Rett Syndrome

A Devastating Neurodevelopmental Disorder

A Clinical Proceedings White Paper

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Clinical Neurological Society of America

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Introduction

Rett syndrome, or RTT, is a rare neurodevelopmental disorder[1,2] that occurs almost exclusively in females and affects all racial and ethnic groups worldwide.[3] It is estimated to affect one in 10,000 females globally,[4] but because cases can go undiagnosed or be misdiagnosed, it is difficult to determine its actual frequency in the population.[5,6]

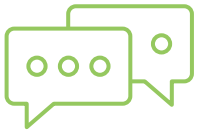
Individuals with RTT are intellectually impaired and also struggle physically with everyday activities like moving, speaking, and eating. They require virtually round-the-clock care. Despite the debilitating nature of the disease, almost three quarters of people with Rett syndrome survive into their 50s,[7] placing a sizeable burden on their families.

No cure is available for RTT, so treatment is focused on managing symptoms and providing support[3]. However, the first Rett syndrome-specific treatment was recently approved by the U.S. Food and Drug Administration.[8] In addition, two gene therapy programs are now active or will be active soon,[9,10] providing new hope for individuals with RTT and their families.

Clinical Features

Although cases are rare, RTT is still the second most identified cause of intellectual disability after Down syndrome.[5] Two different forms of RTT are known: typical (classic) and atypical. **To be diagnosed with the typical form of the disease, individuals must exhibit all of the following criteria:**

An Altered Pattern of Development
that includes a period of regression, then stabilization



Partial or Complete Loss of Spoken Language

TYPICAL RETT SYNDROME

Partial or Complete Loss of Acquired, Purposeful Hand Skills
such as grasping with fingers, reaching for things, or touching things on purpose

Gait Abnormalities
including walking on toes or walking with an unsteady, wide-based, wandering, stiff-legged gait, or the inability to walk at all[11,12]

Repetitive Hand Movements
such as hand wringing, washing, squeezing, clapping, or rubbing

In contrast, those with the atypical form of RTT will experience regression and stabilization, but they will not have all of the additional symptoms of the typical form of the disease.

The progression of typical RTT is often divided into four stages.[13,14]

Stage 1

Individuals exhibit developmental delay; however, the symptoms are subtle and can be easily missed by parents, pediatricians, or family physicians.

Stage 2

Individuals go through a period of regression. In over 90% of those with RTT, this phase starts after 12 months of age.[15] It often includes the loss of controlled hand movements and coordination as well as social interaction and communication, specifically spoken language.[13,14] The disappearance of these skills can occur either rapidly – in just days – or gradually over weeks, months, or even years.[16] Children in this stage may also have slowed head growth and start to exhibit stereotypic hand movements, such as wringing or washing, or breathing problems, such as hyperventilation.

Stage 3

Usually begins between two and 10 years of age and can last for many years. During this stage, individuals continue to have trouble with overall movement, and the development of seizures is common.[13] However, many other symptoms stabilize and stop changing over time, and slight improvements in attention, behavior, hand use, and communication are typical. Scoliosis also typically appears during this phase.[17]

Stage 4

Is characterized by changes in muscle tone, with increased rigidity and stiffness. This stage can also include more difficulty initiating movements and decreased, or even loss of, ability to walk. Individuals may also develop scoliosis that is severe enough to require braces or surgery.[13]

> “Parents often comment that these children are different from their other children in the sense that they eat and sleep but are not very interactive, and, in a sense, they are too good.”
>
> **–Alan K. Percy, MD**

Genetic Features

The diagnosis of RTT is based on meeting the clinical definition of the disease;[6,18,19] however, a mutation in the gene that encodes methyl-CpG-binding protein 2 (MeCP2) is also detected in 95-97% of typical and up to 85% of atypical cases.[6] More than 300 different mutations in the *MECP2* gene have been identified in people with RTT.[11] These mutations tend to be sporadic, which means that they are not passed on from generation to generation and are not found in the parents. Indeed, fewer than 1% of recorded cases of RTT are inherited,[3] so the chance of having more than one child with the disease is small.

RTT affects females and males differently, with the disorder primarily affecting females and much less frequently being seen in males.[3,21] This is because the *MECP2* gene is located on the X-chromosome.

What is MeCP2?

MeCP2 is a protein that is highly expressed in the brain and controls the expression of genes that regulate the development of the central nervous system.[20]

Since males typically have only one X chromosome, it was initially thought that males with mutations in *MECP2* that cause RTT in females are rare because they have more severe conditions and die at a young age. However, the number of males being identified with *MECP2* mutations is increasing, and although these individuals have significant impairments, they are not as severely impaired as previously thought.[22] Therefore, additional work is needed to completely understand the clinical variation in males with *MECP2* mutations. Importantly, there are males with *MECP2* mutations who have two X chromosomes (called Klinefelter syndrome) or they acquired a mutation in *MECP2* during early fetal development (somatic mosaicism) that have exactly the same clinical features as females with RTT and should be clinically classified as having RTT.

In contrast, females have two X chromosomes, so individuals with RTT have both a normal copy of *MECP2* and a mutated copy of *MECP2*. Since the number of normal and mutated proteins present can differ from individual to individual, symptom severity can also vary between them, with people who have more mutant MeCP2 having more severe symptoms.

> “There is a spectrum, but it’s not all over the board. Broadly, all patients are impaired in their ability to speak, use their hands, and walk. There’s a gradation within those groups.”
>
> **–Jeffrey Neul, MD, PhD**

Barriers to Timely Diagnosis

Receiving a diagnosis is critical because it is the first step toward accessing help and services, such as relevant treatments, financial assistance, and social support.[23] Having a diagnosis can also lead to significant decreases in anxiety levels in parents.[24] For these reasons, identifying and addressing the obstacles that prevent the timely diagnosis of RTT is essential.

> “When the diagnosis is made, parents are usually relieved. They have an answer and a target they can address moving forward. On the other hand, they may also be depressed that they have a child with Rett syndrome.”
>
> **–Alan K. Percy, MD**

Lack of Access to Specialized Care

Rett syndrome can be difficult to identify, with many families receiving a definitive diagnosis years after the first symptoms are apparent.[25] Despite the fact that developmental symptoms may show up as early as 6 months of age, typical RTT is often diagnosed between 2.5 to 3 years of age, and the atypical form is often diagnosed between 2.9 and 5.1 years of age.[15] It is also rare for pediatricians to make the diagnosis. Instead, the diagnosis is more often made by a neurologist, developmental pediatrician, or geneticist,[15] indicating that a referral process is often required.

> “Patients are usually referred to me when they are about 2 years old, mainly because of seizures.”
>
> **–J. Richard Gunderman, MD**

Because RTT is rare, it is common for pediatricians and family physicians to have little experience with this disease. But, finding RTT experts or even specialists with experience can be difficult. There are only 18 clinics in the United States that have been designated by the International Rett Syndrome Foundation as Centers of Excellence for treatment. This scarcity is more acutely felt by those who live in the West, since fewer than one third of these clinics are located in the western half of the country.[26]

Difficulty Identifying Disease Features

The variability in the presentation of the disease, as well as misconceptions about its features, can make identifying RTT difficult and potentially delay diagnosis. For example, having delayed regression or acquisition of stereotypical hand movements as well as normal head circumference can increase the chance of being diagnosed at an older age.[15,25]

While children with RTT often experience delays in early developmental milestones, they are usually still within the normal range, at least initially. Therefore, taking a "wait-and-see" approach when a child starts missing milestones can leave them at risk of a later diagnosis.[15] In addition, since RTT is primarily found in females, parents of males with RTT have reported problems getting a diagnosis because the disease is often overlooked.[27]

> "Quite regularly I hear stories of frustration from families that they had been raising concerns to their pediatrician or primary care doctor at a year old that their child was not developing at the same rate as their older siblings did. The pediatrician will say, 'No, it's fine. Different kids acquire these skills at different ages.'"
>
> **– Jeffrey Neul, MD, PhD**

The symptoms of RTT used to be mistaken for those of other disorders,[5,28-30] but now, such mistakes are rare. It is still relatively common, however, that children with RTT, particularly those with less severe forms of the disease, are initially diagnosed with autism.[31] This is because, during the regression stage, they may exhibit social withdrawal, dislike of physical contact, eye contact avoidance, and indifference to visual and aural stimulation, which are generally associated with autism.[31] Over time, however, these autistic features become less pronounced, making the characteristics of RTT more prominent.

> "The diagnosis of autism is often made when these children are between 1 and 2 years of age because, during the period of regression, they are often quite resistant to contact, act like they are in another world, resist being held, and cry a lot. But, once the regression phase passes and they begin to recover, their eye contact is much better, and their communication improves steadily. When you look at a child with Rett syndrome who is 4 or 5, their eye contact is much too good for them to be considered autistic."
>
> **– Alan K. Percy, MD**

The Challenges of Early Genetic Screening

Because of the high incidence of *MECP2* mutations in those with RTT, it is tempting to assume that neonatal or early genetic testing would be helpful in early diagnosis. There are questions, however, surrounding the benefits of using such genetic screening as a predictive diagnostic tool.[32]

MECP2 mutations are neither necessary nor sufficient to diagnose RTT.[6,18,19,33] Indeed, individuals can have the disease without an *MECP2* mutation.[34-36] *MECP2* mutations have also been found in a variety of diseases;[33] thus, having a mutation does not always indicate that the individual has RTT.

It is also possible to have an *MECP2* mutation but be an asymptomatic carrier.[37] Overall, this ambiguity is problematic because, when the results of the genetic screening cannot be clearly linked to defined disease outcomes, acting (or not acting) on the genetic information in the absence of additional symptoms could actually cause emotional and physical harm to children and their families.[38]

> “If a child meets the clinical criteria for Rett syndrome, the likelihood that they will have a mutation is 95% to 97%. However, we don’t know the likelihood of a patient having Rett syndrome if newborn screening finds an *MECP2* mutation. We can’t really say anything with any confidence regarding their overall prognosis.”
>
> **– Jeffrey Neul, MD, PhD**

Individual & Family Challenges

Daily Life

Rett syndrome affects all aspects of the daily life of affected individuals and their families. One study showed that much of the individual's time was spent on basic needs, including sleep, daily care (eating, hygiene, dressing), and medical activities. With all the attention on daily care, little time was spent on social or creative activities, communication, or schoolwork. Indeed, all study participants needed care and support in most if not all activities both at night and during the day, irrespective of age, mobility, or type of housing.[39,40]

> "Those higher-functioning girls can be more difficult to manage because they can get around, they can climb on furniture, they can get to the stove or the water, and some have even exited the house and been injured. So, the higher-functioning children often have greater care issues."
>
> **– Alan K. Percy, MD**

Round-the-clock care can take a toll on families. In fact, parents have described their experience of being a caregiver as an "obstacle course."[41] In the beginning, the focus is on achieving a diagnosis, with the number of tests being a source of pain and suffering for the child and a source of burnout for the caregivers.[27,41] Once families have a diagnosis, they must settle into a pattern of daily life that they must continually adjust as symptoms and needs evolve.[41]

> "From a social standpoint, the biggest challenge is communication. From a treatment standpoint, the most frightening thing is the seizures. In the long run, however, it is the understanding that their child is not normal."
>
> **– J. Richard Gunderman, MD**

Parents often feel that they never have enough time to work, care for their child with RTT and their other children, and take care of their household.[27] Accordingly, studies have shown that caring for a child with RTT can have significant, negative effects on the physical and emotional well-being of parents and caregivers.[42,43]

> "Caregiver quality of life oftentimes is inversely related to the overall severity of the individual with Rett syndrome."
>
> **– Jeffrey Neul, MD, PhD**

With the life expectancy for most individuals with RTT exceeding age 50,[44] aging often results in additional challenges and decreased quality of life for those with RTT and their families.[45,46] Adults with RTT can have more limited mobility, and they may also experience more health issues, such as heart problems, fatigue, dental problems, gastrointestinal problems, changes in mood, and irritability.[47,48] As the parents get older, these changes in their children can become more difficult

to handle because of their own age-related health issues.[47] Parents may also experience increased stress related to determining who will care for their child if or when something happens to them.[49]

> "If the girl is 40 or 50 years of age, the parents are 60, 70, or 80 years old. Their ability to manage their child's care is less and less because of their own issues, such as mobility or ability to lift."
>
> **– Alan K. Percy, MD**

Coordinating Care

For parents, having a child with Rett syndrome often means a lifetime of scheduling and attending health care appointments as well as regular communication with health care professionals to coordinate treatment and make plans for continued care. This process can be even more burdensome for those in less populated areas, since getting appropriate care and services may require traveling to larger cities.[27] While telehealth visits may be helpful for services related to physical activities or communication,[50,51] they may not be used to replace all types of patient evaluations.

> "Staying up to date on preventive care – particularly routine gynecological care starting in the teenage years and continuing through adulthood – is important and should not be overlooked."
>
> **– Alan K. Percy, MD**

Multidisciplinary Treatment Team

Pediatricians/ Primary Care Physicians

Pediatric Neurologists

Behavioral/ Developmental Medicine Physicians

Nutritionists

Specialists
(In Genetics, Cardiology, Dentistry, Gastroenterology, Gynecology, Ophthalmology, Orthopedics, Pulmonology, and Endocrinology.)

Social Workers

Occupational & Physical Therapists

Speech-Language Pathologists

Economic Burdens

The actual monetary cost of RTT is difficult to determine because the disease varies in its severity. It is generally thought to be quite expensive when accounting for medical and therapy appointments, medications and medical devices, as well as respite or long-term residential care.[47,52] The amount that a family pays directly may depend on their insurance coverage as well as the services available in their area.

Families may also experience administrative obstacles that force them to pay more out of pocket for specialized care.[27] The cost can dramatically increase when indirect, non-medical factors, such as lost wages or travel expenses, come into play.[27,47]

Relationships & Social Isolation

The constant care required by a child with RTT can have a significant impact on relationships within the family.[42] One study found that the divorce rate of couples who had a daughter with RTT was approximately 9% higher than the divorce rate of the general population.[53] Furthermore, while the brothers and sisters of those with RTT are often resilient and may help with care, they may also struggle with feelings of resentment when most family time and activities are centered around the care and treatment of their Rett sibling.[27] They may also be bullied or have trouble making friends at school because their Rett sibling is "different."[47,54]

Later in life, siblings may also be involved in conflicts surrounding who will care for their Rett sibling when their parents no longer can.[47] Rett individuals themselves may also experience emotional changes or stress when their siblings grow up, move out, and move on to their adult lives.[47]

> "It will either make or break a family."
>
> **– Laura Lehman, MD, MPH**

> "The divorce rate in parents who have children with Rett syndrome is very high in my experience."
>
> **– J. Richard Gunderman, MD**

Having a child with RTT may also be isolating for families. Attending social events can be difficult because the mood of their child with RTT can be unpredictable.[27,47] Families may also be actively excluded from activities by others because of social stigma or difficulties related to the care of their child.[55] Some families may even choose to isolate themselves because they want to avoid being associated with a child with special needs.

> "We have parents who kept the diagnosis secret because they didn't want to be embarrassed by taking their child out in public."
>
> **– Alan K. Percy, MD**

Alleviating the Burdens of Disease

Earlier Recognition

Earlier diagnosis would benefit individuals with RTT and their families in a number of ways. It would provide them with the peace of knowing what is wrong and help them identify specific providers, research organizations, support groups, and government resources that help families cope with this rare disease.[23]

Some studies suggest that motor and communication impairments may be present before the classic symptoms become obvious.[16,56] More research in this area is needed to confirm these results and potentially develop guidelines for pediatricians and family physicians to consult when they are considering neurodevelopmental disorder diagnoses in their patients.

It is also common for parents to report that their early concerns about their child were dismissed by their pediatrician or family care physician.[16,56] Therefore, getting more information out to first-line providers about what to look for with RTT could shorten the timeline to a diagnosis. Improving access to Rett specialists via pop-up clinics, particularly in areas that have little to no access to such experts, may also be a way to support local providers and facilitate early diagnosis.

> “It is hard is for pediatricians to really recognize Rett syndrome, so education and outreach to them would be helpful.”
>
> **– Laura Lehman, MD, MPH**

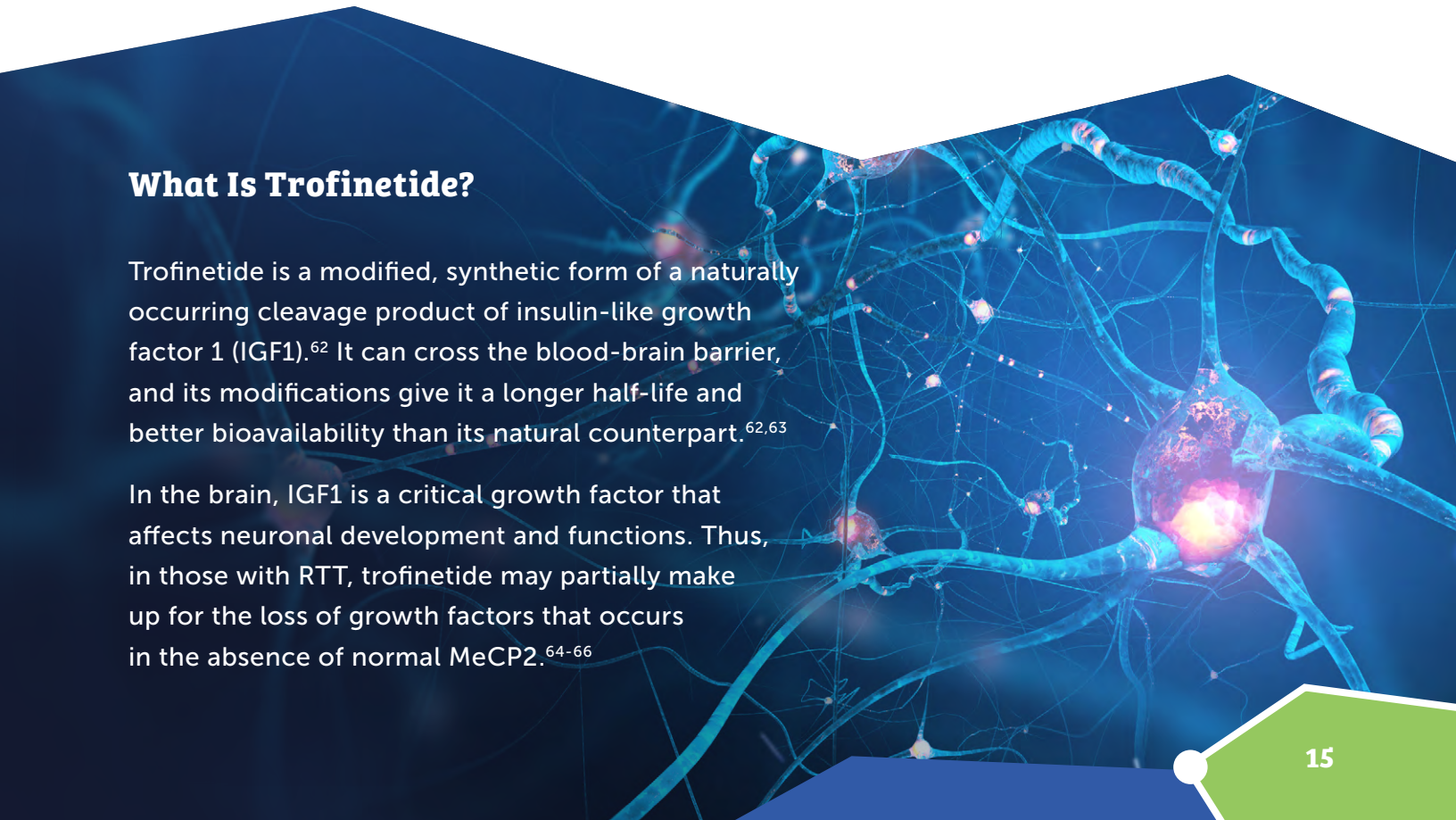
Rett-Specific Treatments

Until recently, the only way to treat RTT was on a symptom-by-symptom basis. However, recent clinical trials have found that a drug called trofinetide was able to improve symptoms of RTT with relatively minor side effects.[57-61] After consideration of these results, in March 2023, the U.S. Food and Drug Administration approved trofinetide for use in RTT individuals two years of age and older.[8] This is a landmark approval since it is the first and only drug approved specifically to treat RTT.[8]

Trofinetide is expected to be a major breakthrough that will help relieve some of the burden of RTT on those suffering from the disease and their families, but some questions still remain. For example, trofinetide has been shown to help relieve some RTT symptoms in the short term, however, additional studies are necessary to determine what these improvements look like in the long term. It is also still unknown whether trofinetide will benefit males with RTT or those without an identified *MECP2* mutation.

Despite having only recently been approved, there are already concerns about insurance companies erecting access barriers to trofinetide. For example, screening questions that would be appropriate for a clinical trial could be misapplied as part of some prior authorization protocols. Now that the medication has received FDA approval, it should be the medical judgement of expert clinicians, in consultation with parents, who decide if the medication is appropriate for each Rett individual.

> “Anything that can help these kids or slow disease progression is wonderful.”
>
> **– J. Richard Gunderman, MD**



What Is Trofinetide?

Trofinetide is a modified, synthetic form of a naturally occurring cleavage product of insulin-like growth factor 1 (IGF1).[62] It can cross the blood-brain barrier, and its modifications give it a longer half-life and better bioavailability than its natural counterpart.[62,63]

In the brain, IGF1 is a critical growth factor that affects neuronal development and functions. Thus, in those with RTT, trofinetide may partially make up for the loss of growth factors that occurs in the absence of normal MeCP2.[64-66]

Improving Daily Quality of Life

Despite the demanding nature of meeting basic needs, spending time on communication, physical activities, rest, and socialization may help improve the quality of life of individuals with RTT and their families. Support groups for caregivers can also be important.

Communication

Spending time working on communication skills using various methods or devices, such as picture boards, body movements, or eye-tracking technologies, could facilitate communication and decrease frustration levels for those with RTT and their caregivers.[47,67,68]

> "A lot of quality of life for the individual and for the caregivers can be improved if there is more dedicated effort put into improving the individual's ability to communicate non-verbally."
>
> **– Jeffrey Neul, MD, PhD**

Physical Activity

More participation in standing and walking activities has been shown to have positive effects on the health and quality of life of those with RTT.[69,70] While there is relatively little scientific evidence to suggest the effectiveness of alternative therapies, including animal-assisted therapy, hydrotherapy, music therapy, massage therapy, or adapted sports,[30] such activities may still be beneficial for recreation, increasing movement, or providing social enrichment.

> "I'm in favor of just about any type of therapy the patient and family are interested in, whether it be swimming, horseback riding, physical therapy, occupational therapy, applied behavior analysis therapy, whatever it is. And the sooner you get it, the better."
>
> **– J. Richard Gunderman, MD**

Socialization

When children with RTT are young, access to early intervention and school programs may be available. Such programs can give parents daily breaks from care and give RTT children opportunities to learn and socialize with their peers. Some schools may even provide additional services, such as occupational therapy, speech-language therapy, physical therapy, or extended school year services.[71]

> "In the US, outside services are available all the way up through the completion of school, which in most states is at age 22."
>
> **– Alan K. Percy, MD**

Respite

Providing constant care for a child with special needs can be overwhelming for the caregiver. Families with special needs children have consistently reported that respite care is an essential support that allows caregivers to lower their stress levels, catch up on sleep, restore their energy reserves, and return some normalcy to their lives.[72]

Support Groups

Connecting with other parents through peer support networks can alleviate stress and feelings of isolation by providing emotional support and coping strategies as well as practical advice for dealing with the challenges of life with their child with RTT.[73,74] Another source of community support is advocacy groups. Belonging to such groups can create a sense of empowerment in parents because it gives them the opportunity to help all families with the same challenges as their own.[75]

> "I think that it's very important to socialize and realize that you're part of a larger problem, and that it's not just you and your family."
>
> **– Alan K. Percy, MD**

> "Something that can help families is being a part of advocacy groups or supporting research in order to try to make something bigger out of the trials or frustration that can occur after having a child diagnosed with Rett syndrome."
>
> **– Laura Lehman, MD, MPH**

Planning for the Future

Because people with RTT often live well into adulthood, making plans for their future is a key step in their care. These plans may include the preparation of legal documents, such as a will, trust, guardianship, or conservatorship, to designate who will make care and financial decisions for the child over the course of their life.[47]

> "We recommend that, as the girls reach their mid-teens, the parents develop a conservatorship and also a guardianship arrangement. It's important that, as these girls become adults, these documents exist."
>
> **– Alan K. Percy, MD**

Conclusion

Rett syndrome is a debilitating disease that affects thousands of people worldwide. Despite the severity of symptoms, most people with this disease are expected to live relatively long lives, meaning years of continuous care.

To alleviate the severe personal, economic, and social burdens of Rett syndrome on affected individuals and their families, further investments in both education and pharmaceutical development are desperately needed. Educating pediatricians, primary care physicians, and neurologists on the clinical criteria of Rett syndrome will enable individuals to receive an early diagnosis that will help facilitate timely access to appropriate care and services, including Rett-specific treatments. Furthermore, using and developing additional Rett-specific treatments, such as trofinetide, is essential for providing meaningful improvements in the quality of life of not only those with Rett syndrome but also their families and caregivers.

CNSA's Clinical Proceedings

The Clinical Neurological Society of America has nearly 50 years of experience bringing together leading experts and clinical neurologists for educational programming. With the launch of CNSA's Clinical Proceedings — a white paper series — the organization expanded its educational resource offerings while raising awareness about unmet needs in neurology.

CNSA recognizes the expert panel members who contributed to the development of this white paper about Rett syndrome.

Jeffrey Neul, MD, PhD
Chair

J. Richard Gunderman, MD

Laura Lehman, MD, MPH

Alan K. Percy, MD

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