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# Characterizing the journey of Rett syndrome among females in the United States: a real-world evidence study using the Rett syndrome natural history study database

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## Abstract

**Background** With the advent of the first targeted therapy for Rett Syndrome (RTT), a comprehensive assessment of the journey of RTT is needed to elucidate on present unmet needs in this population. This study characterized females with RTT in the United States and their disease journey with respect to longitudinal treatment patterns, RTT-related outcomes, and changes in disease severity.

**Methods** This retrospective cohort study used registry data of females with RTT from the 5211 RTT Natural History Study (RNHS) (November 2015–July 2021). Pharmacological and supportive therapy use, RTT-related outcomes, and RTT severity, as measured by the Clinical Severity Scale and Motor Behavioral Assessment scale, were evaluated following the first RNHS visit. Analyses were conducted overall and in subgroups by RTT type (classic and atypical RTT) and age at first visit (pediatric and adult).

**Results** A total of 455 females with RTT were included in the study, of whom 90.5% had classic RTT and 79.8% were pediatric individuals. Over a median follow-up of 4 years, use of pharmacological therapies, including prokinetic agents (42.7% vs. 28.3%), and supportive therapies, including physical therapy (87.3% vs. 40.2%) and speech-language therapy (86.8% vs. 23.9%), were more common in pediatric than adult individuals (all  $p < 0.05$ ). Nearly half (44.6%) of all individuals had a hospital or emergency room visit, with a higher proportion of visits in individuals with classic RTT than atypical RTT and pediatric than adult individuals (both  $p = 0.001$ ). An increasing trend in clinical severity was observed in pediatric individuals (mean change per year: 0.24; 95% confidence interval [CI]: 0.03, 0.44), while an increasing trend in motor-behavioral dysfunction was observed in pediatric individuals (mean change per year: 1.12; 95% CI: 0.63, 1.60) and those with classic RTT (mean change per year: 0.97; 95% CI: 0.53, 1.41).

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**Conclusions** Findings from this study highlight the considerable burden of RTT across disease subtype and age. Despite reliance on supportive therapies and healthcare encounters, individuals with RTT experience increasing disease severity and motor-behavioral dysfunction in childhood and adolescence, underscoring the unmet needs of this population and the value of early intervention to manage RTT in the long-term.

**Keywords** Rett syndrome, Disease progression, Natural history, Registry, Treatment patterns, Clinical manifestations

## Background

Rett syndrome (RTT) is a severe neurodevelopmental disorder that occurs almost exclusively in females, with an estimated incidence of 1 out of every 10,000 to 15,000 live female births worldwide [1–3]. RTT is clinically diagnosed as classic or atypical based on the manifestation of key clinical symptoms [2], with an average age at diagnosis of 2.5 years [2]. In 90–95% of individuals with classic RTT, the disorder is caused by a spontaneous mutation in the *MECP2* gene on the X chromosome [2, 3]. There are four main criteria required for diagnosing classic RTT, including the partial or complete loss of acquired purposeful hand skills, the partial or complete loss of spoken language, stereotypic hand movements, and gait abnormalities [2]. At least two of the four main criteria are required to diagnose atypical RTT, in addition to at least five of 11 supportive criteria [2, 4].

Despite an estimated survival of over 70% at 45 years of age [5], RTT is associated with substantial clinical and humanistic burden that translates to poor quality of life (QoL) [2, 6]. Individuals with RTT often require lifelong care due to a range of symptoms, stemming from neurological, gastrointestinal, cardiac, endocrine, and orthopedic disorders [5, 7]. However, there is limited longitudinal data describing how the severity of RTT changes over time, underscoring a much-needed area of research.

Until recently, treatment options for RTT were limited to symptom management and supportive care for daily activities [2, 4, 8]. To promote childhood development, consensus guidelines recommend early referral to physical, occupational, and speech language therapists, as well as establishment of an individualized education program [2]. Anticonvulsants may be used to treat seizures, and maintaining a healthy body mass and monitoring for scoliosis become important considerations as individuals reach late childhood [2].

In March 2023, the United States (US) Food and Drug Administration (FDA) approved trofinetide as the first pharmaceutical therapy for RTT [9, 10]. With the advent of trofinetide for treatment of RTT, a comprehensive understanding of the characteristics and disease journey of individuals with RTT is needed to elucidate on present unmet needs and inform the integration of novel therapies into the current treatment paradigm for RTT.

The overarching aim of this study was to characterize females with classic or atypical RTT in the US with respect to their demographic and clinical profiles, and

to describe their disease journey with respect to longitudinal patterns of treatment, RTT-related outcomes, and changes in disease severity.

## Methods

### Data source

All analyses were conducted using registry data from the 5211 RTT Natural History Study (RNHS) spanning from November 2015 to July 2021. The 5211 RNHS is a US-based, multi-center, five-year observational registry study that has been comprehensively described in prior literature [5, 6, 11–14]. Briefly, it includes data on measures such as demographics, developmental skills (clinician-recorded or caregiver-reported), RTT clinical features, supportive therapy (e.g., physical therapy), medication logs, and death, as well as clinical severity and motor-behavioral dysfunction, as evaluated by the Clinical Severity Scale (CSS) and Motor Behavioral Assessment (MBA) scales, respectively. Data were de-identified and compliant with the Health Insurance Portability and Accountability Act.

### Study design and population

A retrospective, longitudinal cohort design was used to address the study objectives. The index date was defined as the date of the first RNHS visit. The follow-up period was defined as the time after the index date up to the earliest date of study disenrollment, death, or study completion.

The study population consisted of females with a diagnosis of classic or atypical RTT, at least one follow-up visit, and no history of brain trauma on or before the index date. The overall study sample was further stratified into subgroups by RTT type (classic RTT and atypical RTT) and age at index (pediatric [ $<18$  years of age]) and adult [ $\geq 18$  years of age]).

### Outcomes

Demographics and clinical characteristics were evaluated on the index date and included age at first visit, age at onset of regression, race, *MECP2* mutation status, clinical manifestations of RTT, and gross motor function.

Pharmacological and supportive therapy use were evaluated during the follow-up period. Pharmacological therapies included the use of prokinetic agents, antiepileptics, sedative/hypnotics, and nutritional supplements. Reasons for discontinuation of pharmacologic therapy,

including ineffective treatment, treatment not needed, and side effects, were reported among individuals who discontinued treatment. Supportive therapies included the use of physical therapy, speech-language therapy, occupational therapy, scoliosis treatment (including bracing, serial casting, and surgery), behavioral therapy, vision therapy, and feeding assistance (including feeding tube). Feeding assistance was identified from hospital or emergency room visits that listed feeding assistance as the reason for the visit.

RTT-related outcomes were evaluated during the follow-up period and included hospital and emergency room visits, incident gastrostomy tube (g-tube) surgery, and death. Incident g-tube surgery was evaluated among individuals without a prior g-tube surgery on the index date.

RTT severity was assessed based on the CSS and MBA scale and evaluated at each year following the first visit. The CSS is a clinician-completed questionnaire that uses a Likert-type scale to rank statements in 13 categories related to the features of RTT for a maximum score of 58 [15]. The MBA scale is a clinician-completed questionnaire that uses a Likert-type scale to score 34 items on a severity scale of 0 to 4 (none, 25% of the time, 50% of the time, 75% of the time, 100% of the time) for a maximum total score of 136 [13]. For both the CSS and MBA scale, higher scores represent greater clinical severity.

### Statistical analysis

All statistical analyses were conducted using SAS Enterprise 7.1 software (SAS Institute, Cary, NC, USA). The extent of missing data was summarized for all study measures. All measures in this study were evaluated in the subset of individuals with complete information on these measures. No imputation was conducted for missing data. Demographics, clinical characteristics, use of pharmacological and supportive therapies, RTT-related outcomes, and annual change in RTT severity were summarized using means, standard deviations (SDs), and medians for continuous characteristics and frequencies and proportions for categorical characteristics.

Due to the substantial missingness (>65%) in CSS and MBA scores from years 3–5 of follow up, these measures were only evaluated from the first RNHS visit to year 2 of follow-up. CSS and MBA scores were summarized for each respective year among individuals with available measurements using means SDs, and medians. Separate linear mixed effect models were used to estimate mean change in CSS and MBA scores per year and corresponding 95% confidence intervals (CIs).

Statistical comparisons between individuals with classic RTT vs. atypical RTT and pediatric individuals vs. adult individuals were conducted using t-tests for means and Chi-squared tests or Fisher's exact tests (when the

expected sample size was <5) for proportions. The t-statistic was reported for comparisons conducted using the t-test and the Chi-squared value was reported for comparisons conducted using the Chi-squared test or Fisher's exact test. Nominal  $p$ -values <0.05 were considered statistically significant and were not adjusted for multiple comparisons.

## Results

### Study population

After applying all eligibility criteria, 455 females with RTT were included in the study, of whom 412 (90.5%) had classic RTT and 43 (9.5%) had atypical RTT. Three hundred and sixty-three individuals (79.8%) were pediatric, while 92 (20.2%) were adults.

Demographic and clinical characteristics of the study population are presented in Table 1. Mean (SD) age at first visit was 11.8 (9.5) years in the overall RTT cohort, 7.9 (4.7) years among pediatric individuals, and 27.1 (8.1) years among adult individuals. Mean (SD) age of motor and communication regression was 2.3 (0.8) years overall. Individuals primarily identified as White (87.0%) and nearly all had an *MECP2* mutation (98.2%).

Common clinical manifestations of RTT included loss of language (95.8%), hand stereotypies (92.3%), respiratory dysfunction (75.8%), sleep disturbances (75.6%), and constipation (74.5%). Clinical manifestations were more prevalent in individuals with classic RTT than atypical RTT (loss of language: 99.5% vs. 60.5%,  $p<0.001$ ; hand stereotypies: 94.4% vs. 72.1%,  $p<0.001$ ; respiratory dysfunction: 79.1% vs. 44.2%,  $p<0.001$ ; sleep disturbances: 77.2% vs. 60.5%,  $p=0.015$ ; respectively). At first visit, scoliosis (73.9% vs. 45.7%,  $p<0.001$ ), constipation (83.7% vs. 72.2%,  $p=0.024$ ), and epilepsy (56.5% vs. 43.5%,  $p=0.026$ ) were more prevalent in adult individuals than pediatric individuals, respectively. There were no significant differences in ability to sit, stand, or walk independently between individuals with classic RTT and atypical RTT (classic: 47.3–74.0%; atypical: 58.1–79.1%).

### Use of pharmacological and supportive therapies during the follow-up period

Overall, the most used pharmacological therapies were prokinetic agents (39.8%) and antiepileptic drugs (32.3%) (Table 2). Compared with adult individuals, pediatric individuals were more likely to use prokinetic agents (42.7% vs. 28.3%,  $p=0.011$ ), antiepileptics (35.0% vs. 21.7%,  $p=0.015$ ), sedatives/hypnotics (27.8% vs. 15.2%,  $p=0.013$ ), and nutritional supplements (25.1% vs. 15.2%,  $p=0.045$ ) (Table 2). Use of pharmacological therapies was similar between individuals with classic RTT and individuals with atypical RTT (Table 2).

The most common reason for discontinuing prokinetic agents and sedatives/hypnotics among individuals

**Table 1** Demographics and clinical characteristics among females with RTT, overall and stratified by RTT type and age

Characteristics		Overall RTT		Stratification by RTT type			Stratification by age			
		Cohort	Classic RTT	Atypical RTT	Test statistic	p-value	Pediatric ( $< 18$ years of age)	Adult ( $\geq 18$ years of age)	Test statistic	p-value
Demographics										
Age at first visit, years, mean $\pm$ SD [median]		11.8 $\pm$ 9.5 [9]	11.8 $\pm$ 9.5 [9]	11.7 $\pm$ 9.7 [9]	-0.1	0.943	7.9 $\pm$ 4.7 [7]	27.1 $\pm$ 8.1 [25]	21.9	$< 0.001^*$
Age category at first visit, n (%)										
0–4		110 (24.2)	98 (23.8)	12 (27.9)	0.4	0.548	110 (30.3)	–	–	–
5–10		149 (32.7)	134 (32.5)	15 (34.9)	0.1	0.754	149 (41.0)	–	–	–
11–17		104 (22.9)	97 (23.5)	7 (16.3)	1.2	0.280	104 (28.7)	–	–	–
18–29		61 (13.4)	56 (13.6)	5 (11.6)	0.1	0.719	–	61 (66.3)	–	–
30–39		25 (5.5)	21 (5.1)	4 (9.3)	1.3	0.280	–	25 (27.2)	–	–
40–49		5 (1.1)	5 (1.2)	0 (0.0)	0.5	1.000	–	5 (5.4)	–	–
$\geq 50$		1 (0.2)	1 (0.2)	0 (0.0)	0.1	1.000	–	1 (1.1)	–	–
Age of regression onset, years, mean $\pm$ SD [median]		2.3 $\pm$ 0.8 [2]	2.4 $\pm$ 0.8 [2]	1.9 $\pm$ 1.2 [2]	-2.4	0.021*	2.4 $\pm$ 0.8 [2]	2.2 $\pm$ 0.8 [2]	-1.5	0.143
Race, n (%)										
White		396 (87.0)	357 (86.7)	39 (90.7)	0.6	0.452	310 (85.4)	86 (93.5)	4.2	0.039*
Multiple		21 (4.6)	20 (4.9)	1 (2.3)	0.6	0.709	20 (5.5)	1 (1.1)	3.3	0.093
Black or African American		15 (3.3)	14 (3.4)	1 (2.3)	0.1	1.000	12 (3.3)	3 (3.3)	0.0	1.000
Asian		14 (3.1)	14 (3.4)	0 (0.0)	1.5	0.381	13 (3.6)	1 (1.1)	1.5	0.319
Native Hawaiian and Other Pacific Islander		1 (0.2)	1 (0.2)	0 (0.0)	0.1	1.000	1 (0.3)	0 (0.0)	0.3	1.000
Unknown/unspecified		8 (1.8)	6 (1.5)	2 (4.7)	2.3	0.170	7 (1.9)	1 (1.1)	0.3	1.000
Clinical characteristics										
MECP2 mutation, n (%)		447 (98.2)	406 (98.5)	41 (95.3)	2.3	0.170	358 (98.6)	89 (96.7)	1.5	0.206
Clinical manifestations, n (%)										
Loss of spoken language		436 (95.8)	410 (99.5)	26 (60.5)	148.4	$< 0.001^*$	348 (95.9)	88 (95.7)	0.0	1.000
Hand stereotypes		420 (92.3)	389 (94.4)	31 (72.1)	27.3	$< 0.001^*$	339 (93.4)	81 (88.0)	3.0	0.086
Respiratory dysfunction		345 (75.8)	326 (79.1)	19 (44.2)	25.9	$< 0.001^*$	281 (77.4)	64 (69.6)	2.5	0.116
Sleep disturbances		344 (75.6)	318 (77.2)	26 (60.5)	5.9	0.015*	272 (74.9)	72 (78.3)	0.4	0.507
Constipation		339 (74.5)	308 (74.8)	31 (72.1)	0.1	0.703	262 (72.2)	77 (83.7)	5.1	0.024*
Feeding problems		292 (64.2)	268 (65.0)	24 (55.8)	1.4	0.229	233 (64.2)	59 (64.1)	0.0	0.992
Autonomic symptoms		274 (60.2)	248 (60.2)	26 (60.5)	0.0	0.972	216 (59.5)	58 (63.0)	0.4	0.536
Scoliosis		234 (51.4)	217 (52.7)	17 (39.5)	2.7	0.101	166 (45.7)	68 (73.9)	23.3	$< 0.001^*$
Gastroesophageal reflux		212 (46.6)	198 (48.1)	14 (32.6)	3.8	0.053	164 (45.2)	48 (52.2)	1.4	0.230
Epilepsy		210 (46.2)	196 (47.6)	14 (32.6)	3.5	0.060	158 (43.5)	52 (56.5)	5.0	0.026*
Fractures		17 (3.7)	14 (3.4)	3 (7.0)	1.4	0.210	12 (3.3)	5 (5.4)	0.9	0.356
Gall bladder dysfunction		8 (1.8)	8 (1.9)	0 (0.0)	0.8	1.000	3 (0.8)	5 (5.4)	9.0	0.010*
Gross motor function, n (%)										
Ability to sit		339 (74.5)	305 (74.0)	34 (79.1)	0.5	0.470	277 (76.3)	62 (67.4)	3.1	0.080
Ability to stand		223 (49.0)	198 (48.1)	25 (58.1)	1.6	0.208	177 (48.8)	46 (50.0)	0.0	0.832

**Table 1** (continued)

Characteristics	Overall RTT Cohort (N=455)	Stratification by RTT type		Test statistic	p-value	Stratification by age		Test statistic	p-value
		Classic RTT (N=412)	Atypical RTT (N=43)			Pediatric ( $<18$ years of age) (N=363)	Adult ( $\geq 18$ years of age) (N=92)		
Ambulation	220 (48.4)	195 (47.3)	25 (58.1)	1.8	0.177	173 (47.7)	47 (51.1)	0.3	0.557
Ability to communicate	34 (7.5)	31 (7.5)	3 (7.0)	0.0	1.000	26 (7.2)	8 (8.7)	0.2	0.617

Abbreviations: RTT: Rett syndrome; SD: standard deviation

Asterisks denote statistical significance at  $p < 0.05$ 

who discontinued treatment was that the therapy was no longer needed (63.0% and 44.0%, respectively) (Table 2). Among individuals who discontinued antiepileptic drugs, nearly half (48.8%) stopped use due to ineffective treatment (Table 2).

The most used supportive therapies were physical therapy (77.8%), speech-language therapy (74.1%), and occupational therapy (70.5%) (Fig. 1). Pediatric individuals were more likely than adult individuals to use physical therapy (87.3% vs. 40.2%,  $p < 0.001$ ), speech-language therapy (86.8% vs. 23.9%,  $p < 0.001$ ), and occupational therapy (82.1% vs. 25.0%,  $p < 0.001$ ) (Supplementary Table 1). Use of supportive therapies was similar between individuals with classic RTT and atypical RTT (classic: 1.9–78.4%; atypical: 0.0–72.1%) (Supplementary Table 1).

#### RTT-related outcomes during the follow-up period

Over a median follow-up period of 4 years, nearly half (44.6%) of all individuals had a hospital or emergency room visit (Fig. 2), with a significantly higher proportion of visits observed in individuals with classic RTT than atypical RTT (47.1% vs. 20.9%,  $p = 0.001$ ), and pediatric individuals than adult individuals (48.5% vs. 29.3%,  $p = 0.001$ ) (Supplementary Table 2). Incident g-tube surgeries were observed among 13.7% of individuals, and pediatric individuals had a significantly higher incidence of g-tube surgery than adult individuals (16.7% vs. 2.7%,  $p = 0.002$ ) (Supplementary Table 2). Mortality was rare (0.7%) in the overall RTT cohort, and all observed deaths were due to natural causes, with no specific cause documented (Fig. 2).

#### Change in CSS and MBA scores from first visit to year 2 of follow-up

In the overall RTT cohort, mean CSS score (first visit: 22.7; year 1: 22.0; year 2: 23.2) (Fig. 3) and mean MBA score (first visit: 46.7; year 1: 46.0; year 2: 48.5) (Fig. 4) remained largely unchanged from first visit to year 2 of follow up. Mean CSS scores were significantly higher for individuals with classic RTT than individuals with atypical RTT across all timepoints assessed (classic: 22.5–23.8; atypical: 16.8–17.2, all  $p < 0.05$ ) (Supplementary Table 3); a similar pattern was observed for mean MBA scores (classic: 47.2–49.7; atypical: 34.9–36.5, all  $p < 0.05$ ) (Supplementary Table 4). Mean CSS score was significantly higher for adult individuals than pediatric individuals at year 1 of follow-up (adult: 26.6; pediatric: 21.7,  $p = 0.031$ ) (Supplementary Table 3), while mean MBA scores were significantly higher for adult individuals than pediatric individuals at first visit (adult: 50.5; pediatric: 45.8,  $p = 0.009$ ) and year 1 of follow-up (adult: 53.3; pediatric: 45.6,  $p = 0.046$ ) (Supplementary Table 4).

There were no meaningful changes in clinical severity per year in the overall RTT cohort (mean change per

**Table 2** Pharmacological therapies used among females with RTT, overall and stratified by RTT type and age

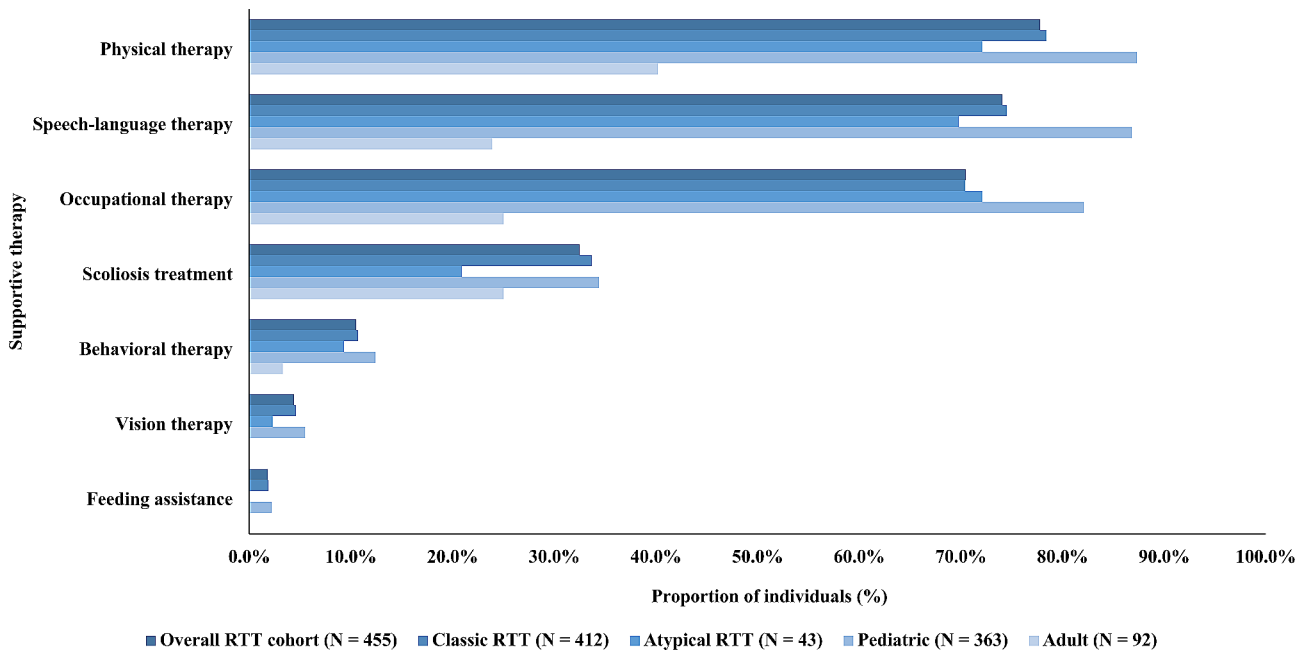
Pharmacological therapies		Overall RTT Cohort	Stratification by RTT type			Stratification by age			Test statistic	p-value
			Classic RTT	Atypical RTT	p-value	Pediatric (<18 years of age)	Adult (≥18 years of age)			
Follow-up period, years, mean ± SD [median]		(N=455)	(N=412)	(N=43)			(N=363)	(N=92)		
Prokinetic agents, n (%)		4.1 ± 1.0 [4]	4.1 ± 1.0 [4]	4.1 ± 1.2 [4]	-0.2	0.833	4.1 ± 1.1 [4]	4.2 ± 0.8 [4]	1.5	0.140
Individuals who discontinued use		181 (39.8)	164 (39.8)	17 (39.5)	0.0	0.972	155 (42.7)	26 (28.3)	6.4	0.011*
Reasons for discontinuing <sup>†</sup>		46 (25.4)	44 (26.8)	2 (11.8)	1.8	0.246	43 (27.7)	3 (11.5)	3.1	0.079
Ineffective		11 (23.9)	10 (22.7)	1 (50.0)	0.8	0.425	11 (25.6)	0 (0.0)	1.0	1.000
Not needed		29 (63.0)	28 (63.6)	1 (50.0)	0.2	1.000	28 (65.1)	1 (33.3)	1.2	0.545
Side effects		10 (21.7)	10 (22.7)	0 (0.0)	0.6	1.000	8 (18.6)	2 (66.7)	3.8	0.115
Missing		2 (4.3)	2 (4.5)	0 (0.0)	0.1	1.000	2 (4.7)	0 (0.0)	0.1	1.000
Antiepileptics, n (%)		147 (32.3)	137 (33.3)	10 (23.3)	1.8	0.182	127 (35.0)	20 (21.7)	5.9	0.015*
Individuals who discontinued use		41 (27.9)	40 (29.2)	1 (10.0)	1.7	0.284	36 (28.3)	5 (25.0)	0.1	0.756
Reasons for discontinuing <sup>†</sup>										
Ineffective		20 (48.8)	20 (50.0)	0 (0.0)	1.0	1.000	17 (47.2)	3 (60.0)	0.3	0.663
Not needed		10 (24.4)	10 (25.0)	0 (0.0)	0.3	1.000	9 (25.0)	1 (20.0)	0.1	1.000
Side effects		13 (31.7)	12 (30.0)	1 (100.0)	2.2	0.317	12 (33.3)	1 (20.0)	0.4	1.000
Missing		3 (7.3)	3 (7.5)	0 (0.0)	0.1	1.000	3 (8.3)	0 (0.0)	0.4	1.000
Sedatives/hypnotics, n (%)		115 (25.3)	101 (24.5)	14 (32.6)	1.3	0.248	101 (27.8)	14 (15.2)	6.2	0.013*
Individuals who discontinued use		25 (21.7)	23 (22.8)	2 (14.3)	0.5	0.731	23 (22.8)	2 (14.3)	0.5	0.731
Reasons for discontinuing <sup>†</sup>										
Ineffective		9 (36.0)	8 (34.8)	1 (50.0)	0.2	1.000	8 (34.8)	1 (50.0)	0.2	1.000
Not needed		11 (44.0)	10 (43.5)	1 (50.0)	0.0	1.000	11 (47.8)	0 (0.0)	1.7	0.487
Side effects		9 (36.0)	8 (34.8)	1 (50.0)	0.2	1.000	7 (30.4)	2 (100.0)	3.9	0.120
Missing		1 (4.0)	1 (4.3)	0 (0.0)	0.1	1.000	1 (4.3)	0 (0.0)	0.1	1.000
Nutritional supplements, n (%)		105 (23.1)	95 (23.1)	10 (23.3)	0.0	0.977	91 (25.1)	14 (15.2)	4.0	0.045*
Individuals who discontinued use		20 (19.0)	19 (20.0)	1 (10.0)	0.6	0.683	20 (22.0)	0 (0.0)	3.8	0.067
Reasons for discontinuing <sup>†</sup>										
Ineffective		1 (5.0)	1 (5.3)	0 (0.0)	0.1	1.000	1 (5.0)	0 (0.0)	–	–
Not needed		16 (80.0)	15 (78.9)	1 (100.0)	0.3	1.000	16 (80.0)	0 (0.0)	–	–
Side effects		3 (15.0)	2 (10.5)	1 (100.0)	6.0	0.150	3 (15.0)	0 (0.0)	–	–
Missing		1 (5.0)	1 (5.3)	0 (0.0)	0.1	1.000	4 (15.0)	0 (0.0)	–	–

Abbreviations: RTT: Rett syndrome; SD: standard deviation

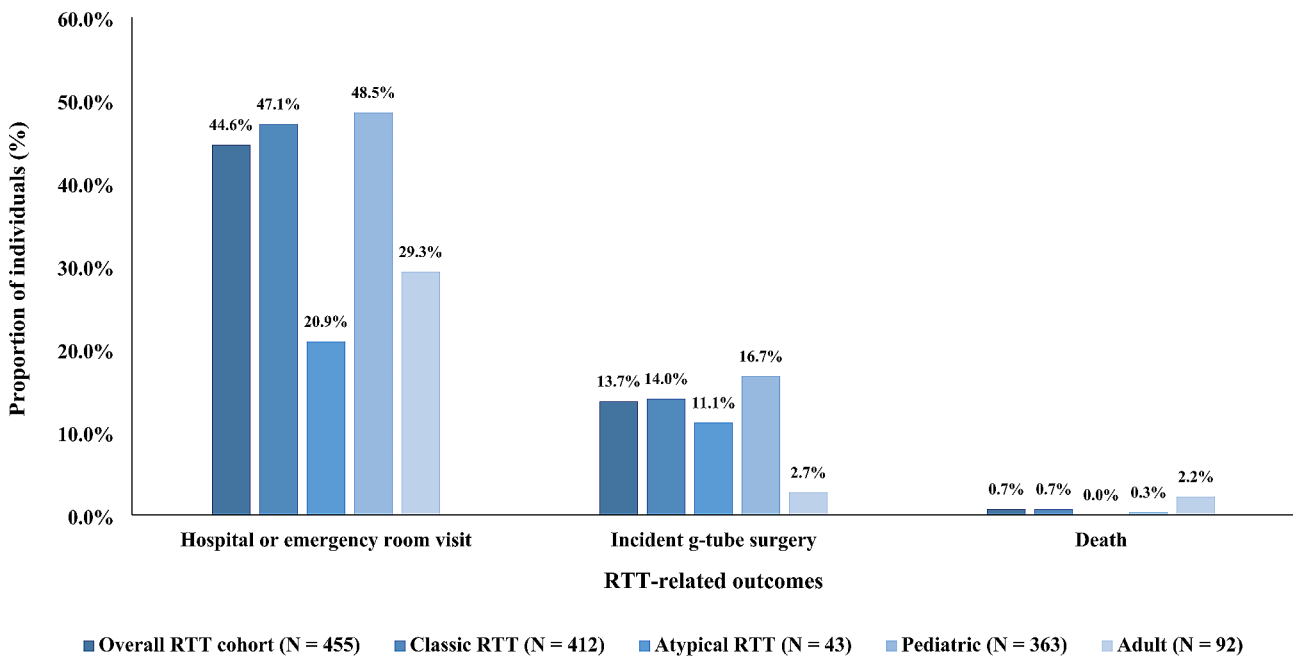
Note:

1. Individuals could have multiple reasons for discontinuing a treatment

Asterisks denote statistical significance at p<0.05



**Fig. 1** Supportive therapies used among females with RTT, overall and stratified by RTT type and age  
Abbreviation: RTT: Rett syndrome



**Fig. 2** RTT-related outcomes among females with RTT, overall and stratified by RTT type and age<sup>1,2</sup>

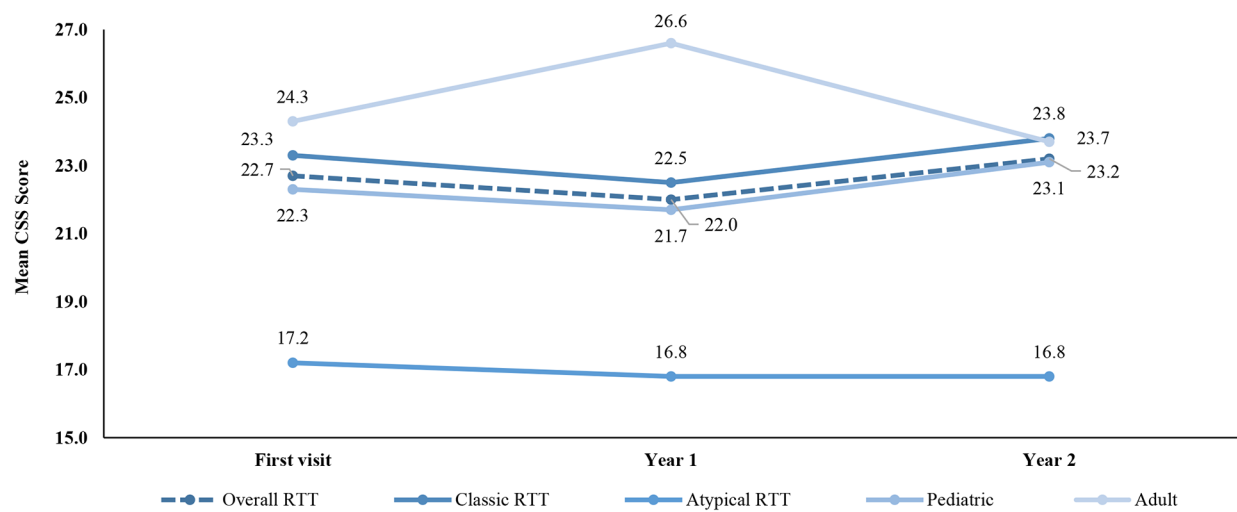
Abbreviations: G-tube: gastrostomy tube; RTT: Rett syndrome. 1. Proportions of individuals with incident g-tube surgery were evaluated among individuals without a g-tube surgery prior to the first visit (overall cohort:  $N=350$ ; classic RTT:  $N=314$ ; atypical RTT:  $N=36$ ; pediatric:  $N=275$ ; adult:  $N=75$ ). 2. G-tube surgeries included endoscopic gastrostomy, gastrostomy with fundoplication, and gastrostomy without fundoplication

year: 0.11; 95% CI: -0.08, 0.30), adult individuals (mean change per year: -0.39; 95% CI: -0.83, 0.05), individuals with classic RTT (mean change per year: 0.12; 95% CI: -0.07, 0.31), or individuals with atypical RTT (mean change per year: 0.00; 95% CI: -0.70, 0.69) (Table 3).

Conversely, an increasing trend in clinical severity per year was observed in pediatric individuals (mean change per year: 0.24; 95% CI: 0.03, 0.44) (Table 3).

An increasing trend in motor-behavioral dysfunction (as evaluated using the MBA scale) per year was observed

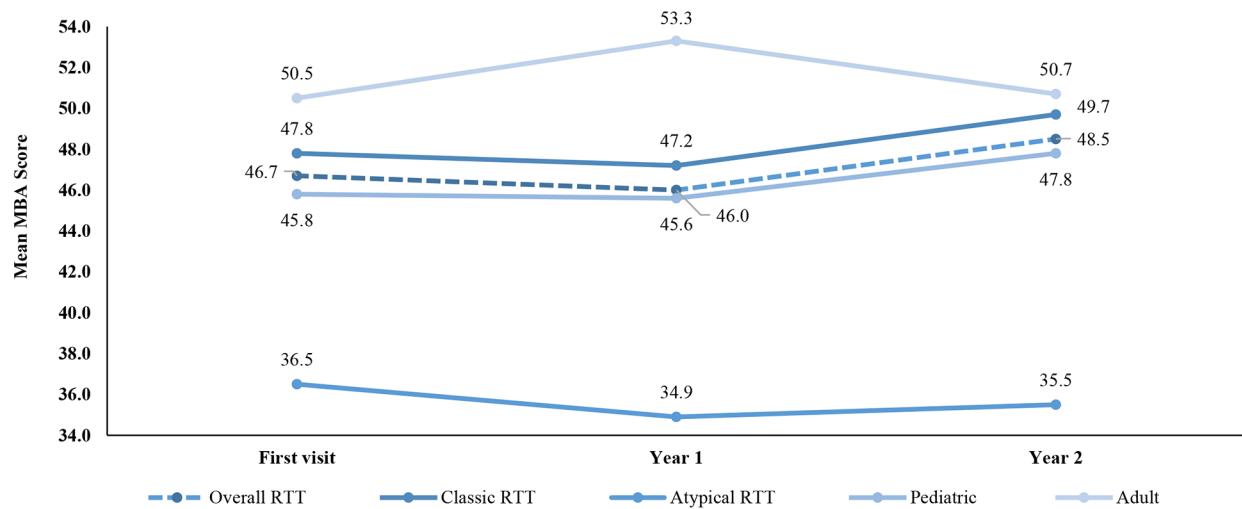




Individuals with available CSS measurement,<sup>1</sup> n (%)

Cohort	First visit	Year 1	Year 2
Overall RTT Cohort	454 (99.8)	218 (47.9)	305 (67.0)
Classic RTT Cohort	411 (99.8)	198 (48.1)	279 (67.7)
Atypical RTT Cohort	43 (100.0)	20 (46.5)	26 (60.5)
Pediatric Cohort	362 (99.7)	207 (57.0)	241 (66.4)
Adult Cohort	92 (100.0)	11 (12.0)	64 (69.6)

**Fig. 3** Trends in CSS score among females with RTT, overall and stratified by RTT type and age  
Abbreviations: CSS: Clinical Severity Scale; RTT: Rett syndrome. Note: 1. CSS score per year was calculated only among individuals with an available CSS measurement in the respective year



Individuals with available MBA measurement,<sup>1</sup> n (%)

Cohort	First visit	Year 1	Year 2
Overall RTT Cohort	453 (99.6)	214 (47.0)	298 (65.5)
Classic RTT Cohort	410 (99.5)	194 (47.1)	272 (66.0)
Atypical RTT Cohort	43 (100.0)	20 (46.5)	26 (60.5)
Pediatric Cohort	361 (99.4)	204 (56.2)	234 (64.5)
Adult Cohort	92 (100.0)	10 (10.9)	64 (69.6)

**Fig. 4** Trends in MBA score among females with RTT, overall and stratified by RTT type and age  
Abbreviations: MBA: Motor Behavioral Assessment; RTT: Rett syndrome. Note: 1. MBA score per year was calculated only among individuals with an available MBA measurement in the respective year



**Table 3** Annual change in CSS and MBA scores among females with RTT, overall and stratified by RTT type and age

Clinical severity measures	Overall RTT Cohort	Stratification by RTT type		Stratification by age	
		Classic RTT	Atypical RTT	Pediatric ( $< 18$ years of age)	Adult ( $\geq 18$ years of age)
		(N = 455)	(N = 412)	(N = 43)	(N = 363)
Follow-up period, years, mean $\pm$ SD [median]	4.1 $\pm$ 1.0 [4]	4.1 $\pm$ 1.0 [4]	4.1 $\pm$ 1.2 [4]	4.1 $\pm$ 1.1 [4]	4.2 $\pm$ 0.8 [4]
Mean change in CSS per year (95% CI)	0.11 (-0.08, 0.30)	0.12 (-0.07, 0.31)	0.00 (-0.70, 0.69)	0.24 (0.03, 0.44)	-0.39 (-0.83, 0.05)
Mean change in MBA score per year (95% CI)	0.92 (0.50, 1.35)	0.97 (0.53, 1.41)	0.34 (-1.06, 1.75)	1.12 (0.63, 1.60)	0.17 (-0.61, 0.94)

Abbreviations: CI: confidence interval; CSS: Clinical Severity Scale; MBA: Motor Behavioral Assessment; RTT: Rett syndrome; SD: standard deviation

in the overall RTT cohort (mean change per year: 0.92; 95% CI: 0.50, 1.35), pediatric individuals (mean change per year: 1.12; 95% CI: 0.63, 1.60), and individuals with classic RTT (mean change per year: 0.97; 95% CI: 0.53, 1.41) (Table 3). No meaningful changes in motor-behavioral dysfunction per year were observed in adult individuals (mean change per year: 0.17; 95% CI: -0.61, 0.94) or individuals with atypical RTT (mean change per year: 0.34; 95% CI: -1.06, 1.75) (Table 3).

Discussion

In this retrospective real-world study, we used registry data from the 5211 RHNS study to gain insights into the disease journey of females with RTT in the US with respect to longitudinal treatment patterns, RTT-related outcomes, and changes in disease severity. Our findings suggest that individuals with RTT experience high disease burden, irrespective of RTT type and age group, as evidenced by the high use of supportive therapies, the need for a hospital or emergency room visit in nearly half of all individuals, and the increasing trend in motor-behavioral dysfunction observed over time. To our knowledge, this is the first real-world study to evaluate changes in RTT severity over time, as measured by the CSS and MBA scale. These findings help advance the understanding of short-term changes in RTT severity across RTT type and age group.

In this study, most individuals with RTT required supportive therapy, with more use observed in pediatric individuals than adult individuals. These findings are consistent with a recent real-world administrative health-care claims study of females with RTT, which found that nearly 60% of the overall RTT cohort relied on pharmacologic and supportive therapies to manage symptoms, and the use of supportive therapies was highest during early childhood (3–4 years of age) and decreased markedly by 18 years of age [16]. The most used pharmacological therapies in this study were prokinetic agents and antiepileptic drugs, which aligns with the high rates of gastrointestinal manifestations and epilepsy reported in this population. In one survey of 983 parents of females with RTT in the North American RTT database, 92% reported symptoms of gastrointestinal dysmotility [17], while epilepsy has been estimated to occur in 60–80%

of individuals with RTT [18]. As the registry data used in this study spanned up to July 2021, prior to the FDA approval of trofinetide in March 2023 [9, 10], future real-world evidence studies that encompass data following the approval of trofinetide or other novel therapies are warranted to shed light on its integration into the treatment paradigm for RTT, and its impact on pharmacologic and supportive therapies currently used to manage RTT symptoms.

Despite the heavy reliance on pharmacologic and supportive therapies, nearly half of all individuals in our study required a hospital or emergency room visit during the follow-up period. While comparable literature is limited, a previous survey study of 399 individuals with RTT from the International Rett Syndrome Phenotype Database (InterRett) database (95.5% female and 82.2% from the US) found that 21.4% of individuals experienced a hospital admission for lower respiratory tract infection (LRTI) over the previous 5 years [19], a figure that is likely lower due to the capture of LRTI-related hospital admissions rather than all-cause hospital or emergency room visits. Moreover, a higher frequency of hospital or emergency room visits was observed in individuals with classic RTT relative to atypical RTT and in pediatric individuals relative to adult individuals. A registry-based study in Australia similarly observed a higher frequency of hospital admissions in individuals with RTT between the ages of 0–17 years relative to individuals with RTT more than 17 years of age (0–7 years: 22.2%, 8–12 years: 23.7%, 13–17 years: 18.0%, >17 years: 9.1%) [20], although these findings are not directly comparable to our frequency estimate given that emergency room visits could not be distinguished from hospital visits in this study. As the present study was unable to separately assess the frequency of emergency room visits and hospital visits, an understanding of the severity of healthcare encounters experienced by individuals in this study is limited.

In this study, approximately 14% of individuals with RTT underwent incident g-tube surgery during the follow-up period, with a greater incidence in pediatric individuals than adult individuals. Although literature on the incidence of g-tube surgery in individuals with RTT is sparse, prior literature have reported a prevalence of

g-tube surgery between 28.0 and 30.3% [17, 21], which aligns with the prevalence of g-tube surgery that can be delineated from our study given that 153 (33.6%) individuals had a g-tube surgery at baseline or during the study period. The need for invasive g-tube surgery to alleviate feeding difficulties among individuals with RTT, particularly younger individuals, further underscores the considerable burden associated with this disease [21].

Mortality in the present study was rare and aligns with prior literature that reported death in 4.3% of individuals with classic and atypical RTT in the RNHS over a 9-year observation period, with survival exceeding 70% at 45 years of age [5]. The low mortality rates observed in this study may have been driven by the larger representation of pediatric individuals in the overall RTT sample (79.8%) and right-censoring of the RNHS data. Although death during the study was ascertained from death certificates in the RNHS [5], deaths among individuals who withdrew from the study or that occurred after the completion of the study were not systematically captured. As such, mortality rates from this study may be underestimated. Future studies could assess cause-specific mortality in RTT, which is often unknown but has been presumed to be related to cardio-respiratory issues [5], and evaluate the potential value of novel treatments for addressing events that are known drivers of mortality in RTT, such as aspiration. Together, our findings underscore an unmet need for improved symptom management earlier on in the lifespan of individuals with RTT to reduce the burden of this disease and potentially increase survival at older ages. Future studies could assess how novel treatments may impact healthcare resource use and mortality among individuals with RTT, and whether these outcomes vary by type of RTT or individuals' age.

A novel aspect of this study was the assessment of the change in RTT severity per year. Among the overall study sample and in individuals with classic RTT, motor-behavioral dysfunction significantly increased per year. Furthermore, both clinical severity and motor-behavioral dysfunction significantly increased per year among pediatric individuals with RTT. Although not unexpected, these findings highlight the increasing burden of RTT over time. Prior literature investigating individuals with RTT aged 5–18 years in the RNHS identified a significant association between clinical impairment in RTT, as measured by the CSS and MBA, and poor physical QoL [6], suggesting that increasing clinical severity and motor-behavioral dysfunction have important negative impacts on individual's QoL. Due to missing data for clinical measures, longer-term assessments of CSS and MBA scores among individuals with RTT were not feasible, and the annual change in RTT severity estimated by our models was limited to 2 years of data. While our findings can elucidate on the short-term changes in RTT severity, an

understanding of the long-term trends in clinical severity and motor-behavioral dysfunction is limited, as developmental changes in RTT are generally slow [6]. Future studies may expand upon this analysis by investigating the annual changes in RTT severity over longer periods of time and using other clinical measures, such as the Rett Syndrome Behavior Questionnaire (RSBQ) to assess neurobehavioral severity [22]. Nonetheless, these findings provide additional insight on the changes in RTT severity in the short-term, and how these changes may vary across RTT type and individual's age.

The findings from our study should be interpreted considering some limitations. First, as most RTT-related outcomes and therapies evaluated in this study were reported by caregivers, there is a potential for mis-specification of endpoints, given the subjectivity in their assessment. However, estimates reported in this study are corroborated by published RTT literature, suggesting that our findings are representative of the real world. Second, our assessments were limited to the subset of individuals with complete information; the high proportion of missingness observed for certain variables could lead to uncertainty in the estimation of endpoints evaluated in this study. Third, the MBA scale has not been validated in individuals with RTT and as such, the reliability, validity, and relevance of this scale in the RTT population have not been established. Future research assessing motor-behavioral dysfunction in individuals with RTT using a validated instrument are warranted.

To our knowledge, this study was the first to assess changes in RTT severity over time and provide novel insights on the short-term trends of this disease in classic and atypical RTT as well as in pediatric and adult individuals. This study used data from the largest registry database specifically designed to collect data on individuals with RTT in the US. The database is uniquely rich in endpoints, such as CSS and MBA scores, allowing for a more comprehensive overview of the treatment and disease journey that might otherwise not be observed in other data sources where data capture may be less complete. Moreover, the results are likely to be generalizable to the broader RTT population. Additionally, the RHNS database has a comprehensive capture of the clinical features of RTT and over-the-counter pharmacologic therapies, which may not be captured in other data sources that necessitate a healthcare encounter or a drug prescription/dispensing, respectively, to be recorded in the database.

## Conclusions

Findings from this study highlight the considerable burden of RTT across classic and atypical RTT as well as pediatric and adult individuals. Reliance on supportive therapies and healthcare resources to manage debilitating

symptoms of RTT was common in the overall study sample and more pronounced in pediatric individuals than adult individuals, highlighting the importance of early interventions to facilitate the long-term management of RTT. Despite the use of pharmacological and supportive therapies, individuals with RTT experience increasing severity of disease with respect to motor-behavioral dysfunction, underscoring the present unmet needs of this population. Future studies may provide additional insights by investigating disease management strategies in the context of novel targeted therapies and elucidate the impact of the evolving treatment landscape on the severity of RTT as well as the QoL of individuals with RTT and their caregivers.

#### Abbreviations

CI	Confidence interval
CSS	Clinical Severity Scale
FDA	Food and Drug Administration
g-tube	Gastrostomy tube
LRTI	Lower respiratory tract infection
MBA	Motor Behavioral Assessment
QoL	Quality of life
RNHS	Rett Syndrome Natural History Study
RSBQ	Rett Syndrome Behavior Questionnaire
RTT	Rett syndrome
SD	Standard deviation
US	United States

#### Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s11689-024-09557-6>.

Supplementary Material 1

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#### Author contributions

DM contributed to study conception and design, as well as data analysis and interpretation. AP and JN contributed to study conception and design and data interpretation. DCP and MK contributed to study conception and design. KKS, MM, ND, and PL contributed to study conception and design, collection and assembly of data, as well as data analysis and interpretation. GC and TW contributed to the data analysis and interpretation. All authors reviewed and approved the final content of this manuscript and its submission to the *Journal of Neurodevelopmental Disorders*.

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#### Data availability

The data that support the findings of this study are available from the International Rett Syndrome Foundation, but restrictions apply to the availability of these data, which were used under license for the current study, and therefore, are not publicly available. Data are however available from the authors upon reasonable request and with permission of the International Rett Syndrome Foundation.

#### Declarations

##### Ethics approval and consent to participate

Data were de-identified and certified as fully compliant with US patient confidentiality requirements outlined in the Health Insurance Portability and Accountability Act (HIPAA). Since this study relied exclusively on de-identified patient records and did not involve the collection, use, or dissemination of individually identifiable data, institutional review board approval was not required as per HIPAA. All methods were carried out in accordance with relevant guidelines and regulations in the Declaration of Helsinki. The data that support the findings of this study are not publicly available online; administrative permissions to access the data were given by the International Rett Syndrome Foundation under license.

##### Consent for publication

Not applicable.

##### Competing interests

DM is an employee of Acadia Pharmaceuticals Inc. DCP and MK are employees of the International Rett Syndrome Foundation. KKS, MM, ND, GC, TW, and PL are employees of Analysis Group, Inc., a consultancy that received funding from Acadia Pharmaceuticals, Inc. to conduct this study. AKP is co-editor of *Translational Science of Rare Diseases*, received research funding from the National Institutes of Health, and is a consultant for Acadia Pharmaceuticals Inc., Anavex Life Sciences Corp., AveXis, and GW Pharmaceuticals, as well as advisor to the International Rett Syndrome Foundation. JLN has received research funding from the International Rett Syndrome Foundation, the National Institutes of Health, and Rett Syndrome Research Trust and personal consultancy fees from Acadia Pharmaceuticals Inc., Analysis Group, AveXis, GW Pharmaceuticals, Hoffmann-La Roche, Myrtelle, Neurogene, Newron Pharmaceuticals, Signant Health, and Taysha Gene Therapies, and for the preparation of CME activities for Medscape and Peer Review Institute; serves on the scientific advisory board of Alcyon Lifesciences; is a scientific cofounder of LizarBio Therapeutics; and was a member of a data safety monitoring board for clinical trials conducted by Ovid Therapeutics.

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#### References

1. Chahil G, Bollu PC. Rett Syndrome. [Updated 2023 Aug 8]. In: StatPearls. StatPearls Publishing; 2023. <https://www.ncbi.nlm.nih.gov/books/NBK482252/>
2. Fu C, Armstrong D, Marsh E, et al. Consensus guidelines on managing Rett syndrome across the lifespan. *BMJ Paediatr Open*. 2020;4(1):e000717. <https://doi.org/10.1136/bmjpo-2020-000717>
3. Ip JPK, Mellios N, Sur M. Rett syndrome: insights into genetic, molecular and circuit mechanisms. *Nat Rev Neurosci Jun*. 2018;19(6):368–82. <https://doi.org/10.1038/s41583-018-0006-3>
4. National Institutes of Health (NIH). Rett syndrome. Accessed October 16, 2023. <https://www.nichd.nih.gov/health/topics/factsheets/rett>
5. Tarquinio DC, Hou W, Neul JL, et al. The changing face of survival in Rett syndrome and MECP2-related disorders. *Pediatr Neurol*. 2015;53(5):402–11. <https://doi.org/10.1016/j.pediatrneurol.2015.06.003>
6. Lane JB, Lee HS, Smith LW, et al. Clinical severity and quality of life in children and adolescents with Rett syndrome. *Neurology*. 2011;77(20):1812–8. <https://doi.org/10.1212/WNL.0b013e3182377dd2>
7. Fu C, Armstrong D, Marsh E, et al. Multisystem comorbidities in classic Rett syndrome: a scoping review. *BMJ Paediatrics open*. 2020;4(1):e000731–000731. <https://doi.org/10.1136/bmjpo-2020-000731>
8. Sandweiss AJ, Brandt VL, Zoghbi HY. Advances in understanding of Rett syndrome and MECP2 duplication syndrome: prospects for future

- therapies. *Lancet Neurol* Aug. 2020;19(8):689–98. [https://doi.org/10.1016/S1474-4422\(20\)30217-9](https://doi.org/10.1016/S1474-4422(20)30217-9)
9. US Food & Drug Administration. FDA approves first treatment for Rett syndrome. Accessed October 18. 2023. <https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-treatment-rett-syndrome>
  10. Neul JL, Percy AK, Benke TA, et al. Trofinetide for the treatment of Rett syndrome: a randomized phase 3 study. *Nat Med* Jun. 2023;29(6):1468–75. <https://doi.org/10.1038/s41591-023-02398-1>
  11. Percy AK, Neul JL, Glaze DG, et al. Rett syndrome diagnostic criteria: lessons from the natural history study. *Ann Neurol* Dec. 2010;68(6):951–5. <https://doi.org/10.1002/ana.22154>
  12. Neul JL, Lane JB, Lee HS, et al. Developmental delay in Rett syndrome: data from the natural history study. *J Neurodev Disord*. 2014;6(1):20. <https://doi.org/10.1186/1866-1955-6-20>
  13. Raspa M, Bann CM, Gwaltney A, et al. A psychometric evaluation of the motor-behavioral assessment scale for use as an outcome measure in Rett syndrome clinical trials. *Am J Intellect Dev Disabil* Nov. 2020;1(6):493–509. <https://doi.org/10.1352/1944-7558-125.6.493>
  14. Buchanan CB, Stallworth JL, Scott AE, et al. Behavioral profiles in Rett syndrome: data from the natural history study. *Brain Dev* Feb. 2019;41(2):123–34. <https://doi.org/10.1016/j.braindev.2018.08.008>
  15. Neul JL, Fang P, Barrish J, et al. Specific mutations in methyl-CpG-binding protein 2 confer different severity in Rett syndrome. *Neurol* Apr. 2008;15(16):1313–21. <https://doi.org/10.1212/01.wnl.0000291011.54508.aa>
  16. May D, Kponee-Shovein K, Mahendran M, et al. Epidemiology and patient journey of Rett syndrome in the United States: a real-world evidence study. *BMC Neurol* Apr. 2023;4(1):141. <https://doi.org/10.1186/s12883-023-03181-y>
  17. Motil KJ, Caeg E, Barrish JO, et al. Gastrointestinal and nutritional problems occur frequently throughout life in girls and women with Rett syndrome. *J Pediatr Gastroenterol Nutr* Sep. 2012;55(3):292–8. <https://doi.org/10.1097/MPG.0b013e31824b6159>
  18. Operto FF, Mazza R, Pastorino GMG, Verrotti A, Coppola G. Epilepsy and genetic in Rett syndrome: a review. *Brain Behav* May. 2019;9(5):e01250. <https://doi.org/10.1002/brb3.1250>
  19. MacKay J, Leonard H, Wong K, Wilson A, Downs J. Respiratory morbidity in Rett syndrome: an observational study. *Dev Med Child Neurol* Sep. 2018;60(9):951–7. <https://doi.org/10.1111/dmcn.13726>
  20. Hendrie D, Bebbington A, Bower C, Leonard H. Measuring use and cost of health sector and related care in a population of girls and young women with Rett syndrome. *Res Autism Spect Dis*. 2011;5(2):901–909. <https://doi.org/10.1016/j.rasd.2010.10.004>
  21. Wong K, Downs J, Ellaway C, et al. Impact of gastrostomy placement on nutritional status, physical health, and parental well-being of females with Rett syndrome: a longitudinal study of an Australian population. *J Pediatr* Sep. 2018;200:188–e1951. <https://doi.org/10.1016/j.jpeds.2018.04.050>
  22. Percy AK, Neul JL, Benke TA, Marsh ED, Glaze DG. A review of the Rett syndrome behaviour questionnaire and its utilization in the assessment of symptoms associated with Rett syndrome. *Front Pediatr*. 2023;11:1229553. <https://doi.org/10.3389/fped.2023.1229553>

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