Overview of the Developmental and Epileptic Encephalopathies (DEEs)

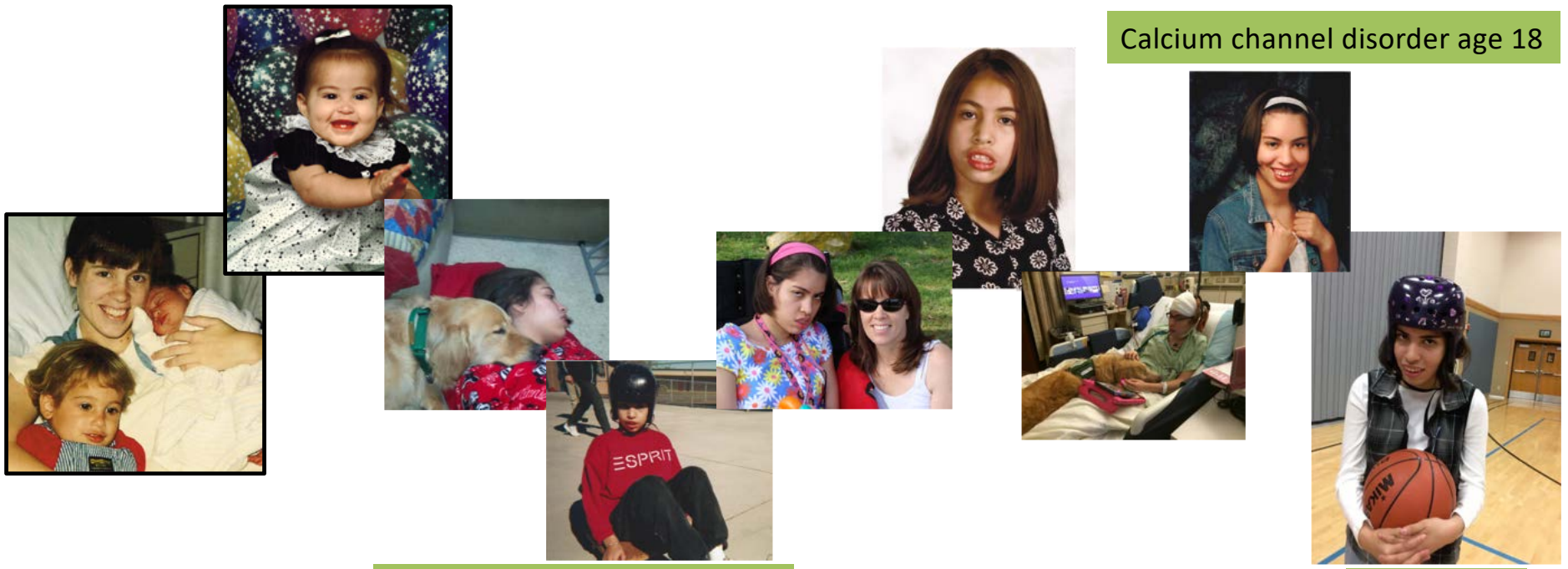
For Families Living with DEEs

Tracy Dixon-Salazar, PhD

Director of Research & Strategy

LGS FOUNDATION
LENNOX-GASTAUT SYNDROME

Savannah – DEE, LGS, and Calcium Channel Overactivation Disorder (my daughter)



Seizures at age 2, LGS at age 5

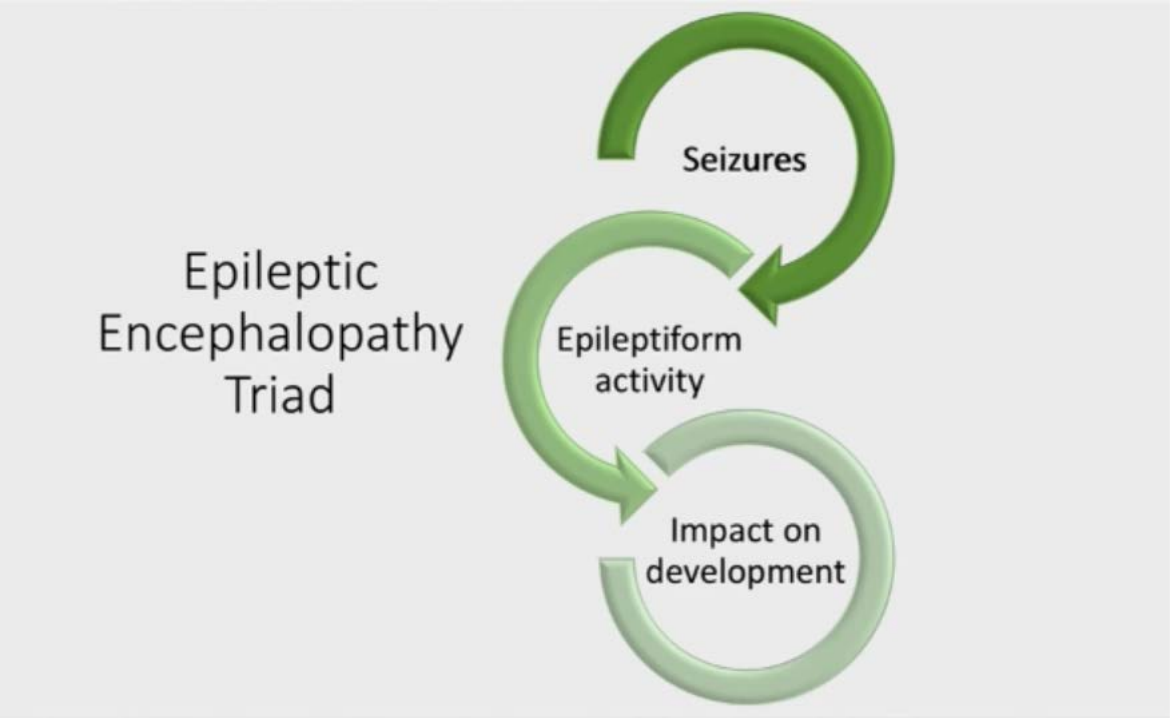
Calcium channel disorder age 18

Age 26 now

What are Epileptic Encephalopathies (EEs)?

Epileptic Encephalopahties (EEs)

Group of epilepsy syndromes where the frequent epileptic activity contributes to the cognitive and behavioral impairments beyond that expected from the underlying cause of the syndrome alone.

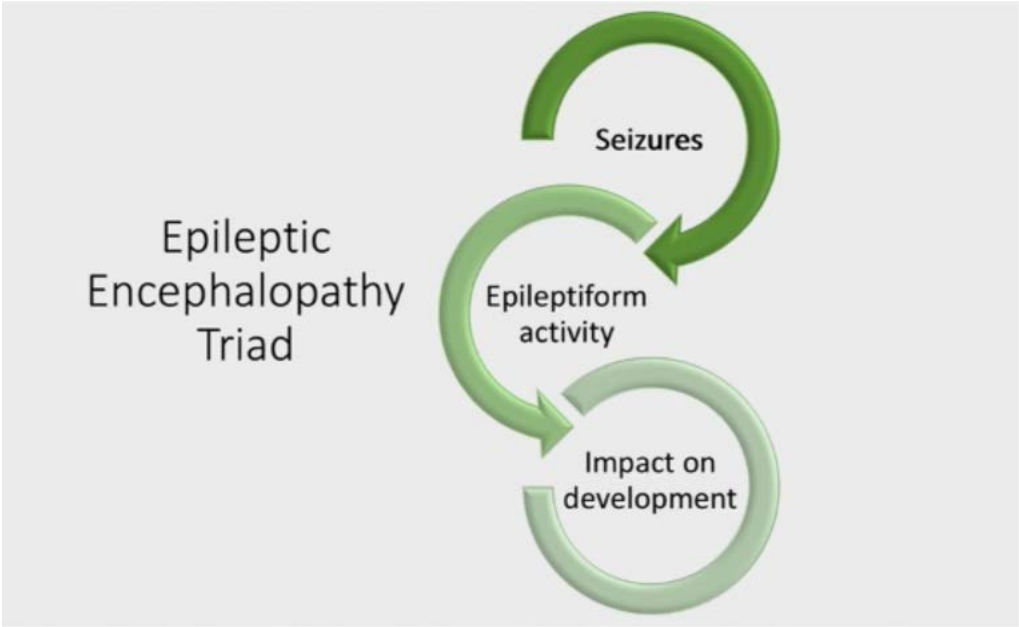


Courtesy of Ingrid Scheffer

Some Epileptic Encephalopathies*

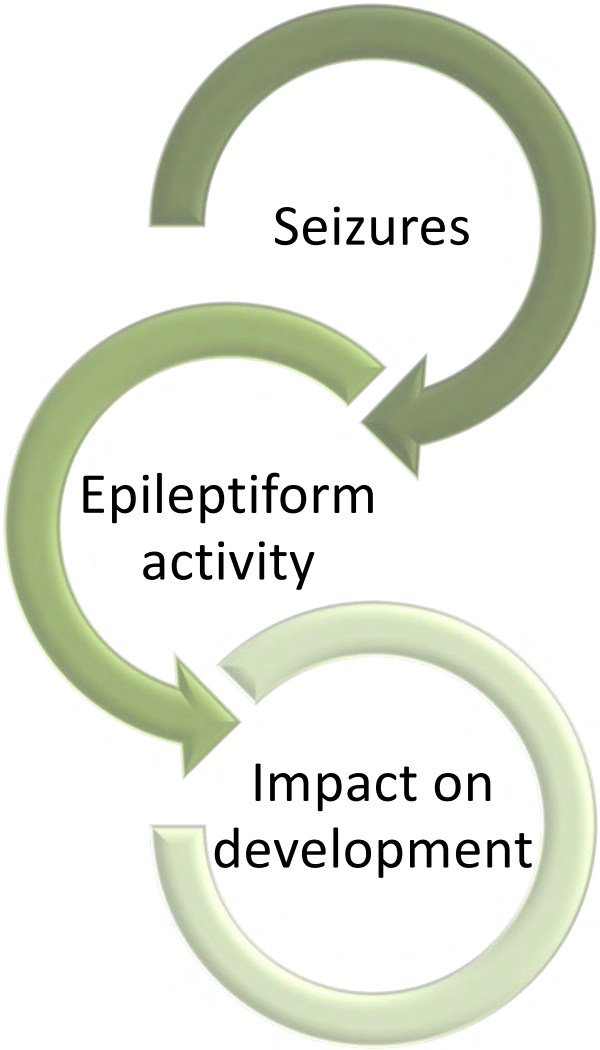
Doose Syndrome
Dravet Syndrome
Early Myoclonic Encephalopathy
Landau-Kleffner Syndrome
Lennox-Gastaut Syndrome
Ohtahara Syndrome
West Syndrome / Infantile Spasms
Gene-specific epilepsy syndromes
- -CDD – CDKL5 Deficiency Disorder
- -Dup15Q Deficiency
- -SCN8A Epilepsy
- -And many more

*To name a few, can have more than one



Courtesy of Ingrid Scheffer

Epileptic Encephalopathy Triad



Berg et al, Epilepsia, 2017
Scheffer et al, Epilepsia, 2017

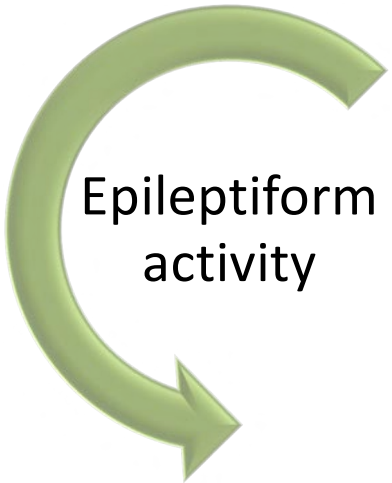
Concept of Epileptic Encephalopathy

Typically present with seizures

- Usually multiple seizure types emerge
  - eg. tonic-clonic, focal, myoclonic, atonic
  - – May be explosive onset
    eg. Myoclonic-Atonic Epilepsy
  - – May be gradual eg. Dravet syndrome
- Sometimes only one seizure type
- But seizures are **not** essential
  - eg. Landau-Kleffner syndrome

Courtesy of Ingrid Scheffer

Concept of Epileptic Encephalopathy



Frequent epileptiform activity

- Distinctive patterns
  - Slow spike wave
  - Hypsarrhythmia
  - Multifocal discharges
- Timing
- How much is enough?
- eg. unilateral in ECSWS
- If never had epileptiform activity

→ not an epileptic encephalopathy

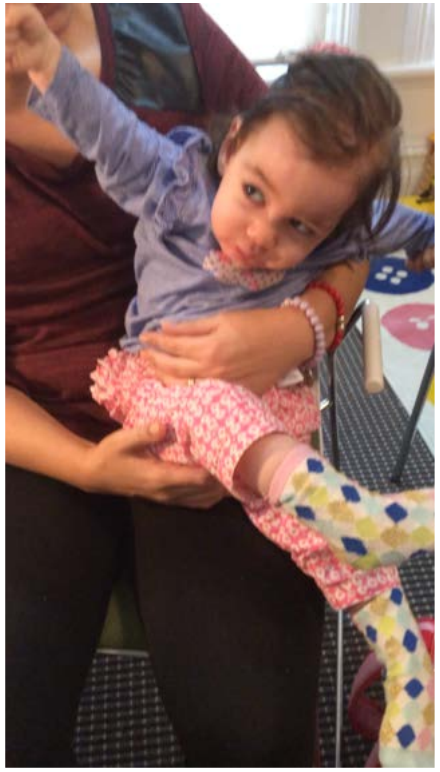
Courtesy of Ingrid Scheffer

Concept of Epileptic Encephalopathy

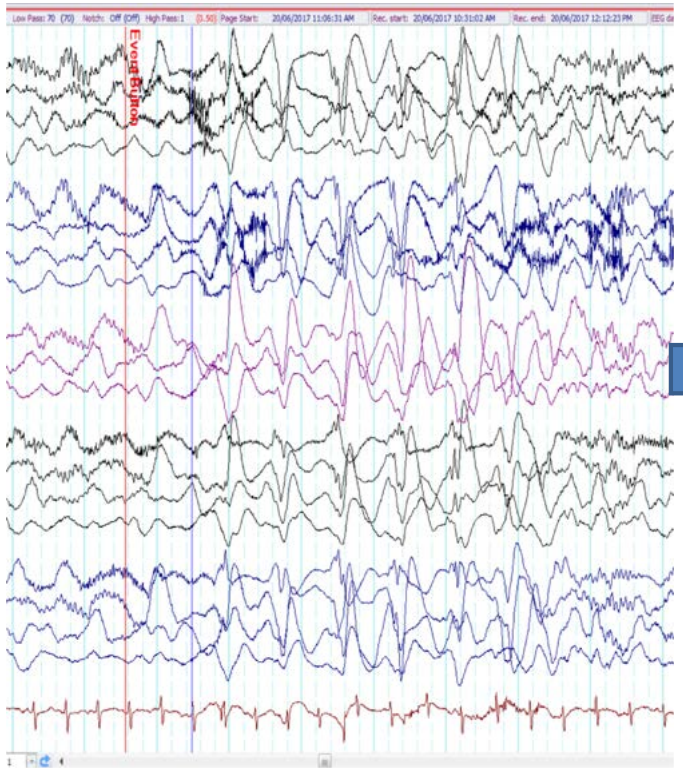
- Preceding development may be
  - Normal
  - Delayed
- Development plateaus
- Or regresses
- Once or stepwise
- Triggers – seizures, infection, brain oedema

Courtesy of Ingrid Scheffer

Epileptic Encephalopathy – any age



Seizures

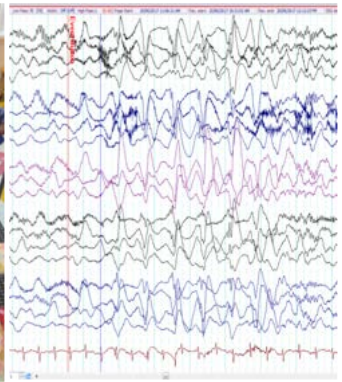


and/or frequent epileptiform activity

Developmental slowing or regression

Courtesy of Ingrid Scheffer

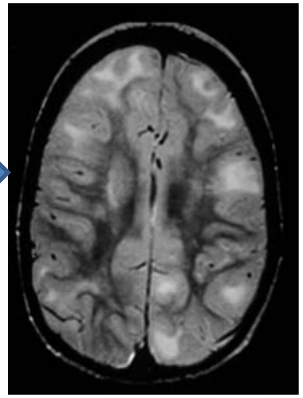
Epileptic Encephalopathy



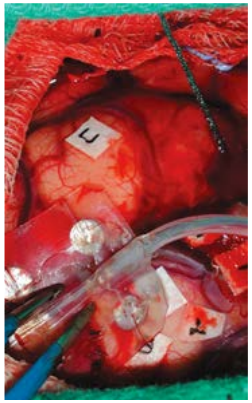
Seizures and/or frequent epileptiform activity

Causes (Etiologies)

Structural

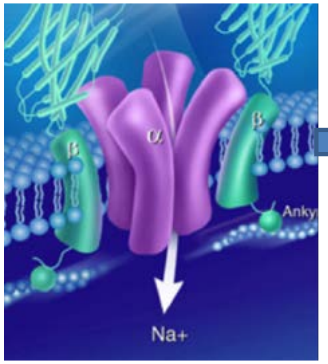


Surgery



Resolution

Genetic



Dravet syndrome:
Stop CBZ,OXC
Start TPM, STP, VPA, FEN

Improve cognition

Courtesy of Ingrid Scheffer

Developmental and/or Epileptic Encephalopathy

Developmental impairment

Epileptic Encephalopathy superimposed
Remediable component? AED selection

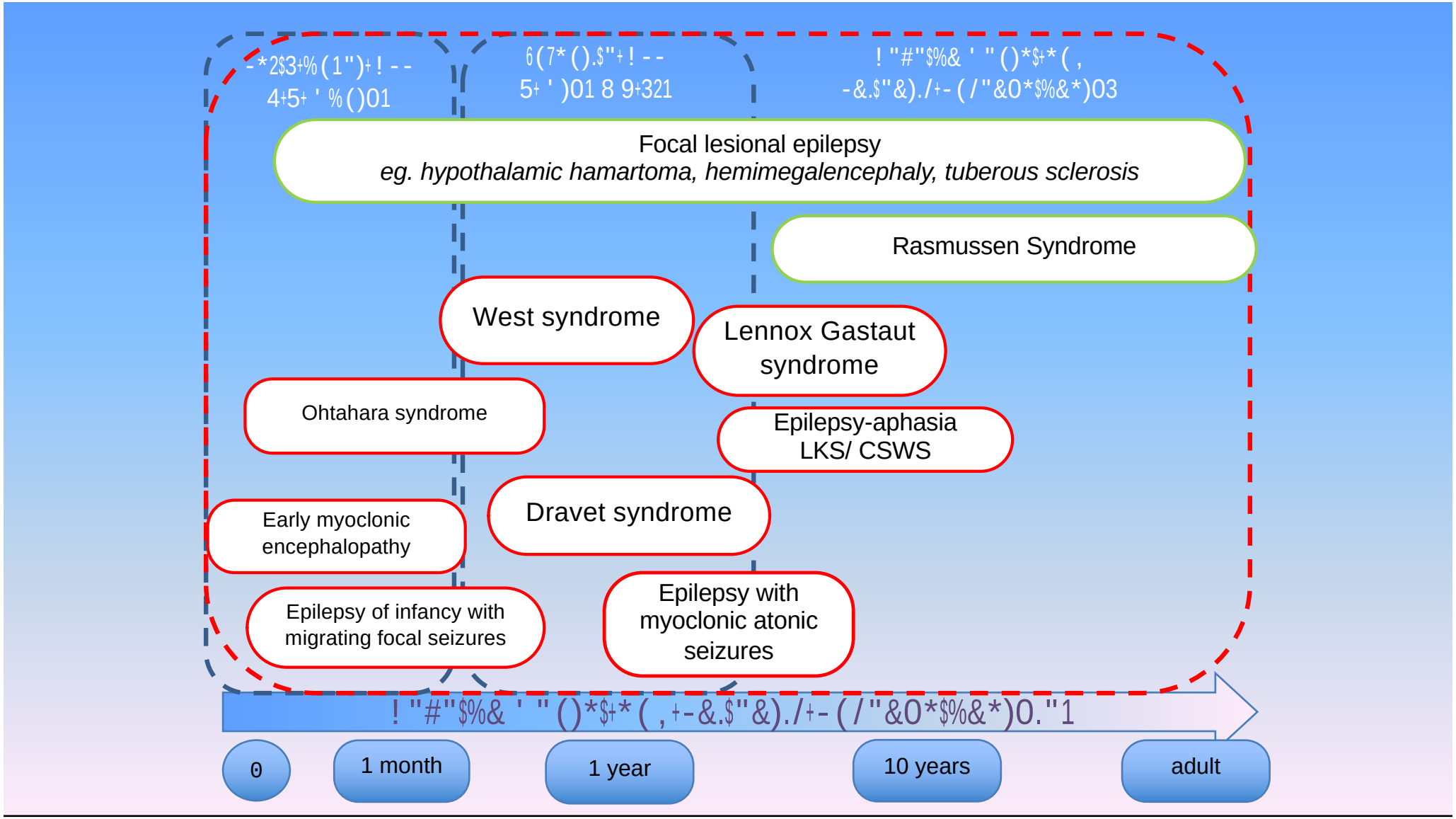
Move to *GENE* encephalopathy

Wide range of comorbidities

Outcome may be poor even though seizures stop

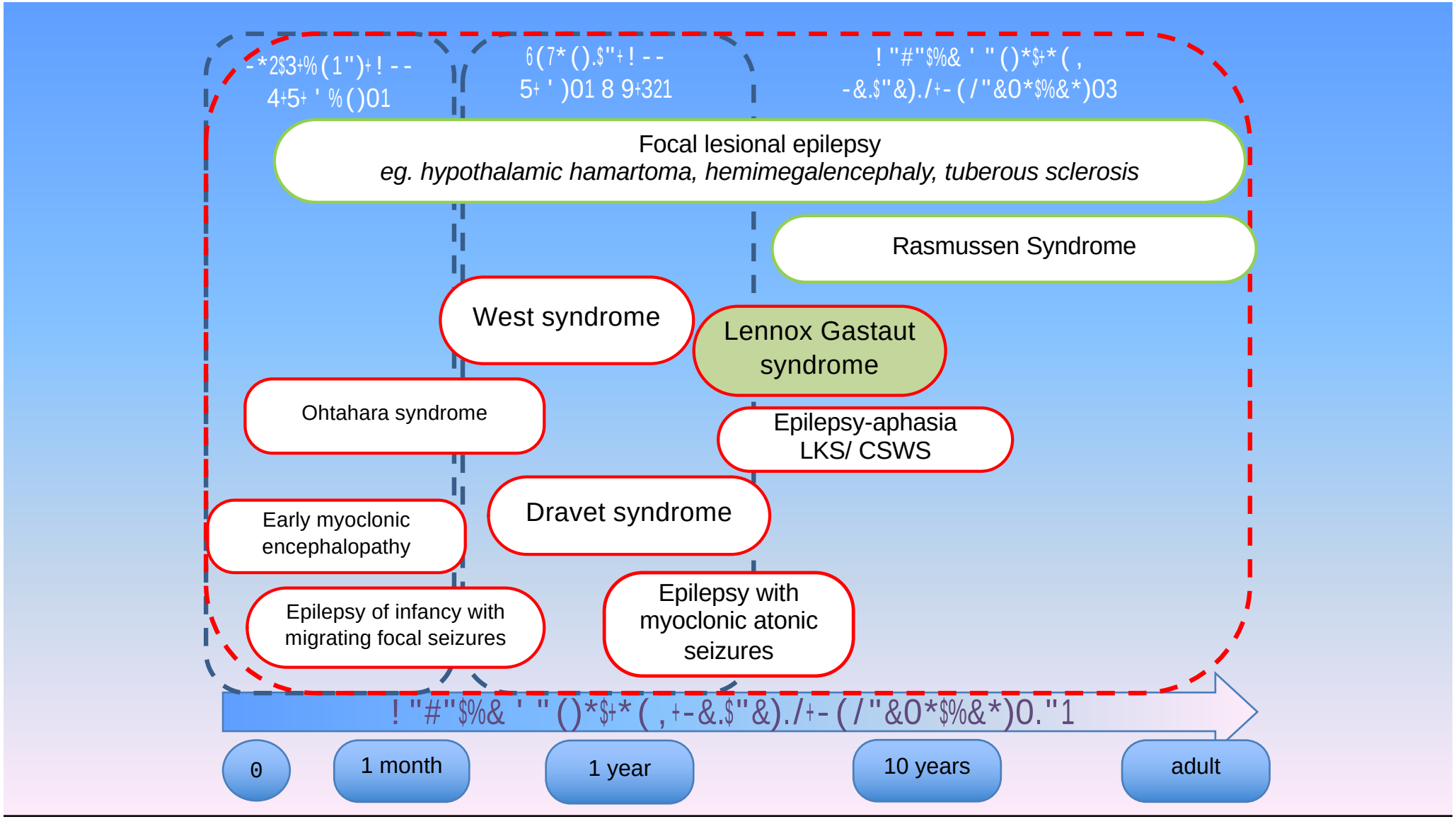
KCNQ2 encephalopathy

Courtesy of Ingrid Scheffer


Focal lesional epilepsy
eg. hypothalamic hamartoma, hemimegalencephaly, tuberous sclerosis
Rasmussen Syndrome
West syndrome
Lennox Gastaut syndrome
Ohtahara syndrome
Epilepsy-aphasia LKS/ CSWS
Dravet syndrome
Early myoclonic encephalopathy
Epilepsy of infancy with migrating focal seizures
Epilepsy with myoclonic atonic seizures
0
1 month
1 year
10 years
adult

Syndromes: Names Change over Time

1939-2004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Evolution of a Name

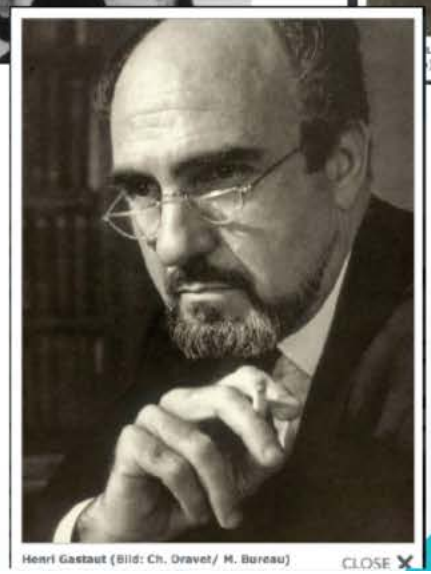
1939 - EEG findings first described by Gibbs, Gibbs and Lennox

1950 – correlation of seizure types and intellectual disability with EEG pattern (Lennox and Davis)

1965 – publication with description of syndrome (Dravet)

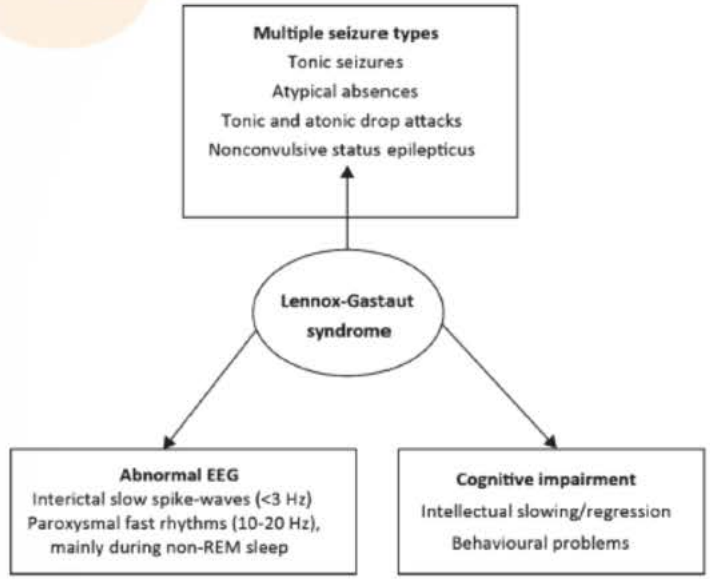
1966 - Lennox Syndrome – 100 cases published (Gastaut et al, 1966)

1969 – Lennox-Gastaut Syndrome (Neidermeyer, 1969)

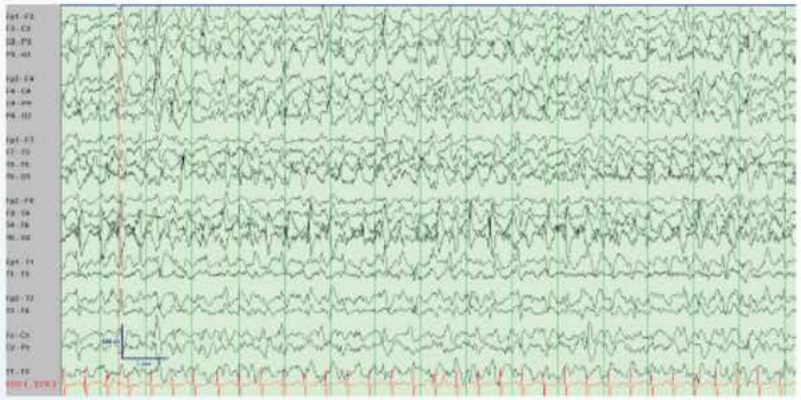


Courtesy of Kelly Knupp

Lennox- Gastaut Syndrome



Bourgeois et al, Epilepsia 2014



ILAE criteria

Must have:

- Tonic seizures during sleep
- Slow spike and wave
- Paroxysmal fast activity
- Abnormal background EEG

May have:

- Any other seizure type

Courtesy of Kelly Knupp

Lennox Gastaut Syndrome – Associated Etiologies

- Brain Malformations
  - Focal cortical dysplasia
  - Double cortex
  - Tumor
- Vascular Abnormalities
  - Hypoxic-Ischemic Injury
  - Stroke
  - Hemorrhage
- Infection
  - Encephalitis
  - Meningitis

10- 25% without an identified cause

- Tuberous sclerosis complex (TSC1, TSC2)
- Tumors (both benign and aggressive)
- Traumatic Brain Injury
- Metabolic
  - Menke syndrome
  - Mitochondrial disorders
- Syndromes
  - Aicardi Syndrome

ARX
RDXP2
ALDH7A1
POLG
CDKL5
STXBP1
SCN2A
FOXG1
PCDH19
SLC2A1
MeCP2
SLC6A1

Courtesy of Kelly Knupp

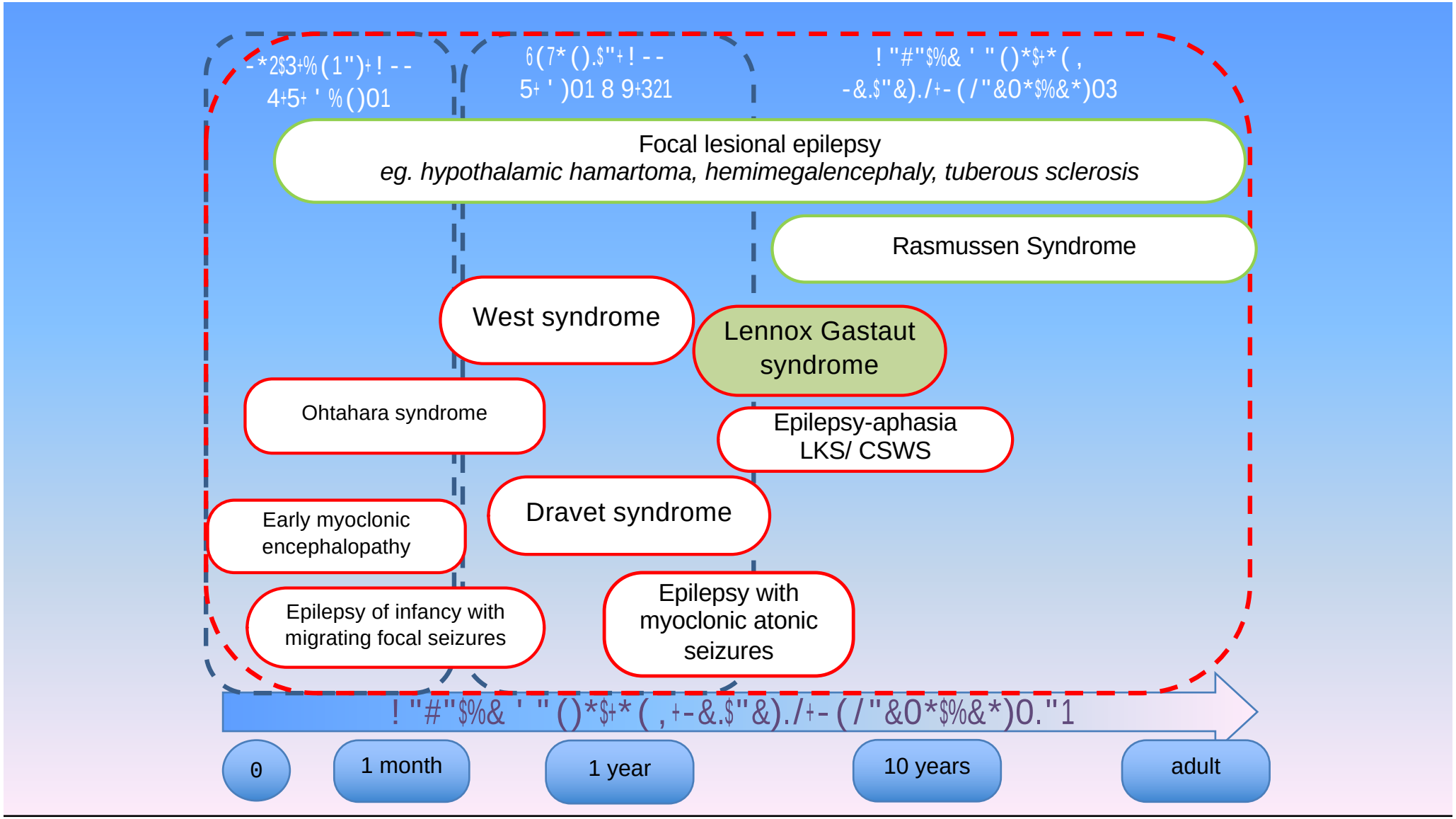
Varied Definitions of LGS

Author	Childhood Onset	IDD	Multiple Seizure Types	Tonic Seizure in Sleep	Diffuse Slow SSW	Fast Rhythms in Sleep
Lennox 1950[1]	✗	✓	✓	✗	✓	✗
Trevathan 1997[2]	✓	✗	✓	✗	✓	✗
Genton 2000[3]	✓	✓	✓	✗	✓	✓
ILAE 2001[4]	✓	✓	✓	✓	✓	✓
French 2004[5]	✗	✓	✓	✗	✓	✗

Abbreviations: IDD, intellectual developmental disorder; ILAE, International League Against Epilepsy; LGS, Lennox-Gastaut syndrome; SSW, slow spike-wave.

1. Lennox WG, Davis JP. *Pediatrics*. 1950;5:626-44.
2. Trevathan E, Murphy CC. *Epilepsia*. 1997;38:1283-8.
3. Genton P, et al. Handbook of Clinical Neurology. 2000;73(29) (reviewed in Van Rijkevorsel K. *Neuropsych Dis Treat*. 2008;4:1001-19).
4. Engel J. *Epilepsia*. 2001;42:796-803.
5. French J, et al. *Neurology*. 2004;62:1261-73.

Courtesy of Jack Pellock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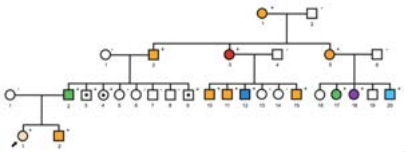
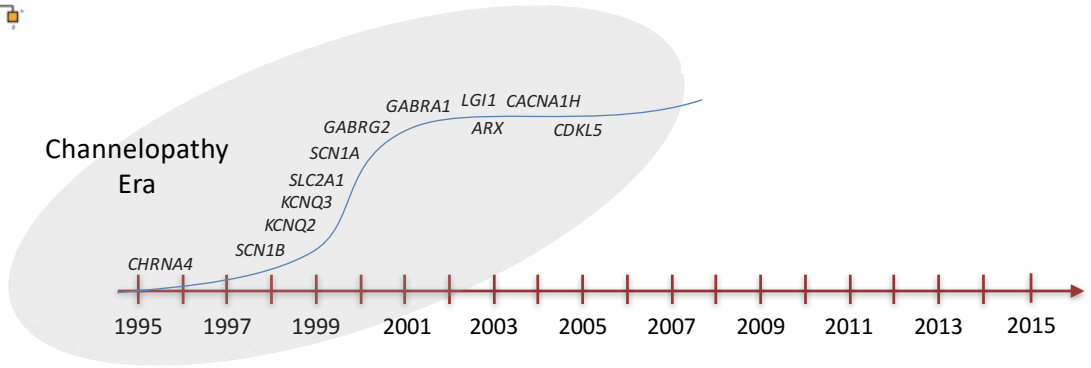
Syndromes and Genes

1995-Present

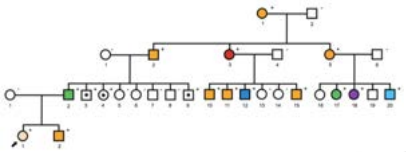
Gene discovery in epilepsy





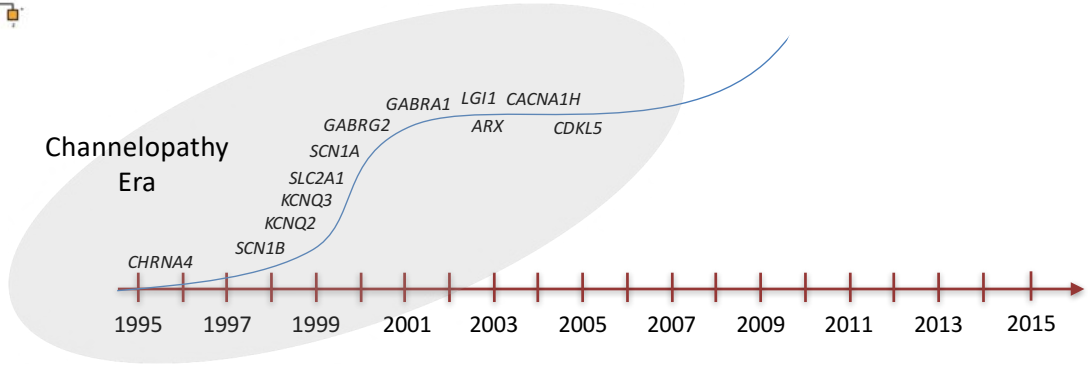
Ingo Helbig & Heather Mefford

Gene discovery in epilepsy



Microdeletions

15q13.3
16p13.11
15q11.2



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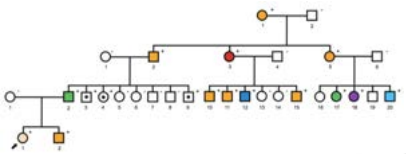


Channelopathy Era

CHRNA4
SCN1B
KCNQ2
KCNQ3
SLC2A1
SCN1A
GABRG2
GABRA1
LGI1
CACNA1H
ARX
CDKL5

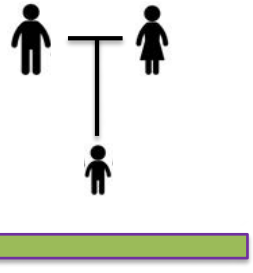
Next-gen Sequencing Era

STX1B
SLC6A1
GABRA1
GABRB3
SIK1
KCNA2
ALG13
GRIN2B
PURA
KCNB1
KCNC1
DNM1
HCN1
CHD2
SCN8A
SCN2A
GRIN2A
DEPDC5
KCNT1
PRRT2
TBC1D24
STXBP1
PCDH19

Microdeletions

15q13.3
16p13.11
15q11.2

1995 1997 1999 2001 2003 2005 2007 2009 2011 2013 2015

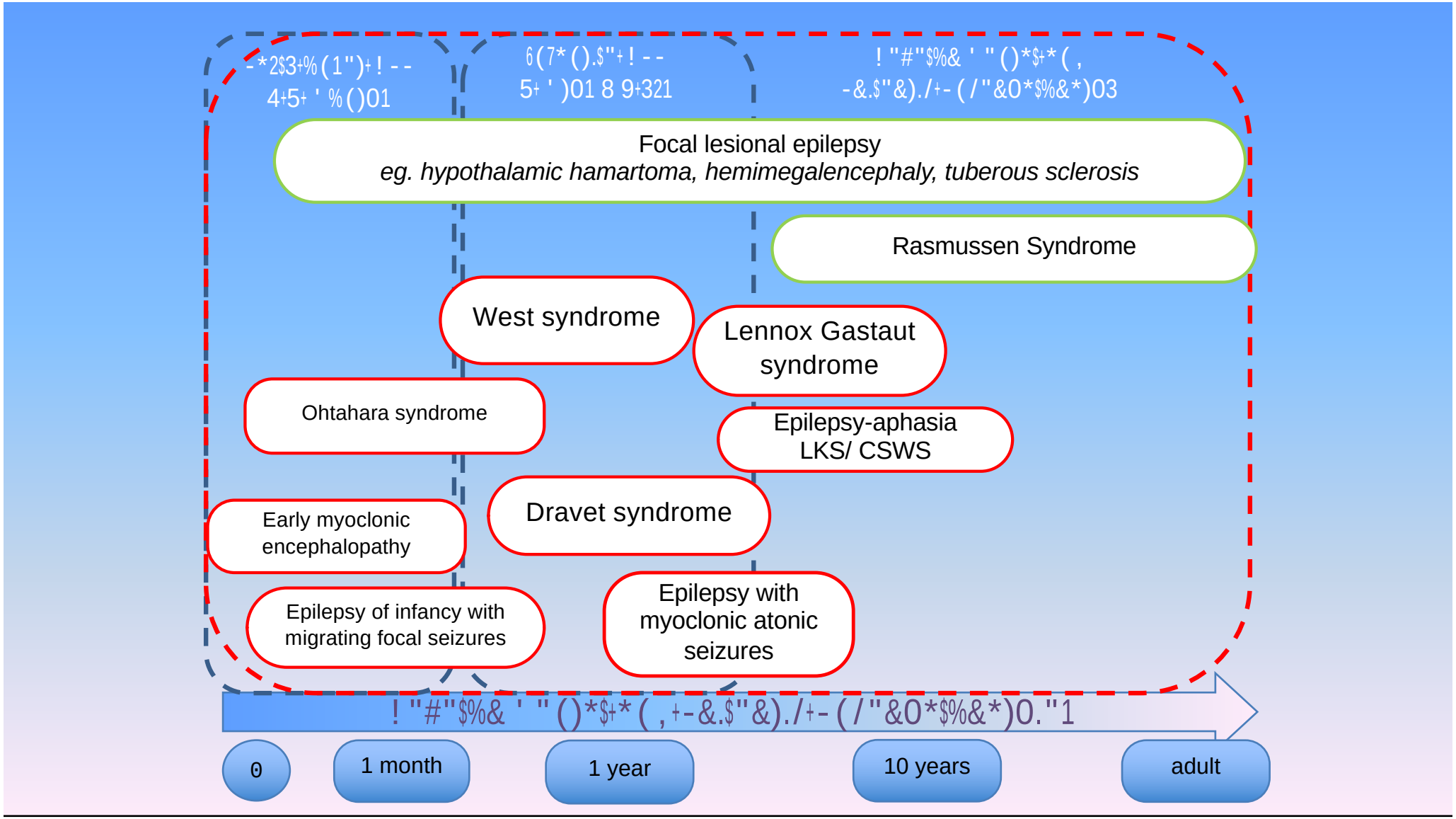


DEEs including **LGS**

Gene panels

Exome sequencing

Ingo Helbig & Heather Mefford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1 month
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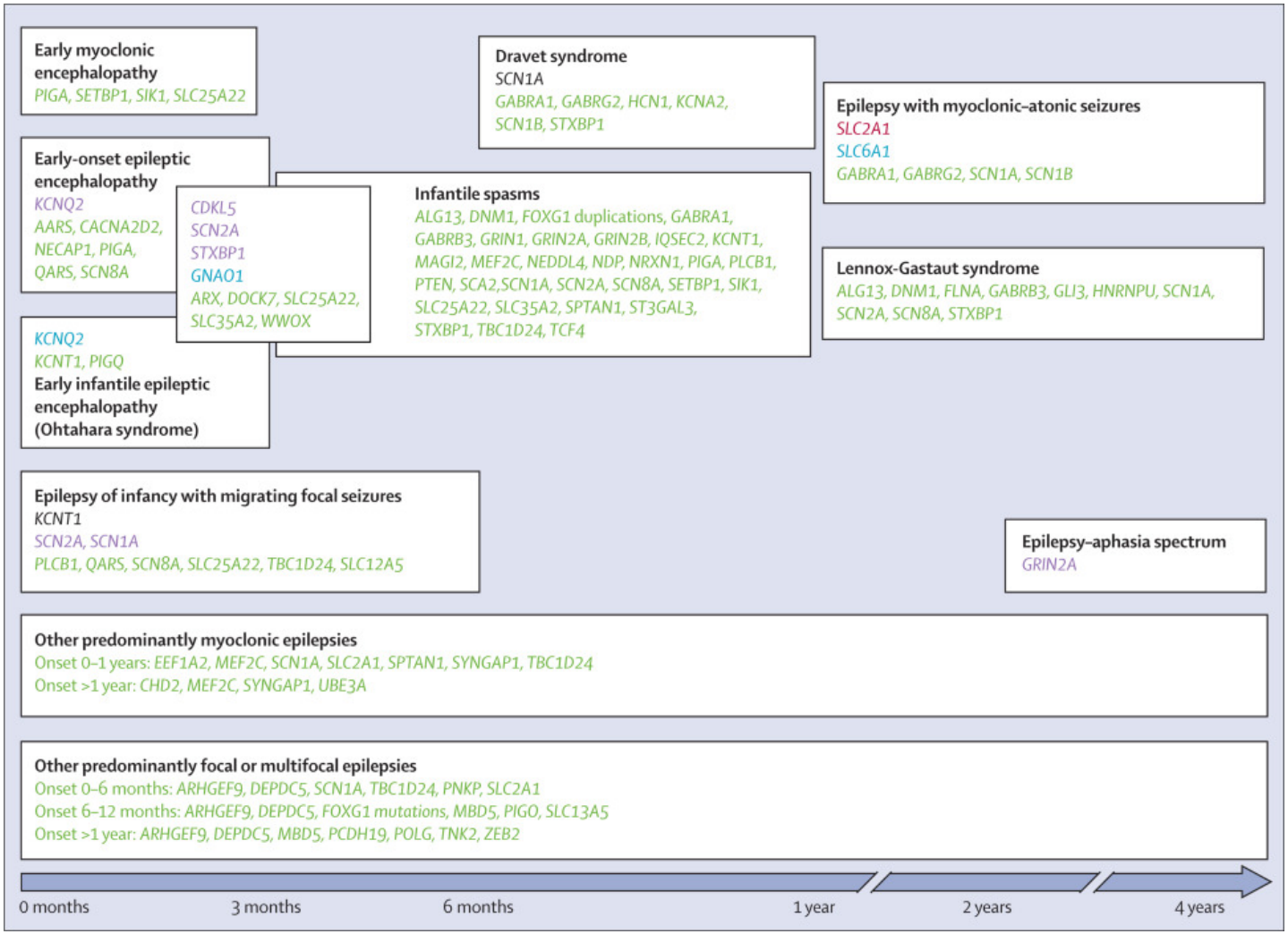
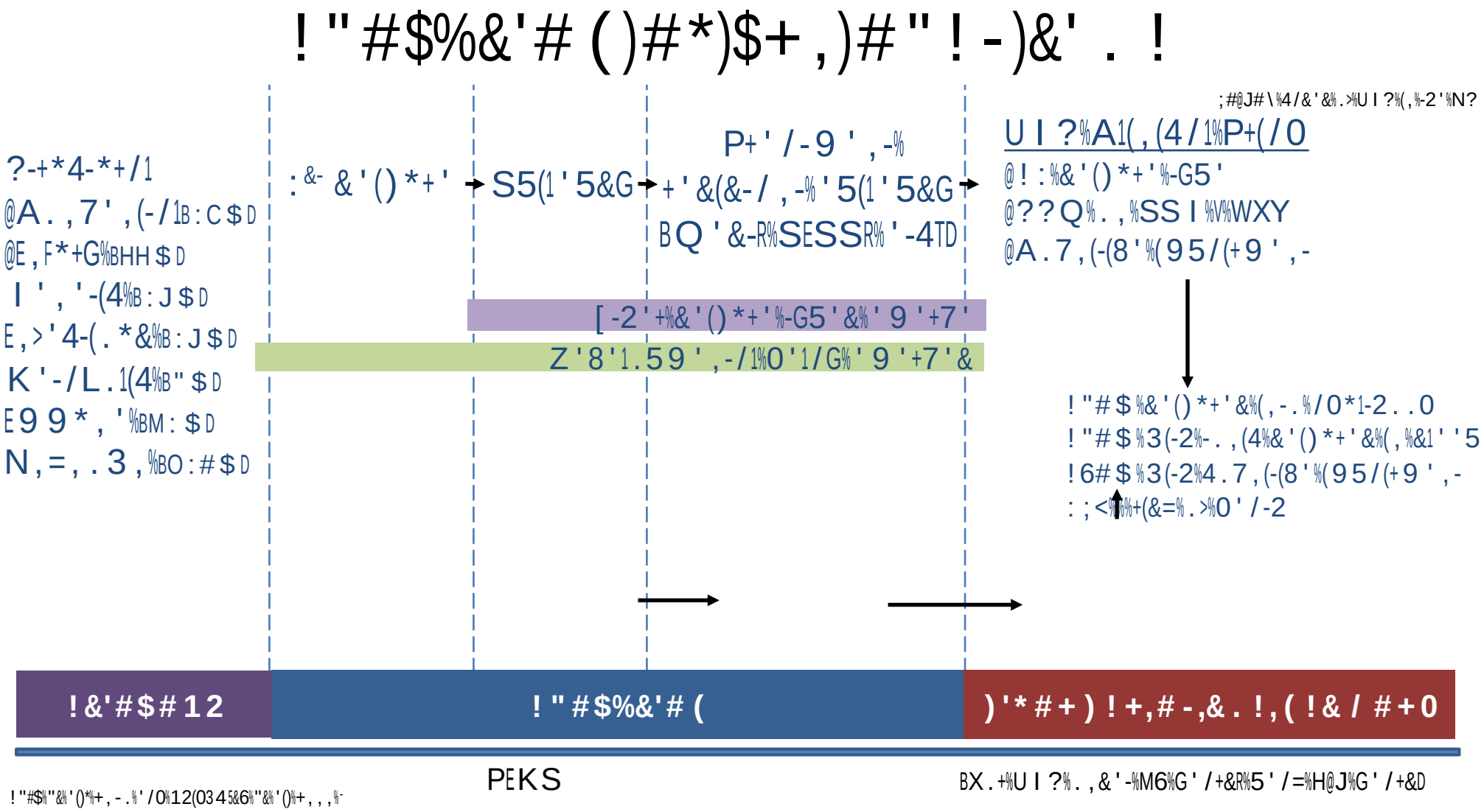
Genetic Landscape of the DEEs



McTague et al, 2016

Why does all this naming craziness matter?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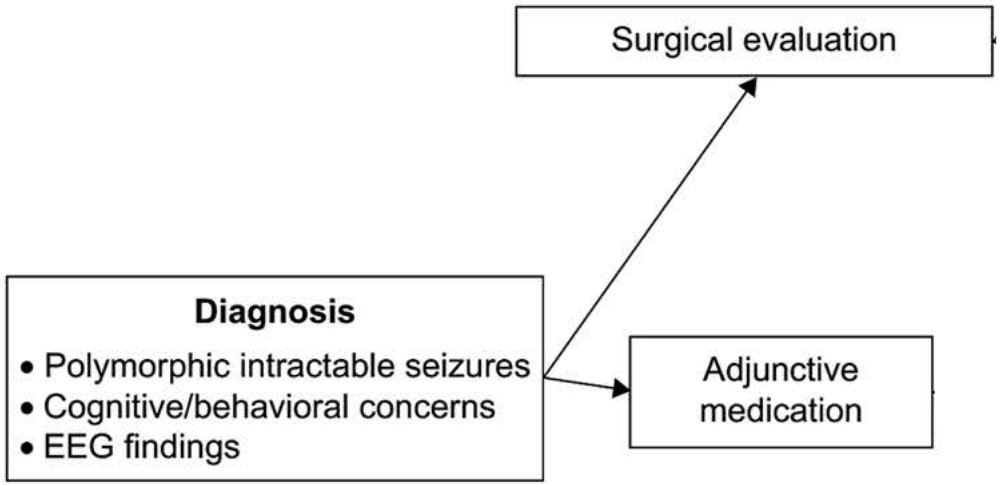
Proposed Management of Seizures in LGS



First-tier preferred medications are in bold; for these, overall seizure reduction in LGS ranges from ~20% to ~70% with considerable variability between patients and seizure types.

*Commonly used medications without level 1 or 2 efficacy evidence

Ostendorf AP, Ng YT. *Neuropsychiatr Dis Treat*. 2017;13:1131-1140.

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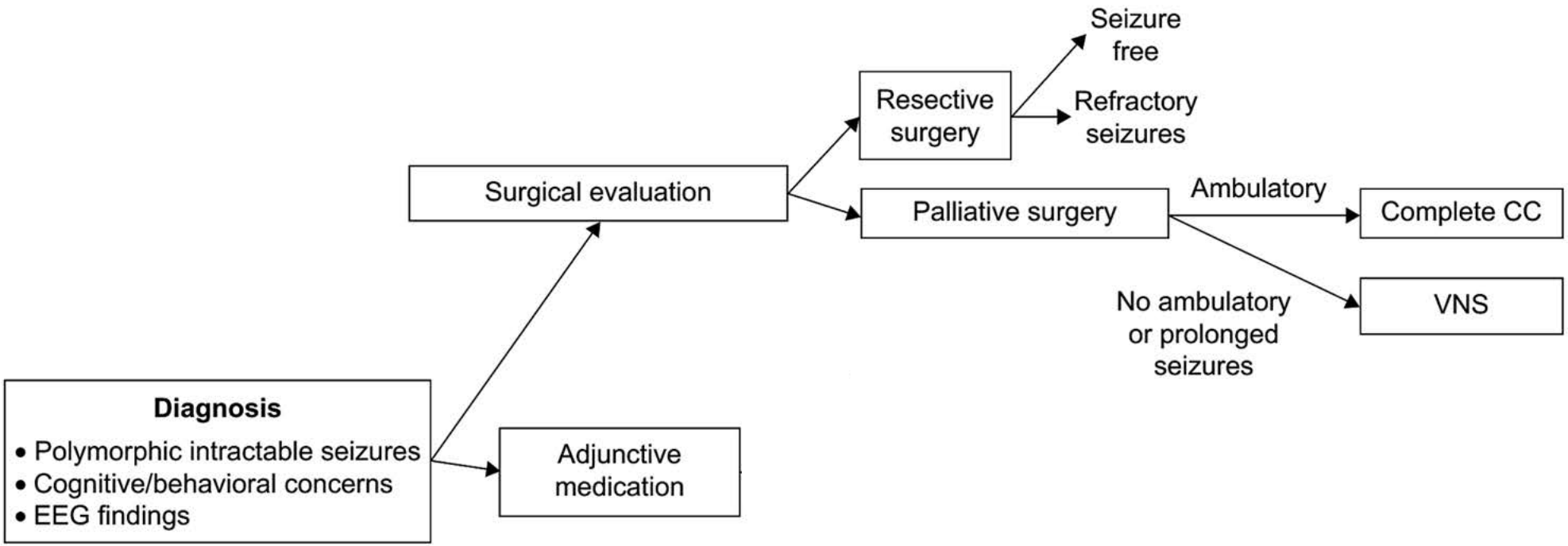

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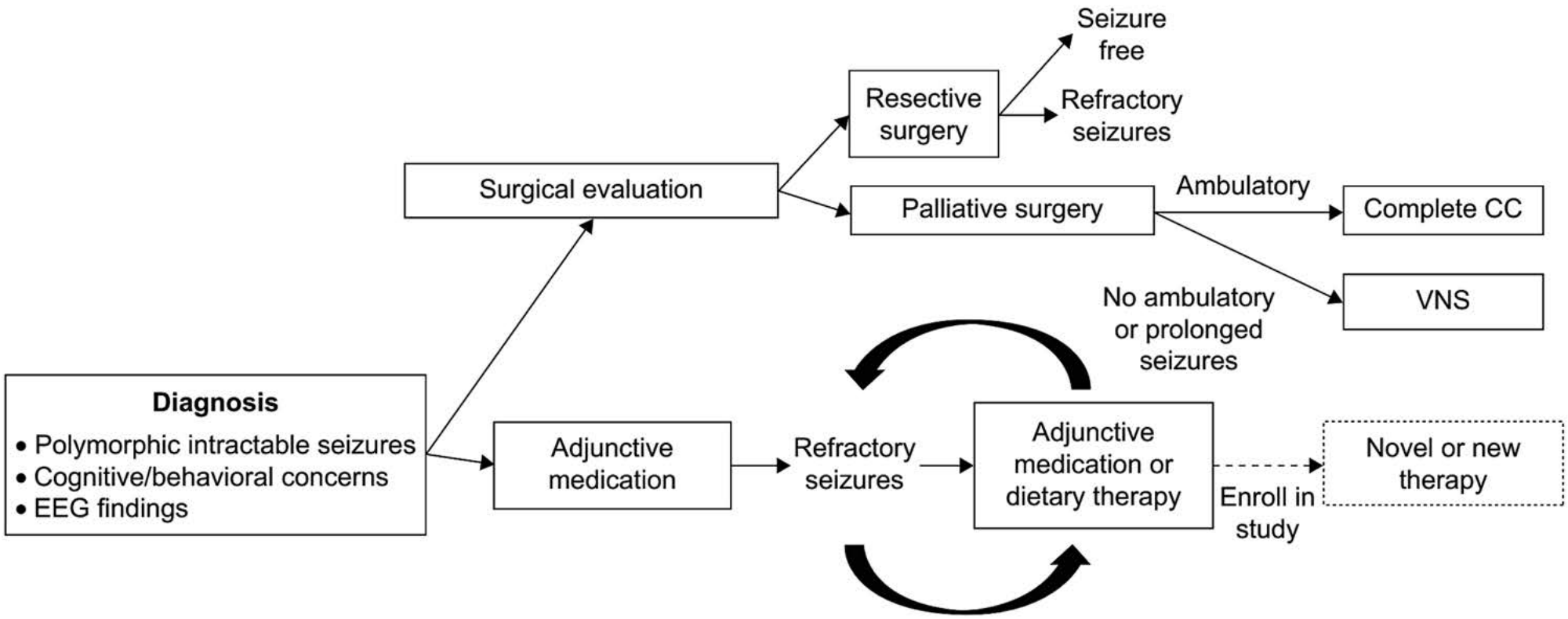

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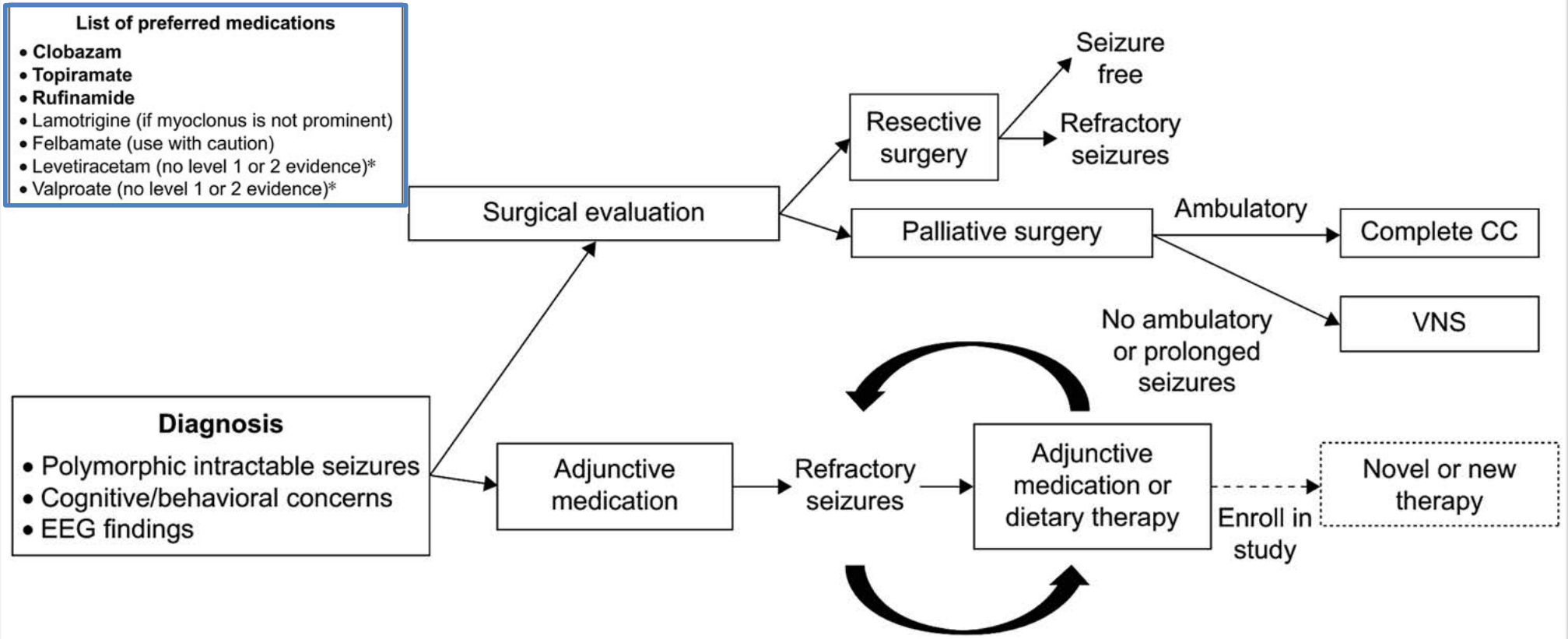

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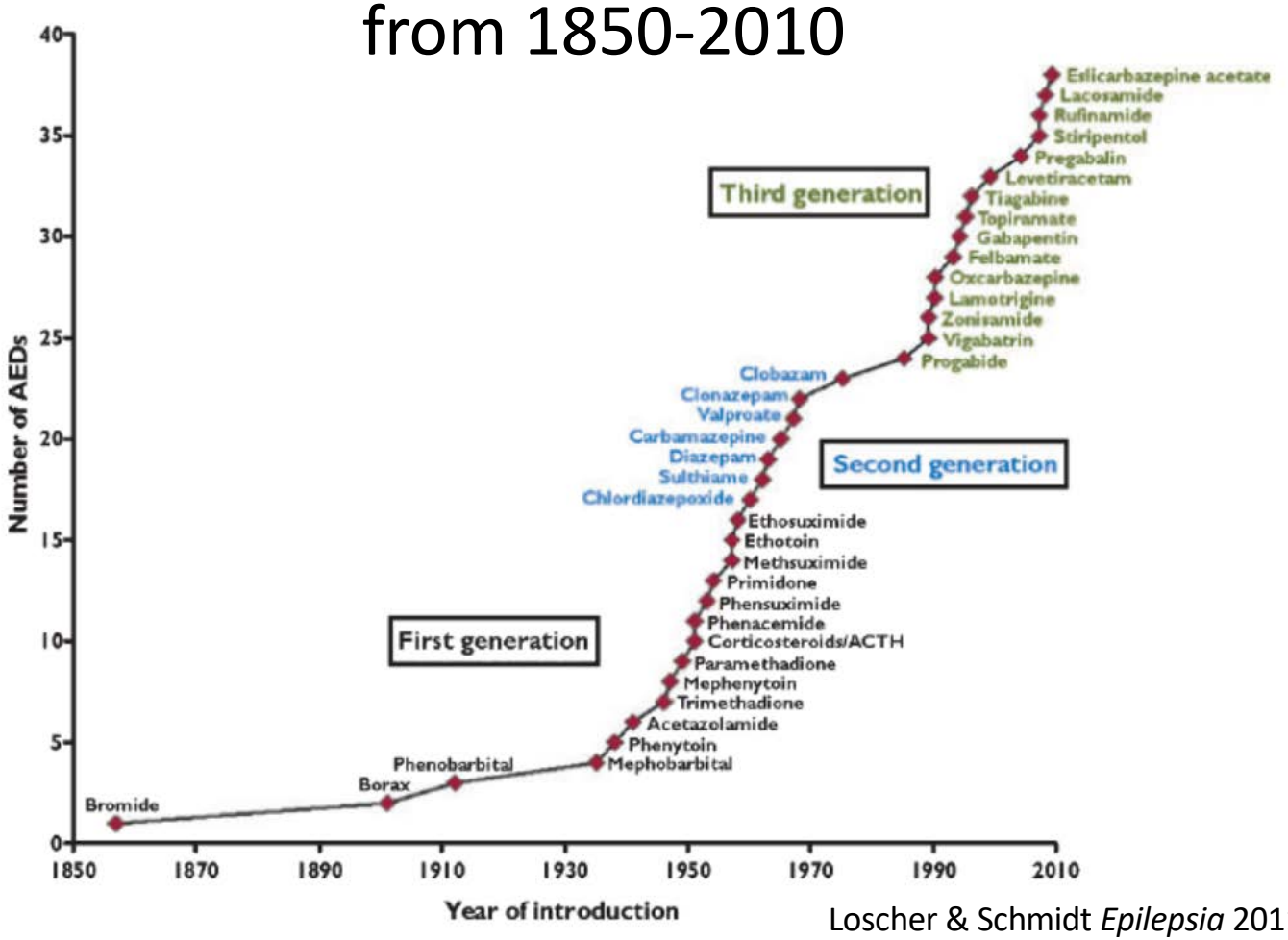
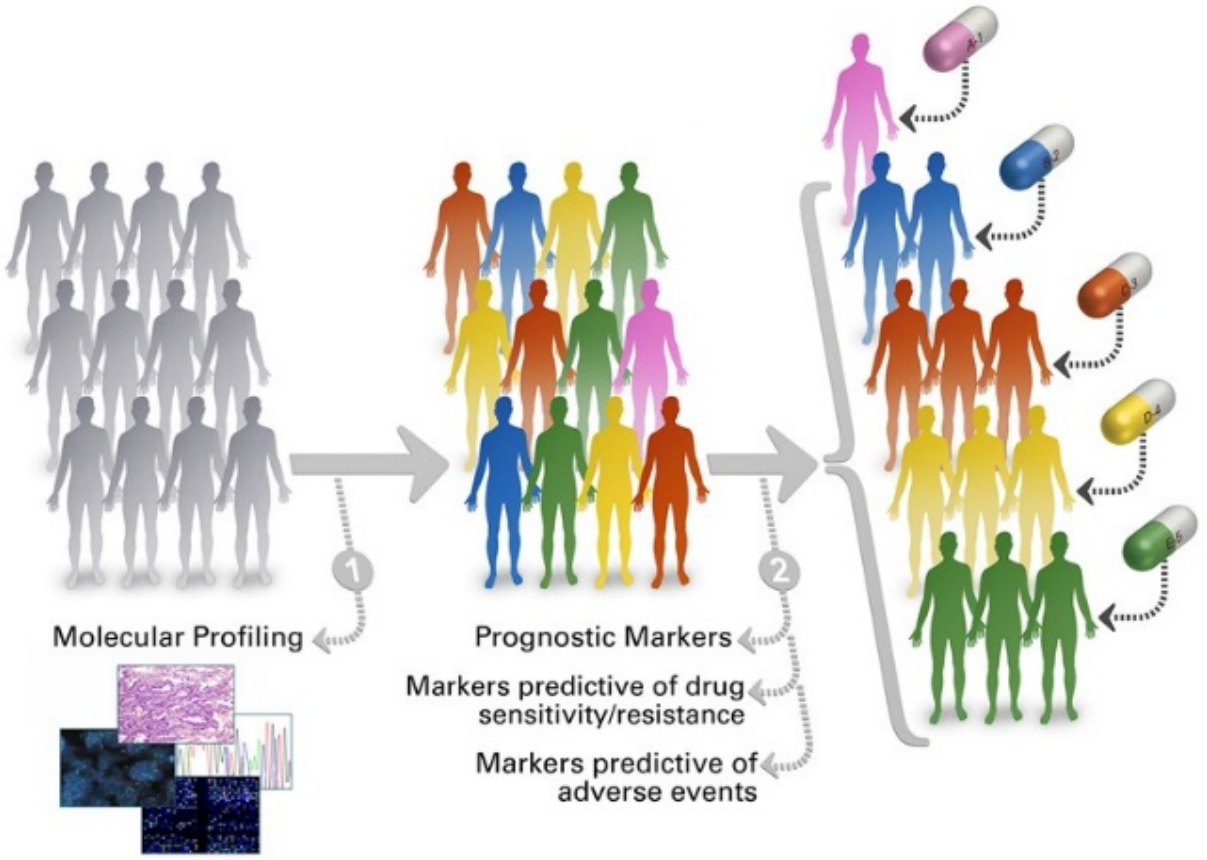
~40 approved epilepsy medications from 1850-2010



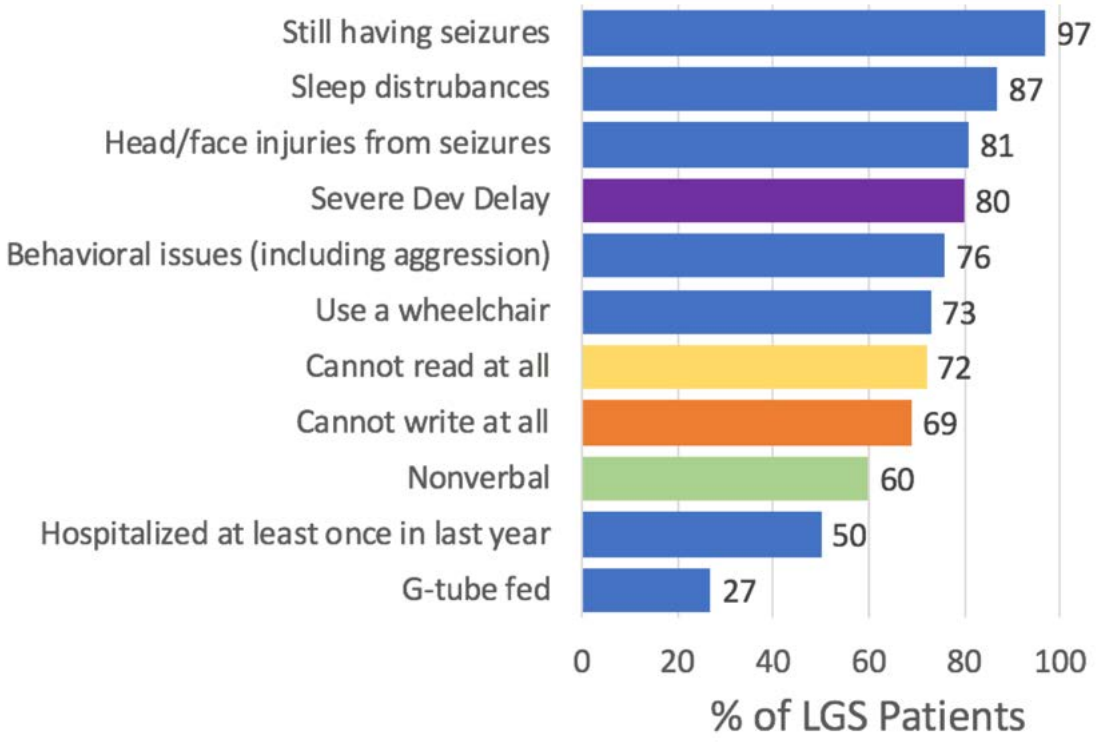
Loscher & Schmidt *Epilepsia* 2011

Genomic & Precision Medicine



LGS and DEEs are more than just counting seizures

Major Issues Reported by LGS Caregivers



Caregiver Priorities:

1. Seizures and safety
2. Delay/ID, especially communication
3. Behavior, especially aggression
4. Mobility and physical care issues
5. Sleep
6. Costs/Access to care
7. Social Isolation

n=416

LGS Foundation Caregiver Survey 2018 (in preparation)

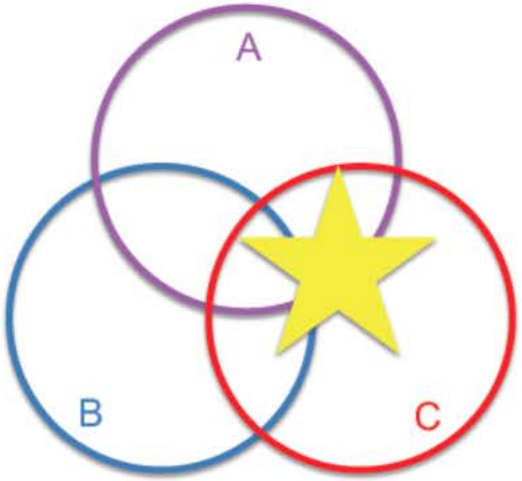
Meanwhile, at today's Feline Engagement Committee, decisions were made on how to increase feline recruitment.

LGS FOUNDATION
LENNOX-GASTAUT SYNDROME

Thank you

Tracy@lgsfoundation.org
www.lgsfoundation.org

How distinct are Epilepsy Syndromes?



Many features might overlap, but the hope is that the cluster of symptoms are "specific" to that epilepsy syndrome...this is often better in theory than practice.

Courtesy of Kelly Knupp