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Guidance for Primary Care Providers in Rett Syndrome

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Guidance for Primary Care Providers in Rett Syndrome

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Abbreviations:
ABR: auditory brainstem response
AAC: augmentative and alternative communication
CVI: cortical visual impairment
DMV: department of motor vehicle
EI: Early Intervention
ICF: International Classification of Functioning, Disability and Health
IEP: Individualized Education Program
NHS: NIH-funded Natural History Study of Rett and related disorders
PCP: primary care provider
RTT: Rett Syndrome
TVI: teacher of the visually impaired

Summary Box:

What is known: Rett syndrome (RTT) is a multi-system and rare genetic disorder with similarities to other developmental encephalopathies. No randomized phase three clinical trials have assessed therapeutics in RTT. There are no peer-reviewed consensus-based therapeutic guidance to care in RTT.

What this study adds: The primary care provider plays a key role in recognizing, treating and directing care of patients with RTT. A consensus on guidance for the primary care provider was developed based on literature review and expert opinion. This guidance is applicable to other rare and often severe neurodevelopmental disorders.

Abstract

Background: Rett syndrome (RTT) is a severe neurodevelopmental disorder with complex medical co-morbidities extending beyond the nervous system requiring the attention of primary care providers. No randomized phase three clinical trials have assessed therapeutics in RTT. There are no peer-reviewed consensus-based therapeutic guidance to care in RTT. The objective was to provide consensus on guidance of best practice for addressing these concerns.

Methods: Informed by the literature and using a modified Delphi approach, a consensus process was utilized to develop guidance for care in RTT by primary care providers.

Results: Typical RTT presents early in childhood in a clinically recognizable fashion. Multisystem co-morbidities evolve throughout the lifespan requiring coordination of care between primary care and often multiple subspecialty providers. To assist primary care providers and families in seeking best practice, a checklist and detailed references for guidance were developed by consensus.

Conclusions: The overall multisystem issues of RTT require the primary care provider to oversee and manage the whole individual and family. Given the median life expectancy well into the 6th decade, guidance is provided to primary care providers to achieve current best possible outcomes for these special-needs individuals.

Introduction

Rett syndrome (RTT)[1] is a severe neurodevelopmental disorder with an estimated worldwide prevalence of between 1 in 20,000 to 40,000 people. The vast majority of individuals with RTT are female with up to 1 in 10,000 girls under the age of 12 affected[2], making it one of the most common genetic causes of developmental and intellectual impairment in females[3]. RTT is considered a progressive disorder involving multisystem symptom evolution over time but, contrary to a long-held misconception, is not a neurodegenerative condition[4]. Research into the molecular pathogenesis has progressed rapidly, symptoms of the disorder have been reversed in mouse models[5,6], and there is burgeoning hope for significant disease modifying therapies in the near future.

Nearly all individuals with RTT have one of >300 distinct loss-of-function mutations in the *MECP2* gene on the X-chromosome[7]. This gene encodes methyl-CpG binding protein-2, an essential transcriptional regulator in the brain required for normal neurodevelopment[8]. Complete genetic testing involves sequencing and methods to detect larger deletions (e.g. multiplex ligation-dependent probe amplification (MLPA)) of the *MECP2* gene. Likely owing to the random nature of X-chromosome inactivation[9] and other genetic modifiers[10-12], genotype-phenotype correlations are imprecise. However, a general pattern exists with some mutations (early truncating mutations such as R168X, R255X, R270X, large deletions and specific point mutations such as R106W) associated with increased severity compared to other mutation groups (R133C, R294X, R306X, and C-terminal truncations)[13]. *MECP2* mutations causing RTT are almost always *de novo* (spontaneous) and as such are not expected to recur in families.

The presentation is initially subtle in the first two years of life involving developmental delays and hypotonia on exam, but subsequent symptom evolution between 18-30 months of age with developmental regression and onset of repetitive, purposeless hand movements is striking[14]. The core clinical diagnostic features of RTT (Table 1)[1] include a period of normal (or near normal) development followed by developmental regression with loss of language and hand function skills, impaired gait, and development of hand stereotypies causing life-long dependence[15,16]. The average age at diagnosis of 2.5 years has been trending downward with increasing availability of diagnostic genetic testing[2]. The

multisystem nature of the disorder has been documented within multiple observational studies with symptom risk evolving across the lifespan. Neurodevelopmental concerns are central in all patients, requiring education and management of: periodic breathing(95%[17]), epilepsy (90%[18]), tone/movement (63-84%[19-21]), sleep (80%[22]), and behavior (14%[23]). Additional clinical domains of relevance to the PCP include gastrointestinal (90%[24]), orthopedic (85%[25-27]), nutritional (40%[24]), endocrine (30%[28,29]), and cardiac (10-18%[30,31]) issues (Supplemental Table 1).

In the past two decades the natural history of RTT has been extensively studied[32]. Perhaps most important to the primary care provider (PCP) is the knowledge that with appropriate care, children with RTT will become adults with RTT; 70% live to at least 50 years of age[15,33]. As such, the PCP is often presented with the daunting task of effectively coordinating attention to the evolving medical comorbidities of the disorder throughout a patient's lifespan. To help address this challenge, based on a review of published literature regarding Rett syndrome symptomatology that identified the concerns most relevant to the PCP, through a modified Delphi consensus approach we developed recommendations regarding guidance for best practice.

Methods

Draft guidance was developed (MJ, KH and PN) and presented and discussed at bimonthly International Rett Syndrome Foundation sponsored North American Rett Syndrome Clinics Network conference calls between January 2016 through September 2018 with input obtained from 22 clinical sites. An initial draft was presented January 2017 for external review by the Network through September 2018; additional public input was obtained from January 2019 to May 2019 through placement on the RettSyndrome.org website. With supervision by the group leader, the guidance was further refined substantially by eight Rett Centers (University of Alabama Birmingham, Vanderbilt University, Children's Hospital Colorado, Children's Hospital of Philadelphia, Cincinnati Children's Hospital, Boston Children's Hospital, UCSF Benioff Children's Hospital Oakland, and Texas Children's Hospital) providing multidisciplinary care for individuals with RTT, in partnership with the NIH-funded Natural

History Study of Rett and related disorders (NHS, U54 HD061222; **ClinicalTrials.gov: NCT00299312/NCT02738281**) and two patient advocacy groups, Rett Syndrome Research Trust and the International Rett Syndrome Foundation. This consensus approach followed a modified Delphi process employed by members of this group previously[34]. The partners were chosen based on clinical experience across primary care, multiple subspecialties, health care delivery, and, importantly, patient-family experience with RTT. Conflicts of interest were vetted by the group leader with full knowledge by the group. A consensus led by the group leader surrounding guidance that should be intended for primary care providers based on published data and clinical opinion was developed through six further rounds of modifications. Search of Pubmed from 2000 to present was performed using the search terms (Rett and *MECP2* AND patient) OR (Rett and *MECP2* AND cohort). Articles related to prevalence of clinical findings were assessed with respect to the size and nature of the cohorts interrogated (Level 3) and their impact on clinical care (Supplemental Table 1). A qualitative review of 104 articles, which included small case series, the experience of the panel (each often with 100s of patients and subjects) informed the guidance (Level 4-5). The following recommendations were created based on an age-dependent health supervision approach to assist primary care providers in fulfilling the goal of effective and meaningful care for individuals with RTT across all ages (Tables 2 and 3). Items are organized by prevalence at each age group. Consistent with International Classification of Functioning, Disability and Health (ICF) guidelines (WHO , 2001)[35], this guidance recognize the inter-relatedness of body function/structure, environment and personal factors to maximize activities and participation (Supplemental Table 2). Thus, in addition to routine assessment of medical issues (body function), several psychosocial, environmental, and educational concerns need to be assessed frequently to achieve the goal of family-centered service:

- The financial, emotional and physical impact on the family as a whole: sibling well-being, parent physical and mental health (sleep, grief, anxiety, depression), quality of life, and marital impacts[36,37].
- Vigilance regarding signs and symptoms of abuse and neglect of an at-risk individual.
- Educational support programs for which the individual may be eligible.

- Supplemental Security Income benefits.
- Personal financial, community, and emotional support available to the family.

Patient involvement

Patients family groups (International Rett Syndrome Foundation and Rett Syndrome Research Trust), represented by parents of individuals with RTT (Ms. Nues and Ms. Coenraads), were involved in the development of the patient care guidance and writing of this manuscript. Their organizations will assist with dissemination of the guidance.

Results

A previously employed modified Delphi approach[34] was utilized to obtain consensus regarding guidance for primary care providers. This was formulated into a checklist (Table 2) with further details and references (Tables 3-7) that informed the checklist and the consensus process. The guidance for management by primary care providers was grouped by relevant features and therapeutic approaches at different ages. The checklist (Table 2) is suitable for use by both the primary care provider and the family as part of their health care records with Tables 3-7 providing further detailed guidance.

Diagnosis to 5 years old--Early Childhood: Most features of RTT may emerge during this age period. Feeding difficulties and growth failure[24,38,39] begin during this age. Additional treatable gastrointestinal issues including dysmotility, gastroesophageal reflux, constipation, gas bloating, often presenting as irritability or apparent discomfort manifest commonly at this age[24,40]. The development of microcephaly or head growth stagnation (as early as 1.5 months)[39] is a common feature, though macrocephaly has also been seen[41]. Tone issues at this age are typically characterized by hypotonia[42]; early referral to therapists (physical, occupational, speech language including augmentative communication[43]) and establishment of an IEP[44] are necessary. Severe hearing loss is uncommon in RTT[45] but there may be delayed auditory processing[46,47] that mimics hearing impairment. There is increased risk of cortical visual impairment (CVI) and ocular apraxia in RTT[48]. There is evidence suggesting increased risk for prolonged QTc interval that may be present from a young age[30,31,49] and may

develop with time[50]. The frequency of epileptic and non-epileptic spells[51,52] wax and wane throughout the course[18,51]. Individuals with RTT generally respond to anticonvulsants[18,51,53] but there have been no randomized, controlled trials of specific anticonvulsants for RTT. If hospitalized, it is important to inform hospital staff that RTT individuals may need lower doses of anesthetics or analgesics[54,55] and may take longer to awaken from anesthesia[56], and potentially confounding baseline issues: cold extremities[57], irregular and disordered breathing with oxygen desaturations[17,58], impaired proprioception, lack of hand use, inability to change position, and increased fall risk.

5 years to the Pre-pubescent Stage--Late Childhood: During the early school years, children with RTT typically have stabilized developmentally; the regression phase has ended[39]. Overall, many of the multisystem issues that arose during the first 5 years of life persist. Preventing undernutrition and maintaining a healthy BMI is important, as this has been associated with better functioning[38,59]. Surveillance for scoliosis becomes an important preventive measure; some children (~20%) ultimately require spinal surgery for this comorbidity[60]. Longitudinal assessment of pubertal development indicates an increased prevalence of early thelarche and adrenarche but delayed menarche[28]. Difficulties with abnormal tone in this age range typically are characterized by hypotonia evolving to rigidity[19,21].

Post-puberty to the end of school (~21 years old)--Post-puberty: Surveillance for scoliosis continues to be an important preventive measure though this lessens with completion of puberty[28]. Surveillance for urinary retention is important[61,62]. Biliary tract disease is seen in young adulthood at rates similar to the general population but due to communication impairment in RTT the presenting symptoms may be limited to irritability, weight loss and vomiting[63,64]. Studies of longevity in RTT demonstrate survival of many into middle age, underscoring the need for the early development of a comprehensive, thoughtful plan for transitioning to adulthood[65]. Longitudinal supervision is required in RTT as physical, behavioral and cognitive limitations will not allow for independent living[15,16]. This may include day programs and respite care.

21 years and older--Adulthood: Overall, individuals with RTT tend to stabilize clinically in young adulthood[66-68]. Frequent causes of hospitalization for women with RTT include pneumonia,

respiratory distress, status epilepticus, rectal bleeding, decline in ambulation, or refusal/inability to eat or drink[16]. While one-third of individuals may have a gastrostomy tube, half of these continue to have some oral intake[33]. With age, concern for low bone mineral mass coupled with long-term use of particular anticonvulsants, raises the risks for osteoporosis and bone fractures[27,69,70] necessitating continued supplementation and monitoring of 25-OH Vitamin D status[71,72]. Musculoskeletal problems and gross motor function may worsen overall[67] possibly due to more parkinsonian features[19] but with overall preservation of intellect and memory[16]; additional study is needed due to relatively low numbers studied. Physical limitations, parkinsonian features, and high prevalence of social withdrawal behaviors lead to abnormal or decreased social interactions consistent with anxiety or depression[23]. Although the majority of women with RTT in the US live at home[15], in other countries only about one-third of women over age 16 with RTT live at home (either full or part-time) with the majority living in a residential facility[16]. Long-term and individually-tailored care that provides social interactions and physical activity should be provided at all ages to reduce age-related deterioration[73].

Discussion

Management of RTT requires input or expertise related to multiple specialties, often necessitating referrals to many providers in addition to the primary care provider. The above health guidance will evolve with further research into the longitudinal course of RTT by the NHS and others. However, there are limitations to the current proposed health guidance, specifically with respect to the lack of needed randomized clinical trials in a rare condition where interventions, such as physical and other therapies, are rarely standardized. At this time, longitudinal prognostic details are not well understood in certain areas of evaluation such as affect, displayed emotion and its meaning, the most appropriate manner to assess intelligence and how it evolves, or the life span of gynecologic concerns. With the relative paucity of older individuals in the NHS and related studies, further study into the care of older individuals is needed to better address guidance more extensively for both older RTT women and for those more severely affected who are not routinely captured in most studies[68]. Additional studies should also address the role

and utility of palliative care and banking of post-mortem tissue. From this breadth of information, quality metrics with benchmarks can be defined to ensure standards of care with best outcomes for individuals with RTT.

Additionally, with current and future clinical trials, the disease course for individuals with RTT may be more modifiable with severity of symptoms and disease progression very different from our current understanding. There is considerable ongoing research in the field of specific RTT therapeutics[74]. It is therefore important for families, caregivers and primary care providers to reach out to Rett Centers and family support group resources to stay up to date on clinical trials, drug approvals, and how this impacts these current care guidance. While the primary care provider may not be able to counsel on the suitability of different clinical trials, actively engaging RTT individuals and families and referring to clinical trials at specialty centers is necessary for the development of improved therapeutics.

With the advances in healthcare and technology, improved and earlier genetic testing, robust research in RTT, and active patient advocacy from families and clinicians, individuals with RTT are surviving well into adulthood while living more healthy and meaningful lives. With the vast amount of medical knowledge emerging from research in RTT today and knowing the complexity of care RTT often requires, this proposed guidance can facilitate the primary care provider in delivering more thorough and well-rounded management and comprehensive surveillance. Importantly, the guidance also help to outline considerations in which the primary provider may want to refer the individual with RTT for more specialized management.

In conclusion, Rett syndrome is a medically complex neurodevelopmental disorder impacting multiple organ systems in an evolving fashion from childhood through the 6th decade of adulthood. Primary care providers are uniquely positioned to most effectively manage the individual and family to coordinate the multidisciplinary requirements of the disorder by drawing on the accumulating knowledge regarding the natural history of the disorder to anticipate these requirements.

Web-links for primary care providers to regional RTT clinics

https://www.rettsyndrome.org/about-rett-syndrome/clinics

https://reverserett.org/newly-diagnosed/#clinics-map

Useful web-links for families

https://www.rettsyndrome.org/

https://reverserett.org/

https://www.rettsyndrome.org/for-families/resources-for-families

Contribution Statement: Ms. Nues, Drs. Marsh, Jones, Neul, Percy and Benke conceptualized and designed the literature search and guidance. Ms. Nues and Dr. Jones initiated a first draft of Tables 2 and 3. Drs. Fu, Armstrong, Lieberman, Marsh and Witt initiated the search and a first draft of the guidance. All authors contributed to subsequent drafts of the figure and guidance as described. Dr. Benke, as group leader, supervised and moderated the search and consensus process, initial drafts, the overall collation of the figure, tables, manuscript, and guidance. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Table 1. Classic (or Typical RTT) and Atypical RTT diagnostic criteria[1].
Classic or Typical RTT diagnostic criteria A period of regression followed by recovery or stabilization
1. Partial or complete loss of acquired purposeful hand skills
2. Partial or complete loss of spoken language
3. Gait abnormalities: impaired or absence of ability
4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms.
Atypical RTT diagnostic criteria A period of regression followed by recovery or stabilization 1. At least 2 of the 4 main criteria 2. 5 of 11 supportive criteria a) Breathing disturbances while awake b) Bruxism while awake c) Impaired sleep d) Abnormal muscle tone e) Peripheral vasomotor disturbances f) Scoliosis/kyphosis g) Growth retardation h) Small cold hands and feet i) Inappropriate laughing/screaming spells j) Diminished response to pain k) Intense eye communication – "eye pointing"

Table 2. Health Supervision guidance as a checklist for individuals and PCP.

• **Individuals with Rett syndrome should be seen for regular wellness checkups, screenings and immunizations (especially influenza vaccinations)*.** • **Inform staff that extra time will be needed for visit, especially to inspecting the individual without braces, shoes and outer clothing.** • **Parents and care-givers should keep a binder of health records to include: genetic testing results, summaries of all doctor visits (including specialist referrals), summaries of hospital admissions, laboratory studies, ECG, x-ray reports and other imaging results.**				
Areas of Assessment	**Assessment Details**	**Yearly Wellness Visit**	**Primary Care every 6 months***	**Baseline**
Genetics/ *MECP2* Testing Results	Counsel family on genetic test results and refer to genetic counselor if appropriate for additional counsel or explanation. Family and PCP to keep a copy of genetic results.			✓
General	Update current medications and allergies	At every visit		
	Weight	At every visit		
	Height or body length Body mass index	At very visit At every visit		
	Head circumference[1]	At every visit		
	Tanner Stage	At yearly wellness		
	Laboratory evaluations (see below)	(see below)		
Gastrointestinal	Review: feeding methods, appetite, chewing ability, choking and length of feeding time.	✓	✓	
	Screen for GE reflux, gas bloating, biliary tract disease, constipation and hemorrhoids, skin tags, or fissures.	✓	✓	
Nutrition	Review nutritional and herbal supplements Nutrition screening[2]: energy, protein, fluids, sodium, potassium, calcium, and vitamin D intake.	✓	✓	
Respiratory	Screen for awake disordered breathing (hyperventilating, breath-holding, color change), and air swallowing.	✓		
Neurology	Screen for presence of seizures and spells suspicious for seizures. Record description and frequency of seizures. Encourage individual to follow-up with neurologist routinely; every 6 months if treated for seizures. If individual's weight fluctuates (more than 10-20%), request neurologist to consider adjusting anticonvulsant doses accordingly.	✓	✓	✓
	Screen for abnormal movements (stereotypies and dystonia).	✓		✓
Cardiology	Check QTc interval with ECG; if abnormal, refer to Cardiology.	✓		✓
Skin	Document temperature and color of hands and feet. Screen for skin breakdown from hand-mouthing or ill-fitting braces. Screen for pressure ulcers.	✓	✓	
Orthopedics Rehabilitation	Estimate curvature of spine. Recheck every 6 months if scoliosis present; refer to Orthopedics if > 20 degrees.	✓	(if scoliosis present✓)	
	Screen for abnormal hip abduction, range of motion and leg length.	✓	✓	

	Screen for contractures and use or need of devices to prevent them (ankle-foot orthoses and splints).	✓		
	Discuss risk of fractures due to osteopenia.	✓		
	Screen for needs and use of mobility aids.	✓		
Urology	Review toilet training, frequency and infrequency of urination, and urinary tract infections. Refer to urology for frequent urinary tract infections or overflow incontinence.	✓		
Development	Documentation of baseline, gains and losses of milestones. Fine motor: hand use: raking grasp, pincer grasp, rake, holding cup or spoon. Gross motor: sitting, standing, and walking. Language: coo, babble, laugh, words.	✓		✓
Communication	Screen communication methods used by family and school: eye pointing, vocalizations, switches, ipad, eye-gaze device.	✓		✓
Behavioral	Screen for symptoms of anxiety and depression, such as withdrawal, screaming and irritability. Inquire about sensory processing difficulties.	✓	✓	✓
Sleep	Review sleep initiation, staying asleep, snoring or coughing, and frequency of nocturnal interventions by caregivers. Review safety of bed and bedroom.	✓	✓	✓
Pain	Discuss delayed pain response and describe individual's response to pain.	✓		
Extremities	Temperature dysregulation. Review environmental factors that might impact comfort.	✓		
Screenings	Vision screening including acuity, spatial, depth, visual fields and cortical visual impairment. Review results with parents.	✓		
	Audiology ABR at birth, PRN if chronic otitis media, consider evaluation for auditory processing delay	✓		✓
	Annual dental health screening; refer for cleaning every 6 months.	✓		
Education/therapies	Review for presence of current IEP (see info on RettSyndrome.org) Documentation of therapies (type and frequency).	✓		✓
Family/Social	Assess for family stress (financial, social, fatigue)	✓	✓	✓
Resources	Review available community, insurance resources (DMV permit, respite care etc.) In adolescent individuals review plans for obtaining guardianship. PCP may be required to write Letters of Medical Necessity for equipment and sign school medication forms.	✓		

*6month follow-up visit is medically necessary to screen for issues that can appear quickly, progress rapidly and require intervention

[1]Please see CDC or Nellhaus head circumference chart for age 0-18 years

[2]Please see **Food and Drink Log** (https://www.rettsyndrome.org/pcg) to ensure adequate calcium, vitamin D, calories and fluid intake

LABORATORY EVALUATIONS: CBC, chemistry panel, 25-OH-vitamin D (yearly), baseline lipid screen (fasting if possible), UA (every 2 years). If disrupted sleep or concern with restless leg syndrome, consider ferritin, serum iron, TIBC, transferrin.

Tables 3-7. Detailed approaches to management and therapy for RTT. References not specific to RTT noted as "See:".

Table 3: Genetics, Neurology, Cardiology, Respiratory, and Urology			
System/Area	**Common concerns and questions**	**Details and suggested approach**	**References**
Genetics	*MECP2* gene	For suspicion of Rett syndrome, *MECP2* gene sequencing and MLPA testing is recommended. MLPA testing is needed to detect deletions otherwise missed by sequencing; this test is necessary if no abnormalities are found by sequencing. Referral to a geneticist or genetic counselor is recommended to review recurrence risks and answer related questions. Genetic testing results are essential for enrollment in clinical trials. Referral to a Rett Center if feasible may be useful to provide multidisciplinary care and access to clinical trials.	2,75,76
Neurology	Seizures and Spells	Refer to neurologist for seizures and spells suspicious for seizures with follow-up every 6 months if treated with an anticonvulsant. It is difficult to differentiate between a non-epileptic Rett Spell and a seizure (both may be present). Individuals can have multiple types of seizures. Seizure logs by the family are needed with careful description of events that includes frequency and duration. Videos of events are helpful to the neurologist. The neurologist may order a video EEG to accurately characterize whether a type of event is a seizure or not. An overnight EEG may be necessary to capture sleep; an EEG is incomplete if sleep is not captured.	18,51-53
	Abnormal movements	Ataxic gait and an impaired spatial awareness (proprioception) are common. Stereotypical hand movements (hand-wringing, mouthing, etc) are typical. These are often disruptive to hand use. Use of splints to elbows or hand guards, which may be prescribed by an OT, may be helpful to improve hand use. Initially, most individuals have low tone that progresses over years to high tone and dystonia. Neurologist or physiatrist may prescribe neuromuscular blockade or other medications to reduce tone to maintain function and prevent contractures.	19-21,77
Cardiology	Abnormal ECG	Yearly ECG to check for prolonged QTc interval which can develop at any time. Referral to cardiologist if the ECG is abnormal, who may consider further studies (Holter monitor, echocardiogram) or treatment. Avoid prescription of medications that can prolong QTc interval (i.e. fluoxetine). A current ECG is needed before anesthesia.	30,31,49,50
	Poor circulation	Distal temperature asymmetries are common and thought to be autonomic in origin; no specific therapy is recommended.	57,78,79
Respiratory	Hyperventilation, air swallowing, breath holding, blowing raspberries	Due to autonomic dysregulation, these may occur during the day. While not purposeful, they may be triggered by anxiety. Currently, there are no medications or treatments for this. If night time apneas are present, check tonsils and consider ordering a comprehensive sleep study and related specialist referral. Breathing abnormalities may disrupt feeding.	17,58,80-82
Urology	Urine retention	Autonomic dysfunction can lead to delayed bladder emptying and bladder distension. If present, referral to urology may be needed. Constipation can increase risk of UTIs. Toilet training can be achieved in some cases. Certain medications or poor fluid intake can cause increase risk of kidney stones.	61,62 See: 83

Table 4: Gastroenterology and Nutrition

System/Area	Common concerns and questions	Details and suggested approach	References
Gastroenterology and Nutrition	Dysmotility	Abdominal pain and discomfort typically are caused by reflux, gas bloating, delayed stomach emptying, biliary tract disease, or constipation; these can be empirically diagnosed and managed (see below). These will present with abdominal fullness (gas or constipation), irritability (reflux or constipation), nocturnal arousals (reflux or constipation), arching (reflux), overt reflux or emesis, burping (reflux or air swallowing). Gall bladder dysfunction, screened by abdominal ultrasound, should be considered. Referral to surgery for cholecystectomy may be necessary for symptomatic gallstones or biliary dyskinesia.	24,38,40,64
	Constipation	This is a very common problem. Laxatives (polyethylene glycol, magnesium hydroxide, glycerin or bisacodyl suppositories) are often a part of long-term treatment with a goal of one soft bowel movement per day.	24,40
	Reflux	This is a very common problem. PPI or H2 blockers are used empirically. Referral to gastroenterologist may be necessary to rule out complications such as esophagitis, ulcer, strictures, or Barrett's esophagus.	24,40
	Poor weight gain	Fatigue and irritability may be signs that dietary requirements are not being met;.consider energy dense foods (oils, syrups, avocado), gastroenterologist, and nutrition consults. Gastrostomy-button may be needed to maintain growth; counsel families that use of a gastrostomy button does not preclude oral feeding as long as oral feeding is safe. Use CDC/WHO growth charts to track growth and try to keep at same BMI percentile on growth curve through adolescent growth spurt. RTT-specific growth charts are also available.	24,38,39,84,85
	Calcium/Vitamin D	Ensure supplemental Vitamin D intake: 600-1000 IU or more daily. Target serum levels of 25-OH-Vitamin D greater than 30-40 ng/ml. Ensure milk and dairy products to provide age-appropriate dietary calcium intakes: 1-3 y, 700 mg/d; 4-8 y, 1000 mg/d; 9-18 y, 1300 mg/d; 19 y and older, 1000 mg/d. One 8-oz glass of milk or 8-oz cup of yogurt contains 300 mg of calcium.	27,69,70 See: 86
	Prolonged feeding times	Long feeding times (more than 30 minutes) can affect quality of life for patient and family; this may be an indication that a gastrostomy button is needed.	59,85 See: 87
	Chewing/swallowing difficulties	Referral to appropriate therapist or gastroenterologist to assess if there is concern for aspiration (coughing, choking, gagging with feeding or aspiration or unexplained pneumonia). In some cases, thickeners for liquids may be helpful to prevent aspiration versus need for a gastrostomy button.	24,38

Table 5: Orthopedics, Rehabilitation, Skin, Endocrine, and Hospitalization

System/Area	Common concerns and questions	Details and suggested approach	References
Orthopedics, Rehabilitation	Scoliosis	Increased risk of neuromuscular scoliosis after age 6; risk typically abates after puberty. This can progress rapidly if present, necessitating re-observation every 6 months if present. Supine x-ray and orthopedic referral when scoliotic curvature greater than 20 degrees; correction may be indicated when greater than 40 degrees. Kyphosis is more common in ambulatory individuals.	25,60,88-90
	Increased risk of hip subluxation	Examine hip range of motion due to high risk for hip subluxation and contractures, as either may be source of pain and cause for irritability. X-ray-AP views of pelvis may be needed to evaluate femoral head coverage.	91
	Contractures	Encourage families and caregivers to inspect all joints and practice daily range of motion, especially if mobility is reduced in an acute setting (illness or hospitalization). Consider OT and PT consults for bracing and splinting. Consider neurology and physiatry consults for neuromuscular blockade or other medications to improve tone.	92,93
	Osteopenia and fractures	There is higher risk of fracture due to immobility and use of anticonvulsants. If fracture occurs, consider DEXA scan and referral to endocrine specialist (in addition to aggressive screen of calcium, vitamin D intake and 25-OH-vitamin D levels). Cause for fractures beyond osteopenia needs investigation in order to eliminate other preventable causes, such as falling out of bed (needs rails), falling at home (needs assessment of home) or non-accidental trauma.	26,27,69-72,84,86,94
	Equipment	There is risks of injury due to outgrown equipment (See Skin above). Family and caregivers may need lifts, shower accommodations, bed-side toilets, etc.; these needs may be best assessed by a physiatry referral.	See: 95
Skin	Breakdown from mouthing or equipment or lack of re-positioning	Redness persisting longer than 20 min after equipment (such as a splint) is removed is of concern for development of pressure ulcers; return to PT to re-fit equipment. OT or PT may prescribe splints on elbows or hands to prevent skin breakdown from mouthing. Decubitus ulcer may need consultation with wound specialist and equipment specialist.	93
Endocrinology, Gynecology	Premature adrenarche	Menarche comes later, but breast buds and pubic hair may begin earlier than in typically developing children. Periods may be irregular due to low body weight or stress; T4, TSH should be checked if periods are irregular. Counsel family to notice whether or not seizure frequency corresponds with menstrual cycle and alert neurologist. Consideration of menses suppression should be considered, especially if it disrupts the interactions with caregivers and family or hormonal fluctuations correspond with increased seizure activity. The impact of menses suppression on bone health should be considered; IUD is a consideration. Avoidance of DEPO-provera is a consideration. Well-woman examination should include breast exam.	28,29 See: 96
Hospitalization	Anesthesia sensitivity, impaired proprioception	Individuals may need lower doses of anesthetics or analgesics. They may take longer to awaken from anesthesia. It is important to ensure anesthesiologist is aware of current medications (especially anticonvulsants and cannabis preparations), type and description of seizures, breathing abnormalities and risk of presence of prolonged QTc; a recent EKG is essential. Hospital needs to be aware of impaired proprioception, lack of hand use, inability to change position and increased fall risk. If hospitalized, family or hospital should perform daily ROM to prevent contractures.	17,30,31,49,54-56,58

Table 6: Psychological, Behavioral, Sleep, Pain, and Screenings

System/Area	Common concerns and questions	Details and suggested approach	References
Psychological, Behavioral	Issues with inattention/anxiety	Auditory processing is delayed and may be misinterpreted as disinterest; allow for this delay when assessing non-verbal language by allowing additional time for responses to questions or commands. Behavioral inconsistency is typical and may be affected by physical factors such as sleep or environment. Assess for intolerance of excessive stimuli (i.e. bright lights, loud noises).	46,47
	Externalizing/internalizing behaviors	Screen for caregiver impressions of anxiety and depression, such as withdrawal; these may become more prominent with age or in individuals with milder clinical presentations. Identify possible contributors (e.g., sedating medications, decreased social interaction, limited access to engaging activities). Consider treatment with an SSRI such as escitalopram which may have a lower risk of inducing a prolonged QTc interval.	16,23,68,97
Sleep	Disrupted sleep	Circadian rhythm is often disrupted; consider melatonin to initiate sleep and trazodone or clonidine to maintain asleep. Patient may be getting out of bed, which could be unsafe; consider a tent-style bed or similar engineering controls to keep child in bed and safe. Consider ferritin, serum iron, TIBC and transferrin levels if there is disrupted sleep or concerns for restless leg syndrome and need for iron replacement. Consider overnight sleep study for snoring or pauses in breathing.	22,98 See: 99-101
Pain	Pain assessment and sensitivity	Individuals have an atypical pain response, with higher thresholds and variable indications of pain (i.e. grimace, crying, increase in repetitive movements); typical pain scales may be difficult to interpret or apply	102
	Increased risk of chronic pain	Often due to GI problems (see above), dental problems, immobility and positioning. Always consider hip subluxation, vertebral compression fractures or other fractures as cause of pain.	24,40,63,64
Screening: Ophthalmology	Difficult vision assessment	Since eye gaze is the main way of communicating, assessment by practitioner familiar with special needs individuals is needed. Practitioner familiar with cortical visual impairment and ocular apraxia is needed.	48,92
Screening: Auditory	Auditory processing delay	Hearing is typically normal and assessments are often difficult to obtain but if chronic otitis media is present, these are needed.,	45
Screening: Dental	Teeth grinding, increased risk of caries	Routine cleanings needed and may require anesthesia. Dental work under anesthesia should be done with proper anesthesia support at major medical institutions. Regular dental care is required to avoid tooth extraction; tooth extraction significantly interferes with oral function and is to therefore be avoided if at all possible.	77,103

Table 7: Development, Education, Therapies, Social, and Alternative Medications

System/Area	Common concerns and questions	Details and suggested approach	References
Development, Education and Therapies	Developmental Milestones	Developmental regression (reduced hand use and language) typically stops between 2-3 years. Skills can be maintained and possibly regained with vigorous therapies. Therapies to consider: speech therapy (ST), feeding therapy (FT), occupational therapy (OT), augmentative communication therapy (AAC), vision therapy (VT), hippotherapy (horse) and swim/pool therapy.	43,44,48,92,104
	IEP and therapy challenges	Educators may not have experience with Rett syndrome. Request they focus on communication, mobility, and socialization with attention to apraxia. Educators and therapists need to be informed that the approach to therapy in Rett syndrome is different: it is about maintaining skills as well as recovery. Therapies for Rett syndrome should include occupational, physical, speech, swallow and augmentative communication. Therapy that maximizes physical activities should be life-long, as these will minimize long-term complications and maximize long-term potentials. Educational opportunities that provide intensive physical, occupational and speech therapy, especially those that provide augmentative communication, allow individuals to learn and make the best progress. If CVI is present, then a Teacher of the Visually Impaired (TVI) should be included in the IEP. This is in accordance with Free Appropriate Public Education (FAPE), an educational right of all students in the United States that is guaranteed by the Rehabilitation Act of 1973 and the Individuals with Disabilities Education Act (IDEA). Families should work with schools to develop an IEP that recognizes this; referral to a Rett Specialist may provide additional assistance in this regard.	43,44
	Non-verbal communication	Alternative and augmentative communication assessments are needed. While this can be done by some speech therapists, a specific referral may be needed. Since eye gaze is typically the most effective form of communication, special eye gaze devices can give individuals a voice. These referrals should be made as early as possible to coincide with typical language development. Devices should be made available to individuals at both home and school. Home use is to be encouraged as this setting may be the longest after the child graduates from the school system.	43,92
Social Concerns	Increased family stress	Family may need respite care. Sibling reactions and their adjustment should be considered; families could provide education for extended family and friends to understand Rett syndrome through patient advocacy group websites. When appropriate, discussion of Rett genetics with older siblings of child-bearing age should be considered by referral to a genetic counselor.	36,37,105,106
Alternative medications	Cannabis, St John's wort, etc.	Families should be encouraged to disclose use of alternative medications (cannabis, oils etc) to all specialists.	

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Supplemental Table 1. Characteristics of studies included in the meta-analysis of RTT comorbidities

RTT Comorbidities	Studies	Country	Study design	Cohort size	Age range (years)	Prevalence (%)
Neurological						
Periodic breathing	Tarquinio et al, 2018[1]	USA	Prospective	778	0.7-66.5	95
Epilepsy	Tarquinio et al, 2017[2]	USA	Prospective	922	0.7-66.5	90
Dysphagia	Motil et al, 2012[3]	USA	Cross-sectional	983	0-40+	90
Sleep dysfunction	Wong et al, 2015[4]	Australia	Prospective	320	2-35.8	80
Movement disorders	Humphreys et al, 2016[5]	Canada	Prospective	51	2.5-54	84
	Temudo et al, 2008[6]	Portugal	Prospective	60	5-13.5	63
	FitzGerald et al, 1990[7]	USA	Prospective	32	2.5-28	63
Behavioral disturbance (on medication)	Buchanan et al, 2019[8]	USA	Prospective	861	3-66	14
Gastrointestinal/Nutrition						
Constipation	Motil et al, 2012[3]	USA	Cross-sectional	983	0-40+	80
Reflux	Motil et al, 2012[3]	USA	Cross-sectional	983	0-40+	40
Failure to thrive	Motil et al, 2012[3]	USA	Cross-sectional	983	0-40+	40
Gall bladder dysfunction	Motil et al, 2019[9]	USA	Cross-sectional	271	7, 19[N.B.]	4
Cardiac						
Prolonged QT interval	McCauley, et al, 2011[10]	USA	Cross-sectional	379	2-46	18
	Crosson et al, 2017[11]	USA	Cross-sectional	100	1-17	10
Endocrine						
Premature adrenarche	Killian et al, 2014[12]	USA	Prospective	802	3-70	28
Premature thelarche	Killian et al, 2014[12]	USA	Prospective	802	3-70	25
Delayed menarche	Killian et al, 2014[12]	USA	Prospective	802	3-70	19
Low bone mineral mass	Motil et al, 2008[13]	USA	Cross-sectional	50	2-38	59
Thyroid dysfunction	Stagi et al, 2015[14]	Italy	Cross-sectional	45	2-26.1	18
Orthopedic						
Scoliosis	Percy et al, 2010[15]	USA	Prospective	554	0-57	80
Hip displacement	Tay et al, 2010[16]	Australia	Cross-sectional	31	7-29	50
Fractures	Jefferson et al, 2011[17]	Australia	Cross-sectional	97	4-30.5	32
	Motil et al, 2008[13]	USA	Cross-sectional	50	2-38	28

N.B.: Reported as 1st, 3rd quartile

Supplementary Table 2. Health supervision goals surrounding individuals with RTT by ICF contextual factors				
	Early Childhood	Late Childhood	Post-puberty	Adulthood
Body Functions and Structure	GI/Nutrition: Maintain adequate growth,bone health, and nutrition; manage reflux and constipation Neurological: Identify and manage epilepsy when present; identify and manage autonomic dysfunction Rehabilitation: develop strength and coordination Cardiology: detect and manage prolonged QT	GI/Nutrition: Maintain adequate growth,bone health, and nutrition; manage reflux and constipation Neurological: Identify and manage epilepsy when present; identify and manage autonomic dysfunction Rehabilitation: regulate tone and prevent contractures Cardiology: detect and manage prolonged QT Orthopedics: detect and manage scoliosis	GI/Nutrition: Maintain nutrition and bone health; manage constipation; detect and manage gall bladder dysfunction Neurological: Identify and manage epilepsy when present; identify and manage autonomic dysfunction Rehabilitation: regulate tone and prevent contractures Cardiology: detect and manage prolonged QT Orthopedics detect and prevent fractures	GI/Nutrition: Maintain nutrition and bone health; manage constipation; detect and manage gall bladder dysfunction Neurological: Identify and manage epilepsy when present; identify and manage autonomic dysfunction Rehabilitation: regulate tone and prevent contractures Cardiology: detect and manage prolonged QT Orthopedics: detect and prevent fractures
Environment	Education: Develop appropriate IEP Therapies: Access to appropriate therapies Socialization: Age-appropriate interactions and activities	Education: Develop appropriate IEP Therapies: Access to appropriate therapies including physical, occupational, and assistive communication technologies Socialization: Age-appropriate interactions and activities	Education: Develop appropriate IEP Therapies: Access to appropriate therapies including physical, occupational, and assistive communication technologies Socialization: Age-appropriate interactions and activities	Education: Transition to Adult Daycare programs. Therapies: Access to appropriate therapies including physical, occupational, and assistive communication technologies Socialization: Age-appropriate interactions and activities

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Guidance for Primary Care Providers in Rett Syndrome

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Abbreviations:
ABR: auditory brainstem response
AAC: augmentative and alternative communication
CVI: cortical visual impairment
DMV: department of motor vehicle
EI: Early Intervention
ICF: International Classification of Functioning, Disability and Health
IEP: Individualized Education Program
NHS: NIH-funded Natural History Study of Rett and related disorders
PCP: primary care provider
RTT: Rett Syndrome
TVI: teacher of the visually impaired

Summary Box:

What is known: Rett syndrome (RTT) is a multi-system and rare genetic disorder with similarities to other developmental encephalopathies. There are no peer-reviewed consensus-based therapeutic guidance to care in RTT.

What this study adds: The primary care provider plays a key role in recognizing, treating and directing care of patients with RTT. A consensus on guidance for the primary care provider was developed based on literature review and expert opinion. This guidance is applicable to other rare and often severe neurodevelopmental disorders.

Abstract

Background: Rett syndrome (RTT) is a severe neurodevelopmental disorder with complex medical co-morbidities extending beyond the nervous system requiring the attention of primary care providers. There are no peer-reviewed consensus-based therapeutic guidance to care in RTT. The objective was to provide consensus on guidance of best practice for addressing these concerns.

Methods: Informed by the literature and using a modified Delphi approach, a consensus process was utilized to develop guidance for care in RTT by primary care providers.

Results: Typical RTT presents early in childhood in a clinically recognizable fashion. Multisystem co-morbidities evolve throughout the lifespan requiring coordination of care between primary care and often multiple subspecialty providers. To assist primary care providers and families in seeking best practice, a checklist and detailed references for guidance were developed by consensus.

Conclusions: The overall multisystem issues of RTT require the primary care provider to oversee and manage the whole individual and family. Given the median life expectancy well into the 6th decade, guidance is provided to primary care providers to achieve current best possible outcomes for these special-needs individuals.

Introduction

Rett syndrome (RTT)[1] is a severe neurodevelopmental disorder with an estimated worldwide prevalence of between 1 in 20,000 to 40,000 people. RTT is one of the most common genetic causes of developmental and intellectual impairment in females[2], affecting up to 1 in 10,000 girls under the age of 12. RTT is not a neurodegenerative condition[3], rather it is a progressive disorder involving multisystem symptom evolution over time. Following demonstration of symptom reversal in mouse models[4,5], there is flourishing hope for further disease modifying therapies.

Nearly all individuals with RTT have one of >300 distinct loss-of-function mutations in the *MECP2* gene on the X-chromosome[6]. This gene encodes methyl-CpG binding protein-2, an essential transcriptional regulator in the brain required for normal neurodevelopment[7]. Complete genetic testing involves sequencing and methods to detect larger deletions (e.g. multiplex ligation-dependent probe amplification (MLPA)) of the *MECP2* gene. Likely owing to the random nature of X-chromosome inactivation[8] and other genetic modifiers[9-11], genotype-phenotype correlations are imprecise. However, a general pattern exists with some mutations (early truncating mutations such as R168X, R255X, R270X, large deletions and specific point mutations such as R106W) associated with increased severity compared to other mutation groups (R133C, R294X, R306X, and C-terminal truncations)[12]. *MECP2* mutations causing RTT are almost always *de novo* (spontaneous) and as such are not expected to recur in families.

The presentation is initially subtle in the first two years of life involving developmental delays and hypotonia on exam, but subsequent symptom evolution between 18-30 months of age with developmental regression and onset of repetitive, purposeless hand movements is striking[13]. The core clinical diagnostic features of RTT (Table 1)[1] include a period of normal (or near normal) development followed by developmental regression with loss of language and hand function skills, impaired gait, and development of hand stereotypies causing life-long dependence[14,15]. The average age at diagnosis of 2.5 years has been trending downward with increasing availability of diagnostic genetic testing[16]. The multisystem nature of the disorder has been documented within multiple observational studies with symptom risk evolving across the lifespan.

In the past two decades the natural history of RTT has been extensively studied[17]. Perhaps most important to the primary care provider (PCP) is the knowledge that with appropriate care, children with RTT will become adults with RTT; 70% live to at least 50 years of age[14,18]. As such, the PCP is often presented with the daunting task of effectively coordinating attention to the evolving medical comorbidities of the disorder throughout a patient's lifespan. To help address this challenge, based on a review of published literature regarding Rett syndrome symptomatology that identified the concerns most relevant to the PCP, through a modified Delphi consensus approach we developed recommendations regarding guidance for best practice.

Methods

Draft guidance was developed (MJ, KH and PN) and presented and discussed at bimonthly International Rett Syndrome Foundation sponsored North American Rett Syndrome Clinics Network conference calls between January 2016 through September 2018 with input obtained from 22 clinical sites. An initial draft was presented January 2017 for external review by the Network through September 2018; additional public input was obtained from January 2019 to May 2019 through placement on the RettSyndrome.org website. With supervision by the group leader, the guidance was further refined substantially by eight Rett Centers (University of Alabama Birmingham, Vanderbilt University, Children's Hospital Colorado, Children's Hospital of Philadelphia, Cincinnati Children's Hospital, Boston Children's Hospital, UCSF Benioff Children's Hospital Oakland, and Texas Children's Hospital) providing multidisciplinary care for individuals with RTT, in partnership with the NIH-funded Natural History Study of Rett and related disorders (NHS, U54 HD061222; **ClinicalTrials.gov: NCT00299312/NCT02738281**) and two patient advocacy groups, Rett Syndrome Research Trust and the International Rett Syndrome Foundation. This consensus approach followed a modified Delphi process employed by members of this group previously[19]. The partners were chosen based on clinical experience across primary care, multiple subspecialties, health care delivery, and, importantly, patient-family experience with RTT. Conflicts of interest were vetted by the group leader with full knowledge by the

group. A consensus led by the group leader surrounding guidance that should be intended for primary care providers based on published data and clinical opinion was developed through six further rounds of modifications. The results of a systematic review were used to inform the guidance (Fu et al, in preparation). The following recommendations were created based on an age-dependent health supervision approach to assist primary care providers in fulfilling the goal of effective and meaningful care for individuals with RTT across all ages (Tables 2 and 3). Items are organized by prevalence at each age group. Consistent with International Classification of Functioning, Disability and Health (ICF) guidelines (WHO , 2001)[20], this guidance recognize the inter-relatedness of body function/structure, environment and personal factors to maximize activities and participation (Supplemental Table 1). Thus, in addition to routine assessment of medical issues (body function), several psychosocial, environmental, and educational concerns need to be assessed frequently to achieve the goal of family-centered service:

- The financial, emotional and physical impact on the family as a whole: sibling well-being, parent physical and mental health (sleep, grief, anxiety, depression), quality of life, and marital impacts[21,22].
- Vigilance regarding signs and symptoms of abuse and neglect of an at-risk individual.
- Educational support programs for which the individual may be eligible.
- Supplemental Security Income benefits.
- Personal financial, community, and emotional support available to the family.

Patient involvement

Patients family groups (International Rett Syndrome Foundation and Rett Syndrome Research Trust), represented by parents of individuals with RTT (Ms. Nues and Ms. Coenraads), were involved in the development of the patient care guidance and writing of this manuscript. Their organizations will assist with dissemination of the guidance.

Results

The guidance was formulated into a checklist (Table 2) with further details and references (Tables 3-7) that informed the checklist and the consensus process. The guidance for management by primary care providers was grouped by relevant features and therapeutic approaches at different ages. The checklist (Table 2) is suitable for use by both the primary care provider and the family as part of their health care records with Tables 3-7 providing further detailed guidance.

Diagnosis to 5 years old--Early Childhood: Most features of RTT may emerge during this age period. Feeding difficulties and growth failure[23-25] begin during this age. Additional treatable gastrointestinal issues including dysmotility, gastroesophageal reflux, constipation, gas bloating, often presenting as irritability or apparent discomfort manifest commonly at this age[23,26]. The development of microcephaly or head growth stagnation (as early as 1.5 months)[25] is a common feature, though macrocephaly has also been seen[27]. Tone issues at this age are typically characterized by hypotonia[28]; early referral to therapists (physical, occupational, speech language including augmentative communication[29]) and establishment of an IEP[30] are necessary. Severe hearing loss is uncommon in RTT[31] but there may be delayed auditory processing[32,33] that mimics hearing impairment. There is increased risk of cortical visual impairment (CVI) and ocular apraxia in RTT[34]. There is evidence suggesting increased risk for prolonged QTc interval that may be present from a young age[35-37] and may develop with time[38]. The frequency of epileptic and non-epileptic spells[39,40] wax and wane throughout the course[39,41]. Individuals with RTT generally respond to anticonvulsants[39,41,42] but there have been no randomized, controlled trials of specific anticonvulsants for RTT. If hospitalized, it is important to inform hospital staff that RTT individuals may need lower doses of anesthetics or analgesics[43,44] and may take longer to awaken from anesthesia[45], and potentially confounding baseline issues: cold extremities[46], irregular and disordered breathing with oxygen desaturations[47,48], impaired proprioception, lack of hand use, inability to change position, and increased fall risk.

5 years to the Pre-pubescent Stage--Late Childhood: During the early school years, children with RTT typically have stabilized developmentally; the regression phase has ended[25]. Overall, many of the multisystem issues that arose during the first 5 years of life persist. Preventing undernutrition and

maintaining a healthy BMI is important, as this has been associated with better functioning[24,49]. Surveillance for scoliosis becomes an important preventive measure; some children (~20%) ultimately require spinal surgery for this comorbidity[50]. Longitudinal assessment of pubertal development indicates an increased prevalence of early thelarche and adrenarche but delayed menarche[51]. Difficulties with abnormal tone in this age range typically are characterized by hypotonia evolving to rigidity[52,53].

Post-puberty to the end of school (~21 years old)--Post-puberty: Surveillance for scoliosis continues to be an important preventive measure though this lessens with completion of puberty[51]. Surveillance for urinary retention is important[54,55]. Biliary tract disease is seen in young adulthood at rates similar to the general population but due to communication impairment in RTT the presenting symptoms may be limited to irritability, weight loss and vomiting[56,57]. Studies of longevity in RTT demonstrate survival of many into middle age, underscoring the need for the early development of a comprehensive, thoughtful plan for transitioning to adulthood[58]. Longitudinal supervision is required in RTT as physical, behavioral and cognitive limitations will not allow for independent living[14,15]. This may include day programs and respite care.

21 years and older--Adulthood: Overall, individuals with RTT tend to stabilize clinically in young adulthood[59-61]. Frequent causes of hospitalization for women with RTT include pneumonia, respiratory distress, status epilepticus, rectal bleeding, decline in ambulation, or refusal/inability to eat or drink[15]. While one-third of individuals may have a gastrostomy tube, half of these continue to have some oral intake[18]. With age, concern for low bone mineral mass coupled with long-term use of particular anticonvulsants, raises the risks for osteoporosis and bone fractures[62-64] necessitating continued supplementation and monitoring of 25-OH Vitamin D status[65,66]. Musculoskeletal problems and gross motor function may worsen overall[60] possibly due to more parkinsonian features[52] but with overall preservation of intellect and memory[15]; additional study is needed due to relatively low numbers studied. Physical limitations, parkinsonian features, and high prevalence of social withdrawal behaviors lead to abnormal or decreased social interactions consistent with anxiety or depression[67]. Although the majority of women with RTT in the US live at home[14], in other countries only about one-third of women over age

16 with RTT live at home (either full or part-time) with the majority living in a residential facility[15]. Long-term and individually-tailored care that provides social interactions and physical activity should be provided at all ages to reduce age-related deterioration[68].

Discussion

Management of RTT requires input or expertise related to multiple specialties, often necessitating referrals to many providers in addition to the primary care provider. The above health guidance will evolve with further research into the longitudinal course of RTT by the NHS and others. However, there are limitations to the current proposed health guidance, specifically with respect to the lack of needed randomized clinical trials in a rare condition where interventions, such as physical and other therapies, are rarely standardized. At this time, longitudinal prognostic details are not well understood in certain areas of evaluation such as affect, displayed emotion and its meaning, the most appropriate manner to assess intelligence and how it evolves, or the life span of gynecologic concerns. Additional studies should also address the role and utility of palliative care and banking of post-mortem tissue. From this breadth of information, quality metrics with benchmarks can be defined to ensure standards of care with best outcomes for individuals with RTT.

With the relative paucity of older individuals in the NHS and related studies, further study into the care of older individuals is needed to better address guidance more extensively for both older RTT women and for those more severely affected who are not routinely captured in most studies[61]. Additionally, with current and future clinical trials, the disease course for individuals with RTT may be more modifiable with severity of symptoms and disease progression very different from our current understanding. There is considerable ongoing research in the field of specific RTT therapeutics[69]. It is therefore important for families, caregivers and primary care providers to reach out to Rett Centers and family support group resources to stay up to date on clinical trials, drug approvals, and how this impacts these current care guidance. While the primary care provider may not be able to counsel on the suitability

of different clinical trials, actively engaging RTT individuals and families and referring to clinical trials at specialty centers is necessary for the development of improved therapeutics.

With the advances in healthcare and technology, improved and earlier genetic testing, robust research in RTT, and active patient advocacy from families and clinicians, individuals with RTT are surviving well into adulthood while living more healthy and meaningful lives. With the vast amount of medical knowledge emerging from research in RTT today and knowing the complexity of care RTT often requires, this proposed guidance can facilitate the primary care provider in delivering more thorough and well-rounded management and comprehensive surveillance. Importantly, the guidance also help to outline considerations in which the primary provider may want to refer the individual with RTT for more specialized management.

In conclusion, Rett syndrome is a medically complex neurodevelopmental disorder impacting multiple organ systems in an evolving fashion from childhood through the 6th decade of adulthood. Primary care providers are uniquely positioned to most effectively manage the individual and family to coordinate the multidisciplinary requirements of the disorder by drawing on the accumulating knowledge regarding the natural history of the disorder to anticipate these requirements.

Web-links for primary care providers to regional RTT clinics

https://www.rettsyndrome.org/about-rett-syndrome/clinics

https://reverserett.org/newly-diagnosed/#clinics-map

Useful web-links for families

https://www.rettsyndrome.org/

https://reverserett.org/

https://www.rettsyndrome.org/for-families/resources-for-families

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Table 1. Classic (or Typical RTT) and Atypical RTT diagnostic criteria[1].
Classic or Typical RTT diagnostic criteria A period of regression followed by recovery or stabilization
1. Partial or complete loss of acquired purposeful hand skills
2. Partial or complete loss of spoken language
3. Gait abnormalities: impaired or absence of ability
4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms.
Atypical RTT diagnostic criteria A period of regression followed by recovery or stabilization 1. At least 2 of the 4 main criteria 2. 5 of 11 supportive criteria a) Breathing disturbances while awake b) Bruxism while awake c) Impaired sleep d) Abnormal muscle tone e) Peripheral vasomotor disturbances f) Scoliosis/kyphosis g) Growth retardation h) Small cold hands and feet i) Inappropriate laughing/screaming spells j) Diminished response to pain k) Intense eye communication – "eye pointing"

Table 2. Health Supervision guidance as a checklist for individuals and PCP.

- **Individuals with Rett syndrome should be seen for regular wellness checkups, screenings and immunizations (especially influenza vaccinations)*.**
- **Inform staff that extra time will be needed for visit, especially to inspecting the individual without braces, shoes and outer clothing.**
- **Parents and care-givers should keep a binder of health records to include: genetic testing results, summaries of all doctor visits (including specialist referrals), summaries of hospital admissions, laboratory studies, ECG, x-ray reports and other imaging results.**

Areas of Assessment	Assessment Details	Yearly Wellness Visit	Primary Care every 6 months*	Baseline
Genetics/ *MECP2* Testing Results	Counsel family on genetic test results and refer to genetic counselor if appropriate for additional counsel or explanation. Family and PCP to keep a copy of genetic results.			✓
General	Update current medications and allergies	At every visit		
	Weight	At every visit		
	Height or body length Body mass index	At very visit At every visit		
	Head circumference[1]	At every visit		
	Tanner Stage	At yearly wellness		
	Laboratory evaluations (see below)	(see below)		
Gastrointestinal	Review: feeding methods, appetite, chewing ability, choking and length of feeding time.	✓	✓	
	Screen for GE reflux, gas bloating, biliary tract disease, constipation and hemorrhoids, skin tags, or fissures.	✓	✓	
Nutrition	Review nutritional and herbal supplements Nutrition screening[2]: energy, protein, fluids, sodium, potassium, calcium, and vitamin D intake.	✓	✓	
Respiratory	Screen for awake disordered breathing (hyperventilating, breath-holding, color change), and air swallowing.	✓		
Neurology	Screen for presence of seizures and spells suspicious for seizures. Record description and frequency of seizures. Encourage individual to follow-up with neurologist routinely; every 6 months if treated for seizures. If individual's weight fluctuates (more than 10-20%), request neurologist to consider adjusting anticonvulsant doses accordingly.	✓	✓	✓
	Screen for abnormal movements (stereotypies and dystonia).	✓		✓
Cardiology	Check QTc interval with ECG; if abnormal, refer to Cardiology.	✓		✓
Skin	Document temperature and color of hands and feet. Screen for skin breakdown from hand-mouthing or ill-fitting braces. Screen for pressure ulcers.	✓	✓	
Orthopedics Rehabilitation	Estimate curvature of spine. Recheck every 6 months if scoliosis present; refer to Orthopedics if > 20 degrees.	✓	(if scoliosis present✓)	
	Screen for abnormal hip abduction, range of motion and leg length.	✓	✓	

	Screen for contractures and use or need of devices to prevent them (ankle-foot orthoses and splints).	✓		
	Discuss risk of fractures due to osteopenia.	✓		
	Screen for needs and use of mobility aids.	✓		
Urology	Review toilet training, frequency and infrequency of urination, and urinary tract infections. Refer to urology for frequent urinary tract infections or overflow incontinence.	✓		
Development	Documentation of baseline, gains and losses of milestones. Fine motor: hand use: raking grasp, pincer grasp, rake, holding cup or spoon. Gross motor: sitting, standing, and walking. Language: coo, babble, laugh, words.	✓		✓
Communication	Screen communication methods used by family and school: eye pointing, vocalizations, switches, ipad, eye-gaze device.	✓		✓
Behavioral	Screen for symptoms of anxiety and depression, such as withdrawal, screaming and irritability. Inquire about sensory processing difficulties.	✓	✓	✓
Sleep	Review sleep initiation, staying asleep, snoring or coughing, and frequency of nocturnal interventions by caregivers. Review safety of bed and bedroom.	✓	✓	✓
Pain	Discuss delayed pain response and describe individual's response to pain.	✓		
Extremities	Temperature dysregulation. Review environmental factors that might impact comfort.	✓		
Screenings	Vision screening including acuity, spatial, depth, visual fields and cortical visual impairment. Review results with parents.	✓		
	Audiology ABR at birth, PRN if chronic otitis media, consider evaluation for auditory processing delay	✓		✓
	Annual dental health screening; refer for cleaning every 6 months.	✓		
Education/therapies	Review for presence of current IEP (see info on RettSyndrome.org) Documentation of therapies (type and frequency).	✓		✓
Family/Social	Assess for family stress (financial, social, fatigue)	✓	✓	✓
Resources	Review available community, insurance resources (DMV permit, respite care etc.) In adolescent individuals review plans for obtaining guardianship. PCP may be required to write Letters of Medical Necessity for equipment and sign school medication forms.	✓		

*6month follow-up visit is medically necessary to screen for issues that can appear quickly, progress rapidly and require intervention

[1]Please see CDC or Nellhaus head circumference chart for age 0-18 years

[2]Please see **Food and Drink Log** (https://www.rettsyndrome.org/pcg) to ensure adequate calcium, vitamin D, calories and fluid intake

LABORATORY EVALUATIONS: CBC, chemistry panel, 25-OH-vitamin D (yearly), baseline lipid screen (fasting if possible), UA (every 2 years). If disrupted sleep or concern with restless leg syndrome, consider ferritin, serum iron, TIBC, transferrin.

Tables 3-7. Detailed approaches to management and therapy for RTT. References not specific to RTT noted as "See:".

Table 3: Genetics, Neurology, Cardiology, Respiratory, and Urology			
System/Area	**Common concerns and questions**	**Details and suggested approach**	**References**
Genetics	*MECP2* gene	For suspicion of Rett syndrome, *MECP2* gene sequencing and MLPA testing is recommended. MLPA testing is needed to detect deletions otherwise missed by sequencing; this test is necessary if no abnormalities are found by sequencing. Referral to a geneticist or genetic counselor is recommended to review recurrence risks and answer related questions. Genetic testing results are essential for enrollment in clinical trials. Referral to a Rett Center if feasible may be useful to provide multidisciplinary care and access to clinical trials.	16,70,71
Neurology	Seizures and Spells	Refer to neurologist for seizures and spells suspicious for seizures with follow-up every 6 months if treated with an anticonvulsant. It is difficult to differentiate between a non-epileptic Rett Spell and a seizure (both may be present). Individuals can have multiple types of seizures. Seizure logs by the family are needed with careful description of events that includes frequency and duration. Videos of events are helpful to the neurologist. The neurologist may order a video EEG to accurately characterize whether a type of event is a seizure or not. An overnight EEG may be necessary to capture sleep; an EEG is incomplete if sleep is not captured.	39-42
	Abnormal movements	Ataxic gait and an impaired spatial awareness (proprioception) are common. Stereotypical hand movements (hand-wringing, mouthing, etc) are typical. These are often disruptive to hand use. Use of splints to elbows or hand guards, which may be prescribed by an OT, may be helpful to improve hand use. Initially, most individuals have low tone that progresses over years to high tone and dystonia. Neurologist or physiatrist may prescribe neuromuscular blockade or other medications to reduce tone to maintain function and prevent contractures.	52,53,72,73
Cardiology	Abnormal ECG	Yearly ECG to check for prolonged QTc interval which can develop at any time. Referral to cardiologist if the ECG is abnormal, who may consider further studies (Holter monitor, echocardiogram) or treatment. Avoid prescription of medications that can prolong QTc interval (i.e. fluoxetine). A current ECG is needed before anesthesia.	35-38
	Poor circulation	Distal temperature asymmetries are common and thought to be autonomic in origin; no specific therapy is recommended.	46,74,75
Respiratory	Hyperventilation, air swallowing, breath holding, blowing raspberries	Due to autonomic dysregulation, these may occur during the day. While not purposeful, they may be triggered by anxiety. Currently, there are no medications or treatments for this. If night time apneas are present, check tonsils and consider ordering a comprehensive sleep study and related specialist referral. Breathing abnormalities may disrupt feeding.	47,48,76-78
Urology	Urine retention	Autonomic dysfunction can lead to delayed bladder emptying and bladder distension. If present, referral to urology may be needed. Constipation can increase risk of UTIs. Toilet training can be achieved in some cases. Certain medications or poor fluid intake can cause increase risk of kidney stones.	54,55 See: 79

Table 4: Gastroenterology and Nutrition

System/Area	Common concerns and questions	Details and suggested approach	References
Gastroenterology and Nutrition	Dysmotility	Abdominal pain and discomfort typically are caused by reflux, gas bloating, delayed stomach emptying, biliary tract disease, or constipation; these can be empirically diagnosed and managed (see below). These will present with abdominal fullness (gas or constipation), irritability (reflux or constipation), nocturnal arousals (reflux or constipation), arching (reflux), overt reflux or emesis, burping (reflux or air swallowing). Gall bladder dysfunction, screened by abdominal ultrasound, should be considered. Referral to surgery for cholecystectomy may be necessary for symptomatic gallstones or biliary dyskinesia.	23,24,26,57
	Constipation	This is a very common problem. Laxatives (polyethylene glycol, magnesium hydroxide, glycerin or bisacodyl suppositories) are often a part of long-term treatment with a goal of one soft bowel movement per day.	23,26
	Reflux	This is a very common problem. PPI or H2 blockers are used empirically. Referral to gastroenterologist may be necessary to rule out complications such as esophagitis, ulcer, strictures, or Barrett's esophagus.	23,26
	Poor weight gain	Fatigue and irritability may be signs that dietary requirements are not being met;.consider energy dense foods (oils, syrups, avocado), gastroenterologist, and nutrition consults. Gastrostomy-button may be needed to maintain growth; counsel families that use of a gastrostomy button does not preclude oral feeding as long as oral feeding is safe. Use CDC/WHO growth charts to track growth and try to keep at same BMI percentile on growth curve through adolescent growth spurt. RTT-specific growth charts are also available.	23-25,80,81
	Calcium/Vitamin D	Ensure supplemental Vitamin D intake: 600-1000 IU or more daily. Target serum levels of 25-OH-Vitamin D greater than 30-40 ng/ml. Ensure milk and dairy products to provide age-appropriate dietary calcium intakes: 1-3 y, 700 mg/d; 4-8 y, 1000 mg/d; 9-18 y, 1300 mg/d; 19 y and older, 1000 mg/d. One 8-oz glass of milk or 8-oz cup of yogurt contains 300 mg of calcium.	62-64 See: 82
	Prolonged feeding times	Long feeding times (more than 30 minutes) can affect quality of life for patient and family; this may be an indication that a gastrostomy button is needed.	49,81 See: 83
	Chewing/swallowing difficulties	Referral to appropriate therapist or gastroenterologist to assess if there is concern for aspiration (coughing, choking, gagging with feeding or aspiration or unexplained pneumonia). In some cases, thickeners for liquids may be helpful to prevent aspiration versus need for a gastrostomy button.	23,24

Table 5: Orthopedics, Rehabilitation, Skin, Endocrine, and Hospitalization

System/Area	Common concerns and questions	Details and suggested approach	References
Orthopedics, Rehabilitation	Scoliosis	Increased risk of neuromuscular scoliosis after age 6; risk typically abates after puberty. This can progress rapidly if present, necessitating re-observation every 6 months if present. Supine x-ray and orthopedic referral when scoliotic curvature greater than 20 degrees; correction may be indicated when greater than 40 degrees. Kyphosis is more common in ambulatory individuals.	50,84-87
	Increased risk of hip subluxation	Examine hip range of motion due to high risk for hip subluxation and contractures, as either may be source of pain and cause for irritability. X-ray-AP views of pelvis may be needed to evaluate femoral head coverage.	88
	Contractures	Encourage families and caregivers to inspect all joints and practice daily range of motion, especially if mobility is reduced in an acute setting (illness or hospitalization). Consider OT and PT consults for bracing and splinting. Consider neurology and physiatry consults for neuromuscular blockade or other medications to improve tone.	89,90
	Osteopenia and fractures	There is higher risk of fracture due to immobility and use of anticonvulsants. If fracture occurs, consider DEXA scan and referral to endocrine specialist (in addition to aggressive screen of calcium, vitamin D intake and 25-OH-vitamin D levels). Cause for fractures beyond osteopenia needs investigation in order to eliminate other preventable causes, such as falling out of bed (needs rails), falling at home (needs assessment of home) or non-accidental trauma.	62-66,80,82,91,92
	Equipment	There is risks of injury due to outgrown equipment (See Skin above). Family and caregivers may need lifts, shower accommodations, bed-side toilets, etc.; these needs may be best assessed by a physiatry referral.	See: 93
Skin	Breakdown from mouthing or equipment or lack of re-positioning	Redness persisting longer than 20 min after equipment (such as a splint) is removed is of concern for development of pressure ulcers; return to PT to re-fit equipment. OT or PT may prescribe splints on elbows or hands to prevent skin breakdown from mouthing. Decubitus ulcer may need consultation with wound specialist and equipment specialist.	90
Endocrinology, Gynecology	Premature adrenarche	Menarche comes later, but breast buds and pubic hair may begin earlier than in typically developing children. Periods may be irregular due to low body weight or stress; T4, TSH should be checked if periods are irregular. Counsel family to notice whether or not seizure frequency corresponds with menstrual cycle and alert neurologist. Consideration of menses suppression should be considered, especially if it disrupts the interactions with caregivers and family or hormonal fluctuations correspond with increased seizure activity. The impact of menses suppression on bone health should be considered; IUD is a consideration. Avoidance of DEPO-provera is a consideration. Well-woman examination should include breast exam.	51,94 See: 95
Hospitalization	Anesthesia sensitivity, impaired proprioception	Individuals may need lower doses of anesthetics or analgesics. They may take longer to awaken from anesthesia. It is important to ensure anesthesiologist is aware of current medications (especially anticonvulsants and cannabis preparations), type and description of seizures, breathing abnormalities and risk of presence of prolonged QTc; a recent EKG is essential. Hospital needs to be aware of impaired proprioception, lack of hand use, inability to change position and increased fall risk. If hospitalized, family or hospital should perform daily ROM to prevent contractures.	35-37,43-45,47,48

Table 6: Psychological, Behavioral, Sleep, Pain, and Screenings

System/Area	Common concerns and questions	Details and suggested approach	References
Psychological, Behavioral	Issues with inattention/anxiety	Auditory processing is delayed and may be misinterpreted as disinterest; allow for this delay when assessing non-verbal language by allowing additional time for responses to questions or commands. Behavioral inconsistency is typical and may be affected by physical factors such as sleep or environment. Assess for intolerance of excessive stimuli (i.e. bright lights, loud noises).	32,33
	Externalizing/internalizing behaviors	Screen for caregiver impressions of anxiety and depression, such as withdrawal; these may become more prominent with age or in individuals with milder clinical presentations. Identify possible contributors (e.g., sedating medications, decreased social interaction, limited access to engaging activities). Consider treatment with an SSRI such as escitalopram which may have a lower risk of inducing a prolonged QTc interval.	15,61,67,96
Sleep	Disrupted sleep	Circadian rhythm is often disrupted; consider melatonin to initiate sleep and trazodone or clonidine to maintain asleep. Patient may be getting out of bed, which could be unsafe; consider a tent-style bed or similar engineering controls to keep child in bed and safe. Consider ferritin, serum iron, TIBC and transferrin levels if there is disrupted sleep or concerns for restless leg syndrome and need for iron replacement. Consider overnight sleep study for snoring or pauses in breathing.	97,98 See: 99-101
Pain	Pain assessment and sensitivity	Individuals have an atypical pain response, with higher thresholds and variable indications of pain (i.e. grimace, crying, increase in repetitive movements); typical pain scales may be difficult to interpret or apply	102
	Increased risk of chronic pain	Often due to GI problems (see above), dental problems, immobility and positioning. Always consider hip subluxation, vertebral compression fractures or other fractures as cause of pain.	23,26,56,57
Screening: Ophthalmology	Difficult vision assessment	Since eye gaze is the main way of communicating, assessment by practitioner familiar with special needs individuals is needed. Practitioner familiar with cortical visual impairment and ocular apraxia is needed.	34,89
Screening: Auditory	Auditory processing delay	Hearing is typically normal and assessments are often difficult to obtain but if chronic otitis media is present, these are needed.,	31
Screening: Dental	Teeth grinding, increased risk of caries	Routine cleanings needed and may require anesthesia. Dental work under anesthesia should be done with proper anesthesia support at major medical institutions. Regular dental care is required to avoid tooth extraction; tooth extraction significantly interferes with oral function and is to therefore be avoided if at all possible.	73,103

Table 7: Development, Education, Therapies, Social, and Alternative Medications			
System/Area	**Common concerns and questions**	**Details and suggested approach**	**References**
Development, Education and Therapies	Developmental Milestones	Developmental regression (reduced hand use and language) typically stops between 2-3 years. Skills can be maintained and possibly regained with vigorous therapies. Therapies to consider: speech therapy (ST), feeding therapy (FT), occupational therapy (OT), augmentative communication therapy (AAC), vision therapy (VT), hippotherapy (horse) and swim/pool therapy.	29,30,34,89,104
	IEP and therapy challenges	Educators may not have experience with Rett syndrome. Request they focus on communication, mobility, and socialization with attention to apraxia. Educators and therapists need to be informed that the approach to therapy in Rett syndrome is different: it is about maintaining skills as well as recovery. Therapies for Rett syndrome should include occupational, physical, speech, swallow and augmentative communication. Therapy that maximizes physical activities should be life-long, as these will minimize long-term complications and maximize long-term potentials. Educational opportunities that provide intensive physical, occupational and speech therapy, especially those that provide augmentative communication, allow individuals to learn and make the best progress. If CVI is present, then a Teacher of the Visually Impaired (TVI) should be included in the IEP. This is in accordance with Free Appropriate Public Education (FAPE), an educational right of all students in the United States that is guaranteed by the Rehabilitation Act of 1973 and the Individuals with Disabilities Education Act (IDEA). Families should work with schools to develop an IEP that recognizes this; referral to a Rett Specialist may provide additional assistance in this regard.	29,30
	Non-verbal communication	Alternative and augmentative communication assessments are needed. While this can be done by some speech therapists, a specific referral may be needed. Since eye gaze is typically the most effective form of communication, special eye gaze devices can give individuals a voice. These referrals should be made as early as possible to coincide with typical language development. Devices should be made available to individuals at both home and school. Home use is to be encouraged as this setting may be the longest after the child graduates from the school system.	29,89
Social Concerns	Increased family stress	Family may need respite care. Sibling reactions and their adjustment should be considered; families could provide education for extended family and friends to understand Rett syndrome through patient advocacy group websites. When appropriate, discussion of Rett genetics with older siblings of child-bearing age should be considered by referral to a genetic counselor.	21,22,105,106
Alternative medications	Cannabis, St John's wort, etc.	Families should be encouraged to disclose use of alternative medications (cannabis, oils etc) to all specialists.	

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Supplementary Table 1. Health supervision goals surrounding individuals with RTT by ICF contextual factors

	Early Childhood	Late Childhood	Post-puberty	Ad
Body Functions and Structure	GI/Nutrition: Maintain adequate growth,bone health, and nutrition; manage reflux and constipation Neurological: Identify and manage epilepsy when present; identify and manage autonomic dysfunction Rehabilitation: develop strength and coordination Cardiology: detect and manage prolonged QT	GI/Nutrition: Maintain adequate growth,bone health, and nutrition; manage reflux and constipation Neurological: Identify and manage epilepsy when present; identify and manage autonomic dysfunction Rehabilitation: regulate tone and prevent contractures Cardiology: detect and manage prolonged QT Orthopedics: detect and manage scoliosis	GI/Nutrition: Maintain nutrition and bone health; manage constipation; detect and manage gall bladder dysfunction Neurological: Identify and manage epilepsy when present; identify and manage autonomic dysfunction Rehabilitation: regulate tone and prevent contractures Cardiology: detect and manage prolonged QT Orthopedics detect and prevent fractures	GI nut ma and dys Ne ma pre aut Re and Ca pro Or pre
Environment	Education: Develop appropriate IEP Therapies: Access to appropriate therapies Socialization: Age-appropriate interactions and activities	Education: Develop appropriate IEP Therapies: Access to appropriate therapies including physical, occupational, and assistive communication technologies Socialization: Age-appropriate interactions and activities	Education: Develop appropriate IEP Therapies: Access to appropriate therapies including physical, occupational, and assistive communication technologies Socialization: Age-appropriate interactions and activities	Ed Da Th app phy ass tec So app act

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Guidance for Health Professionals in Rett Syndrome

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Abbreviations:
ABR: auditory brainstem response
AAC: augmentative and alternative communication
CVI: cortical visual impairment
EI: Early Intervention
ICF: International Classification of Functioning, Disability and Health
IEP: Individualized Education Program (or Plan)
NHS: NIH-funded Natural History Study of Rett and related disorders
PCP: primary care provider
RTT: Rett Syndrome
TVI: teacher of the visually impaired

Summary Box:

What is known: Rett syndrome (RTT) is a multi-system and rare genetic disorder with similarities to other developmental encephalopathies. There are no peer-reviewed consensus-based therapeutic guidance to care in RTT.

What this study adds: Primary care providers and other health professionals caring for patients with RTT frequently have limited first-hand experience managing the disorder due to its rare prevalence. A consensus on guidance for health professionals caring for patients with RTT was developed based on literature review and expert opinion. This guidance is applicable to other rare and often severe neurodevelopmental disorders.

Abstract

Background: Rett syndrome (RTT) is a severe neurodevelopmental disorder with complex medical co-morbidities extending beyond the nervous system requiring the attention of health professionals. There are no peer-reviewed consensus-based therapeutic guidance to care in RTT. The objective was to provide consensus on guidance of best practice for addressing these concerns.

Methods: Informed by the literature and using a modified Delphi approach, a consensus process was utilized to develop guidance for care in RTT by health professionals.

Results: Typical RTT presents early in childhood in a clinically recognizable fashion. Multisystem co-morbidities evolve throughout the lifespan requiring coordination of care between primary care and often multiple subspecialty providers. To assist health professionals and families in seeking best practice, a checklist and detailed references for guidance were developed by consensus.

Conclusions: The overall multisystem issues of RTT require primary care providers and other health professionals to manage complex medical co-morbidities within the context of the whole individual and family. Given the median life expectancy well into the 6th decade, guidance is provided to health professionals to achieve current best possible outcomes for these special-needs individuals.

Introduction

Rett syndrome (RTT)[1] is a severe neurodevelopmental disorder with an estimated worldwide prevalence of between 1 in 20,000 to 40,000 people. RTT is one of the most common genetic causes of developmental and intellectual impairment in females[2], affecting up to 1 in 10,000 girls under the age of 12. RTT is not a neurodegenerative condition[3], rather it is a progressive disorder involving multisystem symptom evolution over time. Following demonstration of symptom reversal in mouse models[4 5], there is flourishing hope for further disease modifying therapies.

Nearly all individuals with RTT have one of >300 distinct loss-of-function mutations in the *MECP2* gene on the X-chromosome[6]. This gene encodes methyl-CpG binding protein-2, an essential transcriptional regulator in the brain required for normal neurodevelopment[7]. Complete genetic testing involves sequencing and methods to detect larger deletions (e.g. multiplex ligation-dependent probe amplification (MLPA)) of the *MECP2* gene. Likely owing to the random nature of X-chromosome inactivation[8] and other genetic modifiers[9-11], genotype-phenotype correlations are imprecise. However, a general pattern exists with some mutations (early truncating mutations such as R168X, R255X, R270X, large deletions and specific point mutations such as R106W) associated with increased severity compared to other mutation groups (R133C, R294X, R306X, and C-terminal truncations)[12]. *MECP2* mutations causing RTT are almost always *de novo* (spontaneous) and as such are not expected to recur in families.

The presentation is initially subtle in the first two years of life involving developmental delays and hypotonia on exam, but subsequent symptom evolution between 18-30 months of age with developmental regression and onset of repetitive, purposeless hand movements is striking[13]. The core clinical diagnostic features of RTT (Table 1, Typical and Atypical)[1] include a period of normal (or near normal) development followed by developmental regression with loss of language and hand function skills, impaired gait, and development of hand stereotypies causing life-long dependence[14 15]. The average age at RTT diagnosis of 2.5 years has been trending downward with increasing availability of diagnostic genetic testing[16]. The multisystem nature of the disorder has been documented within multiple observational studies with symptom risk evolving across the lifespan.

MECP2 mutations have been identified rarely in males with neurodevelopmental disorders, termed "male RTT encephalopathy". The resulting developmental outcome is quite variable though with symptomatology distinct from RTT and ranges in severity from a severe neonatal encephalopathy with minimal developmental improvement to a mild intellectual disability[17]. Male RTT encephalopathy[18] and other distinct developmental encephalopathies (historically linked to RTT)[19] such as *MECP2* duplication syndrome[20-22], *CDKL5* Deficiency Disorder[23-26] and *FOXG1* syndrome[27-30] may have similar approaches (but distinct therapeutics) as more is learned about specific aspects of their clinical care. Alterations in *MECP2, CDKL5* and *FOXG1* should be considered in all individuals, male and female, with developmental delays and intellectual disability.

In the past two decades the natural history of RTT has been extensively studied[31]. Perhaps most important to all health professionals managing this complex disorder is the knowledge that with appropriate care, children with RTT will become adults with RTT; 70% live to at least 50 years of age[14 32]. As such, health professionals are often presented with the daunting task of effectively managing the evolving medical comorbidities of the disorder throughout a patient's lifespan. To help address this challenge, based on a review of published literature regarding RTT symptomatology that identified the most relevant primary care concerns through a modified Delphi consensus approach, we developed recommendations regarding guidance for best practice. These recommendations have been organized based on an age-dependent health supervision approach to facilitate the goal of effective and meaningful care for individuals with RTT across all ages.

Methods

Draft guidance was developed (MJ, KH and PN) and presented and discussed at bimonthly International Rett Syndrome Foundation sponsored North American Rett Syndrome Clinics Network conference calls between January 2016 through September 2018 with input obtained from 22 clinical sites. An initial draft was presented January 2017 for external review by the Network through September 2018; additional public input was obtained from January 2019 to May 2019 through placement on the

RettSyndrome.org website. With supervision by the group leader, the guidance was further refined substantially by eight Rett Centers (University of Alabama Birmingham, Vanderbilt University, Children's Hospital Colorado, Children's Hospital of Philadelphia, Cincinnati Children's Hospital, Boston Children's Hospital, UCSF Benioff Children's Hospital Oakland, and Texas Children's Hospital) providing multidisciplinary care for individuals with RTT, in partnership with the NIH-funded Natural History Study of Rett and related disorders (NHS, U54 HD061222; **ClinicalTrials.gov: NCT00299312/NCT02738281**) and two patient advocacy groups, Rett Syndrome Research Trust and the International Rett Syndrome Foundation. This consensus approach followed a modified Delphi process employed by members of this group previously[33]. The partners were chosen based on clinical experience across primary care, multiple subspecialties, health care delivery, and, importantly, patient-family experience with RTT. Conflicts of interest were vetted by the group leader with full knowledge by the group. A consensus led by the group leader surrounding relevant guidance based on published data and clinical opinion was developed through six further rounds of modifications. The results of a systematic review were used to inform the guidance (Fu et al, in preparation). The following recommendations were created based on an age-dependent health supervision approach to assist health professionals in fulfilling the goal of effective and meaningful care for individuals with RTT across all ages (Tables 2 and 3). Items are organized by prevalence at each age group. Consistent with International Classification of Functioning, Disability and Health (ICF) guidelines (WHO , 2001)[34], this guidance recognizes the inter-relatedness of body function/structure, environment and personal factors to maximize activities and participation (Supplemental Table 1). Thus, in addition to routine assessment of medical issues (body function), several psychosocial, environmental, and educational concerns need to be assessed frequently to achieve the goal of family-centered service:

- The financial, emotional and physical impact on the family as a whole: sibling well-being, parent physical and mental health (sleep, grief, anxiety, depression), quality of life, and marital impacts[35 36].
- Vigilance regarding signs and symptoms of abuse and neglect of an at-risk individual.
- Educational support programs for which the individual may be eligible.

- Government-sponsored income and other support benefits.
- Personal financial, community, and emotional support available to the family.

Patient involvement

Patients family groups (International Rett Syndrome Foundation and Rett Syndrome Research Trust), represented by parents of individuals with RTT (Ms. Nues and Ms. Coenraads), were involved in the development of the patient care guidance and writing of this manuscript. Their organizations will assist with dissemination of the guidance.

Results

The guidance was formulated into a checklist (Table 2) with further details and references (Tables 3-7) that informed the checklist and the consensus process. The guidance for management by health professionals was grouped by relevant features and therapeutic approaches at different ages. The checklist (Table 2) is suitable for use by health professionals as well as the family as part of their health care records with Tables 3-7 providing further detailed guidance.

Diagnosis to 5 years old--Early Childhood: Most features of RTT may emerge during this age period. Feeding difficulties and growth failure[37-39] begin during this age. Additional treatable gastrointestinal issues including dysmotility, gastroesophageal reflux, constipation, gas bloating, often presenting as irritability or apparent discomfort manifest commonly at this age[37 40]. The development of microcephaly or head growth stagnation (as early as 1.5 months)[39] is a common feature, though macrocephaly has also been seen[41]. Tone issues at this age are typically characterized by hypotonia[42]; early referral to therapists (physical, occupational, speech language including augmentative communication[43]) and establishment of an IEP[44] are necessary. Severe hearing loss is uncommon in RTT[45] but there may be delayed auditory processing[46 47] that mimics hearing impairment. There is increased risk of cortical visual impairment (CVI) and ocular apraxia in RTT[48]. There is evidence suggesting increased risk for prolonged QTc interval that may be present from a young age[49-51] and may develop with time[52]. The frequency of epileptic and non-epileptic spells[53 54] wax and wane throughout the

course[53 55]. Individuals with RTT generally respond to anticonvulsants[53 55 56] but there have been no randomized, controlled trials of specific anticonvulsants for RTT. If hospitalized, it is important to inform hospital staff of important issues in RTT individuals that could potentially confound or complicate care. This includes a heightened sensitivity to the effects of anesthetics. potentially requiring lower doses of anesthetic medications to achieve sedation[57 58] or longer time to awaken from general anesthesia[59]. Though response to pain is altered in RTT[60], the approach to analgesia should not be altered. Hospital staff should also be aware of cold extremities[61], irregular and disordered breathing with oxygen desaturations[62 63], impaired proprioception, lack of hand use, inability to change position, and increased fall risk.

5 years to the Pre-pubescent Stage--Late Childhood: During the early school years, children with RTT typically have stabilized developmentally; the regression phase has ended[39]. Overall, many of the multisystem issues that arose during the first 5 years of life persist. Preventing undernutrition and maintaining a healthy BMI is important, as this has been associated with better functioning[38 64]. Surveillance for scoliosis becomes an important preventive measure; some children (~20%) ultimately require spinal surgery for this comorbidity[65]. Longitudinal assessment of pubertal development indicates an increased prevalence of early thelarche and adrenarche but delayed menarche[66]. Difficulties with abnormal tone in this age range typically are characterized by hypotonia evolving to rigidity[67 68].

Post-puberty to the end of school (~21 years old)--Post-puberty: Surveillance for scoliosis continues to be an important preventive measure though this lessens with completion of puberty[66]. Surveillance for urinary retention is important[69 70]. Biliary tract disease is seen in young adulthood at rates similar to the general population but due to communication impairment in RTT the presenting symptoms may be limited to irritability, weight loss and vomiting[71 72]. Studies of longevity in RTT demonstrate survival of many into middle age, underscoring the need for the early development of a comprehensive, thoughtful plan for transitioning to adulthood[73]. Longitudinal supervision is required in RTT as physical, behavioral and cognitive limitations will not allow for independent living[14 15]. This may include day programs and respite care.

21 years and older--Adulthood: Overall, individuals with RTT tend to stabilize clinically in young adulthood[74-76]. Frequent causes of hospitalization for women with RTT include pneumonia, respiratory distress, status epilepticus, rectal bleeding, decline in ambulation, or refusal/inability to eat or drink[15]. While one-third of individuals may have a gastrostomy tube, half of these continue to have some oral intake[32]. With age, concern for low bone mineral mass coupled with long-term use of particular anticonvulsants, raises the risks for osteoporosis and bone fractures[77-79] necessitating continued supplementation and monitoring of 25-OH Vitamin D status[80 81]. Musculoskeletal problems and gross motor function may worsen overall[75] possibly due to more parkinsonian features[67] but with overall preservation of intellect and memory[15]; additional study is needed due to relatively low numbers studied. Physical limitations, parkinsonian features, and high prevalence of social withdrawal behaviors lead to abnormal or decreased social interactions consistent with anxiety or depression[82]. Although the majority of women with RTT in the US live at home[14], in other countries only about one-third of women over age 16 with RTT live at home (either full or part-time) with the majority living in a residential facility[15]. Long-term and individually-tailored care that provides social interactions and physical activity should be provided at all ages to reduce age-related deterioration[83].

Discussion

Management of RTT requires input or expertise related to multiple specialties, often necessitating referrals to many providers in addition to the primary care provider. The above health guidance will evolve with further research into the longitudinal course of RTT by the NHS and others. However, there are limitations to the current proposed health guidance, specifically with respect to the lack of needed randomized clinical trials in a rare condition where interventions, such as physical and other therapies, are rarely standardized. While evaluation of annual ECG for prolonged QT appears supported by the literature[49-52], the impact and outcomes of such surveillance need further study. At this time, longitudinal prognostic details are not well understood in certain areas of evaluation such as affect, displayed emotion and its meaning, the most appropriate manner to assess intelligence and how it evolves, or the life span of

gynecologic concerns. Additional studies should also address the role and utility of palliative care and banking of post-mortem tissue. From this breadth of information, quality metrics with benchmarks can be defined to ensure standards of care with best outcomes for individuals with RTT.

With the relative paucity of older individuals in the NHS and related studies, further study into the care of older individuals is needed to better address guidance more extensively for both older RTT women and for those more severely affected who are not routinely captured in most studies[76]. Additionally, with current and future clinical trials, the disease course for individuals with RTT may be more modifiable with severity of symptoms and disease progression very different from our current understanding. There is considerable ongoing research in the field of specific RTT therapeutics[84]. It is therefore important for families, caregivers and health professionals to reach out to Rett Centers and family support group resources to stay up to date on clinical trials, drug approvals, and how this impacts these current care guidance. While a primary care provider may not be able to counsel on the suitability of different clinical trials, actively engaging RTT individuals and families and referring to clinical trials at specialty centers is necessary for the development of improved therapeutics.

With the advances in healthcare and technology, improved and earlier genetic testing, robust research in RTT, and active patient advocacy from families and clinicians, individuals with RTT are surviving well into adulthood while living more healthy and meaningful lives. With the vast amount of medical knowledge emerging from research in RTT today and knowing the complexity of care RTT often requires, this proposed guidance can facilitate delivery of more thorough and well-rounded management and comprehensive surveillance by primary care providers and other health professionals caring for individuals with RTT. Importantly, the guidance also helps to outline considerations in which health professionals may want to refer the individual with RTT for more specialized management.

In conclusion, Rett syndrome is a medically complex neurodevelopmental disorder impacting multiple organ systems in an evolving fashion from childhood through the 6th decade of adulthood. Primary care providers and other health professionals tasked with coordinating care play an essential role in ensuring the long-term health and well-being of these individuals through effective screening practices,

active management, and thoughtful coordination of subspecialty requirements. The accumulating knowledge regarding the natural history of RTT serves as a vital resource to help providers anticipate the complexities of this disorder.

Web-links to regional RTT clinics for health profressionals

https://www.rettsyndrome.org/about-rett-syndrome/clinics

https://reverserett.org/newly-diagnosed/#clinics-map

https://www.rettsyndrome.eu/

Useful web-links for families

https://www.rettsyndrome.org/

https://reverserett.org/

https://www.rettsyndrome.org/for-families/resources-for-families

https://www.rettsyndrome.eu/

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Table 1. Classic (or Typical RTT) and Atypical RTT diagnostic criteria[1].
Classic or Typical RTT diagnostic criteria A period of regression followed by recovery or stabilization
1. Partial or complete loss of acquired purposeful hand skills
2. Partial or complete loss of spoken language
3. Gait abnormalities: impaired or absence of ability
4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms.
Atypical RTT diagnostic criteria A period of regression followed by recovery or stabilization 1. At least 2 of the 4 main criteria 2. 5 of 11 supportive criteria a) Breathing disturbances while awake b) Bruxism while awake c) Impaired sleep d) Abnormal muscle tone e) Peripheral vasomotor disturbances f) Scoliosis/kyphosis g) Growth retardation h) Small cold hands and feet i) Inappropriate laughing/screaming spells j) Diminished response to pain k) Intense eye communication – "eye pointing"

Table 2. Health Supervision guidance as a checklist for individuals and PCP.

• **Individuals with Rett syndrome should be seen for regular wellness checkups, screenings and immunizations (especially influenza vaccinations)*.** • **Inform staff that extra time will be needed for visit, especially to inspecting the individual without braces, shoes and outer clothing.** • **Parents and care-givers should keep a binder of health records to include: genetic testing results, summaries of all doctor visits (including specialist referrals), summaries of hospital admissions, laboratory studies, ECG, x-ray reports and other imaging results.**				
Areas of Assessment	**Assessment Details**	**Yearly Wellness Visit**	**Primary Care every 6 months***	**Baseline**
Genetics/ *MECP2* Testing Results	Counsel family on genetic test results and refer to genetic counselor if appropriate for additional counsel or explanation. Family and PCP to keep a copy of genetic results.			✓
General	Update current medications and allergies	At every visit		
	Weight	At every visit		
	Height or body length Body mass index	At very visit At every visit		
	Head circumference[1]	At every visit		
	Tanner Stage	At yearly wellness		
	Laboratory evaluations (see below)	(see below)		
Gastrointestinal	Review: feeding methods, appetite, chewing ability, choking and length of feeding time.	✓	✓	
	Screen for GE reflux, gas bloating, biliary tract disease, constipation and hemorrhoids, skin tags, or fissures.	✓	✓	
Nutrition	Review nutritional and herbal supplements Nutrition screening[2]: energy, protein, fluids, sodium, potassium, calcium, and vitamin D intake. Consider nutrition related laboratory screening (yearly): CBC, electrolye panel, 25-OH-vitamin D, fasting lipids	✓	✓	
Respiratory	Screen for awake disordered breathing (hyperventilating, breath-holding, color change), and air swallowing.	✓		
Neurology	Screen for presence of paroxysmal events (seizures or non-epileptic spells suspicious for seizures). Advise caregivers to keep a log with description of distinct event types and frequency. Refer to Neurology if an event occurs repeatedly for diagnostic clarification. Encourage follow-up with neurologist routinely; every 6 months if treated for seizures. If individual's weight fluctuates (more than 10-20%), request neurologist to consider adjusting anticonvulsant doses accordingly. Laboratory follow-up as needed for use of antiseizure medications.	✓	✓	✓
	Screen for abnormal movements (stereotypies and dystonia) and level of impact on daily	✓		✓

	activities.			
Cardiology	12-lead ECG to screen for prolonged QTc interval; if abnormal, refer to Cardiology.	✓		✓
Skin	Document temperature and color of hands and feet. Screen for skin breakdown from hand-mouthing or ill-fitting braces. Screen for pressure ulcers.	✓	✓	
Orthopedics Rehabilitation	Estimate curvature of spine. Recheck every 6 months if scoliosis present; refer to Orthopedics if > 20 degrees.	✓	(if scoliosis present✓)	
	Screen for abnormal hip abduction, range of motion and leg length.	✓	✓	
	Screen for contractures and use or need of devices to prevent them (ankle-foot orthoses and splints).	✓		
	Discuss risk of fractures due to osteopenia.	✓		
	Screen for needs and use of mobility aids.	✓		
Urology	Review toilet training, frequency and infrequency of urination, and urinary tract infections. Refer to Urology for frequent urinary tract infections or urinary retention. Consider Urology related laboratory screening (every 2 years): urinalysis	✓		
Development	Documentation of baseline, gains and losses of milestones. Fine motor: hand use: raking grasp, pincer grasp, rake, holding cup or spoon. Gross motor: sitting, standing, and walking. Language: coo, babble, laugh, words.	✓		✓
Communication	Screen communication methods used by family and school: eye pointing, vocalizations, switches, ipad, eye-gaze device.	✓		✓
Behavioral	Screen for symptoms of anxiety and depression, such as withdrawal, screaming and irritability. Inquire about sensory processing difficulties.	✓	✓	✓
Sleep	Review sleep initiation, staying asleep, snoring or coughing, and frequency of nocturnal interventions by caregivers. Review safety of bed and bedroom. Consider laboratory evaluation for iron deficiency if concerns arise about disrupted sleep or restless leg syndrome: ferritin, serum iron, TIBC, transferrin.	✓	✓	✓
Pain	Discuss delayed pain response and describe individual's response to pain.	✓		
Extremities	Temperature dysregulation. Review environmental factors that might impact comfort.	✓		
Screenings	Screen for vision concerns and consider referral for formal vision assessment including acuity, spatial, depth, visual fields and cortical visual impairment.	✓		
	Review newborn ABR results at baseline, consider repeating ABR if history of chronic otitis media, consider evaluation for auditory processing delay.	✓		✓
	Annual dental health screening; refer for cleaning every 6 months.	✓		
Education/Therapies	Review for presence of current IEP (see info on RettSyndrome.org) Documentation of therapies (type and frequency).	✓		✓
Family/Social	Assess for family stress (financial, social, fatigue)	✓	✓	✓
Resources	Review available community and insurance resources (disabled parking permit, respite care etc.) In adolescent individuals review plans for obtaining guardianship. Clinician may be required	✓		

	to write Letters of Medical Necessity for equipment and sign school medication forms.			

*6month follow-up visit is medically necessary to screen for issues that can appear quickly, progress rapidly and require intervention

[1]Please see CDC or Nellhaus head circumference chart for age 0-18 years

[2]Please see **Food and Drink Log** (https://www.rettsyndrome.org/pcg) to ensure adequate calcium, vitamin D, energy and fluid intake

Tables 3-7. Detailed approaches to management and therapy for RTT. References not specific to RTT noted as "See:".

Table 3: Genetics, Neurology, Cardiology, Respiratory, and Urology			
System/Area	**Common concerns and questions**	**Details and suggested approach**	**References**
Genetics	*MECP2* gene	For suspicion of Rett syndrome, *MECP2* gene sequencing and MLPA testing is recommended. MLPA testing is needed to detect deletions otherwise missed by sequencing; this test is necessary if no abnormalities are found by sequencing. Referral to a geneticist or genetic counselor is recommended to review recurrence risks and answer related questions. Genetic testing results are essential for enrollment in clinical trials. Referral to a Rett Center if feasible may be useful to provide multidisciplinary care and access to clinical trials.	16 85 86
Neurology	Seizures and Spells	Refer to neurologist for seizures and spells suspicious for seizures with follow-up every 6 months if treated with an anticonvulsant. It is difficult to differentiate between a non-epileptic Rett Spell and a seizure (both may be present). Individuals can have multiple types of seizures. Seizure logs by the family are needed with careful description of events that includes frequency and duration. Videos of events are helpful to the neurologist. The neurologist may order a video EEG to accurately characterize whether a type of event is a seizure or not. An overnight EEG may be necessary to capture sleep; an EEG is incomplete if sleep is not captured.	53-56
	Abnormal movements	Ataxic gait and an impaired spatial awareness (proprioception) are common. Stereotypical hand movements (hand-wringing, mouthing, etc) are typical. These are often disruptive to hand use. Use of splints to elbows or hand guards, which may be prescribed by an OT, may be helpful to improve hand use. Initially, most individuals have low tone that progresses over years to high tone and dystonia. Neurologist or physiatrist may prescribe neuromuscular blockade or other medications to reduce tone to maintain function and prevent contractures.	67 68 87 88
Cardiology	Abnormal ECG	Yearly ECG to check for prolonged QTc interval which can develop at any time. Referral to cardiologist if the ECG is abnormal, who may consider further studies (Holter monitor, echocardiogram) or treatment. Avoid prescription of medications that can prolong QTc interval (i.e. fluoxetine). A current ECG is recommended before anesthesia.	49-52
	Poor circulation	Distal temperature asymmetries are common and thought to be autonomic in origin; no specific therapy is recommended.	61 89 90
Respiratory	Hyperventilation, air swallowing, breath holding, blowing raspberries	Due to autonomic dysregulation, these may occur during the day. While not purposeful, they may be triggered by anxiety. Currently, there are no medications or treatments for this. If night time apneas are present, check tonsils and consider ordering a comprehensive sleep study and related specialist referral. Breathing abnormalities may disrupt feeding.	62 63 91-93
Urology	Urine retention	Autonomic dysfunction can lead to delayed bladder emptying and bladder distension. If present, referral to urology may be needed. Constipation can increase risk of UTIs. Toilet training can be achieved in some cases. Certain medications or poor fluid intake can cause increase risk of kidney stones.	69 70 See: 94

Table 4: Gastroenterology and Nutrition

System/Area	Common concerns and questions	Details and suggested approach	References
Gastroenterology and Nutrition	Dysmotility	Abdominal pain and discomfort typically are caused by reflux, gas bloating, delayed stomach emptying, biliary tract disease, or constipation; these can be empirically diagnosed and managed (see below). These will present with abdominal fullness (gas or constipation), irritability (reflux or constipation), nocturnal arousals (reflux or constipation), arching (reflux), overt reflux or emesis, burping (reflux or air swallowing). Gall bladder dysfunction, screened by abdominal ultrasound, should be considered. Referral to surgery for cholecystectomy may be necessary for symptomatic gallstones or biliary dyskinesia.	37 38 40 72
	Constipation	This is a very common problem. Laxatives (polyethylene glycol, magnesium hydroxide, glycerin or bisacodyl suppositories) are often a part of long-term treatment with a goal of one soft bowel movement per day.	37 40
	Reflux	This is a very common problem. PPI or H2 blockers are used empirically. Referral to gastroenterologist may be necessary to rule out complications such as esophagitis, ulcer, strictures, or Barrett's esophagus.	37 40
	Poor weight gain	Fatigue and irritability may be signs that dietary requirements are not being met;.consider energy dense foods (oils, syrups, avocado), gastroenterologist, and nutrition consults. Gastrostomy-button may be needed to maintain growth; counsel families that use of a gastrostomy button does not preclude oral feeding as long as oral feeding is safe. Use CDC/WHO growth charts to track growth and try to keep at same BMI percentile on growth curve through adolescent growth spurt. RTT-specific growth charts are also available.	37-39 95 96
	Calcium/Vitamin D	Ensure supplemental Vitamin D intake: 600-1000 IU or more daily. Target serum levels of 25-OH-Vitamin D greater than 30-40 ng/ml. Ensure milk and dairy products to provide age-appropriate dietary calcium intakes: 1-3 y, 700 mg/d; 4-8 y, 1000 mg/d; 9-18 y, 1300 mg/d; 19 y and older, 1000 mg/d. 240 ml (8 oz) of milk or 240 ml (8 oz) of yogurt contains 300 mg of calcium.	77-79 See: 97
	Prolonged feeding times	Long feeding times (more than 30 minutes) can affect quality of life for patient and family; this may be an indication that a gastrostomy button is needed.	64 96 See: 98
	Chewing/swallowing difficulties	Referral to appropriate therapist or gastroenterologist to assess if there is concern for aspiration (coughing, choking, gagging with feeding or aspiration or unexplained pneumonia). In some cases, thickeners for liquids may be helpful to prevent aspiration versus need for a gastrostomy button.	37 38

Table 5: Orthopedics, Rehabilitation, Skin, Endocrine, and Hospitalization

System/Area	Common concerns and questions	Details and suggested approach	References
Orthopedics, Rehabilitation	Scoliosis	Increased risk of neuromuscular scoliosis after age 6; risk typically abates after puberty. This can progress rapidly if present, necessitating re-observation every 6 months if present. Supine x-ray and orthopedic referral when scoliotic curvature greater than 20 degrees; correction may be indicated when greater than 40 degrees. Kyphosis is more common in ambulatory individuals.	65 99-102
	Increased risk of hip subluxation	Examine hip range of motion due to high risk for hip subluxation and contractures, as either may be source of pain and cause for irritability. X-ray-AP views of pelvis may be needed to evaluate femoral head coverage.	103
	Contractures	Encourage families and caregivers to inspect all joints and practice daily range of motion, especially if mobility is reduced in an acute setting (illness or hospitalization). Consider OT and PT consults for bracing and splinting. Consider neurology and physiatry consults for neuromuscular blockade or other medications to improve tone.	104 105
	Osteopenia and fractures	There is higher risk of fracture due to immobility and use of anticonvulsants. If fracture occurs, consider DEXA scan and referral to endocrine specialist (in addition to aggressive screen of calcium, vitamin D intake and 25-OH-vitamin D levels). Cause for fractures beyond osteopenia needs investigation in order to eliminate other preventable causes, such as falling out of bed (needs rails), falling at home (needs assessment of home) or non-accidental trauma.	77-81 95 97 106 107
	Equipment	There is risks of injury due to outgrown equipment (See Skin above). Family and caregivers may need lifts, shower accommodations, bed-side toilets, etc.; these needs may be best assessed by a physiatry referral.	See: 108
Skin	Breakdown from mouthing or equipment or lack of re-positioning	Redness persisting longer than 20 min after equipment (such as a splint) is removed is of concern for development of pressure ulcers; return to PT to re-fit equipment. OT or PT may prescribe splints on elbows or hands to prevent skin breakdown from mouthing. Decubitus ulcer may need consultation with wound specialist and equipment specialist.	105
Endocrinology, Gynecology	Premature adrenarche	Menarche comes later, but breast buds and pubic hair may begin earlier than in typically developing children. Periods may be irregular due to low body weight or stress; T4, TSH should be checked if periods are irregular. Counsel family to notice whether or not seizure frequency corresponds with menstrual cycle and alert neurologist. Consideration of menses suppression should be considered, especially if it disrupts the interactions with caregivers and family or hormonal fluctuations correspond with increased seizure activity. The impact of menses suppression on bone health should be considered; IUD is a consideration. Avoidance of DEPO-provera is a consideration. Well-woman examination should include breast exam.	66 109 See: 110
Hospitalization	Anesthesia sensitivity, impaired proprioception	Individuals may be more sensitive to effects of anesthetics. They may take longer to awaken from anesthesia. It is important to ensure anesthesiologist is aware of current medications (especially anticonvulsants and cannabis preparations), type and description of seizures, breathing abnormalities and risk of presence of prolonged QTc; a recent ECG is essential. Hospital needs to be aware of impaired proprioception, lack of hand use, inability to change position and increased fall risk. If hospitalized, family or hospital should perform daily ROM to prevent contractures.	49-51 57-59 62 63

Table 6: Psychological, Behavioral, Sleep, Pain, and Screenings

System/Area	Common concerns and questions	Details and suggested approach	References
Psychological, Behavioral	Issues with inattention/anxiety	Auditory processing is delayed and may be misinterpreted as disinterest; allow for this delay when assessing non-verbal language by allowing additional time for responses to questions or commands. Behavioral inconsistency is typical and may be affected by physical factors such as sleep or environment. Assess for intolerance of excessive stimuli (i.e. bright lights, loud noises).	46 47
	Externalizing/internalizing behaviors	Screen for caregiver impressions of anxiety and depression, such as withdrawal; these may become more prominent with age or in individuals with milder clinical presentations. Identify possible contributors (e.g., sedating medications, decreased social interaction, limited access to engaging activities). Consider treatment with an SSRI such as escitalopram which may have a lower risk of inducing a prolonged QTc interval.	15 76 82 111
Sleep	Disrupted sleep	Circadian rhythm is often disrupted; consider melatonin to initiate sleep and trazodone or clonidine to maintain asleep. Patient may be getting out of bed, which could be unsafe; consider a tent-style bed or similar engineering controls to keep child in bed and safe. Consider ferritin, serum iron, TIBC and transferrin levels if there is disrupted sleep or concerns for restless leg syndrome and need for iron replacement. Consider overnight sleep study for snoring or pauses in breathing.	112 113 See: 114-116
Pain	Pain assessment and sensitivity	Individuals have an atypical pain response giving appearance of decreased sensitivity and have variable indications of pain (i.e. grimace, crying, increase in repetitive movements); typical pain scales may be difficult to interpret or apply.	60
	Increased risk of chronic pain	Often due to GI problems (see above), dental problems, immobility and positioning. Always consider hip subluxation, vertebral compression fractures or other fractures as cause of pain.	37 40 71 72
Screening: Ophthalmology	Difficult vision assessment	Since eye gaze is the main way of communicating, assessment by a practitioner familiar with special needs individuals and cortical visual impairment is needed. Practitioner familiar with cortical visual impairment and ocular apraxia is needed.	48 104
Screening: Auditory	Auditory processing delay	Hearing is typically normal and assessments are often difficult to obtain but if chronic otitis media is present, these are needed.	45
Screening: Dental	Teeth grinding, increased risk of caries	Routine cleanings needed and may require anesthesia. Dental work under anesthesia should be done with proper anesthesia support at major medical institutions. Regular dental care is required to avoid tooth extraction; tooth extraction significantly interferes with oral function and is to therefore be avoided if at all possible.	88 117

Table 7: Development, Education, Therapies, Social, and Alternative Medications

System/Area	Common concerns and questions	Details and suggested approach	References
Development, Education and Therapies	Developmental Milestones	Developmental regression (reduced hand use and language) typically stops between 2-3 years. Skills can be maintained and possibly regained with vigorous therapies. Therapies to consider: speech therapy (ST), feeding therapy (FT), occupational therapy (OT), augmentative communication therapy (AAC), vision therapy (VT), hippotherapy (horse) and swim/pool therapy.	43 44 48 104 118
	IEP and therapy challenges	Educators may not have experience with Rett syndrome. Request they focus on communication, mobility, and socialization with attention to apraxia. Educators and therapists need to be informed that the approach to therapy in Rett syndrome is different: it is about maintaining skills as well as recovery. Therapies for Rett syndrome should include occupational, physical, speech, swallow and augmentative communication. Therapy that maximizes physical activities should be life-long, as these will minimize long-term complications and maximize long-term potentials. Educational opportunities that provide intensive physical, occupational and speech therapy, especially those that provide augmentative communication, allow individuals to learn and make the best progress. If CVI is present, then a Teacher of the Visually Impaired (TVI) should be included in the IEP. These essential accomodations to facilitate education are in accordance with disability rights legislation enacted in many countries throughout the world as required by the United Nations Convention on the Rights of Persons with Disabilities (CRPD). This international treaty signed by nearly all 193 U.N. Member States defines access to an inclusive, quality and free education as a basic human right of individuals with disabilities. Families should work with schools to develop an IEP that recognizes this; referral to a Rett Specialist may provide additional assistance in this regard.	43 44
	Non-verbal communication	Alternative and augmentative communication assessments are needed. While this can be done by some speech therapists, a specific referral may be needed. Since eye gaze is typically the most effective form of communication, special eye gaze devices can give individuals a voice. These referrals should be made as early as possible to coincide with typical language development. Devices should be made available to individuals at both home and school. Home use is to be encouraged as this setting may be the longest after the child graduates from the school system.	43 104
Social Concerns	Increased family stress	Family may need respite care. Sibling reactions and their adjustment should be considered; families could provide education for extended family and friends to understand Rett syndrome through patient advocacy group websites. When appropriate, discussion of Rett genetics with older siblings of child-bearing age should be considered by referral to a genetic counselor.	35 36 119 120
Alternative medications	Cannabis, St John's wort, etc.	Families should be encouraged to disclose use of alternative medications (cannabis, oils etc) to all specialists.	

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Supplementary Table 1. Health supervision goals surrounding individuals with RTT by ICF contextual factors

	Early Childhood	Late Childhood	Post-puberty	Ad
Body Functions and Structure	GI/Nutrition: Maintain adequate growth,bone health, and nutrition; manage reflux and constipation Neurological: Identify and manage epilepsy when present; identify and manage autonomic dysfunction Rehabilitation: develop strength and coordination Cardiology: detect and manage prolonged QT	GI/Nutrition: Maintain adequate growth,bone health, and nutrition; manage reflux and constipation Neurological: Identify and manage epilepsy when present; identify and manage autonomic dysfunction Rehabilitation: regulate tone and prevent contractures Cardiology: detect and manage prolonged QT Orthopedics: detect and manage scoliosis	GI/Nutrition: Maintain nutrition and bone health; manage constipation; detect and manage gall bladder dysfunction Neurological: Identify and manage epilepsy when present; identify and manage autonomic dysfunction Rehabilitation: regulate tone and prevent contractures Cardiology: detect and manage prolonged QT Orthopedics detect and prevent fractures	GI nut ma and dys Ne ma pre aut Re and Ca pro Or pre
Environment	Education: Develop appropriate IEP Therapies: Access to appropriate therapies Socialization: Age-appropriate interactions and activities	Education: Develop appropriate IEP Therapies: Access to appropriate therapies including physical, occupational, and assistive communication technologies Socialization: Age-appropriate interactions and activities	Education: Develop appropriate IEP Therapies: Access to appropriate therapies including physical, occupational, and assistive communication technologies Socialization: Age-appropriate interactions and activities	Ed Da Th app phy ass tec So app act

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Consensus guidelines on managing Rett Syndrome across the lifespan

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Abbreviations:
ABR: auditory brainstem response
AAC: augmentative and alternative communication
CVI: cortical visual impairment
EI: Early Intervention
ICF: International Classification of Functioning, Disability and Health
IEP: Individualized Education Program (or Plan)
NHS: NIH-funded Natural History Study of Rett and related disorders
PCP: primary care provider
RTT: Rett Syndrome
TVI: teacher of the visually impaired

Summary Box:

What is known: Rett syndrome (RTT) is a multi-system and rare genetic disorder with similarities to other developmental encephalopathies. There are no peer-reviewed consensus-based therapeutic guidance to care in RTT.

What this study adds: Primary care providers and other health professionals caring for patients with RTT frequently have limited first-hand experience managing the disorder due to its rare prevalence. A consensus on guidance for health professionals caring for patients with RTT was developed based on literature review and expert opinion. This guidance is applicable to other rare and often severe neurodevelopmental disorders.

Abstract

Background: Rett syndrome (RTT) is a severe neurodevelopmental disorder with complex medical co-morbidities extending beyond the nervous system requiring the attention of health professionals. There are no peer-reviewed consensus-based therapeutic guidance to care in RTT. The objective was to provide consensus on guidance of best practice for addressing these concerns.

Methods: Informed by the literature and using a modified Delphi approach, a consensus process was utilized to develop guidance for care in RTT by health professionals.

Results: Typical RTT presents early in childhood in a clinically recognizable fashion. Multisystem co-morbidities evolve throughout the lifespan requiring coordination of care between primary care and often multiple subspecialty providers. To assist health professionals and families in seeking best practice, a checklist and detailed references for guidance were developed by consensus.

Conclusions: The overall multisystem issues of RTT require primary care providers and other health professionals to manage complex medical co-morbidities within the context of the whole individual and family. Given the median life expectancy well into the 6th decade, guidance is provided to health professionals to achieve current best possible outcomes for these special-needs individuals.

Introduction

Rett syndrome (RTT)[1] is a severe neurodevelopmental disorder with an estimated worldwide prevalence of between 1 in 20,000 to 40,000 people. RTT is one of the most common genetic causes of developmental and intellectual impairment in females[2], affecting up to 1 in 10,000 girls under the age of 12. RTT is not a neurodegenerative condition[3], rather it is a progressive disorder involving multisystem symptom evolution over time. Following demonstration of symptom reversal in mouse models[4 5], there is flourishing hope for further disease modifying therapies.

Nearly all individuals with RTT have one of >300 distinct loss-of-function mutations in the *MECP2* gene on the X-chromosome[6]. This gene encodes methyl-CpG binding protein-2, an essential transcriptional regulator in the brain required for normal neurodevelopment[7]. Complete genetic testing involves sequencing and methods to detect larger deletions (e.g. multiplex ligation-dependent probe amplification (MLPA)) of the *MECP2* gene. Likely owing to the random nature of X-chromosome inactivation[8] and other genetic modifiers[9-11], genotype-phenotype correlations are imprecise. However, a general pattern exists with some mutations (early truncating mutations such as R168X, R255X, R270X, large deletions and specific point mutations such as R106W) associated with increased severity compared to other mutation groups (R133C, R294X, R306X, and C-terminal truncations)[12]. *MECP2* mutations causing RTT are almost always *de novo* (spontaneous) and as such are not expected to recur in families.

The presentation is initially subtle in the first two years of life involving developmental delays and hypotonia on exam, but subsequent symptom evolution between 18-30 months of age with developmental regression and onset of repetitive, purposeless hand movements is striking[13]. The core clinical diagnostic features of RTT (Table 1, Typical and Atypical)[1] include a period of normal (or near normal) development followed by developmental regression with loss of language and hand function skills, impaired gait, and development of hand stereotypies causing life-long dependence[14 15]. The average age at RTT diagnosis of 2.5 years has been trending downward with increasing availability of diagnostic genetic testing[16]. The multisystem nature of the disorder has been documented within multiple observational studies with symptom risk evolving across the lifespan.

MECP2 mutations have been identified rarely in males with neurodevelopmental disorders, termed "male RTT encephalopathy". The resulting developmental outcome is quite variable though with symptomatology distinct from RTT and ranges in severity from a severe neonatal encephalopathy with minimal developmental improvement to a mild intellectual disability[17]. Male RTT encephalopathy[18] and other distinct developmental encephalopathies (historically linked to RTT)[19] such as *MECP2* duplication syndrome[20-22], *CDKL5* Deficiency Disorder[23-26] and *FOXG1* syndrome[27-30] may have similar approaches (but distinct therapeutics) as more is learned about specific aspects of their clinical care. Alterations in *MECP2, CDKL5* and *FOXG1* should be considered in all individuals, male and female, with developmental delays and intellectual disability.

In the past two decades the natural history of RTT has been extensively studied[31]. Perhaps most important to all health professionals managing this complex disorder is the knowledge that with appropriate care, children with RTT will become adults with RTT; 70% live to at least 50 years of age[14 32]. As such, health professionals are often presented with the daunting task of effectively managing the evolving medical comorbidities of the disorder throughout a patient's lifespan. To help address this challenge, based on a review of published literature regarding RTT symptomatology that identified the most relevant primary care concerns through a modified Delphi consensus approach, we developed recommendations regarding guidance for best practice. These recommendations have been organized based on an age-dependent health supervision approach to facilitate the goal of effective and meaningful care for individuals with RTT across all ages.

Methods

Draft guidance was developed (MJ, KH and PN) and presented and discussed at bimonthly International Rett Syndrome Foundation sponsored North American Rett Syndrome Clinics Network conference calls between January 2016 through September 2018 with input obtained from 22 clinical sites. An initial draft was presented January 2017 for external review by the Network through September 2018; additional public input was obtained from January 2019 to May 2019 through placement on the

RettSyndrome.org website. With supervision by the group leader, the guidance was further refined substantially by eight Rett Centers (University of Alabama Birmingham, Vanderbilt University, Children's Hospital Colorado, Children's Hospital of Philadelphia, Cincinnati Children's Hospital, Boston Children's Hospital, UCSF Benioff Children's Hospital Oakland, and Texas Children's Hospital) providing multidisciplinary care for individuals with RTT, in partnership with the NIH-funded Natural History Study of Rett and related disorders (NHS, U54 HD061222; **ClinicalTrials.gov: NCT00299312/NCT02738281**) and two patient advocacy groups, Rett Syndrome Research Trust and the International Rett Syndrome Foundation. This consensus approach followed a modified Delphi process employed by members of this group previously[33]. The partners were chosen based on clinical experience across primary care, multiple subspecialties, health care delivery, and, importantly, patient-family experience with RTT. Conflicts of interest were vetted by the group leader with full knowledge by the group. A consensus led by the group leader surrounding relevant guidance based on published data and clinical opinion was developed through six further rounds of modifications. The results of a literature review were used to inform the guidance (paper submitted). The following recommendations were created based on an age-dependent health supervision approach to assist health professionals in fulfilling the goal of effective and meaningful care for individuals with RTT across all ages (Tables 2 and 3). Items are organized by prevalence at each age group. Consistent with International Classification of Functioning, Disability and Health (ICF) guidelines (WHO , 2001)[34], this guidance recognizes the inter-relatedness of body function/structure, environment and personal factors to maximize activities and participation (Supplemental Table 1). Thus, in addition to routine assessment of medical issues (body function), several psychosocial, environmental, and educational concerns need to be assessed frequently to achieve the goal of family-centered service:

- The financial, emotional and physical impact on the family as a whole: sibling well-being, parent physical and mental health (sleep, grief, anxiety, depression), quality of life, and marital impacts[35 36].
- Vigilance regarding signs and symptoms of abuse and neglect of an at-risk individual.
- Educational support programs for which the individual may be eligible.

- Government-sponsored income and other support benefits.
- Personal financial, community, and emotional support available to the family.

Patient involvement

Patients family groups (International Rett Syndrome Foundation and Rett Syndrome Research Trust), represented by parents of individuals with RTT (Ms. Nues and Ms. Coenraads), were involved in the development of the patient care guidance and writing of this manuscript. Their organizations will assist with dissemination of the guidance.

Results

The guidance was formulated into a checklist (Table 2) with further details and references (Tables 3-7) that informed the checklist and the consensus process. The guidance for management by health professionals was grouped by relevant features and therapeutic approaches at different ages. The checklist (Table 2) is suitable for use by health professionals as well as the family as part of their health care records with Tables 3-7 providing further detailed guidance.

Diagnosis to 5 years old--Early Childhood: Most features of RTT may emerge during this age period. Feeding difficulties and growth failure[37-39] begin during this age. Additional treatable gastrointestinal issues including dysmotility, gastroesophageal reflux, constipation, gas bloating, often presenting as irritability or apparent discomfort manifest commonly at this age[37 40]. The development of microcephaly or head growth stagnation (as early as 1.5 months)[39] is a common feature, though macrocephaly has also been seen[41]. Tone issues at this age are typically characterized by hypotonia[42]; early referral to therapists (physical, occupational, speech language including augmentative communication[43]) and establishment of an IEP[44] are necessary. Severe hearing loss is uncommon in RTT[45] but there may be delayed auditory processing[46 47] that mimics hearing impairment. There is increased risk of cortical visual impairment (CVI) and ocular apraxia in RTT[48]. There is evidence suggesting increased risk for prolonged QTc interval that may be present from a young age[49-51] and may develop with time[52]. The frequency of epileptic and non-epileptic spells[53 54] wax and wane throughout the

course[53 55]. Individuals with RTT generally respond to anticonvulsants[53 55 56] but there have been no randomized, controlled trials of specific anticonvulsants for RTT. If hospitalized, it is important to inform hospital staff of important issues in RTT individuals that could potentially confound or complicate care. This includes a heightened sensitivity to the effects of anesthetics. potentially requiring lower doses of anesthetic medications to achieve sedation[57 58] or longer time to awaken from general anesthesia[59]. Though response to pain is altered in RTT[60], the approach to analgesia should not be altered. Hospital staff should also be aware of cold extremities[61], irregular and disordered breathing with oxygen desaturations[62 63], impaired proprioception, lack of hand use, inability to change position, and increased fall risk.

5 years to the Pre-pubescent Stage--Late Childhood: During the early school years, children with RTT typically have stabilized developmentally; the regression phase has ended[39]. Overall, many of the multisystem issues that arose during the first 5 years of life persist. Preventing undernutrition and maintaining a healthy BMI is important, as this has been associated with better functioning[38 64]. Surveillance for scoliosis becomes an important preventive measure; some children (~20%) ultimately require spinal surgery for this comorbidity[65]. Longitudinal assessment of pubertal development indicates an increased prevalence of early thelarche and adrenarche but delayed menarche[66]. Difficulties with abnormal tone in this age range typically are characterized by hypotonia evolving to rigidity[67 68].

Post-puberty to the end of school (~21 years old)--Post-puberty: Surveillance for scoliosis continues to be an important preventive measure though this lessens with completion of puberty[66]. Surveillance for urinary retention is important[69 70]. Biliary tract disease is seen in young adulthood at rates similar to the general population but due to communication impairment in RTT the presenting symptoms may be limited to irritability, weight loss and vomiting[71 72]. Studies of longevity in RTT demonstrate survival of many into middle age, underscoring the need for the early development of a comprehensive, thoughtful plan for transitioning to adulthood[73]. Longitudinal supervision is required in RTT as physical, behavioral and cognitive limitations will not allow for independent living[14 15]. This may include day programs and respite care.

21 years and older--Adulthood: Overall, individuals with RTT tend to stabilize clinically in young adulthood[74-76]. Frequent causes of hospitalization for women with RTT include pneumonia, respiratory distress, status epilepticus, rectal bleeding, decline in ambulation, or refusal/inability to eat or drink[15]. While one-third of individuals may have a gastrostomy tube, half of these continue to have some oral intake[32]. With age, concern for low bone mineral mass coupled with long-term use of particular anticonvulsants, raises the risks for osteoporosis and bone fractures[77-79] necessitating continued supplementation and monitoring of 25-OH Vitamin D status[80 81]. Musculoskeletal problems and gross motor function may worsen overall[75] possibly due to more parkinsonian features[67] but with overall preservation of intellect and memory[15]; additional study is needed due to relatively low numbers studied. Physical limitations, parkinsonian features, and high prevalence of social withdrawal behaviors lead to abnormal or decreased social interactions consistent with anxiety or depression[82]. Although the majority of women with RTT in the US live at home[14], in other countries only about one-third of women over age 16 with RTT live at home (either full or part-time) with the majority living in a residential facility[15]. Long-term and individually-tailored care that provides social interactions and physical activity should be provided at all ages to reduce age-related deterioration[83].

Discussion

Management of RTT requires input or expertise related to multiple specialties, often necessitating referrals to many providers in addition to the primary care provider. The above health guidance will evolve with further research into the longitudinal course of RTT by the NHS and others. However, there are limitations to the current proposed health guidance, specifically with respect to the lack of needed randomized clinical trials in a rare condition where interventions, such as physical and other therapies, are rarely standardized. While evaluation of annual ECG for prolonged QT appears supported by the literature[49-52], the impact and outcomes of such surveillance need further study. At this time, longitudinal prognostic details are not well understood in certain areas of evaluation such as affect, displayed emotion and its meaning, the most appropriate manner to assess intelligence and how it evolves, or the life span of

gynecologic concerns. Additional studies should also address the role and utility of palliative care and banking of post-mortem tissue. From this breadth of information, quality metrics with benchmarks can be defined to ensure standards of care with best outcomes for individuals with RTT.

With the relative paucity of older individuals in the NHS and related studies, further study into the care of older individuals is needed to better address guidance more extensively for both older RTT women and for those more severely affected who are not routinely captured in most studies[76]. Additionally, with current and future clinical trials, the disease course for individuals with RTT may be more modifiable with severity of symptoms and disease progression very different from our current understanding. There is considerable ongoing research in the field of specific RTT therapeutics[84]. It is therefore important for families, caregivers and health professionals to reach out to Rett Centers and family support group resources to stay up to date on clinical trials, drug approvals, and how this impacts these current care guidance. While a primary care provider may not be able to counsel on the suitability of different clinical trials, actively engaging RTT individuals and families and referring to clinical trials at specialty centers is necessary for the development of improved therapeutics.

With the advances in healthcare and technology, improved and earlier genetic testing, robust research in RTT, and active patient advocacy from families and clinicians, individuals with RTT are surviving well into adulthood while living more healthy and meaningful lives. With the vast amount of medical knowledge emerging from research in RTT today and knowing the complexity of care RTT often requires, this proposed guidance can facilitate delivery of more thorough and well-rounded management and comprehensive surveillance by primary care providers and other health professionals caring for individuals with RTT. Importantly, the guidance also helps to outline considerations in which health professionals may want to refer the individual with RTT for more specialized management.

In conclusion, Rett syndrome is a medically complex neurodevelopmental disorder impacting multiple organ systems in an evolving fashion from childhood through the 6th decade of adulthood. Primary care providers and other health professionals tasked with coordinating care play an essential role in ensuring the long-term health and well-being of these individuals through effective screening practices,

active management, and thoughtful coordination of subspecialty requirements. The accumulating knowledge regarding the natural history of RTT serves as a vital resource to help providers anticipate the complexities of this disorder.

Web-links to regional RTT clinics for health profressionals

https://www.rettsyndrome.org/about-rett-syndrome/clinics

https://reverserett.org/newly-diagnosed/#clinics-map

https://www.rettsyndrome.eu/

Useful web-links for families

https://www.rettsyndrome.org/

https://reverserett.org/

https://www.rettsyndrome.org/for-families/resources-for-families

https://www.rettsyndrome.eu/

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Table 1. Classic (or Typical RTT) and Atypical RTT diagnostic criteria[1].
Classic or Typical RTT diagnostic criteria A period of regression followed by recovery or stabilization
1. Partial or complete loss of acquired purposeful hand skills
2. Partial or complete loss of spoken language
3. Gait abnormalities: impaired or absence of ability
4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms.
Atypical RTT diagnostic criteria A period of regression followed by recovery or stabilization 1. At least 2 of the 4 main criteria 2. 5 of 11 supportive criteria a) Breathing disturbances while awake b) Bruxism while awake c) Impaired sleep d) Abnormal muscle tone e) Peripheral vasomotor disturbances f) Scoliosis/kyphosis g) Growth retardation h) Small cold hands and feet i) Inappropriate laughing/screaming spells j) Diminished response to pain k) Intense eye communication – "eye pointing"

Table 2. Health Supervision guidance as a checklist for individuals and PCP.

• **Individuals with Rett syndrome should be seen for regular wellness checkups, screenings and immunizations (especially influenza vaccinations)*.** • **Inform staff that extra time will be needed for visit, especially to inspecting the individual without braces, shoes and outer clothing.** • **Parents and care-givers should keep a binder of health records to include: genetic testing results, summaries of all doctor visits (including specialist referrals), summaries of hospital admissions, laboratory studies, ECG, x-ray reports and other imaging results.**				
Areas of Assessment	**Assessment Details**	**Yearly Wellness Visit**	**Primary Care every 6 months***	**Baseline**
Genetics/ *MECP2* Testing Results	Counsel family on genetic test results and refer to genetic counselor if appropriate for additional counsel or explanation. Family and PCP to keep a copy of genetic results.			✓
General	Update current medications and allergies	At every visit		
	Weight	At every visit		
	Height or body length Body mass index	At very visit At every visit		
	Head circumference[1]	At every visit		
	Tanner Stage	At yearly wellness		
	Laboratory evaluations (see below)	(see below)		
Gastrointestinal	Review: feeding methods, appetite, chewing ability, choking and length of feeding time.	✓	✓	
	Screen for GE reflux, gas bloating, biliary tract disease, constipation and hemorrhoids, skin tags, or fissures.	✓	✓	
Nutrition	Review nutritional and herbal supplements Nutrition screening[2]: energy, protein, fluids, sodium, potassium, calcium, and vitamin D intake. Consider nutrition related laboratory screening (yearly): CBC, electrolye panel, 25-OH-vitamin D, fasting lipids	✓	✓	
Respiratory	Screen for awake disordered breathing (hyperventilating, breath-holding, color change), and air swallowing.	✓		
Neurology	Screen for presence of paroxysmal events (seizures or non-epileptic spells suspicious for seizures). Advise caregivers to keep a log with description of distinct event types and frequency. Refer to Neurology if an event occurs repeatedly for diagnostic clarification. Encourage follow-up with neurologist routinely; every 6 months if treated for seizures. If individual's weight fluctuates (more than 10-20%), request neurologist to consider adjusting anticonvulsant doses accordingly. Laboratory follow-up as needed for use of antiseizure medications.	✓	✓	✓
	Screen for abnormal movements (stereotypies and dystonia) and level of impact on daily	✓		✓

	activities.			
Cardiology	12-lead ECG to screen for prolonged QTc interval; if abnormal, refer to Cardiology.	✓		✓
Skin	Document temperature and color of hands and feet. Screen for skin breakdown from hand-mouthing or ill-fitting braces. Screen for pressure ulcers.	✓	✓	
Orthopedics Rehabilitation	Estimate curvature of spine. Recheck every 6 months if scoliosis present; refer to Orthopedics if > 20 degrees.	✓	(if scoliosis present✓)	
	Screen for abnormal hip abduction, range of motion and leg length.	✓	✓	
	Screen for contractures and use or need of devices to prevent them (ankle-foot orthoses and splints).	✓		
	Discuss risk of fractures due to osteopenia.	✓		
	Screen for needs and use of mobility aids.	✓		
Urology	Review toilet training, frequency and infrequency of urination, and urinary tract infections. Refer to Urology for frequent urinary tract infections or urinary retention. Consider Urology related laboratory screening (every 2 years): urinalysis	✓		
Development	Documentation of baseline, gains and losses of milestones. Fine motor: hand use: raking grasp, pincer grasp, rake, holding cup or spoon. Gross motor: sitting, standing, and walking. Language: coo, babble, laugh, words.	✓		✓
Communication	Screen communication methods used by family and school: eye pointing, vocalizations, switches, ipad, eye-gaze device.	✓		✓
Behavioral	Screen for symptoms of anxiety and depression, such as withdrawal, screaming and irritability. Inquire about sensory processing difficulties.	✓	✓	✓
Sleep	Review sleep initiation, staying asleep, snoring or coughing, and frequency of nocturnal interventions by caregivers. Review safety of bed and bedroom. Consider laboratory evaluation for iron deficiency if concerns arise about disrupted sleep or restless leg syndrome: ferritin, serum iron, TIBC, transferrin.	✓	✓	✓
Pain	Discuss delayed pain response and describe individual's response to pain.	✓		
Extremities	Temperature dysregulation. Review environmental factors that might impact comfort.	✓		
Screenings	Screen for vision concerns and consider referral for formal vision assessment including acuity, spatial, depth, visual fields and cortical visual impairment.	✓		
	Review newborn ABR results at baseline, consider repeating ABR if history of chronic otitis media, consider evaluation for auditory processing delay.	✓		✓
	Annual dental health screening; refer for cleaning every 6 months.	✓		
Education/Therapies	Review for presence of current IEP (see info on RettSyndrome.org) Documentation of therapies (type and frequency).	✓		✓
Family/Social	Assess for family stress (financial, social, fatigue)	✓	✓	✓
Resources	Review available community and insurance resources (disabled parking permit, respite care etc.) In adolescent individuals review plans for obtaining guardianship. Clinician may be required	✓		

	to write Letters of Medical Necessity for equipment and sign school medication forms.			

*6month follow-up visit is medically necessary to screen for issues that can appear quickly, progress rapidly and require intervention

[1]Please see CDC or Nellhaus head circumference chart for age 0-18 years

[2]Please see **Food and Drink Log** (https://www.rettsyndrome.org/pcg) to ensure adequate calcium, vitamin D, energy and fluid intake

Tables 3-7. Detailed approaches to management and therapy for RTT. References not specific to RTT noted as "See:".

Table 3: Genetics, Neurology, Cardiology, Respiratory, and Urology			
System/Area	**Common concerns and questions**	**Details and suggested approach**	**References**
Genetics	*MECP2* gene	For suspicion of Rett syndrome, *MECP2* gene sequencing and MLPA testing is recommended. MLPA testing is needed to detect deletions otherwise missed by sequencing; this test is necessary if no abnormalities are found by sequencing. Referral to a geneticist or genetic counselor is recommended to review recurrence risks and answer related questions. Genetic testing results are essential for enrollment in clinical trials. Referral to a Rett Center if feasible may be useful to provide multidisciplinary care and access to clinical trials.	16 85 86
Neurology	Seizures and Spells	Refer to neurologist for seizures and spells suspicious for seizures with follow-up every 6 months if treated with an anticonvulsant. It is difficult to differentiate between a non-epileptic Rett Spell and a seizure (both may be present). Individuals can have multiple types of seizures. Seizure logs by the family are needed with careful description of events that includes frequency and duration. Videos of events are helpful to the neurologist. The neurologist may order a video EEG to accurately characterize whether a type of event is a seizure or not. An overnight EEG may be necessary to capture sleep; an EEG is incomplete if sleep is not captured.	53-56
	Abnormal movements	Ataxic gait and an impaired spatial awareness (proprioception) are common. Stereotypical hand movements (hand-wringing, mouthing, etc) are typical. These are often disruptive to hand use. Use of splints to elbows or hand guards, which may be prescribed by an OT, may be helpful to improve hand use. Initially, most individuals have low tone that progresses over years to high tone and dystonia. Neurologist or physiatrist may prescribe neuromuscular blockade or other medications to reduce tone to maintain function and prevent contractures.	67 68 87 88
Cardiology	Abnormal ECG	Yearly ECG to check for prolonged QTc interval which can develop at any time. Referral to cardiologist if the ECG is abnormal, who may consider further studies (Holter monitor, echocardiogram) or treatment. Avoid prescription of medications that can prolong QTc interval (i.e. fluoxetine). A current ECG is recommended before anesthesia.	49-52
	Poor circulation	Distal temperature asymmetries are common and thought to be autonomic in origin; no specific therapy is recommended.	61 89 90
Respiratory	Hyperventilation, air swallowing, breath holding, blowing raspberries	Due to autonomic dysregulation, these may occur during the day. While not purposeful, they may be triggered by anxiety. Currently, there are no medications or treatments for this. If night time apneas are present, check tonsils and consider ordering a comprehensive sleep study and related specialist referral. Breathing abnormalities may disrupt feeding.	62 63 91-93
Urology	Urine retention	Autonomic dysfunction can lead to delayed bladder emptying and bladder distension. If present, referral to urology may be needed. Constipation can increase risk of UTIs. Toilet training can be achieved in some cases. Certain medications or poor fluid intake can cause increase risk of kidney stones.	69 70 See: 94

Table 4: Gastroenterology and Nutrition

System/Area	Common concerns and questions	Details and suggested approach	References
Gastroenterology and Nutrition	Dysmotility	Abdominal pain and discomfort typically are caused by reflux, gas bloating, delayed stomach emptying, biliary tract disease, or constipation; these can be empirically diagnosed and managed (see below). These will present with abdominal fullness (gas or constipation), irritability (reflux or constipation), nocturnal arousals (reflux or constipation), arching (reflux), overt reflux or emesis, burping (reflux or air swallowing). Gall bladder dysfunction, screened by abdominal ultrasound, should be considered. Referral to surgery for cholecystectomy may be necessary for symptomatic gallstones or biliary dyskinesia.	37 38 40 72
	Constipation	This is a very common problem. Laxatives (polyethylene glycol, magnesium hydroxide, glycerin or bisacodyl suppositories) are often a part of long-term treatment with a goal of one soft bowel movement per day.	37 40
	Reflux	This is a very common problem. PPI or H2 blockers are used empirically. Referral to gastroenterologist may be necessary to rule out complications such as esophagitis, ulcer, strictures, or Barrett's esophagus.	37 40
	Poor weight gain	Fatigue and irritability may be signs that dietary requirements are not being met;.consider energy dense foods (oils, syrups, avocado), gastroenterologist, and nutrition consults. Gastrostomy-button may be needed to maintain growth; counsel families that use of a gastrostomy button does not preclude oral feeding as long as oral feeding is safe. Use CDC/WHO growth charts to track growth and try to keep at same BMI percentile on growth curve through adolescent growth spurt. RTT-specific growth charts are also available.	37-39 95 96
	Calcium/Vitamin D	Ensure supplemental Vitamin D intake: 600-1000 IU or more daily. Target serum levels of 25-OH-Vitamin D greater than 30-40 ng/ml. Ensure milk and dairy products to provide age-appropriate dietary calcium intakes: 1-3 y, 700 mg/d; 4-8 y, 1000 mg/d; 9-18 y, 1300 mg/d; 19 y and older, 1000 mg/d. 240 ml (8 oz) of milk or 240 ml (8 oz) of yogurt contains 300 mg of calcium.	77-79 See: 97
	Prolonged feeding times	Long feeding times (more than 30 minutes) can affect quality of life for patient and family; this may be an indication that a gastrostomy button is needed.	64 96 See: 98
	Chewing/swallowing difficulties	Referral to appropriate therapist or gastroenterologist to assess if there is concern for aspiration (coughing, choking, gagging with feeding or aspiration or unexplained pneumonia). In some cases, thickeners for liquids may be helpful to prevent aspiration versus need for a gastrostomy button.	37 38

Table 5: Orthopedics, Rehabilitation, Skin, Endocrine, and Hospitalization

System/Area	Common concerns and questions	Details and suggested approach	References
Orthopedics, Rehabilitation	Scoliosis	Increased risk of neuromuscular scoliosis after age 6; risk typically abates after puberty. This can progress rapidly if present, necessitating re-observation every 6 months if present. Supine x-ray and orthopedic referral when scoliotic curvature greater than 20 degrees; correction may be indicated when greater than 40 degrees. Kyphosis is more common in ambulatory individuals.	65 99-102
	Increased risk of hip subluxation	Examine hip range of motion due to high risk for hip subluxation and contractures, as either may be source of pain and cause for irritability. X-ray-AP views of pelvis may be needed to evaluate femoral head coverage.	103
	Contractures	Encourage families and caregivers to inspect all joints and practice daily range of motion, especially if mobility is reduced in an acute setting (illness or hospitalization). Consider OT and PT consults for bracing and splinting. Consider neurology and physiatry consults for neuromuscular blockade or other medications to improve tone.	104 105
	Osteopenia and fractures	There is higher risk of fracture due to immobility and use of anticonvulsants. If fracture occurs, consider DEXA scan and referral to endocrine specialist (in addition to aggressive screen of calcium, vitamin D intake and 25-OH-vitamin D levels). Cause for fractures beyond osteopenia needs investigation in order to eliminate other preventable causes, such as falling out of bed (needs rails), falling at home (needs assessment of home) or non-accidental trauma.	77-81 95 97 106 107
	Equipment	There is risks of injury due to outgrown equipment (See Skin above). Family and caregivers may need lifts, shower accommodations, bed-side toilets, etc.; these needs may be best assessed by a physiatry referral.	See: 108
Skin	Breakdown from mouthing or equipment or lack of re-positioning	Redness persisting longer than 20 min after equipment (such as a splint) is removed is of concern for development of pressure ulcers; return to PT to re-fit equipment. OT or PT may prescribe splints on elbows or hands to prevent skin breakdown from mouthing. Decubitus ulcer may need consultation with wound specialist and equipment specialist.	105
Endocrinology, Gynecology	Premature adrenarche	Menarche comes later, but breast buds and pubic hair may begin earlier than in typically developing children. Periods may be irregular due to low body weight or stress; T4, TSH should be checked if periods are irregular. Counsel family to notice whether or not seizure frequency corresponds with menstrual cycle and alert neurologist. Consideration of menses suppression should be considered, especially if it disrupts the interactions with caregivers and family or hormonal fluctuations correspond with increased seizure activity. The impact of menses suppression on bone health should be considered; IUD is a consideration. Avoidance of DEPO-provera is a consideration. Well-woman examination should include breast exam.	66 109 See: 110
Hospitalization	Anesthesia sensitivity, impaired proprioception	Individuals may be more sensitive to effects of anesthetics. They may take longer to awaken from anesthesia. It is important to ensure anesthesiologist is aware of current medications (especially anticonvulsants and cannabis preparations), type and description of seizures, breathing abnormalities and risk of presence of prolonged QTc; a recent ECG is essential. Hospital needs to be aware of impaired proprioception, lack of hand use, inability to change position and increased fall risk. If hospitalized, family or hospital should perform daily ROM to prevent contractures.	49-51 57-59 62 63

Table 6: Psychological, Behavioral, Sleep, Pain, and Screenings

System/Area	Common concerns and questions	Details and suggested approach	References
Psychological, Behavioral	Issues with inattention/anxiety	Auditory processing is delayed and may be misinterpreted as disinterest; allow for this delay when assessing non-verbal language by allowing additional time for responses to questions or commands. Behavioral inconsistency is typical and may be affected by physical factors such as sleep or environment. Assess for intolerance of excessive stimuli (i.e. bright lights, loud noises).	46 47
	Externalizing/internalizing behaviors	Screen for caregiver impressions of anxiety and depression, such as withdrawal; these may become more prominent with age or in individuals with milder clinical presentations. Identify possible contributors (e.g., sedating medications, decreased social interaction, limited access to engaging activities). Consider treatment with an SSRI such as escitalopram which may have a lower risk of inducing a prolonged QTc interval.	15 76 82 111
Sleep	Disrupted sleep	Circadian rhythm is often disrupted; consider melatonin to initiate sleep and trazodone or clonidine to maintain asleep. Patient may be getting out of bed, which could be unsafe; consider a tent-style bed or similar engineering controls to keep child in bed and safe. Consider ferritin, serum iron, TIBC and transferrin levels if there is disrupted sleep or concerns for restless leg syndrome and need for iron replacement. Consider overnight sleep study for snoring or pauses in breathing.	112 113 See: 114-116
Pain	Pain assessment and sensitivity	Individuals have an atypical pain response giving appearance of decreased sensitivity and have variable indications of pain (i.e. grimace, crying, increase in repetitive movements); typical pain scales may be difficult to interpret or apply.	60
	Increased risk of chronic pain	Often due to GI problems (see above), dental problems, immobility and positioning. Always consider hip subluxation, vertebral compression fractures or other fractures as cause of pain.	37 40 71 72
Screening: Ophthalmology	Difficult vision assessment	Since eye gaze is the main way of communicating, assessment by a practitioner familiar with special needs individuals and cortical visual impairment is needed. Practitioner familiar with cortical visual impairment and ocular apraxia is needed.	48 104
Screening: Auditory	Auditory processing delay	Hearing is typically normal and assessments are often difficult to obtain but if chronic otitis media is present, these are needed.	45
Screening: Dental	Teeth grinding, increased risk of caries	Routine cleanings needed and may require anesthesia. Dental work under anesthesia should be done with proper anesthesia support at major medical institutions. Regular dental care is required to avoid tooth extraction; tooth extraction significantly interferes with oral function and is to therefore be avoided if at all possible.	88 117

Table 7: Development, Education, Therapies, Social, and Alternative Medications

System/Area	Common concerns and questions	Details and suggested approach	References
Development, Education and Therapies	Developmental Milestones	Developmental regression (reduced hand use and language) typically stops between 2-3 years. Skills can be maintained and possibly regained with vigorous therapies. Therapies to consider: speech therapy (ST), feeding therapy (FT), occupational therapy (OT), augmentative communication therapy (AAC), vision therapy (VT), hippotherapy (horse) and swim/pool therapy.	43 44 48 104 118
	IEP and therapy challenges	Educators may not have experience with Rett syndrome. Request they focus on communication, mobility, and socialization with attention to apraxia. Educators and therapists need to be informed that the approach to therapy in Rett syndrome is different: it is about maintaining skills as well as recovery. Therapies for Rett syndrome should include occupational, physical, speech, swallow and augmentative communication. Therapy that maximizes physical activities should be life-long, as these will minimize long-term complications and maximize long-term potentials. Educational opportunities that provide intensive physical, occupational and speech therapy, especially those that provide augmentative communication, allow individuals to learn and make the best progress. If CVI is present, then a Teacher of the Visually Impaired (TVI) should be included in the IEP. These essential accomodations to facilitate education are in accordance with disability rights legislation enacted in many countries throughout the world as required by the United Nations Convention on the Rights of Persons with Disabilities (CRPD). This international treaty signed by nearly all 193 U.N. Member States defines access to an inclusive, quality and free education as a basic human right of individuals with disabilities. Families should work with schools to develop an IEP that recognizes this; referral to a Rett Specialist may provide additional assistance in this regard.	43 44
	Non-verbal communication	Alternative and augmentative communication assessments are needed. While this can be done by some speech therapists, a specific referral may be needed. Since eye gaze is typically the most effective form of communication, special eye gaze devices can give individuals a voice. These referrals should be made as early as possible to coincide with typical language development. Devices should be made available to individuals at both home and school. Home use is to be encouraged as this setting may be the longest after the child graduates from the school system.	43 104
Social Concerns	Increased family stress	Family may need respite care. Sibling reactions and their adjustment should be considered; families could provide education for extended family and friends to understand Rett syndrome through patient advocacy group websites. When appropriate, discussion of Rett genetics with older siblings of child-bearing age should be considered by referral to a genetic counselor.	35 36 119 120
Alternative medications	Cannabis, St John's wort, etc.	Families should be encouraged to disclose use of alternative medications (cannabis, oils etc) to all specialists.	

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Supplementary Table 1. Health supervision goals surrounding individuals with RTT by ICF contextual factors

	Early Childhood	Late Childhood	Post-puberty	Ad
Body Functions and Structure	GI/Nutrition: Maintain adequate growth,bone health, and nutrition; manage reflux and constipation Neurological: Identify and manage epilepsy when present; identify and manage autonomic dysfunction Rehabilitation: develop strength and coordination Cardiology: detect and manage prolonged QT	GI/Nutrition: Maintain adequate growth,bone health, and nutrition; manage reflux and constipation Neurological: Identify and manage epilepsy when present; identify and manage autonomic dysfunction Rehabilitation: regulate tone and prevent contractures Cardiology: detect and manage prolonged QT Orthopedics: detect and manage scoliosis	GI/Nutrition: Maintain nutrition and bone health; manage constipation; detect and manage gall bladder dysfunction Neurological: Identify and manage epilepsy when present; identify and manage autonomic dysfunction Rehabilitation: regulate tone and prevent contractures Cardiology: detect and manage prolonged QT Orthopedics detect and prevent fractures	GI nut ma and dys Ne ma pre aut Re and Ca pro Or pre
Environment	Education: Develop appropriate IEP Therapies: Access to appropriate therapies Socialization: Age-appropriate interactions and activities	Education: Develop appropriate IEP Therapies: Access to appropriate therapies including physical, occupational, and assistive communication technologies Socialization: Age-appropriate interactions and activities	Education: Develop appropriate IEP Therapies: Access to appropriate therapies including physical, occupational, and assistive communication technologies Socialization: Age-appropriate interactions and activities	Ed Da Th app phy ass tec So app act

Consensus guidelines on managing Rett Syndrome across the lifespan~~Guidance for Health Professionals in Rett Syndrome~~

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Abbreviations:
ABR: auditory brainstem response
AAC: augmentative and alternative communication
CVI: cortical visual impairment
EI: Early Intervention
ICF: International Classification of Functioning, Disability and Health
IEP: Individualized Education Program (or Plan)
NHS: NIH-funded Natural History Study of Rett and related disorders
PCP: primary care provider
RTT: Rett Syndrome
TVI: teacher of the visually impaired

Summary Box:

What is known: Rett syndrome (RTT) is a multi-system and rare genetic disorder with similarities to other developmental encephalopathies. There are no peer-reviewed consensus-based therapeutic guidance to care in RTT.

What this study adds: Primary care providers and other health professionals caring for patients with RTT frequently have limited first-hand experience managing the disorder due to its rare prevalence. A consensus on guidance for health professionals caring for patients with RTT was developed based on literature review and expert opinion. This guidance is applicable to other rare and often severe neurodevelopmental disorders.

Abstract

Background: Rett syndrome (RTT) is a severe neurodevelopmental disorder with complex medical co-morbidities extending beyond the nervous system requiring the attention of health professionals. There are no peer-reviewed consensus-based therapeutic guidance to care in RTT. The objective was to provide consensus on guidance of best practice for addressing these concerns.

Methods: Informed by the literature and using a modified Delphi approach, a consensus process was utilized to develop guidance for care in RTT by health professionals.

Results: Typical RTT presents early in childhood in a clinically recognizable fashion. Multisystem co-morbidities evolve throughout the lifespan requiring coordination of care between primary care and often multiple subspecialty providers. To assist health professionals and families in seeking best practice, a checklist and detailed references for guidance were developed by consensus.

Conclusions: The overall multisystem issues of RTT require primary care providers and other health professionals to manage complex medical co-morbidities within the context of the whole individual and family. Given the median life expectancy well into the 6th decade, guidance is provided to health professionals to achieve current best possible outcomes for these special-needs individuals.

Introduction

Rett syndrome (RTT)[1] is a severe neurodevelopmental disorder with an estimated worldwide prevalence of between 1 in 20,000 to 40,000 people. RTT is one of the most common genetic causes of developmental and intellectual impairment in females[2], affecting up to 1 in 10,000 girls under the age of 12. RTT is not a neurodegenerative condition[3], rather it is a progressive disorder involving multisystem symptom evolution over time. Following demonstration of symptom reversal in mouse models[4 5], there is flourishing hope for further disease modifying therapies.

Nearly all individuals with RTT have one of >300 distinct loss-of-function mutations in the *MECP2* gene on the X-chromosome[6]. This gene encodes methyl-CpG binding protein-2, an essential transcriptional regulator in the brain required for normal neurodevelopment[7]. Complete genetic testing involves sequencing and methods to detect larger deletions (e.g. multiplex ligation-dependent probe amplification (MLPA)) of the *MECP2* gene. Likely owing to the random nature of X-chromosome inactivation[8] and other genetic modifiers[9-11], genotype-phenotype correlations are imprecise. However, a general pattern exists with some mutations (early truncating mutations such as R168X, R255X, R270X, large deletions and specific point mutations such as R106W) associated with increased severity compared to other mutation groups (R133C, R294X, R306X, and C-terminal truncations)[12]. *MECP2* mutations causing RTT are almost always *de novo* (spontaneous) and as such are not expected to recur in families.

The presentation is initially subtle in the first two years of life involving developmental delays and hypotonia on exam, but subsequent symptom evolution between 18-30 months of age with developmental regression and onset of repetitive, purposeless hand movements is striking[13]. The core clinical diagnostic features of RTT (Table 1, Typical and Atypical)[1] include a period of normal (or near normal) development followed by developmental regression with loss of language and hand function skills, impaired gait, and development of hand stereotypies causing life-long dependence[14 15]. The average age at RTT diagnosis of 2.5 years has been trending downward with increasing availability of diagnostic genetic testing[16]. The multisystem nature of the disorder has been documented within multiple observational studies with symptom risk evolving across the lifespan.

MECP2 mutations have been identified rarely in males with neurodevelopmental disorders, termed "male RTT encephalopathy". The resulting developmental outcome is quite variable though with symptomatology distinct from RTT and ranges in severity from a severe neonatal encephalopathy with minimal developmental improvement to a mild intellectual disability[17]. Male RTT encephalopathy[18] and other distinct developmental encephalopathies (historically linked to RTT)[19] such as *MECP2* duplication syndrome[20-22], *CDKL5* Deficiency Disorder[23-26] and *FOXG1* syndrome[27-30] may have similar approaches (but distinct therapeutics) as more is learned about specific aspects of their clinical care. Alterations in *MECP2, CDKL5* and *FOXG1* should be considered in all individuals, male and female, with developmental delays and intellectual disability.

In the past two decades the natural history of RTT has been extensively studied[31]. Perhaps most important to all health professionals managing this complex disorder is the knowledge that with appropriate care, children with RTT will become adults with RTT; 70% live to at least 50 years of age[14 32]. As such, health professionals are often presented with the daunting task of effectively managing the evolving medical comorbidities of the disorder throughout a patient's lifespan. To help address this challenge, based on a review of published literature regarding RTT symptomatology that identified the most relevant primary care concerns through a modified Delphi consensus approach, we developed recommendations regarding guidance for best practice. These recommendations have been organized based on an age-dependent health supervision approach to facilitate the goal of effective and meaningful care for individuals with RTT across all ages.

Methods

Draft guidance was developed (MJ, KH and PN) and presented and discussed at bimonthly International Rett Syndrome Foundation sponsored North American Rett Syndrome Clinics Network conference calls between January 2016 through September 2018 with input obtained from 22 clinical sites. An initial draft was presented January 2017 for external review by the Network through September 2018; additional public input was obtained from January 2019 to May 2019 through placement on the

RettSyndrome.org website. With supervision by the group leader, the guidance was further refined substantially by eight Rett Centers (University of Alabama Birmingham, Vanderbilt University, Children's Hospital Colorado, Children's Hospital of Philadelphia, Cincinnati Children's Hospital, Boston Children's Hospital, UCSF Benioff Children's Hospital Oakland, and Texas Children's Hospital) providing multidisciplinary care for individuals with RTT, in partnership with the NIH-funded Natural History Study of Rett and related disorders (NHS, U54 HD061222; **ClinicalTrials.gov: NCT00299312/NCT02738281**) and two patient advocacy groups, Rett Syndrome Research Trust and the International Rett Syndrome Foundation. This consensus approach followed a modified Delphi process employed by members of this group previously[33]. The partners were chosen based on clinical experience across primary care, multiple subspecialties, health care delivery, and, importantly, patient-family experience with RTT. Conflicts of interest were vetted by the group leader with full knowledge by the group. A consensus led by the group leader surrounding relevant guidance based on published data and clinical opinion was developed through six further rounds of modifications. The results of a ~~systematic~~ literature review were used to inform the guidance (~~Fu et al, in preparation~~paper submitted). The following recommendations were created based on an age-dependent health supervision approach to assist health professionals in fulfilling the goal of effective and meaningful care for individuals with RTT across all ages (Tables 2 and 3). Items are organized by prevalence at each age group. Consistent with International Classification of Functioning, Disability and Health (ICF) guidelines (WHO , 2001)[34], this guidance recognizes the inter-relatedness of body function/structure, environment and personal factors to maximize activities and participation (Supplemental Table 1). Thus, in addition to routine assessment of medical issues (body function), several psychosocial, environmental, and educational concerns need to be assessed frequently to achieve the goal of family-centered service:

- The financial, emotional and physical impact on the family as a whole: sibling well-being, parent physical and mental health (sleep, grief, anxiety, depression), quality of life, and marital impacts[35 36].
- Vigilance regarding signs and symptoms of abuse and neglect of an at-risk individual.
- Educational support programs for which the individual may be eligible.

- Government-sponsored income and other support benefits.
- Personal financial, community, and emotional support available to the family.

Patient involvement

Patients family groups (International Rett Syndrome Foundation and Rett Syndrome Research Trust), represented by parents of individuals with RTT (Ms. Nues and Ms. Coenraads), were involved in the development of the patient care guidance and writing of this manuscript. Their organizations will assist with dissemination of the guidance.

Results

The guidance was formulated into a checklist (Table 2) with further details and references (Tables 3-7) that informed the checklist and the consensus process. The guidance for management by health professionals was grouped by relevant features and therapeutic approaches at different ages. The checklist (Table 2) is suitable for use by health professionals as well as the family as part of their health care records with Tables 3-7 providing further detailed guidance.

Diagnosis to 5 years old--Early Childhood: Most features of RTT may emerge during this age period. Feeding difficulties and growth failure[37-39] begin during this age. Additional treatable gastrointestinal issues including dysmotility, gastroesophageal reflux, constipation, gas bloating, often presenting as irritability or apparent discomfort manifest commonly at this age[37 40]. The development of microcephaly or head growth stagnation (as early as 1.5 months)[39] is a common feature, though macrocephaly has also been seen[41]. Tone issues at this age are typically characterized by hypotonia[42]; early referral to therapists (physical, occupational, speech language including augmentative communication[43]) and establishment of an IEP[44] are necessary. Severe hearing loss is uncommon in RTT[45] but there may be delayed auditory processing[46 47] that mimics hearing impairment. There is increased risk of cortical visual impairment (CVI) and ocular apraxia in RTT[48]. There is evidence suggesting increased risk for prolonged QTc interval that may be present from a young age[49-51] and may develop with time[52]. The frequency of epileptic and non-epileptic spells[53 54] wax and wane throughout the

course[53 55]. Individuals with RTT generally respond to anticonvulsants[53 55 56] but there have been no randomized, controlled trials of specific anticonvulsants for RTT. If hospitalized, it is important to inform hospital staff of important issues in RTT individuals that could potentially confound or complicate care. This includes a heightened sensitivity to the effects of anesthetics. potentially requiring lower doses of anesthetic medications to achieve sedation[57 58] or longer time to awaken from general anesthesia[59]. Though response to pain is altered in RTT[60], the approach to analgesia should not be altered. Hospital staff should also be aware of cold extremities[61], irregular and disordered breathing with oxygen desaturations[62 63], impaired proprioception, lack of hand use, inability to change position, and increased fall risk.

5 years to the Pre-pubescent Stage--Late Childhood: During the early school years, children with RTT typically have stabilized developmentally; the regression phase has ended[39]. Overall, many of the multisystem issues that arose during the first 5 years of life persist. Preventing undernutrition and maintaining a healthy BMI is important, as this has been associated with better functioning[38 64]. Surveillance for scoliosis becomes an important preventive measure; some children (~20%) ultimately require spinal surgery for this comorbidity[65]. Longitudinal assessment of pubertal development indicates an increased prevalence of early thelarche and adrenarche but delayed menarche[66]. Difficulties with abnormal tone in this age range typically are characterized by hypotonia evolving to rigidity[67 68].

Post-puberty to the end of school (~21 years old)--Post-puberty: Surveillance for scoliosis continues to be an important preventive measure though this lessens with completion of puberty[66]. Surveillance for urinary retention is important[69 70]. Biliary tract disease is seen in young adulthood at rates similar to the general population but due to communication impairment in RTT the presenting symptoms may be limited to irritability, weight loss and vomiting[71 72]. Studies of longevity in RTT demonstrate survival of many into middle age, underscoring the need for the early development of a comprehensive, thoughtful plan for transitioning to adulthood[73]. Longitudinal supervision is required in RTT as physical, behavioral and cognitive limitations will not allow for independent living[14 15]. This may include day programs and respite care.

21 years and older--Adulthood: Overall, individuals with RTT tend to stabilize clinically in young adulthood[74-76]. Frequent causes of hospitalization for women with RTT include pneumonia, respiratory distress, status epilepticus, rectal bleeding, decline in ambulation, or refusal/inability to eat or drink[15]. While one-third of individuals may have a gastrostomy tube, half of these continue to have some oral intake[32]. With age, concern for low bone mineral mass coupled with long-term use of particular anticonvulsants, raises the risks for osteoporosis and bone fractures[77-79] necessitating continued supplementation and monitoring of 25-OH Vitamin D status[80 81]. Musculoskeletal problems and gross motor function may worsen overall[75] possibly due to more parkinsonian features[67] but with overall preservation of intellect and memory[15]; additional study is needed due to relatively low numbers studied. Physical limitations, parkinsonian features, and high prevalence of social withdrawal behaviors lead to abnormal or decreased social interactions consistent with anxiety or depression[82]. Although the majority of women with RTT in the US live at home[14], in other countries only about one-third of women over age 16 with RTT live at home (either full or part-time) with the majority living in a residential facility[15]. Long-term and individually-tailored care that provides social interactions and physical activity should be provided at all ages to reduce age-related deterioration[83].

Discussion

Management of RTT requires input or expertise related to multiple specialties, often necessitating referrals to many providers in addition to the primary care provider. The above health guidance will evolve with further research into the longitudinal course of RTT by the NHS and others. However, there are limitations to the current proposed health guidance, specifically with respect to the lack of needed randomized clinical trials in a rare condition where interventions, such as physical and other therapies, are rarely standardized. While evaluation of annual ECG for prolonged QT appears supported by the literature[49-52], the impact and outcomes of such surveillance need further study. At this time, longitudinal prognostic details are not well understood in certain areas of evaluation such as affect, displayed emotion and its meaning, the most appropriate manner to assess intelligence and how it evolves, or the life span of

gynecologic concerns. Additional studies should also address the role and utility of palliative care and banking of post-mortem tissue. From this breadth of information, quality metrics with benchmarks can be defined to ensure standards of care with best outcomes for individuals with RTT.

With the relative paucity of older individuals in the NHS and related studies, further study into the care of older individuals is needed to better address guidance more extensively for both older RTT women and for those more severely affected who are not routinely captured in most studies[76]. Additionally, with current and future clinical trials, the disease course for individuals with RTT may be more modifiable with severity of symptoms and disease progression very different from our current understanding. There is considerable ongoing research in the field of specific RTT therapeutics[84]. It is therefore important for families, caregivers and health professionals to reach out to Rett Centers and family support group resources to stay up to date on clinical trials, drug approvals, and how this impacts these current care guidance. While a primary care provider may not be able to counsel on the suitability of different clinical trials, actively engaging RTT individuals and families and referring to clinical trials at specialty centers is necessary for the development of improved therapeutics.

With the advances in healthcare and technology, improved and earlier genetic testing, robust research in RTT, and active patient advocacy from families and clinicians, individuals with RTT are surviving well into adulthood while living more healthy and meaningful lives. With the vast amount of medical knowledge emerging from research in RTT today and knowing the complexity of care RTT often requires, this proposed guidance can facilitate delivery of more thorough and well-rounded management and comprehensive surveillance by primary care providers and other health professionals caring for individuals with RTT. Importantly, the guidance also helps to outline considerations in which health professionals may want to refer the individual with RTT for more specialized management.

In conclusion, Rett syndrome is a medically complex neurodevelopmental disorder impacting multiple organ systems in an evolving fashion from childhood through the 6th decade of adulthood. Primary care providers and other health professionals tasked with coordinating care play an essential role in ensuring the long-term health and well-being of these individuals through effective screening practices,

active management, and thoughtful coordination of subspecialty requirements. The accumulating knowledge regarding the natural history of RTT serves as a vital resource to help providers anticipate the complexities of this disorder.

Web-links to regional RTT clinics for health profressionals

https://www.rettsyndrome.org/about-rett-syndrome/clinics

https://reverserett.org/newly-diagnosed/#clinics-map

https://www.rettsyndrome.eu/

Useful web-links for families

https://www.rettsyndrome.org/

https://reverserett.org/

https://www.rettsyndrome.org/for-families/resources-for-families

https://www.rettsyndrome.eu/

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Table 1. Classic (or Typical RTT) and Atypical RTT diagnostic criteria[1].
Classic or Typical RTT diagnostic criteria A period of regression followed by recovery or stabilization
1. Partial or complete loss of acquired purposeful hand skills
2. Partial or complete loss of spoken language
3. Gait abnormalities: impaired or absence of ability
4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms.
Atypical RTT diagnostic criteria A period of regression followed by recovery or stabilization 1. At least 2 of the 4 main criteria 2. 5 of 11 supportive criteria a) Breathing disturbances while awake b) Bruxism while awake c) Impaired sleep d) Abnormal muscle tone e) Peripheral vasomotor disturbances f) Scoliosis/kyphosis g) Growth retardation h) Small cold hands and feet i) Inappropriate laughing/screaming spells j) Diminished response to pain k) Intense eye communication – "eye pointing"

Table 2. Health Supervision guidance as a checklist for individuals and PCP.

• **Individuals with Rett syndrome should be seen for regular wellness checkups, screenings and immunizations (especially influenza vaccinations)*.** • **Inform staff that extra time will be needed for visit, especially to inspecting the individual without braces, shoes and outer clothing.** • **Parents and care-givers should keep a binder of health records to include: genetic testing results, summaries of all doctor visits (including specialist referrals), summaries of hospital admissions, laboratory studies, ECG, x-ray reports and other imaging results.**				
Areas of Assessment	**Assessment Details**	**Yearly Wellness Visit**	**Primary Care every 6 months***	**Baseline**
Genetics/ *MECP2* Testing Results	Counsel family on genetic test results and refer to genetic counselor if appropriate for additional counsel or explanation. Family and PCP to keep a copy of genetic results.			✓
General	Update current medications and allergies	At every visit		
	Weight	At every visit		
	Height or body length Body mass index	At very visit At every visit		
	Head circumference[1]	At every visit		
	Tanner Stage	At yearly wellness		
	Laboratory evaluations (see below)	(see below)		
Gastrointestinal	Review: feeding methods, appetite, chewing ability, choking and length of feeding time.	✓	✓	
	Screen for GE reflux, gas bloating, biliary tract disease, constipation and hemorrhoids, skin tags, or fissures.	✓	✓	
Nutrition	Review nutritional and herbal supplements Nutrition screening[2]: energy, protein, fluids, sodium, potassium, calcium, and vitamin D intake. Consider nutrition related laboratory screening (yearly): CBC, electrolye panel, 25-OH-vitamin D, fasting lipids	✓	✓	
Respiratory	Screen for awake disordered breathing (hyperventilating, breath-holding, color change), and air swallowing.	✓		
Neurology	Screen for presence of paroxysmal events (seizures or non-epileptic spells suspicious for seizures). Advise caregivers to keep a log with description of distinct event types and frequency. Refer to Neurology if an event occurs repeatedly for diagnostic clarification. Encourage follow-up with neurologist routinely; every 6 months if treated for seizures. If individual's weight fluctuates (more than 10-20%), request neurologist to consider adjusting anticonvulsant doses accordingly. Laboratory follow-up as needed for use of antiseizure medications.	✓	✓	✓
	Screen for abnormal movements (stereotypies and dystonia) and level of impact on daily	✓		✓

	activities.			
Cardiology	12-lead ECG to screen for prolonged QTc interval; if abnormal, refer to Cardiology.	✓		✓
Skin	Document temperature and color of hands and feet. Screen for skin breakdown from hand-mouthing or ill-fitting braces. Screen for pressure ulcers.	✓	✓	
Orthopedics Rehabilitation	Estimate curvature of spine. Recheck every 6 months if scoliosis present; refer to Orthopedics if > 20 degrees.	✓	(if scoliosis present✓)	
	Screen for abnormal hip abduction, range of motion and leg length.	✓	✓	
	Screen for contractures and use or need of devices to prevent them (ankle-foot orthoses and splints).	✓		
	Discuss risk of fractures due to osteopenia.	✓		
	Screen for needs and use of mobility aids.	✓		
Urology	Review toilet training, frequency and infrequency of urination, and urinary tract infections. Refer to Urology for frequent urinary tract infections or urinary retention. Consider Urology related laboratory screening (every 2 years): urinalysis	✓		
Development	Documentation of baseline, gains and losses of milestones. Fine motor: hand use: raking grasp, pincer grasp, rake, holding cup or spoon. Gross motor: sitting, standing, and walking. Language: coo, babble, laugh, words.	✓		✓
Communication	Screen communication methods used by family and school: eye pointing, vocalizations, switches, ipad, eye-gaze device.	✓		✓
Behavioral	Screen for symptoms of anxiety and depression, such as withdrawal, screaming and irritability. Inquire about sensory processing difficulties.	✓	✓	✓
Sleep	Review sleep initiation, staying asleep, snoring or coughing, and frequency of nocturnal interventions by caregivers. Review safety of bed and bedroom. Consider laboratory evaluation for iron deficiency if concerns arise about disrupted sleep or restless leg syndrome: ferritin, serum iron, TIBC, transferrin.	✓	✓	✓
Pain	Discuss delayed pain response and describe individual's response to pain.	✓		
Extremities	Temperature dysregulation. Review environmental factors that might impact comfort.	✓		
Screenings	Screen for vision concerns and consider referral for formal vision assessment including acuity, spatial, depth, visual fields and cortical visual impairment.	✓		
	Review newborn ABR results at baseline, consider repeating ABR if history of chronic otitis media, consider evaluation for auditory processing delay.	✓		✓
	Annual dental health screening; refer for cleaning every 6 months.	✓		
Education/Therapies	Review for presence of current IEP (see info on RettSyndrome.org) Documentation of therapies (type and frequency).	✓		✓
Family/Social	Assess for family stress (financial, social, fatigue)	✓	✓	✓
Resources	Review available community and insurance resources (disabled parking permit, respite care etc.) In adolescent individuals review plans for obtaining guardianship. Clinician may be required	✓		

	to write Letters of Medical Necessity for equipment and sign school medication forms.			

*6month follow-up visit is medically necessary to screen for issues that can appear quickly, progress rapidly and require intervention

[1]Please see CDC or Nellhaus head circumference chart for age 0-18 years

[2]Please see **Food and Drink Log** (https://www.rettsyndrome.org/pcg) to ensure adequate calcium, vitamin D, energy and fluid intake

Tables 3-7. Detailed approaches to management and therapy for RTT. References not specific to RTT noted as "See:".

Table 3: Genetics, Neurology, Cardiology, Respiratory, and Urology			
System/Area	**Common concerns and questions**	**Details and suggested approach**	**References**
Genetics	*MECP2* gene	For suspicion of Rett syndrome, *MECP2* gene sequencing and MLPA testing is recommended. MLPA testing is needed to detect deletions otherwise missed by sequencing; this test is necessary if no abnormalities are found by sequencing. Referral to a geneticist or genetic counselor is recommended to review recurrence risks and answer related questions. Genetic testing results are essential for enrollment in clinical trials. Referral to a Rett Center if feasible may be useful to provide multidisciplinary care and access to clinical trials.	16 85 86
Neurology	Seizures and Spells	Refer to neurologist for seizures and spells suspicious for seizures with follow-up every 6 months if treated with an anticonvulsant. It is difficult to differentiate between a non-epileptic Rett Spell and a seizure (both may be present). Individuals can have multiple types of seizures. Seizure logs by the family are needed with careful description of events that includes frequency and duration. Videos of events are helpful to the neurologist. The neurologist may order a video EEG to accurately characterize whether a type of event is a seizure or not. An overnight EEG may be necessary to capture sleep; an EEG is incomplete if sleep is not captured.	53-56
	Abnormal movements	Ataxic gait and an impaired spatial awareness (proprioception) are common. Stereotypical hand movements (hand-wringing, mouthing, etc) are typical. These are often disruptive to hand use. Use of splints to elbows or hand guards, which may be prescribed by an OT, may be helpful to improve hand use. Initially, most individuals have low tone that progresses over years to high tone and dystonia. Neurologist or physiatrist may prescribe neuromuscular blockade or other medications to reduce tone to maintain function and prevent contractures.	67 68 87 88
Cardiology	Abnormal ECG	Yearly ECG to check for prolonged QTc interval which can develop at any time. Referral to cardiologist if the ECG is abnormal, who may consider further studies (Holter monitor, echocardiogram) or treatment. Avoid prescription of medications that can prolong QTc interval (i.e. fluoxetine). A current ECG is recommended before anesthesia.	49-52
	Poor circulation	Distal temperature asymmetries are common and thought to be autonomic in origin; no specific therapy is recommended.	61 89 90
Respiratory	Hyperventilation, air swallowing, breath holding, blowing raspberries	Due to autonomic dysregulation, these may occur during the day. While not purposeful, they may be triggered by anxiety. Currently, there are no medications or treatments for this. If night time apneas are present, check tonsils and consider ordering a comprehensive sleep study and related specialist referral. Breathing abnormalities may disrupt feeding.	62 63 91-93
Urology	Urine retention	Autonomic dysfunction can lead to delayed bladder emptying and bladder distension. If present, referral to urology may be needed. Constipation can increase risk of UTIs. Toilet training can be achieved in some cases. Certain medications or poor fluid intake can cause increase risk of kidney stones.	69 70 See: 94

Table 4: Gastroenterology and Nutrition

System/Area	Common concerns and questions	Details and suggested approach	References
Gastroenterology and Nutrition	Dysmotility	Abdominal pain and discomfort typically are caused by reflux, gas bloating, delayed stomach emptying, biliary tract disease, or constipation; these can be empirically diagnosed and managed (see below). These will present with abdominal fullness (gas or constipation), irritability (reflux or constipation), nocturnal arousals (reflux or constipation), arching (reflux), overt reflux or emesis, burping (reflux or air swallowing). Gall bladder dysfunction, screened by abdominal ultrasound, should be considered. Referral to surgery for cholecystectomy may be necessary for symptomatic gallstones or biliary dyskinesia.	37 38 40 72
	Constipation	This is a very common problem. Laxatives (polyethylene glycol, magnesium hydroxide, glycerin or bisacodyl suppositories) are often a part of long-term treatment with a goal of one soft bowel movement per day.	37 40
	Reflux	This is a very common problem. PPI or H2 blockers are used empirically. Referral to gastroenterologist may be necessary to rule out complications such as esophagitis, ulcer, strictures, or Barrett's esophagus.	37 40
	Poor weight gain	Fatigue and irritability may be signs that dietary requirements are not being met;.consider energy dense foods (oils, syrups, avocado), gastroenterologist, and nutrition consults. Gastrostomy-button may be needed to maintain growth; counsel families that use of a gastrostomy button does not preclude oral feeding as long as oral feeding is safe. Use CDC/WHO growth charts to track growth and try to keep at same BMI percentile on growth curve through adolescent growth spurt. RTT-specific growth charts are also available.	37-39 95 96
	Calcium/Vitamin D	Ensure supplemental Vitamin D intake: 600-1000 IU or more daily. Target serum levels of 25-OH-Vitamin D greater than 30-40 ng/ml. Ensure milk and dairy products to provide age-appropriate dietary calcium intakes: 1-3 y, 700 mg/d; 4-8 y, 1000 mg/d; 9-18 y, 1300 mg/d; 19 y and older, 1000 mg/d. 240 ml (8 oz) of milk or 240 ml (8 oz) of yogurt contains 300 mg of calcium.	77-79 See: 97
	Prolonged feeding times	Long feeding times (more than 30 minutes) can affect quality of life for patient and family; this may be an indication that a gastrostomy button is needed.	64 96 See: 98
	Chewing/swallowing difficulties	Referral to appropriate therapist or gastroenterologist to assess if there is concern for aspiration (coughing, choking, gagging with feeding or aspiration or unexplained pneumonia). In some cases, thickeners for liquids may be helpful to prevent aspiration versus need for a gastrostomy button.	37 38

Table 5: Orthopedics, Rehabilitation, Skin, Endocrine, and Hospitalization

System/Area	Common concerns and questions	Details and suggested approach	References
Orthopedics, Rehabilitation	Scoliosis	Increased risk of neuromuscular scoliosis after age 6; risk typically abates after puberty. This can progress rapidly if present, necessitating re-observation every 6 months if present. Supine x-ray and orthopedic referral when scoliotic curvature greater than 20 degrees; correction may be indicated when greater than 40 degrees. Kyphosis is more common in ambulatory individuals.	65 99-102
	Increased risk of hip subluxation	Examine hip range of motion due to high risk for hip subluxation and contractures, as either may be source of pain and cause for irritability. X-ray-AP views of pelvis may be needed to evaluate femoral head coverage.	103
	Contractures	Encourage families and caregivers to inspect all joints and practice daily range of motion, especially if mobility is reduced in an acute setting (illness or hospitalization). Consider OT and PT consults for bracing and splinting. Consider neurology and physiatry consults for neuromuscular blockade or other medications to improve tone.	104 105
	Osteopenia and fractures	There is higher risk of fracture due to immobility and use of anticonvulsants. If fracture occurs, consider DEXA scan and referral to endocrine specialist (in addition to aggressive screen of calcium, vitamin D intake and 25-OH-vitamin D levels). Cause for fractures beyond osteopenia needs investigation in order to eliminate other preventable causes, such as falling out of bed (needs rails), falling at home (needs assessment of home) or non-accidental trauma.	77-81 95 97 106 107
	Equipment	There is risks of injury due to outgrown equipment (See Skin above). Family and caregivers may need lifts, shower accommodations, bed-side toilets, etc.; these needs may be best assessed by a physiatry referral.	See: 108
Skin	Breakdown from mouthing or equipment or lack of re-positioning	Redness persisting longer than 20 min after equipment (such as a splint) is removed is of concern for development of pressure ulcers; return to PT to re-fit equipment. OT or PT may prescribe splints on elbows or hands to prevent skin breakdown from mouthing. Decubitus ulcer may need consultation with wound specialist and equipment specialist.	105
Endocrinology, Gynecology	Premature adrenarche	Menarche comes later, but breast buds and pubic hair may begin earlier than in typically developing children. Periods may be irregular due to low body weight or stress; T4, TSH should be checked if periods are irregular. Counsel family to notice whether or not seizure frequency corresponds with menstrual cycle and alert neurologist. Consideration of menses suppression should be considered, especially if it disrupts the interactions with caregivers and family or hormonal fluctuations correspond with increased seizure activity. The impact of menses suppression on bone health should be considered; IUD is a consideration. Avoidance of DEPO-provera is a consideration. Well-woman examination should include breast exam.	66 109 See: 110
Hospitalization	Anesthesia sensitivity, impaired proprioception	Individuals may be more sensitive to effects of anesthetics. They may take longer to awaken from anesthesia. It is important to ensure anesthesiologist is aware of current medications (especially anticonvulsants and cannabis preparations), type and description of seizures, breathing abnormalities and risk of presence of prolonged QTc; a recent ECG is essential. Hospital needs to be aware of impaired proprioception, lack of hand use, inability to change position and increased fall risk. If hospitalized, family or hospital should perform daily ROM to prevent contractures.	49-51 57-59 62 63

Table 6: Psychological, Behavioral, Sleep, Pain, and Screenings

System/Area	Common concerns and questions	Details and suggested approach	References
Psychological, Behavioral	Issues with inattention/anxiety	Auditory processing is delayed and may be misinterpreted as disinterest; allow for this delay when assessing non-verbal language by allowing additional time for responses to questions or commands. Behavioral inconsistency is typical and may be affected by physical factors such as sleep or environment. Assess for intolerance of excessive stimuli (i.e. bright lights, loud noises).	46 47
	Externalizing/internalizing behaviors	Screen for caregiver impressions of anxiety and depression, such as withdrawal; these may become more prominent with age or in individuals with milder clinical presentations. Identify possible contributors (e.g., sedating medications, decreased social interaction, limited access to engaging activities). Consider treatment with an SSRI such as escitalopram which may have a lower risk of inducing a prolonged QTc interval.	15 76 82 111
Sleep	Disrupted sleep	Circadian rhythm is often disrupted; consider melatonin to initiate sleep and trazodone or clonidine to maintain asleep. Patient may be getting out of bed, which could be unsafe; consider a tent-style bed or similar engineering controls to keep child in bed and safe. Consider ferritin, serum iron, TIBC and transferrin levels if there is disrupted sleep or concerns for restless leg syndrome and need for iron replacement. Consider overnight sleep study for snoring or pauses in breathing.	112 113 See: 114-116
Pain	Pain assessment and sensitivity	Individuals have an atypical pain response giving appearance of decreased sensitivity and have variable indications of pain (i.e. grimace, crying, increase in repetitive movements); typical pain scales may be difficult to interpret or apply.	60
	Increased risk of chronic pain	Often due to GI problems (see above), dental problems, immobility and positioning. Always consider hip subluxation, vertebral compression fractures or other fractures as cause of pain.	37 40 71 72
Screening: Ophthalmology	Difficult vision assessment	Since eye gaze is the main way of communicating, assessment by a practitioner familiar with special needs individuals and cortical visual impairment is needed. Practitioner familiar with cortical visual impairment and ocular apraxia is needed.	48 104
Screening: Auditory	Auditory processing delay	Hearing is typically normal and assessments are often difficult to obtain but if chronic otitis media is present, these are needed.	45
Screening: Dental	Teeth grinding, increased risk of caries	Routine cleanings needed and may require anesthesia. Dental work under anesthesia should be done with proper anesthesia support at major medical institutions. Regular dental care is required to avoid tooth extraction; tooth extraction significantly interferes with oral function and is to therefore be avoided if at all possible.	88 117

Table 7: Development, Education, Therapies, Social, and Alternative Medications

System/Area	Common concerns and questions	Details and suggested approach	References
Development, Education and Therapies	Developmental Milestones	Developmental regression (reduced hand use and language) typically stops between 2-3 years. Skills can be maintained and possibly regained with vigorous therapies. Therapies to consider: speech therapy (ST), feeding therapy (FT), occupational therapy (OT), augmentative communication therapy (AAC), vision therapy (VT), hippotherapy (horse) and swim/pool therapy.	43 44 48 104 118
	IEP and therapy challenges	Educators may not have experience with Rett syndrome. Request they focus on communication, mobility, and socialization with attention to apraxia. Educators and therapists need to be informed that the approach to therapy in Rett syndrome is different: it is about maintaining skills as well as recovery. Therapies for Rett syndrome should include occupational, physical, speech, swallow and augmentative communication. Therapy that maximizes physical activities should be life-long, as these will minimize long-term complications and maximize long-term potentials. Educational opportunities that provide intensive physical, occupational and speech therapy, especially those that provide augmentative communication, allow individuals to learn and make the best progress. If CVI is present, then a Teacher of the Visually Impaired (TVI) should be included in the IEP. These essential accomodations to facilitate education are in accordance with disability rights legislation enacted in many countries throughout the world as required by the United Nations Convention on the Rights of Persons with Disabilities (CRPD). This international treaty signed by nearly all 193 U.N. Member States defines access to an inclusive, quality and free education as a basic human right of individuals with disabilities. Families should work with schools to develop an IEP that recognizes this; referral to a Rett Specialist may provide additional assistance in this regard.	43 44
	Non-verbal communication	Alternative and augmentative communication assessments are needed. While this can be done by some speech therapists, a specific referral may be needed. Since eye gaze is typically the most effective form of communication, special eye gaze devices can give individuals a voice. These referrals should be made as early as possible to coincide with typical language development. Devices should be made available to individuals at both home and school. Home use is to be encouraged as this setting may be the longest after the child graduates from the school system.	43 104
Social Concerns	Increased family stress	Family may need respite care. Sibling reactions and their adjustment should be considered; families could provide education for extended family and friends to understand Rett syndrome through patient advocacy group websites. When appropriate, discussion of Rett genetics with older siblings of child-bearing age should be considered by referral to a genetic counselor.	35 36 119 120
Alternative medications	Cannabis, St John's wort, etc.	Families should be encouraged to disclose use of alternative medications (cannabis, oils etc) to all specialists.	

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