The IFCR Centers of Excellence: the Rett Clinic at Children’s Hospital Colorado

Standards of Care

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The Rett Clinic Team:
Scott Demarest MD; Margarita Saenz MD; Katie Angione MSGC;
Laura Watne MS RD, Margaret Spring MS OT, Meghan Roe M Ed,
CCC-SLP et al.
Disclosures

1. RO1 NS076577 (Benke)
   NIH/NINDS
   Molecular mechanisms linking early life seizures, autism and intellectual disability
   Role: PI.

2. Questcor Pharmaceuticals (Benke)
   Whole-exome sequencing and ACTH responsiveness in Infantile Spasms
   Role: PI.

3. 1U10NS077277(Vollmer)
   NIH/NINDS
   Rocky Mountain Network for Neuroscience Clinical Studies (NeuroNext Clinical Site)
   Role: Co-I.

4. U54 HD061222 (Percy)
   NICHD
   Rett syndrome, MECP2 Duplication Disorder, and Rett-related Disorders Natural History.
   Role: Site Director, Co-I.

5. Rett Clinic at Children’s Hospital Colorado (Benke)
   Rocky Mountain Rett Association
   Role: PI/Medical Director

6. CDKL5 Center of Excellence (Benke)
   International Foundation for CDKL5 Research
   Role: PI

7. Neuren: Study of trofinetide, also known as NNZ-2566, for females with Rett Syndrome
   Role: site PI
Topics today

• IFCR CDKL5 Centers of Excellence

• The Rett Clinic at Children’s Hospital Colorado
  • Clinic profile
  • Research approach in a clinical setting
CDKL5 research consortium: IFCR Centers of Excellence

3 Teams
University of Colorado/Children’s Hospital Colorado
  Lead: Benke
Boston Children’s/Harvard
  Lead: Olson/Kaufmann
Cleveland Clinic
  Lead: Parikh

Goals: Clinical Care tailored to CDKL5 syndrome, Advancing Research, determining Standards of Care
The Rett Clinic at Children’s Hospital Colorado:

Established thanks to a generous and repeated gifts from the Rocky Mountain Rett Association (RMRA). Started December 14, 2011.

Purpose:

- Consultation and evaluation for all people with Rett Syndrome and genetically related disorders (MeCP2, CDKL5 and FOXG1)
- Ensure they are receiving the needed therapies, treatments and services to live a quality life.
- We serve people of all ages.
- Provide up-to-date information on Rett Syndrome, CDKL5 and FOXG1 to parents, physicians, therapists and care providers.
- Participate in ground-breaking clinical research trials.
- Work as a team with the family and the primary care providers.
- Train future providers
- Family support
What it looks like:

Integration through a multi-disciplinary approach to provide optimal care

RN coordinator driven (Tristen Dinkel RN BSN)

6x/year clinic

Providing new and follow-up assessments

Clinic appointment involves a four hour block with consultation by all pertinent specialists in one centralized location

The patient/family stays in one room with providers moving to the families’ location in a round-robin format. Specialized Multi-D area.

4-5 new and 4-5 follow-up patients seen per session-

Intake packets filled out prior to visit (3 weeks)

• Team reviews over lunch 1 week prior to clinic
• Outside records reviewed and archived for completion
• Parent/therapist/provider questions

➢ Team addresses questions/concerns while in clinic.
Our Team:

18 members representing individual professional disciplines:

- Timothy Benke, PhD, MD
  - Neurology/Medical Director
- Tristen Dinkel, RN, BSN
  - Nurse Clinic Coordinator
- Anne Stratton, MD
  - Rehabilitation
- Sandra Friedman, MD, MPH
  - Developmental Pediatrics
- Sumeet Garg, MD
  - Orthopedic Surgery
- Terry Katz, PhD
  - Neurodevelopment & Behavioral Pediatrics
- Margarita Saenz, MD
  - Clinical Genetics
- Michael Schaffer, MD
  - Cardiology
- Oren Kupfer, MD
  - Pulmonary
- Jaime Guthrie, PT, DPT, CFMT
  - Physical Therapy
- Margaret Spring, M.S., OT
  - Occupational Therapy
- Meghan Roe M.Ed., CCC-SLP
  - Augmentative Communication Specialist
- Laura Watne, MS RD
  - Nutrition
- Ed Liu, MD
  - GI/Nutrition
- Scott Demarest, MD
  - Neurology/Epilepsy
- Katie Angione, MS, CGC
  - Certified Genetic Counselor
- Joanna Reeder, LCSW
  - Social Work
- Carrie Rose-Matens
  - RMRA Representative
Our Team:

Who is missing?

- Ophthalmology (Neurology)
- Gynecology
- Movement specialist (Neurology)
- Immunologist (Pulmonary)
- Sleep (Neurology, Pulmonary, Development/Behavior)
- Other?
Research Questions, Specific Aims and Hypotheses and Issues

• Questions (not exclusive) to determine standards of care:
  • What is the natural history?
    • What are the associated features?
    • What predicts natural history?
      • Epilepsy?
      • Biomarkers?
      • Specific mutations?
    • How does this impact families?
      • How can we positively affect this?
  • What are the best treatments?
Specific Aims and Hypotheses

1. Longitudinal and very structured evaluations can define the natural history of CDKL5 syndromes. *We will perform structured clinical evaluations in our CDKL5 patients.*

2. Structured laboratory (MRI, EEG, etc) data collection obtained from clinical evaluations will define biomarkers that can predict clinical course. *We will collect structured laboratory data in our CDKL5 patients.*

3. A defined natural history is necessary to determine the efficacy of future clinical trials. *We will serve as sites for future clinical trials.*
Research Questions, Specific Aims and Hypotheses and Issues

Approach (IRB approved):
• Implement structured clinical questionnaire
  • REDCAP
  • Must address research questions, amenable to statistics/quantitative
• Efficient
  • Patient elements completed during “standard visit”
  • Family elements complete but not overly burdensome
• Perfect not enemy of good
• Review of outside records (EEG, MRI, genetics, etc)
  • Completed outside of clinic
• Common, shared international data instrument, single database (or multiple linked dbs)
  • Governance, ownership, authorship, IRBs, standardization
  • Collaboration/Confederation/Federation
Issues

• Threading together the data across sites
• New sites/collaborations
• New questions/adding to the forms/circling back
• Similar/dissimilar approaches
• Time
  • Record review especially EEG review (not just reports)
  • Data entry, analysis
Emerging standards of care: Quick view

- Multidisciplinary team; every 1-2 years
  - Convenient, accessible, interested
- Genetic consultation and counseling
  - Missense mutations: parental confirmation
- Yearly EKG (looking for prolonged QTc)
  - Referral, prolonged/halter if abnormal
- Yearly clinical spine evaluation; every 6 months if abnormal
  - Imaging if abnormal; referral to orthopedics if > 10deg; correction > 30-40deg
- Prolonged EEG; sleep studies
  - For new spell types, evolving spell types; sleep issues
- Therapies
  - Lifelong, Multifaceted
  - Accommodations for visual impairment in the classroom
- Bone health (Vitamin D 400-800U/calcium/day)
- Regular dental exams; regular eye exams
- GYN health
## Rett Program Recommendations Childhood Through Adulthood

### Cardiac Evaluations
- **RET1**: EKG every 1-2 Years
- Cardiology referral for any abnormality
- EKG every 1-2 Years
- Cardiology referral for any abnormality
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- Cardiology referral for any abnormality
- EKG every 1-2 Years
- Cardiology referral for any abnormality

### Spine Evaluations
- Yearly Physical Exam after age 4yo
- Upright (sitting or standing) Spine x-ray imaging if curvature appears, then Physical Exam every 6 months until stable through puberty
- Orthopedics referral for curvature >10 degrees
- If corrected, yearly Physical Exam
- Yearly Physical Exam after age 4yo
- Upright (sitting or standing) Spine x-ray imaging if curvature appears
- Orthopedics referral for curvature >10 degrees
- If corrected, yearly Physical Exam
- Yearly Physical Exam after age 4yo
- Upright (sitting or standing) Spine x-ray imaging if curvature appears
- Orthopedics referral for curvature >10 degrees
- If corrected, yearly Physical Exam

### Vitamin D and Calcium Supplements
- At least 400-800 U Vitamin D and calcium daily
- Follow levels yearly
- BMI
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### Eye and Dental Exams
- Regular Eye exams
- Dental exams every 6 months/as needed
- Yearly Eye exams
- Dental exams every 6 months/as needed
- Yearly Eye exams
- Dental exams every 6 months/as needed
- Regular Eye exams
- Dental exams every 6 months/as needed

### Therapies
- Lifelong PT (ranging from 1-2x/week- 1x/month)
- AAC assessment
- Occupational Therapy
- Regular seating assessments
- Lifelong PT (ranging from 1-2x/week- 1x/month)
- AAC assessment
- Occupational Therapy
- Regular seating assessments
- Lifelong PT (ranging from 1-2x/week- 1x/month)
- AAC assessment
- Occupational Therapy
- Regular seating assessments
- Lifelong PT (ranging from 1-2x/week- 1x/month)
- AAC assessment
- Occupational Therapy

### Other
- Regular Vaccines including Flu
- Boosters in adolescence and adulthood
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- Boosters in adolescence and adulthood
Summary

IFCR: COE

• Diagnostic and therapeutic support for patients and families

• Clinical tools/Future publications

• Emerging standards of care
Special Thanks!!!

Our patients and families

IFCR-COE collaborators:
Heather Olson, Sumit Parikh, Walter Kaufmann, Elia Pestana-Knight

NHS-Natural History Study:
Eric Marsh, Alan Percy, Jeff Neul, Alex Paciorkowski, Laura Mamounas, Tim Roberts, Chuck Nelson, Sar Peters, Michaela Fagiolini, etc

Rocky Mountain Rett Association
Ponzio Family Chair in Neuroscience Research
questions