KCNT1 EPILEPSY

HOPE IS ON THE HORIZON

KCNT1 gene mutations can result in debilitating seizures and profound developmental stagnation.
Most children never learn to walk or talk.

Urgent Need for Better Treatments

Treatments that **relieve signs and symptoms** and improve **quality of life**

Treatments that do not sedate infants during key developmental periods

Disease-modifying treatments that allow children to…

- **Interact** with their families
- Use their hands
- Lift their heads
- **Communicate** their basic needs
- Continue to learn
- Smile for their families

KCNT1 EPILEPSY
FOUNDATION

Our Mission

Accelerate Drug Development for KCNTI-Related Epilepsies

Create a clinical trial-ready community

Patient identification, education and support

De-risk research by providing...

Longitudinal patient data

Biorepository

Funding

Roundtable Agenda

Speaker	Topic
Sophie Hill, PhD Children's Hospital of Philadelphia / University of Michigan	Reduction of Kcnt1 is therapeutic in mouse models of SCN1A and SCN8A epilepsy
Dr. Jitendra Kumar Sahu, DM Professor, Pediatric Neurology Unit, Postgraduate Institute of Medical Education & Research, India	KCNT1-related Infantile Epileptic Spasms Syndrome
Dr. David Bearden Department of Neurology and Pediatrics, University of Rochester Medical Center	Natural History of KCNT1-related Epilepsy
Rebecca Schapiro, M.S. Candidate Human Genetics and Genetic Counseling, Stanford University School of Medicine	Cardiovascular Risks for Individuals with KCNT1-Related Epilepsy
Jay Pathmanathan, MD, PhD Neurology and Epilepsy, Beacon Biosignals	Longitudinal EEG data acquisition for the development of EEG biomarkers of KCNT1
Dr. Michael Alber University Hospital and Faculty of Medicine Tübingen	Pimozide therapy of single patients with KCNT1 encephalopathy
Jacopo C. DiFrancesco, M.D., Ph.D. Neurology, Fondazione IRCCS San Gerardo dei Tintori, University of Milano-Bicocca, Monza	Precision medicine approach with fluoxetine in a patient with KCNT1-related drug-resistant focal epilepsy
Professor Rima Nabbout Hôpital Necker – Enfants Malades	• EGG biomarkers in KCNT1 related epilepsy infancy with migrating focal seizures • Systematic review of therapies in KCNT1-related epilepsies
Dr. David Bearden, Department of Neurology and Pediatrics, University of Rochester Medical Center	KCNT1-related Epilepsy: Where are we now, and where are we going?
All	Open Q and A to all speakers, discussion

Please Participate!

- Captions are available live
  - Click the three dots in lower right corner > “More” > “Captions”
  - Choose your language
- Please use the chat during the presentations
  - Add comments, questions, discussion items, useful resources, desires to collaborate, kudos to speakers
- Create community
  - Foundation can make connections for you

KCNT1 Epilepsy Foundation Update: Population

KCNT1 EPILEPSY

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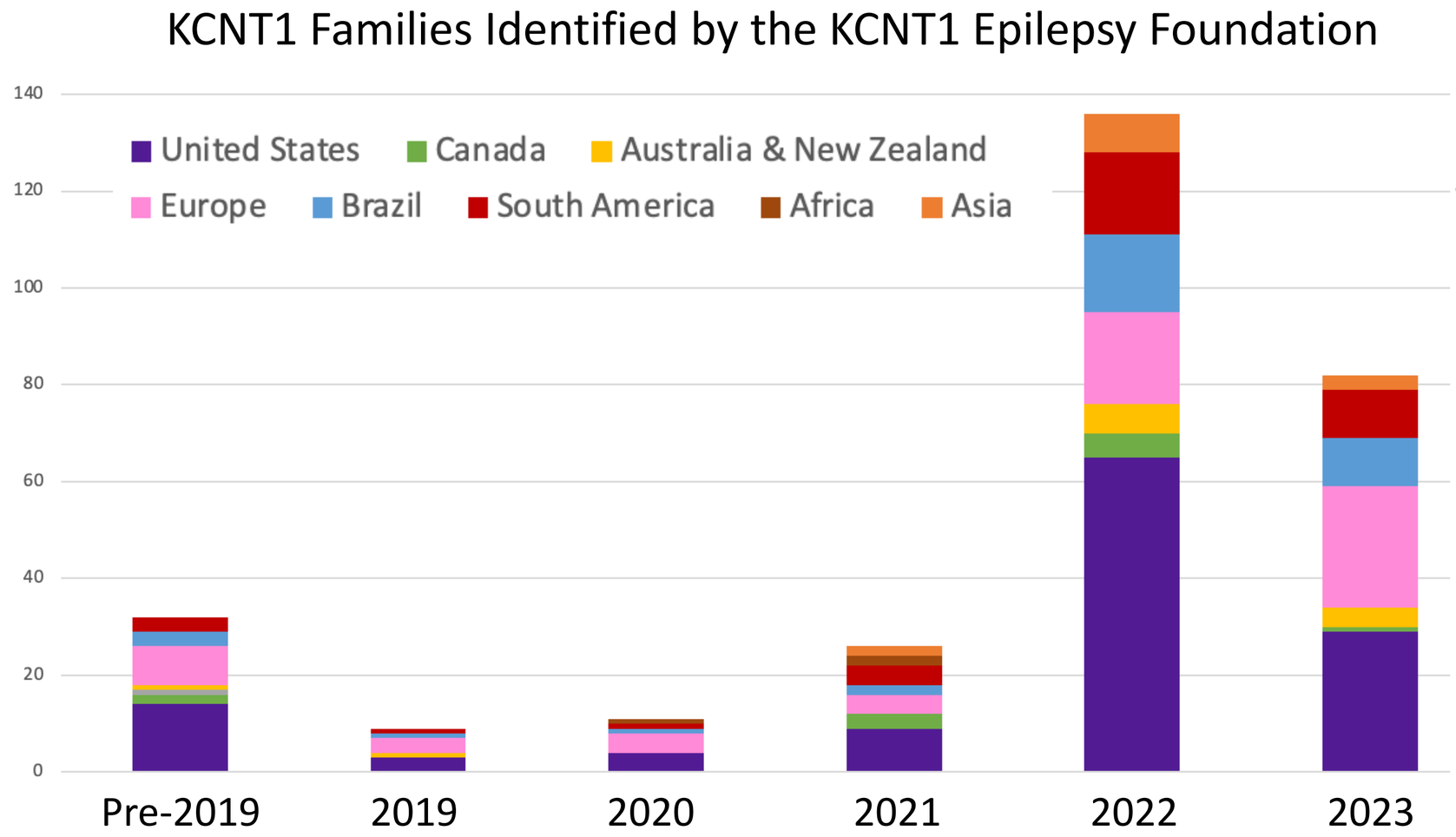
Our Families and Estimated Prevalence

- 300 families in 38 countries[1]
- Estimated 1,000 - 2,500 individuals in U.S. and 33,000 worldwide[1]

- 24 known deaths since tracking started in 2021
- 7 deaths in 2023

1. KCNT1 Epilepsy Foundation Database. 2. Ambit.

New Families Identified Around the World



- ~80 new families registered in 2023
  - ~80% joined Foundation through Facebook, website, genetic testing companies
  - ~20% newly diagnosed

KCNT1 Epilepsy Foundation Update: Initiatives

KCNT1 EPILEPSY

HOPE IS ON THE HORIZON

Data Initiatives

Electronic Medical Record Analysis

- Patient families allow import of electronic medical records through Invitae's Ciitizen platform
- 62 patients from USA enrolled
- Upcoming: analysis by Foundation and CHOP
- **Data available by request for your own analysis!**

Facebook data analysis by Trend Community

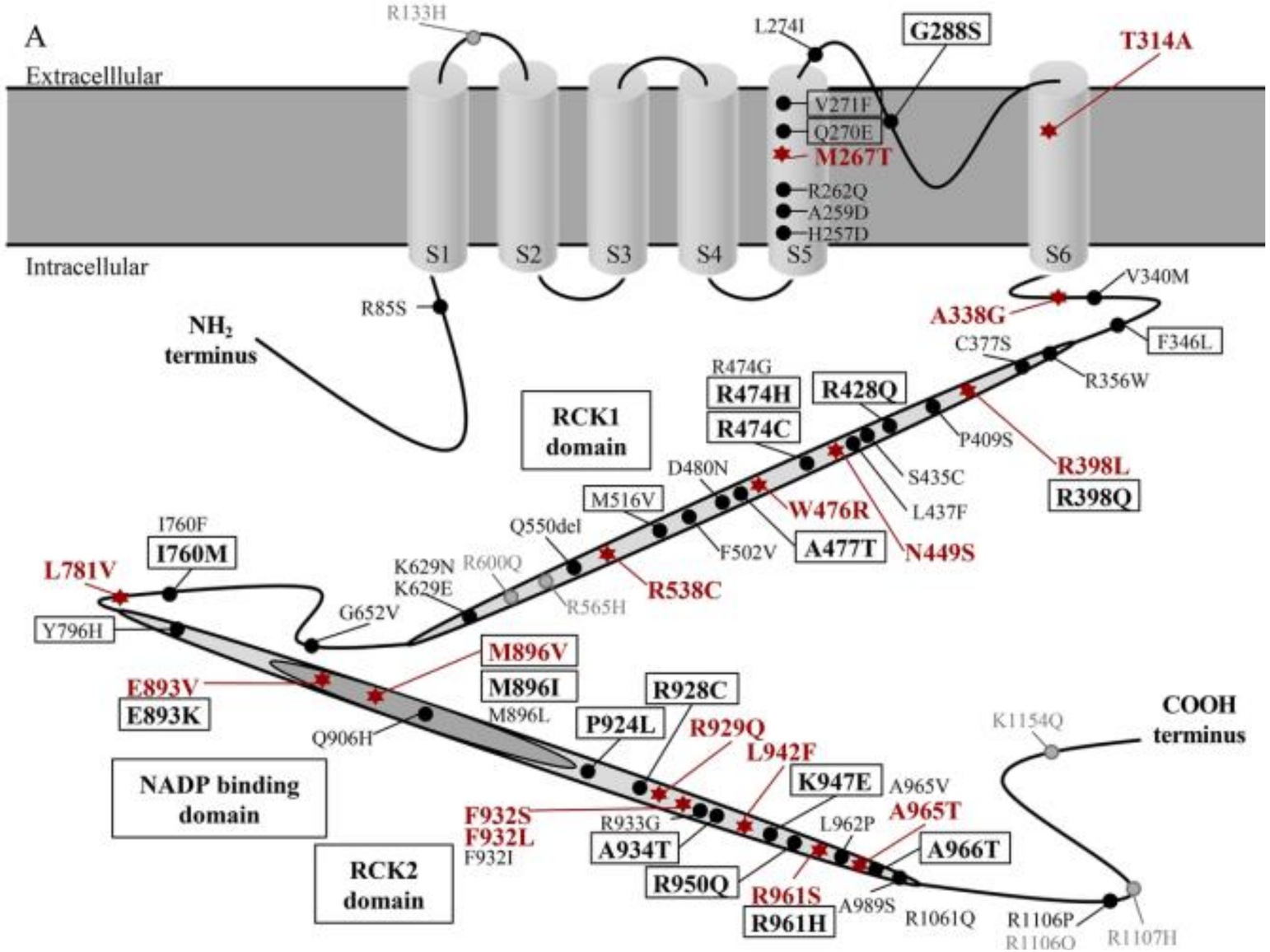
- Deidentified data
- Consent from private group admins

Electronic seizure diary

- Chosen in collaboration with other developmental epilepsies
- Familiarize families with use as part of Clinical Trial Readiness program

KCNT1 Variants of Unknown Significance Need Classification

- 248 individuals
- 64 mutations identified
  - 24 recurrent mutations represent nearly half of cohort
  - G288S, A934T, R474H, R428Q, R398Q, R950Q
- Many reported variants are VUS
- **Seeking approaches to recategorize VUS**
  - Important for clinical trial initiation



Bonardi et al. Brain. 2021 Dec 31;144(12):3635-3650.

KCNT1 Assets: Patient-Derived Samples

Variant	Biosample type	Location
c.2797 C>G; p.Arg993Gly	PBMCs, plasma, and white blood cell pellets	Van Andel Institute
c.1421 G>A; p.Arg474His	PBMCs, plasma, and white blood cell pellets	Van Andel Institute
c.1421 G>A; p.Arg474His	PBMCs, plasma	Van Andel Institute
	PBMCs, plasma, whole blood	Van Andel Institute
c.2849G>A; p.Arg950Gln		
c.1421 G>A; p.Arg474His		
c.1283G>A; p.Arg428Gln		
c.820C>A; p.Leu274Ile		
c.1421 G>A; p.Arg474His		
c.1193G>A; p.Arg398Gln		
c.862G>A; p.Gly288Ser		
	Post-mortem brain tissue	University of Maryland Brain Bank

KCNT1 Assets: Human Cell Lines

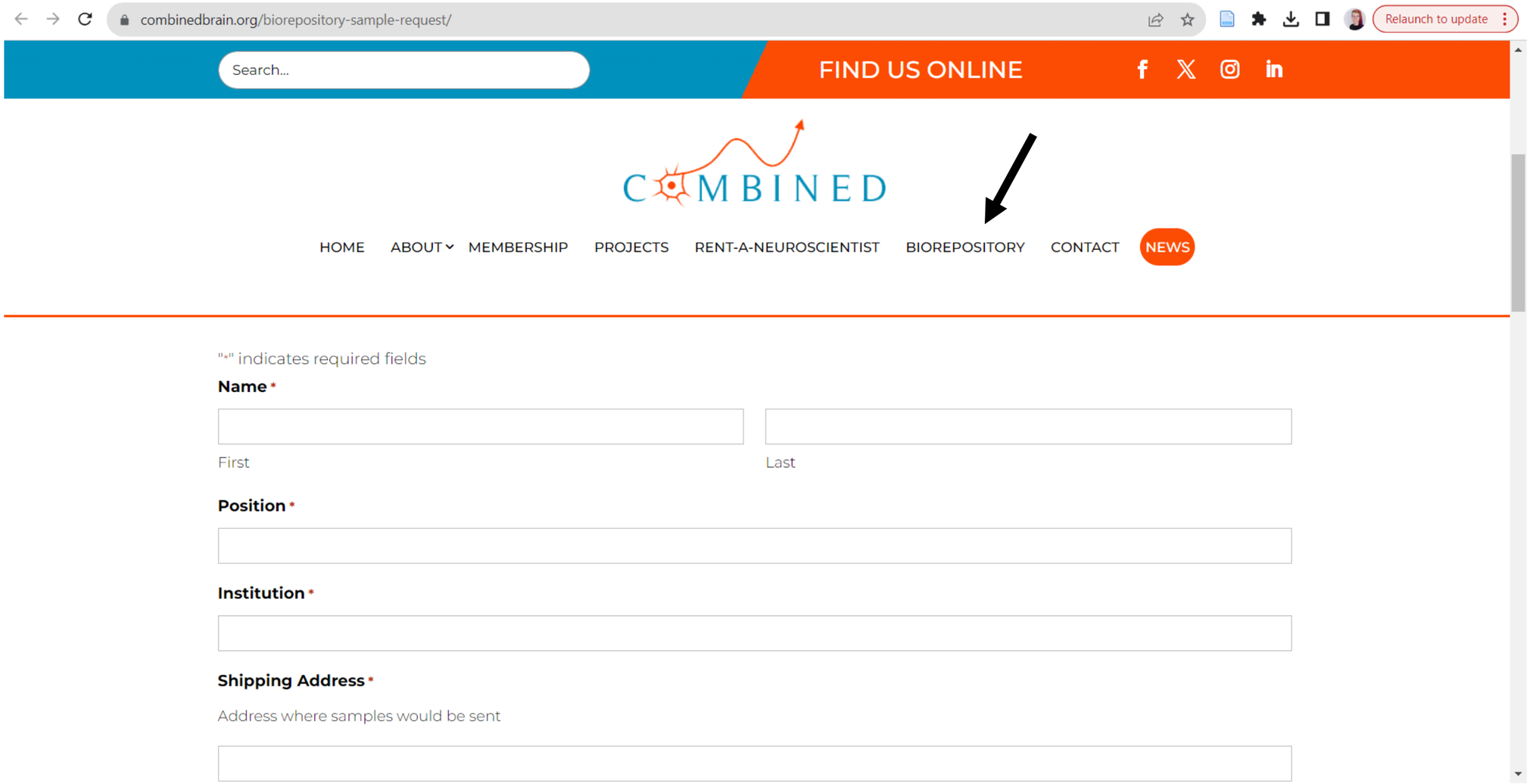
Variant	Cell line type	Location
c.1283G>A; p.Arg428Gln	fibroblast	Tim Yu, BCH
c.1661G>A; p.Gly554Glu	fibroblast	Tim Yu, BCH
c.2849G>A; p.Arg950Gln	fibroblast	Tim Yu, BCH
c.1421 G>A; p. Arg474His	IPSC, fibroblast	Tim Yu, BCH
c.1421 G>A; p. Arg474His	IPSC, fibroblast	Tim Yu, BCH
c.862G>A; p.Gly288Ser	IPSC	Al George, Northwestern
c.2849G>A; p.Arg950Gln	IPSC	Al George, Northwestern
c.2800 G>A; c.Ala934Thr	IPSC	Yucai Chen, Shanghai Children's Hospital
Pro924Leu	Engineered IPSC	Leonard Kaczmarek, Yale

- Working to transfer lines to Van Andel Institute

KCNT1 Assets: Mouse Models

Mouse variant	Human variant equivalent	Location
L437F	L456F	Tracey Gertler, Lurie Children's
R455H	R474H	Matt Weston, Virginia Tech
Y777H	Y796H	Matt Weston, Virginia Tech
R409Q	R428Q	Matt Weston, Virginia Tech
P905L	P924L	Steve Petrou, Florey Institute
Y777H	Y796H	Leonard Kaczmarek, Yale
R409Q	R428Q	Jon Lippiat, Leeds
Knockout		Christopher Lingle, Washington University
Conditional KO		Christopher Lingle, Washington University

Requesting Assets



https://combinedbrain.org/biorepository-sample-request/

Foundation Grant Initiatives

- Million Dollar Bike Ride 2023
  - June Ride in Philadelphia
  - Call for Grants September
  - Announcing winner in December
  - Repeat in 2024
- Internal grant- to launch in Q1 of 2024

RIDE
FOR RESEARCH
TEAM KCNT1
2023

Other 2024 Foundation Projects

Research/Medicine Directed

- Consensus treatment recommendations
- Investigate cardiac involvement in KCNT1
- Applied for FDA patient Listening Session
- Conceptual model development

Patient/Family Facing

- Enhancing parent support programs
  - Bereavement support group
- Clinical Trial readiness education programs

Shared

- Family meeting/Conference

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