BUILDING COORDINATED CARE PATHWAYS FOR RETT SYNDROME: A CALL TO ACTION IN EUROPE

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CRA Charles River Associates

EBC European Brain Council

rse rett syndrome europe

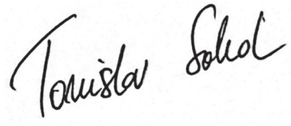
FOREWORD

Rett syndrome is a compelling example of why Europe must act decisively to strengthen coordinated care for rare diseases. Children and adults living with this complex neurological disorder depend on multiple specialists throughout their lives - yet caregivers too often find themselves navigating fragmented systems, facing delayed diagnosis, unequal access to expert centres, and significant personal and financial strain. These challenges illustrate broader shortcomings that affect millions of Europeans living with a rare disease.

The EU has already laid important foundations. European Reference Networks, cross-border healthcare frameworks, and recent Council calls for a comprehensive EU approach to rare diseases show a growing recognition that expertise must be shared, not limited by geography. At the same time, progress remains uneven. Access to diagnosis, care coordination, and innovation still depends heavily on where a person lives. This is incompatible with the principle of equity that underpins our European health cooperation.

This white paper outlines policy solutions for improving care for Rett syndrome patients. Coordinated national Rett pathways anchored in expert centres, rapid access to diagnosis, digital tools and data collection, and stronger support for caregivers are not aspirational goals - they are feasible measures that could improve outcomes and reduce inefficiencies across health and social systems. Investment in research and readiness for upcoming therapies is also essential to ensure that Europe remains competitive and that innovation reaches all patients, not a select few.

By advancing these actions, Member States can move towards a shared European standard of care for Rett syndrome - consistent, multidisciplinary, and centred on what truly matters to patients and families. I welcome this paper as an essential contribution to our ongoing policy efforts. It offers a clear message: with coordinated pathways, targeted investment, and commitment to equity, we can transform the experience of people living with Rett syndrome - and strengthen rare disease care across Europe as a whole.



Tomislav Sokol, PhD,
Member of the European Parliament

OBJECTIVES AND CONTRIBUTIONS TO THE PAPER

The aim of this white paper is to shed light on the urgent challenges faced by individuals with Rett syndrome, their families and the healthcare systems that support them. It seeks to provide policymakers with clear evidence on how fragmented care pathways contribute to unequal access, delays in diagnosis, unnecessary costs and avoidable burdens on families. By examining these issues through the lens of Rett syndrome, the paper highlights broader lessons for rare disease care across Europe and proposes practical policy solutions to move from fragmented to coordinated care.

Acadia Pharmaceuticals GmbH commissioned this white paper to support and broaden the understanding of care coordination–related challenges for Rett syndrome. Experts in Rett syndrome, spanning policy, health research and patient advocacy, advised on the research underpinning this paper, ensuring that both lived experience and system-level expertise informed its findings. An Acadia-commissioned study engaging primary caregivers of individuals with Rett syndrome across Europe provided additional context and insights for the paper.

Contributors

- Prof. Nadia Bahi-Buisson, Professor of Paediatric Neurology, Necker-Enfants Malades Hospital & Imagine Institute, Université Paris Cité (France)
- Frédéric Destrebecq, Executive Director, European Brain Council (Belgium)
- Becky Jenner, Former President, Rett Syndrome Europe; Trusts & Foundations Fundraiser, Rett UK; Caregiver Advocate (UK)
- Bojana Milanov, Board Member & Scientific Advisory Board, Rett Syndrome Europe; Caregiver Advocate (Serbia)
- Prof. Justyna Paprocka, MD, PhD, Head of Paediatric Neurology, Faculty of Medical Sciences, Medical University of Silesia, Katowice (Poland)
- Claudia Petzold, Founder & Chair, Rett-Syndrom Deutschland e.V.; Communications Specialist in Augmentative Communication; Caregiver Advocate (Germany)
- Pedro Rocha, President, Rett Syndrome Europe; Caregiver Advocate (Spain)
- Heidi Sejr, Chair, Landsforeningen Rett Syndrom; Caregiver Advocate (Denmark)
- Danijela Szili, Chairwoman, Hungarian Rett Syndrome Foundation; Pharmacist & Patient Advocate; Secretary of Scientific Advisory Board, Rett Syndrome Europe; Caregiver Advocate (Hungary)
- Sheela Upadhyaya, Life Sciences Consultant Specialising in Rare Diseases (UK)
- Mariëlle van den Berg, MD, Orthopaedic Surgeon and IDD Physician ST; Chair, Scientific Advisory Board, Rett Syndrome Europe; Science and Medical Adviser of Netherlands Rett Syndrome Association (Netherlands)
- Aglaia Vignoli, Associate Professor of Child Neuropsychiatry, University of Milan; Director, Child & Adolescent Neurology and Psychiatry, ASST Grande Ospedale Metropolitano Niguarda (Italy)
- Prof. Dimitrios Zafeiriou, Professor of Paediatric Neurology & Developmental Paediatrics; Chair, First Department of Paediatrics, Hippokratio General Hospital, Aristotle University, Thessaloniki (Greece)

CRA Authors: Angela De Martini (Vice President, Zurich), Michele Pistollato (Principal, London), Antun Sablek (Associate Principal, Brussels), Yiannis Pantelides (Senior Associate, London)

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EXECUTIVE SUMMARY

Building Coordinated Care Pathways for Rett Syndrome: A Call to Action in Europe

Rett syndrome (RTT) is a rare, life-limiting neurodevelopmental disorder that profoundly affects children, most often girls. After an apparently normal early development, children can experience a regression of skills and develop a range of severe impairments, requiring care from multiple specialists throughout life. With more individuals now living into adulthood—although mortality can still be high in childhood—RTT highlights the urgent need for coordinated, multidisciplinary care across the lifespan.

Across Europe, families encounter fragmented systems that make accessing care uneven and unpredictable. Diagnosis is frequently delayed due to low awareness among frontline professionals and the absence of clear referral pathways. Once a patient is diagnosed, care often remains inconsistent, with limited access to expert centres and a lack of structured coordination across specialities. Transition from paediatric to adult services is especially challenging, forcing families to navigate unfamiliar systems with little to no support. This fragmentation places heavy burdens on families, who must often act as care coordinators themselves, and leads to inefficiencies and avoidable costs for families and healthcare systems.

The impact extends beyond healthcare. Caregivers, siblings and families face significant emotional and financial strains and reduced quality of life, and many are reducing or leaving employment to meet their child's complex needs. Social isolation, anxiety and burnout are common, while gaps in financial coverage mean families frequently carry costs for therapies, equipment, transportation and home adaptations. These burdens highlight why better coordination of RTT care is both a health and social policy priority.

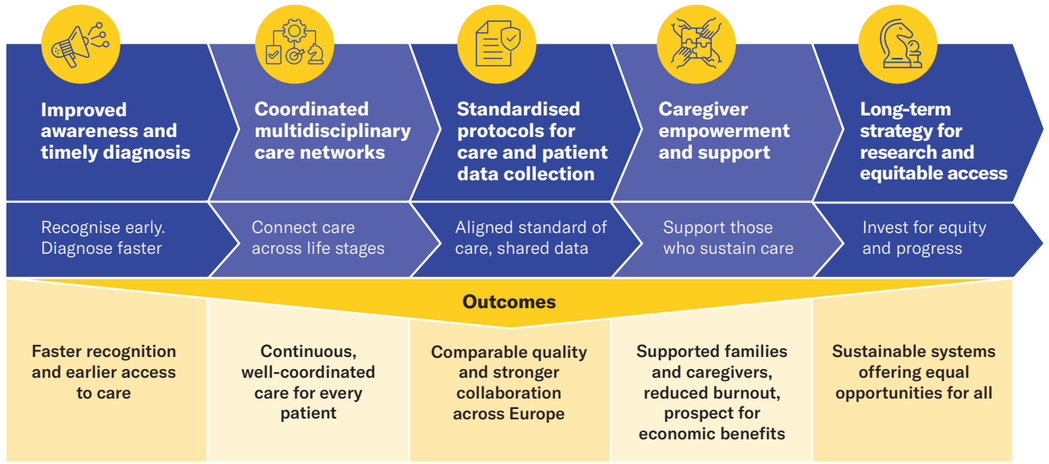
Europe has already laid important foundations. Initiatives such as the European Reference Networks (ERNs) show how expertise can be shared across borders, and a forthcoming European Action Plan on Rare Diseases provides a framework for greater coordination. What is now needed is for national health systems to turn these ambitions into practice by setting clear standards for RTT care.

Key policy recommendations (Figure 1):

To pave the way towards coordinated care pathways for RTT in Europe, we propose several cross-cutting policy actions that all countries should adopt as a baseline:

- **Improved awareness and timely diagnosis:** Increase awareness and ensure timely diagnosis by training healthcare professionals and standardising referral protocols.
- **Coordinated multidisciplinary care networks:** Establish coordinated national RTT care pathways preferably anchored in expert centres, with care coordinators and structured transitions across the lifespan.
- **Standardised protocols for care and patient data collection:** Adopt standardised care protocols and shared data systems by developing national standards, building patient registries and supporting a cross-region EU registry.
- **Caregiver empowerment and support:** Empower and support caregivers and families through financial assistance, respite services, education and psychosocial support, and strengthen the role of patient advocacy organisations as essential partners. Such support is also economically beneficial, helping families remain in employment and reducing long-term societal costs.
- **Long-term strategy for research and equitable access:** Develop a strategy to advance RTT research, deepen understanding of disease progression, and ensure equitable access to high-quality care and innovation. Continued investment in research and workforce training will help guarantee that all individuals with RTT, regardless of where they live, have equal opportunities for diagnosis, treatment and lifelong care.

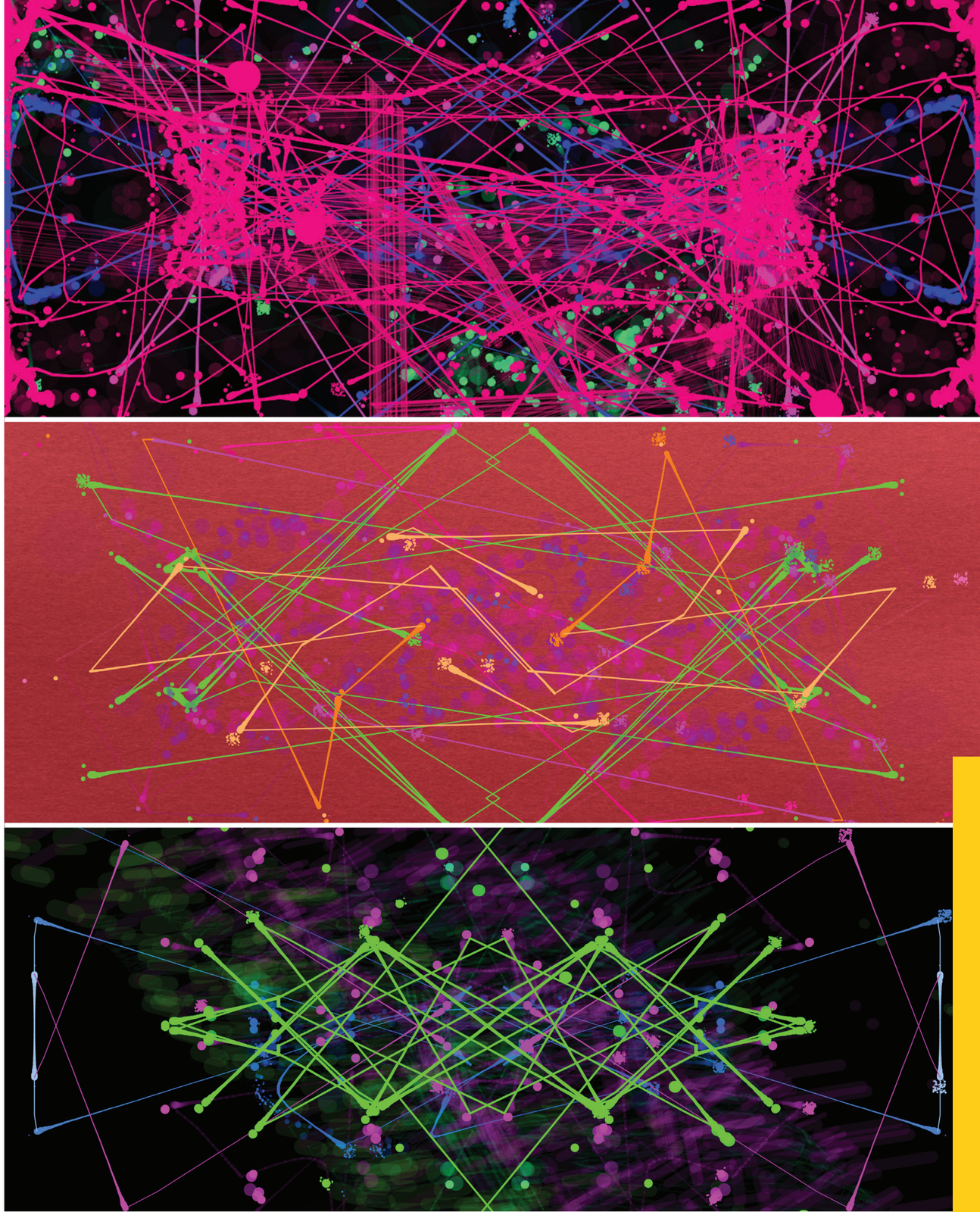
Figure 1: Key policy recommendations



Source: CRA (2025)

Moreover, because the current level of preparedness to address RTT varies across healthcare systems, tailored actions are also needed. Overall, we observe that the policy and care environments fall into three broad archetypes: (1) integrated (advanced and well structured), (2) evolving (partial progress towards integration) and (3) foundational (major structural and policy gaps) systems. Integrated systems should consolidate their strengths and address remaining gaps, such as coordinated care, transition to adulthood and long-term planning. Evolving systems should expand successful pilots into coherent national programmes with consistent standards. Foundational systems should urgently establish reference centres and access to diagnosis while leveraging European cross-border expertise to bridge immediate gaps. Across all systems, where relevant and operationally feasible, countries should learn from one another and draw on existing best practices.

Ultimately, RTT is a test case for how Europe manages rare multisystemic genetic diseases; the challenges are complex, but the solutions are clear. By committing to coordinated care pathways, equitable access and strong support for families, policymakers can transform fragmented care into sustainable systems that deliver less burden and better outcomes and quality of life for patients, caregivers and society.



***Everyone Is An Artist*, Istanbul, Rett Syndrome Europe. From top to bottom: Asel Erattir, Ebru Bicak, and Rümeysa Ayse Gencer**

1. BACKGROUND: RETT SYNDROME AND CARE CHALLENGES

Rett syndrome (RTT) is a rare, complex, multi-organ and life-shortening neurodevelopmental disorder (X-linked MECP2 mutations) that affects approximately 1 in 10,000 live female births and impacts a smaller number of males.[1] Symptoms typically emerge between 6 and 18 months of age, but because the condition is rare, diagnosis is often delayed. Although children with RTT may lose previously acquired skills—a process that can look degenerative—this is due to abnormal development and dysfunction of neurons. Neurons in the brain remain largely intact, suggesting the disorder affects neuronal function and communication rather than causing neurodegeneration (Figure 2).[2,3]

Figure 2: What is RTT?

Neurodevelopmental, meaning that it affects how the brain functions and develops

Not neurodegenerative, meaning brain cells will not become damaged or die as a direct result of Rett syndrome

Complex, and can have a variety of symptoms that may change over time

Typically caused by a gene mutation of the X chromosome on a gene called MECP2

Usually recognized in children between 6 to 18 months of age, as they begin to miss developmental milestones or lose abilities they had gained

Source: Figure adapted from Rettlife. What is Rett syndrome?. Retrieved 15 October, 2025, from https://rettlife.ca/what-is-rett-syndrome

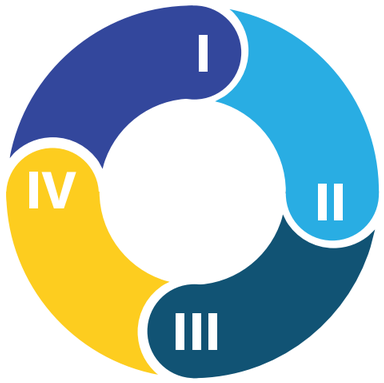
RTT manifestation varies, although overall signs and symptoms largely fall into three categories: (1) core onset symptoms that are hallmarks of RTT; (2) frequent, nonspecific manifestations that surface variably; and (3) associated comorbidities related to disease progression. After a period of otherwise apparently normal early development, children with RTT experience a regression of speech and motor skills and develop a range of severe impairments, including loss of purposeful hand use, gait abnormalities, seizures, breathing irregularities, orthopaedic impairments (including scoliosis) and gastrointestinal problems (Figure 3). Some individuals may have some level of intellectual disability.

This complex and evolving clinical picture means that individuals require multidisciplinary care (neurology, pulmonology, gastroenterology, orthopaedics, endocrinology, cardiology, rehabilitation and therapy [physical/occupational, speech], dentistry, nutrition, and psychosocial support). Given that many people with RTT can live into their 50s, coordination of care across the lifespan is crucial.[4] Clinical priorities evolve throughout life. In childhood, the focus is on timely diagnosis of new symptoms that emerge and demand timely intervention, such as controlling seizures. During adolescence, emphasis shifts to skeletal and hormonal health, while in adulthood the main goals include managing chronic comorbidities, supporting quality of life and keeping the condition as stable as possible.[5]

Figure 3: Signs and symptoms of RTT

Stage I

Early stagnation tends to begin between 6 and 18 months with **low muscle tone, mobility problems, difficulty feeding and delay in speech development.**



Stage II

Some children progress to **lose skills rapidly** – others more gradually – exhibiting **loss of purposeful hand movements, periods of distress, disinterest in people, problems sleeping and difficulty eating**.

Stage III

Even in Stage III, fine motor abilities **decline with increasing age**. Some domains may remain more stable. Additional symptoms can include **epileptic seizures and spinal issues such as scoliosis.**

Stage IV

Later motor deterioration begins after age 10, and individuals who were able to walk may no longer be able to do so. Patients may experience **new issues, including scoliosis, muscle weakness, and involuntary or slow movements.**

Source: Figure adapted from RARE Revolution Magazine. (2025, September). Rett syndrome infographic. Retrieved 15 October, 2025, from https://rarerevolutionmagazine.com/wp-content/uploads/2025/09/Rett-syndrome-infographic.pdf

The complex needs of individuals with RTT also place significant and sustained demands on family caregivers in terms of time, emotional resilience and financial resources (in this context, "caregivers" primarily means family members who provide day-to-day support, though formal caregivers [e.g. paid nurses or aides] may also play a role). Fragmented and poorly coordinated care services compound this burden, requiring families to take on substantial organisational responsibilities in addition to direct care.

The difficulties in managing RTT are compounded by barriers in delivering effective treatment to patients. Clinical trials to develop treatments for RTT face significant challenges due to the disorder's rarity, wide symptom variability and reliance on caregiver observations to measure the impact of the treatment. Because most patients have limited speech and mobility, trials depend on tools like the Rett Syndrome Behaviour Questionnaire and the Clinical Global Impression–Improvement scale to capture both caregiver and clinician perspectives on change.[6] Regulators have recognised this combined approach as an appropriate way to assess treatment benefit.[7] However, defining what constitutes a meaningful clinical improvement remains difficult, as small functional gains, such as improved communication or breathing, may be highly significant to families but remain hard to quantify, and the interpretation of the benefits varies across research studies.[8] Achieving consensus on meaningful change and harmonising outcome measures across studies will be crucial to advancing therapy development and regulatory approval in RTT.

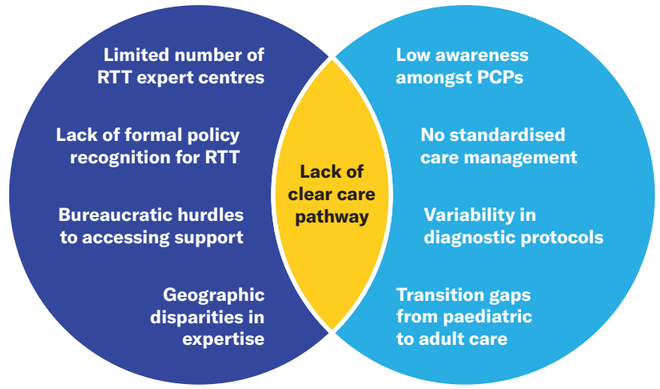
Even though a coordinated approach could more effectively address these needs, care for RTT remains highly fragmented across Europe. "Fragmented care" describes the challenges that occur at multiple levels: at the system level, where expertise, specialist centres and funding structures are unevenly distributed; at the clinical management level, where referral routes, protocols and day-to-day clinical practices vary across countries, regions and treatment centres due to the lack of expertise and standardisation; and at the intersection between the two, where poor coordination often leaves families to bridge the gaps themselves. For instance, providing the right care at the right time often requires multiple referrals to specialists in different locations, alongside frequent primary care visits where knowledge of RTT is limited.[9,10] This process is resource-intensive for health systems and exhausting for families, who must navigate complex pathways in the face of uncertainty. Ultimately, the lack of structured referral routes and low awareness among frontline healthcare providers lead to delays in accessing appropriate interventions and negative consequences for individuals with RTT and their families, especially when they are misdirected to the wrong care pathway.[11] In summary, RTT care requires lifelong management, coordination across multiple disciplines and support during critical transition periods.

Examining these challenges provides insight into how fragmented care affects not only individuals living with RTT but also their caregivers and health systems more broadly. To structure this analysis, we adopt a conceptual framework (Figure 4) that categorises the main barriers to coordinated care. This analysis is the result of a targeted literature review, interviews and policy discussions. An Acadia-commissioned study engaging the primary caregivers of individuals with Rett syndrome across Europe provided additional context and insights for this paper (full details of the methodology are provided in the appendix). The next sections first present evidence on the drivers of fragmentation and then examine their consequences for patients, families and healthcare systems.

Figure 4: Conceptual framework to categorise challenges in care coordination

System challenges

Challenges stemming from fragmentation in health system infrastructure and lack of capacity across Europe



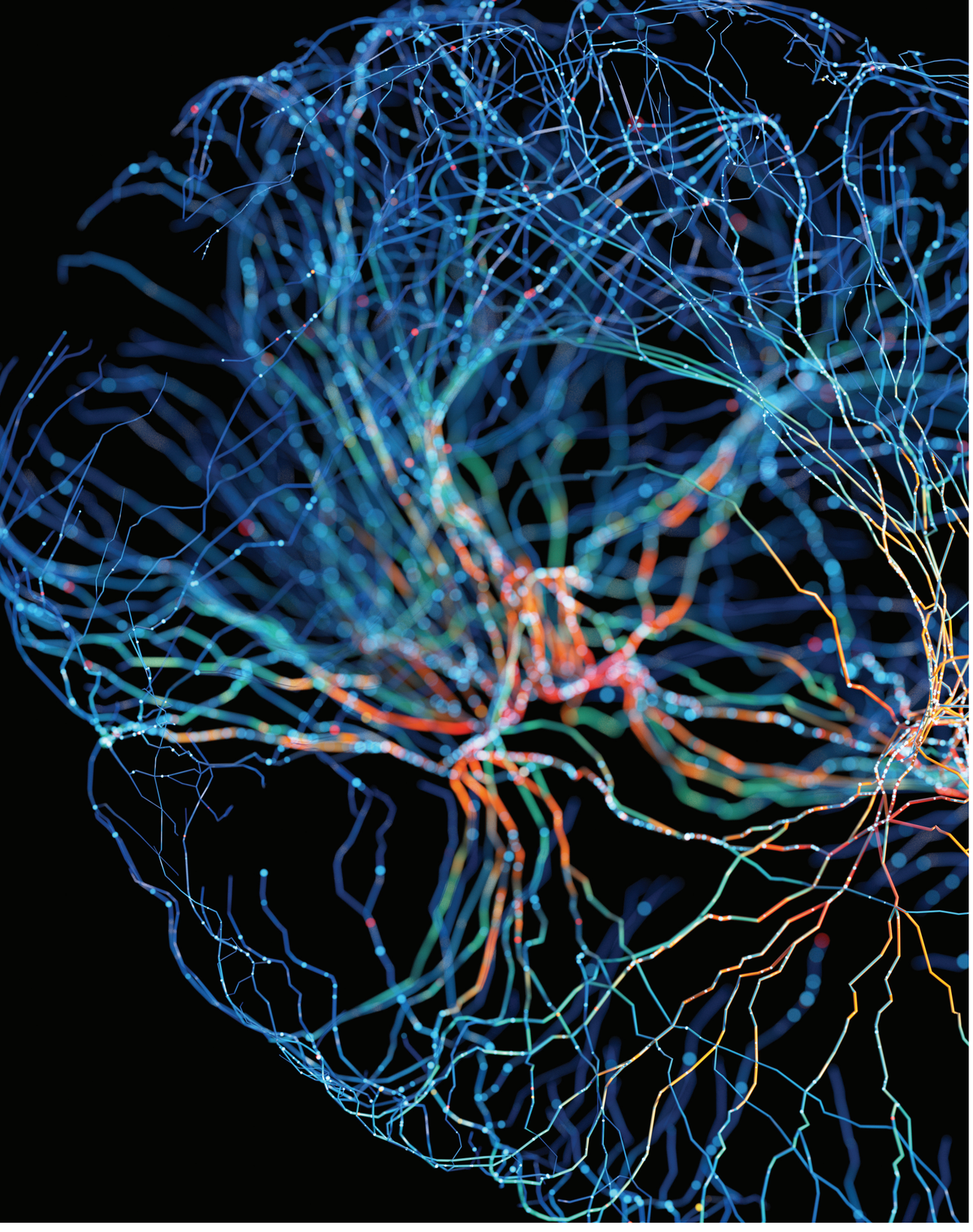
Clinical management challenges

Challenges stemming from the inherent complexity of the disease pathophysiology hindering adequate and coordinated management

Coordination (system–management interface) challenges

Challenges stemming from both systemic and management-related issues

Source: CRA (2025)



2. EVIDENCE OF FRAGMENTED RETT SYNDROME CARE ACROSS EUROPE

Our research reveals multiple factors contributing to the fragmented care of RTT across Europe. These factors operate at different levels, ranging from limitations in access and specialist infrastructure to gaps in primary care expertise and inconsistent care delivery. Taken together, these factors reinforce one another and intensify fragmentation, ultimately exacerbating how care is managed for individuals with RTT. Importantly, countries vary widely in their capacity to coordinate RTT care services. It is also important to note that these categories refer to levels of care coordination and fragmentation—they are not fixed classifications of entire health systems. A country may appear integrated in some respects (for example, having specialist centres) but remain fragmented in others (such as lack of transition to adult care or access to social care). Likewise, even in the most integrated systems, we observed persistent challenges—for instance, ensuring smooth transition to adult care or guaranteeing equitable access to care and rehabilitation across all countries. We observed that the policy and care environments across countries generally fall into three broad archetypes:

- **Integrated system:** Advanced, well-structured systems with formalised policies, care pathways and equitable access across life stages for individuals with RTT
- **Evolving system:** Partial progress towards integration—some foundational elements (e.g. a specialist clinic or regional programme), but inconsistent care quality across regions within the country; policies or practices developed in one region not consistently implemented or scaled nationally, leading to uneven access and quality of care
- **Foundational system:** Major structural and policy gaps, little to no specialised framework for RTT care, placing full burden on families, requiring an urgent need for investment and RTT recognition

Below, we outline the key challenges driving fragmented care, accompanied by country examples that illustrate how different aspects of care can align with different archetypes in practice.

2.1 Health System Challenges Result in Fragmented, Unequal and Hard-to-Navigate RTT Care

At the healthcare system level, three major issues bolster fragmentation of RTT care, related to capacity and infrastructure, geographical distance from treatment centres, and administrative hurdles.

Limited Specialist Capacity and Diagnostic Infrastructure Lead to Uneven Diagnosis and Fragmented Care across Europe

The shortage of dedicated RTT clinics and experts in many countries leads to uneven care availability. Only between five and ten European countries benefit to varying degrees from the services of a national RTT expertise centre or specialised multidisciplinary RTT clinics, some of which are part of broader rare disease centres.[12] In several other countries, one or more hospitals may provide diagnostic services through one or two medical experts, but RTT-specific expertise remains scarce.[13] For example, Denmark and Sweden each operate a national RTT centre, and France has developed RTT clinic networks.[14] The scarcity of RTT expert centres creates “huge variability in knowledge and expertise” between countries, meaning that where a patient lives largely determines

the quality of care they can access.[15] Furthermore, limited diagnostic infrastructure and capacity constrain timely diagnosis.[16] The uneven levels of diagnostic expertise contribute to fragmentation not only within countries but also across Europe as a whole, resulting in stark inequalities between health systems.

Geography Becomes a Barrier to Continuous, Coordinated RTT Care

Even when expertise exists, it is often concentrated in major cities or single centres, forcing families to travel long distances to obtain adequate care. In Spain, for instance, parents and their children with RTT who live in smaller peripheral cities must travel long distances to access adequate care, incurring additional costs in the process.[17] Similarly, an Italian caregiver survey (AIRETT) found that individuals with RTT were often followed by multiple specialists located far apart, causing work disruptions and additional travel expenses for parents.[18] In effect, geography can be a barrier to continuous integrated care, as families in outlying regions struggle to reach care providers.

Administrative Hurdles Create Care Gaps and Add Significant Stress for Caregivers

Caregivers often face bureaucratic challenges and lengthy legal processes to access support services or assistive equipment, such as adapted beds, wheelchairs or day programmes. Parents in Spain described navigating the system as "a continuous struggle" to secure their children's right to appropriate care and social support.[19] Obtaining approvals often demands excessive paperwork and persistent advocacy (support). Access to and affordability of communication devices (such as eye gaze devices) highlight the problem. Although these tools can greatly improve quality of life, they are expensive and difficult to obtain. Despite laws requiring social security coverage, provision is limited, and many families must purchase and maintain devices at their own personal expense. Grants, patient associations and charitable support exist, but caregivers describe these supports as insufficient compared to demand; many report significant unmet needs for equipment and therapies and often rely on their own resources.[20] The time lost to bureaucratic wrangling and unmet promises is itself a form of care fragmentation, forcing families to bridge systemic gaps and adding a heavy strain, compounding the already significant challenges of managing RTT.

COUNTRY SNAPSHOTS - SPECIALIST CAPACITY AND EXPERTISE

The degree of healthcare system preparedness for RTT varies significantly across Europe. Denmark and Sweden benefit from integrated approaches, each having a National Centre for Rett Syndrome that provides one-stop, high-speciality care: multidisciplinary clinics offering medical expertise, therapy, family support, and even research and provider training.[21,22] In France, care is organised within the national rare disease health network (DéfiScience), which focuses on rare developmental brain disorders and intellectual disabilities. RTT care specifically falls under a dedicated subnetwork for intellectual and multiple disabilities of rare causes, coordinated by four reference centres—one of which, Hôpital de la Timone in Marseille, serves as the national coordinating centre—and 11 affiliated regional competence centres. The AP-HP Necker–Enfants Malades Hospital in Paris also holds a specific role as the recognised national RTT reference centre.[23] Italy has established a few RTT clinics and introduced regional protocols to promote multidisciplinary evaluation and follow-up, although families there still report challenges with long-distance travel and coordination between services.[24] Germany has developed an extensive network of Sozialpädiatrische Zentren (SPZs, or social paediatric centres) that provide multidisciplinary care for children with rare and complex conditions, including RTT. Despite this strong infrastructure, awareness and RTT-specific expertise remain limited, underlining the

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(CONT.)

need for continued knowledge sharing and cross-country learning.[25] By contrast, Spain relies on a single specialised clinic in Barcelona and Madrid, which creates a stark regional disparity—families in other areas have little access to RTT-focused care.[26] Austria, similar to Greece, has no dedicated RTT centre or expert network at all, aside from ad hoc resources for specific manifestations of the syndrome (e.g. clinics for rare epilepsies or other neurodevelopmental disorders). Consequently, Austrian and Greek families must depend on general healthcare services that are often ill-equipped to manage RTT's complexities and rely on a few physicians with interest in RTT trying to organise a small circle of supporting subspecialities in order to provide the best-available standards of care.[27,28]

These differences illustrate how countries across Europe can learn from one another's models, combining the structured networks seen in France and the Nordic countries with greater awareness, specialist training and equitable access to expertise across regions.

2.2 Clinical Management Gaps Lead to Delayed Recognition and Fragmented Care

In addition to system-wide shortcomings, several challenges in day-to-day clinical management contribute to fragmented care. These challenges often overlap and are interconnected: gaps in awareness, diagnosis and management protocols reinforce one another and compound the burden on caregivers and their quality of life.

Low Awareness Among Nonspecialist Care Providers Leads to Missed Early Signs and Late Referrals

Nonspecialist care providers, such as general practitioners (GPs), have limited direct clinical experience with RTT due to its rarity; hence, awareness is low, which delays early identification and coordinated management.[29] Caregivers are typically the first to recognise early signs, such as developmental delays or autism-like symptoms, but frequently report that healthcare providers dismiss their concerns.[30] In many cases, providers may not recognise these early symptoms or know where to refer patients for further evaluation. For example, a Spanish study found primary care "unsuitable" for RTT individuals because local doctors had little understanding of the disorder.[31] Such limited awareness among nonspecialist providers delays referral to appropriate specialists and can lead to misdiagnoses (e.g. labelling early RTT as autism or other developmental disorders). The immediate effect of low awareness is that children are not referred, or are referred late, to appropriate specialists. This contributes to fragmentation by breaking the chain of coordinated care: children may see some specialists but not all those required for comprehensive management, leaving families outside a structured, multidisciplinary pathway.

Challenges in Delivering Correct and Timely Diagnoses Lead to Lost Time and Fragmented Early Management

Diagnosing RTT can be complex, and many children experience significant delays before receiving a definitive and correct diagnosis. One third of families initially receive a misdiagnosis, most often autism, which postpones appropriate care. As discussed above, early signs of RTT are often missed or mistaken for other conditions, and long waiting times for referrals and specialist appointments further delay recognition. Confirming an RTT diagnosis typically requires sequential input from multiple specialists, and when referrals are slow or communication is inconsistent, the time to diagnosis may be delayed further.[32,33] In summary, the time to RTT diagnosis remains suboptimal across many parts of Europe. In some countries, like Ireland, the average age of RTT diagnosis remains around five years, notably higher than in Denmark (average two years) and Poland (average 3.5 years), but lower than in Belgium and the Netherlands; parts of the comparative datasets trace back

to 2012, and arguably the diagnostic pathways may have improved since. Broader international caregiver survey data reinforce these national findings, reporting a mean diagnostic age of 4.3 years and a median age of 2.8 years across cohorts in Europe, North America and Australia, underlining that delays in timely clinical recognition are a widespread issue rather than isolated to particular countries.[35]

Lack of Standardised Protocols for Diagnosis and Management Lead to Uneven Care, Poor Communication and Inconsistent Follow-up

There are few formal guidelines or care pathways for RTT, resulting in inconsistent practices across and within countries. For example, absent national protocols for RTT care in Greece, care is guided by international guidelines and the place-based experience of individual centres and/or physicians; most European countries take a similar approach. In fact, no internationally agreed-upon clinical guidelines existed for the overall management of RTT until 2020, when the first international consensus guidelines on managing RTT were published; additional care guidelines were published in 2024 by the International Rett Syndrome Foundation.[36,37] At the national level, only a handful of countries (such as France and Italy) have developed any RTT-specific country protocols or care standards.[38] However, there are international resources and guidelines to manage specific RTT concerns (e.g. communication challenges, scoliosis management, nutrition and growth, bone health).[39] In most of Europe, clinicians must rely on general rare disease frameworks or their own experience, which means important aspects of care (e.g. screening for scoliosis or managing feeding difficulties) may be handled differently depending on the provider or region.

In the absence of clear protocols, caregivers often seek assistance in multiple settings where the lack of a consistent, homogeneous level of assistance increase the difficulties of finding the right level of care.[40] Parents also highlight inadequate communication and follow-up by healthcare professionals, leaving parents to navigate the complexities of the syndrome largely on their own. Survey evidence reinforces this gap: in a survey of 55 parents from the AIRETT, many reported feeling poorly informed by their providers, particularly the fathers of severely affected girls. Strikingly, this sentiment persisted even among those who otherwise rated their satisfaction with coordinated care as "intermediate."[41] Such findings underscore how the lack of standardised protocols translates directly into poor communication, limited follow-up and uneven support for families.

Placed alongside low awareness and diagnostic difficulties, the lack of standardised protocols exacerbates both problems: it prevents consistent early recognition, slows referrals and leaves specialists without common standards for coordination. As a result, it amplifies fragmentation by making care uneven, unpredictable and heavily dependent on where families live.

COUNTRY SNAPSHOTS - STANDARDISED PROTOCOLS FOR DIAGNOSIS AND MANAGEMENT

France has a clearly defined protocol for RTT. The French national diagnosis and care protocol (PNDS), publicly available on the French National Authority for Health's website, provides standardised criteria for diagnosis and recommendations for multidisciplinary management.[42] In the Lombardy and Tuscany regions of Italy, a comprehensive clinical care pathway (PDTA) for Rett syndrome is available, outlining diagnostic criteria, therapeutic strategies and care coordination protocols.[43,44] The pathway promotes standardised and consistent care across institutions and regions, although the extent to which it is implemented more broadly across Italy is unclear. These countries are the exceptions rather than the rule.

2.3 Coordination Gaps Across the Care Pathway Intensify Fragmentation and Burden Families

Finally, numerous challenges arise at the intersection of healthcare system infrastructure and routine clinical management, with deficiencies in each domain compounding and reinforcing one another.

Weak Multidisciplinary Care Coordination Leaves Families to Bridge System Gaps

Since RTT is a complex disorder affecting multiple body systems, effective management requires well-coordinated multidisciplinary care involving many different specialists, such as paediatric neurologists, physiotherapists, occupational and speech therapists, geneticists, gastroenterologists, cardiologists, and GPs. Ideally, a paediatric neurologist or a paediatrician with knowledge of hereditary and congenital abnormalities would act as the central coordinator for paediatric patients; however, in practice, this is seldom the case. Specialists often communicate only on an ad hoc basis, and parents are left to bridge gaps, acting as de facto care coordinators.[45]

Coordination is further hindered by limited access to specialised services, long travel distances and extended waiting times. Even where multidisciplinary clinics exist, communication breakdowns often persist. Polish caregivers highlight the need for embedded teams and formal protocols to reduce poor coordination and "fragmented care."[46] By contrast, some countries, such as France, Spain and the Netherlands, have established interdisciplinary care units where specialists meet jointly to discuss cases, demonstrating how structured coordination can improve outcomes.[47,48]

Fragmented Transition from Childhood to Adulthood Creates Major Breaks in Continuity of Care

The general absence of a structured childhood-to-adulthood transition worsens care gaps for RTT patients. A structured transition should involve a planned, gradual handover, with paediatric teams preparing families and coordinating with adult providers to ensure continuity. Such systems are largely missing. When paediatric eligibility ends, caregivers must navigate unfamiliar services and identify new specialists, often without guidance from paediatric providers who themselves lack transition protocols.

Unlike paediatric clinics, where multiple specialists are often colocated, most adult clinics operate independently, requiring referrals to different providers and adding complexity to coordination.[49] This shift places a heavy burden on families, who frequently assume the role of coordinator without professional or financial support. Caregivers report heightened anxiety about the future, particularly regarding symptom progression, long-term care arrangements as they age and the affordability of professional services, hence impacting overall quality of life.

More broadly, the lack of structured transition protocols is a common challenge across neurodevelopmental disorders, leading to inconsistent or absent handovers that fail to address patients' complex, lifelong needs.[50]

COUNTRY SNAPSHOTS - CHILDHOOD TO ADULTHOOD TRANSITION

In the UK, a troubleshooting RTT specialist clinic was set up to provide practical advice and support caregivers with transitioning to adult services. Although the clinic was established temporarily and not intended as a site for regular follow-up, families described an "excellent" experience with integrated care.[51] In Italy, the San Paolo University Hospital in Milan established a formal transitional programme from paediatric to adult care for girls with RTT, with positive outcomes in terms of managing all main comorbidities. Specifically, a core team comprising a paediatric neurologist, paediatrician and neurologist is responsible for monitoring and scheduling clinical follow-ups for individuals based on their needs and local guidance.[52] The Netherlands officially recognises physicians who serve people with intellectual disabilities as a distinct medical speciality—a role that focuses on comprehensive care for individuals with intellectual disabilities, including transition from paediatric to adult care that can support individuals with RTT.[53] In contrast, in Poland, where there is no evidence of support systems (e.g. transition coordinators), Polish RTT caregivers describe the lack of support and challenges when transitioning to adult care and highlight the need for infrastructure to mitigate fragmented childhood to adulthood care planning (e.g. residential care homes for adults with RTT).[54]

3. CONSEQUENCES FOR PATIENTS, CAREGIVERS, AND HEALTHCARE SYSTEMS

Ultimately, patients, caregivers and healthcare systems bear the burden of a lack of coordinated care. This section sheds light on the central consequence of care fragmentation—worsened health outcomes—and outlines the main ways fragmented care creates additional burdens for caregivers, education systems and society.

3.1 Fragmented Care Directly Worsens Health Outcomes for Patients

For patients, challenges in care coordination can contribute to worsened health outcomes and reduced quality of life for the whole family. Fragmented coordination can lead to delays in diagnosis and accessing care, as well as increased medical errors when communication and information exchange between providers breaks down.

A survey of UK caregivers and patients with rare diseases highlights the negative impact on patients' physical health when, for reasons related to lack of care coordination, they experience delays in diagnosis and treatment.[55] Arguably, these negative consequences and associated risks are exacerbated in the context of RTT and other rare neurodevelopmental disorders, where accurate diagnosis can be particularly challenging. Delayed diagnostic confirmation or slow access to coordinated care increases the time before appropriate seizure management, feeding safety assessment and spinal surveillance are in place—raising the risk of uncontrolled epilepsy, nutritional compromise and more advanced scoliosis at presentation. Cohort- and clinic-based evidence documents high epilepsy burden without timely management, frequent dysphagia with documented aspiration pneumonia and rapidly progressing scoliosis that would have otherwise benefitted from early orthopaedic monitoring and intervention.[56,57,58]

Regarding ineffective communication between providers, one study found that poor communication of patient information between healthcare professionals is associated with more than 80% of medical errors that take place during transitions of care.[59] For RTT, where many different types of providers are involved to manage the diversity of complications individuals with RTT experience, information exchange and communication become even more critical. This is not limited to physicians. For example, oral health problems such as bruxism, caries and dental abscesses are highly prevalent in RTT, yet families often struggle to find dentists willing or able to provide care due to behavioural challenges and the need for sedation. A recent case study showed that interprofessional collaboration between medical and dental teams, coordinating sedation, surgical timing and shared goals of care, led to significant improvements in quality of life for a young adult with RTT. Following collaborative treatment, the patient's agitation decreased, self-injurious behaviours resolved and her sleep improved, underscoring that even dental care, when integrated with medical care, can have profound impacts on overall health and wellbeing.[60] This illustrates the broader principle that without structured collaboration, important aspects of RTT management risk being overlooked, whereas integrated multidisciplinary care can directly improve outcomes and quality of life.

Pathways Through Which Fragmented Care Worsens Outcomes

3.2 Caregivers Shoulder Significant Emotional and Economic Burden Due to Poor Care Coordination

The emotional and financial burden of RTT on families is considerable, underscoring the need for comprehensive support systems. Families who must navigate fragmented care are often compelled to reduce their professional commitments to meet the complex needs of their loved ones. The result of this loss of productivity yields a cascade of indirect costs: financial strain, increased stress and risk of burnout for the broader family (e.g. siblings), and hence a reduced quality of life. Qualitative research from caregivers in Spain noted that the financial burden on families is "worsened by one of the caregivers abandoning their work" to care for their child.[61] Studies from Poland and Italy also

capture the significant psychosocial burden on caregivers navigating a fragmented and convoluted care system.[62,63] The lack of disease-specific treatments for RTT exacerbates this burden. A European (Italy, Germany and France) rare disease burden study found that for complex disorders like RTT, where no disease-specific treatments are available, indirect costs due to lost productivity can be even higher relative to rare diseases where treatment options are available; one study noted costs rising from approximately 30% to around 45% in untreated rare diseases.[64]

Families of individuals with RTT face significant out-of-pocket expenses. RTT-specific studies show high annual costs, with spending on therapies, equipment (e.g. communication devices), diapers and home modifications (e.g. wheelchair ramps, lifts) creating "undue financial stress"[65,66] Due to the complexity of symptoms, this nonmedical equipment is essential, yet, as previously discussed, under current health and social protection policies in most countries, it is rarely reimbursed. Caregivers must also cover frequent travel to specialist clinics, a common burden given the scarcity of coordinated RTT expertise, which further adds to the financial strain.[67]

In addition, recent evidence highlights the significant psychological toll on parents of children with RTT. A 2024 scoping review found that parents consistently report high levels of stress, with around 40% reaching clinical levels. Depression and anxiety are also prevalent, particularly among mothers, and are associated with the severity of the child's condition and years of caregiving. Mental health outcomes were consistently lower than population norms, with contributing factors including sleep disturbances, gastrointestinal problems and the child's behavioural issues. Caregivers often describe profound self-sacrifice and loss of identity, with daily caretaking tasks leaving little room for their personal or professional life. While some parents also reported positive aspects such as resilience and family closeness, these do not offset the heavy psychological burden. Importantly, the fragmented nature of care intensifies these pressures, as parents must act not only as caregivers but also as advocates and coordinators within underprepared health systems.[68]

3.3 Fragmented Support Limits Educational Access and Lifelong Learning Opportunities for Individuals with RTT

Across Europe, children and young adults with Rett syndrome face persistent and systemic obstacles to participating in learning throughout their lives. Communication and motor impairments mean that children and students with RTT require tailored support, including augmentative and alternative communication (AAC) technologies, one-on-one assistance, and adapted learning materials.[69] However, families consistently report limited access to AAC devices, insufficient staff training, and inadequate speech therapy, despite evidence that such tools significantly improve engagement and decision-making in the classroom.[70] Many teachers feel unprepared to manage the complex needs of RTT students, and support centres tasked with advising educators are often under-resourced. Funding for classroom aides is inconsistent, forcing some families to rely on private resources to ensure appropriate care.[71] Although most European countries endorse inclusion, actual implementation is fragmented: special schools still dominate for students with profound disabilities, and mainstream settings often lack the capacity to deliver high-quality support.[72] These gaps extend across the lifespan. Early intervention services are unevenly distributed, and adult education or vocational pathways for people with RTT remain rare.

3.4 Fragmented Care Amplifies Healthcare Costs and System Inefficiencies

Reliable RTT-specific cost-of-illness data are scarce, but existing evidence and broader rare disease research point to a substantial burden on both healthcare systems and society. RTT individuals often require frequent hospitalisations - 21% are admitted for respiratory infections within five years - and scoliosis surgery typically involves 12–18 days of inpatient care, generating significant costs.[73,74] International real-world evidence suggests that individuals with RTT face annual healthcare costs of roughly €37,000–€42,000 per patient, with children generally requiring more resources than adults.[75,76,77] These estimates reflect costs associated with standard medical care, such as antiepileptic and other supportive medications.

A recent multi-country study highlights the scale of the challenge: across nine European countries, the average annual cost of living with a rare disease is €121,900 per person - six times higher than for the general population.[78] Direct medical costs account for the largest share (€78,900 per year), but inefficiencies and fragmentation amplify indirect costs. At the system level, rare diseases cost Europe €249.3 billion annually - more than cardiovascular disease (€176.8 billion annually). Neurological rare diseases, such as RTT, contribute disproportionately to these excess financial costs.

Fragmented care drives these numbers even higher. Families affected by rare diseases often interact with 10–30 social and healthcare professionals, and most report difficulty in coordinating services.[79] The absence of structured care pathways leads to duplication, delayed interventions, and preventable complications, all of which inflate system costs. Evidence shows that integrated care models improve outcomes while reducing expenditure. Hospital initiatives found that after implementing care integration measures, inpatient charges dropped from 48% of total spend to 41% in year 1 for an RTT cohort.[80]

The burden extends beyond the healthcare system to families and society at large. Rare disease caregivers lose on average 625 work hours annually (~16 weeks), compared to 199 hours in the general population - a 9.7-fold higher productivity loss. More than half of patients (53%) and nearly a third of caregivers (29%) report that their rare disease is the reason they work part-time instead of full-time.[81] Absenteeism averages 34 workdays per year, compared with 13 days in the general population. Families also shoulder disproportionate financial strain, with 26% of healthcare spending paid out-of-pocket compared to 15% in the general population.

Given its complexity, RTT likely imposes a comparable burden to other rare neurodevelopmental disorders, with costs and responsibilities shifted silently from healthcare systems to families, and from families to society.

4. CALL TO ACTION: POLICY RECOMMENDATIONS TO ADVANCE COORDINATED CARE IN RTT

Across Europe, families of individuals with RTT face a shared reality: navigating a fragmented healthcare landscape. Accessing even basic services often brings personal financial strain and logistical hurdles, placing additional pressure on families already managing complex needs. These challenges are not unique to RTT; they mirror the broader struggles of more than 30 million Europeans living with a rare disease.[82]

The EU has acknowledged this burden. In 2024, the European Council called for a comprehensive EU-level approach, including a European Action Plan on Rare Diseases.[83] Initiatives such as the European Reference Networks (ERNs) already connect expertise across borders, offering a framework for how complex conditions like RTT can be better managed. Now, national healthcare systems need to translate these ambitions into practice by setting minimum standards of RTT care across Europe.

Today, RTT care remains fragmented, leading to unequal access, heavy burdens on caregivers and families, and avoidable costs for health systems. Policymakers can reverse these consequences through better coordination, efficiency and equity in care. To achieve these aims, we propose two tiers of action:

- Priorities that all countries should adopt as a baseline for coordinated RTT care
- Tailored actions that account for the varying levels of integration across healthcare systems—whether integrated, evolving or foundational

Together, these steps provide a road map for every country to transition from its current position towards a fully coordinated care system, aiming to make comprehensive, supportive care and lifelong planning the norm rather than the exception.

Cross-Country Coordination of Care Priorities for RTT

To address care coordination gaps, we propose several cross-cutting policy actions that all countries should adopt as a baseline for coordinated RTT care:

- **Improved awareness and timely diagnosis:** Raise awareness of RTT among frontline healthcare professionals to improve early recognition of symptoms and reduce misdiagnosis, as well as delays in correct diagnosis. Implement standardised referral protocols so that once a case is suspected, families are directed to the appropriate specialists. Where feasible, explore the integration of RTT into broader rare disease awareness campaigns and early childhood screening initiatives.
- **Coordinated multidisciplinary care networks:** Create coordinated national RTT care pathways anchored in specialised expert centres (often part of ERNs). Multidisciplinary teams should work collaboratively to guide patients through key stages of care, from early intervention to adult services and long-term planning. To support this, national frameworks should include digital care-monitoring tools and clearly defined referral pathways that facilitate communication across specialities and ensure continuity. This approach promotes proactive, age-appropriate management while reducing the burden on families to coordinate complex care themselves.

- **Standardised protocols for care and patient data collection:** Develop and adopt standardised care protocols for RTT management. Additionally, invest in real-world evidence programmes, such as patient registries and consistent outcome monitoring, to continuously learn what works in supportive care and to prepare health systems for upcoming innovative therapies. Given the rarity of RTT, taking examples from ERNs and establishing a cross-region EU registry would maximise available data, enable stronger research collaboration and support more consistent care across borders.
- **Caregiver empowerment and support:** Empower and support caregivers who are the backbone of RTT care. This includes providing financial assistance and psychosocial support services to reduce burnout and loss of productivity. Provide accessible information and training for families to manage complex needs at home. Critically, ERNs and national specialist centres should involve and recognise patient advocacy organisations as key partners; they serve as hubs for peer support and knowledge exchange and can help disseminate best practices to hard-to-reach families.
- **Long-term strategy for research and equitable access:** Develop a European and national strategy to strengthen RTT research, improve understanding of disease progression and comorbidities, and ensure equitable access to high-quality care and innovation across countries. This includes continued investment in clinical research and workforce training so that all individuals with RTT, regardless of where they live, benefit from the same opportunities for diagnosis, treatment and lifelong care.

Recommended Policy Changes in Delivery of Coordinated Care Tailored to National Contexts

European countries differ in how integrated their services are for complex conditions like RTT. Some have highly organised rare disease networks, while others are still building basic support. To account for this, we outline priorities for three broad archetypes of healthcare system integration: Integrated, Evolving and Foundational. This approach recognises that a country might be integrated in one aspect (e.g. having a strong paediatric centre) but foundational in another (e.g. adult care or research). Every country can thus identify where it stands in each area and progress from its current baseline. The table below summarises key priorities for each archetype, offering a road map that guides each country to advance RTT care within its context and realities on the ground.

Policy priorities for RTT at the national level, adjusted to health system maturity levels

Policy Component	Integrated Systems (advanced & structured)	Evolving Systems (building integration)	Foundational Systems (urgent basics needed)
Improved awareness and timely diagnosis	Maintain high awareness of RTT among primary care providers through continuous education. Provide telemedicine and cross-border specialist consultations to reach patients in underserved or rural areas, achieving more equitable access.	Implement nationwide training for general practitioners and paediatricians about RTT. Standardise referral pathways so any suspected case quickly reaches specialists; consider newborn or early childhood screening if feasible (challenging in absence of treatment). Use ERNs or tele-expertise services to fill gaps where local specialist knowledge is lacking.	**Launch broad awareness campaigns** for healthcare workers and the public to improve early recognition of RTT signs. **Create simple referral pathways** linking local clinics to the national RTT centre and to ERNs, so that patients see all necessary specialists (not just a subset), minimising fragmentation.
Coordinated multidisciplinary care networks	Refine the existing multidisciplinary care pathways to include **specific precautions** (e.g. safe sedation/anaesthesia protocols, guidance on alternative therapies) and to introduce palliative care and guardianship planning early in the care journey. **Ensure structured transition plans for adulthood**—for instance, via joint paediatric-adult clinics—and integrate social services and mental health supports into care plans for adults with RTT.	Develop and disseminate official **national RTT management guideline**s. Pilot the use of dedicated care coordinators to organise appointments and communication across specialities for each patient. **Include sedation safety and palliative care** in all standard care protocols, and start preparing families for transition to adult care well before the child ages out of paediatric services.	**Establish basic multidisciplinary teams** (neurology, orthopaedics, gastroenterology, etc.) at least in the main centre, and outline basic care protocols covering diagnosis, first-line medical management and when to refer to specialists or ERNs. **Provide immediate caregiver/ family supports** such as respite services and family counselling, and train emergency and hospital staff on RTT care basics.
Standardised protocols for care and patient data collection	Incorporate RTT in national **rare disease plans**, and ensure sustained funding for specialist centres. **Adopt nationwide protocols for safe sedation, early palliative care and legal guardianship** in all regions. Invest in RTT research and patient registries; encourage participation in European clinical trials to contribute to and benefit from new treatments.	Expand pilot programmes into formal national networks. Establish more multidisciplinary expertise clinics. Harmonise social and care reimbursement policies to fund **assistive technologies and home modifications** for families.	Acknowledge RTT as a priority in the rare disease strategy. **Designate at least one national reference centre** for RTT, and ensure basic access to core therapies. **Leverage ERNs and cross-border care** to obtain expertise and treatments that are not available domestically, avoiding delays for patients.
Caregiver empowerment and support	**Sustain and enhance** an already advanced system: Keep what works (expert centres, funding) and fill remaining gaps. Key tasks include smoothing the youth-to-adult transition and supporting caregivers navigating the transitions independently.	**Scale and standardise** an evolving system: Build on successful pilots by unifying them into a national programme. Priorities include creating one consistent set of care standards, ensuring **equitable services across regions** and instituting roles (like care coordinators) and funding that make the network sustainable.	**Build the fundamentals:** Focus on **identification, diagnosis and basic care**. The first steps are to find patients (awareness), diagnose them (clinical expertise) and connect them to a multidisciplinary care hub. In parallel, use international support (ERNs, partnerships) so RTT individuals are not left waiting for care improvements that will take time to develop domestically.
Long-term strategy for research and equitable access	**Expand resources** dedicated to maintaining an optimal research environment to better understand RTT. **Continue to actively engage in research and trials** to keep pushing care quality forward.	**Elevate the importance of RTT clinical research** further at the national level, embedding it as a priority within existing rare disease action plans and strategies. **Enhance clinical workforce training** to ensure clinicians have the support needed to deliver care to all individuals with RTT who need it.	**Leverage cross-border expertise and establish knowledge transfer partnerships** to broaden local foundational scientific understanding of RTT. **Build capabilities for the national reference centre** to act both as a clinical and research centre of excellence.

5. APPENDIX – METHODOLOGY

Methodology

This white paper was developed through a mixed-methods approach that combined a targeted literature review with stakeholder consultations and policy dialogue.

Targeted literature search

We conducted a targeted search using Google Scholar and the Google search engine to identify evidence relevant to the challenges and opportunities in Rett syndrome (RTT) care across Europe. Search terms included combinations of "Rett syndrome", "fragmented care", "care coordination", "multidisciplinary care", "rare disease policy", "transition to adult care", "diagnosis delay", "awareness of rare diseases" and "economic burden of rare diseases." To capture the breadth of perspectives, we drew on:

- Peer-reviewed academic literature (clinical and health policy journals)
- Official government reports and health authority documents
- Publications from patient associations and advocacy groups
- Grey literature, including think-tank reports, conference proceedings and professional society statements

Sources were included in both English and local languages (French, German, Spanish, Danish and Italian). In total, 51 sources were reviewed and synthesised.

Expert and caregiver input

To complement the desk research and validate key findings, feedback was gathered from rare disease experts (including clinicians, policy specialists and patient advocates) and caregivers of individuals with RTT across several European countries. Their insights helped contextualise the evidence on care fragmentation, reflect national realities and assess the feasibility of proposed policy actions. Experts and caregivers also provided input on the policy recommendations developed by CRA, ensuring that the final proposals are both evidence-based and grounded in lived experience.

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CRA Charles River Associates

EBC European Brain Council

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