Evolving Treatment Landscape of Rett Syndrome: Emerging Therapies to Address Critical Clinical Gaps

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Faculty and Staff Disclosures

Abigail Jastrab, PharmD, BCPS has no relevant financial relationships with commercial interests to disclose.

Alan K. Percy, MD, has the following relevant financial relationships with commercial interests to disclose:

- Site investigator for the clinical trials of Trofinetide, Acadia Pharmaceuticals.
- Member of the medical advisory boards of Acadia Pharmaceuticals, Taysha, and Neurogene

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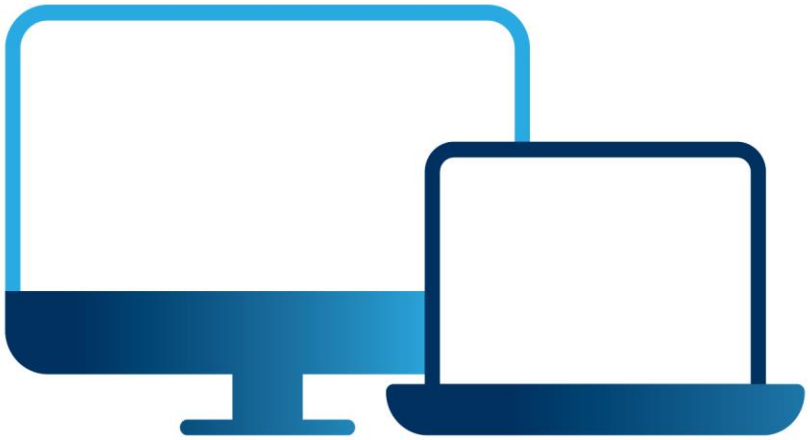

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- ✓Workbook
- ✓Faculty biographies
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Release Date: May 1, 2023

Activity Type: Application

Fee: Free

This activity is supported by an educational grant from Acadia.

Educational Objectives

After completion of this activity, participants will be able to:

- Examine the clinical and economic burden of Rett syndrome
- Review current guidelines on managing Rett syndrome across the lifespan
- Analyze current treatment limitations and the efficacy and safety of emerging novel agents for Rett syndrome
- Identify effective strategies for medication management as well as patient and caregiver education to improve care in patients with Rett syndrome

Pretest Questions

Pretest Question 1

Which of the following accurately characterizes the clinical burden of disease for Rett syndrome?

A. Neurodegenerative condition with progressive loss of communication skills
B. Progressive neurodevelopmental disorder with multisystem symptom evolution overtime
C. Acute sleep disorder
D. Cognitive disorder only presenting with chronic intellectual disability

Pretest Question 2

The lifelong management of Rett syndrome is dependent on

A. the parent
B. the school system
C. multiple providers
D. social service programs

Pretest Question 3

The principal concern of parents in improving the life of their child relates to

A. Awake breathing patterns
B. Communication
C. Scoliosis
D. Pubertal development

Pretest Question 4

RS is a 12-year-old with classic Rett syndrome. Trofinetide has been newly prescribed by her neurologist. Her caregiver reports she is taking the following medications: polyethylene glycol, calcium/vitamin D, esomeprazole, and melatonin.

Which is the most important counseling point to provide RS and her caregiver?

A. Potential adverse effect of diarrhea and plan for polyethylene glycol
B. Category X interaction between trofinetide and esomeprazole
C. Contraindication of calcium and vitamin D supplements in Rett syndrome
D. Potential adverse effect of seizures and potential need for anticonvulsant therapy

Pretest Question 5

Before participating in this activity, how confident are you in your knowledge of Rett syndrome and how to manage it?

A. Not at all
B. Somewhat
C. Moderately
D. Very
E. Extremely

Understanding Rett Syndrome

Abigail Jastrab, PharmD, BCPS

What is Rett Syndrome?

Rare, severe, neurodevelopmental disorder

Prevalence: 1 in 10,000 to 15,000 live female births

2nd leading cause of intellectual disability in girls

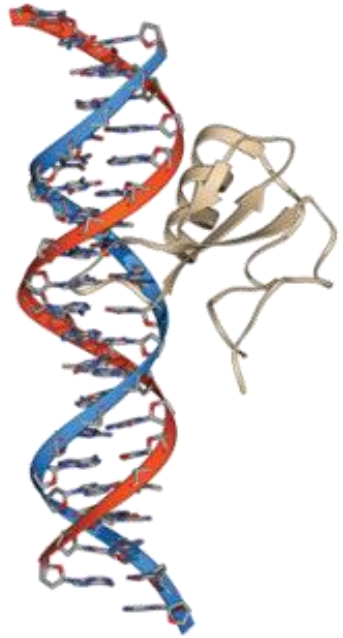
Normal development in first 12-18 months, followed by apraxia, repetitive hand movements, gait abnormalities, and cognitive impairment

Mutation in the *MECP2* gene on X chromosome

- <2% of cases observed in males
- Majority will have 1 of ≥300 distinct loss-of-function mutations in *MECP2* gene

MECP2 = critical reader of DNA methylation and regulating gene expression

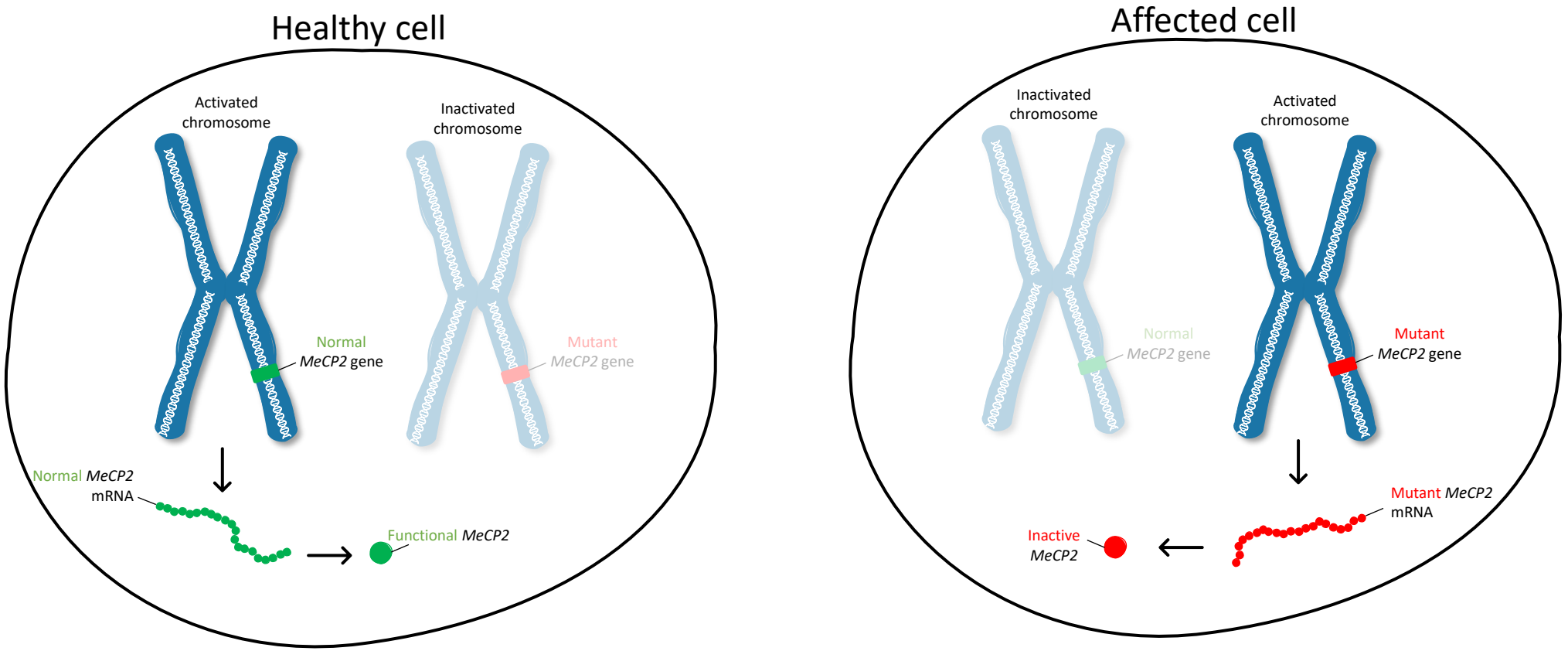
MECP2 = **methyl-CpG-binding protein 2**



Neul J, et al. *Contemp Clin Trials.* 2022;114:1-9; Parisi L, et al. *Mental Illness*. 2016;8(6302):5-9; Fu C, et al. *BMJ Paediatr Open.* 2020;4:e000717; Kirby R, et al. *J Pediatr*. 2010;156(1):135-138; Skinner, et al. Males with MECP2 mutations. International Rett Syndrome Foundation. Accessed February 23, 2023. www.rettsyndrome.org/about-rett-syndrome/boys-with-rett/; Ramirez J, et al. *Physiol.* 2020;35:375-390.

Pathophysiology: Rett Syndrome

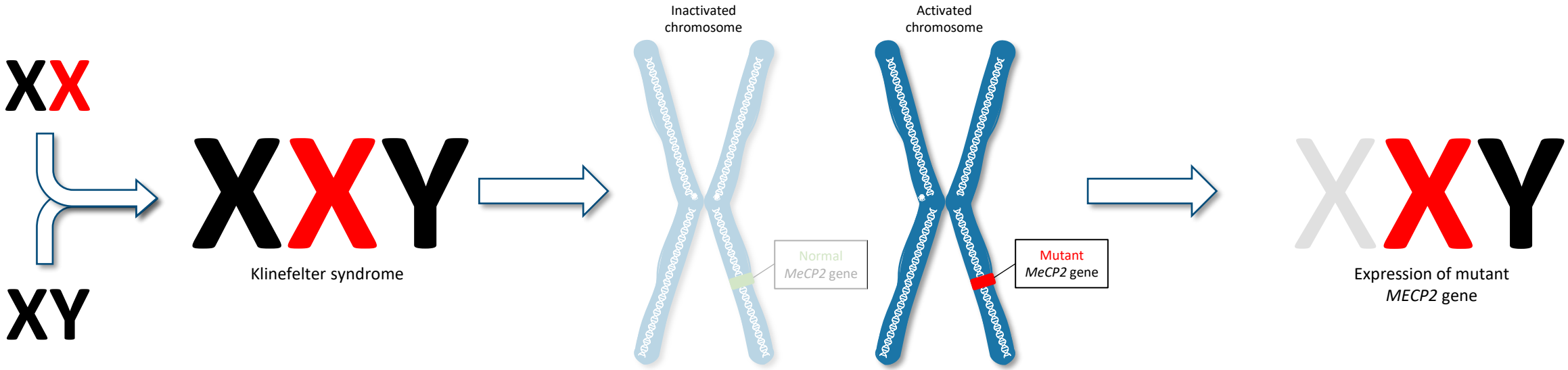
Female X chromosome inactivation



Torrice M. Reversing Rett Syndrome in Mice Gave Hope for Treatments. Chemical & Engineering News. Published December 18, 2017. Accessed February 24, 2023. https://cen.acs.org/articles/95/i49/look-back-at-2007.html

Pathophysiology: Rett Syndrome

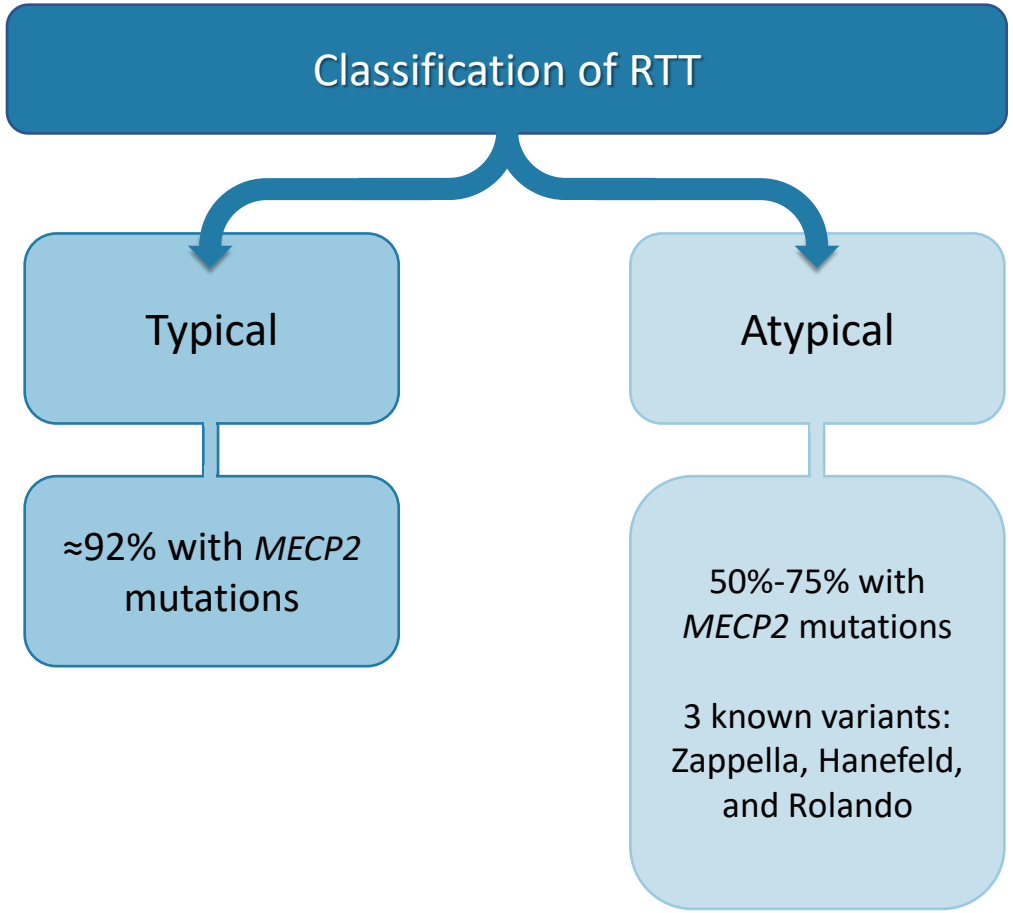
- Males with Klinefelter syndrome carry 2 copies of the X chromosome and 1 Y chromosome
  → Undergo X chromosome inactivation, as seen in females



Inuzuka LM, et. al. *European J of Paediatric Neurology.* 2021;34:7-13; Kinjo K, et. al. *Molecular and Cellular Pediatrics.* 2020;7:1.

Classification of Rett Syndrome

- *MECP2* genetic link to Rett syndrome (RTT) first discovered in 1999
  - To date, RTT largely remains a clinical diagnosis
  - *MECP2* mutations alone are insufficient for an RTT diagnosis
- Average age of diagnosis: 2.5 years



Fu C, et al. *BMJ Paediatr Open*. 2020;4:e000717; Ramirez J, et al. *Physiol*. 2020;35:375-390; Neul JL, et al. *Ann Neurol*. 2010;68(6):944-950.

Diagnosis: Typical vs Atypical Rett Syndrome

Typical RTT must meet the following criteria:

1. A period of regression followed by recovery or stabilization
2. **All** 4 main criteria and **both** exclusion criteria
3. Supportive criteria not required although often present for typical RTT

Atypical RTT must meet the following criteria:

1. A period of regression followed by recovery or stabilization
2. At least **2** of **4** main criteria
3. **5** of **11** supportive criteria

Main

1. Partial/complete loss of acquired purposeful hand skills
2. Partial/complete loss of acquired spoken language
3. Gait abnormalities: impaired or absence of ability
4. Stereotypic hand movements: hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms

Exclusion

1. Brain injury secondary to trauma (peri or postnatally), neurometabolic disease, or severe infection that causes neurological problems
2. Grossly abnormal psychomotor development in first 6 months of life

Supportive

1. Breathing disturbances when awake
2. Bruxism when awake
3. Impaired sleep pattern
4. Abnormal muscle tone
5. Peripheral vasomotor disturbances
6. Scoliosis/kyphosis
7. Growth retardation
8. Small cold hands and feet
9. Inappropriate laughing/screaming spells
10. Diminished response to pain
11. Intense eye communication – "eye pointing"

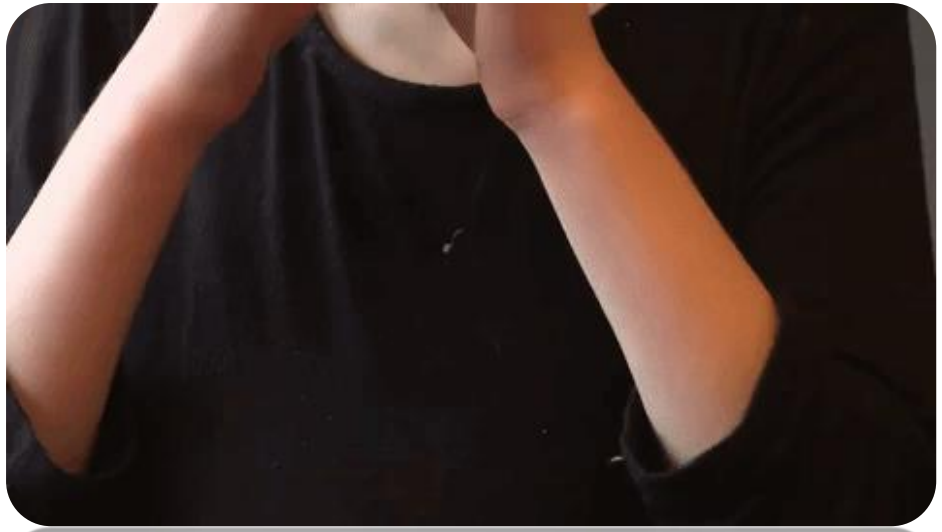
Neul J, et al. *Ann Neurol*. 2010;68(6):944-950.

Hallmark Symptoms

4 main categories

- Cognitive impairment
- Communication dysfunction
- Stereotypic movements*
- Pervasive growth problems

*hallmark symptoms



Roidi M, et al. *Child Care Health Dev*. 2019;45:417-22; Rett Syndrome News. Stages of Rett syndrome. Accessed February 24, 2023. https://rettsyndromenews.com/stages-of-rett-syndrome/; Cincinnati Children's. Rett Syndrome: A Mother's Perspective and Advice. Accessed on March 5, 2023. https://blog.cincinnatichildrens.org/rare-and-complex-conditions/rett-syndrome-mothers-perspective-advice/

Other Symptoms and Comorbidities

Poor growth

Stereotypic hand movements

Osteoporosis

Epilepsy

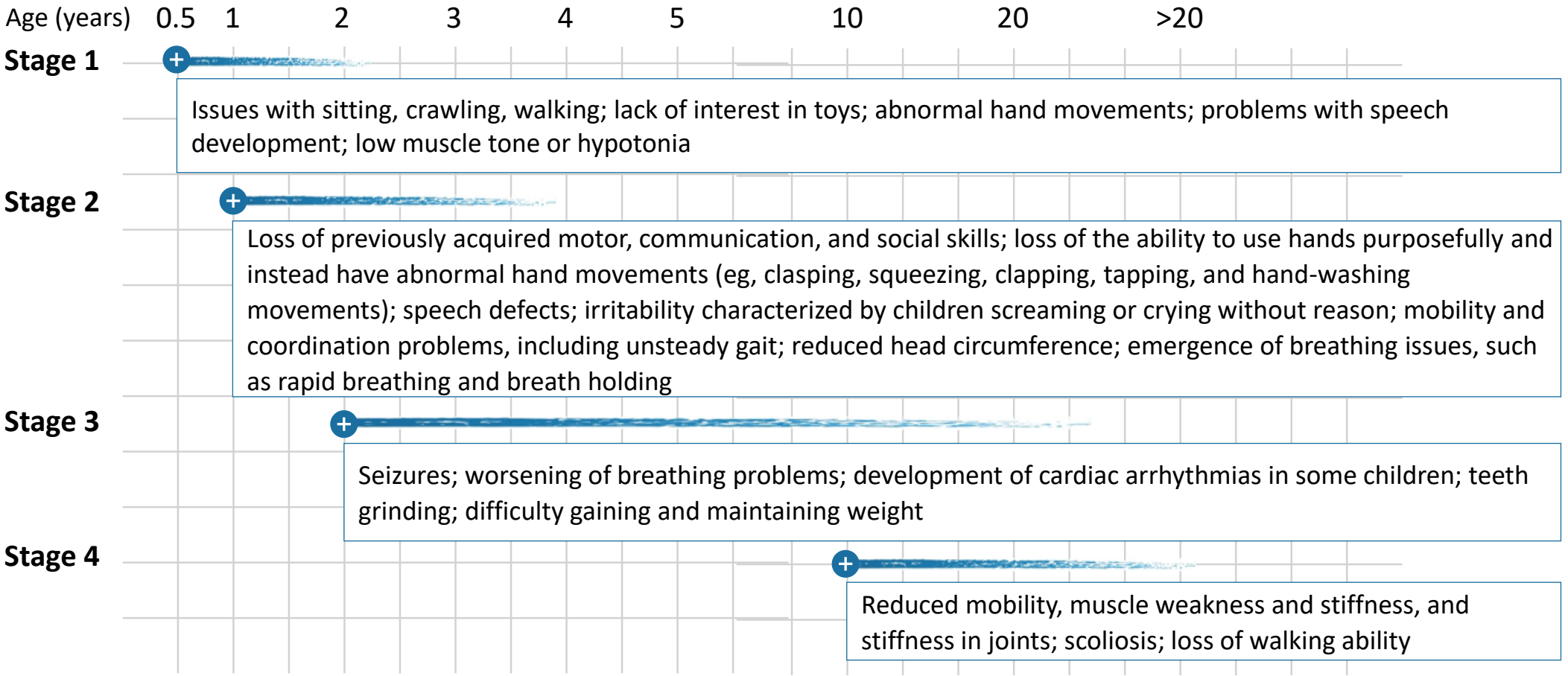
Constipation

Breathing **irregularity**

Shorter life expectancy through the 4th and 5th decades

Roidi M, et al. *Child Care Health Dev.* 2019;45:417-422; Kirby R, et al. *J Pediatr*. 2010;156(1):135-138.

Symptom Evolution



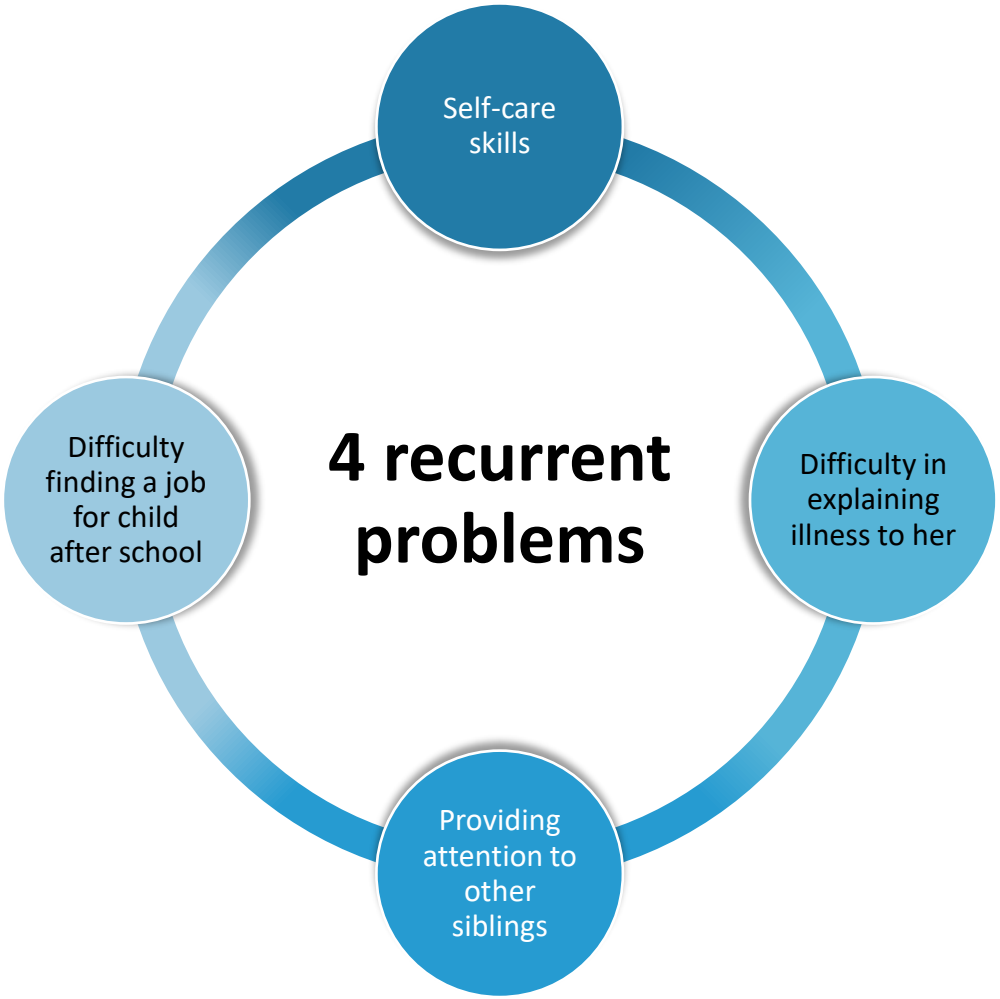
Rett Syndrome News. Stages of Rett syndrome. Accessed February 24, 2023. https://rettsyndromenews.com/stages-of-rett-syndrome/

Disease Burden

2016 study on the quality of life of girls with RTT, and their families

Impact of Childhood Illness Scale
(30 questions divided into 4 sections)

Impact of illness and its treatment (questions 1-5)	Impact on development and child's adjustment (questions 6-15)	Impact on parents (questions 16-20)	Impact on the family (questions 21-30)



Parisi L, et al. *Mental Illness*. 2016;8(6302):5-9.

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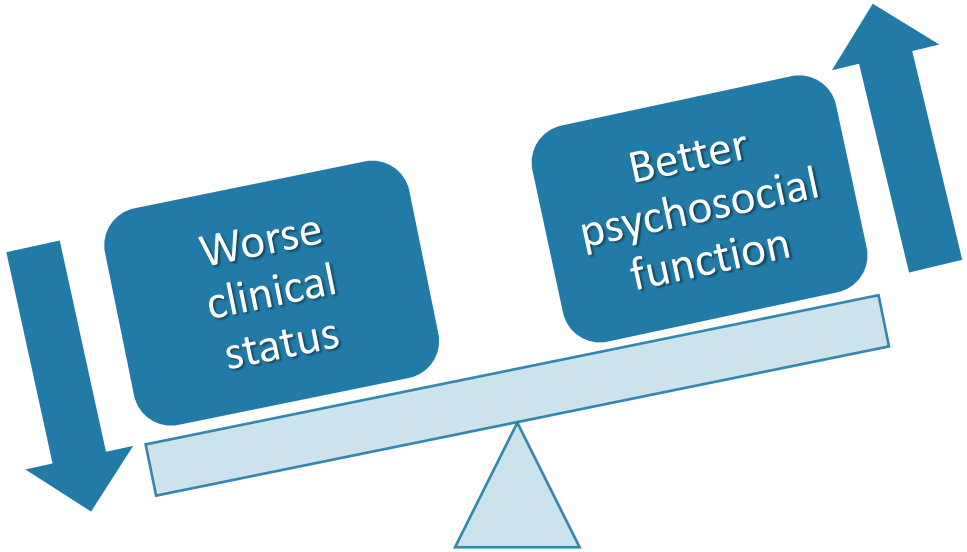
Disease Burden

2016 study

- Studied the physical and mental quality of life over a 5-year period
- More severe disease was associated with poorer physical health component scores ($P = 0.006$) but improved mental health component scores ($P = 0.003$)
- Feeding difficulties were associated with poorer caretaker physical health component scores ($P = 0.007$) and mental health component scores ($P = 0.018$)

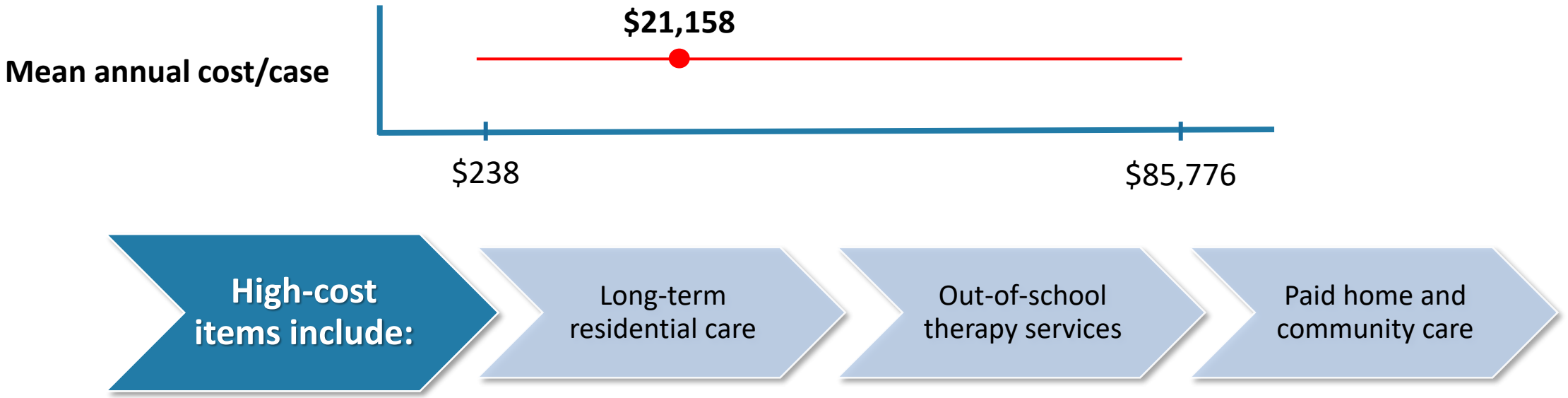


Killian JT, et al. *Pediatr Neurol*. 2016;58:67-74.

Financial Burden

Measuring use and cost of health sector and related care in a population of girls and young women with RTT

- Australian Rett Syndrome Database in 2004



Hendrie D. *Res Autism Spectr Disord*. 2011;5(2):901-909.

Financial Burden

2 systemic literature reviews on the economic burden of care and treatment options for patients with RTT

Enteral feeding ↑ risk of respiratory-related hospital admissions (ARR, 1.79; 95% CI, 1.21-2.65)	Inability to walk independently was associated with 6-fold ↑ risk of respiratory-related hospital admissions (AR, 6.73; 95% CI, 3.42-13.25)	Frequent hospitalizations due to pneumonia, respiratory distress, status epilepticus, rectal bleeding, decline in ambulation, refusal/inability to eat/drink

ARR = adjusted relative risk

Fu C, et al. *BMJ Paediatr Open*. 2020;4:e000717; Dabbous O, et al. Economic burden of care and treatment options for patients with Rett syndrome: two systematic literature reviews. 10th European Conference on Rare Diseases & Orphan Products 2020; May 14-16, 2020.

Current Guidelines for Management

Alan Percy, MD

Rett Syndrome
Longevity

- Overall longevity double Andy Rett's original group

Age in years	% survival
0-10	normal
20	90
30	>75
40	>65
50	>50

Kirby et al., J Pediatr 2010;156:135-138.

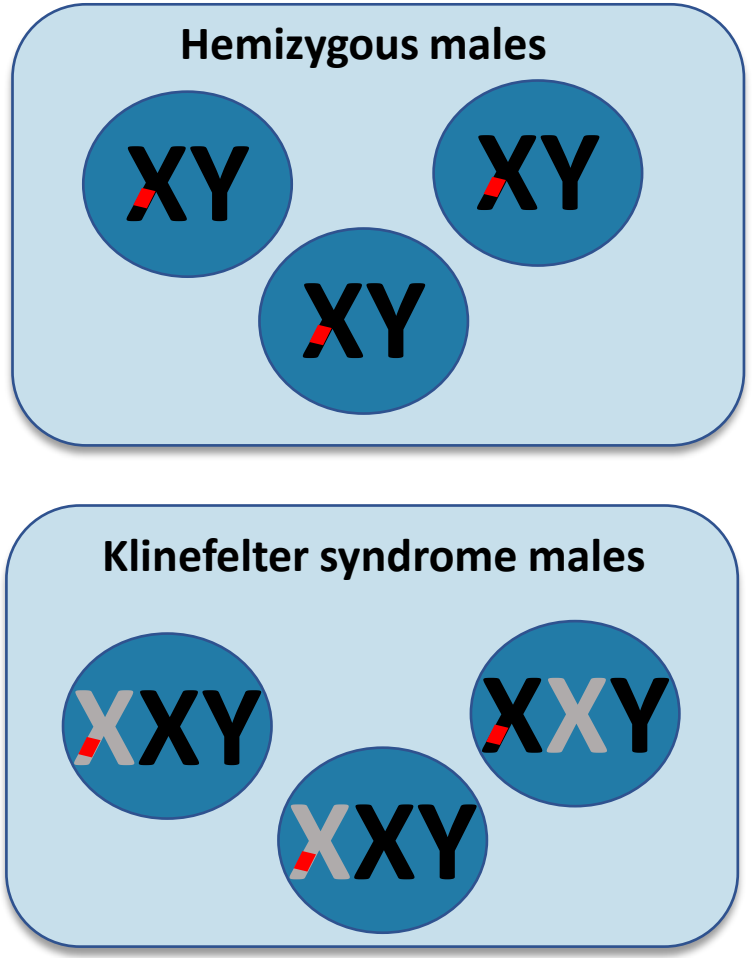
Mortality in Males

Initially thought to be lethal in males

Males who are hemizygous for *MECP2* mutations have an expected lifespan of ≈2 years

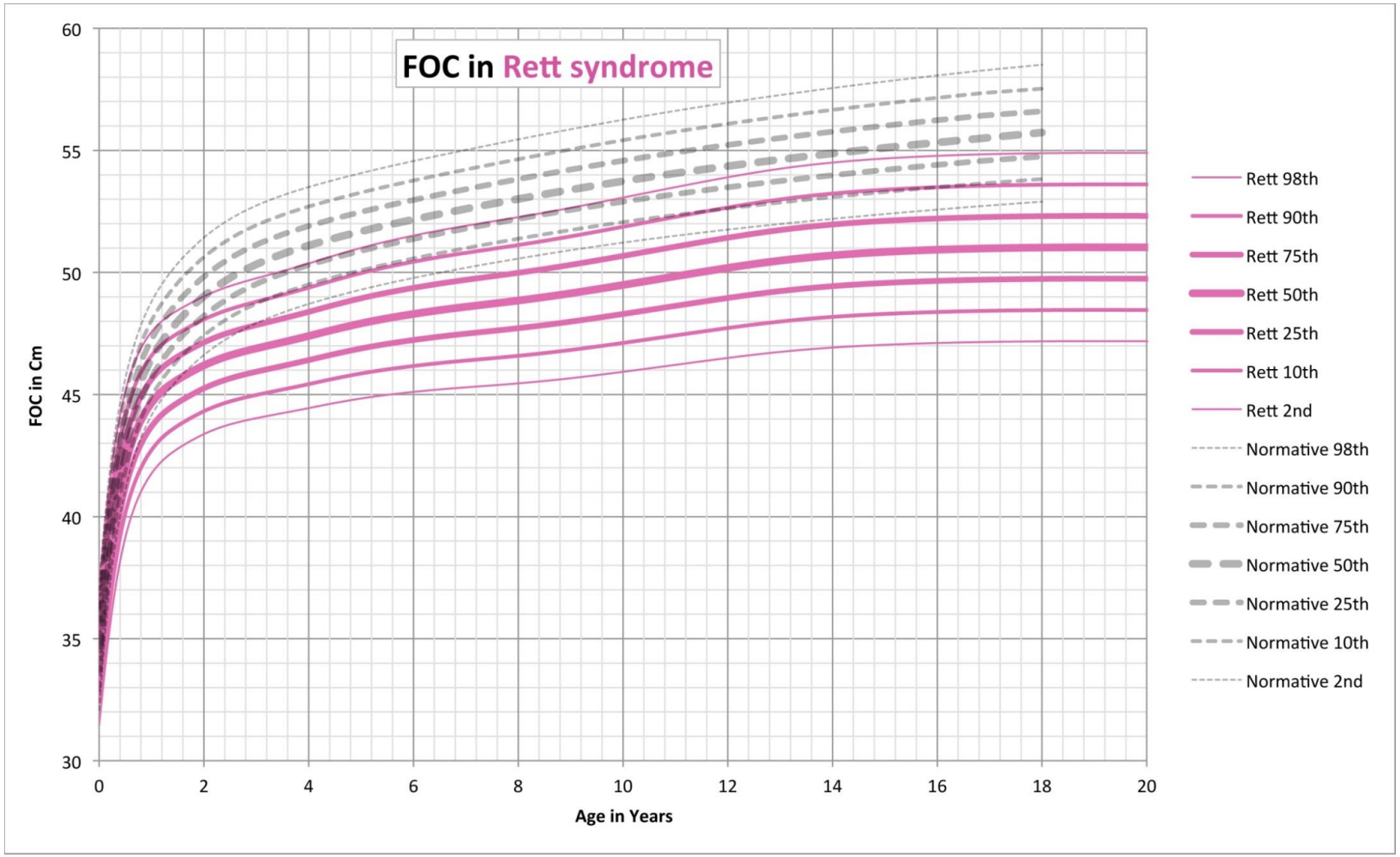
- Somatic mosaicism
- Typically develop congenital encephalopathy
- Can survive into late childhood with aggressive medical care

Males with Klinefelter syndrome (extra X chromosome) may present with a milder phenotype and survive into adulthood



Villard L. *J Med Genet*. 2007;44:417-423; Na E, et al. *Horm Behav*. 2011;59(3):364-368; Skinner, et al. Males with MECP2 mutations. International Rett Syndrome Foundation. Accessed February 24, 2023. https://www.rettsyndrome.org/about-rett-syndrome/boys-with-rett/

Head Growth



Tarquinio DT et al., Neurol 2012;79:1653-1661.

Rett Syndrome
Co-morbidities

- Cognitive impairment – 100%
- Epilepsy - 90%
- Gastrointestinal Issues – 80%
- Ambulation – ~50%
- Self-abuse – ~20%
- Cold hands and feet – 50-70%
- Growth failure – 90%
- Breathing abnormalities – 95%
- Scoliosis – 80-85%
- Sleep – 80-90%
- Bruxism (teeth grinding) – ??
- Dystonia – 60-80%
- Others include cardiac, endocrine, and bone health issues

Fu C et al. BMJ Paediatr Open. 2020;4:e000731 DOI 10.1136/bmjpo-2020-000731

Rett Syndrome
Consensus Guidelines

Due to rare occurrence of RTT, primary care providers and other health professionals may have significant limitations providing appropriate care

Consensus guidelines generated to aid this issue

Guidelines promote integration of care across the range of primary and subspecialty providers

Offer age-based guides for managing range of issues

Fu C et al., BMJ Paediatr Open. 2020;4:e000717. DOI:10.1136/bmjpo-2020-000717

Specific Guidelines

- Genetics/*MECP2* testing: Current recommendations support genome-wide screening at time of first diagnosis
- If positive, parents should be tested for carrier status
- Family counseling on test results essential
- May require referral to genetic counselor
- Critical for primary care physicians and family to receive and maintain copy of test(s)

Fu C et al., BMJ Open. 2020;4:e000717. DOI:10.1136/bmjpo-2020-000717

Specific Guidelines - 2

As with any person, individuals with RTT require regular health wellness checks with general assessments and appropriate immunizations

Providers should recognize need for extra time due to complex issues

Parents and caregivers should maintain binder including all health records: clinic visits, genetic testing, growth assessments, and immunizations

Fu C et al., BMJ Paediatr Open. 2020;4:e000717. DOI:10.1136/bmjpo-2020-000717

Specific Guidelines -3

- Primary care provider should be the quarterback
- Provide annual visits and any acute care assessments
- General assessments should occur annually
- Review general health, medications, and allergies
- Check growth including height, weight, head circumference
- Evaluate Tanner stage
- Lab tests: CBC, metabolic profile, vitamin D level; ECG for prolonged QTc: refer to cardiologist if abnormal

Fu C et al., BMJ Paediatr Open. 2020;4:e000717. DOI:10.1136/bmjpo-2020-000717

Specific Guidelines - GI

- Screen for gastroesophageal reflux, delayed stomach emptying, and constipation
- Review feeding (~1/3 have a G-tube) including appetite, feeding time, and evidence of feeding difficulty
- Also, evaluate for bloating secondary to air swallowing
- Prescribe medications as indicated for above problems
- Annual follow-ups for any problems identified

Fu C et al., BMJ Paediatr Open. 2020;4:e000717. DOI:10.1136/bmjpo-2020-000717

Specific Guidelines - Pulmonary

Screen for awake breath-holding and hyperventilation

Screen for associated air swallowing and color change with prolonged breath-holding

Minimal evidence of effective medications to modify

Fu C et al., BMJ Paediatr Open. 2020;4:e000717. DOI:10.1136/bmjpo-2020-000717

Specific Guidelines - Neurology

Screen for presence of paroxysmal events	May be seizures or non-epileptic events	Caregiver should keep log of events; videos if possible	May require referral to neurologist
Diagnosis may require video-EEG monitoring	Anti-seizure management will require regular follow-up	Recommend every 6 months	Neurologist should assess muscle tone, dystonia, gait

Fu C et al., BMJ Paediatr Open. 2020;4:e000717. DOI:10.1136/bmjpo-2020-000717

Specific Guidelines - Orthopedics

Referral based on curvature as early as preschool age

May require spine X-ray: should be supine, not sitting

If >20°, follow-up every 6 months

Consider surgery if >40°

Additional issues include hip position, contractures, and dystonia

Fracture risk should be discussed; as many as 30% non-accidental; may require bone density assessment

Fu C et al., BMJ Paediatr Open. 2020;4:e000717. DOI:10.1136/bmjpo-2020-000717

Specific Guidelines - Sleep

Review sleep pattern including initiation and maintenance	Interruption in sleep pattern frequent; may relate to hunger, GI issues – GE-reflux or constipation	Consider sleep study for snoring or disrupted breathing
Can check ferritin levels for disrupted sleep or restless legs	For sleep aids: trazodone, gabapentin recommended; antihistamines for short-term use	Review safety of bed/bedroom

Fu C et al., BMJ Paediatr Open. 2020;4:e000717. DOI:10.1136/bmjpo-2020-000717

Specific Guidelines - Others

Urologic issues: Urinary tract infections, frequency or hesitancy

Pain tolerance: Typically high – can mask fractures, injuries

Extremity temperatures: hand and feet often cool or mixed

Skin integrity: often follows hand mouthing or self-biting

Behavior: self abuse or abusing others; anxiety: recommend escitalopram or other SSRIs

Review current IEP, guardianship, conservatorship

Fu C et al., BMJ Paediatr Open. 2020;4:e000717. DOI:10.1136/bmjpo-2020-000717

Age-based Recommendations

- Early childhood: attention to growth, nutrition, GI issues
- Late childhood: regression ended; multisystem issues
- Adolescence: puberty, scoliosis, seizures, nutrition
- Adulthood: post-school daycare, bone health, motor issues
- Lifelong: Assess therapy programs: physical, occupational, speech/language: augmentative communication
- Assess need for group home or other care provider

Fu C et al., BMJ Paediatr Open. 2020;4:e000717. DOI:10.1136/bmjpo-2020-000717

Conclusions

Rett syndrome is a complex, progressive neurodevelopmental disorder with prolonged survival

Multiple health issues require a multidisciplinary approach

Attention to consensus guidelines is critical for long-term health maintenance.

Fu C et al., BMJ Paediatr Open. 2020;4:e000717. DOI:10.1136/bmjpo-2020-000717

Current Treatment Limitations

Alan Percy, MD

Treatments for Rett Syndrome

- Treatment for Rett syndrome is multifactorial
- Based primarily on symptomatic management to promote optimal health
- Specific therapeutic strategies based on recent clinical trial results and additional clinical trials
- Involve pharmaceutical products and gene therapies

Percy AK. Health Care for People with Intellectual and Developmental Disabilities across the Lifespan, 3rd ed, Rubin, Merrick, Greydanus, Patel. Springer. 2016. DOI 10.1007/978-3-319-18096-0.

Rett Syndrome: Symptomatic Therapies

- Epilepsy: Multiple agents: valproic acid, lamotrigine, oxcarbazepine, levetiracetam among others
- GE-reflux: H_2-blockers and proton pump inhibitors
- Constipation: polyethylene glycol, magnesium sulfate, senna among others
- Sleep: trazodone, gabapentin, melatonin, clonazepam, clonidine
- Nutrition: Nutritional formulas, vitamins incl. D

Personal communication

Rett Syndrome: Recent Clinical Trials

- Neuren/Acadia – Trofinetide – phase III
- Anavex – phase II/III
- Investigator-initiated – Ketamine – phase II
- Newron – Sarizotan – phase II/III – failure

Personal communication

Rett Syndrome: Key Caregiver Concerns

- Among the caregiver concerns, five stand out as critical across the disease and age spectrum
- The top five concerns are communication, seizures, hand function, ambulation, and constipation
- Communication is highlighted as fundamental to managing care throughout daily activities including school

Neul JL et al. Personal communication, 2023

Rett Syndrome: Outcome Measures

- Clinical Global Impression Scales of Severity and Improvement
- Clinician generated: 7-point Likert scales, accepted by FDA/EMA
- Must establish rater reliability: training and reliability assessment

Score	CGI-S (Severity)	CGI-I (Improvement)
1	Normal (not ill)	Very much improved
2	Borderline ill	Much improved
3	Mildly ill	Minimally improved
4	Moderately ill	No change
5	Markedly ill	Minimally worse
6	Severely ill	Much worse
7	Extremely ill	Very much worse

Neul JL, et al. J Ch Neurol 2015;30(13):1743-1748

Rett Syndrome: Outcome Measures

- Rett Syndrome Behavioral Questionnaire
- Caregiver reported, 45 items, 3-point Likert scale
- Based on co-morbidities prevalent in RTT
- Pros
  - Undergone psychometric evaluation (factor analysis, test-retest)
  - Simple to complete
  - Accepted by FDA/EMA
- Cons
  - Does not cover all domains of interest
  - Limited response range (not at all, sometimes, always)
  - Concerns about some psychometric elements

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Neul JL, et al. J Ch Neurol 2015;30(13):1743-1748

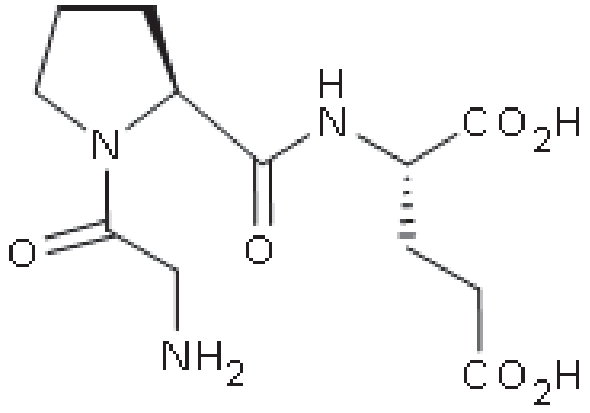
Rett Syndrome: Other Measures

- Breathing assessment with band plethysmography
- Gait assessment Video-based assessment
- Development of new clinician outcome measure from the Rett Syndrome Motor Behavior Assessment (MBA)
- Developed in 1990 by Fitzgerald, Percy, and Jankovic
- From RTT Natural History Study data (1075 participants), original 37 items reduced to 21 items plus 3 additional clinically important items by factor analysis: termed the Revised MBA (R-MBA)
- Internal consistency good (overall Cronbach's α=0.78)
- Correlated well with parent reports of clinical domains (validity)

Neul JL, et al. J Ch Neurol 2015;30(13):1743-1748

Rett Syndrome: Clinical Trials

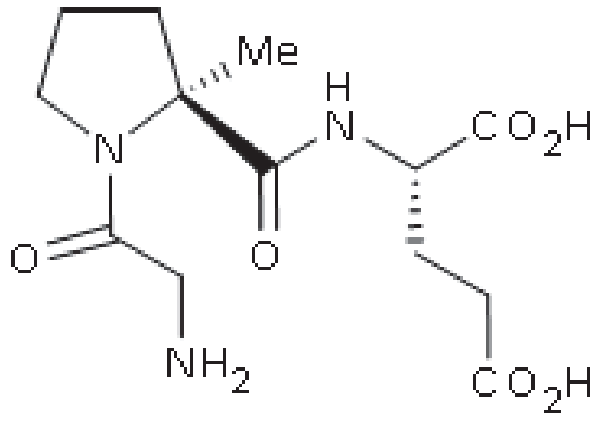
- Partial reversal of Rett Syndrome-like symptoms in MeCP2 mutant mice
- Based on co-morbidities prevalent in RTT
- Male *Mecp2* mice treated with tripeptide from N-terminus of IGF-I: IGF-I [1-3] = Gly-Pro-Glu



Tropea D et al. PNAS 2009:106(6):2029-2034

Rett Syndrome: Clinical Trials

- Initial human trial with full-length IGF-1 (mecasermin) showed no efficacy
- Two phase 2 trials (one in adults, the other in children) by Neuren Pharmaceuticals showed the modified product, Trofinetide, was safe, well-tolerated, and showed positive signal on CGI-I and RSBQ
- Methyl group allowed
- Preparation of oral agent



Glaze DG et al. Pediatr Neurol 2017;76:37-46; Glaze DG et al. Neurol 2019;92:e1912-e1925. DOI: 10.1212/WNL.0000000000007316

Rett Syndrome: Trofinetide

- Trofinetide Phase 3:
- Double-blind, placebo-controlled: 94 in placebo arm; 93 in treatment arm; baseline characteristics similar
- After 12 weeks, trofinetide showed statistically better results on CGI-I and RSBQ than control group, Cohen's d effect sizes of 0.47 and 0.37, respectively
- Communication significantly improved as well
- Side effects: diarrhea in ~80% and vomiting 27% in treatment arm; 19.2% and 9.6%, respectively, in placebo group; most mild or moderate

Neul JL et al. Poster Presented at Child Neurology Society Meeting October 2022.

Rett Syndrome: Trofinetide/DayBue

- FDA granted approval on March 11, 2023
- First approved disease-modifying pharmaceutical for a rare neurodevelopmental disorder
- Expect marketing to have begun by May 1, 2023

Personal communication

Rett Syndrome: Blarcamesine

- Placebo-controlled phase 2/3 trial and a phase 3 trial, both in adults
- ANAVEX-273: muscarinic and sigma 1 receptor agonist
- Results from Phase 2/3 trial demonstrated safety and tolerability with significant benefit on CI-I and RSBQ
- Results from ongoing phase 2/3 trial not known
- No word on potential FDA submission

Rett Syndrome: Gene Replacement Trials

- Critical study in 2007 indicated reversal of neurological deficits in a mouse model of RTT
- Phenotypic improvements were impressive in young and mature mice
- Subsequent studies established AAV9 vector mediated transfer in mice and non-human primates yielding reasonable penetration of the brain and brainstem
- Two companies have or expect to receive approval for clinical trials: Taysha trial in Canada; Neurogene trial in US

Guy J et al. Science 2007;315(5815):1143-1147; Taysha January 2023 www.tayshgtc.com; Neurogene , Inc. January 2023 www.neurogene.com

Role of the Specialty Pharmacist in Improving Outcomes in Rett Syndrome

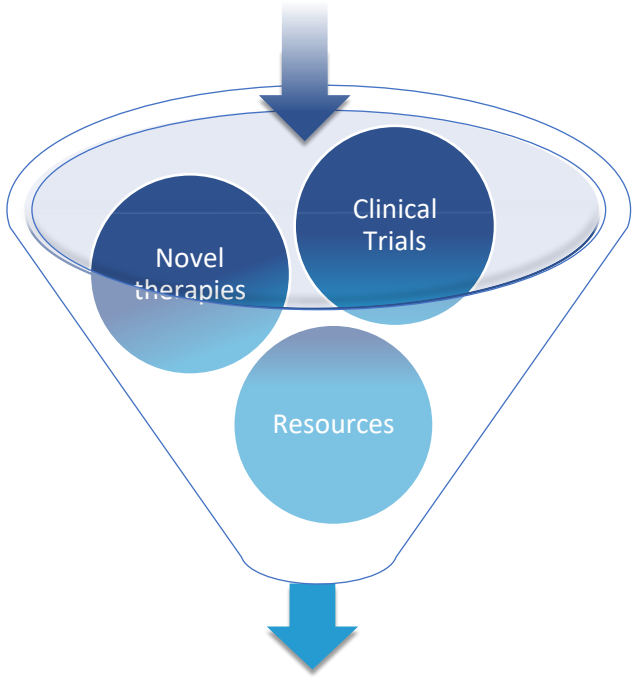
Abigail Jastrab, PharmD, BCPS

Rare Disease Treatment Gaps

FDA-approved therapies

- Less than 10% of rare diseases have an FDA-approved treatment option
- Greater than 90% of rare diseases are without an FDA-approved therapy
- In 2022, 54% of novel drug approvals were for rare disease

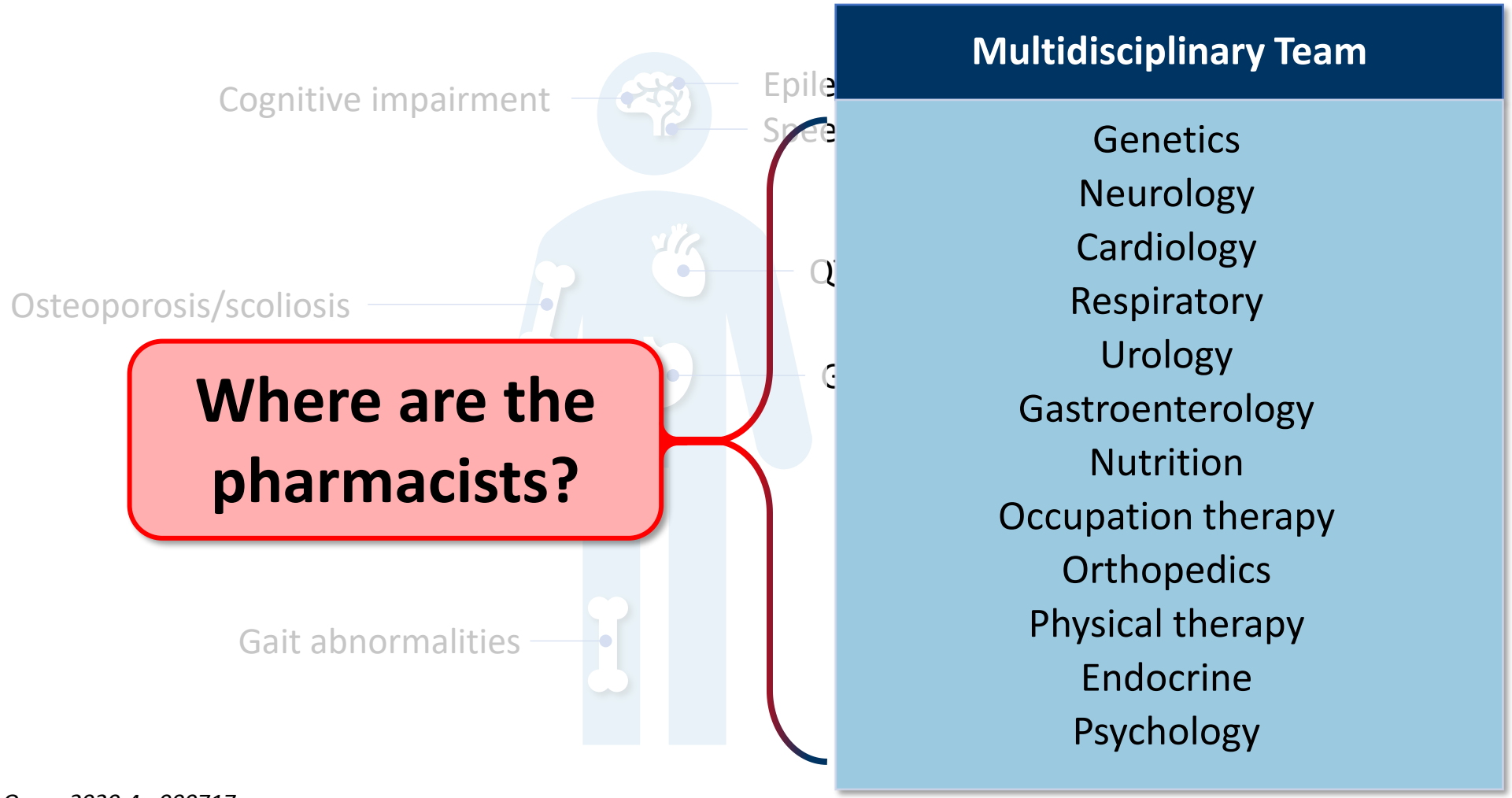
No FDA-approved treatments



FDA-approved treatment options

FDA. New drug therapy approvals 2022. Updated January 10, 2023. Accessed February 24, 2023. https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/new-drug-therapy-approvals-2022; New study investigates the number of available orphan products, generics and biosimilars. Published March 24, 2021. Accessed February 24, 2023. https://rarediseases.org/new-study-investigates-the-number-of-available-orphan-products-generics-and-biosimilars/; PANTHERx Rare Pharmacy. Rare pharmacy emerges from specialty (pharmacy). Accessed February 24, 2023. https://prx.pantherxrare.com/rarepharmacywhitepaper

Pharmacist Role in Treatment Management



Fu C, et al. *BMJ Paediatr Open. 2020;4:e000717.*

PTce

Guiding Treatment Selection

Medically managed symptoms of RTT

Constipation (affects 80%)

Treatment options: Laxatives (polyethylene glycol, magnesium hydroxide, glycerin or bisacodyl suppositories)

Pharmacist considerations

- Route of administration and drug-drug interactions
- Constipation induced by other medications

GERD (affects 39%)

Treatment options: Proton pump inhibitor or H2 blockers are used empirically

Pharmacist considerations

- Route of administration and drug-drug interactions
- Heartburn induced by other medications

GERD, gastroesophageal reflux disease.

Baikie G, et al. *Gastroenterology*. 2014;58:237-244.

PTce

Guiding Treatment Selection

Medically managed symptoms of RTT

Epilepsy (affects 60-80%):

Treatment options: carbamazepine; valproate; lamotrigine; levetiracetam; oxcarbazepine; and topiramate depending on seizure type.

Considerations

Route of administration and drug-drug interactions

Adverse effect (AE) profile

- Weight/appetite loss: valproic acid (weight ↑↓), topiramate
- Nausea: ↑ with carbamazepine
- Vomiting: ↑ with valproic acid
- Heartburn/GERD: ↑ with carbamazepine, phenobarbital

Krajnc N. *Ther Clin Risk Manag.* 2015;11:925-932; Jahromi S, et al. *Seizure.* 2011;20:343-346; Glaze DG, et al. *Neurology.* 2010;74:909-912.

Guiding Treatment Selection

Medically managed symptoms of RTT

Prolonged QTc: possible treatment with β-blockers if persistent

Considerations:

- Reserved for patients who are determined by a pediatric cardiologist to have long QT, and the best treatment approach is routine follow-up and avoidance of QTc-prolonging medications
- Drug interactions and route of administration
- Review other QTc prolonging medications and alert the multidisciplinary team as appropriate

Osteoporosis: supplemental vitamin D intake: 600-1000 IU or more daily

Considerations

- Ensure age-appropriate 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 intake
- Drug interactions and route of administration
- Review for chronic medications contributing to low bone mineral density (eg, certain antiepileptic drugs)

Fu C, et al. *BMJ Paediatr Open.* 2020;4:e000717; Crosson J, et al. *An J Med Genet A.* 2017;173(6):1495-1501.

Pharmacist Role on The Multidisciplinary Team

- Pharmacologic expertise to navigate treatment options
- Guide physicians with off-label prescribing
- Remain updated on evolving guidelines and novel therapies to guide therapy selection
- Address and communicate patient-specific barriers
- Final step between the providers prescribing medication and the patient receiving it

Waszyk-Nowaczyk M, et al. *J Multidiscip Healthc.* 2021;14:2101-2110; Basak R, et al. *Social Science & Medicine.* 2015;132:181-189; Ilardo ML and Speciale A. *Int. J. Environ. Res. Public Health*. 2020;17:536.

Trofinetide Counseling Pearls

Trofinetide

- Large multidose bottle store under refrigeration
- Oral solution: 200 mg/mL
- Indicated in ≥ 2 years of age
- Stop laxatives prior to starting

Counseling points

- May need to solve for storage solutions
- Weight-based dosing given twice daily
- Most common AEs: diarrhea, vomiting
- Monitor: 1) nutrition, 2) dehydration, 3) skin breakdown, 4) guide on antidiarrheal use, 5) dose adjustments for AE's or weight changes

Glaze DG, et al. *Neurology.* 2019;92(16):e1912-1925.

Potential Blarcamesine Counseling Pearls

Blarcamesine

- Liquid oral solution dosed up to 30 mg once daily
- Treatment-emergent AE rates similar to placebo

Counseling points

- Most common AE: dizziness
  - Monitor: fall risk
- Clinical trials also underway for infantile spasms → may need to monitor for any changes needed to antiepileptic regimen

Anavex Life Science. Anavex 2-73 Avatar phase 3 trial met primary and secondary efficacy endpoints. Published February 1, 2022. Accessed February 24, 2023. www.anavex.com/post/anavex-2-73-blarcamesine-avatar-phase-3-trial-met-primary-and-secondary-efficacy-endpoints; ANAVEX2-73 study in pediatric patients with rett syndrome (EXCELLENCE). ClinicalTrials.org. Updated February 8, 2023. Accessed February 24, 2023. https://clinicaltrials.gov/ct2/show/NCT04304482; Anavex Life Science. Anavex 2-73 phase 2b/3 study met primary and key secondary endpoints. Published December 1, 2022. Accessed February 24, 2023. www.anavex.com/post/anavex-2-73-blarcamesine-phase-2b-3-study-met-primary-and-key-secondary-endpoints; Anavex Life Science. Therapeutic candidates. Accessed February 24, 2023. www.anavex.com/therapeutic-candidates

Educating on New and Evolving Treatment Options

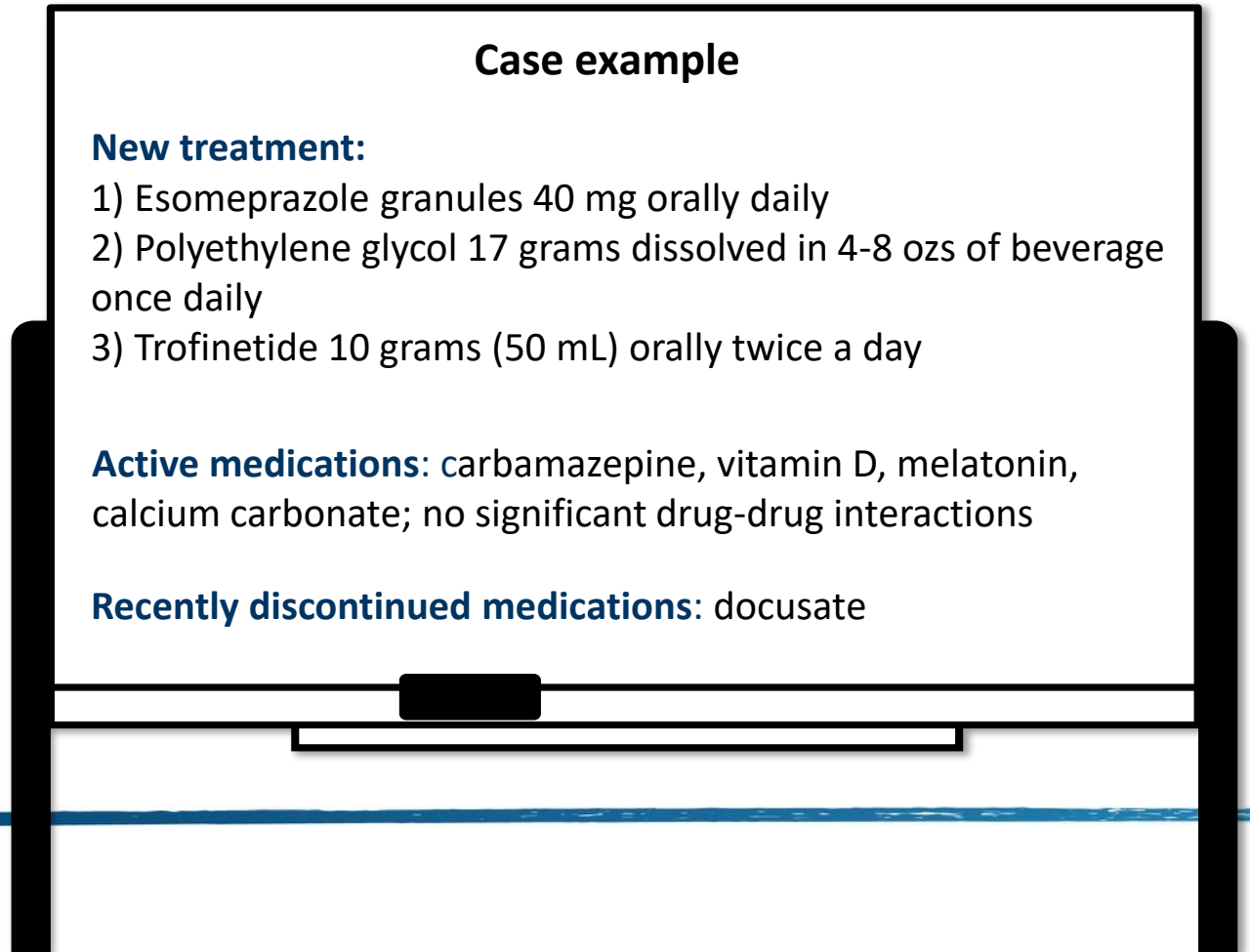
EB is a 12-year-old girl with typical RTT (weight: 36 kg)

Case example

New treatment:
1) Esomeprazole granules 40 mg orally daily
2) Polyethylene glycol 17 grams dissolved in 4-8 ozs of beverage once daily
3) Trofinetide 10 grams (50 mL) orally twice a day

Active medications: carbamazepine, vitamin D, melatonin, calcium carbonate; no significant drug-drug interactions

Recently discontinued medications: docusate



Additional information learned after further inquiry…

→ Significant heartburn previously controlled with OTC calcium carbonate 3x a day-4x a day as needed

→ Worsening constipation previously controlled

Educating on New and Evolving Treatment Options

Pharmacist potential interventions

- Inquire about carbamazepine due to association with significant heartburn
- Chronic calcium carbonate can lead to worsening constipation, but patient should be taking calcium and vitamin D
- Educate patient and provider on AE profile of trofinetide and how that may impact treatment plan

Pharmacist outreach to provider

- Monitor heartburn
- Discontinue calcium carbonate, and consider combination calcium-vitamin D product
- Educate on AE profile on trofinetide and recommend to discontinue polyethylene glycol

Case example

EB is a 12-year-old girl with typical RTT (weight: 36 kg)

Jahromi S, et al. *Seizure.* 2011;20:343-346; Fu C, et al. *BMJ Paediatr Open. 2020;4:e000717;* Naciu AM, et. al. *JBMR.* 2022;37(7): 1251-1259.

Monitoring of AEs and Response to Therapy

Refilling treatment

Trofinetide 10 grams (50 mL) orally twice a day

Active medications

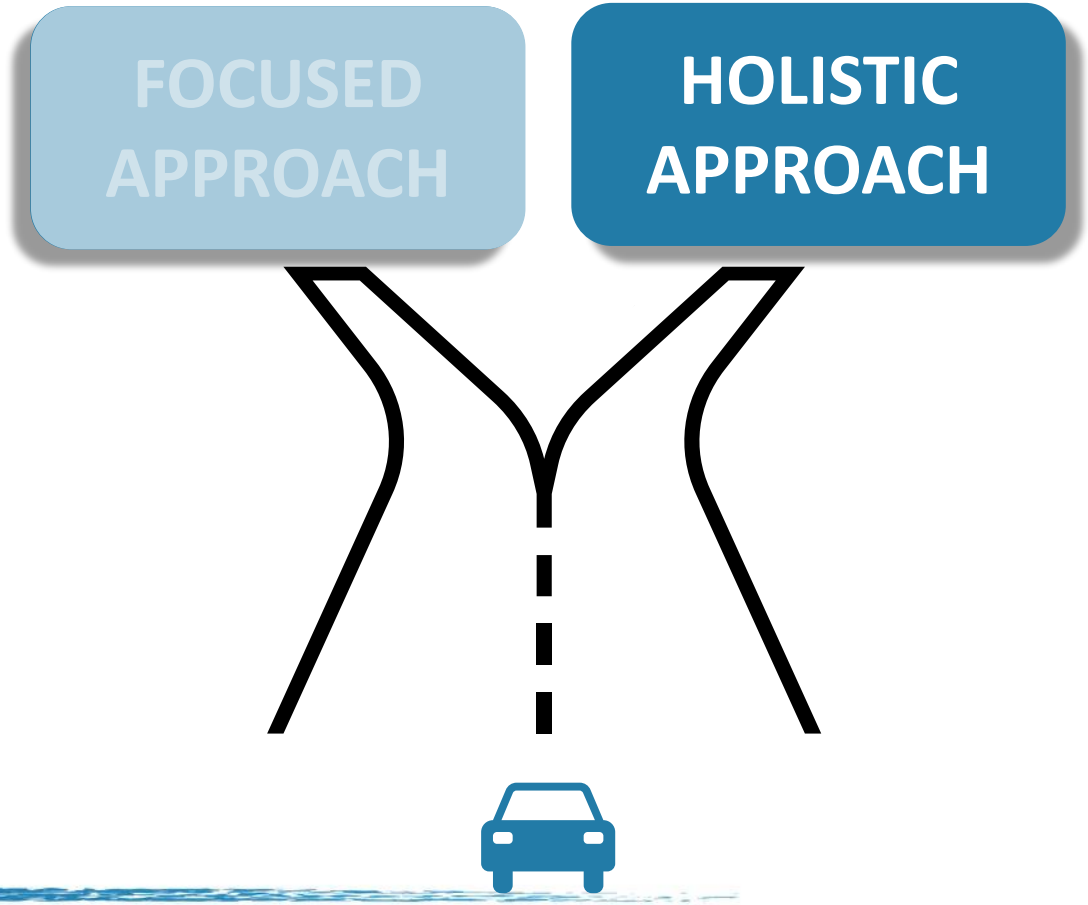
- Trofinetide
- Esomeprazole
- Carbamazepine
- Calcium/vitamin D
- Melatonin
- (No drug interactions)

Discontinued medications

- Polyethylene glycol
- Calcium carbonate

New weight

32 kg



Case example

EB is a 12-year-old girl with typical RTT (weight: 36 kg)

Monitoring of AEs and Response to Therapy

Focused approach

Alert provider of ↓ weight and get new treatment for dose ↓

RTT may present with an abundance of comorbidities and therapeutic complexities; and therefore, require a multidisciplinary care team approach

Holistic approach

Determine reason for weight loss

- → AE related (eg, diarrhea)?
- → Is nutrition or dehydration a concern?
- → If chronic diarrhea, are there wound care issues?
- → Are other medications causing the weight loss?

Make recommendations based on patient's unique needs

Case example

EB is a 12-year-old girl with typical RTT (weight: 32 kg)

Singh J and Santosh P. *Orphanet J Rare Diseases.* 2018;13:128

The Pharmacist's Role on the Patient Journey

Rare conditions present with complex treatment needs:

- Understanding medication dosing
- Administration
- Payor requirements
- 82% prescribed specialty therapies spent ≥1 hour on the phone coordinating care (≥one-third spending at least 3 hours)

It takes time to break down barriers!

PANTHERx Rare Pharmacy. Rare pharmacy emerges from specialty (pharmacy). Accessed February 24, 2023. https://prx.pantherxrare.com/rarepharmacywhitepaper; CoverMyMeds LLC. 2021 medication access report. Accessed February 24, 203. https://assets.ctfassets.net/70w6ftfzv4je/5slQIbN5JquiQpuBvRA7yA/f8b16f6a0ff1d57591f50cc63d007923/CMM_77721_MedicationAccessReport21_FINAL__1_.pdf

The Pharmacist's Role on the Patient Journey

Improving treatment access

- Access is already limited, with less than 10% of rare disease patients having access to FDA-approved treatment options
- 2019 NORD Survey: 61% of patients were denied or delayed in accessing treatments requiring pre-approval
- According to a 2021 statistic reported by CoverMyMeds: Up to 27% of new specialty Rx's are abandoned
- According to a 2022 statistic reported by CoverMyMeds: 84% of pharmacists are helping patients with benefit information in a given week
- Specialty medications account for ≈2% of prescriptions but represent ≈50% of total pharmacy expenditure

CoverMyMeds LLC. 2021 medication access report. Accessed February 24, 2023. https://assets.ctfassets.net/70w6ftfzv4je/5slQIbN5JquiQpuBvRA7yA/f8b16f6a0ff1d57591f50cc63d007923/CMM_77721_MedicationAccessReport21_FINAL__1_.pdf; NORD. New study investigates the number of available orphan products, generics and biosimilars. Published March 25, 2021. Accessed February 24, 2023. https://rarediseases.org/new-study-investigates-the-number-of-available-orphan-products-generics-and-biosimilars/; Vanscoy G, et al. Specialty pharmacy today: improving the lives of patients with rare diseases through orphan drug management. Pharmacy Times. Published September 11, 2017. Accessed February 24, 2023. www.pharmacytimes.com/view/specialty-pharmacy-today-improving-the-lives-of-patients-with-rare-diseases-through-orphan-drug-management. 2022 medication access report; CoverMyMeds LLC. 2022 medication access data guide. Accessed February 24, 2023. https://assets.ctfassets.net/70w6ftfzv4je/6E13LC9SBkokbavq06lUfZ/18d7d06a512c03f6a74ce52771f567b3/CoverMyMeds_2022MedicationAccess_DataGuide__1_.pdf; IQVIA. Medicine use and spending in the US. Published May 9, 2019. Accessed February 24, 2023. www.iqvia.com/insights/the-iqvia-institute/reports/medicine-use-and-spending-in-the-us-a-review-of-2018-and-outlook-to-2023; ASPE. Trends in prescription drug spending, 2016-2021. Published September 2022. Accessed February 24, 2023. https://aspe.hhs.gov/sites/default/files/documents/88c547c976e915fc31fe2c6903ac0bc9/sdp-trends-prescription-drug-spending.pdf

The Pharmacist's Role on the Patient Journey

Pharmacists are partners on the disease management journey	Untangle challenges
	Provide ongoing support
	Promote adherence to therapeutic regimens
	Educate patients and caregivers on disease and medication(s)

Putting patients first allows specialty-focused pharmacists to better support patients and achieve optimal patient experiences

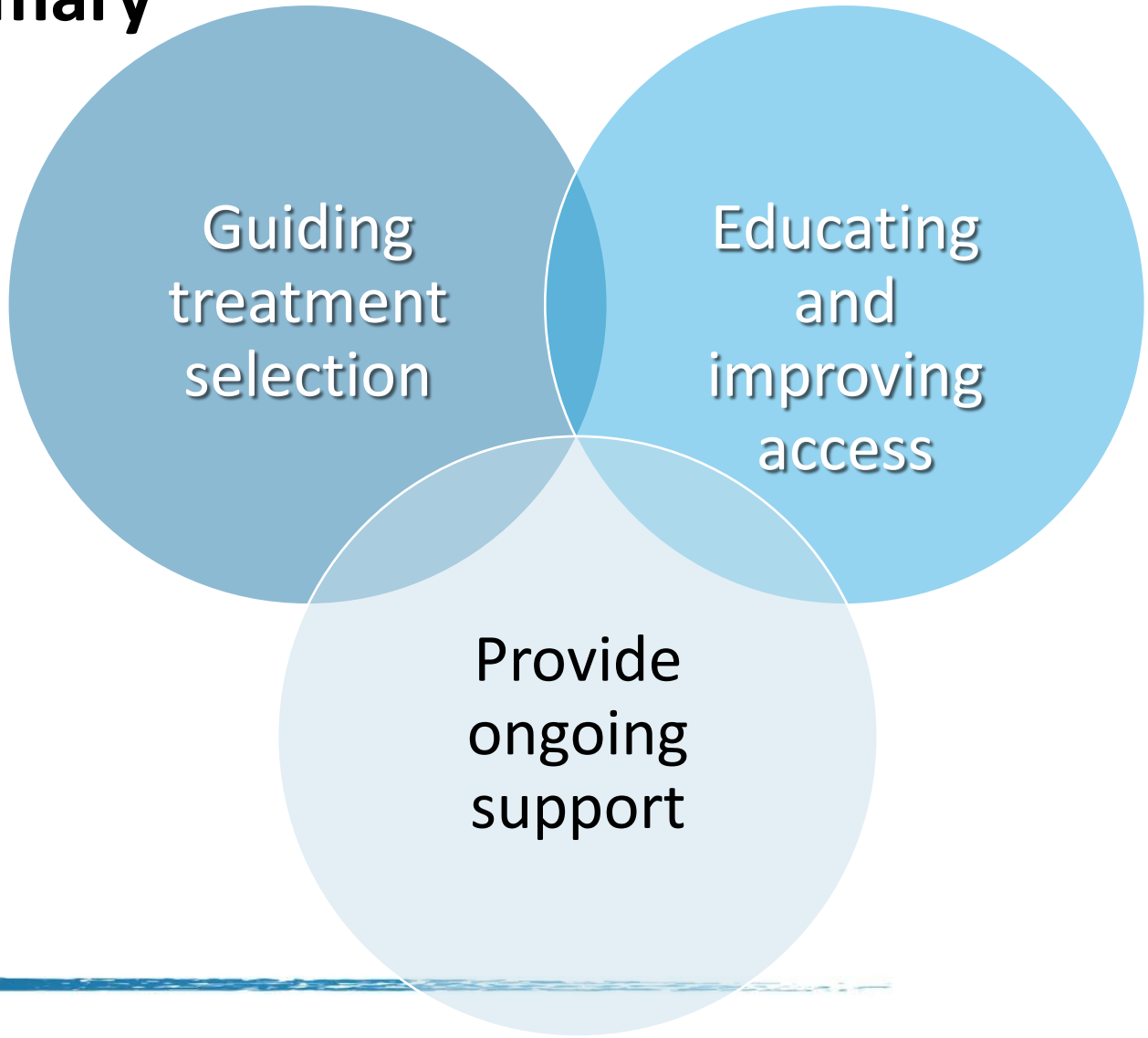
Zuckerman AD, et. al. *AJHP.* 2022;79:1906-1918.

The Pharmacist's Role on the Patient Journey

The Pharmacist's Role on the Patient Journey

Summary

Specialty pharmacists are essential to the RTT multidisciplinary team



Zuckerman AD, et. al. *AJHP.* 2022;79:1906-1918.

Conclusions

- Rett syndrome, a complex, progressive neurodevelop-mental disorder with prolonged survival, depends on symptomatic management
- Caregiver concerns list communication, seizures, hand function, ambulation, and constipation as top 5
- Current therapies address the overall core features of RTT
- Clinical trials have progressed with one agent, Trofinetide (DayBue) now receiving FDA approval
- Additional trials including gene therapy are on-going

Additional Resources

- International Rett Syndrome Foundation: rettsyndrome.org
- Rett Syndrome Research Trust: reverserett.org
- National Organization for Rare Disorders: rarediseases.org

Posttest Questions

Posttest Question 1

Which of the following accurately characterizes the clinical burden of disease for Rett syndrome?

A. Neurodegenerative condition with progressive loss of communication skills
B. Progressive neurodevelopmental disorder with multisystem symptom evolution overtime
C. Acute sleep disorder
D. Cognitive disorder only presenting with chronic intellectual disability

Posttest Question 2

The lifelong management of Rett syndrome is dependent on

A. the parent
B. the school system
C. multiple providers
D. social service programs

Posttest Question 3

The principal concern of parents in improving the life of their child relates to

A. Awake breathing patterns
B. Communication
C. Scoliosis
D. Pubertal development

Posttest Question 4

RS is a 12-year-old with classic Rett syndrome. Trofinetide has been newly prescribed by her neurologist. Her caregiver reports she is taking the following medications: polyethylene glycol, calcium/vitamin D, esomeprazole, and melatonin.

Which is the most important counseling point to provide RS and her caregiver?

A. Potential adverse effect of diarrhea and plan for polyethylene glycol
B. Category X interaction between trofinetide and esomeprazole
C. Contraindication of calcium and vitamin D supplements in Rett syndrome
D. Potential adverse effect of seizures and potential need for anticonvulsant therapy

Posttest Question 4

After participating in this activity, how confident are you in your knowledge of Rett syndrome and how to manage it?

A. Not at all
B. Somewhat
C. Moderately
D. Very
E. Extremely

Question and Answer Session

Thank you!