MECP2 DUPLICATION SYNDROME

Patient-led Listening Session

April 3, 2025

Objectives and Goals

Our objectives were to educate the FDA on MECP2 Duplication Syndrome (MDS) by:

- Explaining the devastating impact of MECP2 Duplication Syndrome on the daily life of our community
- Highlighting the lack of any current FDA approved treatment for effective symptom management for the disorder
- Sharing families' preferences for research and treatments that lead to meaningful change for our children.

Overall, our goal was to provide better understanding of the syndrome, show the impact it has on daily life for children and their caregivers, and illustrate the need for treatments to address the unmet medical challenges of those diagnosed.

Introduction

by Aron Schmidt – Board President, MECP2 Duplication Foundation

Aron began the family portion of the session with introductory remarks:

On behalf of the MECP2 Duplication Syndrome community, thank you for taking the time and providing this opportunity. My name is Aron Schmidt, and I serve as the Board President for the MECP2 Duplication Foundation. My wife Amelia and I also have a wonderful child named Everett who was diagnosed with MECP2 Duplication Syndrome in 2018. As a patient advocate and a caregiver, we appreciate the investment of time the FDA is providing and look forward to working with you in the future.

Our objectives as we move through our agenda are to share the devastating impact of MECP2 Duplication Syndrome, or MDS, on the daily life of our community, highlight the lack of any current FDA-approved treatment for effective symptom management for the disorder, and to share families' preferences for research and treatments that lead to meaningful change for our children.

Our goal is to provide better understanding of the syndrome and to show the impact it has on daily life for children and their caregivers and to illustrate the need for treatments to address the unmet medical challenges of those diagnosed.

Today you will hear what it is like to walk through an MDS family's shoes. You will meet families who unconditionally love their MDS-affected child. You will hear how their child lights up their life. However, you will also hear a nagging, "what's next" that prevents families from finding happiness and joy. The story of an MDS patient is often one that is waiting until the onset of seizures, infection, and regression. The burden on patients and caregivers is immense. The MDS story is also one of incredible resilience and compassion. You will find that parents and caregivers are relentless in the support of MDS patients.

MDS has a small but robust global community made up of caregivers, patients, and researchers. This community is strengthened by virtual and in-person family conferences and forums in the US as well as abroad. Today we represent not only our community but have received letters of support from major domestic and international patient advocacy groups. Globally, we are committed to working together to improve the quality of life in our community.

Our most pressing need is the lack of FDA approved therapies and treatments for our community. It is so hard in our community to schedule just about anything as families are constantly tending to the unpredictable medical and "life" needs of an MDS patient. We have created videos for each of our families to ensure that you are able to hear their story. We have met with a diverse group of families that we feel confident will give you a full picture of MDS. Thank you to each of the families for sharing their story.

Disease Overview

by Davut Pehlivan, MD – Clinical Expert on MECP2 Duplication Syndrome

Davut gave a clinical overview and shared information about the disorder:

Hi, I'm Dr. Davut Pehlivan. I am an Assistant Professor of Pediatrics and Neurology at Baylor College of Medicine and the Director of the MECP2 Duplication Syndrome Clinic at Texas Children's Hospital. As a neurogeneticist, I have been working on MECP2 Duplication Syndrome (MDS) since 2008, focusing on both bench and clinical aspects. My conflicts of interest are listed on the next slide.

The MECP2 protein regulates thousands of genes in the DNA through methylation and is critical for the maintenance of the central nervous system. Both a deficiency and an excess of MECP2 can cause severe neurodevelopmental disorders. A lack of MECP2 causes Rett syndrome, while duplications of the Xq28 chromosomal region cause MECP2 Duplication Syndrome (MDS). MDS is a multisystem disorder characterized by severe to profound developmental delay/intellectual disability, drug-resistant seizures, recurrent respiratory infections, and gastrointestinal problems such as constipation, reflux, and feeding/chewing difficulties. Due to refractory seizures and respiratory infections, survival into the 20s to 30s is common. MDS is an ultra-rare disease with an estimated frequency of 1 in 150,000.

We previously conducted a burden and meaningfulness survey with support from the MECP2 Duplication Syndrome Foundation (Ak et al., Pediatr Neurol, 2022). Given the ultra-rarity of MDS, about 84% of families have difficulty finding medical professionals familiar with the condition. Since patients mostly die in their 20s to 30s, our study showed that 85% of caregivers feel moderate to severe anxiety about the progression of the disease. Regarding the impact of MDS on their lives, 85% reported that caring for an individual with MDS moderately to severely affects their social life. Similarly, caring for an MDS individual moderately to severely affects their job and personal aspirations, financial wellbeing, and personal health, ranging from 60-80%. Over 90% reported that it affects their mental health, with 85% feeling moderate to severe emotional exhaustion and 80% reporting moderate to severe anxiety.

Two independent studies (Peters et al., Am Journal of Med Genet, 2021, and Ak et al., Mol Genet Genomic Med, 2022) identified the most bothersome problems in MDS. Both studies showed that the following six symptoms/domains are the most troublesome for caregivers and patients: epilepsy, difficulty in gross motor skills, lack of communication, frequent and severe infections, difficulty in fine motor skills, and constipation.

We have developed a parental burden survey and a gastrointestinal health scale, which are at least partially validated. We are also in the process of developing a Clinical Global Impression Scale and an Observer Reported Communication Ability scale, which are commonly used tools for neurodevelopmental disorders.

Davut also recommended two papers as supplementary materials:

Ak, M., Suter, B., Akturk, Z., Harris, H., Bowyer, K., Mignon, L., Pasupuleti, S., Glaze, D. G., & Pehlivan, D. (2022). Exploring the characteristics and most bothersome symptoms in MECP2 duplication syndrome to pave the path toward developing parent-oriented outcome measures. Molecular Genetics & Genomic Medicine, 10, e1989. https://doi.org/10.1002/mgg3.1989

Ak, M., Akturk, Z., Bowyer, K., Mignon, L., Pasupuleti, S., Glaze, D. G., Suter, B., & Pehlivan, D. (2022). Assessing the burden on caregivers of MECP2 duplication syndrome. Pediatric Neurology, Volume 133, 1-8, https://doi.org/10.1016/j.pediatrneurol.2022.05.008

Summary of Family Perspectives

Seven parents of children diagnosed with MECP2 Duplication Syndrome shared their lived experiences in the listening session. Each family's story is summarized and anonymized:

JOANN | mother of the first child diagnosed with MDS in the U.S.
My son was the first child diagnosed with MECP2 Duplication Syndrome, a disease which left a painful legacy of the disease in my family as it also claimed the lives of three brothers and a nephew. My child lived until age 20, enduring years of worsening symptoms including developmental delays, loss of motor and cognitive functions, uncontrollable seizures, and respiratory failure. Despite intensive therapies and treatments, including multiple seizure medications, a G-tube, breathing support, and homebound education, MDS progressively stole his abilities and quality of life. I did everything I could and would have done anything—any research, any risk—to ease his suffering. Now I am advocating for other families. We need broader access for more children to participate in clinical trials and faster processes for drug approval to manage symptoms or even cure this disease. I urge the FDA to take action to change the devastating outcomes of this syndrome and give families like mine more time with their children.

MAKENZIE | mother of two sons with MDS
Our journey with MECP2 Duplication Syndrome began at birth for each of our sons as both began life with severe medical issues requiring extensive hospitalizations, specialist care, and genetic testing that ultimately revealed MDS. In addition to MDS, my children live with multiple concurrent diagnoses, including severe intellectual disability, epilepsy, chronic lung disease, autism, and extreme behavioral and cognitive challenges. They require constant supervision and an incredible amount of medical equipment, therapies, and physical assistance for all basic needs. Both boys are non-verbal, making it difficult to understand or respond to their medical distress. Seizures can be frequent, violent, and life-threatening, requiring emergency intervention. MDS brings on fear and exhaustion as we witness our sons regress and suffer. Despite all of this, we are devoted parents with hope for a different future with fewer symptoms and less heartbreak. We implore the FDA to fast-track research, include more patients in clinical trials, and expand access to experimental treatments. We want more choices to help our kids and offer a better future for every child facing this disease.

BETHANY | mother of twin sons with MDS
With identical twins who are both affected by MECP2 Duplication Syndrome, parenting is a full-time job requiring around-the-clock care, coordination with over 20 specialists, a house full of medical equipment, and multiple home nursing agencies. Despite sharing a diagnosis, the twins' symptoms and progression differ significantly, with each boy alternating between respiratory and gastrointestinal complications, frequent seizures, and increasing physical decline. Illness intensifies their seizures, disrupts multiple body systems, and often results in hospitalizations. I am eager for treatments that could profoundly enhance my boys' quality of life by reducing seizures, preventing gastrointestinal issues, and improving mobility.

SUMMARY OF FAMILY PERSPECTIVES CONTINUED

More research, increased access to clinical trials, and approval of new treatments—whether they address symptoms or cure the disease—would bring real, meaningful relief to my children and others with MDS.

LAURA | mother of one son with MDS

Our family's multi-generational journey with MECP2 Duplication Syndrome began with my brother Billy—whose severe disabilities and early death deeply impacted my childhood—and continues with my son Lance, who was diagnosed about 15 years ago. As a family, we have faced overwhelming challenges, made more complex by our life as an active-duty military household, which meant constant relocations and limited access to specialized care. As our son's condition progressively worsened, he developed seizures, lost mobility, and became fully dependent on continuous medical support. Along with repeated hospitalizations, the emotional and financial toll of caregiving has been high, but we fight to give our son a meaningful life. We want more for him and every kid with MDS. We urge the FDA to prioritize research, expand clinical trial access, create compassionate-use pathways, approve treatments that can give families hope, and better support military families caring for children with rare diseases. Our plea is for urgent action to improve the lives of those affected by MECP2 Duplication Syndrome.

DANIELLE | mother of one son with MDS

I finally learned that my son has MECP2 Duplication Syndrome after years of misdiagnosis. This rare, debilitating genetic disorder causes developmental delays, epilepsy, respiratory and gastrointestinal complications, hypotonia, and feeding difficulties—all requiring constant, complex medical care and 24/7 supervision. Despite joyful moments, daily life is consumed by managing an exhaustive regimen of therapies, equipment, and medications. Without treatment, the progression of MECP2 Duplication Syndrome means that seizures and respiratory infections will eventually take my son's life. The risks of participating in research are worth any potential benefit because I am deeply concerned for my child's future. We need action now so we have treatment options to help our kids. I call on the FDA to fast-track drug development and approval, expand access to clinical trials and experimental treatments, include broader patient representation, and incorporate caregiver perspectives into regulatory decisions. Children like my son deserve more than survival; they deserve the chance to thrive.

JUCEL | mother of one son with MDS

Our son was born seemingly healthy, but he soon began experiencing severe respiratory issues and developmental delays, ultimately leading to a diagnosis of MECP2 Duplication Syndrome—a rare, life-limiting genetic disorder. Our son now requires intensive daily care, including feeding through a G-tube, respiratory therapy, and physical support, while facing frequent hospitalizations from common illnesses that escalate quickly into serious complications. Despite his joyful spirit, our child's future is uncertain, with risks of seizures and a reduced life expectancy. We are deeply committed to his care and participating in research. The risks of a trial far outweigh the devastation brought by this disease. We urgently call on the FDA to accelerate treatment development and access to experimental therapies, as time is critical to saving our child's life and changing the course of this devastating disease.

AMY | mother of one daughter with MDS & CureMDS advocacy group representative

Our youngest daughter was born after a typical pregnancy but immediately faced life-threatening health issues, which led to a MECP2 Duplication Syndrome diagnosis. Her life has since been filled with incredible medical challenges—chronic lung disease, frequent pneumonias, multiple cardiac arrests, epilepsy, and a 217-day hospital stay, including ECMO and intubation. She cannot walk, talk, eat by mouth, or breathe independently, requiring 24/7 care through a trach, G-tube, ventilator, and extensive medications. Her condition dictates every aspect of our family's life, and the toll on her quality of life and that of our family—especially her older sister—is profound. Once playful and mischievous, our daughter with MECP2 is now withdrawn due to the progression of her disease and side effects of seizure medications. I am asking the FDA to prioritize MECP2 research and give us more options. We

want the choice to try any possible treatments, including those still deemed experimental, because they can make a big difference for children like mine. Changes that seem small to researchers are huge for parents like me. We want inclusive clinical trials that include girls. The risks are worth it because I have nothing to lose...but my daughter's life.

Session Summary

by Katie Wester-Neal, PhD – Board Member, MECP2 Duplication Foundation

After all seven family representatives shared their stories of living with MECP2 Duplication Syndrome, Katie summarized the meeting with the following comments:

Hello, I'm Katie Wester-Neal—mom to Charlie, a 9-year-old with MECP2 Duplication Syndrome. As you have heard from families and a clinical expert, MECP2 (for short) is a rare disorder with overwhelming consequences for children and their families.

Affecting all aspects of daily life, you have heard how this unrelenting disorder includes severe developmental delays. Children with MECP2 often rely on feeding tubes and various medical devices just to survive. Seizures, respiratory issues, and gastrointestinal complications are common, leading to frequent medical intervention, intensive monitoring, and a limited life expectancy.

I echo the parents you've already heard from. Our diagnosis journey and accessing ongoing care for Charlie has been confusing because not enough is known about this disease. Beyond the terrible neurological issues, Charlie faces challenges with many of the systems throughout his body.

For a handful of years post-diagnosis, we—like many families—lived in fear of seizure onset, which is sometimes called "the beginning of the end" in the MECP2 community. Seizures started for Charlie at age 6. In the three years since then, his skills have regressed significantly. We have watched as this disease takes and takes and takes from him. One day, we know he will have nothing left to give.

Our children are generally non-verbal, adding to the challenge of understanding and meeting their needs. Charlie, for example, has never spoken a word. As other parents have described, we have to guess at his needs and do our best to understand him—and the uncertainty of it all weighs heavily on us.

MECP2 Duplication Syndrome exacts an immense physical, emotional, and financial toll. Compounding these difficulties is the knowledge that there is little help currently available in the form of medications or devices to ameliorate symptoms or change the course of the disease itself. The makeshift symptom management we have today is NOT enough—and more effective options are urgently needed.

Families in our community have repeatedly expressed their willingness to participate in clinical trials—even when considering the risks involved—in hopes of finding treatments that could change the progression of the disease or improve quality of life. We parents know what happens without any treatment—and now you've seen it too. We call on the FDA to help our community in three key ways:

1 **First, accelerate drug development and clinical trial processes.** We are asking for faster approval pathways for potential research studies and treatments. The first patient was diagnosed about 25 years ago. Since then, researchers and families have banded together to make trials a current reality. Decisive action is also needed from the FDA because MECP2 is such a devastating disease.

2 **Second, expand access to trials and experimental treatments.** We encourage the FDA to give families more opportunities because the risks of trial are less than the risks of disease progression. We want trials to have more participants, be opened up to boys and girls with the disease and include a broader range of kids all along the spectrum of disease severity. Families want a chance to try potential treatments in trials and through expanded access or compassionate use programs.

3 **Third, the desire for approved treatments is immense.** Families need options to help their children. Of course we want a cure, but you've also heard so much from families about the importance of symptom reduction.

You've learned about the ground-breaking work toward disease-specific outcome measures—but we acknowledge that these and other clinical trial endpoints don't always capture just how much small, incremental improvements make a huge difference in our kids' daily lives. We know that change can look small in terms of data, but the magnitude of numerical difference isn't always the best indicator of meaningful change in our kids' symptoms. We are asking for recognition that doing any possible good for our kids is much more important to us than perfection when considering new drug applications.

As parents, we want the power to decide if a treatment could work for us. We know our children best, and we want to work with our children's doctors to decide what might increase quality of life. Seemingly small improvements can make a big difference in our lives. We urge you to consider decision-making that reflects this reality, so families have the choice to decide what meaningful change looks like for them.

The difficult times are far too easy to come by with MECP2. We want more good days—because like all the families shared in their stories today, our kids light up our lives.

With your help, we have hope for new breakthroughs. We are enthusiastic about continuing to develop our ongoing relationship with you and looking forward to a better future. We appreciate your time today. Thank you for meeting with us!

Q&A Session

by Aron Schmidt – Board President, MECP2 Duplication Foundation

Aron led the question-and-answer session. He began by asking two moderated questions, which were answered by Amy and Laura:

1 **Outside of a complete cure, what does a successful treatment look like?**

Amy: If we were not able to receive a cure for my daughter, I would wish first for a reduction in the severity and quantity of seizures she has. She is taking four different anti-seizure medications, and they all profoundly limit her ability to move and to focus. She no longer reaches for anything and shows very few signs of happiness or pleasure anymore. Without the medications, she would be seizing constantly.

Secondly, I would wish to improve my daughter's respiratory condition by decannulating her from the trach. She cannot talk or eat by mouth like she used to. She also requires 24/7 care with the trach, so we have sacrificed our jobs and sleep and have nurses in our home most days and nights. She cannot attend school without a nurse either because of the trach. With the current shortage of private duty nurses, she is often forced to miss school which is where she receives most of her therapies.

Laura: For us as a family, a successful outcome would be for Lance to enjoy life and smile again. He should be able to look into our eyes with his head held high, using his own strength. I would love for there to be a complete end to his seizures or a significant reduction, allowing him to communicate with us using his voice. I want him to enjoy eating by mouth once more and to stand and walk wherever his heart desires. I know he would be thrilled not to wear diapers ever again. This syndrome is incredibly toxic to our children. I would honestly celebrate any outcome, big or small.

2 Are there specific risks or a clear line for a potential risk you would not accept?

Amy: There are no risks that we would not accept, because we know the progression of MECP2 Duplication Syndrome is worse than any possible risks of research and experimental treatments. My daughter has a very high pain tolerance, so we know she would be able to withstand many types of treatments – lumbar punctures, infusions, blood draws, etc. In addition, we are confident that the ultimate result of the trials and treatments that are in development for this horrible disease would provide some relief from many, if not all, of the symptoms she has.

Laura: At this point, there is no cure for this syndrome, so I see us as pioneers in this new field of scientific research, willing to accept just about any risks. We have been contributing to research since 2010, marking 15 years of MECP2 Duplication Syndrome investigation, and it has been incredible to witness our progress from nothing to something. I allow Lance to guide us regarding what he will or won't tolerate as research continues and his body keeps growing. So far, all the blood draws, LPs, eye exams, EEGs, sleep studies, and assessments have been relatively easy. All that remains is to solve the problem. I have experienced the other side personally with my brother, where nothing has been done, and all of it leads to an early death as the outcome.

FDA Public Engagement Staff opened the floor to live questions. Several FDA staffers commented on the presentation and what they learned. Another question was raised by FDA in the chat and answered by Amy, Bethany, and Danielle:

Question-What is the biggest obstacle in accessing trials in MDS for patients and families in your experiences?

Answers- Amy: "Females with MDS are not currently allowed in the MDS trials. HUGE obstacle for us personally. I would do anything to have her participate in the ATTUNE trial. No other obstacle is too large for our family."

Bethany: "Huge obstacles for families with MDS are:

1. not all children fit into the simple duplication [a more-easily malleable and targetable type of duplication]
2. patients' progression can occur faster and changes may occur faster than 6 months, so stability is challenging
3. having a site nearby due to complexities with travel and meeting their needs."

Laura: "I think the biggest obstacle for us is making sure the number of participants is large, there are sites open throughout the whole country, and it includes all ages."

To finish the discussion, several FDA staff members expressed their thoughts, and JoAnn reiterated several main points discussed in the meeting, reminding us all that the journey of MDS can be painful and difficult, but there are so many blessings along the way. She encouraged the FDA to think of Brody and all those diagnosed with MDS in their work because families are looking forward to a better future.

Family Representatives in Attendance

JOANN | mother of the first child diagnosed with MDS in the U.S.

MAKENZIE | mother of two sons with MDS

BETHANY | mother of twin sons with MDS

LAURA | mother of one son with MDS

DANIELLE | mother of one son with MDS

JUCEL | mother of one son with MDS

AMY | mother of one daughter with MDS & CureMDS advocacy group representative

Organizers/Others in Attendance

ARON SCHMIDT | father to one son with MDS & MECP2 Duplication Foundation representative

KATIE WESTER-NEAL, PHD | mother to one son with MDS & MECP2 Duplication Foundation representative

STEPHEN BAIRD | father to two sons with MDS & MECP2 Duplication Foundation representative

DAVUT PEHLIVAN, MD | clinical expert - Baylor College of Medicine

AMELIA DECKER, MD | mother to one son with MDS & MECP2 Duplication Foundation representative

TINA NEIL | technical producer - MECP2 Duplication Foundation representative

REAGAN UDALL FOUNDATION

NATIONAL INSTITUTES OF HEALTH (NIH): NIH/NCATS – NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

FDA Divisions Represented

Office of the Commissioner (OC) – 3 offices

- OC/OEA/PES - Office of External Affairs/Public Engagement Staff (organizer)
- OC/OCMO/OPT - Office of the Chief Medical Officer/Office of Pediatric Therapeutics
- OC/OCS/ACOMS – Office the Chief Scientist/Advisory Committee Oversight and Management Staff

Center for Biologics Evaluation and Research (CBER) – 4 offices

- CBER/OCBQ/DIS/PSB – Office of Compliance and Biologics Quality/Division of Inspections and Surveillance/Program Surveillance Branch
- CBER/OCD – Office of the Center Director
- CBER/OTP/OCE/DCEGM/GMB1 – Office of Therapeutic Products/Office of Clinical Evaluation/ Division of Clinical Evaluation General Medicine/General Medicine Branch 1

FDA DIVISIONS REPRESENTED CONTINUED

- CBER/OTP/PSPS – Office of Therapeutic Products/Office of Therapeutic Products/Policy and Special Projects Staff

Center for Drug Evaluation and Research (CDER) – 8 offices

- CDER/OND/ODES/DCOA – Office of New Drugs/Office of Drug Evaluation Science/Division of Clinical Outcome Assessment
- CDER/OND/ON/DNI - Office of New Drugs/Office of Neuroscience/Division of Neuroscience I
- CDER/OND/ON/DNII - Office of New Drugs/Office of Neuroscience/Division of Neuroscience II
- CDER/OND/ORDPURM/DRDMG - Office of New Drugs/Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine/Division of Rare Diseases and Medical Genetics
- CDER/OTS/OB/DBI – Office of Translational Science/Office of Biostatistics/Division of Biostatistics I
- CDER/OTS/DBIII – Office of Translational Science/Office of Biostatistics/Division of Biostatistics III
- CDER/OTS/OCP – Office of Translational Science/Office of Clinical Pharmacology
- CDER/OTS/OCP/DTPM - Office of Translational Science/Office of Clinical Pharmacology/Division of Translational and Precision Medicine

Center for Devices and Radiological Health (CDRH) – 1 office

- CDRH/OSPTI/OEID/DPCD – Office of Strategic Partnership and Technological Innovation/Office of Equity and Innovative Development/Division of Patient Centered Development

Human Foods Program (HFP) – 1 office

- HFP/OPIE/OIE/PHTS – Office of Policy and International Engagement/Office of International Engagement/Public Health and Trade Staff

Partner & Support Organizations

Larry Bauer and James Valentine from Hyman, Phelps & McNamara provided guidance during the meeting planning process.

MECP2 Duplication Syndrome advocacy organizations from around the world lent their support to this meeting:

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Disclaimer

Discussions in FDA Patient Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects the MECP2 Duplication Foundation's account of the perspectives of patients and caregivers who participated in the Patient Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of MECP2 Duplication Syndrome, health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire MECP2 Duplication Syndrome patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.