RETT SYNDROME:
Primary Care Guidelines

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Areas of Assessment

- Patients with Rett syndrome should be seen for regular wellness checkups, screenings and immunizations (especially flu vaccinations)*.
- Inform staff that extra time will be needed for visit.
- Examining the patient without braces, shoes and outer clothing is imperative.
- Allow time for removal of equipment/clothing and provide time and space for probable personal care needs.
- Parents and care-givers should keep a binder of health records. Help them to include: genetic testing results, summaries of all doctor visits (including specialist referrals), summaries of hospital admissions, laboratory studies, EKG, x-ray reports and other imaging results.
- **Medical Disclaimer: All information, content, and material provided in this document is for informational purposes only and is not intended to serve as a substitute for the consultation, diagnosis, and/or medical treatment of a qualified physician or healthcare provider. Always seek the advice of your physician or other qualified health provider with any questions you may have regarding a medical condition.**

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	●		
	Head circumference[1],	At every visit		
	Tanner Stage	●		
	Laboratory evaluations (see below)			
GASTROINTESTINAL	Review: feeding methods, appetite, chewing ability, choking and length of feeding time.	●	●	
	Screen for GE reflux, constipation and hemorrhoids or fissures.	●	●	
NUTRITION	Nutrition screening[2]: calories, fluids, 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 patient to follow-up with neurologist routinely; every 6 months if treated for seizures. If patient weight fluctuates (more than 10-20%), request neurologist to consider adjusting anti-convulsant doses accordingly.	●	●	
	Screen for abnormal movements (stereotypies and dystonia).	●		
CARDIOLOGY	Check QtC interval with EKG; 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.	●	●	

*6 month 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 attached Food and Drink Log to ensure adequate calcium, vitamin D, calories and fluid intake

LABS: CBC, chemistry panel, 25-OH-vitamin D (yearly), baseline lipid screen (fasting if possible), UA (every 2 years). If disrupted sleep or concerned with restless leg syndrome consider ferritin, serum iron, TIBC, transferrin. Ensure that Neurologist is sharing anti-convulsant levels and related labs with PCP.

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AREAS OF ASSESSMENT	ASSESSMENT DETAILS	YEARLY WELLNESS VISIT	PRIMARY CARE EVERY 6 MONTHS*	BASELINE
ORTHOPEDICS/ REHABILITATION	Estimate curvature of spine. Recheck every 6 months if scoliosis present; refer to Orthopedics if > 20 degrees.	●	●	
	Screen for abnormal hip abduction (ROM) and leg length.	●	●	
	Screen for contractures and use or need of devices to prevent them (AFOs and splints).	●		
	Discuss risk of fractures due to osteopenia.	●		
	Screen for needs and use of mobility aids	●		
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 higher pain threshold and describe individual's response to pain.	●		
SCREENINGS	Vision screening that includes: acuity, spatial, depth, visual fields and cortical visual impairment. Review results with parents.	●		
	Audiology ABR at birth, PRN if chronic otitis media.	●		●
	Annual dental health screening	●		
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 (aka DMV permit, respite care etc.) In adolescent patients review plans for obtaining guardianship. PCP may be required to write Letters of Medical Necessity for equipment and sign school medication forms.	●		

Suggested Approaches for Common Concerns

GENETICS

- MECP2 gene: For suspicion of Rett syndrome, MeCP2 gene sequencing and MLPA testing is recommended. MLPA testing is needed to detect deletions other-wise 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.

GROWTH, DEVELOPMENT AND NUTRITION

- Poor weight gain: Fatigue and irritability may be signs that dietary requirements are not being met. Consider highly caloric foods (oils, syrups, avocado) and GI and nutrition consults. May need gastrostomy-tube to maintain growth. Counsel families that use of a gastrostomy tube does not preclude oral feeding as long as oral feeding is safe (see below).

  Use CDC/WHO growth charts to track growth and try to keep at same percentile on growth or curve.
- 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.
- Calcium/Vitamin D: Ensure recommended Vitamin D intake: 400-800 or more IU daily with a supplement containing calcium. Target serum levels of 25-OH-Vitamin D around 40-50 ng/ml.
- Prolonged feeding times: Long feeding times can affect quality of life for patient and family; this may be an indication that a gastrostomy tube is needed.
- Chewing/swallowing difficulties: Referral to appropriate therapist or GI consult to assess, especially 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 and need for a gastrostomy tube.

GASTROENTEROLOGY

- Dysmotility: Abdominal pain and discomfort is typically caused by reflux, gas, delayed stomach emptying 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 GGT, should be considered; need for cholecystectomy is not uncommon.
- Constipation: *This is a very common problem.* Laxatives (Miralax, Milk of Magnesia, glycerin suppositories) are often a part of long term treatment with a goal of one soft BM per day.
- Reflux: *This is a very common problem.* PPI or H2 blockers are used empirically. Referral to GI may be necessary to rule out complications such as ulcer and strictures.

RESPIRATORY

- Hyperventilation, air swallowing, breath holding, blowing raspberries: 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 or related referral (ENT or pulmonary). Breathing abnormalities may disrupt feeding.

NEUROLOGY

- Seizures and Spells: Refer to Neurology for seizures and spells suspicious for seizures. Neurology 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). Patients 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.
- 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 patients have low tone that progresses over years to high tone and dystonia. Neurologist or Rehabilitation specialist may prescribe botox or other medications to reduce tone to maintain function and prevent contractures.

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CARDIOVASCULAR

- Abnormal EKG: Yearly EKG to check for prolonged QTc which can develop at any time. Referral to cardiologist if the EKG is abnormal, who may consider further studies (Holter, echocardiogram) or treatment. Avoid prescription of medications that can prolong QTc (i.e. Fluoxetine). A current EKG is needed before anesthesia.

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.

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. Consider Orthopedic referral when present. Correction may be indicated when greater than 40 degrees. Kyphosis is more common in ambulatory individuals.
- Increased risk of hip subluxation: Examine hip ROM due to high risk for hip subluxation and contractures, as either may be source of pain and cause for irritability. Xray-AP views of pelvis may be needed to evaluate femoral head coverage.
- Prevent contractures: Encourage families and care-givers to inspect all joints and practice daily ROM, especially if mobility is reduced in an acute setting (illness or hospitalization). Consider OT and PT consults for bracing and splinting. Consider Neurology and Rehabilitation consults for Botox or other medications to improve tone.
- Osteopenia and fractures: Higher risk of fracture due to immobility and use of anticonvulsants. If fracture occurs, consider Dexascan and referral to endocrine (in addition to aggressive screen of calcium, vitamin D intake and 25-OH-vitamin D levels). Cause for fractures beyond osteopenia needs to be investigated in order to eliminate other preventable causes, such as falling out of bed (needs rails) or entrapment, falling at home (needs assessment of home) or non-accidental trauma.
- Equipment: Risks of injury due to outgrown equipment (See Skin above). Family and care-givers may need lifts, shower accommodations, bed-side toilets, etc.; these needs may be best assessed by a rehabilitation referral.

ENDOCRINOLOGY/GYNECOLOGY

- Premature adrenarche: Menarche comes at usual time, 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 full impact of menses suppression on bone and circulatory health should be discussed and understood; IUD is a consideration. Well-woman examination should include breast exam.

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 and time toilet training can be achieved in some cases. Certain medications can cause increase risk of kidney stones.

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).

SLEEP

- Disrupted sleep: Circadian rhythm is often disrupted; consider melatonin to get to sleep and trazodone or clonidine to stay asleep. Patient may be getting out of bed, which could be unsafe if able to wander; consider a tent-style bed or similar engineering controls to keep child in bed and safe.

PAIN

- Pain assessment and sensitivity: Patients 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
- Increased risk of chronic pain: Often due to GI problems (see above), immobility and positioning. Always consider hip subluxation, vertebral compression fractures or other fractures as cause of pain.

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SCREENING: OPHTHALMOLOGY

- Difficult vision assessment: Since eye gaze is the main way of communicating, assessment by practitioner familiar with special needs patients is needed. Practitioner familiar with cortical visual impairment and ocular apraxia is needed.

SCREENING: AUDITORY

- Auditory processing delay is typically present. Refer to ENT for chronic otitis media.

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.

EDUCATION/THERAPIES

- IEP and therapy challenges: Educators may not have experience with Rett syndrome. Request they focus on communication, mobility, and socialization with attention to apraxia and neurosensory needs. 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 patients to learn and make the best progress. Families should work with schools to develop an IEP that recognizes this; referral to a Rett Specialist may provide additional assistance in this regard.
- 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 patients a voice. These referrals should be first made as early as possible to coincide with typical language development. Devices should be made available to patients 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.

SOCIAL CONCERNS

- Increased family stress: Family may need respite care.
- Siblings reactions and their adjustment should be considered,
- Families could provide education for extended family and friends to understand Rett syndrome through web-based sites such as RettSyndrome.org and others.
- When appropriate, discussion of Rett genetics with older siblings of child bearing age should be considered by referral to a genetic counselor.

HOSPITALIZATION CONCERNS

- Anesthesia sensitivity, impaired proprioception: Patients may need lower doses of anesthetics or analgesics. Patients 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.

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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Food and Drink Log

In order to help us provide the best care to you, please do the following:

1. Record all foods and drinks that your child has during a typical 24 hour period.
2. Record the amounts of food or drink that are consumed. You can use measuring cups or common items to describe the size.
   Example: 1 apple, 1/2 cup Cheerios, chicken breast the size of a computer mouse.
3. Record as many details as possible about the food and how it was prepared.
   Example: 8 ounces of whole milk, 1 fried chicken thigh, 1/4 cup mashed potatoes with gravy.
4. If possible, record if eaten by mouth or through G-tube.

DATE:	DATE:	DATE:
BREAKFAST	BREAKFAST	BREAKFAST
BETWEEN MEALS	BETWEEN MEALS	BETWEEN MEALS
LUNCH	LUNCH	LUNCH
BETWEEN MEALS	BETWEEN MEALS	BETWEEN MEALS
DINNER	DINNER	DINNER
AFTER DINNER	AFTER DINNER	AFTER DINNER

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References

Chahrour, M. and H. Y. Zoghbi (2007). "The story of Rett syndrome: from clinic to neurobiology." Neuron **56**(3): 422-437.

Council on Children with, D. and C. Medical Home Implementation Project Advisory (2014). "Patient- and family-centered care coordination: a framework for integrating care for children and youth across multiple systems." Pediatrics **133**(5): e1451-1460.

Cuddapah, V. A., R. B. Pillai, K. V. Shekar, J. B. Lane, K. J. Motil, S. A. Skinner, D. C. Tarquinio, D. G. Glaze, G. McGwin, W. E. Kaufmann, A. K. Percy, J. L. Neul and M. L. Olsen (2014). "Methyl-CpG-binding protein 2 (MECP2) mutation type is associated with disease severity in Rett syndrome." J Med.Genet **51**(3): 152-158.

Downs, J., A. Bergman, P. Carter, A. Anderson, G. M. Palmer, D. Roye, B. H. van, A. Bebbington, E. L. Larsson, B. G. Smith, G. Baikie, S. Fyfe and H. Leonard (2009). "Guidelines for management of scoliosis in Rett syndrome patients based on expert consensus and clinical evidence." Spine (Phila Pa 1976.) **34**(17): E607-E617.

Downs, J., D. Young, K. N. de, A. Bebbington, G. Baikie and H. Leonard (2009). "Impact of scoliosis surgery on activities of daily living in females with Rett syndrome." J Pediatr. Orthop. **29**(4): 369-374.

Glaze, D. G., A. K. Percy, S. Skinner, K. J. Motil, J. L. Neul, J. O. Barrish, J. B. Lane, S. P. Geerts, F. Annese, J. Graham, L. McNair and H. S. Lee (2010). "Epilepsy and the natural history of Rett syndrome." Neurology **74**(11): 909-912.

Halbach, N., E. Smeets, C. Steinbusch, M. Maaskant, W. D. van and L. Curfs (2012). "Aging in Rett syndrome: a longitudinal study." Clin.Genet.

Katz, D. M., A. Bird, M. Coenraads, S. J. Gray, D. U. Menon, B. D. Philpot and D. C. Tarquinio (2016). "Rett Syndrome: Crossing the Threshold to Clinical Translation." Trends Neurosci **39**(2): 100-113.

Killian, J. T., J. B. Lane, G. R. Cutter, S. A. Skinner, W. E. Kaufmann, D. C. Tarquinio, D. G. Glaze, K. J. Motil, J. L. Neul and A. K. Percy (2014). "Pubertal development in Rett syndrome deviates from typical females." Pediatr Neurol **51**(6): 769-775.

Kirby, R. S., J. B. Lane, J. Childers, S. A. Skinner, F. Annese, J. O. Barrish, D. G. Glaze, P. Macleod and A. K. Percy (2010). "Longevity in Rett syndrome: analysis of the North American Database." J Pediatr **156**(1): 135-138 e131.

Lombardi, L. M., S. A. Baker and H. Y. Zoghbi (2015). "MECP2 disorders: from the clinic to mice and back." J Clin Invest **125**(8): 2914-2923.

Lotan, M. (2006). "Rett syndrome. Guidelines for individual intervention." ScientificWorldJournal **6**: 1504-1516.

Motil, K. J., E. Caeg, J. O. Barrish, S. Geerts, J. B. Lane, A. K. Percy, F. Annese, L. McNair, S. A. Skinner, H. S. Lee, J. L. Neul and D. G. Glaze (2012). "Gastrointestinal and nutritional problems occur frequently throughout life in girls and women with Rett syndrome." J Pediatr.Gastroenterol.Nutr. **55**(3): 292-298.

Neul, J. L. (2012). "The relationship of Rett syndrome and MECP2 disorders to autism." Dialogues Clin Neurosci **14**(3): 253-262.

Neul, J. L., J. B. Lane, H. S. Lee, S. Geerts, J. O. Barrish, F. Annese, L. M. Baggett, K. Barnes, S. A. Skinner, K. J. Motil, D. G. Glaze, W. E. Kaufmann and A. K. Percy (2014). "Developmental delay in Rett syndrome: data from the natural history study." J Neurodev Disord **6**(1): 20.

Percy, A. K., J. L. Neul, D. G. Glaze, K. J. Motil, S. A. Skinner, O. Khwaja, H. S. Lee, J. B. Lane, J. O. Barrish, F. Annese, L. McNair, J. Graham and K. Barnes (2010). "Rett syndrome diagnostic criteria: lessons from the Natural History Study." Ann.Neurol. **68**(6): 951-955.

Tarquinio, D. C., W. Hou, A. Berg, W. E. Kaufmann, J. B. Lane, S. A. Skinner, K. J. Motil, J. L. Neul, A. K. Percy and D. G. Glaze (2017). "Longitudinal course of epilepsy in Rett syndrome and related disorders." Brain **140**(2): 306-318.

Tarquinio, D. C., W. Hou, J. L. Neul, G. K. Berkmen, J. Drummond, E. Aronoff, J. Harris, J. B. Lane, W. E. Kaufmann, K. J. Motil, D. G. Glaze, S. A. Skinner and A. K. Percy (2018). "The course of awake breathing disturbances across the lifespan in Rett syndrome." Brain Dev **40**(7): 515-529.

Tarquinio, D. C., W. Hou, J. L. Neul, W. E. Kaufmann, D. G. Glaze, K. J. Motil, S. A. Skinner, H. S. Lee and A. K. Percy (2015). "The Changing Face of Survival in Rett Syndrome and MECP2-Related Disorders." Pediatr Neurol **53**(5): 402-411.

Tarquinio, D. C., K. J. Motil, W. Hou, H. S. Lee, D. G. Glaze, S. A. Skinner, J. L. Neul, F. Annese, L. McNair, J. O. Barrish, S. P. Geerts, J. B. Lane and A. K. Percy (2012). "Growth failure and outcome in Rett syndrome: specific growth references." Neurology **79**(16): 1653-1661.

Van Esch, H., M. Bauters, J. Ignatius, M. Jansen, M. Raynaud, K. Hollanders, D. Lugtenberg, T. Bienvenu, L. R. Jensen, J. Gecz, C. Moraine, P. Marynen, J. P. Fryns and G. Froyen (2005). "Duplication of the MECP2 region is a frequent cause of severe mental retardation and progressive neurological symptoms in males." Am J Hum Genet **77**(3): 442-453.

Weese-Mayer, D. E., S. P. Lieske, C. M. Boothby, A. S. Kenny, H. L. Bennett, J. M. Silvestri and J. M. Ramirez (2006). "Autonomic nervous system dysregulation: breathing and heart rate perturbation during wakefulness in young girls with Rett syndrome." Pediatr Res **60**(4): 443-449.

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