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Current Standards and Future Directions of Duchenne Muscular Dystrophy Respiratory Care: The PPMD Italy Meeting Report

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ABSTRACT

Objective: This report summarizes key discussions from the meeting "Current Standards and Future Directions of Respiratory Assessment and Management of Duchenne Muscular Dystrophy (DMD)," organized by Parent Project Muscular Dystrophy (PPMD) Italy and the United States to address current challenges and opportunities in DMD respiratory care.

Methods: The meeting brought together researchers, clinicians, and patient advocates who shared experiences, discussed advancements in DMD respiratory management, and identified areas of debate that require further research.

Results: The speakers emphasized routine assessment of pulmonary function and of breathing during sleep to achieve timely diagnosis of respiratory complications. Therapeutic discussions focused on airway clearance and assisted ventilation, highlighting noninvasive ventilation (NIV) as the preferred modality, even for advanced respiratory failure. The respiratory implications of new pharmacological therapies were discussed. The speakers endorsed the importance of cardiorespiratory outcomes in assessments of drug efficacy. To assess a drug's clinical impact and to define current respiratory phenotypes, the

Abbreviations: AAV, Adeno-associated viral vector; ACT, airway clearance technique; AI, artificial intelligence; ARF, acute respiratory failure; CPF, cough peak flow; DMD, Duchenne muscular dystrophy; dSDB, diaphragmatic sleep disordered breathing; $EtCO_2$, exhaled end-tidal CO_2; FEV1, forced expiratory volume at 1 s; FVC, forced vital capacity; GC, glucocorticoid therapy; HDU, high dependency unit; HFNC, high-flow nasal cannula; ICU, intensive care unit; LVR, lung volume recruitment; MAC, manually assisted coughing; MIP, maximum inspiratory pressure; MI-E, mechanical insufflation-exsufflation; NH, nocturnal hypoventilation; NIV, noninvasive mechanical ventilation; OSA, obstructive sleep apnea; PPMD, parent project muscular dystrophy; RTI, respiratory tract infection; SNIP, sniff nasal inspiratory pressure; SpO2, oxyhemoglobin saturation measured by pulse oximetry; $tcPCO_2$, transcutaneous carbon dioxide; TV, tracheostomy ventilation.

For a complete list of the Members of PPMD Respiratory Group, see the Acknowledgments section.

trajectory of the absolute value of forced vital capacity (FVC) was proposed as a potentially better parameter than FVC percent predicted, which is favored in current drug studies. In regard to management of acute respiratory failure and perioperative situations, standards of care and areas needing future research were identified.

Conclusion: In this meeting, many points of consensus emerged, as well as areas requiring further research. The necessity to involve patients and their families in all aspects of respiratory care was emphasized, as well as the need for patient centered outcomes in medical decision making and research.

1 | Introduction

The meeting "Current Standards and Future Directions of Respiratory Assessment and Management of Duchenne Muscular Dystrophy (DMD)" was organized by the Parent Project Muscular Dystrophy Italy (PPMD aps) with the support of PPMD in the United States (PPMD US). The conference was held in Rome, Italy, on September 26–27, 2024. The panel consisted of an international group of 28 clinicians and researchers—14 adult pulmonologists, 7 pediatric pulmonologists, 3 anesthesiologists/intensivists, 3 pediatricians, and 1 pediatric neurologist— specialized in the management of pediatric and adult neuromuscular patients. The panel also included one respiratory therapist and four representatives from PPMD aps and PPMD US. The meeting reviewed current standards and the latest advancements in respiratory management for individuals with DMD.

This paper summarizes the key presentations and discussions that occurred during the meeting. The meeting was divided into the following topics: (i) routine respiratory diagnostics; (ii) chronic respiratory therapeutics; (iii) respiratory aspects of new DMD therapies; (iv) acute respiratory failure (ARF) and perioperative management. Closing remarks from the final session are summarized, including areas of agreement, as well as areas of debate that require additional research, and the perspective of patient advocates, representing individuals with DMD and their families.

2 | Routine Respiratory Diagnostics

Dr. Finder discussed the routine assessment of pulmonary function. Early detection of respiratory muscle weakness by routine pulmonary function testing can guide interventions and is recommended for all patients able to perform the testing [1, 2]. While pulmonary function testing is often used to assess disease control in asthma and cystic fibrosis, in individuals with DMD, it is a way of assessing the functional status of the respiratory muscles. Use of ulnar length to predict height was endorsed in nonambulatory individuals, but since steroid therapy can alter long bone growth, a modification of this equation is necessary [3].

Spirometry is the primary method used to measure lung function and is typically performed in children aged 6 years and older. It requires effort and cooperation and can be difficult to obtain if there is significant developmental delay or intellectual disability. Forced vital capacity (FVC) is the most studied spirometric parameter, as it reflects both inspiratory and expiratory muscle strength [1]. However, forced expiratory volume at 1 s (FEV1) tracks closely with FVC and can serve as an alternative, especially in less cooperative individuals, as it is based on just the first second of effort. Threshold reduced FVC levels can be used as a criterion for initiating noninvasive ventilation (NIV), as well as the need to perform a diagnostic sleep study, even in individuals who do not yet have symptoms of sleep-related hypoventilation.

Cough peak flow (CPF) measures the highest rate of flow that can be generated with cough. This is helpful to assess an individual's airway clearance capability, which is important for respiratory health and prevention of pneumonia. CPF can predict the need for manual or mechanically assisted coughing, and tracks with FVC [3, 4]. The use of mechanical insufflation-exsufflation (MI-E) is recommended before patients experience severe respiratory issues, with a cautionary note that some standard thresholds of CPF (i.e., 270 L/min) lack a strong evidence base. Ambulatory monitoring of exhaled CO_2 is a simple, inexpensive, and noninvasive tool that can be used to determine the need for daytime NIV. An individual with an awake, daytime CO_2 level over 45 mmHg should start daytime respiratory support. Sniff nasal pressure (SNIP) [5] and maximal inspiratory/expiratory pressures (MIP/MEP) are additional means of assessing respiratory muscle strength. MIP and MEP are subject to effort-related variability and require a cooperative patient; valid results can be used as criteria for starting MI-E. SNIP is an emerging assay of diaphragm strength and can be performed in patients as young as 3 years of age.

In the next talk, Dr. Crescimanno focused on sleep physiology and its impact on breathing in individuals with DMD. During sleep, there are significant changes in ventilation and breathing patterns due to reduced cortical input, chemoreceptor sensitivity, muscle contractility, lung function, and supine position [6]. REM sleep suppresses all respiratory muscles except the diaphragm, underscoring the importance of intact diaphragm function [7]. Both obstructive sleep apnea (OSA) and nocturnal hypoventilation (NH) are common in DMD [8]. OSA may be associated with increased body mass index (BMI), corticosteroid use, and anatomical factors like macroglossia. It is usually mild, but symptoms can mimic attention deficit hyperactivity disorder or autism.

Dr. Crescimanno distinguished between OSA and diaphragmatic sleep disordered breathing (dSDB), an entity with specific diagnostic criteria [9] (Figure 1). In dSDB, individuals may generate shallow breaths due to reduced muscle strength rather than upper airway obstruction—especially, but not exclusively, during REM sleep. Diaphragmatic events are diagnosed as either apnea or hypopnea via overnight cardiorespiratory polygraphy or polysomnography and are characterized by reduction in inspiratory effort compared with baseline.

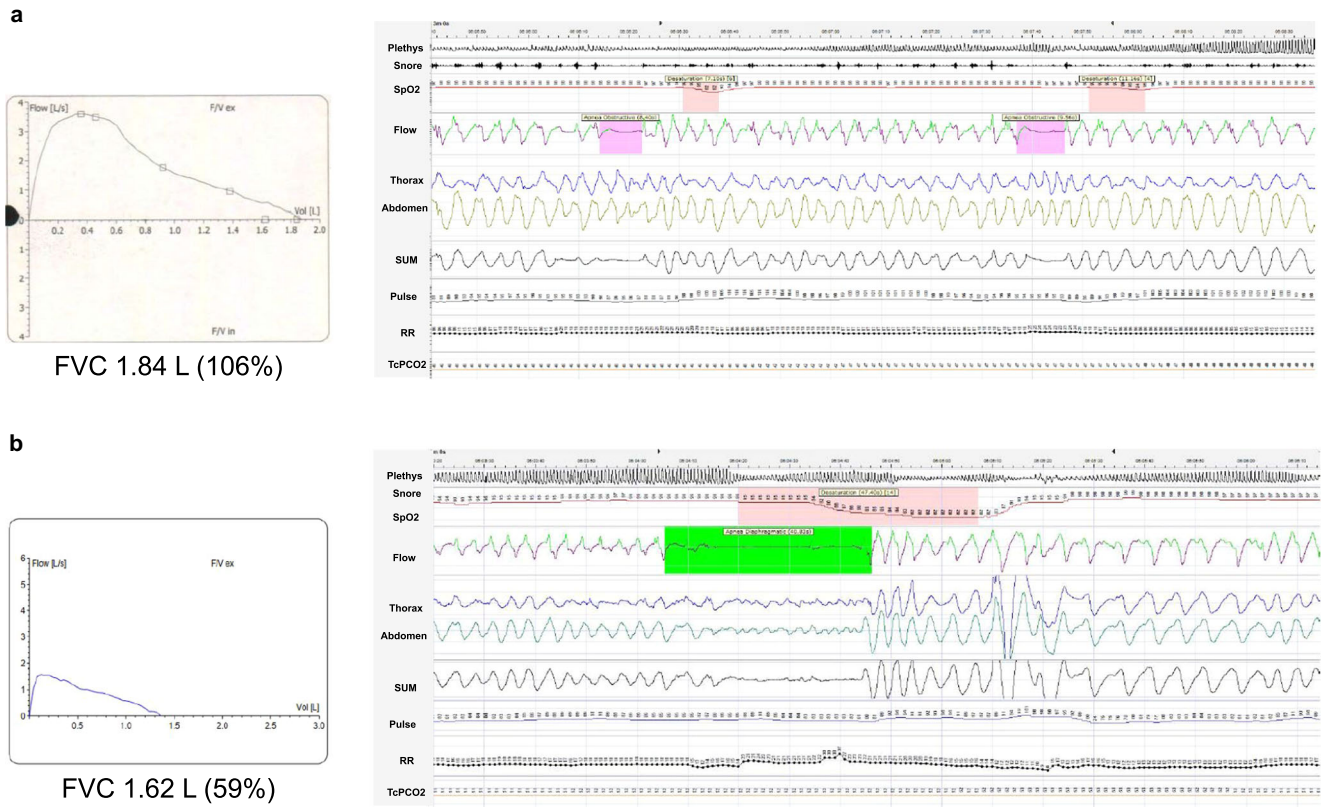

FIGURE 1 | Sleep disordered breathing across the clinical stages of disease progression in Duchenne muscular dystrophy (DMD). Upper panel (a) Example of a sleep event consistent with obstructive sleep apnea according to the American Academy of Sleep Medicine definition (AASM, Berry et al. [24]) in a 9-year-old boy with normal pulmonary function. The reduction of airflow lasts > 2 breaths and is associated with the presence of paradoxical breathing (out-of-synch thoracic and abdominal movements) without a reduction in the amplitude of either thoracic or abdominal traces and without an increased respiratory rate (RR). Lower panel (b) Example of a sleep event consistent with diaphragmatic apnea according to the newly defined scoring criteria for diaphragmatic events in DMD (Trucco et al. [9]) in a 17-year-old boy with restrictive lung disease. The reduction of airflow is associated with reduction in inspiratory effort throughout the entire duration of the event, increased RR and a relative reduction in thoracic versus abdominal effort. RR, respiratory rate; SUM, respiratory inductive plethysmography sum. [Color figure can be viewed at wileyonlinelibrary.com]

Dr. Crescimanno emphasized the importance of using overnight polysomnography and oxy-capnography (i.e., an overnight recording of oxygen saturations and transcutaneous carbon dioxide levels) to assess for sleep-related breathing disorders (i.e, OSA, dSDB, and NH), because their impact can be significant [8], including sleep disruption, weight loss, and failure to thrive. In terms of future research, evolving guidelines for diagnosing NH disorders using oxy-capnography were discussed, Diagnostic criteria customized for individuals with DMD are still needed as those criteria guide treatment decisions [10]. For example, in DMD, less strict criteria for NH (e.g., in comparison to the current standards of the American Academy of Sleep Medicine) may be more clinically relevant.

During the subsequent discussion, FVC thresholds that are commonly used to guide the timing of overnight sleep studies and respiratory interventions were reviewed. However, most participants agreed that FVC alone is inadequate and stressed the need for CO_2 monitoring to assess ventilation needs. During the session, several areas needing additional research were discussed. A debate arose regarding transcutaneous carbon dioxide ($tcPCO_2$) versus exhaled CO_2 ($EtCO_2$) for nocturnal monitoring, highlighting concerns about the accuracy and reliability of $EtCO_2$ measurements, particularly in patients who experience air leaks related to NIV therapy (during NIV, the higher the rate of air leak, the lower the accuracy of the $EtCO_2$ measurement). Dr. Trucco also noted that in Europe, capillary blood gas and $tcPCO_2$, rather than $EtCO_2$, are commonly used in outpatient settings to assess the need for daytime NIV. Finally, it was noted that dSDB requires additional investigation, as its onset likely precedes the development of NH, and dSBD might have a role in decision-making regarding initiation of NIV. If confirmed by prospective studies in an appropriately sized study group, the quantification of dSDB could be a useful respiratory outcome measure in clinical trials, particularly as a measure of respiratory function in nonambulant individuals with DMD and in those who have difficulty performing routine pulmonary function tests.

3 | Standards of Care for Chronic Respiratory Therapeutics

Dr. Chatwin presented a lecture focused on airway clearance techniques (ACTs), highlighting the need for early intervention and correct targeting of ACTs in managing the respiratory decline associated with DMD. Individuals with DMD

experience progressive respiratory muscle weakness, which leads to decreased lung volumes, ineffective cough, and sputum retention, making them vulnerable to lower respiratory tract infections (RTIs). Respiratory therapy can treat the consequences of respiratory muscle weakness. The first step is to improve lung volumes with lung volume recruitment (LVR) techniques. LVR has been shown to improve respiratory system compliance [11, 12]; however, long-term effects on hospitalizations and other outcomes are still areas of debate [13, 14]. The effectiveness of LVR may depend on consistent use and a learning curve [15]; the optimal time to initiate LVR remains unknown [2].

As the disease progresses, cough becomes less effective and ACTs are vital. ACTs can be categorized as peripheral ACTs, which mobilize secretions from the smaller airways to the central airways, and proximal ACTs that clear the central airways (cough augmentation) [16, 17]. Before commencing ACTs optimal hydration should be ensured. Proximal ACTs are initiated first, to compensate for ineffective coughing. However, as the disease progresses microaspiration and recurrent RTIs can cause atelectasis and require addition of peripheral ACTs, to mobilize secretions into the large airways, where they can be extracted with proximal techniques [18, 19].

Guidelines for DMD patients recommend early respiratory intervention [2, 20], including use of proximal ACTs when CPF is ≤ 270 L/min [2, 18, 21]. Proximal ACTs include inspiratory support with a resuscitation bag, ventilator or glossopharyngeal breathing and manually assisted coughing (MAC) [16, 17]. When these fail, MI-E devices are recommended [17]. However, in the later stages of DMD, individuals may experience upper airway closure [22] and re-evaluation of MI-E treatment is warranted. Guidelines support MI-E in acute care [20], increasing the frequency during RTIs or when oxygen saturation drops below 95% [18, 20]. Recent guidelines endorse flexible approaches, tailored to patient-specific needs.

The lecture by Dr. Amaddeo covered a range of topics related to long-term NIV in individuals with DMD, focused on initiation and monitoring of therapy, and areas requiring future research.

Although there are guidelines for starting NIV based on the results of sleep studies [2], there is no standardized, evidence-based definition of NH in children or adults that can be used for diagnosis and management [23]. Moreover, studies are lacking on the end-organ morbidity of chronic hypoventilation. Table 1 shows different definitions of NH currently in use [24–30]. While most neuromuscular specialists agree that the AASM definition of NH (> 25% of sleep time with a $PtcCO_2 > 50$ mmHg) may be too permissive, there is an ongoing debate regarding the best threshold values to use for the diagnosis of NH and initiation of NIV [23, 31, 32]. Dr. Amaddeo highlighted the need for proactive intervention, especially in cases of REM hypoventilation. He discussed the study of Ward et al. showing that when NH was defined by a transcutaneous level of CO_2 over 48 mmHg, it predicted the need for NIV within 2 years [27]. Dr. Amaddeo proposed that use of a low threshold to define NH (i.e., > 2% sleep time with a $PtcCO_2 > 50$ mmHg) could enable early detection of chronic respiratory insufficiency, and enable an anticipatory approach to clinical follow-up and NIV treatment.

TABLE 1 | Definitions of nocturnal hypercapnia and nocturnal hypoventilation in the literature.

Definitions	References
A percentage of sleep time with a $PtcCO_2 > 50$ mmHg > 25%	Berry et al. [24]
A percentage of sleep time with a $PtcCO_2 > 50$ mmHg > 2%	Amaddeo et al. [25]
A percentage of sleep time with a $PtcCO_2 > 50$ mmHg > 10%	Paiva et al. [26]
A $PtcCO_2 > 50$ mmHg > 5 min	Paiva et al. [26]
A $PtcCO_2 > 55$ mmHg > 10 min	Berry et al. [24]
A peak $PtcCO_2 > 49$ mmHg	Ward et al. [27]
A mean $PtcCO_2 > 50$ mmHg	Simonds [28]
A $PtcCO_2 > 10$ mmHg above waking baseline level	Berry et al. [24]
SpO2 < 90% for 2% of total sleep time	Hukins et al. [29]

Abbreviations: $PtcCO_2$, transcutaneous carbon dioxide pressure; SpO2, oxyhemoglobin saturation by pulse oximetry.

Dr. Amaddeo stated that individuals with DMD who are clinically stable should have NIV initiated in an outpatient setting, with provision of necessary home care and monitoring, stressing the need for adequate outpatient support [33]. In individuals with DMD, effective NIV can generally be achieved using a relatively narrow range of conventional device settings, with minor adjustments occurring with aging, such as reduction in the back-up respiratory rate [34].

Dr. Amaddeo touched upon the current state of telemonitoring platforms, stating that they lack detailed breath-by-breath analysis, which is a crucial for effective patient monitoring [35]. He spoke of the utility of built-in ventilator software to monitor patients remotely, combined with tools like home oxycapnography [36]. In Italy, there are many options for ventilators, allowing personalized care for each patient.

He also speculated on the future integration of artificial intelligence (AI) into NIV systems [37]. Dr. Amaddeo expressed concerns about the potential for AI to make autonomous decisions, such as changing ventilator settings autonomously. He emphasized the importance of human involvement and oversight. Dr. Amaddeo concluded with the idea that despite advancements in technology and AI, medical professionals must continue to play an active role in patient care. He raised thought-provoking questions about whether healthcare professionals will actively guide these changes or passively accept current trends, including those related to AI.

Dr. Vianello's lecture was on the topic of continuous NIV. Daytime ventilatory failure commonly occurs in individuals with DMD who are at an advanced stage of the disease. Specifically, the onset of diurnal hypoventilation and the need for daytime ventilatory support has been associated with a decline of FVC below 30% predicted, and a high risk of life-threatening RTI [38]. Diurnal CO_2 retention is related to reduced respiratory muscle competence in the setting of increased respiratory

muscle load due to microatelectasis, ribcage stiffness, and scoliosis [39]. In most cases, full-time NIV is begun when, despite nocturnal ventilation, symptoms of hypoventilation occur during wakefulness. Daytime NIV is then added to address those symptoms, often in the setting of abnormally high $PaCO_2$ levels [40]. According to current guidelines, full-time ventilation should be considered when VC drops below 20% predicted, diurnal $PaCO_2$ levels rise and/or clinical signs of respiratory muscle fatigue are detected [1]. Due to a lower risk of tracheobronchial infection and the possibility of maintaining the ability to speak, full-time NIV has potential advantages over tracheostomy-based ventilation (TV) [38]. However, successful NIV requires intact bulbar muscle function and the ability to cooperate with assisted coughing techniques. Under these conditions, NIV via a mouthpiece was found to reduce severe complications compared with TV [38]. Considering that most patients with DMD prefer a noninvasive treatment approach, NIV should be considered the default option in cases of full-time ventilator dependency. Of importance, several major complications can be associated to 24 h NIV use, including the risk of fatality due to equipment failure, and severe gastric or colonic distension [1]. Although there are conflicting findings on its impact on survival rate and quality of life, tracheostomy remains a viable option for individuals who fail full-time NIV [41].

During the subsequent discussion, participants emphasized the importance of standardizing the timing for initiating nocturnal NIV. Although this remains a debated issue, wider dissemination of institutional and regional practices could encourage uniform standards and enhance patient care. Some attendees debated the choice between full-time NIV and tracheostomy ventilation. Most participants favored NIV for its positive impact on speech and quality of life, while highlighting the importance of respecting patient preferences. All participants endorsed early identification of weak cough and implementation of ACTs.

4 | Respiratory Aspects of New DMD Therapies

Professor Mercuri's lecture focused on advancements and challenges in treating DMD. The overview initially focused on dystrophin restoration using DNA/RNA strategies, including Adeno-associated viral vectors (AAVs) gene therapy and antisense oligonucleotides. Gene Therapy focuses on delivering shortened versions of the dystrophin gene via AAVs [42, 43]. Exon skipping was also discussed, that is, the possibility to skip additional exons to convert out-of-frame mutations into in-frame mutations that can produce some functional dystrophin [44]. An overview of the different approaches and related trial results were critically discussed [43–45].

The results of first-generation of Oligonucleotides (ASOs) and early results from studies of the new generation of these drugs were also discussed. Data were also presented on Ataluren, which aims to restore functional dystrohin production by targeting premature stop codons. Despite positive long-term data, the renewal of the drug in Europe is under threat [45].

The review also included approaches based on drugs with nongenetic mechanisms of action, like Vamorolone, a new glucocorticoid which offers similar efficacy to traditional steroids but fewer adverse effects, like diminished bone health and delayed puberty; and Givinostat, a histone deacetylase inhibitor which showed statistically significant slowing of disease progression by reducing inflammation and fibrosis [46, 47].

Lastly, Professor Mercuri highlighted some lessons learned from previous trials, such as the need for longer study durations; and the need to combine short-term placebo-controlled studies with long-term observational studies, to assess key outcome measures like loss of ambulation, hand-to-mouth function, and ventilation requirements.

Next, Drs. Birnkrant and Katz examined potential problems in the regulatory pathway by which new DMD drugs are approved, with a focus on the outcome measures used to assess drug effectiveness. In DMD, patient survival is determined by cardiorespiratory function, and the most impactful clinical complications are cardiorespiratory in nature [2, 48]. They occur in older individuals, who are in the late nonambulatory stage of the disease. Thus, to be considered truly effective, a new DMD drug should show that it improves *cardiorespiratory function*. Instead, new DMD drugs can be approved through the Accelerated Regulatory pathway [49] based on small improvements in timed tests and muscle strength scales and on surrogate outcome measures, like tissue levels of nonbiologic dystrophin, without considering cardiorespiratory data. Moreover, these studies usually involve a young, ambulatory population, who essentially never experiences the cardiorespiratory complications that occur in the late nonambulatory stage of DMD [50–53].

Drs. Birnkrant and Katz also discussed the methodological limitations of studies that do include respiratory outcomes. One such outcome is a delay in reaching certain threshold pulmonary function values [45, 54]. For example, if a drug delays the decline of FVC to < 50% predicted, the level at which assisted ventilation is recommended by current guidelines. However, these thresholds have never been clinically validated; they were intended as a clinical strategy, not an outcome measure [2, 55]. For example, it has never been established that starting assisted ventilation right when FVC falls below 50% predicted mitigates morbidities or prolongs survival. Next, problems with historical controls were discussed. Historical control data are observational in nature. Therapies that impact cardiorespiratory function, including glucocorticoids, cardiac medications, and assisted ventilation, are not prescribed or administered in a standardized way, and become uncontrolled variables [56, 57].

Another methodological problem is that historical databases use statistical smoothing to report a single, constant rate of decline in FVC % predicted as their respiratory outcome measure. However, this single rate of decline is inaccurate. In fact, pulmonary function in DMD is heterogeneous, reflecting the progressive weakness that occurs with aging. As an example, respiratory data from the Canadian Neuromuscular Data Registry (CNDR) show that individual rates of decline in FVC % predicted are quite variable—variability that is masked by the single rate of decline reported by historical control databases (Figure 2a,b) [58–60]. With their uncontrolled variables and statistical smoothing, respiratory results from historical datasets vary widely; drug studies can select the most pessimistic results

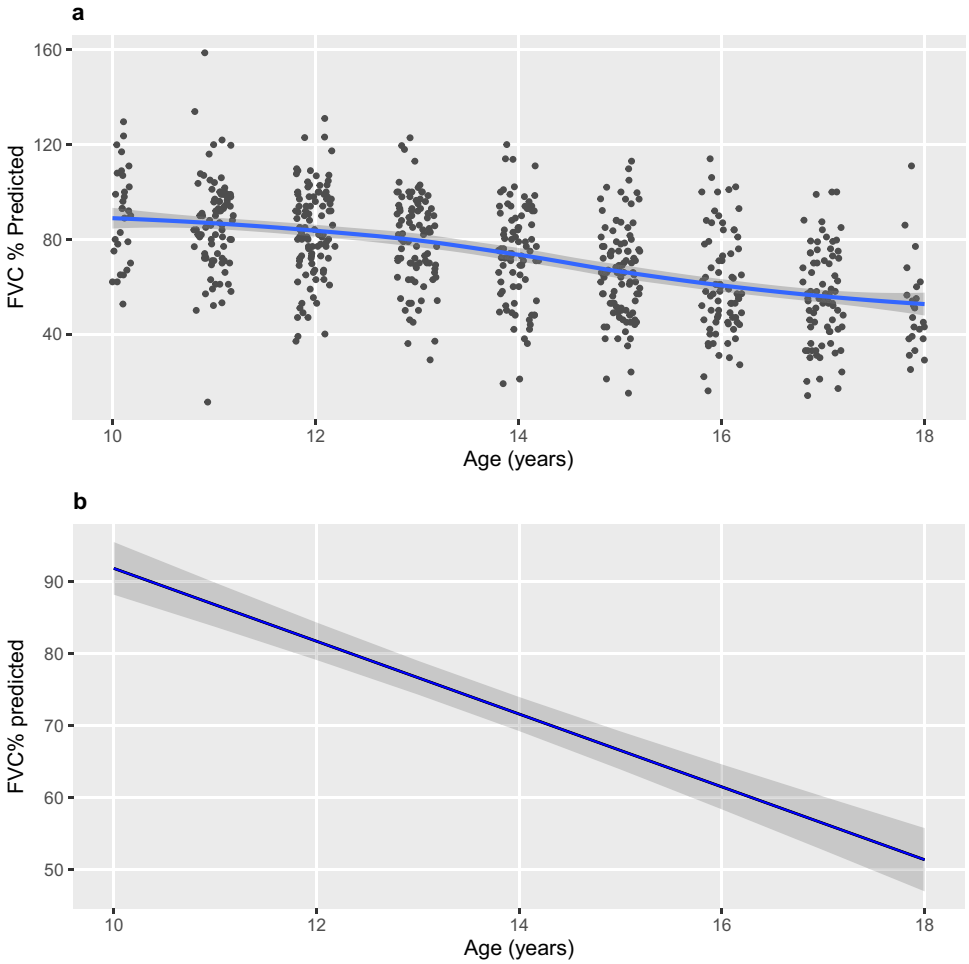

FIGURE 2 | Trajectory of forced vital capacity (FVC) of individuals in the Canadian Neuromuscular Disease Registry (CNDR), expressed as FVC percent predicted for each age. (a) Observed data with a superimposed LOESS smooth curve. (b) Fitted linear model using generalized estimating equations. In each panel, the grey band represents 95% confidence intervals. Reproduced with permission. From: Birnkrant, DJ, Black, JB, Sheehan, DW et al. A New Perspective on Drugs for Duchenne Muscular Dystrophy: Proposals for Better Respiratory Outcomes and Improved Regulatory Pathways. *Pediatr Drugs* (2024). https://doi.org/10.1007/s40272-024-00673-3. Under license CC BY-NC 4.0. https://creativecommons.org/licenses/by-nc/4.0/. [Color figure can be viewed at wileyonlinelibrary.com]

as their historical controls, making it easier to claim that a drug is effective [60].

Drs. Birnkrant and Sheehan discussed broader problems with FVC %predicted, the respiratory outcome measure used in current DMD drug studies. Pulmonary function in DMD can be thought of as the product of two competing forces: growth (which increases pulmonary function) versus progressive weakness (which impairs pulmonary function). The relative influence of these forces changes with aging. In the youngest individuals, the influence of growth predominates. As a result, ambulatory individuals are in the rising stage of pulmonary function. When the early nonambulatory stage begins, growth and weakness are in equilibrium, and pulmonary function enters the plateau stage. Finally, weakness predominates as individuals enter the late, nonambulatory stage of DMD, and pulmonary function begins its final decline (Figure 3) [60]. This heterogenous pattern of pulmonary function with aging is lost when pulmonary function is portrayed by FVC % predicted, which involves a single, constant rate of decline across the lifespan (Figure 4a,b) [59–61]. Those changes are more accurately portrayed using the *absolute value* of FVC over time (the "Rideau Plot"), *instead of FVC % predicted*, making Rideau Plots a potentially better respiratory outcome measure that deserves further study.

To illustrate, the speakers showed a "mock drug trial," assessing the respiratory effect of glucocorticoid therapy (GCs) [60, 62]. When portrayed with FVC % predicted, the improvement is barely noticeable—annual decline changes from −6.06%/year to −5.44%/year, a finding of uncertain clinical significance. In contrast, Rideau Plots show that GC-treated individuals retain favorable pulmonary function into their late teens, an age when the untreated individuals experience a rapid decline (Figure 5) [60]. Rideau Plots show that GCs allow FVC to remain higher for longer, exerting their benefits at the age when respiratory complications occur. It thus becomes apparent that GCs are likely to confer impactful clinical benefits, a conclusion that is obscured when the data are portrayed using FVC % predicted.

Drs. Birnkrant and Sheehan proposed various improvements in study methodologies involving the use of Rideau

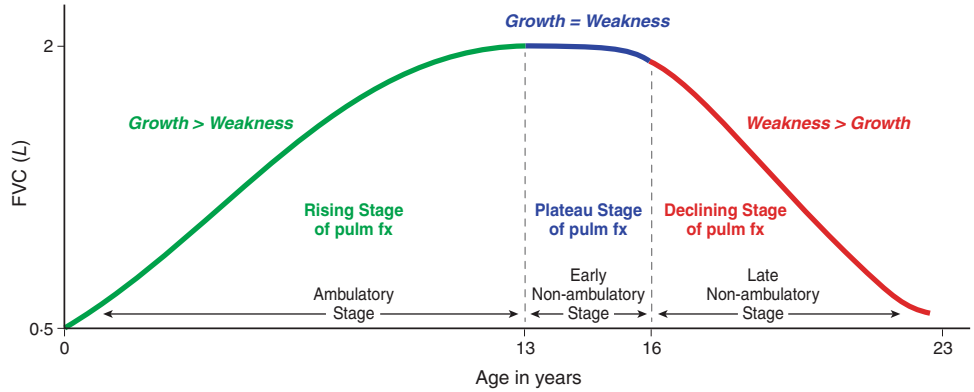

FIGURE 3 | Lung function modified by DMD portrayed with a Rideau Plot (Absolute value of forced vital capacity [FVC] by age), showing three stages of pulmonary function: rising (green), plateau (blue), and declining (red). Reproduced with permission. From: Birnkrant, DJ, Black, JB, Sheehan, DW et al. A New Perspective on Drugs for Duchenne Muscular Dystrophy: Proposals for Better Respiratory Outcomes and Improved Regulatory Pathways. *Pediatr Drugs* (2024). https://doi.org/10.1007/s40272-024-00673-3. Under license CC BY-NC 4.0. https://creativecommons.org/licenses/by-nc/4.0/. [Color figure can be viewed at wileyonlinelibrary.com]

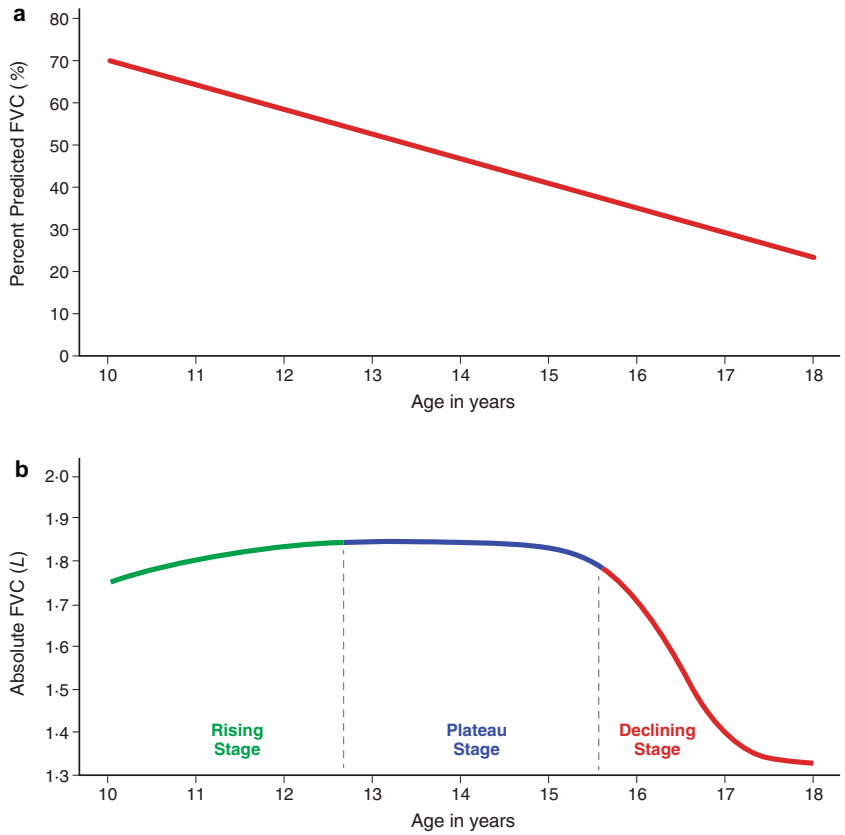

FIGURE 4 | Trajectory of forced vital capacity (FVC) among individuals 10–18 years of age expressed as (a) percent predicted, where the rate of decline is portrayed as constant throughout the age range, and (b) absolute values, where it can be seen that FVC changes with age and spans three stages of pulmonary function: rising (green), plateau (blue), and declining (red). Reproduced with permission. From: Birnkrant, DJ, Black, JB, Sheehan, DW et al. A New Perspective on Drugs for Duchenne Muscular Dystrophy: Proposals for Better Respiratory Outcomes and Improved Regulatory Pathways. *Pediatr Drugs* (2024). https://doi.org/10.1007/s40272-024-00673-3. Under license CC BY-NC 4.0. https://creativecommons.org/licenses/by-nc/4.0/. [Color figure can be viewed at wileyonlinelibrary.com]

Plots as the preferred respiratory outcome measure, in place of FVC % predicted [60]. For example, the speakers showed Rideau Plots from two brothers with identical dystrophin mutations and unexpectedly divergent respiratory function (Figure 6) [63]. If the brother with the beneficial phenotype had been treated with a new drug, one might conclude that the drug was effective; instead, his superior pulmonary function was due to a favorable respiratory phenotype. To define contemporary respiratory phenotypes, new natural history studies are needed that are done prospectively [60]. Key features of Rideau Plots, such as the level of peak FVC and the individual's age at its acquisition, could be used to

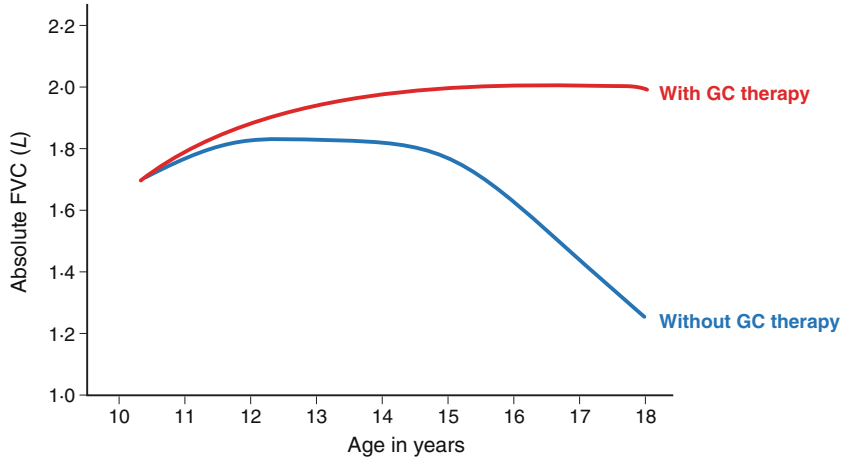

FIGURE 5 | Absolute forced vital capacity (FVC) in individuals 10–18 years of age, with glucocorticoid therapy (red) and without glucocorticoid therapy (blue). Reproduced with permission. From: Birnkrant, DJ, Black, JB, Sheehan, DW et al. A New Perspective on Drugs for Duchenne Muscular Dystrophy: Proposals for Better Respiratory Outcomes and Improved Regulatory Pathways. *Pediatr Drugs* (2024). https://doi.org/10.1007/s40272-024-00673-3. Under license CC BY-NC 4.0. https://creativecommons.org/licenses/by-nc/4.0/. [Color figure can be viewed at wileyonlinelibrary.com]

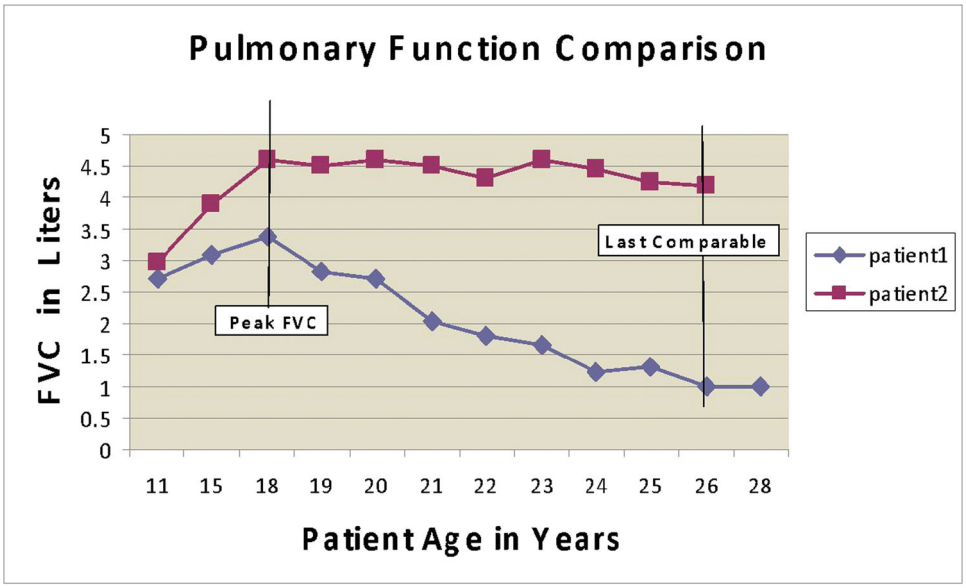

FIGURE 6 | Forced vital capacity (FVC) with aging in two brothers with discordant pulmonary function. Reproduced with permission. From: Birnkrant DJ, Ashwath ML, Nortiz GH, Merrill MC, Shah TA, Crowe CA, Bahler RC. Cardiac and pulmonary function variability in Duchenne muscular dystrophy: an initial report. J Child Neurol 2010; 25: 1110–1115. [Color figure can be viewed at wileyonlinelibrary.com]

group study subjects into phenotypically homogeneous cohorts.

A prospective study design would assure that the study population is treated with current standards of care, minimizing the effect of uncontrolled variables that can confound historical control databases, such as variable dosing of, and adherence to GC therapy; and variations in the therapeutic details of, and adherence to assisted ventilation [60].

Dr. Birnkrant then discussed why it is crucial to include cardiac outcomes in studies of drug effectiveness. Although cardiac function is a key determinant of survival, cardiac outcomes are currently undervalued. *Phenotypic discordance* is when cardiac function diverges from respiratory function in a single individual—as if the heart and lung were expressing "opposite phenotypes." Phenotypic discordance was illustrated by four individuals with identical dystrophin mutations [63]. Two of the individuals had unexpectedly good heart function despite unmeasurably low pulmonary function. Two of the individuals had the opposite type of discordance—unexpectedly poor heart function, despite adequate pulmonary function (Figure 7) [60, 63]. In one study, "Very Prolonged Survivors" of DMD (alive, at mean age 34.3 years) had "Good Heart/Bad Lung" discordance. Good heart function allowed them to achieve prolonged survival, with use of assisted ventilation to compensate for respiratory failure. By contrast, individuals experiencing "Early Death" (at a mean age of 21.7 years) had the opposite type of discordance—"Bad Heart/Good Lung." Their progressive heart failure was life-limiting, despite adequate pulmonary function. Overall, cardiac function was the

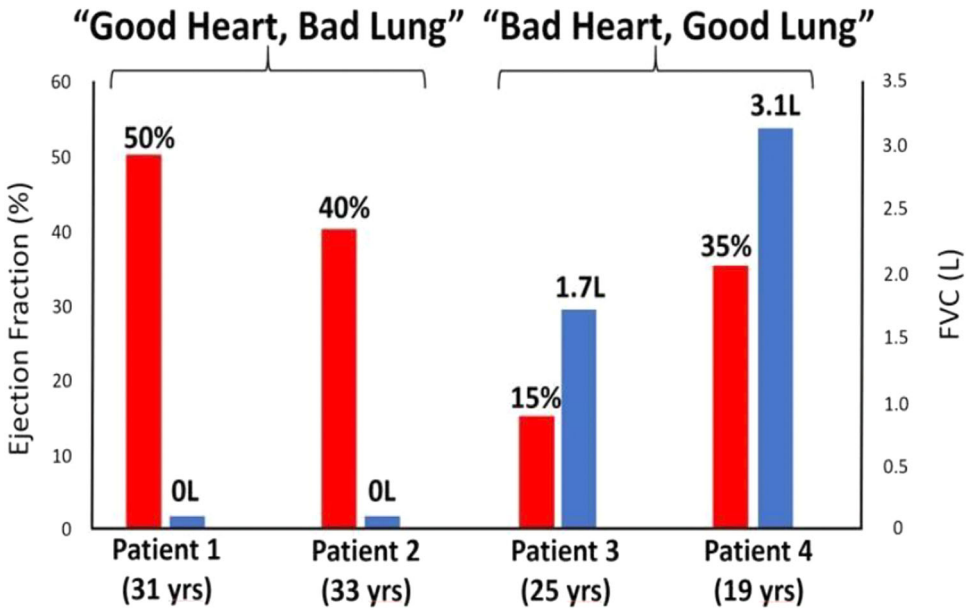

FIGURE 7 | Phenotypic discordance in patients with identical dystrophin mutations. Four patients with deletion of exon 44 show diametrically different profiles in heart and lung function despite an identical dystrophin genotype. EF, ejection fraction. FVC, forced vital capacity. Reproduced with permission. From: Jin JB, Carter JC, Sheehan DW, Birnkrant DJ. Cardiopulmonary discordance is common in Duchenne muscular dystrophy. Pediatr Pulmonol 2019; 54: 186–193. [Color figure can be viewed at wileyonlinelibrary.com]

main determinant of survival when individuals with DMD were treated with assisted ventilation (the current standard of care) [64].

In conclusion, the speakers suggested that new DMD drugs should show they can improve *cardiorespiratory function* to demonstrate their true effectiveness. The speakers presented proposals designed to improve study methodologies and outcome measures, and they endorsed prospective data acquisition instead of historical controls. Their proposals will require further study and validation.

During the subsequent discussion, participants focused on the need for longer studies, prospective data acquisition and better respiratory outcome measures. Professor Mercuri highlighted the idea that upper limb strength and prolongation of ambulation are key outcome measures in young individuals, and they may be more clinically relevant than cardiorespiratory function in that age group.

5 | Standards of Care for Perioperative Management and ARF

Dr. Racca discussed the fact that individuals with DMD are at high risk of intra- and postoperative complications such as ARF, upper airway obstruction, congestive heart failure and difficulty weaning from mechanical ventilation [65–67]. Anesthetic drugs can depress respiratory and cardiac function, which may already be compromised. Additionally, exaggerated sensitivity to sedatives and muscle relaxants can have prolonged postoperative effects. Finally, there is a risk of acute rhabdomyolysis when exposed to inhaled anesthetics or succinylcholine. Key recommendations for preoperative evaluation are summarized in Table 2. In particular, preoperative consultation with cardiologists and pulmonologists is critical [65–67]. Dr. Racca also discussed different anesthesia techniques. Regional anesthesia is preferred when possible, to minimize respiratory complications, but caution is needed for spinal anesthesia in cases of severe cardiac dysfunction [65–67]. If general anesthesia is necessary, a total intravenous anesthesia technique should be used, avoiding inhalational agents and succinylcholine [65, 68, 69]. Ultrashort-acting anesthetic drugs should be chosen when possible. Rocuronium is the nondepolarizing muscle relaxant of choice, because its effects can be reversed with sugammadex [65, 67]. The depth of anesthesia and neuromuscular function should be carefully monitored to adjust the drug dosage appropriately. Cardiovascular function requires close observation, particularly in patients with low ejection fractions (< 35%), as they are at increased risk of intraoperative hypotension and other cardiac complications.

After surgery, admission to an Intensive Care Unit (ICU) or to High Dependency Unit (HDU) should be considered in any patient who is at risk for respiratory or cardiac complications [65, 67]. Patients with significant respiratory muscle weakness should be extubated directly to NIV, using MI-E to assist in clearing bronchial secretions. The use of multimodal pain relief is essential to limit opioid use, especially in patients with reduced respiratory function.

The presentation by Dr. Trucco focused on the home management of ARF in individuals with DMD, highlighting the importance of anticipatory home care and personalized treatment to reduce hospital admissions and improve outcomes. RTIs are responsible for over 90% episodes of ARF [19]. The initial presentation can be subtle. Initially, increased respiratory secretions, changes in the level of consciousness, and dyspnea can all be mild, but the severity can quickly escalate [20, 70]. In adult patients with DMD, the risk of silent aspiration should be always considered [71].

TABLE 2 | Preoperative assessment and management [65–68].

RESPIRATORY MANAGEMENT
✓ Respiratory assessment allows to identify DMD patients with significant respiratory muscle weakness who require NIV and MI-E in the postoperative period to prevent postoperative pulmonary complications such as atelectasis, pneumonia, or extubation failure.
✓ Preoperative training and postoperative use of NIV are strongly recommended for patients with a baseline FVC of less than 50% predicted and are considered essential for those with an FVC of less than 30% predicted
✓ Preoperative training in and postoperative use of manual and mechanical assisted cough techniques are necessary for patients whose baseline PCF is < 270 L/min or whose baseline maximum expiratory pressure is < 60 cm water
✓ Obstructive sleep apnea should be ruled out
CARDIAC MANAGEMENT
✓ An echocardiogram and electrocardiogram should be performed close to the time of surgery.
✓ Consultations with cardiologists allows to optimize cardiac therapies before surgery
ASSESMENT FOR DIFFICULT AIRWAY MANAGEMENT
✓ Difficult airway management should be ruled out
PREVENTION OF ADRENAL CRISIS
✓ In case of long-term corticosteroid therapy, acute adrenal insufficiency may develop after surgical stress.
✓ It should be prevented by a supplemental hydrocortisone dose, based on degree of the surgical stress
DYSPHAGIA ASSESSMENT
✓ Signs and symptoms of swallowing difficulties such as choughing while eating or drinking should be be excluded, especially in the later stages of the disease.
OPTIMIZATION OF NUTRITIONAL STATUS
✓ Nutritional status should also be evaluated and optimized before surgery, because poor nutrition can increase postoperative morbidity, such as prolonged healing of the wound
✓ Optimization of preoperative nutritional status may involve the use of NIV because patients with untreated respiratory failure may become malnourished due to increased work of breathing, or they may be unable to eat due to dyspnea.
DISCUSS THE RISKS AND BENEFITS OF SURGICAL INTERVENTIONS AND ADVANCE DIRECTIVES
✓ The risks and benefits of surgical interventions and anesthesia should be discussed with the patient.
✓ Advanced directives, in particular their attitudes toward tracheostomy, should be considered. Decisions concerning these issues should be easily found in the medical records

Abbreviations: FVC, forced vital capacity; DMD, Duchenne muscular dystrophy; MI-E, mechanical insufflation-exsufflation; NIV, noninvasive mechanical ventilation; PCF, peak cough flow

It is recommended that all patients have access to pulse oximetry at home [20]. Oxygen levels should be measured regularly via pulse oximetry, with levels of SpO2 below 95% indicating the need for escalation of respiratory support and < 92% triggering potential hospital admission. The treatment of ARF should include early, empirical use of broad-spectrum antibiotics, especially when there are increased respiratory secretions or abnormal oxyhemoglobin saturations. For individuals already using NIV, adjustments should include increased time on NIV, and adjustments in the device settings, such as a higher inspiratory pressure and/or an increase in the back up rate of breathing.

Increased time on NIV can result in the development of pressure sores. As a precaution, two different masks should be alternated, and hydrocolloid patches should be applied to protect pressure points, such as the nasal bridge. ACTs such as MI-E should be applied frequently to prevent mucus plugging and atelectasis. In the home, oxygen can be administered by connecting it to the ventilator circuit, but should only be used briefly to support patients with hypoxia, such as before and after airway clearance treatments. Suggested criteria for hospital admission include a persistent decrease in oxyhemoglobin saturation below 92%, changes in mental status, dehydration, or lack of response to home management.

Dr. Trucco emphasized the role of nonrespiratory strategies that are preventative, particularly adherence to age-appropriate immunizations, and good dental hygiene. The benefits of a written emergency health care plan were discussed, and the need to train families and caregivers to recognize the early signs of RTI, so that timely therapy can be instituted. Finally, telemonitoring may be effective in improving the home management of respiratory exacerbations in individuals with DMD who are treated with assisted ventilation [72].

In his second talk, Dr. Racca discussed the hospital management of ARF in individuals with DMD. If home management fails, hospital admission is required [20, 67]. NIV is the first-line treatment, but potential contraindications such as severe dysphagia, reduced consciousness, and severe hypoxemia should be assessed [67, 73]. NIV alone may be insufficient if respiratory secretions are increased. In this case, combining NIV with MI-E can treat and prevent mucus plugging [74].

Patients should be treated in an ICU or HDU to assure continuous monitoring, adequate staffing and rapid physician availability. As MI-E could be used up to every 10 min, professional staffing can be augmented by suitably skilled home caregivers, so that MI-E is available on-demand [75].

Noninvasive strategies should not delay intubation. If NIV fails or is contraindicated, early intubation is crucial, especially in cases of severe hypoxemia. Given the risks associated with the difficult airway management intrinsic to DMD, emergency intubations should be avoided whenever possible [67, 73].

Another key factor is diagnosing the underlying cause of ARF, to implement targeted therapy. If clinical presentation is consistent with pulmonary edema, it is essential to consider congestive heart failure and fat embolism sydrome. Although rare, pneumothorax should always be ruled out, as it can become life-threatening [76]. In patients with scoliosis, chest CT or

ultrasound may be more reliable than plain chest radiographs, which can be difficult to interpret in cases of pneumothorax.

After recovery from an acute illness involving endotracheal intubation, extubation directly to NIV is critical to avoid re-intubation, with MI-E for mucus clearance [77]. Tracheotomy may be considered in patients with severe bulbar dysfunction or repeated extubation failures [77].

Safe management of acute respiratory situations depends on the skills of the local emergency care team, who may not have experience with DMD, due to its rarity. Additionally, emergency teams may hesitate to provide needed treatments due to misconceptions about life expectancy and quality of life, inappropriately limiting therapeutic interventions. This is why it is important for individuals with DMD to carry a pocket guide provided by their neuromuscular team, that includes individualized protocols for management of acute illness, for the benefit of emergency medical personnel [20, 78]. In 2020, an Italian Emergency Card for Individuals with DMD was produced by the Parent Project Italy (PPMD aps), and in April 2022 that document was improved based on a consensus conference [79].

The specialized care needed by individuals with DMD experiencing acute respiratory illness highlights the critical importance of establishing a network of ICUs and HDUs with knowledge regarding the treatment of individuals with neuromuscular disorders.

During the subsequent discussion, panelists emphasized that elective surgery should be performed in a hospital with appropriate experience in the management of DMD. When urgent surgical interventions must be performed in nonspecialized centers, it is crucial that current recommendations for anesthesia and perioperative management are implemented.

The discussion also emphasized the importance of anticipatory care to minimize the frequency and severity of acute clinical deteriorations, by training patients and families to intensify therapy with NIV and MI-E at home, early in the course of any respiratory illnesses. Dr. Trucco underscored the need to customize management guidelines for individuals treated chronically with NIV versus those in whom NIV is newly initiated with an acute illness. The need for standardized criteria for hospital admission and ICU management was also discussed.

In regard to the use of high-flow nasal cannula therapy (HFNC), Dr. Vianello described a pilot retrospective case series of nine patients with neuromuscular diseases intolerant to NIV who were admitted to an HDU for ARF [80]. HFNC was successfully provided during daytime hours and NIV at night. Dr. Vianello suggested that, whenever HFNC is provided to individuals with DMD, $PaCO_2$ levels need to be closely monitored. HFNC may have a role in treating NIV-intolerant individuals with ARF.

6 | Closing Remarks and Future Goals

During the final session of the meeting, a summary was created of the key points of consensus that emerged throughout the conference regarding standards of respiratory management of

TABLE 3 | Standards of care for respiratory management of patients with DMD.

RESPIRATORY DIAGNOSTICS
✓ Spirometry should be initiated when the patient is 5–6 years of age.
✓ Reduction of inspiratory muscle strength results in restrictive pulmonary impairment with a progressive decrease in FVC and development of sleep disordered breathing, including OSA, dSDB and NH.
✓ Serial monitoring of pulmonary function is critical for respiratory management.
✓ Indications for nocturnally assisted ventilation include the signs or symptoms of NH. However, some individuals remain asymptomatic despite the presence of hypoventilation
✓ NH should be considered when a patient have symptoms of sleep-related breathing dysfunction or when a patient's FVC is less than 50% predicted.
✓ Overnight polysomnography or cardiorespiratory polygraphy and transcutaneous carbon dioxide ($tcPCO_2$) measurements allow to recognize sleep-related breathing disorders (i.e, OSA, NH and dSDB)
✓ Proximal ACTs are recommended when cough peak flow (CPF) is ≤ 270
CHRONIC RESPIRATORY FAILURE
✓ DMD patients experience progressive respiratory muscle weakness. The involvement of expiratory muscles impairs the ability to clear airway secretions, inducing ineffective cough and sputum retention. The weakness of inspiratory muscles leads to decreased lung volumes and affects the ability to ventilate leading to alveolar hypoventilation and hypercapnia.
✓ At onset, ventilatory insufficiency may be only nocturnal. Daytime ventilatory failure commonly occurs at a far advanced stage of the disease
✓ LVR techniques improve lung volumes
✓ Nocturnal NIV and proximal ACTs (cough augmentation) improves patient outcomes.
✓ Stable DMD patients can be initiated on NIV in an outpatient setting
✓ Overnight cardiorespiratory polygraphy and oxy-capnography monitoring enable the evaluation of nocturnal NIV effectiveness, favoring outpatient assessment when feasible
✓ Day time ventilation is administered as a result of an empirical extension of nocturnal ventilation when diurnal $PaCO_2$ levels rise and/or clinical signs of respiratory muscle fatigue are detected.
✓ Full-time NIV should be considered the default treatment approach. TV may be necessary when full-time NIV fails, although it does not necessarily improve survival rates.
✓ Flexible approaches tailored to patient-specific needs should be always considered.
PERIOPERATIVE PERIOD
✓ Elective surgery should be conducted in a fully equipped hospital with experience in the management of

(Continues)

TABLE 3 | (Continued)

PERIOPERATIVE PERIOD
neuromuscular disorders. For urgent procedures performed in non-specialized centers, adherence to the updated recommendations is essential.
✓ Preoperative evaluations by cardiologists and pulmonologists are critical
✓ Difficult airway management should be always considered
✓ Acute adrenal insufficiency should be prevented with supplemental hydrocortisone if on long-term corticosteroids
✓ Regional anesthesia is preferred, when possible, with caution for spinal anesthesia in cases of severe cardiac dysfunction
✓ If required, total intravenous anesthesia should be used, avoiding inhalational agents and succinylcholine to prevent rhabdomyolysis.
✓ Ultrashort-acting anesthetic drugs should be preferred.
✓ Rocuronium should be used as a muscle relaxant, because it can be completely reversed with sugammadex
✓ NIV should be used after extubation and during deep sedation if the patient is at risk for respiratory complications. MI-E should be used in these patients to assist bronchial secretions clearance.
✓ After surgery, admission to an ICU or to HDU should be considered if the patient is at risk for respiratory or cardiac complications
✓ Multimodal pain relief should be administered to minimize opioid use, especially in patients with reduced respiratory function
ACUTE RESPIRATORY FAILURE
✓ A proactive immunization and good dental hygiene is crucial to prevent ARF
✓ RTIs cause over 90% of ARF episodes.
✓ Patients and families should be trained in using NIV, pulse oximetry and MI-E
✓ NIV is the first-line treatment for both home and hospital management; MI-E aids in clearing airway secretions.
✓ In the event of hospitalization, it is crucial to ensure the continuous presence of trained caregivers, enabling the use of MI-E at any time
✓ To prevent pressure sores two different masks should be alternated during NIV, and hydrocolloid patches should be used to protect the pressure points
✓ Oxygen should only be delivered via the ventilator, and $PaCO_2$ levels must be closely monitored
✓ In case of increased secretions, a broad-spectrum antibiotic should be administered early, especially if SaO2 < 95%
✓ Acute adrenal insufficiency should be prevented with supplemental hydrocortisone if on long-term corticosteroids
✓ Patients need to be placed in an ICU or HDU if home management fails
✓ Identifying the underlying cause of ARF is essential for targeted therapy

(Continues)

TABLE 3 | (Continued)

ACUTE RESPIRATORY FAILURE
✓ Although rare, pneumothorax should always be ruled out
✓ Difficult airway management should be always considered and emergent intubation should be avoided
✓ Continuous presence of relatives or trained caregivers should be allowed
✓ Extubation with preventive application of NIV and MI-E is critical to avoid reintubation

Abbreviations: ACT, airway clearance technique; AI, artificial intelligence; ARF, acute respiratory failure; CPF, cough peak flow; DMD, Duchenne muscular dystrophy; dSDB, diaphragmatic sleep disordered breathing; FVC, forced vital capacity; HDU, high dependency unit; ICU, intensive care unit; LVR, lung volume recruitment; MI-E, mechanical insufflation-exsufflation; NH, nocturnal hypoventilation; NIV, noninvasive mechanical ventilation; OSA, obstructive sleep apnea; PCF, peak cough flow; RTI, respiratory tract infection; $tcPCO_2$, transcutaneous carbon dioxide; TV, tracheostomy ventilation.

DMD patients. These points are listed in Table 3. Of note: they are a product of the meeting's discussions, and not a formal consensus methodology.

The meeting also raised many unanswered questions regarding the assessment and the management of individuals with DMD that are areas requiring further research. The answers to these questions were viewed as a "to-do list" for the DMD community. This list is shown in Table 4.

The necessity to apply a patient-centered perspective was explored in regard to both standards of care and questions needing further study. For example, centralization of care at DMD centers has great advantages, as it can assure a high standard of disease management. On the other hand, centralized care is not always possible. Two common, high stakes examples are when individuals with DMD experience acute respiratory illness, and present to their local emergency department; or, when individuals with DMD transition out of pediatric care and subsequently require admission to an adult ICU, where individuals with DMD are rarely encountered.

There was consensus on the need for further efforts to train emergency medical teams to deal effectively with the complications of DMD, and to create a network of ICUs to improve hospital management both during ARF and in the postoperative period. These are a few examples of how existing standards require further dissemination, to assure optimal care by the diverse group of clinicians who interact with individuals with DMD.

Another aspect of standards of care is the need for practicality in terms of their implementation. For example, chronic and acute management of respiratory complications has now been well-described in multiple consensus statements [1, 2, 71]. However, implementation of those standards must be patient-centric, to assure tolerability and adherence.

A patient perspective on drug development was discussed. This is a complex and important subject that requires open discussion and debate in the DMD community, involving the need to balance a strong desire for rapid availability of new treatment options with study methodologies and regulatory decisions that ensure the safety and effectiveness of the new drugs reaching individuals with DMD.

TABLE 4 | Community to-do list.

RESPIRATORY DIAGNOSTICS
✓ Modify the equation for predicting height using ulnar length in steroid-treated patients, as steroid use affects long bone growth.
✓ Investigate whether assessment of dSDB progression over time can serve as an early marker of disease progression, especially in non-ambulant patients.
✓ Establish formal consensus criteria for diagnosing nocturnal hypoventilation in DMD patients.
CHRONIC RESPIRATORY FAILURE
✓ Develop a formal consensus on the optimal timing for implementing lung volume recruitment techniques.
✓ Conduct studies to assess the efficacy of ventilators' built-in software for monitoring nocturnal NIV effectiveness at home.
✓ Explore the potential of AI-driven ventilators for future respiratory management.
RESPIRATORY ASPECTS OF NEW DMD THERAPIES
✓ Need for longer studies and better respiratory outcome measures.
✓ Combine short-term placebo-controlled trials with long-term observational studies assessing milestones (e.g., loss of ambulation, hand-to-mouth function, and ventilation needs).
✓ Use prospective data acquisition instead of relying on historical controls
✓ Consider to use absolute FVC values (Rideau Plots) rather than FVC % predicted to assess respiratory function
✓ Consider to apply Rideau Plots to group study participants into phenotypically homogeneous cohorts.
✓ Include respiratory and cardiac outcomes as part of drug effectiveness studies
ACUTE RESPIRATORY FAILURE AND PERIOPERATIVE PERIOD
✓ Develop formal consensus on the timing for training patients and families in the use of NIV and MI-E for ARF home management
✓ Establish formal criteria for hospital admission during ARF episodes
✓ Conduct clinical trials to evaluate the efficacy and safety of HFNC in exacerbated DMD patients
✓ Enhance training for emergency medical teams to effectively handle patients with DMD
✓ Promote the widespread adoption and use of emergency cards
✓ Create and expand a network of ICUs and HDUs specializing in neuromuscular disorder care

Abbreviations: AI, artificial intelligence; ARF, acute respiratory failure; DMD, Duchenne muscular dystrophy; dSDB, diaphragmatic sleep disordered breathing; FVC, forced vital capacity; HDU, high dependency unit; HFNC, high-flow nasal cannula; ICU, intensive care unit; LVR, lung volume recruitment; MI-E, mechanical insufflation-exsufflation; NH, nocturnal hypoventilation; NIV, noninvasive ventilation; OSA, obstructive sleep apnea; $tcPCO_2$, transcutaneous carbon dioxide.

Overall, some Key Points that emerged included the following:

1. Respiratory diagnostic and therapeutic approaches to DMD are well-established and they have helped to improve survival. However, there are still areas that require further research, including the most accurate way to diagnose and treat sleep disordered breathing.
2. Dissemination of respiratory guidelines to clinicians, and the fostering of patient adherence, are areas that require continued emphasis and creative solutions.
3. New drugs for DMD are emerging at an unprecedented rate. It is crucial to include cardiorespiratory outcomes in studies of their effectiveness and in their regulatory approval.
4. Guidelines for optimal perioperative management and treatment of ARF in individuals with DMD require wider dissemination, and further study.

Finally, some of the larger themes that emerged from this conference were: (1) the importance of maintaining respiratory function to mitigate the life-limiting complications of DMD and (2) the crucial need to include the patient perspective in clinical initiatives and research activities, so that the goals of patients and their families inform current and future care.

Author Contributions

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Conflicts of Interest

Federica Trucco reports participation in Scientific Advisory Boards for Roche UK and teaching initiatives for Biogen, Avexis, Roche, and BREAS. Michelle Chatwin discloses the fact that she works in a non-commercial role for Breas Medical as Head of Education and Research 3 days a week. Her participation was in her own time, and Breas Medical has had no input into any aspects of the workshop or manuscript. David J. Birnkrant reports a financial interest in granted (US patents 8,651,107; 8,844,530; 9,795,752; and 10,814,082, and related international patents) and pending patents for respiratory devices, licensed to Advanced Bio Machines PTE LTD (ABM Respiratory Care). The remaining authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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