THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Can we be clairvoyants? Predicting epilepsy in infants with TSC

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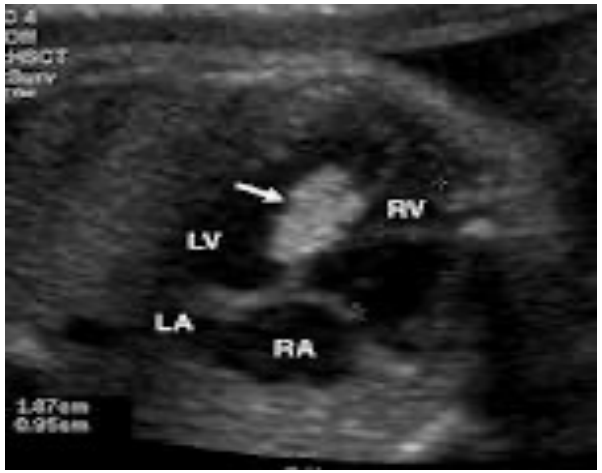
Background Information and Goals of Preventative Therapy

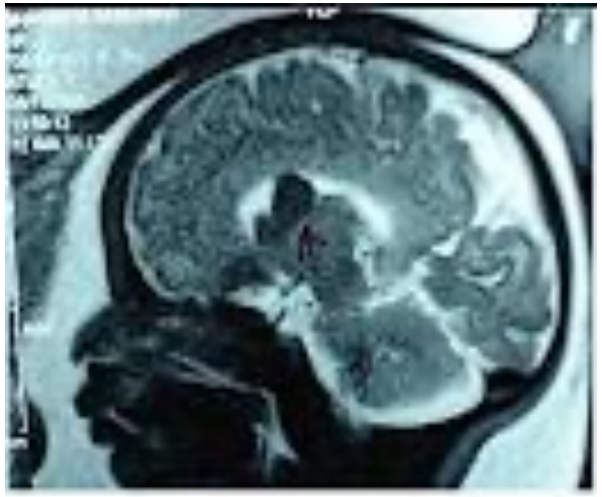
- TSC and the Impact of epilepsy:
  - Overall 90% of individuals with TSC have epilepsy with 65% beginning before the age of 12 months, 60% have an intellectual disability and 50% suffer from psychiatric and behavioral comorbidities (i.e.-Autism)
  - What is the potential impact of preventative therapy for epilepsy?
    - Is it possible to prevent, delay or ameliorate the onset of epilepsy?
    - How does preventative therapy impact developmental outcomes and risk for Autism in TSC infants?
    - Which factors impact developmental outcomes and risk for refractory seizures?
      - TSC mutation
      - MRI brain tuber load
      - Epilepsy type and age of onset

Capal JK, et al. Epilepsy Behav 2017;70(Pt A):245-252; Wu, JY et al. Epilepsia 2019;60(12):2428-2436

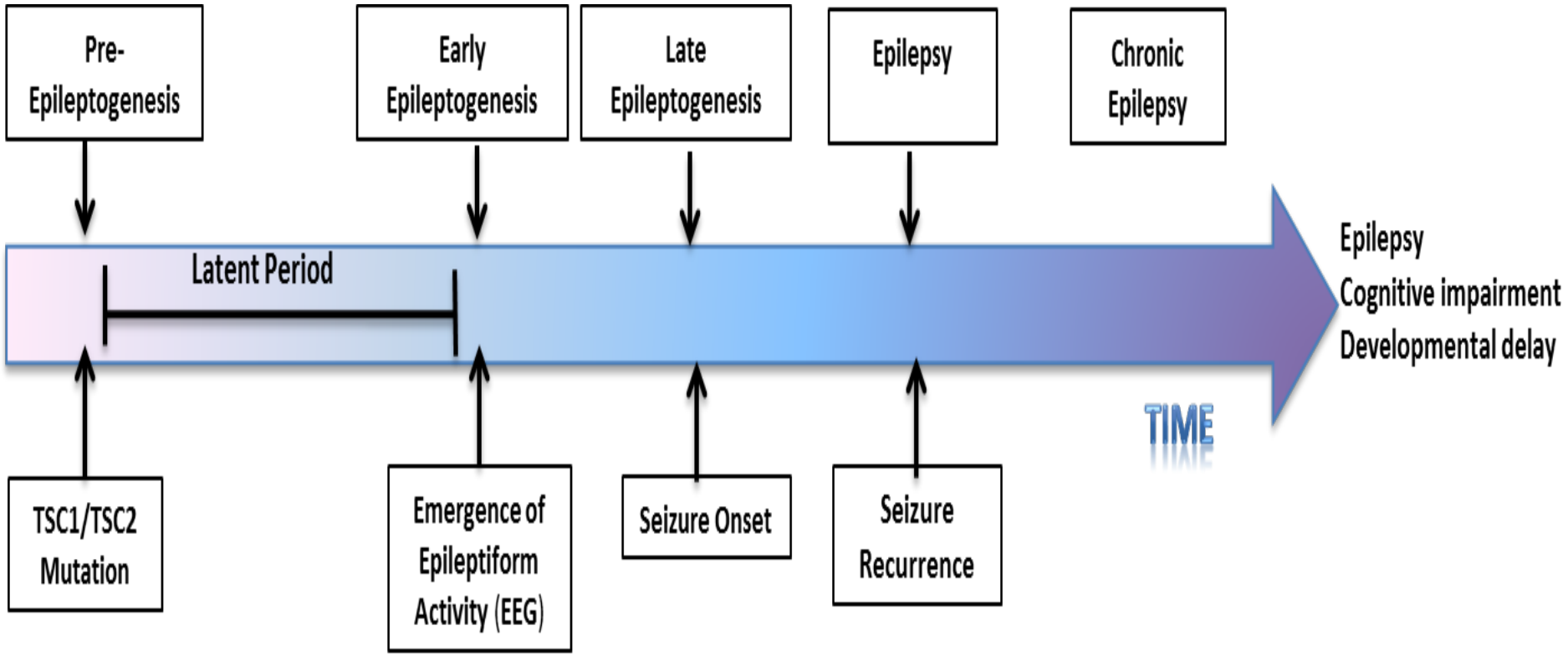
Feasibility of Prevention Therapy

- Ability to Dx TSC prenatally
  - Heart-Cardiac Rhabdomyoma-47% of infants also have cardiac dysrhythmias
    - 80% fetuses and infants with TSC have cardiac rhabdomyomas
    - Brain-cortical tubers, subependymal nodules on prenatal brain MRI (60-70% positive exams)
  - Early Diagnosis and referral to neurologist
  - Education of parents and care givers on seizure recognition
  - EEG at the time of TSC diagnosis

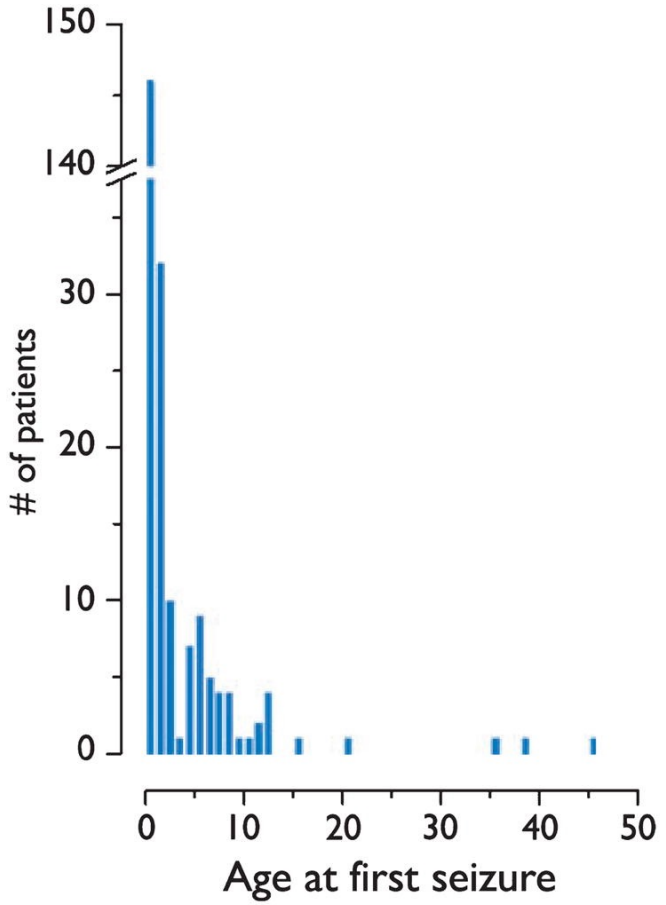




Epileptogenesis in TSC



Onset of Seizures in TSC

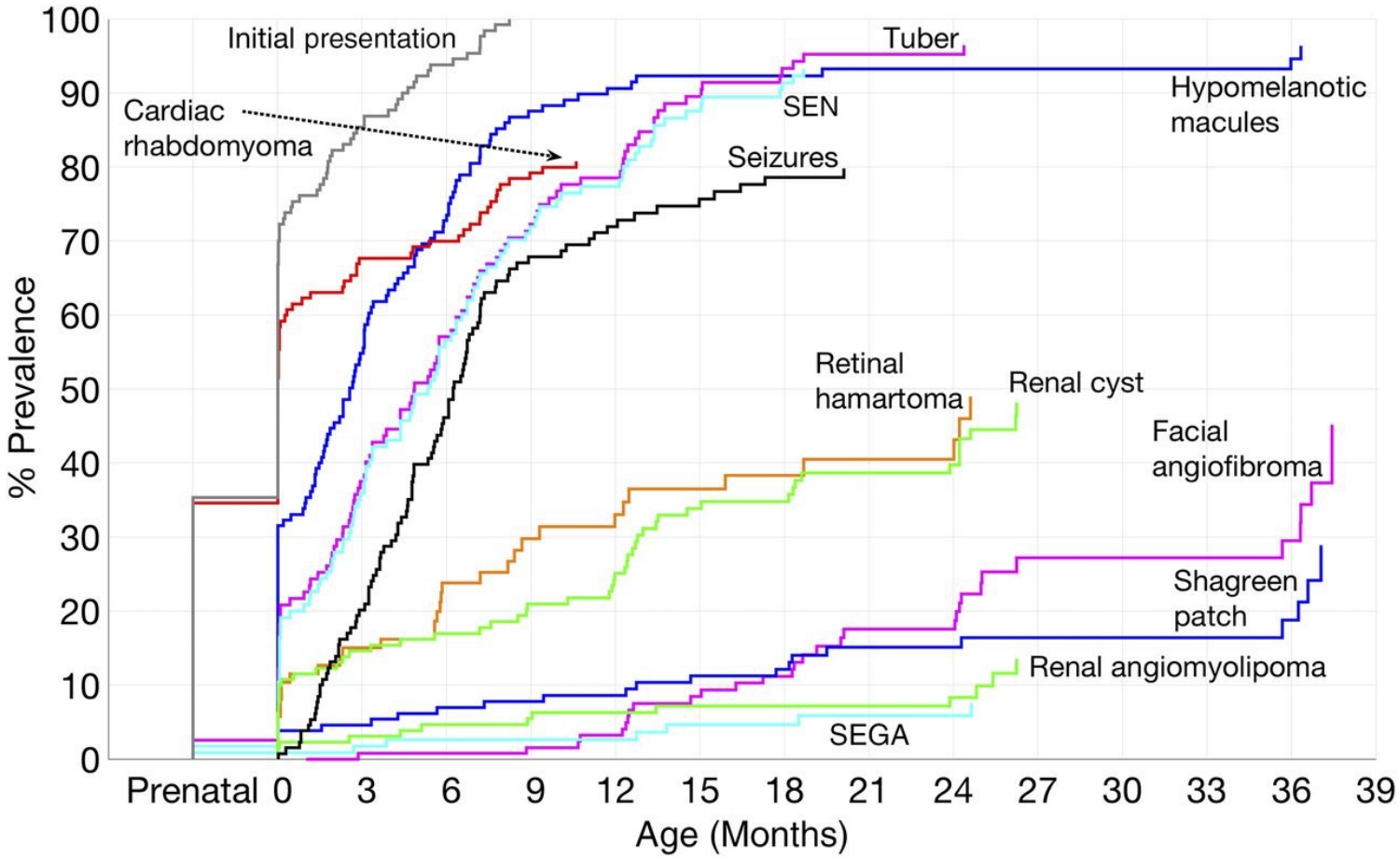


Epilepsia. 2010 Jul; 51(7): 1236–1241.

Seizure Types in TSC

- Up to 85% of individuals with tuberous sclerosis complex (TSC) have epilepsy
  - Birth to 12 months- focal seizures, infantile spasms or a combination of both types
  - Febrile seizures and/or status epilepticus can occur
  - Untreated early-onset seizures are associated with an increased risk of autism and intellectual disability.
  - More than 60% of individuals with TSC and seizures do not achieve seizure control.
    - Compared to 30-40% of individuals with epilepsy who do not have TSC.

Age of onset of TSC symptoms and Manifestations



Age of onset or recognition of the most prevalent TSC features in infants. Hypomelanotic macules, tubers, SENs, and cardiac rhabdomyomas are often seen before the onset of seizures, whereas other manifestations are more commonly first seen later in life.

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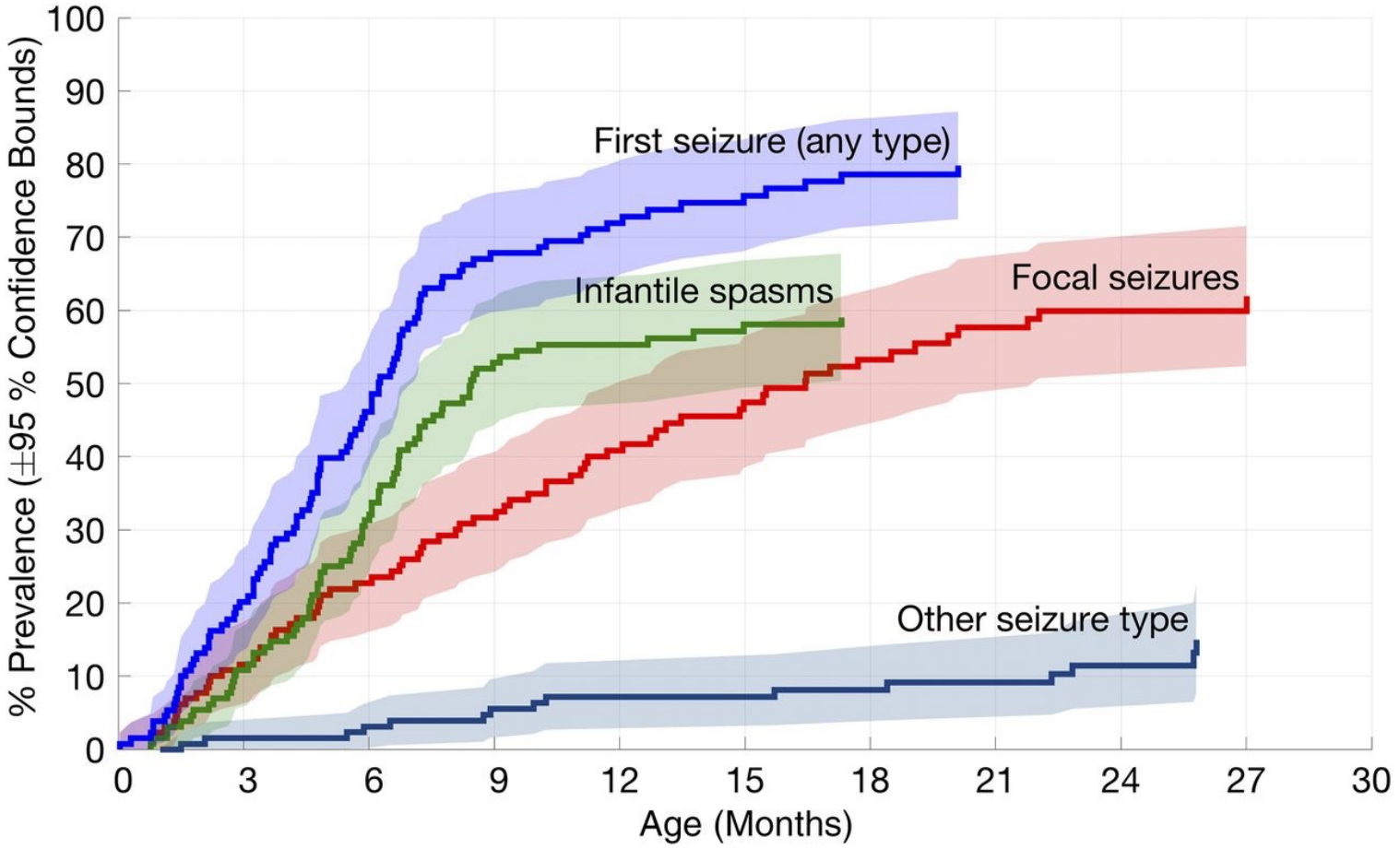
Seizure onset prevalence in TSC by age and seizure type.



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Original article

Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous sclerosis complex

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Comparison of electroencephalographic findings

	Standard group (n=31)	Preventative group (n=14)
Patients with medication (epilepsy or epileptiform discharges on EEG)	22 (71%)	10 (71%)
Normal EEG at age of 24 months	11/31	12/14 p=0.005
Patients receiving AEDs whose EEG turned to normal	2/22	8/10 p=0.0018

Jozwiak et al. Eur.J.Paediatr.Neurol, 2011,

Pediatric Neurology 54 (2016) 29–34

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Original Article

Clinical Electroencephalographic Biomarker for Impending Epilepsy in Asymptomatic Tuberous Sclerosis Complex Infants

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ABSTRACT

BACKGROUND: We assessed the clinical utility of routine electroencephalography (EEG) in the prediction of epilepsy onset in asymptomatic infants with tuberous sclerosis complex. **METHODS:** This multicenter prospective observational study recruited infants younger than 7 months, seizure-free and on no antiepileptic drugs at enrollment, who all underwent serial physical examinations and video EEGs throughout the study. Parental education on seizure recognition was completed at the time of initial enrollment. Once seizure onset occurred, standard of care was applied, and subjects were followed up until 24 months. **RESULTS:** Forty patients were enrolled, 28 older than 12 months with completed EEG evaluation at the time of this interim analysis. Of those, 19 (67.8%) developed seizures. Epileptic spasms occurred in 10 (52.6%), focal seizures in five (26.3%), generalized tonic-clonic seizure in one (5.3%), and a combination of epileptic spasms and focal seizures in three (15.7%). Fourteen infants (73.6%) had the first emergence of epileptiform abnormalities on EEG at an average age 4.2 months, preceding seizure onset by a median of 1.9 months. Hypsarrhythmia or modified hypsarrhythmia was not found in any infant before onset of epileptic spasms. All children with epileptiform discharges subsequently developed epilepsy (100% positive predictive value), and the negative predictive value for not developing epilepsy after a normal EEG was 64%. **CONCLUSIONS:** Serial routine EEGs in infants with tuberous sclerosis complex is a feasible strategy to identify individuals at high risk for epilepsy. The most frequent clinical presentation was epileptic spasms followed by focal seizures, and then a combination of both seizure types.

Keywords: epileptic spasms, EEG, video EEG use in epilepsy, partial seizures

Pediatr Neurol 2016; 54: 29-34

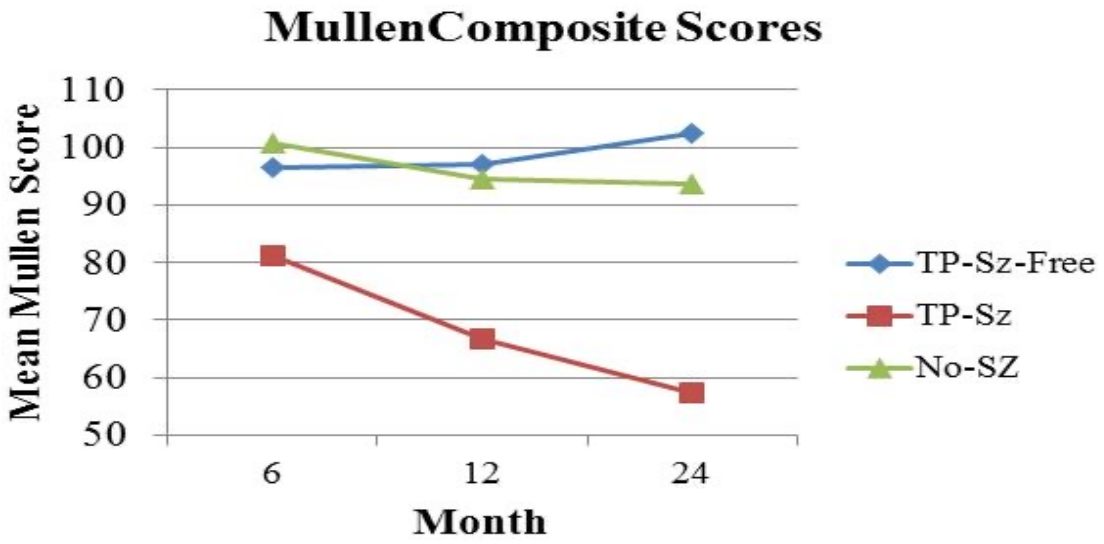
Summary of EEG Characteristics and Statistical Analysis

EEG Characteristics:		
Seventeen of 38 (45%) had epileptiform activity detected on EEG before onset of clinical seizures		
	Average (months)	Median (months)
Age at time of first epileptiform discharges	4.5 (S.D.=4)	4.0
Age at time of first clinical seizure	7.5 (S.D.=4.4)	6.0
Time interval between epileptiform discharges and seizure	3.6 (S.D.=3.4)	
Three of 38 (7%) had no epileptiform activity detected on EEG before the onset of clinical seizures		

Statistical Analysis Summary			
	Clinical seizure	No clinical seizure	
Epileptiform discharges	17	5	
No epileptiform discharges/Normal EEG	3	7	
Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
85	58.3	77.3	70

Wu et al. 2016

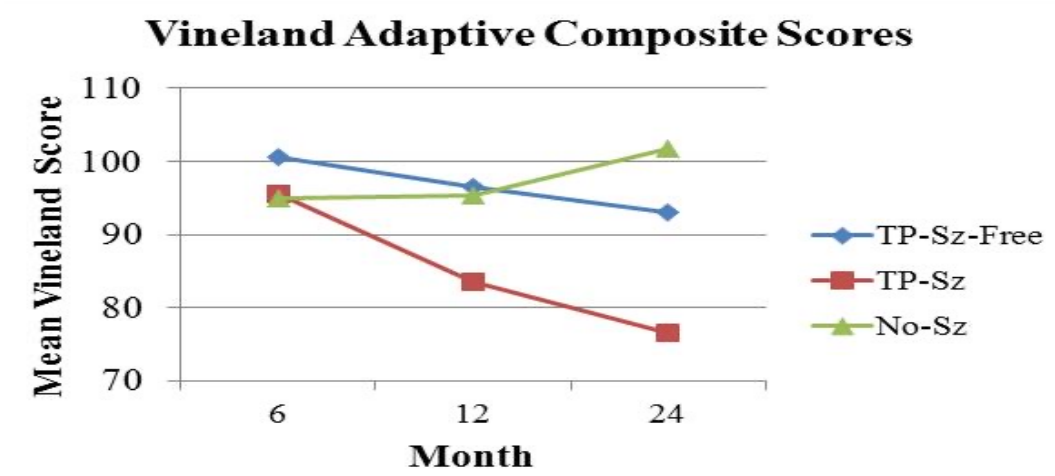
Mullen Scale of Early Learning Composite Scores



Age (months)	TP-Sz-Free	TP-Sz	No-Sz
6	96.63 (19.73)	81.25 (18.23)	100.85 (21.64)
12	97.14 (25.96)	66.57 (13.23)	94.50 (12.82)
24	102.5 (18.09)	57.33 (6.83)	93.62 (25.60)

Wu et al.-2016

Vineland Adaptive Composite Scores



Age (months)	TP-Sz-Free	TP-Sz	No-Sz
6	100.5 (12.00)	95.62 (18.10)	94.62 (13.02)
12	96.57 (17.10)	83.50 (24.48)	95.36 (8.15)
24	93.00 (11.22)	76.50 (13.93)	101.77 (8.89)

Wu et al.-2016

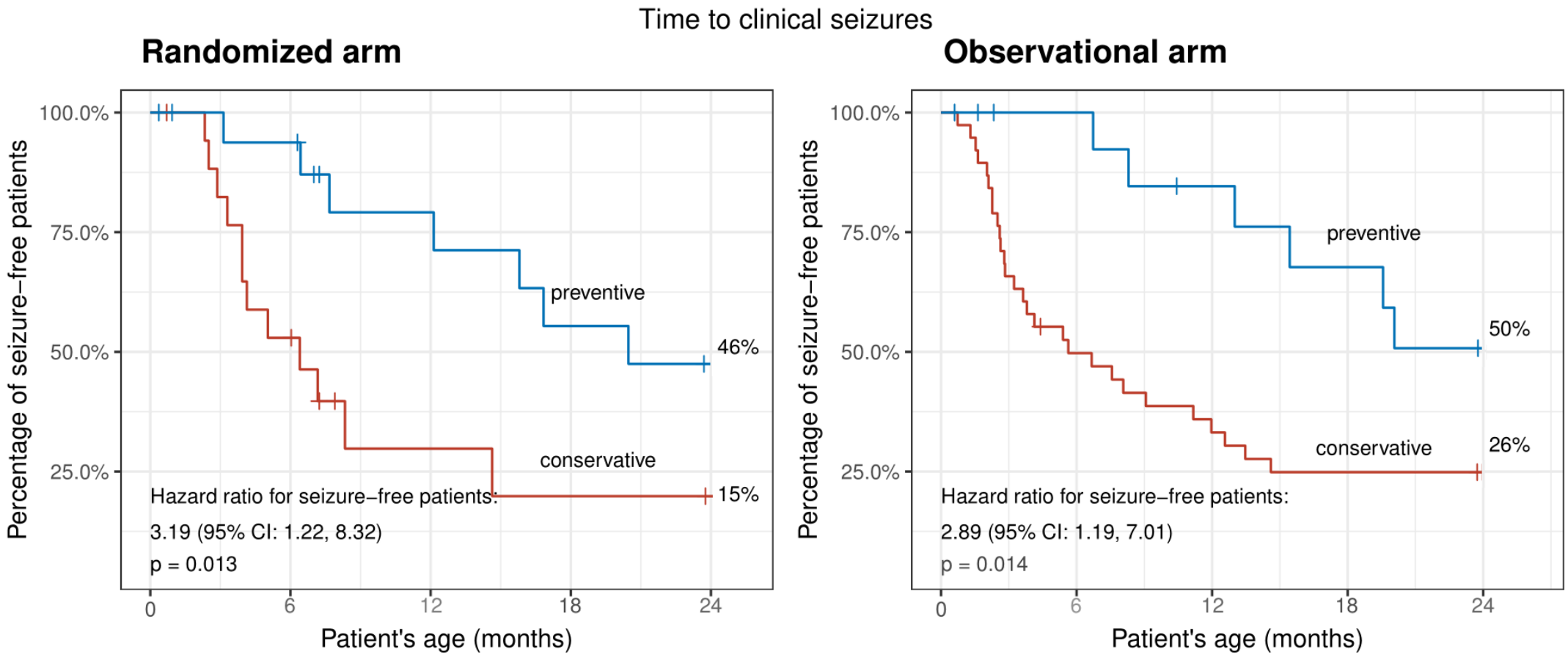
EPISTOP Study Design

European Preventative Study of Vigabatrin (VGB)

Enrolled -101 subjects and included 97 in the study

- 26 subjects were randomized based on their EEG to preventative treatment with VGB or initiation of treatment with VGB at seizure onset
- 43 followed an observational treatment path
  - 22 receiving preventative Rx, 21 Rx at seizure onset with vigabatrin
  - No placebo control for the vigabatrin
  - EEG results were blinded to the physician and subject's family
- Results of the study focused on:
  - Risk to develop epilepsy- focal seizures, Infantile Spasms
  - Percentage in risk for refractory epilepsy
- Developmental Outcomes at 12 and 24 months
  - Value of developmental testing at 6, 12 and 24 months to determine risk for Dev. Delays and ASD risk.

EPISTOP Time to clinical seizure



EPISTOP Epilepsy and Neurodevelopmental Outcomes

Table 1. Demographic and neurodevelopmental data, genetic status, and diagnostic classification at the final follow-up (two years of age) of the 82 infants with Tuberous Sclerosis Complex (TSC).

	N (%)
M	45 (55%)
F	37 (45%)
TSC1 mutation	20 (24%)
TSC2 mutation	59 (72%)
No Mutation Identified	3 (4%)
Normal development at 24 months	44 (54%)
ASD * at 24 months	25 (30%)
ASD * with DQ >70	11 (13%)
ASD * with DQ < 70	14 (17%)
DQ < 70 at 24 months without ASD	13 (16%)

Legend: ASD: Autism Spectrum Disorder; DQ: Developmental Quotient. * ASD diagnosed with ADOS and/or DSM5 criteria.

J. Clinical Medicine 2019; 8:788

EPISTOP Neurodevelopmental Outcomes

- Early developmental assessments at 6 and 12 months of age identified those at risk for Autism and neurodevelopmental co-morbidities
- Risk for neurodevelopmental delays is determined by TSC1/2 mutation, MRI features, epilepsy history and monitoring the early developmental trajectories of each TSC infant.
- *TSC2* pathogenic variants are associated with a more severe clinical phenotype than mosaic *TSC2* or *TSC1* variants in TSC infants. Early assessment of gene variant status and mosaicism might have benefit for clinical management in infants and young children with TSC.

EPISTOP RESULTS

- Preventative Treatment with vigabatrin reduced the risk for clinical seizures and drug resistant epilepsy when compared to treatment after the onset of clinical or electrographic seizures.
- Early EEG monitoring and preventative treatment reduces the risk for severe epilepsy and neurodevelopmental co-morbidities.
- In those patients in which epilepsy was prevented, seizure medication maybe withdrawn at a younger age reducing their lifetime exposure to medication.

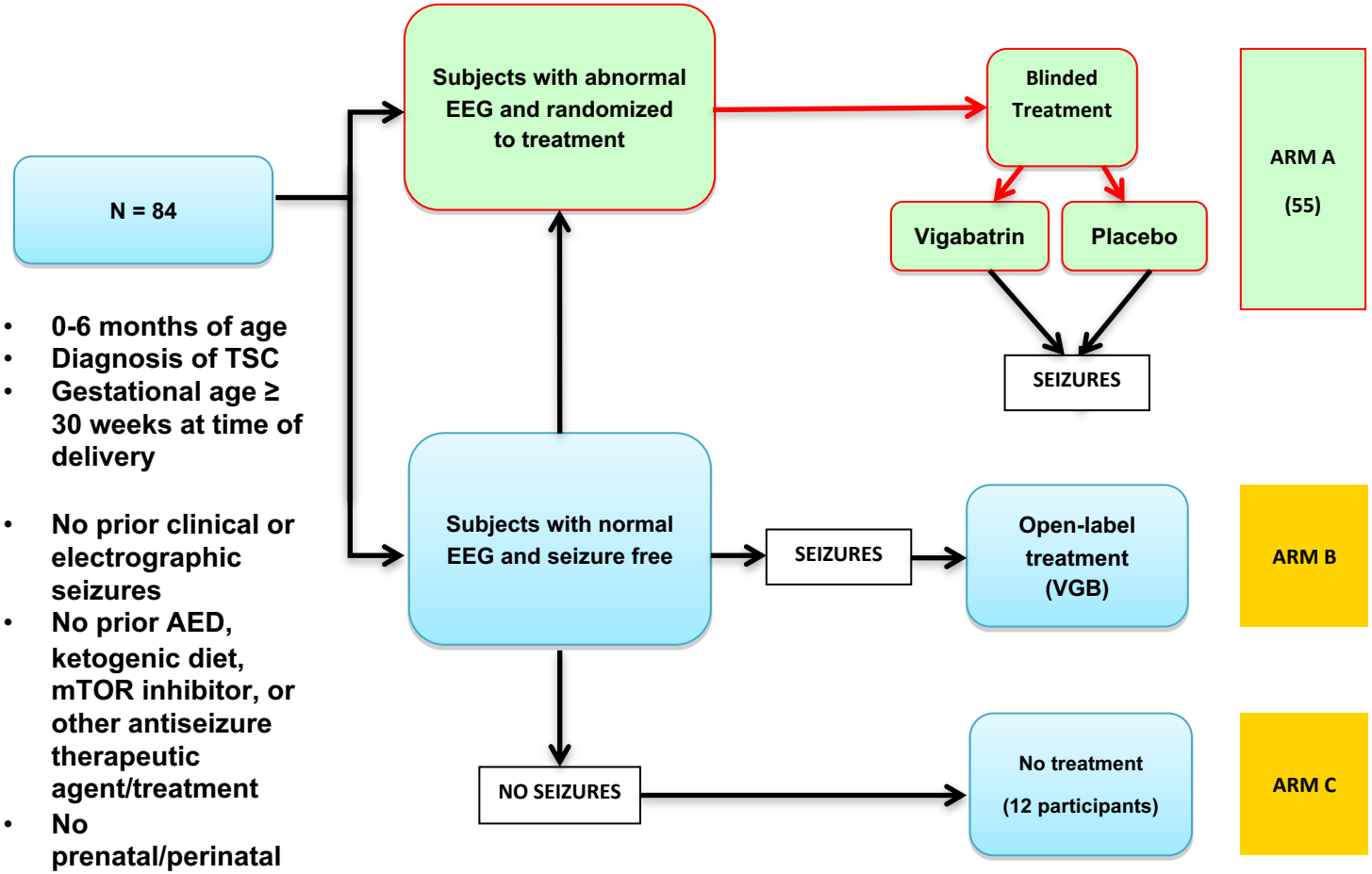
EPISTOP. https://cordis.europa.eu/project/id/602391/reporting

PREVeNT Trial

- Phase IIb clinical trial-blinded randomized controlled trial
- Enrollment Closed March 2020
- Final Results available Q2 -2023
- Multicenter: 13 sites across the U.S.
- **Primary Study Objective**: Developmental Impact of early vs. delayed treatment with vigabatrin. Effect on development at 24 and 36 months

PREVeNT:

PReventing Epilepsy using Vigabatrin in iNfants with TSC



- 0-6 months of age
- Diagnosis of TSC
- Gestational age ≥ 30 weeks at time of delivery

- No prior clinical or electrographic seizures
- No prior AED, ketogenic diet, mTOR inhibitor, or other antiseizure therapeutic agent/treatment
- No prenatal/perinatal medical complications

- EEG every 6 weeks (0-12 months), then every 3 months (13-24 months), then once at 36 months
- Treatment with vigabatrin or placebo until 24 months of age
- Final clinical outcome assessment at 36 months of age

Preventative Epilepsy Key Questions:

- Does Preventative treatment with vigabatrin change the risk for epilepsy in infants with TSC?
  - Lower rates of IS, and value in serial EEG monitoring for focal seizures which maybe the presenting symptoms
  - Lower rates of refractory epilepsy- with preventative therapy (reduction of about 15-20%)
- How does Preventative therapy change the developmental outcomes at 24 and 36 months of age?
  - Risk for Autism and Developmental Disabilities
- Role of Early Intervention Services
- What other factors influence the epilepsy and developmental outcomes for infants with TSC?
  - TSC mutation, MRI brain tuber load, age of onset of seizures and type(s)

EPISTOP. https://cordis.europa.eu/project/id/602391/reporting
Wu et al. Epilepsia. 2019;60:2428-2436

The identification of an early Biomarker, how important?

- The EEG biomarker and use of iEEG allowed for centralized EEG review with 1 hour, by uploading the data to the UPENN server.
- Inter Rater Reliability was emphasized throughout the study
  - Selection of 2 primary EEG reviewers and 1 adjudicator
  - EEG readers were selected based on IRR scores from a set of TSC-EBS EEGs reviewed focused on 5 elements.
- EEG acquisition standardized
  - Critical to obtain at least 20min of sleep during the EEG for completeness

How do we gain definitive evidence of change in disease trajectory?

- Important to follow these participants over a 2-3year time period given the possible evolution of their epilepsy
- TSC- from the TSC-EBS study we found that approximately 1/3 of participants would remain seizure free
- Developmental outcomes need to include both assessments at important developmental periods 12, 24 and 36mos, as well as, the developmental trajectory over time
- Development of epileptogenesis can be accessed with serial EEG and throughout the study.
- PREVeNT EEG schedule:
  - EEG were done every 6 weeks up to 12months of age
  - Every 3months from 12-24months of age
  - Every 6months 24-36months of age
  - EEG data can then be correlated with neuroimaging data

Questions?