for standardizing treatment and monitoring protocols, such as a 40-minute cardiac MRI protocol described at the meeting. However, site staff will need to be trained before the collection of useful natural history data.

Next steps

Nandi closed the meeting highlighting next steps for meeting attendees, including:

- The establishment of Duchenne Heart Network engaging all the centers represented at the meeting to:
    - Gather natural history in their patients, with an emphasis on collecting data on imaging and circulating biomarkers
    - Standardize cardiac MRI and advanced monitoring approaches, including event monitors
    - Standardize treatment to the extent possible
    - Gather data on the use of ICDs and VADs in patients with dystrophic cardiomyopathy
- Quickly apply this network's infrastructure for clinical trials, potentially beginning with a trial of SGLT2 inhibitors in dystrophic cardiomyopathy
- Issue updated treatment and monitoring guidance, or at least develop a Delphi consensus statement with scored recommendations
- Engage care providers to have a follow-up plan for their patients in GT trials
- Advocate that industry and investigators performing skeletal muscle trials in Duchenne gather imaging and biomarker data on the heart

1. McNally EM, Kaltman JR, Benson DW, et al. Contemporary cardiac issues in Duchenne muscular dystrophy. Working Group of the National Heart, Lung, and Blood Institute in collaboration with Parent Project Muscular Dystrophy. *Circulation*. May 5 2015;131(18):1590-8. doi:10.1161/circulationaha.114.015151

2. Greene SJ, Mentz RJ, Fiuzat M, et al. Reassessing the Role of Surrogate End Points in Drug Development for Heart Failure. *Circulation*. Sep 4 2018;138(10):1039-1053. doi:10.1161/circulationaha.118.034668

3. Wu SS, Fernando K, Allerton C, Jansen KU, Vincent MS, Dolsten M. Reviving an R&D pipeline: a step change in the Phase II success rate. *Drug Discov Today*. Feb 2021;26(2):308-314. doi:10.1016/j.drudis.2020.10.019

4. Shaddy R, Canter C, Halnon N, et al. Design for the sacubitril/valsartan (LCZ696) compared with enalapril study of pediatric patients with heart failure due to systemic left ventricle systolic dysfunction (PANORAMA-HF study). *Am Heart J*. Nov 2017;193:23-34. doi:10.1016/j.ahj.2017.07.006

5. Fleming TR, Garnett CE, Conklin LS, et al. Innovations in Pediatric Therapeutics Development: Principles for the Use of Bridging Biomarkers in Pediatric Extrapolation. *Ther Innov Regul Sci*. Jan 2023;57(1):109-120. doi:10.1007/s43441-022-00445-6

6. Brunklaus A, Parish E, Muntoni F, et al. The value of cardiac MRI versus echocardiography in the pre-operative assessment of patients with Duchenne muscular dystrophy. *Eur J Paediatr Neurol*. Jul 2015;19(4):395-401. doi:10.1016/j.ejpn.2015.03.008

7. Buddhe S, Lewin M, Olson A, Ferguson M, Soriano BD. Comparison of left ventricular function assessment between echocardiography and MRI in Duchenne muscular dystrophy. *Pediatr Radiol*. Sep 2016;46(10):1399-408. doi:10.1007/s00247-016-3622-y

8. Soslow JH, Xu M, Slaughter JC, et al. Evaluation of Echocardiographic Measures of Left Ventricular Function in Patients with Duchenne Muscular Dystrophy: Assessment of Reproducibility and Comparison to Cardiac Magnetic Resonance Imaging. *J Am Soc Echocardiogr*. Oct 2016;29(10):983-991. doi:10.1016/j.echo.2016.07.001

9. Wittlieb-Weber CA, Knecht KR, Villa CR, et al. Risk Factors for Cardiac and Non-cardiac Causes of Death in Males with Duchenne Muscular Dystrophy. *Pediatr Cardiol*. Apr 2020;41(4):764-771. doi:10.1007/s00246-020-02309-y

10. Murphy AP, Johnson A, Straub V, Heads-Baister A, Lord S, Bourke JP. Effects of cardiac medications on ventricular function in patients with Duchenne muscular dystrophy-related cardiomyopathy. *Muscle Nerve*. Aug 2021;64(2):163-171. doi:10.1002/mus.27336

11. Raucci FJ, Jr., Xu M, George-Durrett K, et al. Non-contrast cardiovascular magnetic resonance detection of myocardial fibrosis in Duchenne muscular dystrophy. *J Cardiovasc Magn Reson*. Apr 29 2021;23(1):48. doi:10.1186/s12968-021-00736-1

12. Lao K HW, Hor KN. Prevalence of Cardiac Disease in Duchenne Muscular Dystrophy Patients by Age: A Cardiac Magnetic Resonance Natural History Study. *Circulation*. 2021;(144)

13. Hor KN, Wansapura J, Markham LW, et al. Circumferential strain analysis identifies strata of cardiomyopathy in Duchenne muscular dystrophy: a cardiac magnetic resonance tagging study. *J Am Coll Cardiol*. Apr 7 2009;53(14):1204-10. doi:10.1016/j.jacc.2008.12.032

14. Siddiqui S, Alsaied T, Henson SE, et al. Left Ventricular Magnetic Resonance Imaging Strain Predicts the Onset of Duchenne Muscular Dystrophy-Associated Cardiomyopathy. *Circ Cardiovasc Imaging*. Nov 2020;13(11):e011526. doi:10.1161/circimaging.120.011526

15. Tandon A, Villa CR, Hor KN, et al. Myocardial fibrosis burden predicts left ventricular ejectionraction and is associated with age and steroid treatment duration in duchenne muscular dystrophy. *J Am Heart Assoc*. Mar 26 2015;4(4)doi:10.1161/jaha.114.001338

16. Nishimura T, Yanagisawa A, Sakata H, et al. Thallium-201 single photon emission computed tomography (SPECT) in patients with duchenne's progressive muscular dystrophy: a histopathologic correlation study. *Jpn Circ J*. Feb 2001;65(2):99-105. doi:10.1253/jcj.65.99

17. Soslow JH, Damon SM, Crum K, et al. Increased myocardial native T1 and extracellular volume in patients with Duchenne muscular dystrophy. *J Cardiovasc Magn Reson*. Jan 21 2016;18:5. doi:10.1186/s12968-016-0224-7

18. Olivieri LJ, Kellman P, McCarter RJ, Cross RR, Hansen MS, Spurney CF. Native T1 values identify myocardial changes and stratify disease severity in patients with Duchenne muscular dystrophy. *J Cardiovasc Magn Reson*. Oct 28 2016;18(1):72. doi:10.1186/s12968-016-0292-8

19. Puchalski MD, Williams RV, Askovich B, et al. Late gadolinium enhancement: precursor to cardiomyopathy in Duchenne muscular dystrophy? *Int J Cardiovasc Imaging*. Jan 2009;25(1):57-63. doi:10.1007/s10554-008-9352-y

20. United States Food and Drug Administration (FDA). *Clinical Trial Imaging Endpoint Process Standards: Guidance for Industry*. 2018. https://www.fda.gov/media/81172/download. Accessed November 22, 2022

21. Willcocks RJ, Rooney WD, Triplett WT, et al. Multicenter prospective longitudinal study of magnetic resonance biomarkers in a large duchenne muscular dystrophy cohort. *Ann Neurol*. Apr 2016;79(4):535-47. doi:10.1002/ana.24599

22. Arpan I, Willcocks RJ, Forbes SC, et al. Examination of effects of corticosteroids on skeletal muscles of boys with DMD using MRI and MRS. *Neurology*. Sep 9 2014;83(11):974-80. doi:10.1212/wnl.0000000000000775

23. Rooney WD, Berlow YA, Triplett WT, et al. Modeling disease trajectory in Duchenne muscular dystrophy. *Neurology*. Apr 14 2020;94(15):e1622-e1633. doi:10.1212/wnl.0000000000009244

24. Willcocks RJ, Forbes SC, Walter GA, et al. Assessment of rAAVrh.74.MHCK7.micro-dystophin Gene Therapy Using Magnetic Resonance Imaging in Children With Duchenne Muscular Dystrophy. *JAMA Netw Open*. Jan 4 2021;4(1):e2031851. doi:10.1001/jamanetworkopen.2020.31851

25. Barnard AM, Willcocks RJ, Triplett WT, et al. MR biomarkers predict clinical function in Duchenne muscular dystrophy. *Neurology*. Mar 3 2020;94(9):e897-e909. doi:10.1212/wnl.0000000000009012

26. Raman SV, Hor KN, Mazur W, et al. Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. Feb 2015;14(2):153-61. doi:10.1016/s1474-4422(14)70318-7

27. Feingold B, Mahle WT, Auerbach S, et al. Management of Cardiac Involvement Associated With Neuromuscular Diseases: A Scientific Statement From the American Heart Association. *Circulation*. Sep 26 2017;136(13):e200-e231. doi:10.1161/cir.0000000000000526

28. Villa C, Auerbach SR, Bansal N, et al. Current Practices in Treating Cardiomyopathy and Heart Failure in Duchenne Muscular Dystrophy (DMD): Understanding Care Practices in Order to Optimize DMD Heart Failure Through ACTION. *Pediatr Cardiol*. Jun 2022;43(5):977-985. doi:10.1007/s00246-021-02807-7

29. Duboc D, Meune C, Lerebours G, Devaux JY, Vaksmann G, Bécane HM. Effect of perindopril on the onset and progression of left ventricular dysfunction in Duchenne muscular dystrophy. *J Am Coll Cardiol*. Mar 15 2005;45(6):855-7. doi:10.1016/j.jacc.2004.09.078

30. Duboc D, Meune C, Pierre B, et al. Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years' follow-up. *Am Heart J*. Sep 2007;154(3):596-602. doi:10.1016/j.ahj.2007.05.014

31. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol*. Apr 2018;17(4):347-361. doi:10.1016/s1474-4422(18)30025-5

32. Porcher R, Desguerre I, Amthor H, et al. Association between prophylactic angiotensin-converting enzyme inhibitors and overall survival in Duchenne muscular dystrophy-analysis of registry data. *Eur Heart J*. May 21 2021;42(20):1976-1984. doi:10.1093/eurheartj/ehab054

33. Silva MC, Magalhães TA, Meira ZM, et al. Myocardial Fibrosis Progression in Duchenne and Becker Muscular Dystrophy: A Randomized Clinical Trial. *JAMA Cardiol*. Feb 1 2017;2(2):190-199. doi:10.1001/jamacardio.2016.4801

34. Lamendola P, Lanza GA, Melita V, et al. Duchenne muscular dystrophy: preliminary experience with sacubitril-valsartan in patients with asymptomatic left ventricular dysfunction. *Eur Rev Med Pharmacol Sci*. Sep 2020;24(17):9112-9115. doi:10.26355/eurrev_202009_22857

35. Adorisio R, Calvieri C, Cantarutti N, et al. Heart rate reduction strategy using ivabradine in end-stage Duchenne cardiomyopathy. *Int J Cardiol*. Apr 1 2019;280:99-103. doi:10.1016/j.ijcard.2019.01.052

36. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med*. Mar 2022;28(3):568-574. doi:10.1038/s41591-021-01659-1

37. Ganesan AN, Gunton J, Nucifora G, McGavigan AD, Selvanayagam JB. Impact of Late Gadolinium Enhancement on mortality, sudden death and major adverse cardiovascular events in ischemic and nonischemic cardiomyopathy: A systematic review and meta-analysis. *Int J Cardiol*. Mar 1 2018;254:230-237. doi:10.1016/j.ijcard.2017.10.094

38. Gami AS, Olson EJ, Shen WK, et al. Obstructive sleep apnea and the risk of sudden cardiac death: a longitudinal study of 10,701 adults. *J Am Coll Cardiol*. Aug 13 2013;62(7):610-6. doi:10.1016/j.jacc.2013.04.080

39. McCulloch MA, Lal AK, Knecht K, et al. Implantable Cardioverter Defibrillator Use in Males with Duchenne Muscular Dystrophy and Severe Left Ventricular Dysfunction. *Pediatr Cardiol*. Jun 2020;41(5):925-931. doi:10.1007/s00246-020-02336-9

40. Fayssoil A, Lazarus A, Wahbi K, et al. Cardiac implantable electronic devices in tracheotomized muscular dystrophy patients: Safety and risks. *Int J Cardiol*. Nov 1 2016;222:975-977. doi:10.1016/j.ijcard.2016.08.040

41. Hiermeier UM, Baker C, Bourke JP. Exploring the acceptability of implantable defibrillators in patients with cardiac dystrophinopathy and carers. *Open Heart*. 2020;7(1):e001230. doi:10.1136/openhrt-2019-001230

42. Servais L, Camino E, Clement A, et al. First Regulatory Qualification of a Novel Digital Endpoint in Duchenne Muscular Dystrophy: A Multi-Stakeholder Perspective on the Impact for Patients and for Drug Development in Neuromuscular Diseases. *Digit Biomark*. May-Aug 2021;5(2):183-190. doi:10.1159/000517411

43. van der Geest A, Essers JMN, Bergsma A, Jansen M, de Groot IJM. Monitoring daily physical activity of upper extremity in young and adolescent boys with Duchenne muscular dystrophy: A pilot study. *Muscle Nerve*. Mar 2020;61(3):293-300. doi:10.1002/mus.26763

44. Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. *Lancet*. Jan 30 2016;387(10017):453-61. doi:10.1016/s0140-6736(15)00723-0

45. Nandi D, Auerbach SR, Bansal N, et al. Initial multicenter experience with ventricular assist devices in children and young adults with muscular dystrophy: An ACTION registry analysis. *J Heart Lung Transplant*. Sep 20 2022;doi:10.1016/j.healun.2022.09.003

46. Masat E, Pavani G, Mingozzi F. Humoral immunity to AAV vectors in gene therapy: challenges and potential solutions. *Discov Med*. Jun 2013;15(85):379-89.

47. Shin'Ichi T, Takashi O. Progress and Challenges in AAV-Mediated Gene Therapy for Duchenne Muscular Dystrophy. In: Ke X, ed. *Viral Gene Therapy*. IntechOpen; 2011:Ch. 11.

48. Mendell JR, Sahenk Z, Lehman K, et al. Assessment of Systemic Delivery of rAAVrh74.MHCK7.micro-dystrophin in Children With Duchenne Muscular Dystrophy: A Nonrandomized Controlled Trial. *JAMA Neurol*. Sep 1 2020;77(9):1122-1131. doi:10.1001/jamaneurol.2020.1484

49. Xu H, Van Remmen H. The SarcoEndoplasmic Reticulum Calcium ATPase (SERCA) pump: a potential target for intervention in aging and skeletal muscle pathologies. *Skelet Muscle*. Nov 12 2021;11(1):25. doi:10.1186/s13395-021-00280-7

50. Greenberg B, Butler J, Felker GM, et al. Calcium upregulation by percutaneous administration of gene therapy in patients with cardiac disease (CUPID 2): a randomised, multinational, double-blind, placebo-controlled, phase 2b trial. *Lancet*. Mar 19 2016;387(10024):1178-86. doi:10.1016/s0140-6736(16)00082-9

51. Bellinger AM, Reiken S, Carlson C, et al. Hypernitrosylated ryanodine receptor calcium release channels are leaky in dystrophic muscle. *Nat Med*. Mar 2009;15(3):325-30. doi:10.1038/nm.1916