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Treatment of a Broader Population of Patients With DMD

Announcer:
Welcome to CME on ReachMD. This activity titled, “Treatment of a Broader Population of Patients with DMD,” is provided by the France Foundation. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Proud:
Thank you for joining us today. Today, we're going to review expanding DMD treatment horizons and new evidence. I'm Crystal Proud, neuromuscular neurologist and director of Neurology at the Children's Hospital of the King's Daughters in Norfolk, Virginia.

Dr. Finanger:
My name is Erika Finanger. I'm a pediatric neurologist at Oregon Health and Sciences University in Portland, Oregon.

Dr. Proud:
Learning objectives include evaluating real-world case-based scenarios for patients with DMD to help determine therapeutic candidacy across the age spectrum, in addition to assessing the latest data from clinical studies with Duchenne treatments to help inform clinical decision-making, and describing best practices for ongoing monitoring of patients at various ages receiving treatment for Duchenne muscular dystrophy.

Duchenne muscular dystrophy is the result of a reduction or absence of dystrophin protein. Recall that dystrophin protein is usually transcribed and translated by the DMD gene, which is constructed of 79 exons. When there are mutations within any of these exons, it can lead to reduction in the dystrophin protein production and instability of the muscle structural membrane. This leads to progressive segmental necrosis and, over time, muscle degeneration. Unfortunately, DMD has been demonstrated to be a progressive neuromuscular disease, leading to the inability for patients to maintain ambulation as well as impacts on cardiac health and pulmonary health.

Our goal for the treatment of DMD is to individualize therapy to each patient. We can do this by attempting to intervene at various different ways along the pathophysiologic pathway. We know that DMD is the result of genetic mutations leading to absent dystrophin protein production. So could we perhaps intervene with genetic modifying therapies, things like exon skipping or gene transfer therapies? Absent dystrophin within the muscle leads to an inflammatory cascade. And can we intervene through corticosteroids and mechanisms to reduce this inflammatory response, perhaps by things like NF-kappa beta inhibition? Inflammation within the muscle progresses to involve muscle fiber injury and degeneration with difficulty upon regeneration, ultimately leading to fat and fibrotic tissue formation. Other approaches to treatment include things like HDAC inhibitors, antifibrotics, and the potential to improve biogenesis and further immunomodulate.

Here are the available therapeutic classes for the treatment of DMD, including gene transfer therapy, exon skipping therapies, glucocorticoids, as well as small molecule therapies.

We can see that there has been quite a pathway of approval from the FDA for treatments for the indication of Duchenne muscular

dystrophy, beginning in 2016 with the FDA approval of eteplirsen, which was designed to exon skip 51. In 2017, there was FDA approval of deflazacort, which is a corticosteroid to treat DMD. And then in 2019, there was an expanded indication reducing the age at minimum of being 2 years or older. In December of 2019, another exon skipping agent golodirsen was FDA approved. And in 2020, viltolarsen was approved for skipping exon 53 as well. In 2021, casimersen was approved to skip exon 45. And in June 2023, we had the first FDA approval for a gene transfer therapy, delandistrogene moxeparvovec. This was initially indicated for treatment of boys ages 4 and 5 years old, ultimately with expansion to boys ages 4 and over in August of 2024. And in the meantime, we had vamorolone approval in 2023, which was a corticosteroid treatment. In March of 2024, givinostat was approved as an HDAC inhibitor. And then in June of 2024, deflazacort transitioned to a generic option. Much progress has been made in the past 10 years for the treatment of DMD.

We have to consider each phase of DMD in considerations for potential treatment outcomes. In our younger patients who are still ambulatory, the goal of treatment from a motor perspective may be to prevent their progression of muscular weakness and perhaps even prevent or prolong their time to loss of ambulation. We hope to intervene from a neuromuscular restrictive lung mechanic perspective by perhaps avoiding the need for noninvasive ventilation. And then from a cardiac perspective, perhaps we could reduce that risk for progression to heart failure eventually later in life.

In our early nonambulatory patients, we're hoping to preserve arm function, including things like hand to mouth, perhaps avoiding the need or prolonging time until we need noninvasive ventilation for those patients, and then maintaining cardiac health over time.

For our later, older, nonambulatory patients we hope to be able to preserve activities of daily living and quality of life as much as possible by preserving hand function like hand to mouth and propelling independent mobility through use of a power chair, avoidance of or maintenance of their settings of their noninvasive ventilation, and then maintenance of their cardiac status as well.

There's much to consider when we prescribe or consider prescribing a DMD therapy for an individual patient, and here are some of those considerations. Are there biomarkers that could predict which patients might respond to the therapy? And how might we assess this for our individual patient? Do we prescribe approved therapies that are commercially available? Or do we enroll the patient in a clinical trial with the hopes of optimizing therapy that way and pursuing commercial options later? What combination therapies are safe for patients to receive? And is there an appropriate sequencing order where we would start with one therapy and then add on another? Could the patient tolerate the adverse events that are associated with the therapy that we're considering for treatment? And which product might be the best tolerated for a particular patient given the side effect profile. We have to consider each patient individually.

Let's discuss a patient, Ben. He is a 12-year-old male with a deletion in exon 44 who was diagnosed at age 6 when he presented with challenges going upstairs and his teachers noticed that he ran differently compared to his peers. He was started on deflazacort at daily dosing at the time of his diagnosis. He participated in a clinical trial for and then continued commercial dosing of an exon 45 skipping therapy.

We'll return to Ben's case in a moment, but first let's consider baseline patient assessments which may impact how we consider pursuing treatment for each individual patient. We first need to confirm a genetic mutation in the DMD gene. This will confirm a specific mutation that allows us to consider various therapies. We will consider performing functional assessments appropriate to the patient, such as looking at ambulatory status, upper limb function, and timed testing. It will be important to assess cardiac function with EKG, echocardiogram, and/or a cardiac MRI looking for cardiac fibrosis. Pulmonary function testing including the forced vital capacity will allow us to look for evidence of neuromuscular restrictive lung mechanics. And then laboratory testing may be appropriate given certain therapies that are being considered.

Patients and caregivers will also consider various components when selecting a DMD therapy after discussing options with their clinicians. Do they have access to that therapy? Is it financially viable for them to pursue this treatment? What are the long-term side effects? And if we don't know, how willing are they to pursue a treatment that has only several years of experience? Might there be variability in the response to treatment? And what are those components? And what biomarkers are there for us to assess response over time? What might the side effects be that they experience? And do they think that they might be able to tolerate those for the potential benefit? They have to consider the psychosocial impact of therapies as well, as well as the need for potential additional therapies even after selecting one. And over time they will still need to continue monitoring within a multidisciplinary setting.

There are various ways that we can assess motor function when it comes to treatment modalities. Here are a few that we conduct in some of our clinical scenarios, including the time to rise, which is what it sounds like, whereby a patient lies down on the floor and then assumes an upright posture during which time they are timed. The 10-meter walk is the time in which it takes for a person to ambulate 10 meters. And then the 4-stair climb assesses how long it takes an individual to ascend a standard set of 4 stairs. There are standardized values that have been utilized to assess where a boy is in his trajectory with Duchenne muscular dystrophy based on these timed motor function tests. These provide objective measures of ambulatory function and disease progression.

The North Star Ambulatory Assessment score is a standardized test comprised of 17 items which assess motor function. They go from least difficult including standing to most difficult including hopping. And each item is scored either as a 0 for being unable to perform, a 1 which is that the patient could perform it but with accommodations or difficulty, or 2 they were able to perform the task in a typical fashion. We know that based on natural history studies, Duchenne patients have an average peak score of 26 at 6.3 years of age, with an expected decline in function thereafter.

Let's return back to our discussion of Ben. We can keep in mind that he's 12 years and 4 months of age. He is ambulatory. He has a genetic confirmation of a deletion of exon 44 which makes him exon 45 skippable. He has been on daily deflazacort, an exon 45 skipping treatment since age 9. And here, we see his baseline laboratories, including that he is AAVrh74 antibody negative. He has an unremarkable baseline complete blood count. His transaminases are elevated, typical for a boy with Duchenne muscular dystrophy arising from muscle, and his GGT is normal at 17, indicating a baseline normal liver function. His CK is understandably elevated because of his muscular dystrophy at 7895, and his troponin I is normal at 0.03.

Let's discuss gene transfer therapy as a modality for treatment of DMD. The goal of gene therapy is to deliver a shortened microdystrophin transgene to permit protein expression within muscle cells, leading to improved integrity of the muscle membrane. Here, we see gene therapies under investigation currently. Of note, patients with detectable AAV titers were excluded from these clinical trials.

GNT0004 is being evaluated in patients ages 6 through 10 years old who are ambulatory and have mutations in exons 18 and above. This utilizes an AAV8 vector and a specific promoter to drive expression of the protein.

RGX-202 is being studied in patients ages 1 through 11 years old, including those with mutations in exon 18 and up who are also ambulatory. This uses a novel AAV8 vector and includes an exon encoding for Beta-spectrin.

SGT-003 is being evaluated in patients ages 4 to less than 12 years of age who are ambulatory, utilizing a novel vector, and this includes a neuronal nitric oxide synthase binding domain.

Delandistrogene moxeparvovec has been FDA approved for the treatment of patients 4 years of age and older. It utilizes an rhAAV74 vector and an MHCK7 promoter to drive expression.

Announcer:
Commercial and noncommercial dosing of nonambulatory patients have been paused until an enhanced immunosuppressive regimen is approved and available.

Dr. Proud:
Here, we see that in 2023, this was FDA approved for ambulatory individuals 4 through 5 years of age with a diagnosis of DMD. And then in 2024, the FDA expanded approval to include patients who were 4 years of age and older with a diagnosis of DMD. This is contraindicated to be administered to those with active infections and currently contraindicated in those who have mutations, including a deletion in exons 8 or 9. It is also contraindicated for patients who have elevated antibodies at baseline up greater than 1 to 400.

Delandistrogene moxeparvovec has been studied in several clinical trials, including the EMBARK study. This is an ongoing phase 3, multinational, double-blind, randomized, placebo-controlled study evaluating the safety and efficacy of delandistrogene moxeparvovec compared to placebo in boys with DMD ages 4 to 7 years of age; 125 boys were randomized to receive, in Part 1, either a single IV infusion of the treatment or a single IV infusion of placebo. And then after 52 weeks, these groups were swapped, such that those that received the active drug were given a single IV infusion of placebo, and those that received a single IV infusion of placebo during Part 1 received active product in Part 2. Outcome measures included the NSAA results, microdystrophin protein expression, and other functional motor assessments.

Here, we see 2-year data from the EMBARK clinical trial, whereby patients who received delandistrogene moxeparvovec in Part 1 were monitored regarding their motor function for 2 years. In the treatment group, after 2 years boys improved on their NSAA by 2.63 points, whereby an external control cohort declined by 0.25 points, and this difference was statistically significant. During the time to rise from the floor, the boys in the treatment group had a prolongation over 2 years of 0.65 seconds, whereby the patients in an external control cohort demonstrated a prolongation of this time by 2.71 seconds, and the difference between these 2 groups was statistically significant. In the 10-meter Walk-Run test, the boys who had received delandistrogene moxeparvovec in Part 1 decreased in the time it took them to ambulate 10 meters by 0.04 seconds. And in the external control cohort, these boys had a prolonged time by 1.32 seconds, and this difference was also statistically significant. In addition, at week 104, muscle MRI changes from baseline generally favored delandistrogene moxeparvovec over the week-52 placebo, despite some progression of muscle pathology.

Over time, Ben has been looking to further optimize his therapy and long-term outcomes, and he's considering other therapies. He's

considering gene transfer therapy, but his family is worried about the side effects. After consulting with his clinician about risk mitigation strategies, they decide to pursue gene transfer therapy. He hopes that gene transfer therapy will prolong his ability to walk and preserve lung and cardiac function.

There are several things to consider regarding pre-infusion preparation for Ben prior to gene transfer therapy. It was discussed with him the need to start additional prednisone a day before the infusion and continuing this treatment for at least 60 days, with the possibility that he might need to adjust dosing if adverse effects occur. In addition, there were plans explored for continuing corticosteroid options after treatment with gene transfer therapy.

At baseline, from a motor function perspective, Ben had a performance of upper limb score of 25, and the plan was to monitor this over time, looking for impacts of treatment. He has a goal of pursuing stability of his muscle strength or slowing decline over time. And it was reviewed that each person with Duchenne is an individual, and results will be individual to that person.

From a cardiac perspective, Ben had baseline assessments performed, including an EKG which showed normal sinus rhythm, an echocardiogram showed an ejection fraction of 62% which was normal, and he had a cardiac MRI demonstrating only a subtle small area of late gadolinium enhancement with normal function. He was maintained on eplerenone and enalapril. It was discussed that there are some potential cardiac risks associated with gene transfer therapy, and lab monitoring would be necessary. It was also reviewed that safety data showed no increased risk with delandistrogene moxeparvovec. It was emphasized that it was important to start at an appropriate cardiac baseline to optimize tolerability of systemic stressors.

Ben's baseline pulmonary status was evaluated through pulmonary function testing, which demonstrated an FVC of 98% and an FEV1 of 100%. Considerations for airway protection were reviewed as well, given the potential for nausea and vomiting and the goal of overall maintenance of lung health was reviewed.

From a GI and nutritional perspective, it was noted that Ben had a history of intermittent reflux. He weighed 42.5 kg, and it was discussed that he needed to have an option for intervention to address nausea and vomiting, as these were a risk with gene transfer therapy. These were the most common adverse effects noted in the clinical trial program. In addition, it was discussed that he could consider adding famotidine routinely versus just as needed if he had any GI upset. In addition to discussing each of his organ systems and how gene transfer therapy might need to be considered in light of these, he had baseline labs reviewed as well.

Here we see an outline of the experience with timing of adverse events in clinical trial as it pertains to gene transfer therapy. We can see that the most common adverse event is nausea and vomiting, which are most likely within the first week or two after treatment. In addition, there may be a risk for thrombocytopenia within the first week as well. Events of myocarditis were seen within the first 4 weeks, and liver events were demonstrated to occur at week 4 to week 8 most commonly. There were cases of immune-mediated myositis and rhabdomyolysis that ultimately led to exclusion of patients with deletions in exons 8 and 9 from being treated with this particular gene transfer therapy.

Ben pursued treatment with gene transfer therapy but did experience an infusion reaction. About 8 minutes into the infusion, he demonstrated flushing of his cheeks, a rash over his chest, abdomen, and some itching, coughing, and wheezing. He was given diphenhydramine 50 mg IV times 1, albuterol 5 mg inhaled times 1, and famotidine 10 mg by mouth times 1. His symptoms fortunately resolved shortly thereafter, and his infusion was restarted at a slower rate until it returned back to the goal rate, and the entirety of the infusion was completed.

Here are considerations for managing and monitoring strategies for gene therapy patients. It's important to monitor labs every week on a weekly basis for at least 3 months post-treatment, or at least until values become normal thereafter. Cardiac evaluations are important as well, including routine cardiac assessments such as EKGs and echocardiograms. These should be conducted sooner if symptoms of clinical concern arise.

Baseline pulmonary function testing should be pursued per standards of care and then following gene transfer therapy as well to assess the treatment impact.

Glucocorticoids should be administered for at least the first 60 days after treatment with gene transfer therapy. These can have their own side effects as well and require monitoring for things such as weight gain and hypertension. They may require a dosage adjustment based on adverse events that occur following gene transfer therapy. It's important to know that steroids should never be stopped abruptly as this would place the patient at risk for adrenal dysfunction and adrenal crisis.

After gene transfer therapy monitoring is complete, we can consider addition of other therapies like exon skipping or an HDAC inhibitor depending on the clinical scenario.

Dr. Finanger:

Thank you, Dr. Proud. Now we're going to transition to exon skipping therapies, which you recall our patient Ben was treated with prior to initiating gene transfer therapy.

So let's begin by reviewing how exon skipping works. Exon skipping therapies utilize antisense oligonucleotides which are targeted to a specific RNA sequence within the dystrophin transcript to include skipping specific exons during RNA splicing. This effectively restores a functional reading frame in the mRNA and allows for production of a modified but at least partially functional dystrophin protein. Here, we can see that with normal dystrophin mRNA, a fully functional dystrophin protein is produced. However, if the patient's DMD results from out-of-frame deletion exemplified here by exons 48 to 50 deletion, the resulting reading frame is disrupted, and we are unable to produce a functional dystrophin protein. With exon skipping therapies here on the bottom, we see that by excluding a specific exon, in this case exon 51, the reading frame is restored, and there is production of a shortened but partially functional dystrophin protein.

In the previous example, we used exon 51 skipping, but currently there are approved therapies for both exons 45 and 53. In addition, there are a number of additional exons under investigation and improved—what we're calling next-generation exon skipping therapies which use modified ASOs to promote muscle intake and uptake as well as improve efficacy, ideally with less frequent delivery and improved dystrophin protein production.

Here, we can see the four approved exon skipping therapies, again one for exon 51, two for exon 53, and one for exon 45 skipping.

While the percentage of dystrophin production listed here is quite low, generally from about 1 to 6%, we can see particularly for the first three drugs that there is evidence of an efficacy benefit even with these very low levels of dystrophin production.

Importantly, just to review, all four of the medications are delivered via IV or Port-A-Cath weekly, so there is a significant burden of care delivery for these current medications.

The first exon skipping therapy was approved in 2016. And overall, these medications have an excellent safety profile. Here, you can see a summary of the adverse events from clinical trials. Generally speaking, in my experience, they are exceptionally well tolerated. But I would like to bring your attention specifically to the risk for renal toxicity, for which we have regular laboratory monitoring, and I'll review that on the next slide, as well as the risk for hypersensitivity reactions. And of course, all patients should have a protocol in place for the potential occurrence of a hypersensitivity reaction.

So here, again we can review some of the strategies used for the potential side effects associated with exon skipping. I already mentioned the potential for kidney dysfunction, so serum cystatin C is typically monitored, as patients with Duchenne muscular dystrophy and other muscle conditions have a very low creatinine at baseline, and this is an unreliable measure for monitoring of dysfunction.

Again, here we see called out to the risk of hypersensitivity reactions as well as restrictions with regards to concurrent duplicative exon skipping agents. And then finally—we'll allude to this later—to combination therapy strategies. These exon skipping drugs have not been tried in combination, at least in a study, a controlled study setting with regards to other approved medications with the exception of steroids. I should call out they were certainly tested in patients treated with baseline corticosteroids, which we will review next.

So transitioning to corticosteroids. This is the disease therapy mechanism that we have used for the longest time, dating back to the 1990s. The mechanism of action here for corticosteroids, we can see called out on the left what we are calling standard of care glucocorticoids, which are prednisone or deflazacort. And we can see that, as we know for corticosteroids, there is typically both the desired effect, which in this case here is inhibition of the NF-kappa B pathway, as well partially some anti-inflammatory action, as well as the undesired additional effects which lead to the side effects known to be associated with this class of drugs.

On the right, we see the newly approved drug, vamorolone, which is an engineered steroid designed to primarily target the NF-kappa B pathway with inhibition of this pathway, with theoretically less effect on the other pathways known to be associated with corticosteroids.

Here, we can see data from the phase 3 placebo-controlled trial of vamorolone. On the top, you're seeing vamorolone efficacy compared to placebo. The darker purple lines indicate vamorolone at the recommended dose of 6 mg/kg per day. The lighter blue is a lower dose that was studied. And on the bottom, you see the placebo. These graphs clearly indicate the efficacy of vamorolone as compared to placebo. On the bottom, we are showing the comparison of vamorolone. Again, the dark purple being the approved dose of 6 mg/kg, and on the bottom prednisone at the recommended daily dosing.

Here, we're looking at height changes over the 48 weeks. Again placebo-controlled for 24 weeks, we can see that height was preserved in patients treated with vamorolone as compared to those treated with prednisone.

Here, comparing the two more standard of care medications or at least the ones we've been using longer, deflazacort and prednisone, this is a recent study showing that patients treated with deflazacort as compared to those treated with prednisone had a prolonged age

of ambulation extending the age by about 2.5 years in those treated with deflazacort as compared to those treated with prednisone.

As we all know, and I alluded to earlier, corticosteroids come with a range of known side effects and certainly this is something that we encounter with all of our patients. Here, we describe some of the monitoring strategies which we use to try to ameliorate or at least identify these known side effects. So first, we see growth and development issues. Again, I've already spoken briefly about the effect on linear growth in particular which is well known with deflazacort, and to a lesser extent seen with others, and perhaps not seen at all with vamorolone although this is yet to still be followed up.

Blood pressure, so cardiovascular risks as well as risks to the kidneys then from chronic high blood pressure. Metabolic health, again we're primarily focused on glucose here. That's something that's important. And important to remember that, though it's not listed here, we do think about adrenal insufficiency. So at this dose of steroids, steroids should never be stopped abruptly and families should be counseled as to the risk of adrenal insufficiency. Again, musculoskeletal health. Infection risk. I do not see this as a major problem in my clinic but of course that's always a risk when you are immunosuppressing patients. And then I can't overemphasize the risk of psychiatric and behavioral issues with this. Again, young boys exposed to large doses of corticosteroids and the difficulties that creates for them both in the school and the home setting. So important to really be aware of these and try whatever we can to ameliorate these issues. Sometimes that is changing a dosing schedule, perhaps reducing the dose, though we hate to do that because of loss of efficacy, hooking them up with appropriate psychological and social work resources as well.

Alright, we're going to move to our last category of disease-modifying therapies. This is HDAC inhibition. So we have a relatively newly approved drug givinostat, whose mechanism of action is HDAC inhibition. As neurologists, we're fairly familiar with this mechanism but in this specific case of Duchenne we see that givinostat leads to transcription of proteins, not dystrophin directly but other proteins related to muscle health. In particular, the proteins are thought to be related to muscle regeneration as well as reducing inflammation and scarring within the muscle.

Here we can see the data from a very well-designed phase 3 trial in which we see that patients treated with givinostat had improved functional outcomes as compared to those treated with placebo. Patients with givinostat maintained the ability to rise from the floor on average 2 years longer than those not treated. And as seen on the right, there was a benefit in other outcome measures such as the 4-stair climb, the age at loss of ambulation, and the ability to rise from the floor.

In addition, not pictured here but also studied in the study, we see that there is reduced scar tissue formation and fat infiltration as demonstrated by muscle MRI.

As with all medications, we know there are several known adverse effects associated with givinostat. On the left, you can see here the most commonly seen side effects and the anticipated or recommended monitoring based upon these. So platelets are known to fall after initiation of givinostat. And typically, this happens within the first 2 weeks after therapy so there is very close follow-up for the first couple months of therapy, particularly following platelet counts. In the studies, the platelets did not fall to a clinically significant level but it is important that we monitor that. And of course, as it is now within commercial use, we will get a better idea of in the general population if this trend is different.

I'm going to skip to the bottom. The other laboratory monitoring we typically do is for triglycerides, which again typically will increase within the first 2 to 4 weeks. And there are recommended parameters for monitoring for this.

Finally, I will address the moderate or severe diarrhea. I will say that for most patients—and certainly in the clinical trial—we did see a change in stools after initiation of therapy. Typically, this will stabilize and be tolerable but there are patients who have significant diarrhea which is very difficult to manage in a young man with Duchenne. We do recommend monitoring the EKG, particularly if the patient is exposed to any other QTc-prolonging agents. And there are other medications which may lead to changes in the blood levels, and so these need to be monitored based on their mechanism of which the OCT2 transporter is the substrate in particular that we are looking for.

So now that we've reviewed all of our treatments and we come back to our patient Ben. So after a gene transfer therapy, he did have some nausea and vomiting, prompting the initiation of ondansetron daily for 1 week. This vomiting was worse in the morning. His labs remained reassuring over the 12 weeks of stipulated monitoring. He did have some behavioral changes noted with his additional prednisone, not unsurprisingly, which resolved with discontinuation. And steroids were tapered per protocol. They should not be tapered prematurely even with the behavioral issues. But again, once we are able to taper based on the laboratory evaluation, generally the behavior which is exacerbated with the increased doses does resolve.

So now he has undergone gene transfer therapy, he's on daily deflazacort, and the family is interested in understanding where to go from here; if there’s additional options and how they should consider these options. So if we think about his options currently, he could

continue his daily deflazacort at his weight-appropriate dose. We could transition to a high-dose weekend regimen. This is really a twice-weekly regimen at a much higher dose where again they are treated only on those 2 days and the other 5 days they do not take a steroid. They could transition to vamorolone as an alternative corticosteroid. And they could think about other therapies. So recall that he was on exon skipping therapy prior to gene transfer therapy which could be continued or discontinued at this point. We could add givinostat as an additional agent with a totally separate mechanism of action. Or he could consider additional clinical trial opportunities as there continue to be more and more clinical trials within Duchenne which is encouraging.

Alright, so finally, here, we're going to just review the four therapeutic approach categories as we've discussed today. They are presented here in a little bit different order than we went through, but they are presented in the order of approval by the FDA.

You can see here the pros and cons for each, and I'm not going to read through them all, but I would emphasize that glucocorticoids, though they come with significant cons, are well known and are standard of care within Duchenne muscular dystrophy and, in my opinion, should be instituted for all patients.

Exon skipping therapies, again, the pros are that they are addressing specifically the underlying issue with dystrophin production. Cons, I would say, primarily resolve around the fact that they are IV dosed on a weekly basis currently, and that the protein production, dystrophin particularly, is quite low at this point. But as I mentioned, there are products under development for higher levels.

Gene transfer therapy, Dr. Proud covered extensively today. There are some exclusions for who can receive this therapy based on their specific mutation and/or their antibody positivity. And there are significant risks which were reviewed earlier in the presentation today. So patients should be chosen carefully and monitored very carefully afterwards.

And finally, we talked about HDAC inhibition therapy. This is a mechanism which is not directly addressing the underlying dystrophin but does come with known side effects that we have talked about here but is potentially available for all patients with Duchenne, which this and corticosteroids are the only two therapies that are truly available to everyone, regardless of their mutation.

So key takeaways for today: dystrophin restoration therapies can serve as a foundational treatment for patients with Duchenne muscular dystrophy to be built upon. Combining different therapies for Duchenne holds the potential to improve patient outcomes and reduce the overall disease burden by targeting multiple pathways associated with the disease spectrum.

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