Short Communication

Future Rare Diseases

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Characteristics, conditions, and healthcare service utilization patterns of individuals diagnosed with Rett Syndrome: an analysis of administrative claims data

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Aim: To date, no studies have used a commercially available claims dataset to examine the characteristics, conditions, and healthcare service utilization of individuals with Rett syndrome. **Objective:** To improve understanding of the Rett population using data available to health insurance plans. **Methods:** Data were integrated medical and pharmacy claims from the Real-World Evidence data repository licensed from the Decision Resources Group. Individuals had claims for ≥2 visits which included a diagnosis of Rett and were stratified into three age groups: 1 (<5 years), 2 (>5 and <10 years) and 3 (>10 years). Co-occurring conditions and healthcare service utilization were measured. Diagnoses prior to Rett were evaluated. **Results:** Most were female. Epilepsy, incontinence, and scoliosis were common co-occurring conditions. Individuals averaged 4.6 office and 2.5 outpatient visits, and 2.1 emergency and 2.9 inpatient admissions. Group 1 used more physical, occupational and speech therapy and averaged more inpatient days compared with others ($p < 0.05$). **Conclusion:** This study improves understanding of Rett using data that is typically available to health insurance companies.

Plain language summary: Rett syndrome (RTT) is a genetic developmental disorder that is mainly found in female individuals. We used data from commercial claims to group these individuals into three groups based on their age (1–5 years, 5–10 years and 10+ years). Each age group was analyzed for their characteristics and usage of healthcare services (including medical equipment and pharmacy). The results of this study add to the available information on how RTT presents itself in the claims database which provides valuable insight on this population for the scientific research community, payers, and other healthcare stakeholders. Future studies on RTT should continue to use claims data to better understand the patient journey.

Tweetable abstract: Rett syndrome is a rare genetic disorder that primarily affects female individuals. Data from commercial claims were analyzed for demographics and healthcare resource utilization. This expands the current knowledge of how Rett syndrome presents in a claims database.

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Keywords: administrative claims data • patient characteristics • Rett syndrome

Rett syndrome (RTT) is a rare, complex and progressive neurodevelopmental disorder [1]. Rett disorder occurs in approximately 1 in every 10,000 female children worldwide [2] and is much rarer in male children [3]. Rett is a genetic disorder caused by one or more loss-of-function mutations in a gene encoding MeCP2, a DNA binding protein and transcriptional regulator with roles in gene regulation, synaptic development and maintenance of neuronal circuitry [4,5]. As it is a rare disease, little population level information useful to care management policy and care practices is available.

Rett is characterized by the appearance of normal, psychomotor development during the first 6–18 months of life [2], which is followed by a gradual decrease in mental and/or physical abilities [1,2]. Children with RTT

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often lose previously acquired developmental skills including the ability to crawl, walk, communicate, use their hands, and maintain eye contact [1,2,6]. As the child develops, additional symptoms manifest including repetitive, stereotypic hand movements; fits of screaming and inconsolable crying; autistic features; panic-like attacks; teeth grinding; episodic apnea and/or hyperpnea; gait abnormalities and apraxia; tremors; seizures; and slowed head growth [2]. Mutations in the gene MeCP2 have been found among 95–97% of individuals with typical RTT, and among 50–70% of individuals with atypical Rett [7].

Management of the disorder often involves addressing symptoms through a multidisciplinary team-based approach [6]. For example, occupational therapists can help children develop skills needed for performing self-directed activities (e.g., dressing, eating, and practicing arts and crafts), while physical therapy (PT) and hydrotherapy may help prolong mobility [6]. Dieticians and nurses perform nutritional assessments to help with feeding difficulties and to ensure that children gain weight [8]. Speech-language therapy (ST) and alternative and augmentative communication can provide nonverbal ways of communicating and promote social interaction [9]. Anticonvulsant drugs may be used to control seizures, while other medications are often prescribed to address breathing irregularities, and motor difficulties [6]. Regular monitoring by physicians is necessary to detect worsening scoliosis and possible gastrointestinal and heart abnormalities.

While much is known about RTT, prior studies investigating patient characteristics, the frequency of co-occurring conditions, and treatment patterns have been collected from surveys, case reports [10–13] or patient registries [14–20]. While RettBASE [17] and InterRett [17], the Rett Networked Database [18], and IRSF's Natural History Study [19] are invaluable resources replete with important longitudinal genetic and clinical information; currently, little information is available to help payers (health insurance companies) understand what to expect in service utilization, comorbidities and cost of care using claims data which are one of their main sources of information. As new therapies for RTT are approved, it will be essential to understand the landscape of evidence available within commercially available databases as these will influence reimbursement. Furthermore, as approval of new therapies occur, these databases will be used more regularly to examine the safety, efficacy, persistence, and adherence of the therapy; as well as their impact on healthcare utilization and cost.

The objective of the current study was to use a medical and pharmacy claims database to understand the characteristics, co-occurring conditions, and healthcare service utilization among patients diagnosed with RTT in the US healthcare system.

Methods

Study design

A cross-sectional, retrospective analysis similar to that used elsewhere [3] of individuals diagnosed with RTT was conducted using administrative claims data as derived from the Real-World Evidence (RWE) data repository licensed from Decision Resources Group (DRG) [21]. DRG is a global information and technology services company that manages a large repository of proprietary healthcare data, including data representing coverage from 98% of payers, >300 M patients, and >2 M healthcare providers. The data variables in this database include patient age, gender, or insurance type from all 50 states and the District of Columbia and comply with the Health Insurance Portability and Accountability Act (HIPAA).

The time period used to evaluate data was 1 January 2014–31 December 2020. The standard for case identification within claims data was employed [22,23]. Individuals were required to have claims for ≥2 visits at least 330 days apart that include Rett diagnosis (ICD-10 F84.2) to be included in the study. Additionally, cases were required to have minimally 12-months of study data before and after index, and no differential diagnoses (e.g., cerebral palsy or autism) following the last Rett diagnosis on record. Index was defined as the date of the first visit that included a Rett diagnosis. Table 1 presents the study attrition analysis.

Individuals were stratified by age: group 1 (<5 years (yrs.)), group 2 (≥5 and <10 yrs.), group 3 (≥10 yrs.). Demographics, co-occurring conditions, and healthcare service utilization (per patient per year [PPPY]) were measured during the 12-months following index. Diagnoses prior to the index Rett diagnosis were evaluated as a patient journey during the 12-month period leading up to the Rett diagnosis index date. Chi-square and one-way ANOVA were used to test for statistical differences for categorical and continuous variables respectively across age groups. The alpha level was set at 0.05 to identify statistical significance among the different groups. Standard deviation is presented throughout the text in parenthesis. All analysis was performed using SAS version v9.4 (Cary, NC).

Table 1. Attrition criteria and selection of Rett patient cohort.

Step	Reason for selection	Rett syndrome patients: Members remaining, n (%)
1	Patient must have 1 Rett diagnosis during the study period 1 January 2016–31 December 2020	4,446 (100.0%)
2	Exclude patients without one-year of study data before and after the index Rett diagnosis, during the study period	3,656 (82.2%)
3	Include patients with at least one-additional Rett diagnosis, following the index diagnosis, during the follow-up period	988 (22.2%)
4	Exclude patients with a differential diagnosis following last Rett diagnosis on record	702 (15.8%)
	Final Rett cohort	**702 patients**

Table 2. Demographic characteristics of patients with Rett syndrome.

	Full sample (n = 702), n (%)	1–5 years (n = 44), n (%)	>5 years–10 years (n = 120), n (%)	>10 years (n = 538), n (%)	p-value
Age (years), mean (SD) [median]	19.9 (12.6) [17.0]	3.9 (1.0) [4.0]	7.8 (1.4) [7.9]	23.8 (11.7) [20.5]	<0.05
Gender:					ns
Male	35 (5.0%)	4 (9.1%)	9 (7.5%)	22 (4.1%)	
Female	667 (95.0%)	40 (90.9%)	111 (92.5%)	516 (95.9%)	
Region:					ns
Northeast	156 (22.2%)	12 (27.3%)	21 (17.5%)	123 (22.9%)	
Midwest	175 (24.9%)	9 (20.5%)	29 (24.2%)	137 (25.5%)	
South	242 (34.5%)	15 (34.1%)	54 (45.0%)	173 (32.2%)	
West	129 (18.4%)	8 (18.2%)	15 (12.5%)	106 (19.7%)	
Insurance type:					ns
Commercial	71 (10.1%)	6 (13.6%)	16 (13.3%)	49 (9.1%)	
Medicaid	623 (88.7%)	38 (86.4%)	103 (85.8%)	482 (89.6%)	
Medicare	8 (1.1%)	0 (0.0%)	1 (0.8%)	7 (1.3%)	

All demographic characteristics determined at index Rett diagnosis.
Chi-square analysis used to test for statistically significant differences for categorical variables among age groups.
One-way ANOVA used to test for statistically significant differences for continuous variables among age groups.
Alpha level set at 0.05.
ns: Not statistically different at $p \leq 0.05$.

Results

Demographic & patient characteristics

The study sample included 702 patients diagnosed with RTT, of which 667 (95.0%) were female individuals (Table 2). The mean (SD) patient age was 19.9 (±12.6) years: 44 (6.3%) patients having an age of 1–5 years; 120 (17.1%) greater than 5 years and less than 10 years; and 538 (76.6%) greater than 10 years of age. Most patients (34.5%) were from the Southern region of the United States. Just over 50% of individuals diagnosed with RTT resided within 10 US states (Figure 1, Table 3). Less than half of patients (46.9%) resided in a state with a Rett center of excellence (COE) (Figure 2). Just over half (56.4%) of patients resided in a state with a COE or Rett clinical center (Figure 2). Most patients (88.7%) had Medicaid, while 10.1% had commercial insurance coverage. There were no statistically significant differences in gender, region, or insurance among the three age groups (Table 2).

Diagnosis history prior to a Rett syndrome

Prior to the index Rett diagnosis, most patients (87.7%) received an alternative earlier diagnosis. The most frequently occurring diagnoses were epilepsy (16.4%), convulsions (11.1%), cerebral palsy (7.0%), intellectual disability (6.4%), delayed milestone in childhood development or lack of normal physiological development in childhood (6.0%), failure to thrive (4.1%), autism (3.7%), disorders of psychological development (3.7%), delays in development (3.6%), encephalopathy (3.6%), language disorder (3.6%), degenerative disease of the nervous system (3.1%) and Leigh's disease (2.7%) (Table 4).

Among the above diagnoses, no statistically significant differences were observed among age groups for epilepsy, convulsions, cerebral palsy, autism, delays in development, or encephalopathy. Conversely, statistically significant

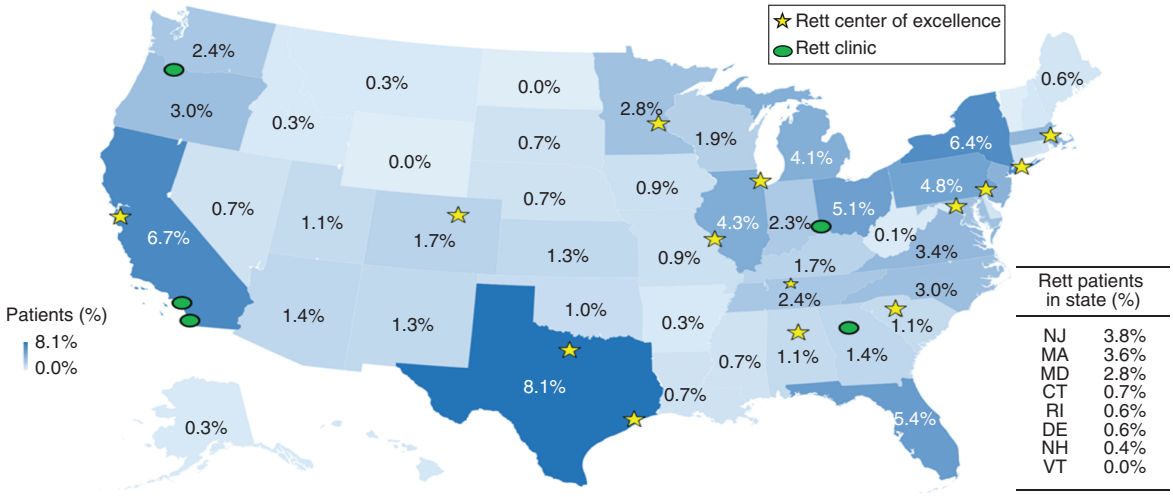

Figure 1. Rett syndrome patient heatmap with Rett clinics and Rett centers of excellence in the USA.

Table 3. Rett syndrome patient distribution by state.

State	n	%	State	n	%
TX	57	8.1%	NM	9	1.3%
CA	47	6.7%	AL	8	1.1%
NY	45	6.4%	SC	8	1.1%
FL	38	5.4%	UT	8	1.1%
OH	36	5.1%	OK	7	1.0%
PA	34	4.8%	IA	6	0.9%
IL	30	4.3%	MO	6	0.9%
MI	29	4.1%	CT	5	0.7%
NJ	27	3.8%	LA	5	0.7%
MA	25	3.6%	MS	5	0.7%
VA	24	3.4%	NE	5	0.7%
NC	21	3.0%	NV	5	0.7%
OR	21	3.0%	SD	5	0.7%
MD	20	2.8%	DE	4	0.6%
MN	20	2.8%	ME	4	0.6%
TN	17	2.4%	RI	4	0.6%
WA	17	2.4%	HI	3	0.4%
IN	16	2.3%	NH	3	0.4%
WI	13	1.9%	AK	2	0.3%
CO	12	1.7%	AR	2	0.3%
KY	12	1.7%	DC	2	0.3%
AZ	10	1.4%	ID	2	0.3%
GA	10	1.4%	MT	2	0.3%
KS	9	1.3%	WV	1	0.1%

differences in frequency were observed among the age cohorts for intellectual disabilities, delayed milestone in childhood development or lack of normal physiological development in childhood, failure to thrive (all $p < 0.05$). Table 4 outlines the frequency of the above alternative diagnoses overall, and by age cohort for over 40 additional alternative diagnoses present prior to the index RTT diagnosis.

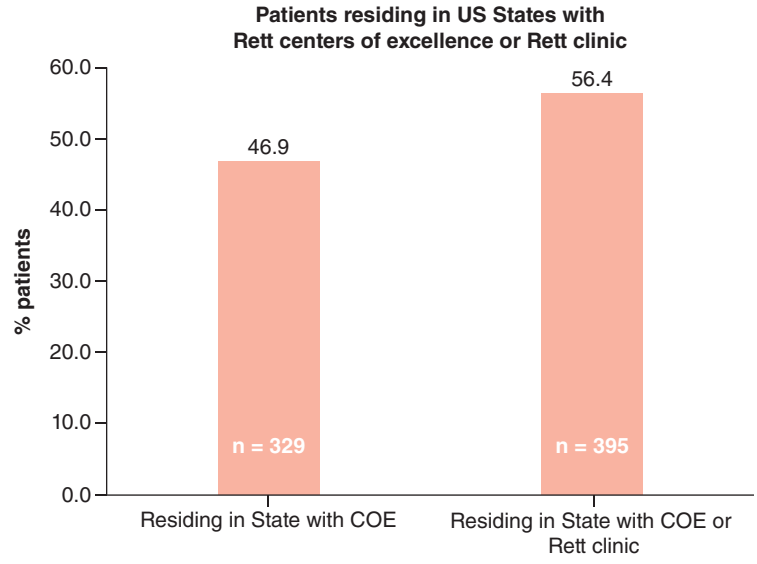

Figure 2. Rett syndrome patients who reside in US states with Rett centers of excellence or Rett syndrome clinic.
COE: Center of excellence.

Frequency of co-occurring conditions associated with Rett syndrome

Following the index Rett diagnosis, most individuals had a co-occurring condition or diagnosis often associated with RTT (Table 5). For example, 268 (38.2%) were diagnosed with some form of epilepsy, 118 (16.8%) with incontinence, 88 (12.5%) with scoliosis, and 74 (10.5%) with dysphagia.

Among the conditions and disorders listed in Table 5, no statistical differences were observed among age groups for epilepsy, scoliosis, constipation, gastroesophageal reflux disease, dyspnea, extrapyramidal-movement, anxiety, long-QT syndrome, restlessness and agitation, and depression. Higher frequencies and statistically significant differences were observed for younger cohorts versus older cohorts for dysphagia, speech language, sleep disorders, muscle weakness and anemia (all $p < 0.05$). Conversely, a higher frequency and statistically significant difference for incontinence was observed for older versus younger cohorts ($p < 0.05$).

Healthcare service utilization

Individuals diagnosed with RTT averaged 4.6 (±10.3) office visits and 2.5 (±7.3) outpatient hospital visits per patient per year (Table 6). Patients utilized on average 2.1 (±2.5) emergency department (ED) visits and 2.9 (±5.4) inpatient (IP) admissions per patient per year. The mean number of inpatient days were 11.8 (±21.7) per patient per year among patients having at least one IP admission. The youngest cohort (1–5 years) averaged the most IP days 31.5 (±38.8), followed by the middle-aged cohort 10.8 (±25.8) and the oldest cohort 9.4 (±15.2) ($p < 0.05$).

Among the patients, 97 (13.9%) utilized PT, 91 (13.0%) occupational therapy (OT) and 46 (6.6%) ST services (Table 7). Patients utilized an average of 12.4 (±16.0) PT visits, 12.4 (±17.4) OT visits and 14.7 (±16.1) ST visits per patient per year (Table 7). There were no differences between age groups for PT and OT utilization, however, utilization of ST services was higher among the youngest age cohort ($p < .05$), (Table 6).

Two-hundred sixty-two patients (37.3%) utilized some form of medical or durable medical equipment (Table 8). The frequency of equipment utilization was highest among the middle age (>5–10 year) cohort (Table 8). Patients 1–5 years utilized 5.8 (±9.4) pieces of equipment, while the middle age (>5–10 years) and oldest cohort (>10 years) averaged 6.9 (±10.0) and 5.8 (±7.5) pieces of equipment, respectively. Oxygen equipment and accessories were the most frequently used among all age groups (Tables 8).

Pharmacy utilization

Levetiracetam (9.5%), lamotrigine (5.0%) and clonazepam (4.8%) were the most frequently prescribed anti-convulsant medications. Diazepam (7.7%) and lorazepam (3.0%) were the most frequently prescribed anxiolytics. Trazodone (1.6%) and fluoxetine (1.4%) were the most frequently prescribed anti-depressants. The frequency of additional medications prescribed are found in Table 9.

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Table 4. Diagnosis history of Rett patients up to 12 months prior to index Rett diagnosis.

	Full sample (n = 702)		1–5 years (n = 44)		>5 years–10 years (n = 120)		>10 years (n = 538)		p-value
	n	%	n	%	n	%	n	%	
Epilepsy	115	16.4%	11	25.0%	22	18.3%	82	15.2%	ns
Convulsions	78	11.1%	10	22.7%	16	13.3%	52	9.7%	ns
Cerebral palsy	49	7.0%	4	9.1%	6	5.0%	39	7.2%	ns
Intellectual disabilities	45	6.4%	0	0.0%	2	1.7%	43	8.0%	<0.05
Delayed milestone in childhood or lack of normal physiological development in childhood	42	6.0%	10	22.7%	17	14.2%	15	2.8%	<0.05
Failure to thrive (Child)	29	4.1%	5	11.4%	11	9.2%	13	2.4%	<0.05
Autism	26	3.7%	2	4.5%	5	4.2%	19	3.5%	ns
Disorders oF psychological development	26	3.7%	10	22.7%	9	7.5%	7	1.3%	<0.05
Delays in development	25	3.6%	7	15.9%	7	5.8%	11	2.0%	ns
Encephalopathy	25	3.6%	5	11.4%	5	4.2%	15	2.8%	ns
Language disorder	25	3.6%	9	20.5%	8	6.7%	8	1.5%	<0.05
Degenerative disease of nervous system	22	3.1%	0	0.0%	2	1.7%	20	3.7%	<0.05
Leigh's disease	19	2.7%	0	0.0%	2	1.7%	17	3.2%	<0.05
Chromosomal abnormalities	16	2.3%	3	6.8%	5	4.2%	8	1.5%	ns
Muscle weakness (generalized)	15	2.1%	5	11.4%	6	5.0%	4	0.7%	<0.05
Specific developmental disorder of motor function	14	2.0%	5	11.4%	4	3.3%	5	0.9%	<0.05
Developmental disorder of scholastic skills	12	1.7%	1	2.3%	2	1.7%	9	1.7%	ns
Pervasive Development Disorder	12	1.7%	1	2.3%	3	2.5%	8	1.5%	ns
Adult failure to thrive	10	1.4%	0	0.0%	0	0.0%	10	1.9%	ns
Alpers disease	7	1.0%	1	2.3%	0	0.0%	6	1.1%	ns
Cerebral or brain degeneration	7	1.0%	1	2.3%	1	0.8%	5	0.9%	ns
Mood disorder	7	1.0%	0	0.0%	1	0.8%	6	1.1%	ns
Creutzfeldt-Jakob disease	5	0.7%	0	0.0%	1	0.8%	4	0.7%	ns
Dystonia	5	0.7%	1	2.3%	0	0.0%	4	0.7%	ns
Encounter for general adult medical examination	5	0.7%	0	0.0%	0	0.0%	5	0.9%	ns
Mixed development disorder	5	0.7%	4	9.1%	1	0.8%	0	0.0%	<0.05
Attention-deficit/hyperactivity disorder	4	0.6%	0	0.0%	2	1.7%	2	0.4%	ns
Microcephaly	4	0.6%	1	2.3%	2	1.7%	1	0.2%	ns
Asperger's syndrome	3	0.4%	0	0.0%	0	0.0%	3	0.6%	ns
Developmental coordination disorder	3	0.4%	0	0.0%	1	0.8%	2	0.4%	ns
Disorder of brain or CNS	3	0.4%	2	4.5%	0	0.0%	1	0.2%	<0.05
Down syndrome	3	0.4%	0	0.0%	1	0.8%	2	0.4%	ns
Myoneural disorders, unspecified	3	0.4%	0	0.0%	1	0.8%	2	0.4%	ns
Myopathy	3	0.4%	0	0.0%	1	0.8%	2	0.4%	ns
Tourette's disorder	3	0.4%	0	0.0%	1	0.8%	2	0.4%	ns
Unspecified disturbance of conduct	3	0.4%	0	0.0%	0	0.0%	3	0.6%	ns
Angelman syndrome	2	0.3%	0	0.0%	1	0.8%	1	0.2%	ns
Ataxia	2	0.3%	0	0.0%	1	0.8%	1	0.2%	ns
Childhood disintegrative disorder	2	0.3%	0	0.0%	0	0.0%	2	0.4%	ns
Extrapyramidal and movement disorder	2	0.3%	1	2.3%	0	0.0%	1	0.2%	ns
Adjustment disorder	1	0.1%	0	0.0%	0	0.0%	1	0.2%	ns
Compression of brain	1	0.1%	1	2.3%	0	0.0%	0	0.0%	<0.05

All diagnoses determined during the 12-month period prior to index diagnosis.
Chi-square analysis used to test for statistically significant differences for categorical variables among age groups.
One-way ANOVA used to test for statistically significant differences for continuous variables among age groups.
Alpha level set at 0.05.
ns: Not statistically different at $p \leq 0.05$.

Table 4. Diagnosis history of Rett patients up to 12 months prior to index Rett diagnosis (cont.).

	Full sample (n = 702)		1–5 years (n = 44)		>5 years–10 years (n = 120)		>10 years (n = 538)		p-value
	n	%	n	%	n	%	n	%	
Congenital anomalies	1	0.1%	0	0.0%	0	0.0%	1	0.2%	ns
Congenital malformation, unspecified	1	0.1%	0	0.0%	0	0.0%	1	0.2%	ns
Fussy infant (baby)	1	0.1%	0	0.0%	1	0.8%	0	0.0%	ns
Huntington's chorea	1	0.1%	0	0.0%	0	0.0%	1	0.2%	ns
Mild cognitive impairment, so stated	1	0.1%	0	0.0%	0	0.0%	1	0.2%	ns
Other acquired torsion dystonia	1	0.1%	0	0.0%	0	0.0%	1	0.2%	ns
Other conditions of brain	1	0.1%	1	2.3%	0	0.0%	0	0.0%	<0.05
Other motor neuron disease	1	0.1%	0	0.0%	0	0.0%	1	0.2%	ns
Psychological and behavioral factors	1	0.1%	0	0.0%	0	0.0%	1	0.2%	ns
Spinal muscular atrophy, unspecified	1	0.1%	0	0.0%	0	0.0%	1	0.2%	ns
Unspecified persistent mental disorder	1	0.1%	0	0.0%	0	0.0%	1	0.2%	ns

All diagnoses determined during the 12-month period prior to index diagnosis.
Chi-square analysis used to test for statistically significant differences for categorical variables among age groups.
One-way ANOVA used to test for statistically significant differences for continuous variables among age groups.
Alpha level set at 0.05.
ns: Not statistically different at $p \leq 0.05$.

Table 5. Co-occurring conditions among individuals diagnosed with Rett syndrome during the 12-month follow-up period.

	Full sample (n = 702)		1–5 years (n = 44)		>5 years–10 years (n = 120)		>10 years (n = 538)		p-value
	n	%	n	%	n	%	n	%	
Epilepsy	268	38.2%	19	43.2%	50	41.7%	199	37.0%	ns
Incontinence	118	16.8%	1	2.3%	20	16.7%	97	18.0%	<0.05
Scoliosis	88	12.5%	4	9.1%	17	14.2%	67	12.5%	ns
Dysphagia	74	10.5%	12	27.3%	19	15.8%	43	8.0%	<0.05
Constipation	60	8.5%	4	9.1%	10	8.3%	46	8.6%	ns
GERD	44	6.3%	4	9.1%	10	8.3%	30	5.6%	ns
Speech language disorders	33	4.7%	7	15.9%	15	12.5%	11	2.0%	<0.05
Dyspnea	32	4.6%	4	9.1%	5	4.2%	23	4.3%	ns
Sleep disorders	28	4.0%	8	18.2%	5	4.2%	15	2.8%	<0.05
Muscle weakness	27	3.8%	4	9.1%	11	9.2%	12	2.2%	<0.05
Extrapyramidal-movement disorder	22	3.1%	2	4.5%	4	3.3%	16	3.0%	ns
Anemia	19	2.7%	3	6.8%	0	0.0%	16	3.0%	<0.05
Anxiety	17	2.4%	0	0.0%	1	0.8%	16	3.0%	ns
Long QT syndrome	14	2.0%	2	4.5%	4	3.3%	8	1.5%	ns
Restlessness and agitation	11	1.6%	1	2.3%	0	0.0%	10	1.9%	ns
Depression	6	0.9%	0	0.0%	0	0.0%	6	1.1%	ns

Diagnoses measured during the 12-month period following the index Rett diagnosis.
Chi-square analysis used to test for statistically significant differences for categorical variables among age groups.
One-way ANOVA used to test for statistically significant differences for continuous variables among age groups.
Alpha level set at 0.05.
GERD: Gastroesophageal reflux disease; ns: Not statistically different at $p \leq 0.05$.

Discussion

RTT is a severe, progressive, dominant X chromosome-linked neurodevelopmental disorder with a characteristic clinical picture that mostly occurs in girls [24]. To our knowledge, this is the first retrospective database study using commercially available medical claims to examine the demographic characteristics, pre-diagnosis medical history, co-occurring conditions, and treatment utilization of individuals diagnosed with RTT. Similar to most studies on RTT, we found that patients were predominantly female individuals [25], although 5% of our study population were

Table 6. Healthcare service utilization occurring during the 12-month follow-up period.

	Full sample (n = 702)			1–5 years (n = 44)			>5–10 years (n = 120)			>10 years (n = 538)			p-value
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	
Office visits (PPPY)	702	4.6	10.3	44	5.1	8.3	120	6.2	13.4	538	4.1	9.7	ns
Outpatient hospital visits (PPPY)	702	2.5	7.3	44	3.4	7.6	120	3.2	6.0	538	2.3	7.6	ns
ED visits (PPPY)													
Mean (SD)	–	0.5	1.4	–	1.0	2.4	–	0.5	1.2	–	0.4	1.3	$p < 0.05$
Among patients with 1+ visits	156	2.1	2.5	15	2.9	3.4	34	1.9	1.6	107	2.0	2.6	ns
Inpatient admission (PPPY)													
Mean (SD)	–	0.5	2.5	–	1.0	2.5	–	0.4	1.2	–	0.5	2.8	ns
Among patients with 1+ admission	126	2.9	5.4	12	3.6	4.0	27	2.0	1.8	87	3.1	6.2	ns
Inpatient days (among total)													
Mean (SD)	–	2.1	10.2	–	8.6	24.4	–	2.4	12.9	–	1.5	7.0	$p < 0.05$
Among patients with 1+ admission	126	11.8	21.7	12	31.5	38.8	27	10.8	25.8	87	9.4	15.2	$p < 0.05$

Measured during the 12-month period following the index Rett diagnosis.
Chi-square analysis used to test for statistically significant differences for categorical variables among age groups.
One-way ANOVA used to test for statistically significant differences for continuous variables among age groups.
Alpha level set at 0.05.
GERD: Gastroesophageal reflux disease; ns: Not statistically different at $p \leq 0.05$; PPPY: Per patient per year.

male individuals. Most were insured by Medicaid (a program dedicated to providing health coverage for low-income individuals in the US states, US territories, and District of Columbia [26]). While the frequency of co-occurring conditions typically associated with RTT were lower than in other published sources, we attribute differences to an examination of lifetime prevalence in most studies versus our examination of the 12 months following the index diagnosis. Over time, we expect the frequencies of co-occurring conditions to increase and mirror other studies. Finally, we found that many patients do not reside within a state with a COE or Rett clinic implying that patients, parents, and guardians would need to travel significant distances to receive optimal care from Rett specialists. However, it is not clear from these data whether patients were treated at COEs or Rett specialty clinics nor is the relationship between treatment at a COE and treatment outcomes and cost.

Early identification of developmental disorders is an important role of pediatricians; since they are the gatekeepers for access to additional services. However, due in part to its rare nature, few pediatricians have significant knowledge, familiarity, or experience with RTT and how to appropriately diagnose and provide care for patients [25]. In 2010, Neul *et al.* simplified diagnostic criteria in an attempt to eliminate confusion regarding the diagnosis of RTT [27]. Despite this, studies published in 2015 by Tarquinio *et al.* demonstrated that only 5.4% and 3.0% of classic and atypical Rett diagnoses were made by pediatricians or other primary care providers respectively [28]. In the current study we found that nearly 90% of patients had a "significant" alternative diagnosis preceding the index Rett diagnosis. Diagnoses included various forms of epilepsy, cerebral palsy, intellectual disabilities, autism, delays in development, failure to thrive and more (Table 4). The aforementioned alternative diagnoses (and delays in a classic or atypical Rett diagnosis) have important treatment-related implications that can prevent, or delay children from receiving optimal care by specialists available at COEs or Rett clinics. Furthermore, these delays can prevent enrollment in important clinical trials and other research studies and even reduce caregiver support through formal and informal channels. Taken together, these data suggest that additional training and greater awareness of RTT is necessary for all providers, particularly pediatricians and primary care providers. The goal of training should be to ensure that a diagnosis of RTT is made as early as possible to ensure the best possible care.

We also found that a small minority of patients had medical claims for any PT, OT or ST, during the 12 months following the index diagnosis. Utilization of PT and OT services was greatest among the youngest cohort and declined with age. While it is likely that most individuals will eventually engage these services during their patient journey, the aforementioned frequencies are surprising given the body of work highlighting the impact that PT, OT, and ST services can have on patient outcomes [28–30]. Because individuals with Rett have a variety of co-occurring

Table 7. Therapy service utilization occurring during the 12-month follow-up period.

Office visits	Full sample (n = 702)				1–5 years (n = 44)				>5–10 years (n = 120)				>10 years (n = 538)				p-value
	n	%	Mean	SD	n	%	Mean	SD	n	%	Mean	SD	n	%	Mean	SD	
Physical therapy (PPPY), mean (SD)			1.7	7.3			5.3	12.2			2.9	8.5			1.2	6.2	<0.05
Among those who have at least one	97	13.8%	12.4	16.0	12	27.3%	19.6	16.8	29	24.2%	12.0	14.2	56	10.4%	11.1	16.6	ns
Occupational therapy (PPPY), mean (SD)			1.6	7.4			5.6	13.6			2.6	10.6			1.1	5.6	<0.05
Among those who have at least one	91	13.0%	12.4	17.4	14	31.8%	17.5	19.6	20	16.7%	15.4	22.2	57	10.6%	10.1	14.8	ns
Speech therapy (PPPY), mean (SD)			1.0	5.4			4.6	14.5			1.7	6.1			0.5	3.5	<0.05
Among those who have at least one	46	6.6%	14.7	16.1	6	13.6%	33.7	25.3	20	16.7%	10.4	11.6	20	3.7%	13.3	13.1	<0.05

Measured during the 12-month period following the index Rett diagnosis.
Chi-square analysis used to test for statistically significant differences for categorical variables among age groups.
One-way ANOVA used to test for statistically significant differences for continuous variables among age groups.
Alpha level set at 0.05.
ns.: Not statistically different at $p \leq 0.05$; PPPY: Per patient per year.

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Table 8. Medical equipment and durable medical equipment utilization during the 12-month follow-up period

	Full sample (n = 702)		1–5 years (n = 44)		>5–10 years (n = 120)		>10 years (n = 538)		p-value
	n	%	n	%	n	%	n	%	
Medical equipment and durable medical equipment utilization during the 12-month follow-up period									
Any medical equipment	262	37.3%	19	43.2%	60	50.0%	183	34.0%	ns
Medical equipment									
Orthotic and prosthetic devices	135	19.2%	13	29.5%	35	29.2%	87	16.2%	$p < 0.05$
Cranial orthotic device	3	0.4%	1	2.3%	0	0.0%	2	0.4%	ns
Durable medical equipment									
Walkers and canes	1	0.1%	0	0.0%	1	0.8%	0	0.0%	ns
Wheelchairs and scooters (non-electric)	27	3.8%	0	0.0%	3	2.5%	24	4.5%	ns
Power wheelchairs	0	0.0%	0	0.0%	0	0.0%	0	0.0%	–
Speech generating devices	8	1.1%	1	2.3%	5	4.2%	2	0.4%	$p < 0.05$
Patient lifts	22	3.1%	0	0.0%	2	1.7%	20	3.7%	ns
Oxygen equipment and accessories	116	16.5%	7	15.9%	26	21.7%	83	15.4%	ns
Commode chairs	2	0.3%	0	0.0%	1	0.8%	1	0.2%	ns
Number of medical equipment and durable medical equipment utilization during the 12-month follow-up period									
Any medical equipment	2.3	5.8	2.5	6.7	3.5	7.9	2.0	5.2	$p < 0.05$
Among those who have at least 1	6.0	8.3	5.8	9.4	6.9	10.0	5.8	7.5	ns
Medical equipment									
Orthotic and prosthetic devices	0.4	0.9	0.4	0.8	0.5	1.0	0.3	0.9	$p < 0.05$
Among those who have at least 1	1.8	1.4	1.5	0.7	1.9	1.0	1.9	1.6	ns
Cranial orthotic device	0.0	0.1	0.0	0.2	0.0	0.0	0.0	0.1	ns
Among those who have at least 1	1.0	0.0	1.0	–	–	–	1.0	–	ns
Durable medical equipment									
Walkers and canes	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	–
Among those who have at least 1	1.0	–	–	–	1.0	–	–	–	–
Wheelchairs and scooters (non-electric)	0.1	0.8	0.0	0.0	0.0	0.2	0.1	0.9	ns
Among those who have at least 1	2.7	3.0	–	–	1.0	–	2.9	3.1	ns
Power wheelchairs	0.0	0.0	–	–	–	–	–	–	–
Among those who have at least 1	–	–	–	–	–	–	–	–	–
Speech generating devices	0.0	0.2	0.0	0.3	0.1	0.4	0.0	0.1	$p < 0.05$
Among those who have at least 1	1.8	0.9	2.0	–	1.6	0.9	2.0	1.4	ns
Patient lifts	0.1	1.1	0.0	0.0	0.1	1.1	0.2	1.2	ns
Among those who have at least 1	4.6	4.4	–	–	6.5	7.8	4.5	4.2	ns
Oxygen equipment and accessories	1.6	5.6	2.0	6.7	2.7	7.6	1.4	4.8	$p < 0.05$
Among those who have at least 1	9.8	10.3	12.6	13.1	12.5	12.3	8.8	9.3	ns
Commode chairs	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.0	ns
Amongst those who have at least 1	1.0	–	–	–	1.0	–	1.0	–	ns

Measured during the 12-month period following the index Rett diagnosis.
Chi-square analysis used to test for statistically significant differences for categorical variables among age groups.
One-way ANOVA used to test for statistically significant differences for continuous variables among age groups.
Alpha level set at 0.05.
ns.: Not statistically different at $p \leq 0.05$.

conditions that can be mitigated by PT, OT and ST; these services should be a part of the patient's treatment regimen as early as possible. As above, additional work should be dedicated to raising the awareness of the impact of these therapies and working with PT, OT and STs to outline best practices for patients with specific co-occurring conditions.

Finally, we found that individuals with RTT used physician office visits and outpatient hospital visits at a rate higher than national averages of well and problem focused care visits according to the CDC National Center for Health Statistics [31]. In 2012, children under 18 years of age averaged 232 visits per 100 children, or 2.32 visits per person, while those ages 1–5 years averaged 277 office visits per 100 children, or 2.77 visits per child [32]. In our

Table 9. Pharmacy utilization among patients with Rett syndrome during the 12-month follow-up period.

	Full sample (n = 702)		1–5 years (n = 44)		>5–10 years (n = 120)		>10 years (n = 538)		p-value
	n	%	n	%	n	%	n	%	
Anticonvulsants									ns
Levetiracetam	67	9.5%	7	15.9%	15	12.5%	45	8.4%	
Lamotrigine	35	5.0%	1	2.3%	2	1.7%	32	5.9%	
Clonazepam	34	4.8%	0	0.0%	2	1.7%	32	5.9%	
Clobazam	27	3.8%	1	2.3%	10	8.3%	16	3.0%	
Carbamazepine	25	3.6%	0	0.0%	1	0.8%	24	4.5%	
Topiramate	24	3.4%	0	0.0%	6	5.0%	18	3.3%	
Valproic acid	24	3.4%	0	0.0%	6	5.0%	18	3.3%	
Divalproex sodium	23	3.3%	0	0.0%	2	1.7%	21	3.9%	
Oxcarbazepine	20	2.8%	2	4.5%	4	3.3%	14	2.6%	
Lacosamide	19	2.7%	1	2.3%	3	2.5%	15	2.8%	
Zonisamide	14	2.0%	0	0.0%	3	2.5%	11	2.0%	
Rufinamide	8	1.1%	0	0.0%	3	2.5%	5	0.9%	
Gabapentin	8	1.1%	1	2.3%	0	0.0%	7	1.3%	
Felbamate	4	0.6%	0	0.0%	1	0.8%	3	0.6%	
Perampanel	4	0.6%	0	0.0%	2	1.7%	2	0.4%	
Primidone	1	0.1%	0	0.0%	0	0.0%	1	0.2%	
Fosphenytoin sodium	1	0.1%	0	0.0%	0	0.0%	1	0.2%	
Ethosuximide	1	0.1%	0	0.0%	0	0.0%	1	0.2%	
Phenytoin	1	0.1%	0	0.0%	0	0.0%	1	0.2%	
Anxiolytics									ns
Diazepam	54	7.7%	5	11.4%	13	10.8%	36	6.7%	
Lorazepam	21	3.0%	1	2.3%	4	3.3%	16	3.0%	
Alprazolam	5	0.7%	0	0.0%	0	0.0%	5	0.9%	
Midazolam hydrochloride	4	0.6%	0	0.0%	1	0.8%	3	0.6%	
Clorazepate dipotassium	3	0.4%	0	0.0%	0	0.0%	3	0.6%	
Triazolam	1	0.1%	0	0.0%	0	0.0%	1	0.2%	
Temazepam	1	0.1%	0	0.0%	0	0.0%	1	0.2%	
Antidepressants									ns
Trazodone HCl	11	1.6%	1	2.3%	3	2.5%	7	1.3%	
Fluoxetine HCl	10	1.4%	1	2.3%	0	0.0%	9	1.7%	
Escitalopram oxalate	9	1.3%	0	0.0%	2	1.7%	7	1.3%	
Citalopram hydrobromide	4	0.6%	0	0.0%	0	0.0%	4	0.7%	
Mirtazapine ODT	2	0.3%	0	0.0%	0	0.0%	2	0.4%	
Lexapro	2	0.3%	0	0.0%	0	0.0%	2	0.4%	
Sertraline HCl	2	0.3%	0	0.0%	0	0.0%	2	0.4%	
Amitriptyline HCl	2	0.3%	0	0.0%	0	0.0%	2	0.4%	
Mirtazapine	1	0.1%	0	0.0%	0	0.0%	1	0.2%	
Doxepin HCl	1	0.1%	0	0.0%	0	0.0%	1	0.2%	
Antiarrhythmics									
Metoprolol	2	0.3%	0	0.0%	0	0.0%	2	0.4%	
Acebutolol	1	0.1%	0	0.0%	0	0.0%	1	0.2%	
Diltiazem	1	0.1%	0	0.0%	0	0.0%	1	0.2%	
Laxatives									ns
Polyethylene glycol	32	4.6%	3	6.8%	6	5.0%	23	4.3%	
Lactulose	9	1.3%	0	0.0%	3	2.5%	6	1.1%	
Potassium chloride	1	0.1%	0	0.0%	0	0.0%	1	0.2%	

Measured during the 12-month period following the index Rett diagnosis.
Chi-square analysis used to test for statistically significant differences for categorical variables among age groups.
One-way ANOVA used to test for statistically significant differences for continuous variables among age groups.
Alpha level set at 0.05.
Not statistically different at $p \leq 0.05$.

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study, the youngest individuals with RTT (1–5 years) averaged just over a month, 31.5 (±38.8) days in inpatient care. While these data reaffirm that individuals with RTT use significant healthcare related resources, future studies will directly compare healthcare utilization to a group of children without RTT to understand the magnitude of the difference in utilization. Further, future studies should quantify the relationship between treatment at COEs and treatment outcomes and cost of care.

Study limitations

Many of the study limitations in other manuscripts using administrative claims data to study RTT apply here [3]. The first limitation is that causality cannot be inferred. Also, it is always possible that an unknown number of coding errors are contained within the database, however, that reimbursement depends upon correct coding provides some safeguard against coding errors. Additionally, neither disease severity nor results of genetic testing are available in commercially available medical claims. Though we did not perform a clinical assessment and gene-based phenotyping was not possible orthodox methods for diagnosis based case-finding produced a sample that was within expected limits. These limitations should be considered when evaluating these data.

Conclusion

Two therapies targeting RTT recently demonstrated promising results in clinical studies [32–35]. The emergence of these therapies, and others in the future, create the need to better understand the Rett patient journey. Commercially available administrative claims databases, like the one used here, can provide general descriptions of healthcare needs and services utilized by large populations of patients and will be central to evaluating future real-world outcomes related to these new therapies. Compared with individuals without an RTT diagnosis, the RTT group used on average twice the number of office-based physician visits and approximately 30 days per year of hospital based services. The current study is the first to our knowledge that illustrates the clinical characteristics and healthcare service utilization of people with RTT as would be seen by health insurance companies attempting to make care management decisions directly affecting treatment of people with RTT.

Summary points

- Significant numbers of Rett cases have alternative diagnoses prior to the Rett diagnosis manifesting delays in a classic or atypical Rett diagnosis.
- Delays in correct Rett diagnosis have important treatment-related implications that can prevent, or delay children from receiving optimal care by specialists and entering clinical trials.
- Additional training and greater awareness of Rett syndrome may be of benefit for all providers, particularly pediatricians and primary care providers.
- Though the impact of PT, OT and ST is well documented, small minority of patients in our sample had medical claims for any PT, OT or ST, during the 12-months following the index diagnosis with utilization greatest among the youngest cohort and declining with age.
- Because individuals with Rett have a variety of co-occurring conditions that can be mitigated by PT, OT, and ST; these services should be a part of the patient's treatment regimen as early as possible.
- Finally, we found that individuals with Rett syndrome used physician office visits and outpatient hospital visits at a rate higher than national averages of well and problem focused care visits.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors confirm that the study protocol was approved by Advarra's Institutional Review Board.

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