



Precision medicine in genetic epilepsy from childhood to adulthood

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Research Institutes, Melbourne, Australia

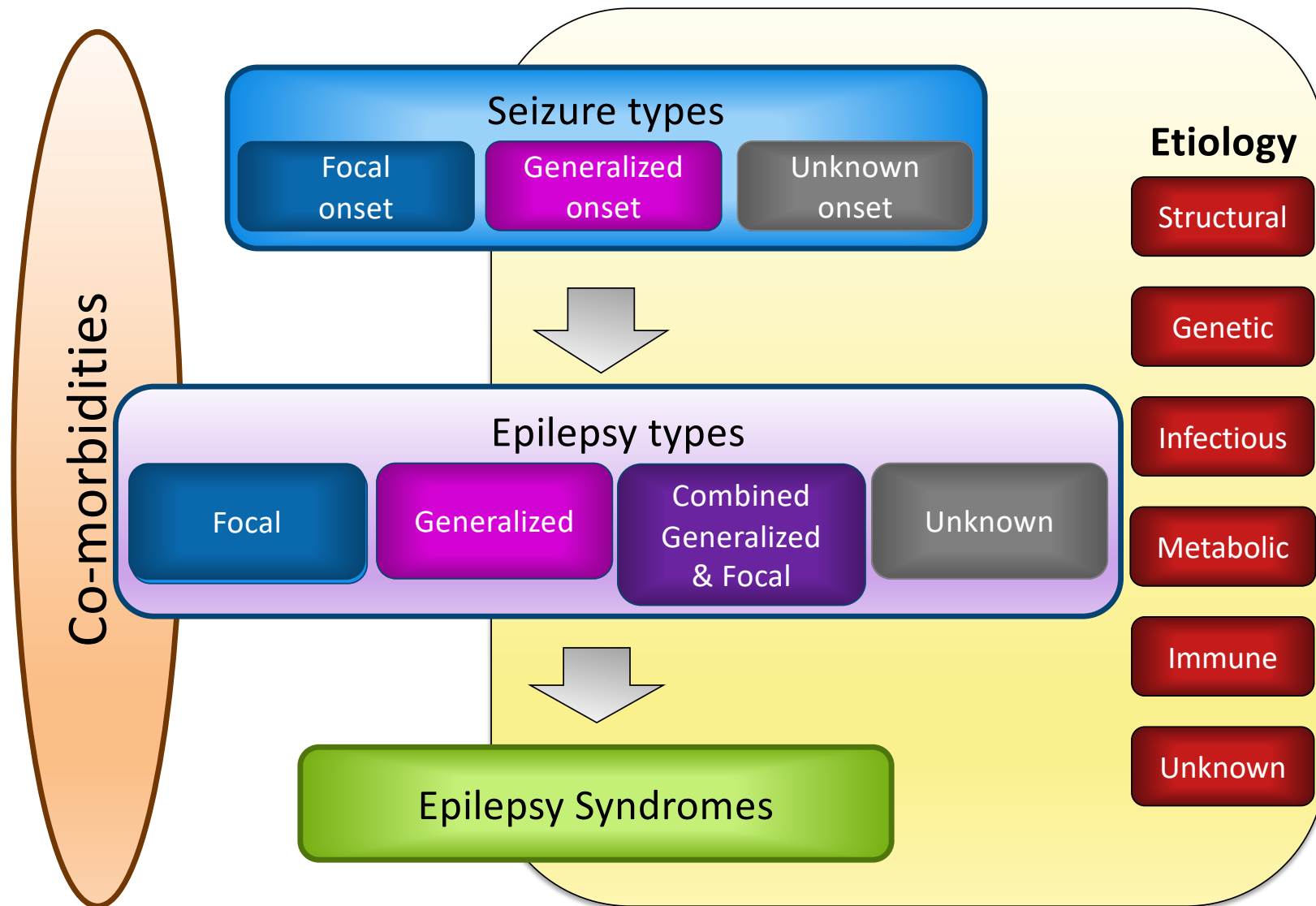
Outline

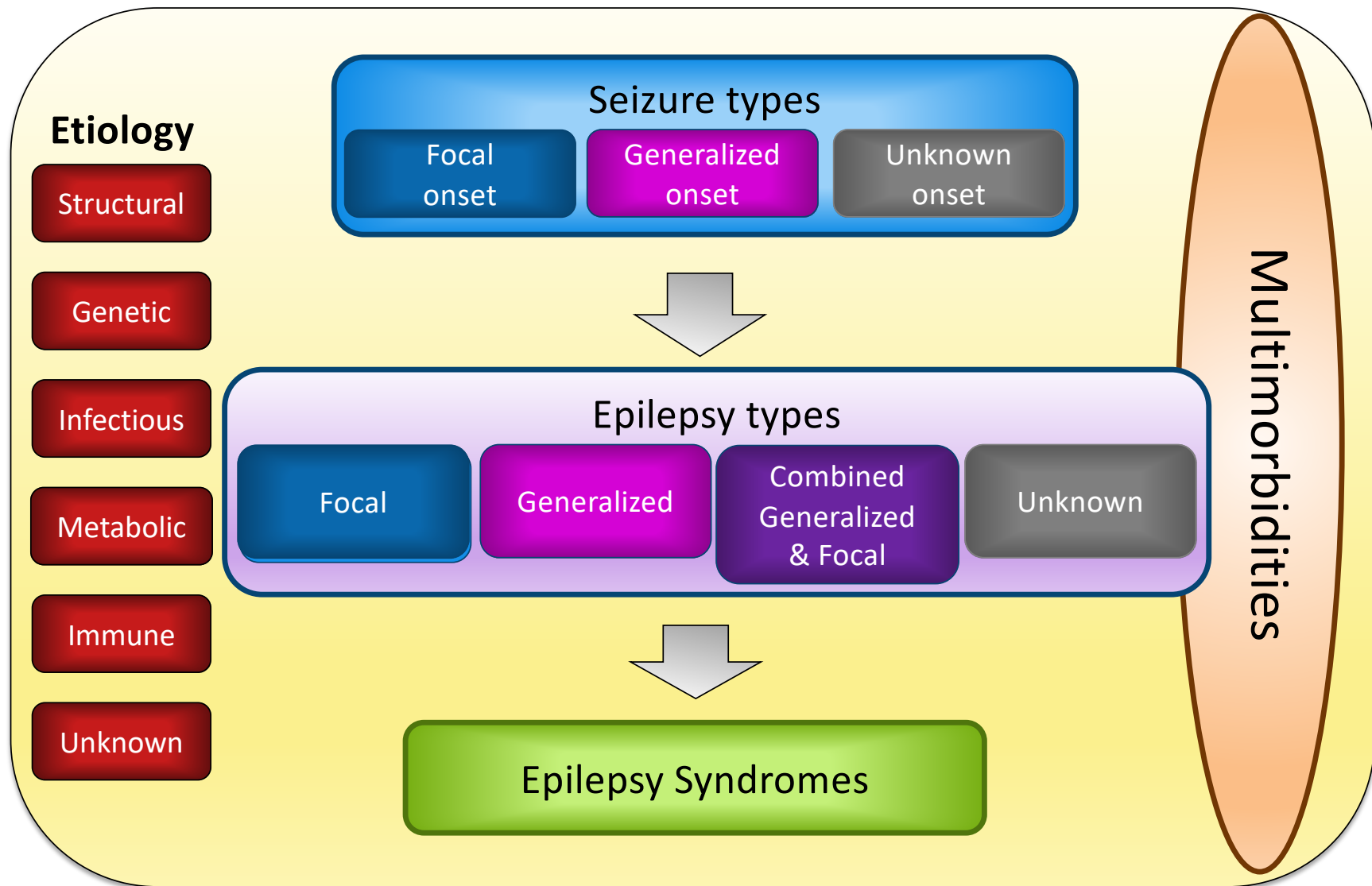
Diagnosing epilepsy syndrome and aetiology

Etiology specific spectrum of epilepsy syndromes

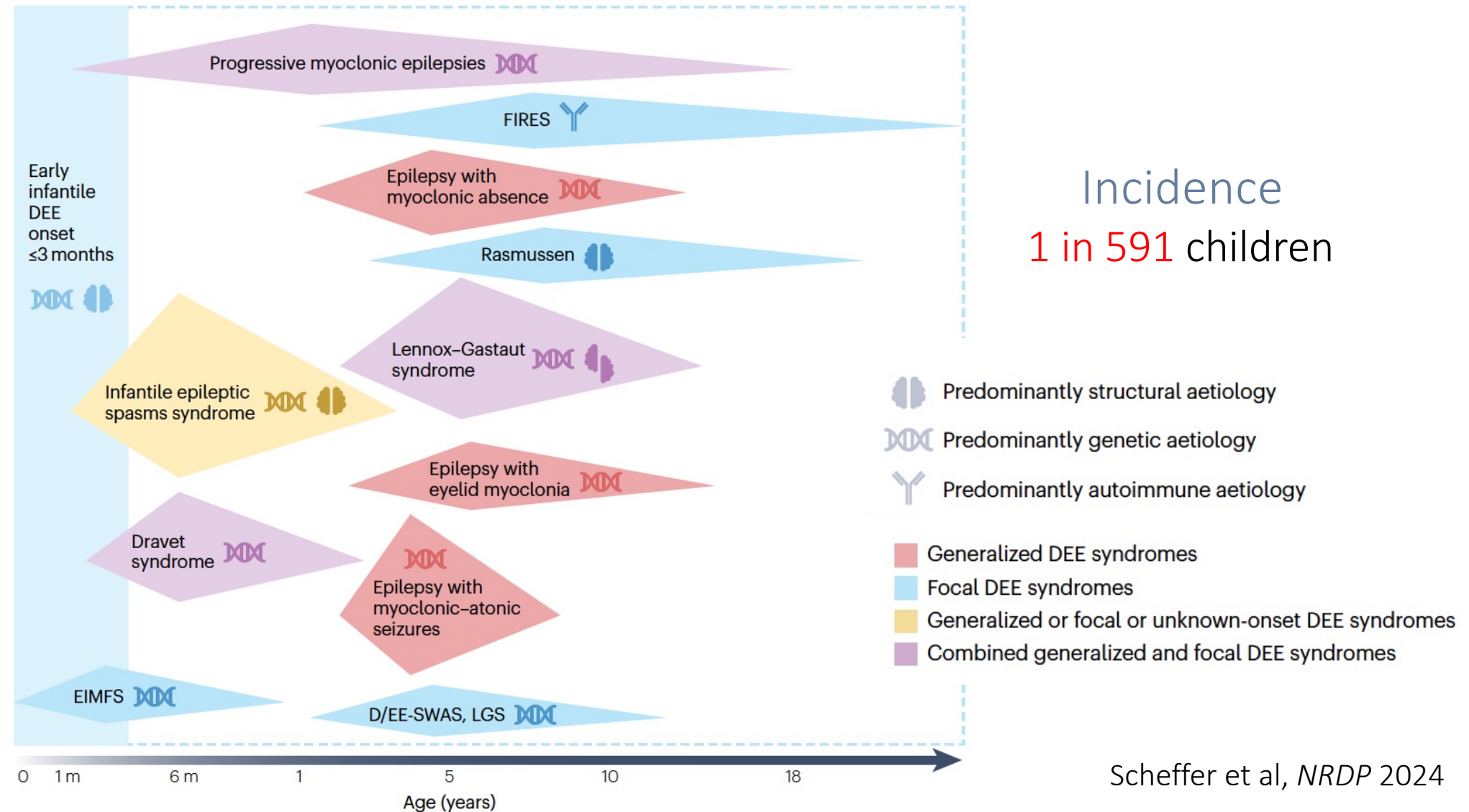
Natural history studies

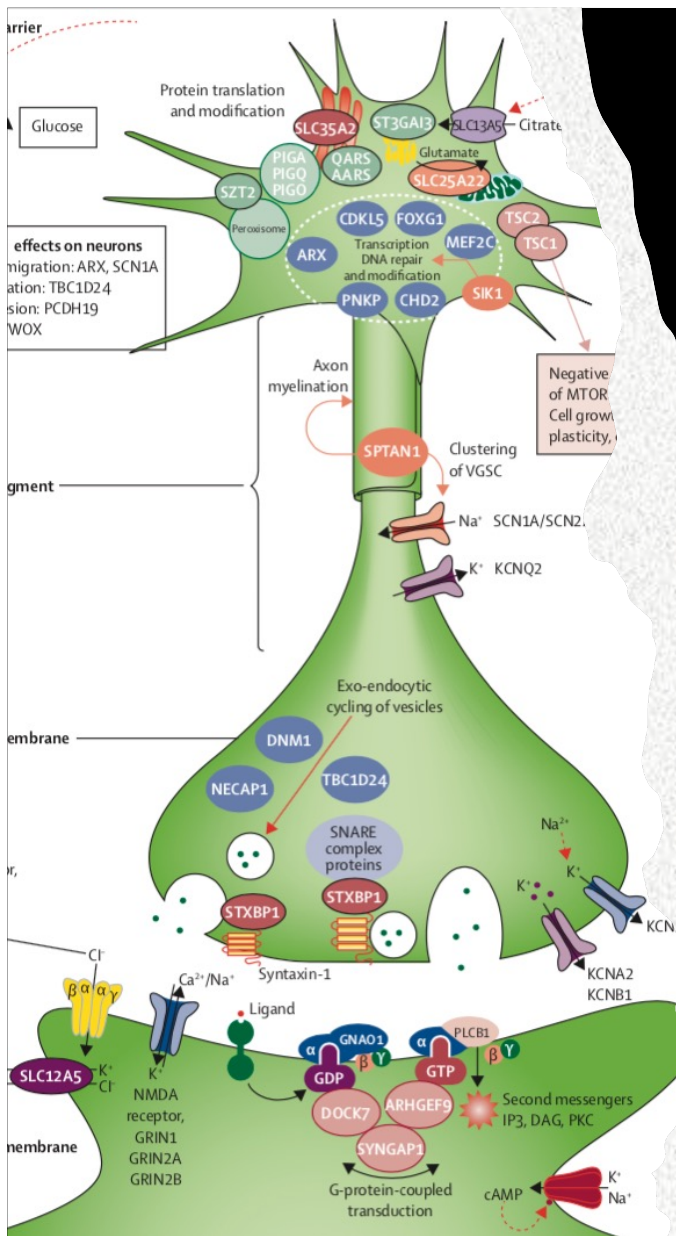
Precision medicine –many approaches





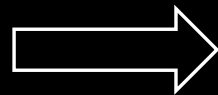
Developmental and Epileptic Encephalopathies





Genes for Developmental and Epileptic Encephalopathies

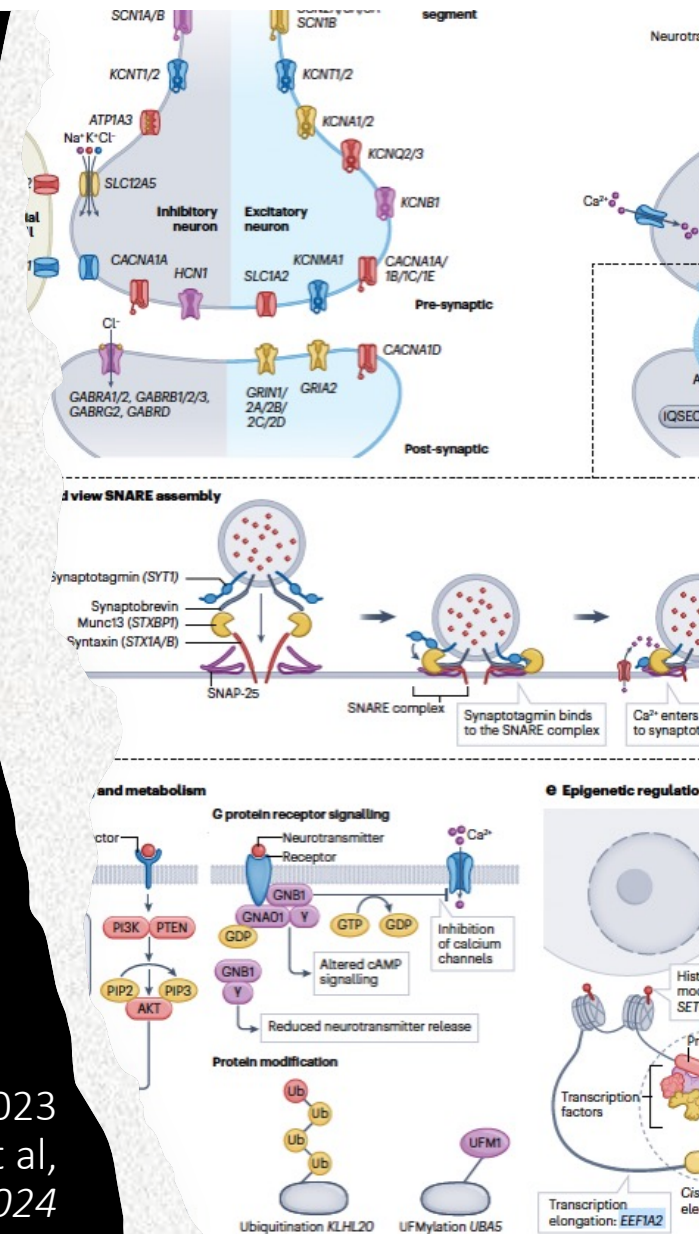
60
2016



>970
2026

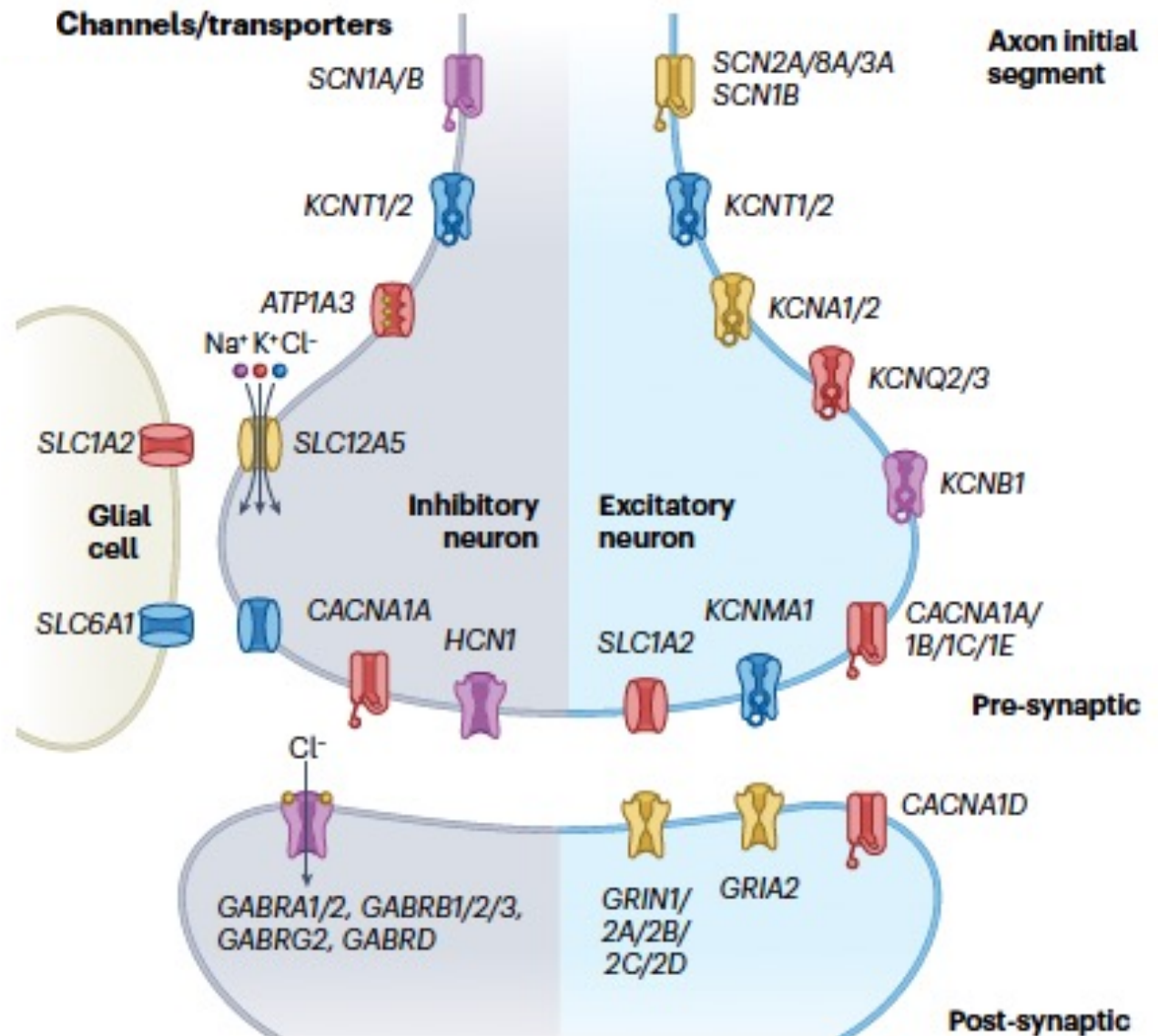
McTague et al,
Lancet Neurol 2016

Oliver et al 2023
Scheffer et al,
NRDP 2024



Developmental and Epileptic Encephalopathies Mechanisms:

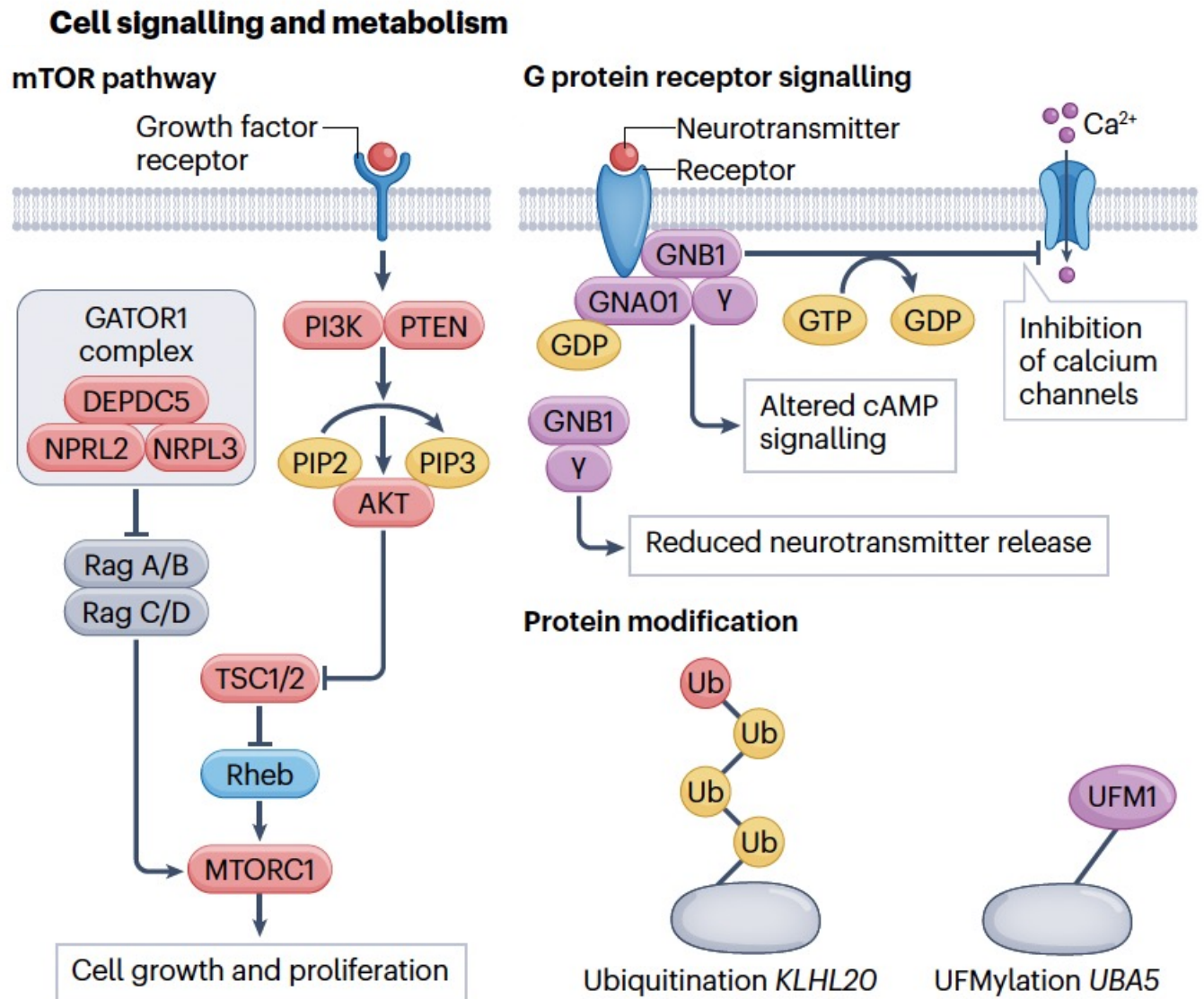
Channels and transporters



Developmental and Epileptic Encephalopathies Mechanisms:

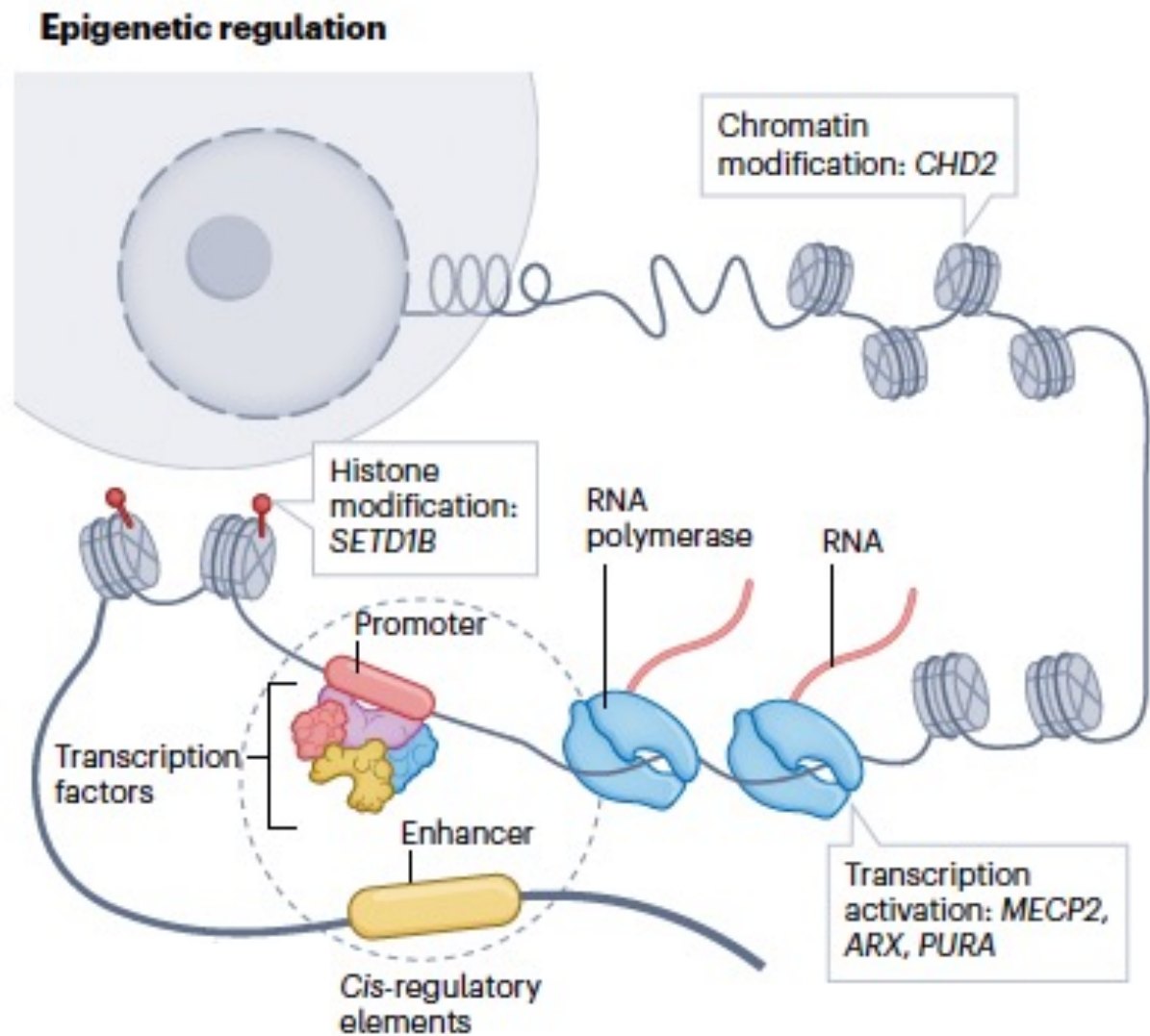
Cell signalling and metabolism

Scheffer, McTague et al, *NRDP* 2024

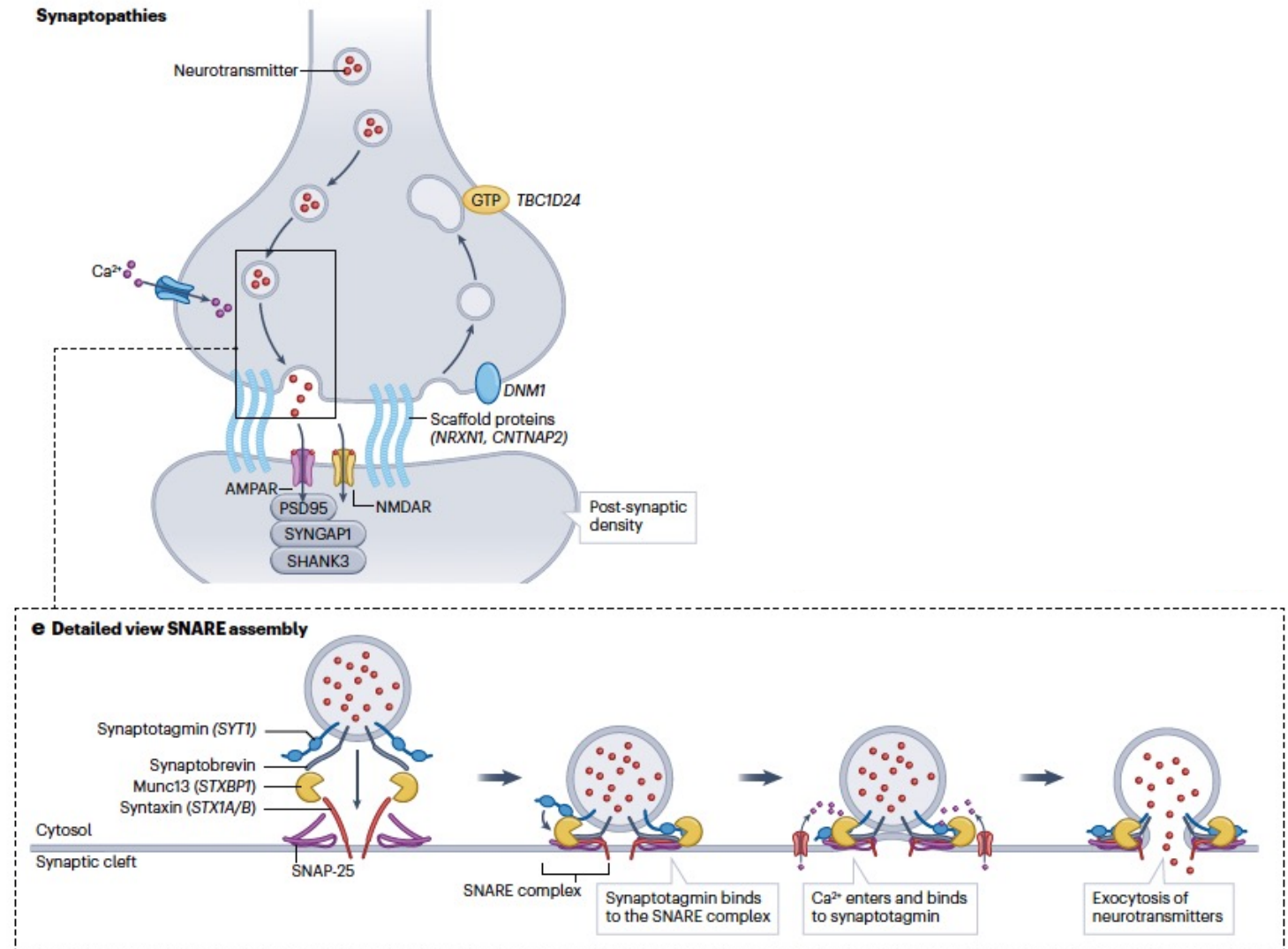


Developmental and Epileptic Encephalopathies Mechanisms:

Epigenetic regulation



Developmental and Epileptic Encephalopathies Mechanisms: Synaptopathies



Epilepsy Syndromes

ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: Position statement by the ILAE Task Force on Nosology and Definitions

Zuberi et al Epilepsia, 2022

Etiology-specific syndromes

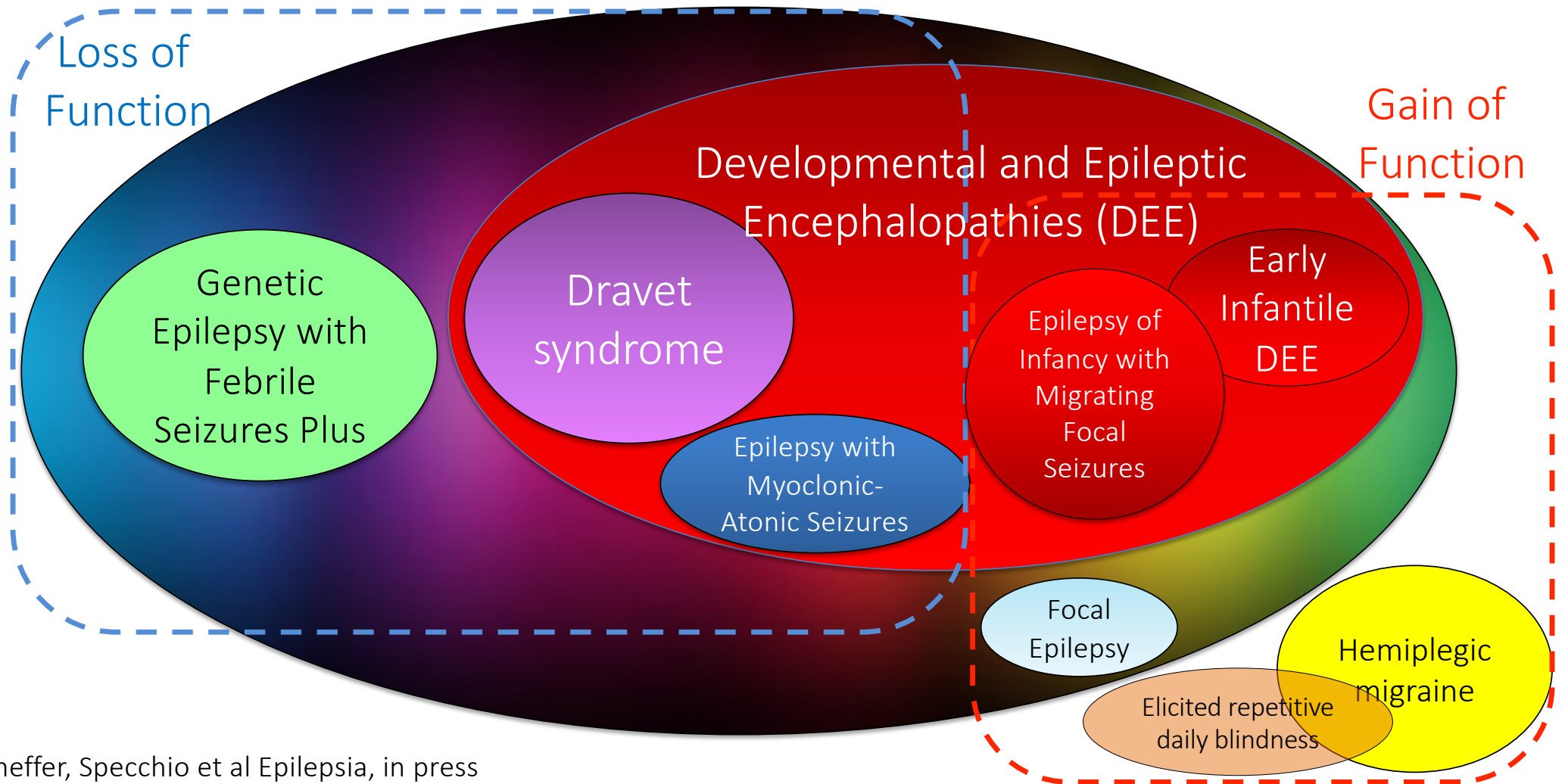
- *KCNQ2*-DEE
- Pyridoxine-dependent (*ALDH7A1*)-DEE (PD-DEE)
- Pyridox(am)ine 5'-Phosphate Deficiency (PNPO)-DEE (PSPD-DEE)
- *CDKL5*-DEE

Etiology-specific spectrum of epilepsy syndromes (ESSES)

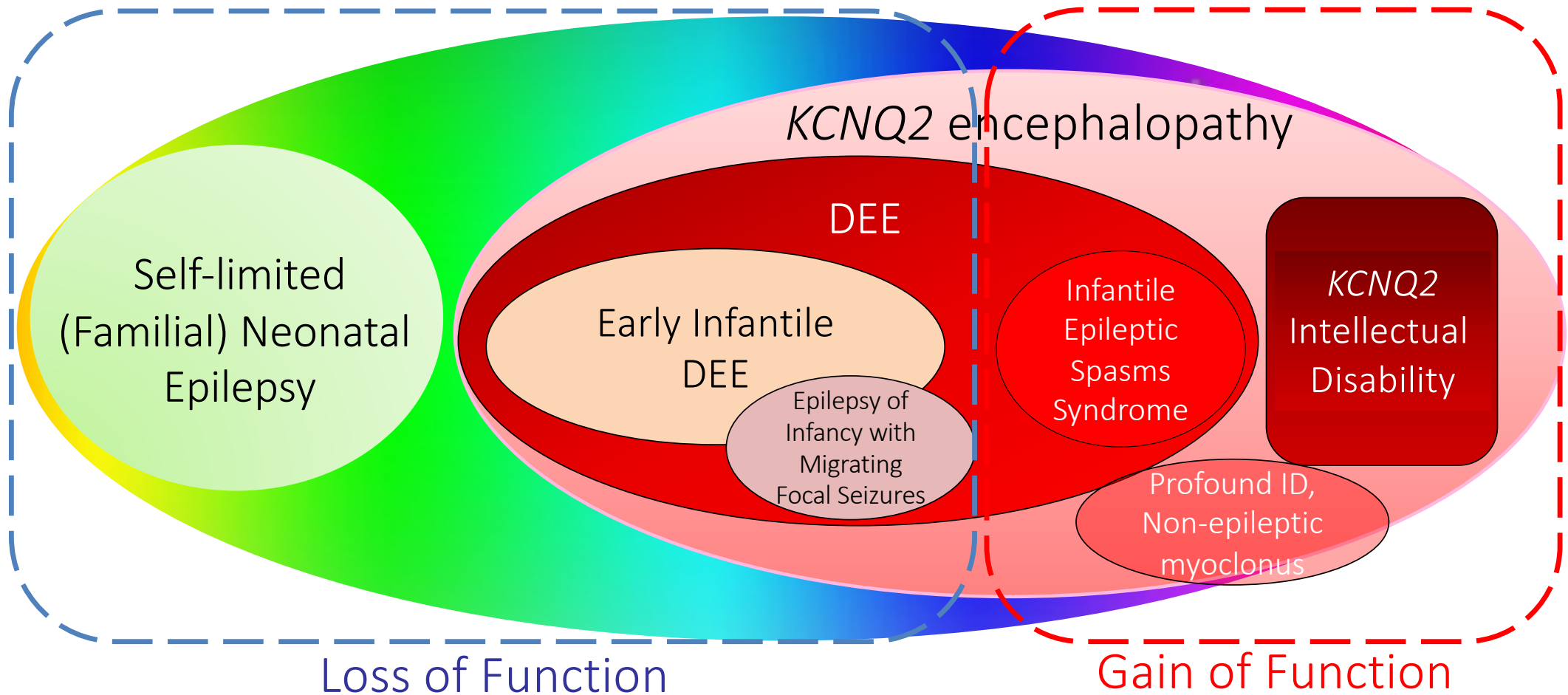
(*GLUT1DS*)

- Sturge Weber syndrome (SWS)
- Gelastic seizures with hypothalamic hamartoma (GS-HH)

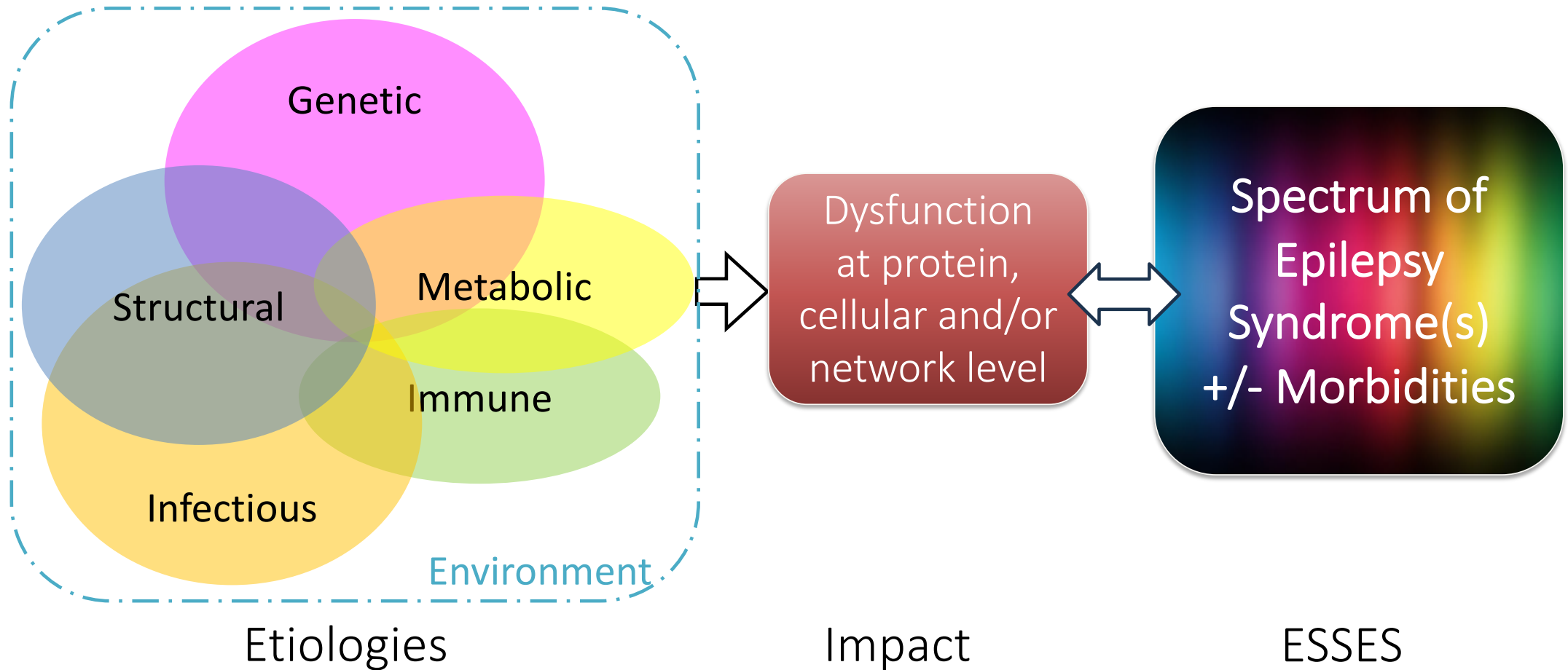
SCN1A spectrum of epilepsy syndromes and related disorders



KCNQ2 spectrum of epilepsy syndromes and related disorders



Etiology-specific spectrum of epilepsy syndromes (ESSES)



Outline

Diagnosing epilepsy syndrome and aetiology

Etiology specific spectrum of epilepsy syndromes

Natural history studies

Precision medicine –many approaches

Natural History
Studies of each
genetic epilepsy are
critical to measure if
new therapies are
effective



Describe the natural history of each genetic DEE
> 970 diseases!



With impact of novel therapy



Health economics, national standards of care



Psychosocial impacts

Natural History Studies



Include all morbidities



Timelines of evolution



Global collaborative studies

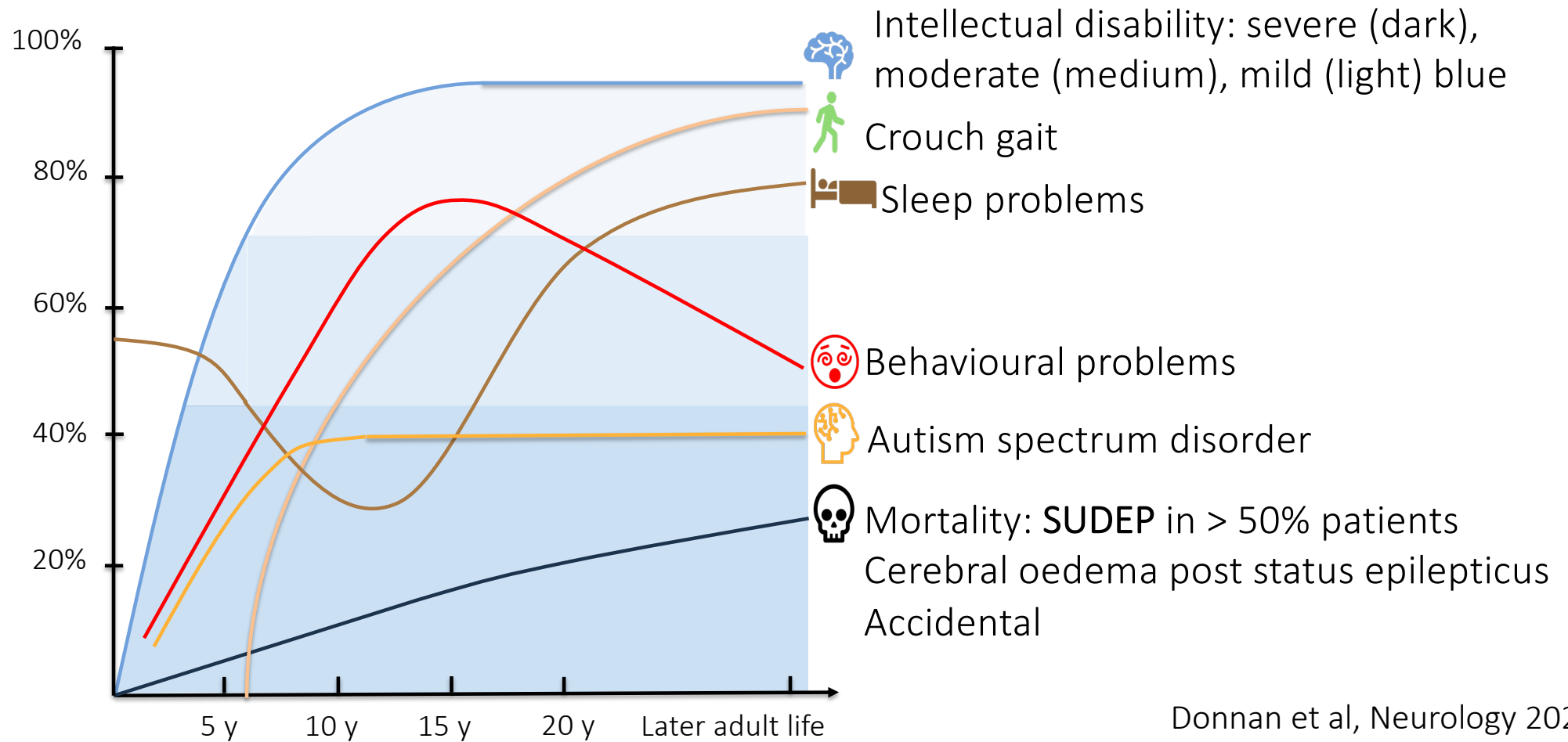


Use same measures



Regular monitoring 6-12 monthly

Dravet syndrome: Morbidities across the lifespan



Donnan et al, Neurology 2023
Myers et al, Pediatrics 2017

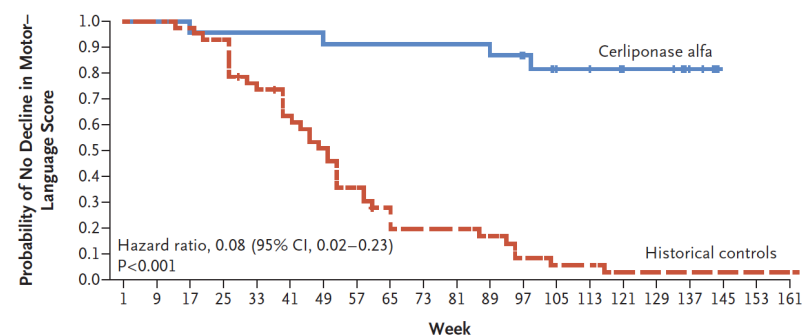
Natural history study needed to get approval for Precision Therapy by US FDA

ORIGINAL ARTICLE

Study of Intraventricular Cerliponase Alfa for CLN2 Disease

Angela Schulz, M.D., Temitayo Ajayi, M.D., Nicola Specchio, M.D., Ph.D., Emily de Los Reyes, M.D., Paul Gissen, M.B., Ch.B., Ph.D., Douglas Ballon, Ph.D., Jonathan P. Dyke, Ph.D., Heather Cahan, M.D., Peter Slasor, Sc.D., David Jacoby, M.D., Ph.D., and Alfried Kohlschütter, M.D., for the CLN2 Study Group*

A Motor–Language Score



No. at Risk
Cerliponase alfa
Historical controls

Neuronal ceroid lipofuscinosis - CLN2 disease

Enzyme replacement therapy

Genetic epilepsies
Natural History Studies

What are we trying to
modify?

Improve **all** aspects of
disease



Reduce seizures



Stop development slowing/regressing



Prevent **all** morbidities

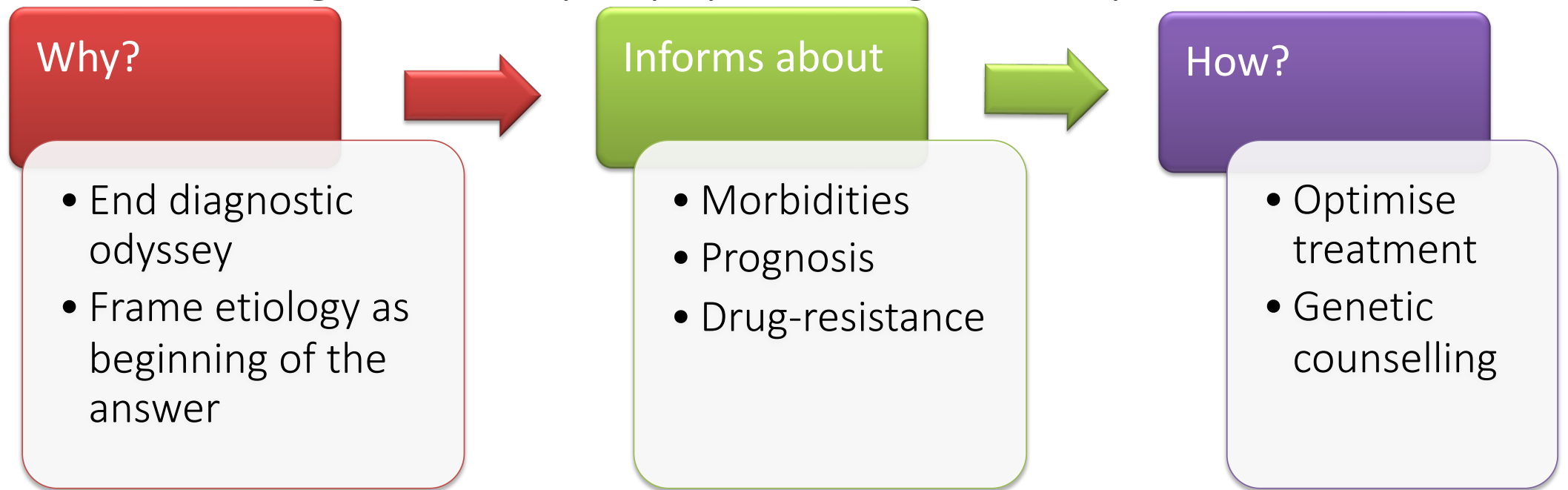


Eliminate high mortality risk



Global impact

Making an epilepsy syndrome and etiological diagnosis in epilepsy at all ages is important



Finding the cause

- Precision Diagnosis – epilepsy syndrome *and* etiology
- New therapies → Precision Medicine



Genetic epilepsies: Natural history may improve with



Repurposed therapies



New drugs



Genetic therapies

Randomised Controlled Trials

- Not disease modifying
- Not anti-epileptogenic

Precision therapies

- Genetic therapies
- Small molecules

Outline

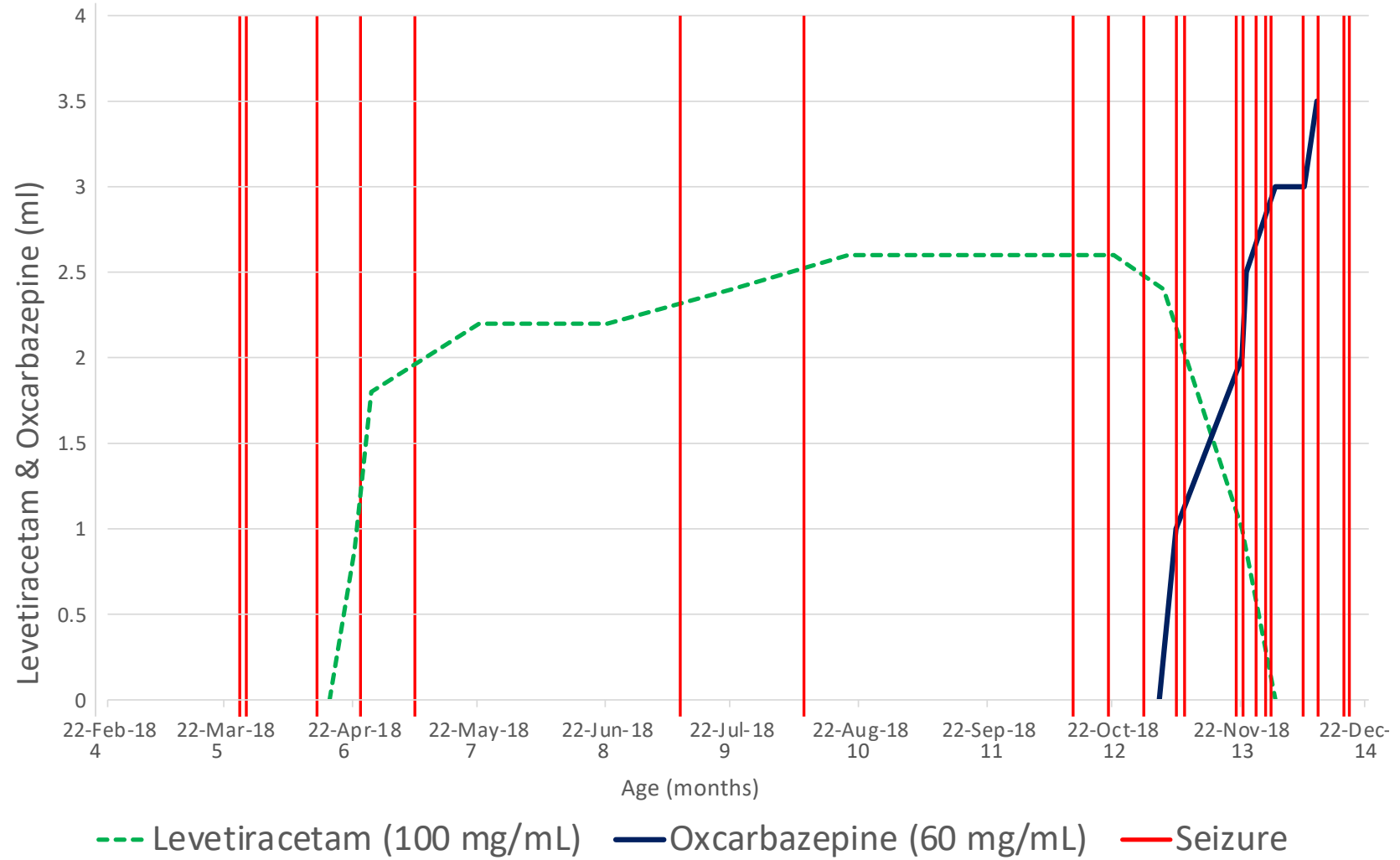
Diagnosing epilepsy syndrome and aetiology

Etiology specific spectrum of epilepsy syndromes

Natural history studies

Precision medicine –many approaches

2018 Seizure diary



Does the specific sodium channelopathy matter?

SCN1A DEE

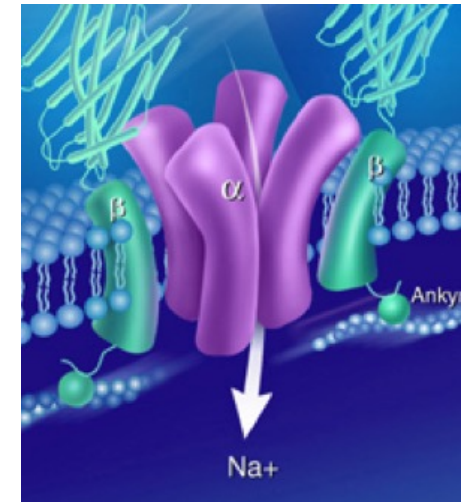
- Dravet
- Loss of function
- Seizure exacerbation with sodium channel blockers
 - ✗ carbamazepine
 - ✗ oxcarbazepine
 - ✗✓ lamotrigine

SCN8A Early Infantile DEE

SCN2A Early Infantile DEE

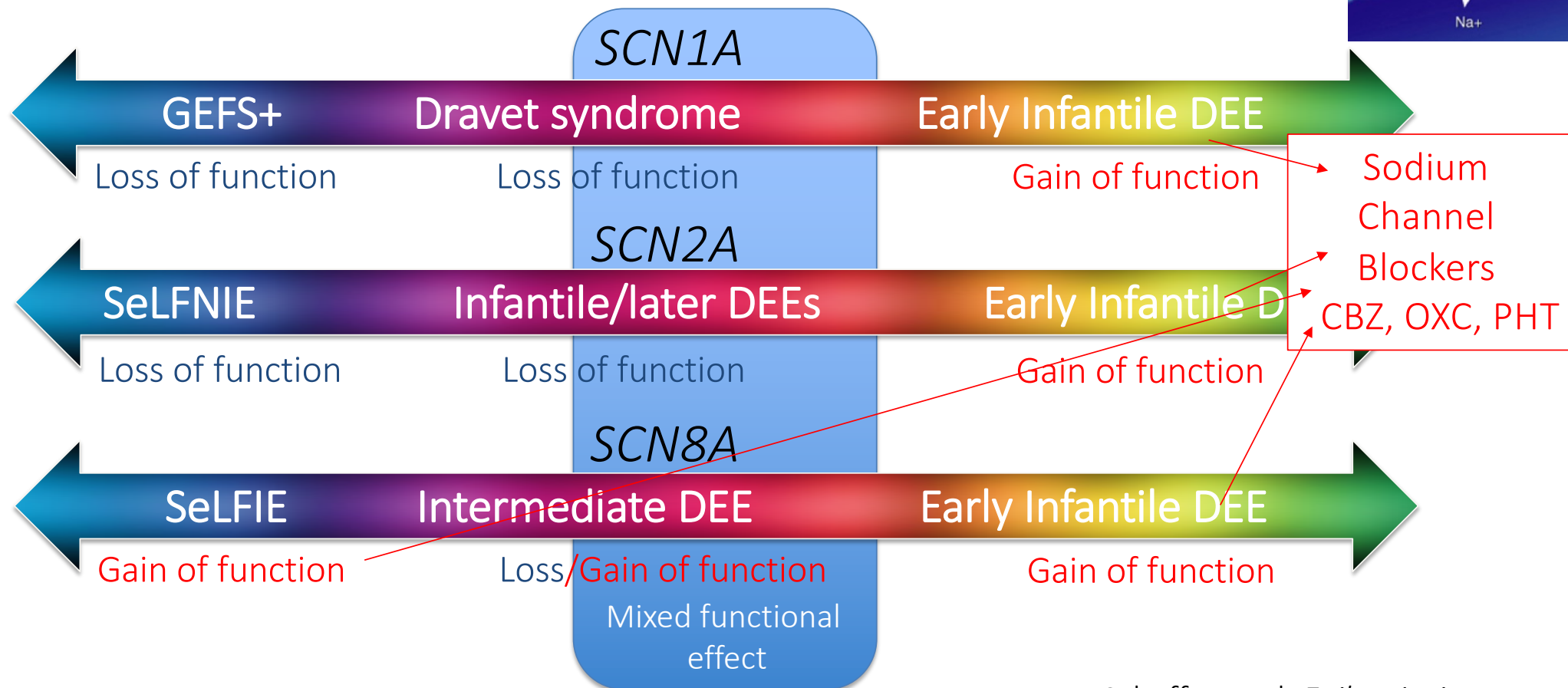
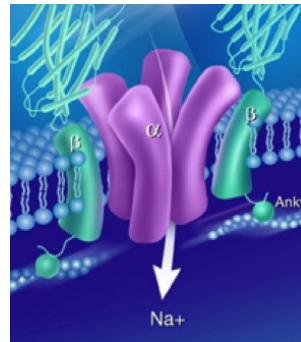
Gain of function

- Seizure control with sodium channel blockers
 - ✓ carbamazepine
 - ✓ phenytoin
 - ✓ oxcarbazepine

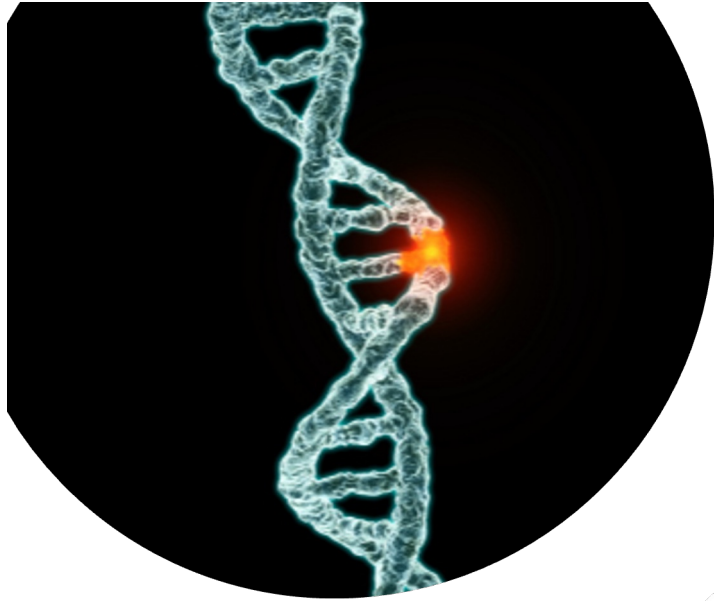


Dalic et al DMCN 2014
Larsen et al Neurology 2015
Howell et al Neurology 2015

Spectrum of Epilepsy Syndromes in sodium channel epilepsies



Scheffer et al, *Epilepsia*, in press

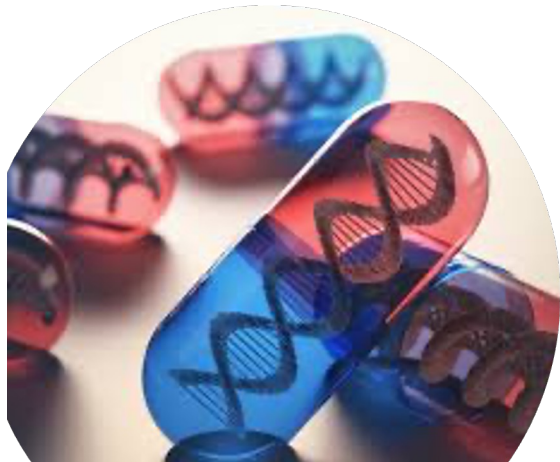


Genetic diagnosis

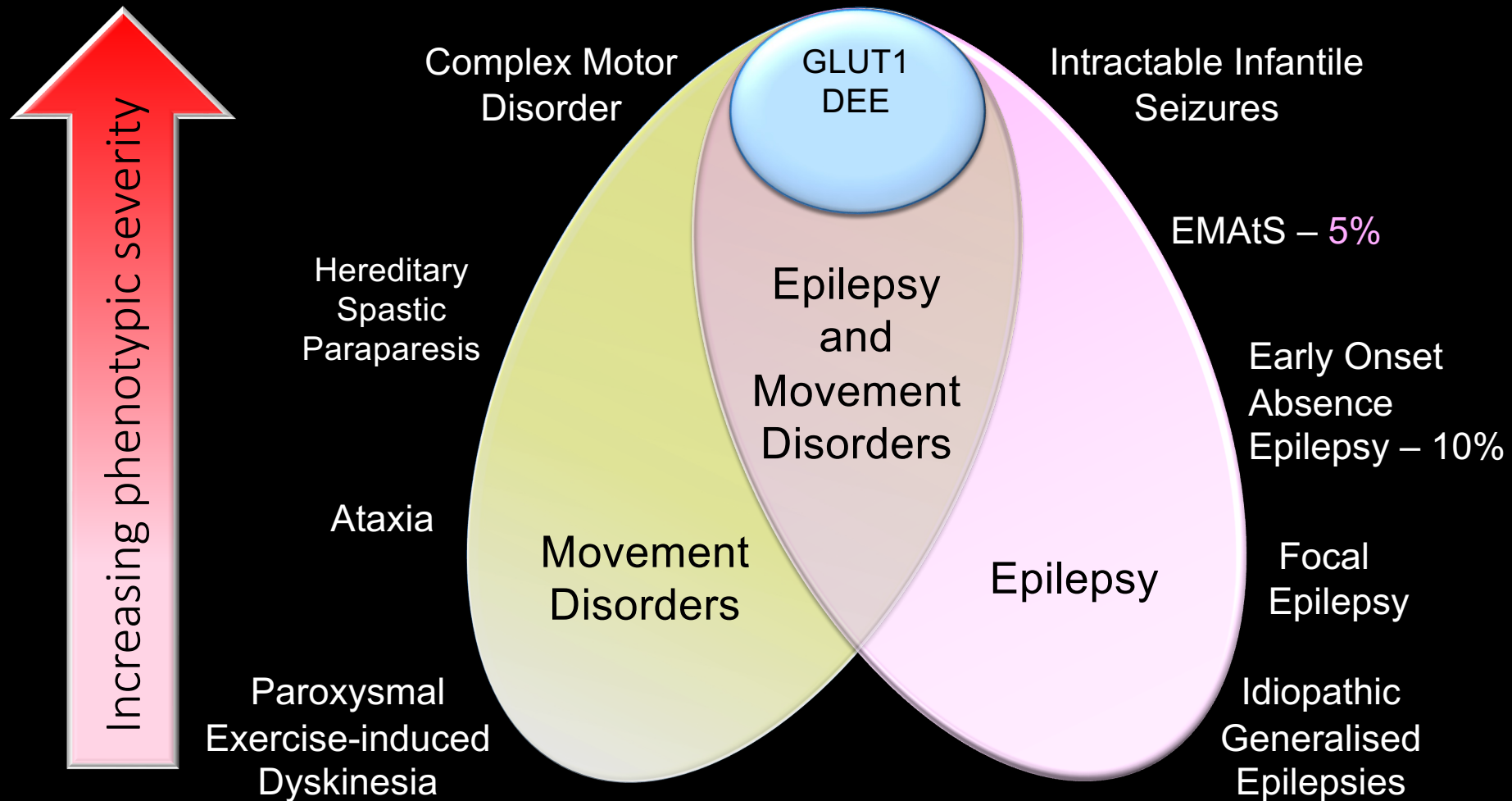
→ address pathophysiology



Precision medicine



Spectrum of GLUT1 Deficiency



GLUT1 deficiency syndrome



From “Ketocooking” –Nation, Cross, Scheffer 2012

Metabolic encephalopathy due to abnormal glucose transport across blood brain barrier

GLUT1 encoded by *SLC2A1*

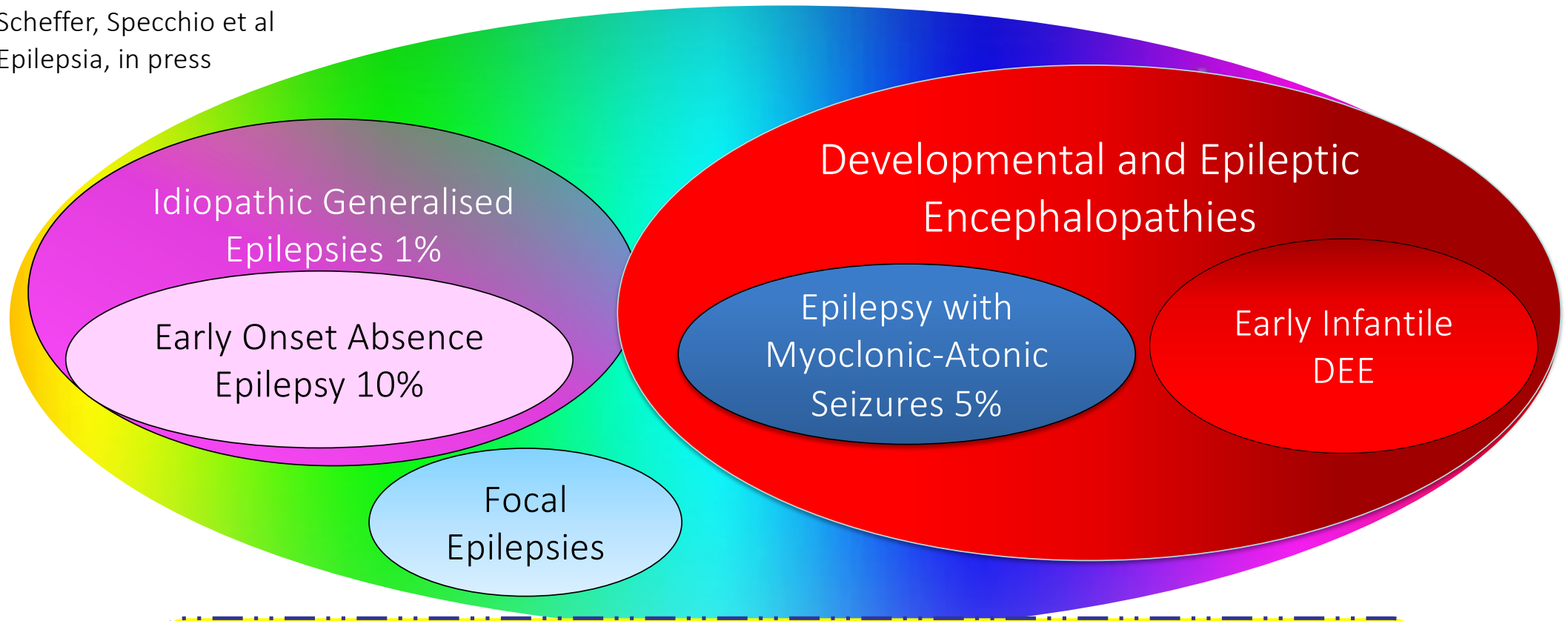
Fasting CSF glucose < 2.2 mmol/L (< 40 mg/dL)

CSF/plasma glucose ratio < 0.45

Precision Medicine: Ketogenic diet

Glucose Transporter 1 Deficiency Spectrum of Epilepsy Syndromes

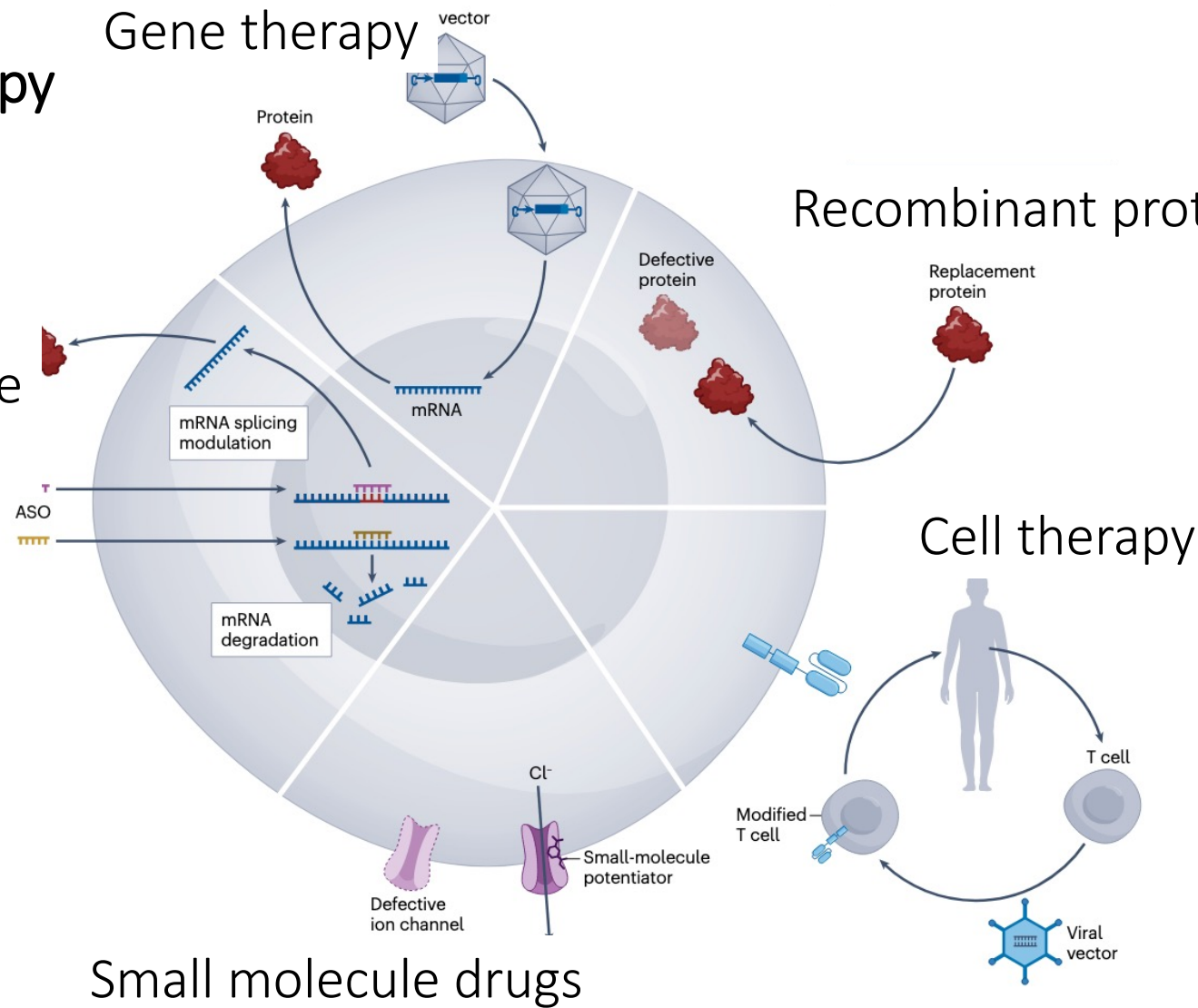
Scheffer, Specchio et al
Epilepsia, in press



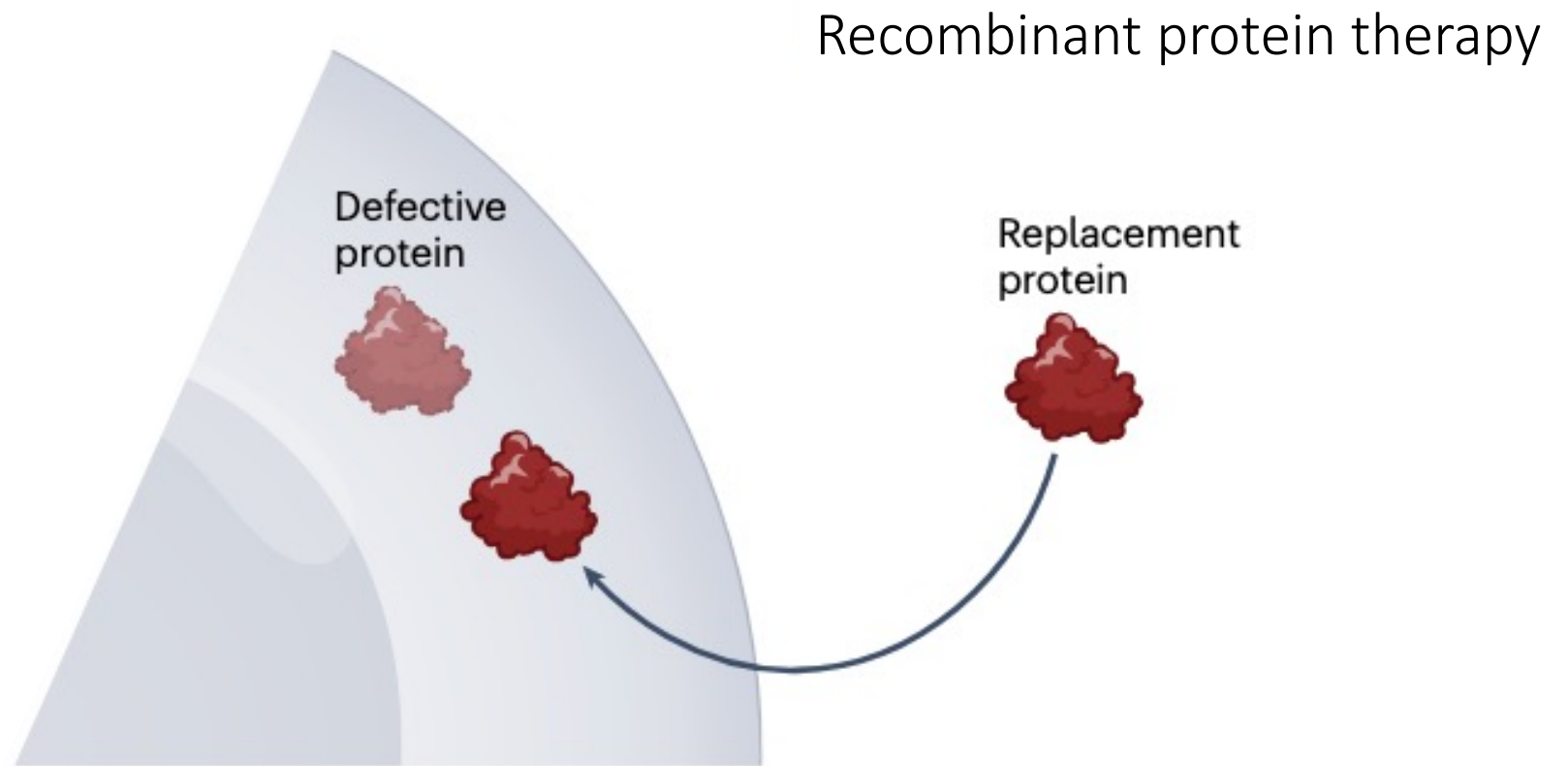
Movement disorders – Paroxysmal exercise-induced dyskinesia, neonatal eye movements. Motor disorders: Ataxia, Spastic paraplegia; Intellectual Disability, Dyspraxia, Dysarthria; Hemolytic anemia

Precision therapy approaches

Antisense oligonucleotide therapy



Precision therapy approaches

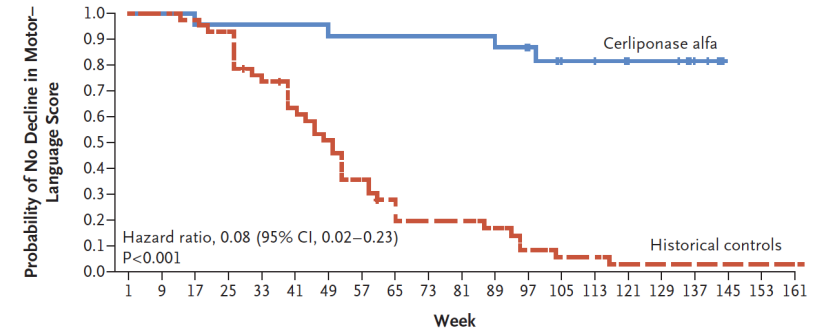


ORIGINAL ARTICLE

Study of Intraventricular Cerliponase Alfa for CLN2 Disease

Angela Schulz, M.D., Temitayo Ajayi, M.D., Nicola Specchio, M.D., Ph.D., Emily de Los Reyes, M.D., Paul Gissen, M.B., Ch.B., Ph.D., Douglas Ballon, Ph.D., Jonathan P. Dyke, Ph.D., Heather Cahan, M.D., Peter Slasor, Sc.D., David Jacoby, M.D., Ph.D., and Alfried Kohlschütter, M.D., for the CLN2 Study Group*

A Motor–Language Score

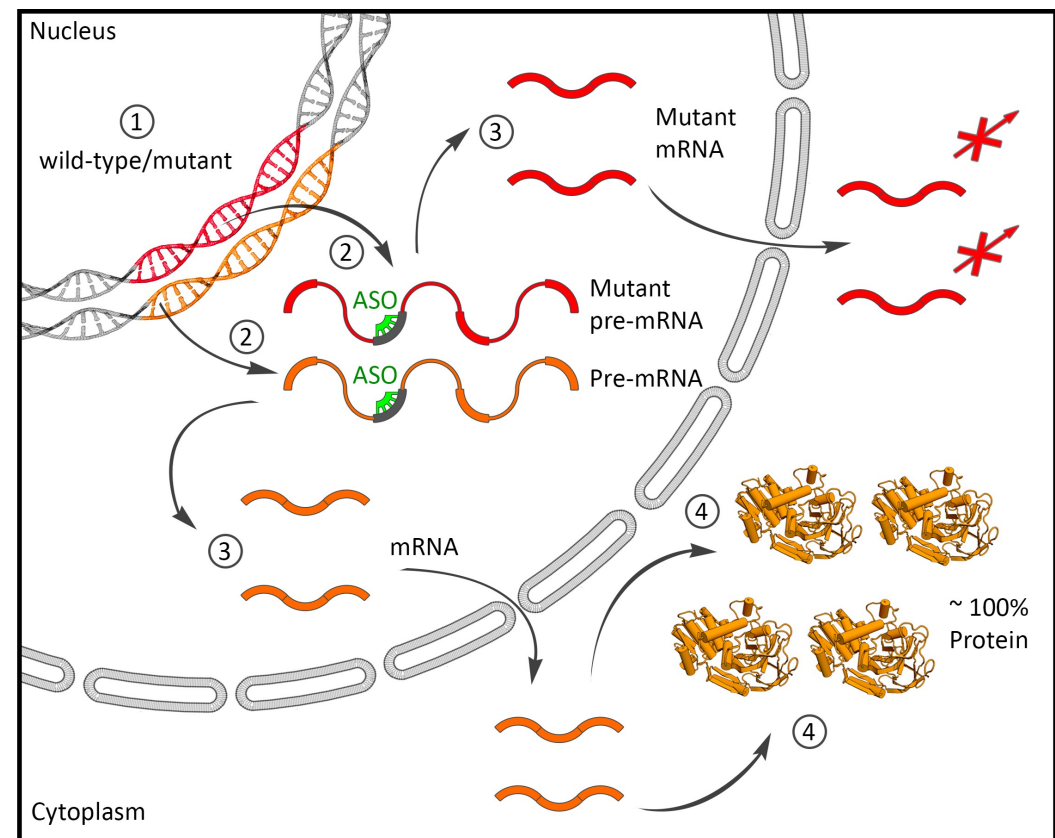
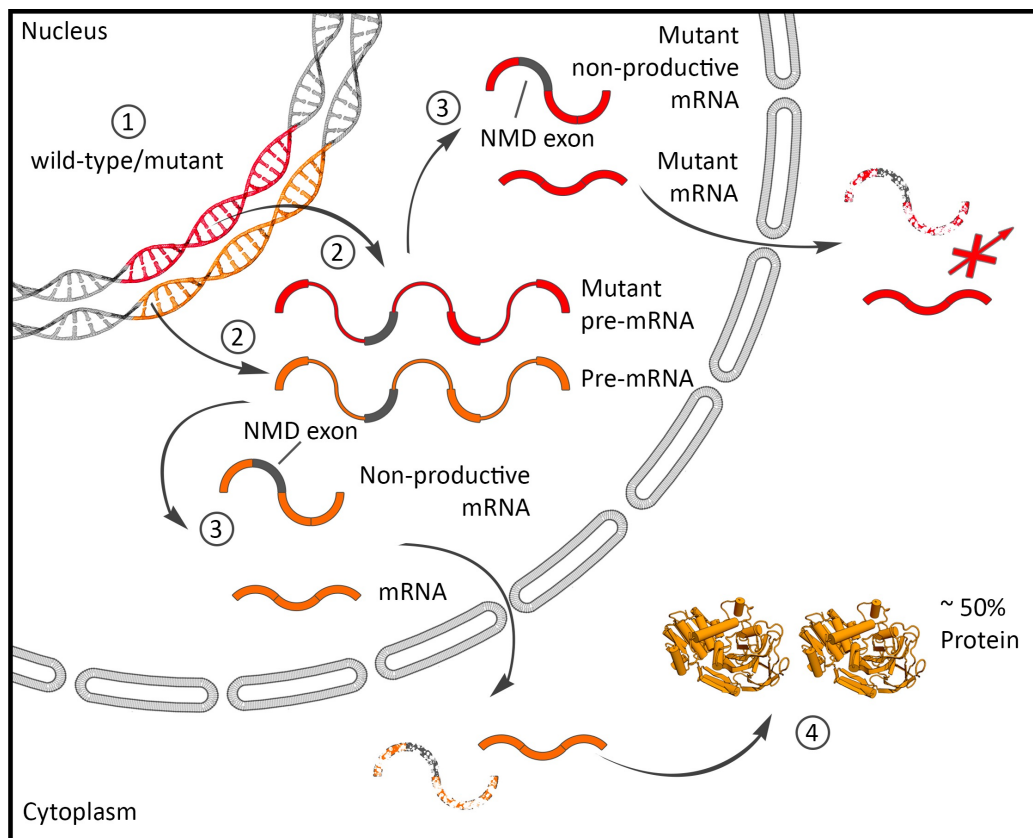


No. at Risk
Cerliponase alfa
Historical controls

Neuronal ceroid lipofuscinosis - CLN2 disease

Enzyme replacement therapy

Anti-Sense Oligonucleotide (ASO) targets non-productive splicing to increase mRNA



Anti-Sense Oligonucleotide (ASO) targets non-productive splicing to increase mRNA



The NEW ENGLAND JOURNAL *of* MEDICINE

2026

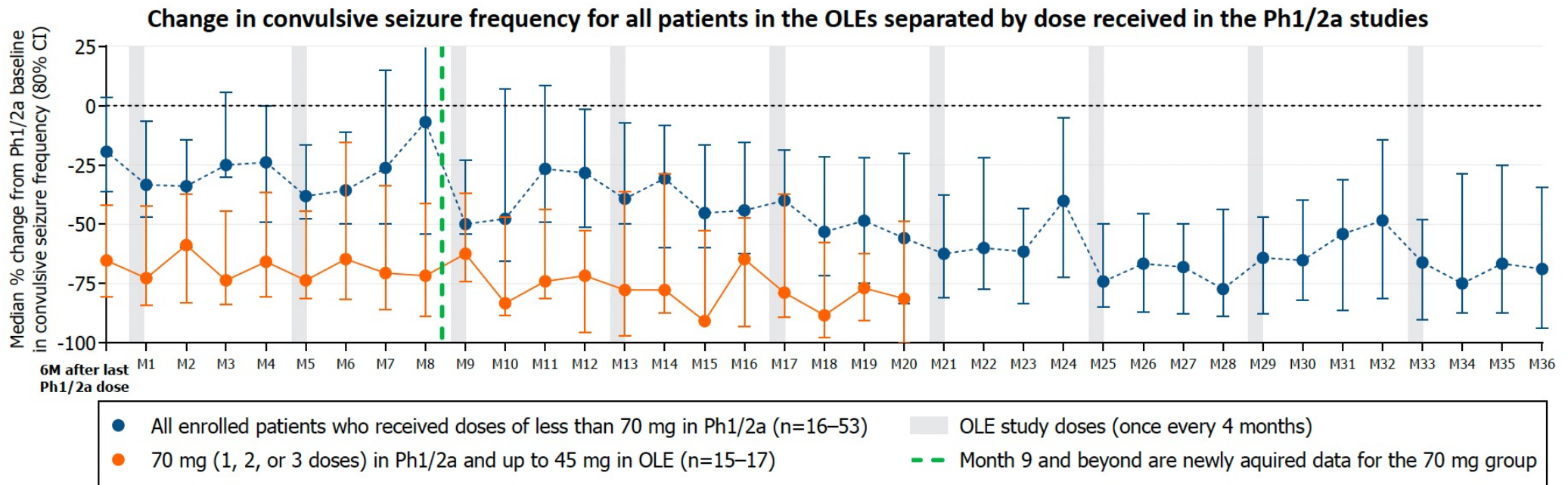
ORIGINAL ARTICLE

Zorevunersen in Children and Adolescents with Dravet Syndrome

L. Laux,¹ J. Sullivan,² M.S. Perry,³ A. Brunklaus,⁴ A. Desurkar,⁵ J.M. Schreiber,⁶ C.M. Roberts,⁷ K.G. Knupp,⁸ J.W. Wheless,⁹ E.C. Wirrell,¹⁰ P. Ventola,¹¹ F. Wang,¹² Meena,¹² J. Lynch,¹² K.A. Parkerson,¹² B. Ticho,¹² and J.H. Cross,¹³ for the MONARCH, ADMIRAL, SWALLOWTAIL, and LONGWING Study Groups*

Phase 1-2a: 4 monthly intrathecal injections long term

Reductions in convulsive seizure frequency were maintained through 3 years of treatment with zorevunersen on top of standard of care in the OLE studies



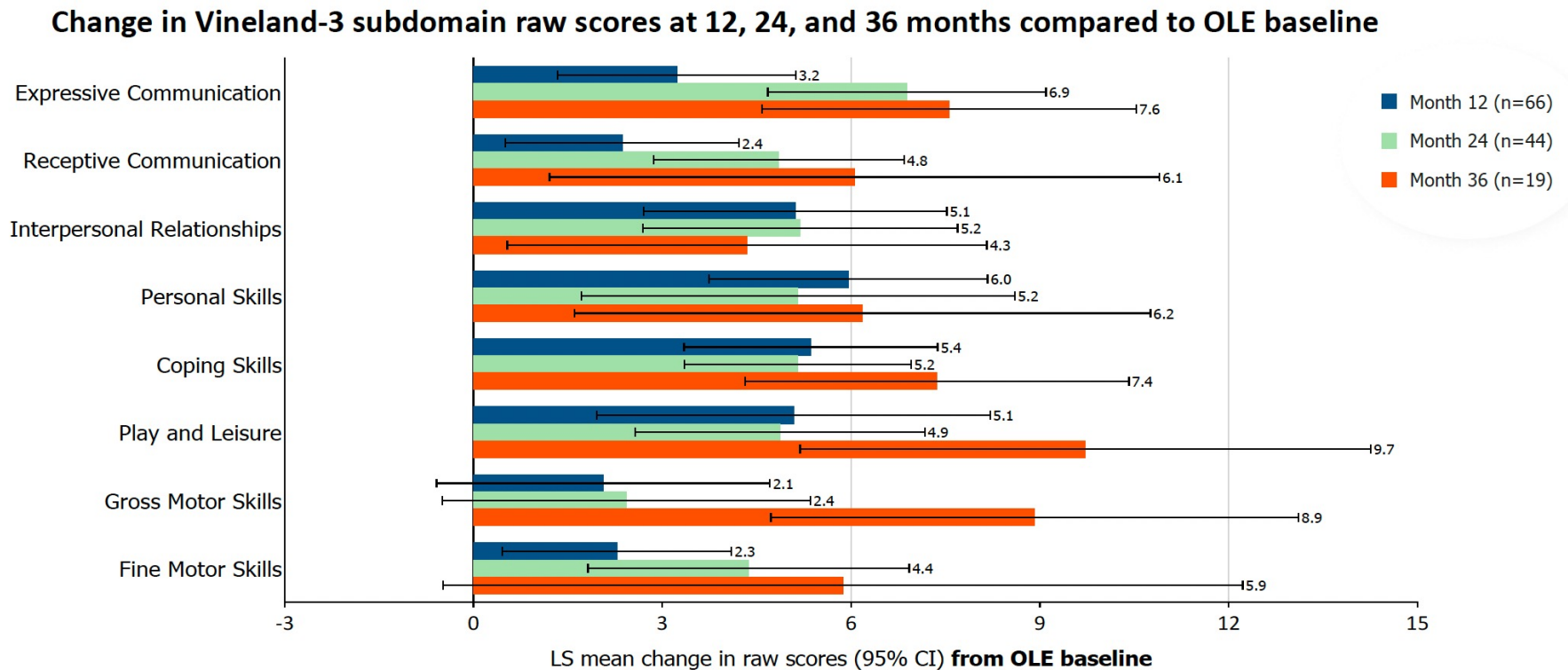
Reductions were greater in patients who received loading doses of 70 mg followed by maintenance doses of ≤ 45 mg

No. of Patients

<70 mg (1 or 3 doses)	52	53	53	53	53	52	52	52	46	46	47	47	45	45	45	41	38	41	41	40	38	39	39	39	36	36	36	36	32	30	30	30	25	20	19	19	16
70 mg (1, 2, or 3 doses)	16	17	17	17	17	17	17	17	17	17	17	17	16	17	17	17	15	16	16	16	16																

Laux et al, NEJM 2026

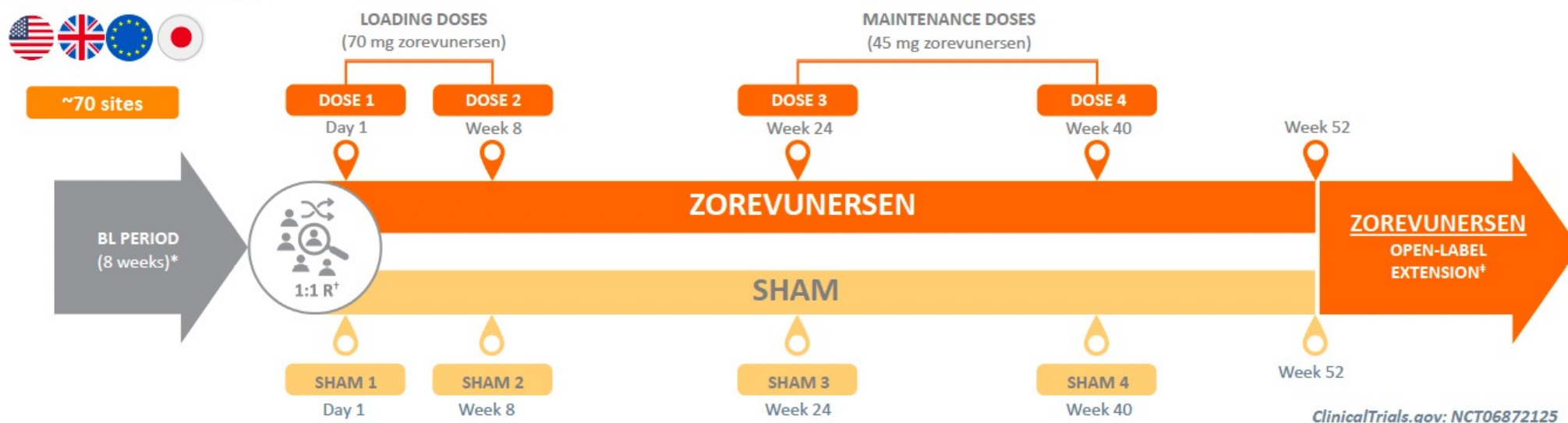
Substantial improvements in cognition and behavior continued through 3 years of treatment with zorevunersen in the OLE studies



Continued improvements in Vineland-3 subdomains were observed through 36 months of the OLE studies

EMPEROR Phase 3 study design: Evaluation of zorevunersen as a potential disease-modifying therapy for Dravet syndrome

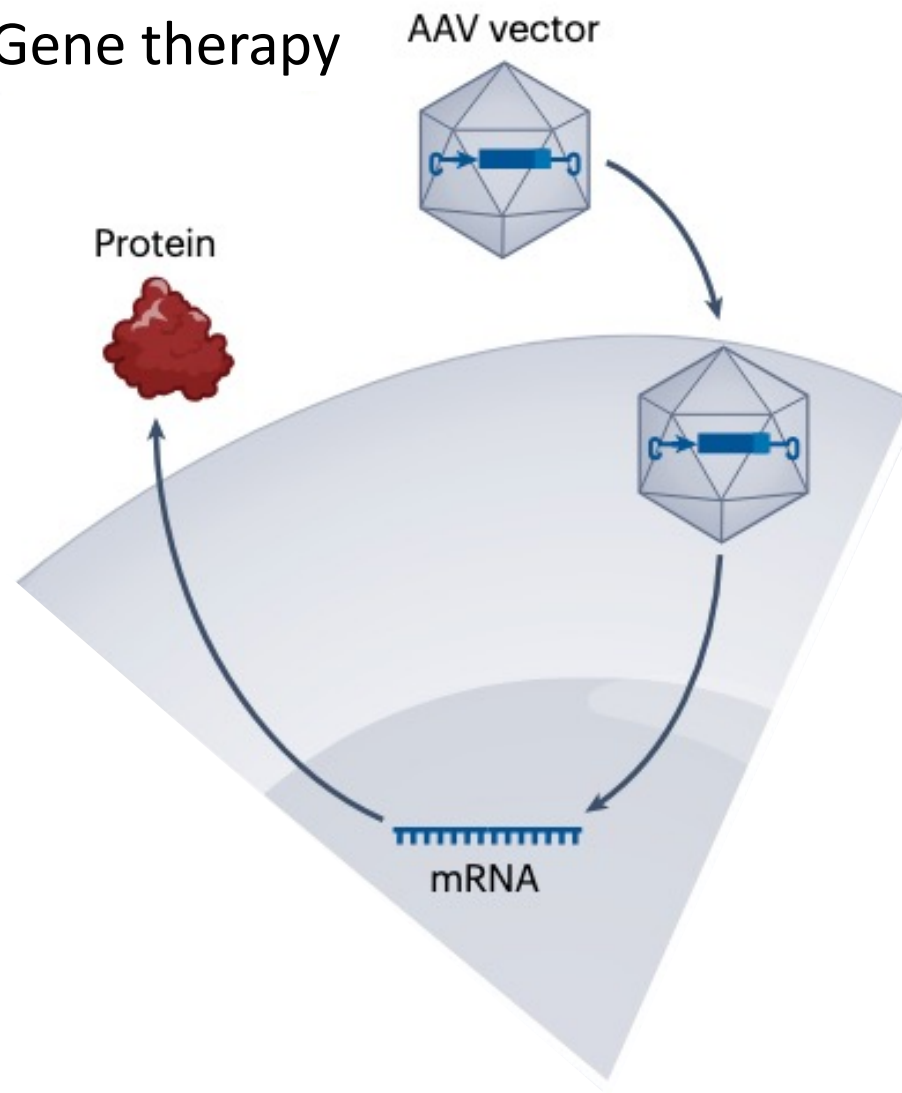
Figure 1. EMPEROR study design



The duration of the study is anticipated to be approximately 60 weeks, including an 8-week baseline period and a 52-week double-blind efficacy period. *The 8-week baseline period consists of screening Visit A, screening Visit B, and observation for 6 weeks. [†]Following eligibility confirmation, patients will be randomized in a 1:1 ratio (zorevunersen:sham). [‡]Patients will have the option to receive zorevunersen in an open-label extension study if they meet eligibility criteria. BL, baseline; R, randomization.

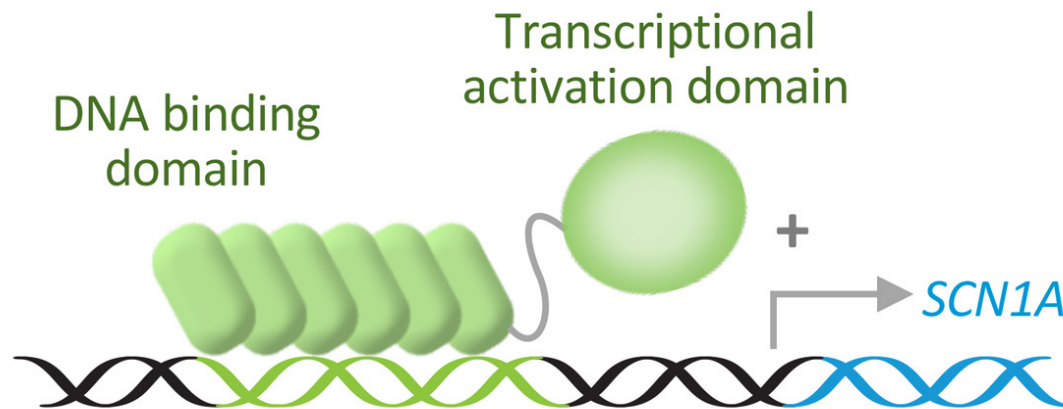
Precision therapy approaches

Gene therapy



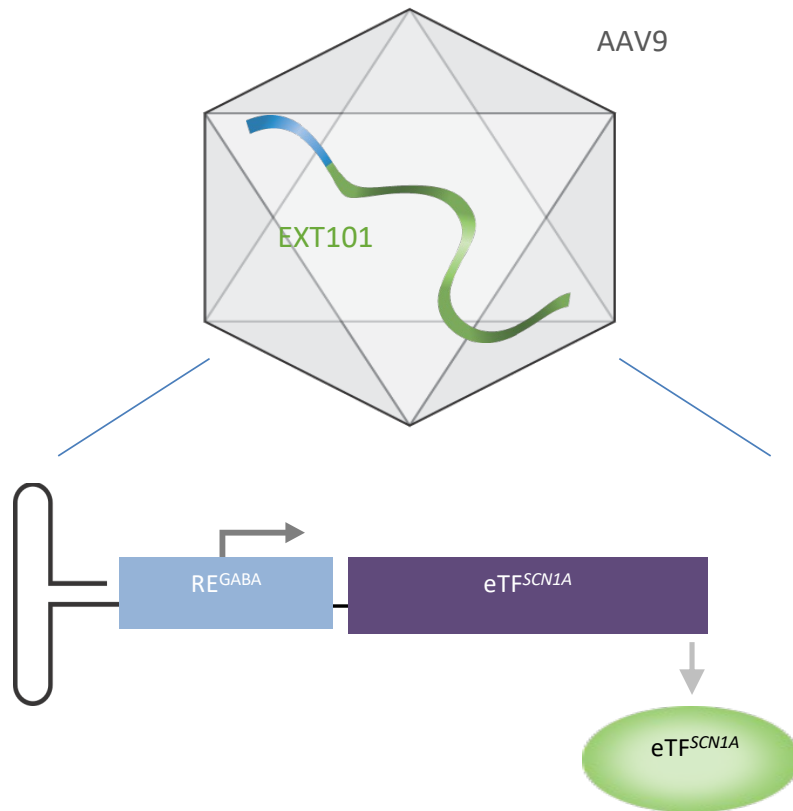
Phase 1/2 clinical trial epigenetic targeting using zinc fingers with an engineered transcription factor regulatory element

Engineered Transcription Factor (eTF^{SCN1A}) Transgene



- Zinc-finger DNA-binding domain (DBD) fused to transcriptional activator domain via a short linker sequence
- DNA-Binding Domain recognizes unique DNA sequence upstream of the *SCN1A* transcription start site

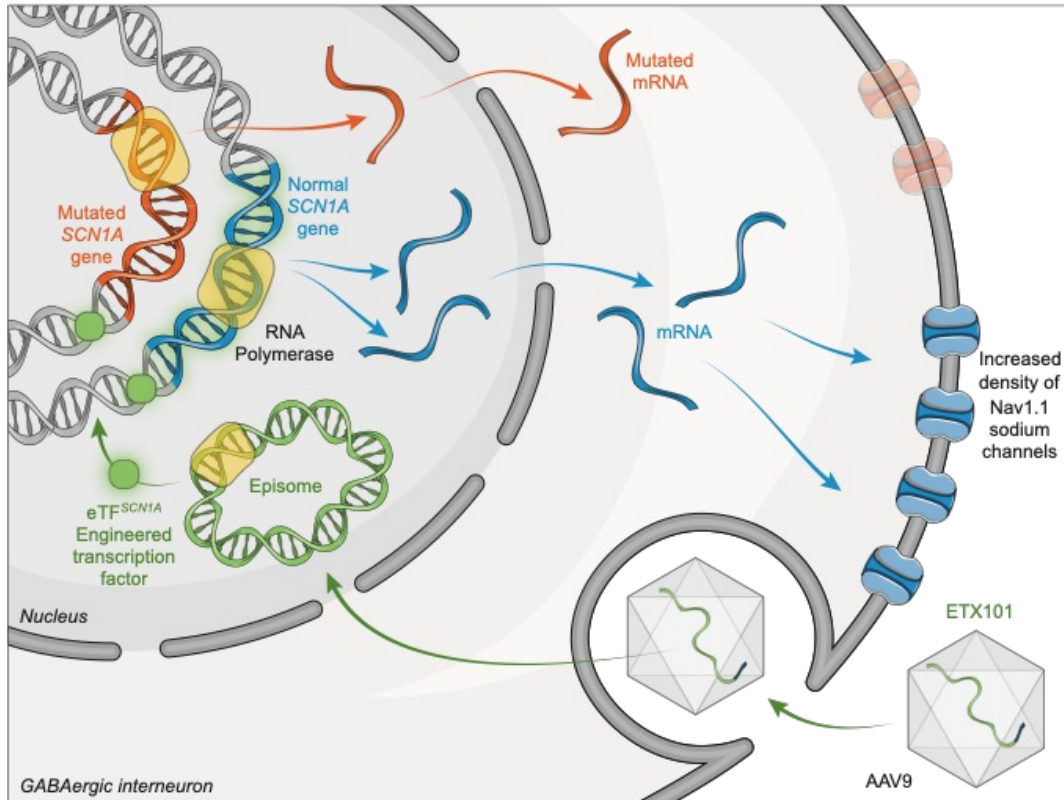
ETX101 - Cell Selective Gene Regulation Therapy



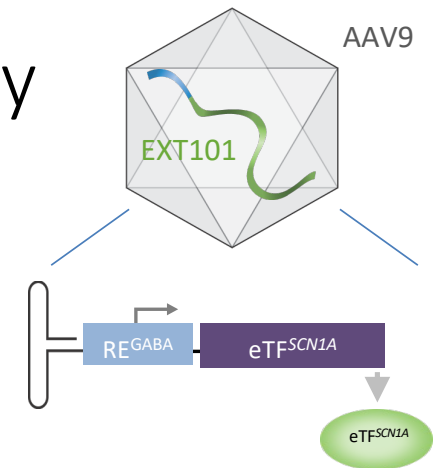
- ETX101 is **not** gene replacement therapy
- ETX101 is **A**deno-**A**ssociated **V**irus-mediated gene therapy
- RE^{GABA} and eTF^{SCN1A} components of ETX101 → precise upregulation of *SCN1A* expression within target cell, GABAergic inhibitory interneurons

eTF, engineered transcription factor; RE, regulatory element

ETX101 - Cell Selective Gene Regulation Therapy

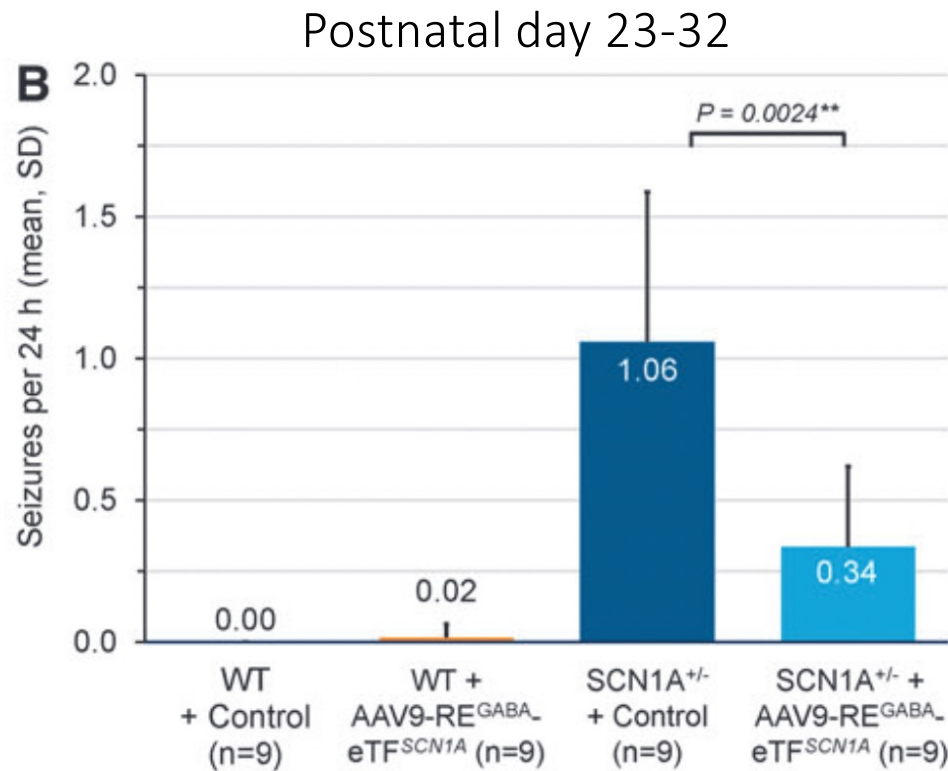


AAV, Adeno-associated virus; eTF, engineered transcription factor; mRNA, messenger RNA; RE, regulatory element;

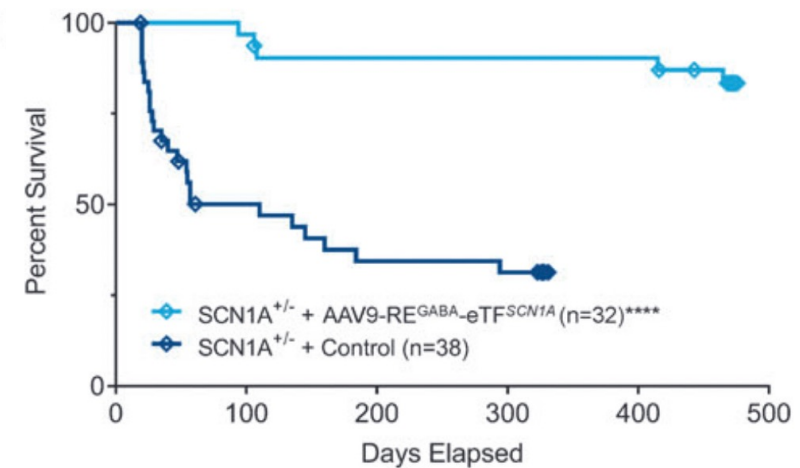
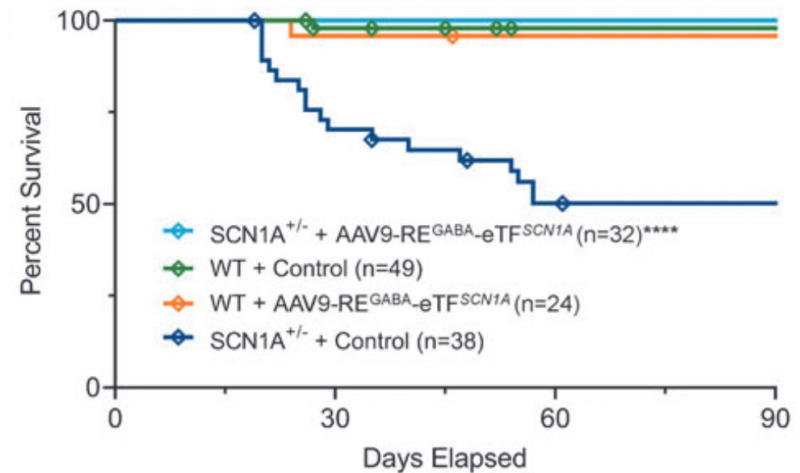
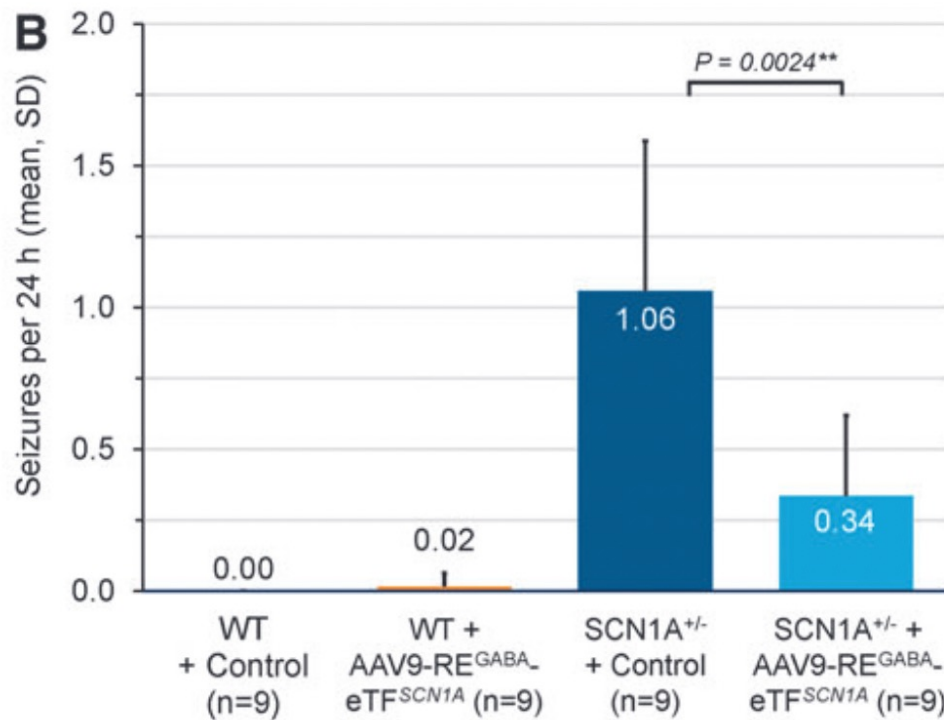


- AAV9 vector recognized by cell surface receptors, taken via endosome into neurons
- Forms episome ready for transcription
- Transcription initiated under regulation of RE^{GABA} promoter to produce eTF^{SCN1A} (engineered transcription factor) in GABAergic neurons only
→ upregulation of endogenous Na_v1.1

ETX-101 regulatory gene therapy rescues seizures and mortality in Dravet mouse model



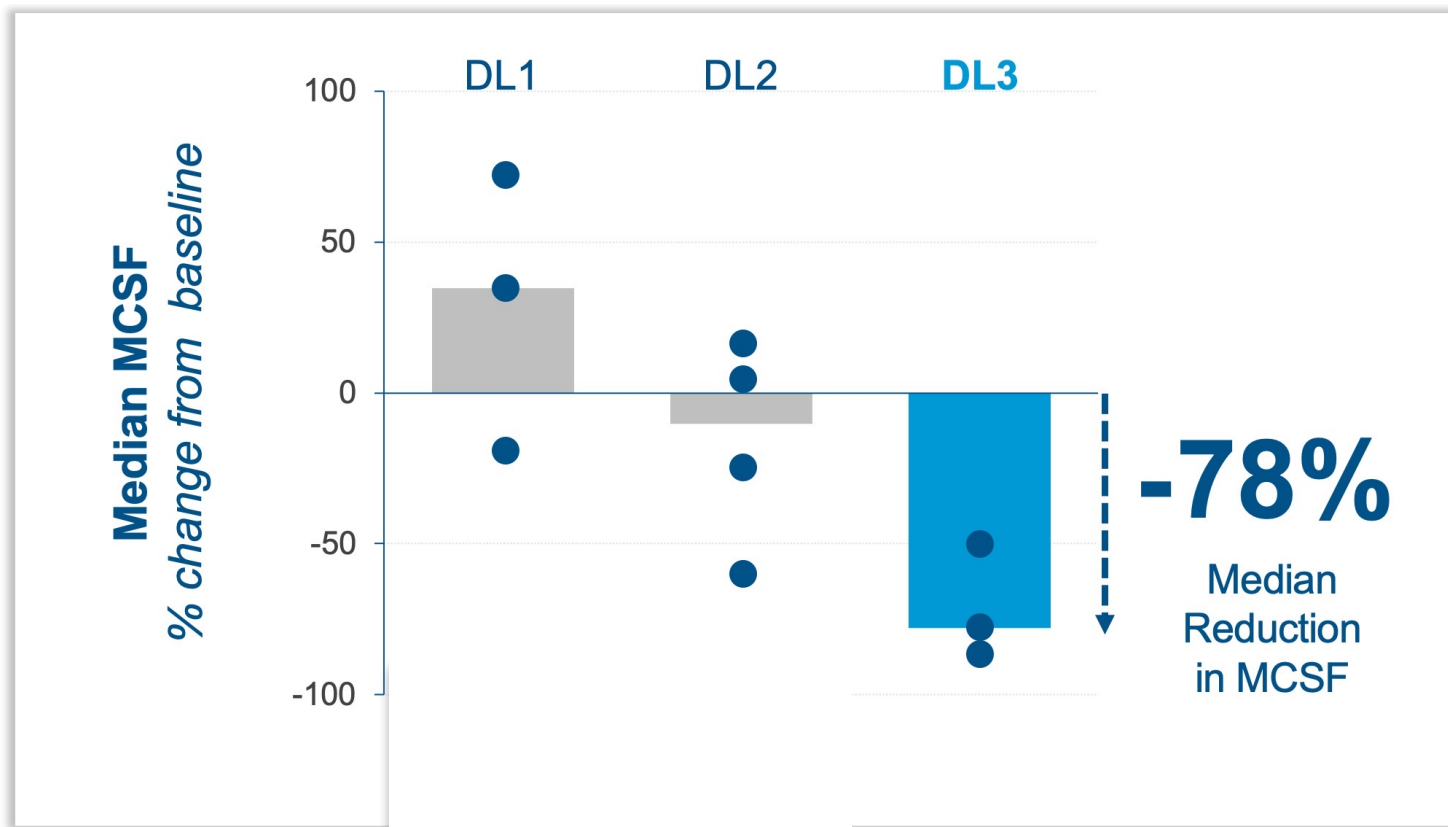
ETX-101 regulatory gene therapy rescues seizures and mortality in Dravet mouse model



ETX101: Single dose results in seizure reduction over 32 weeks

POLARIS
ETX101 in Dravet Syndrome

Encoded
THERAPEUTICS



Substantial and sustained reduction through >7 months of observation

Data presented at the American Epilepsy Society Annual Meeting 2025, December 5, 2025, Atlanta, GA, USA.

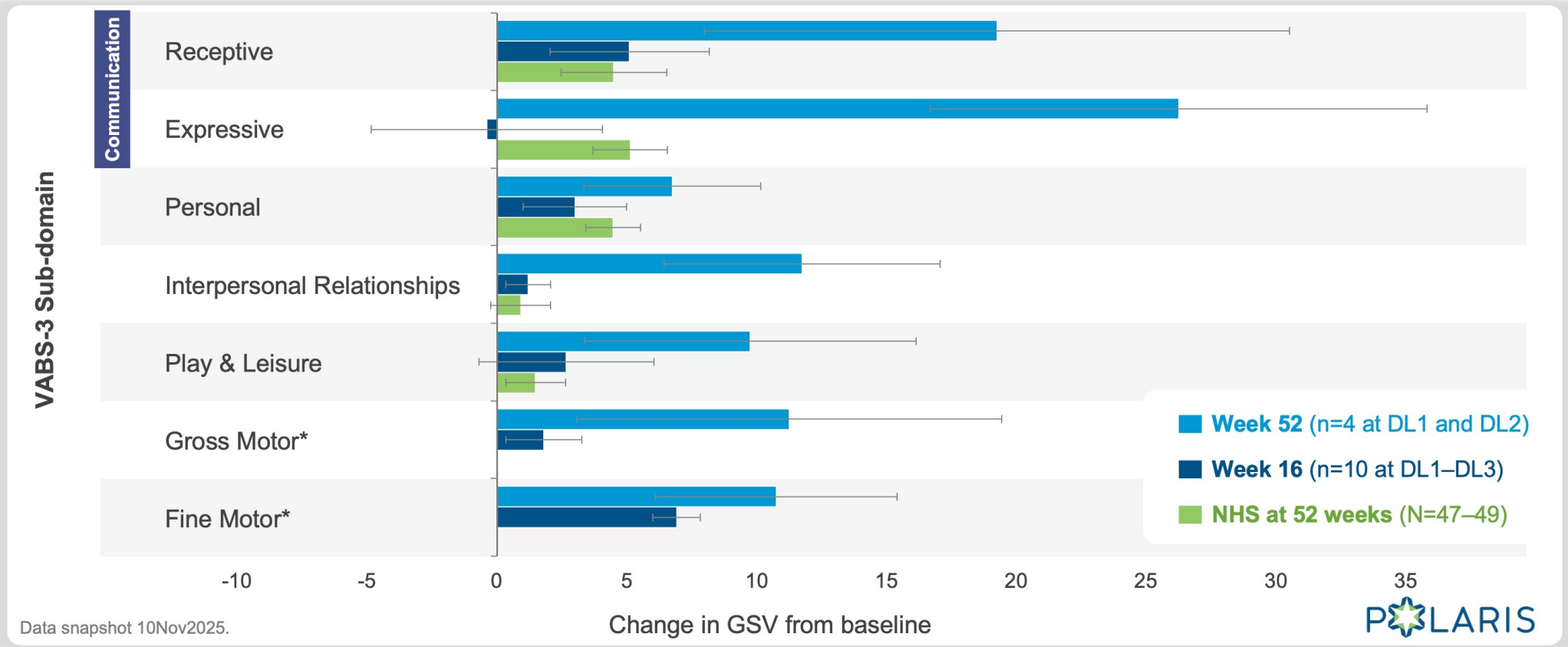
DL, dose level; MCSF, monthly countable seizure frequency.
Analysis includes data from cohorts that have completed 32 weeks of observation.
Note: Data are from a live database and subject to change during monitoring or QC check.
Data snapshot 10Nov2025.

© 2026 ENCODED THERAPEUTICS | ETX101 is an investigational gene regulation therapy. Its safety and efficacy have not yet been established.



Clinically significant gains in Vineland-3 outcomes in children treated with ETX101

Rapid onset of effect by 16 weeks post-treatment, with increased communication skill acquisition and meaningful gains across all domains within one year, even at lower dose levels



Data shown are mean $\pm$ standard error. ENVISION uses VABS-3 Parent/Caregiver Form, whereas POLARIS uses VABS-3 Interview Form.*Motor domains not obtained in ENVISION.
 Note: Data are from a live database and subject to change during monitoring or QC check.
 DL, dose level; GSV, growth scale value; NHS, natural history study; VABS-3, Vineland Adaptive Behavior Scales Version 3.
 © 2026 ENCODED THERAPEUTICS | ETX101 is an investigational gene regulation therapy. Its safety and efficacy have not yet been established.

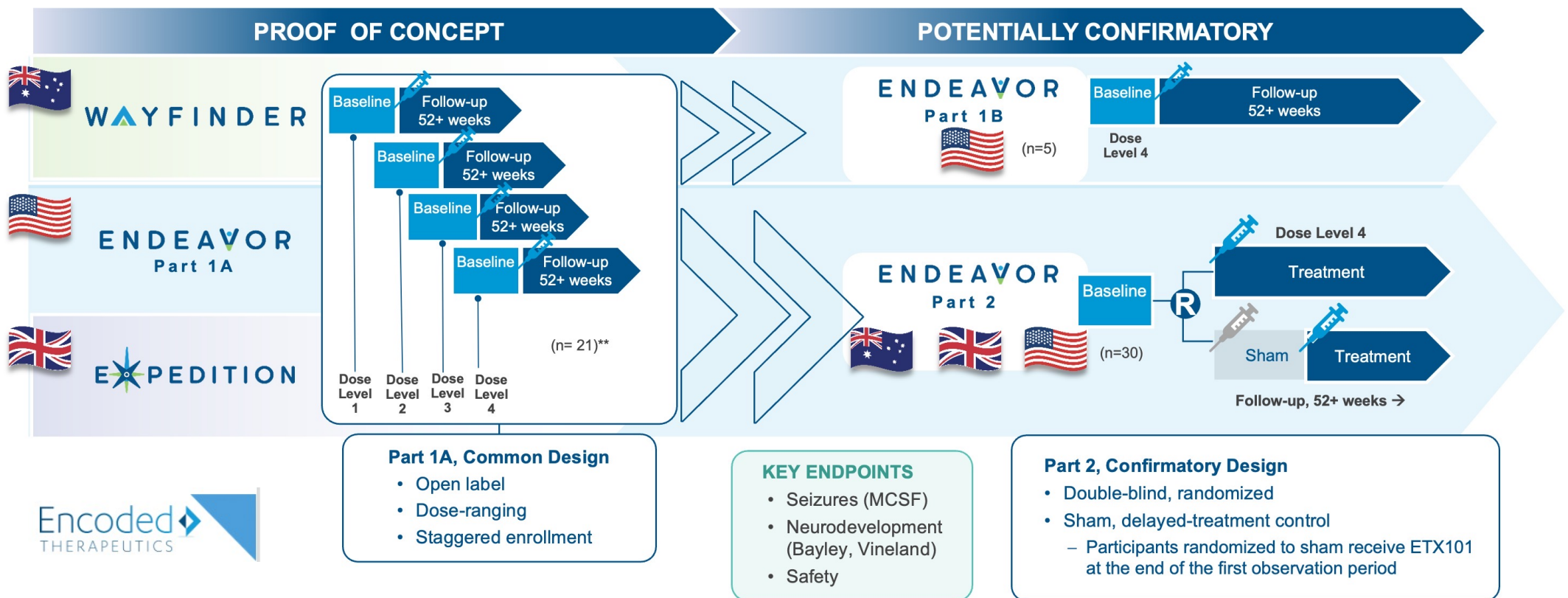
Data presented at the American Epilepsy Society Annual Meeting 2025, December 5, 2025, Atlanta, GA, USA.

POLARIS: ETX101 Clinical Program Overview

Designed to transition seamlessly from POC to potentially confirmatory trial



Three clinical trials will evaluate safety and efficacy in patients aged 6 months to <18 years



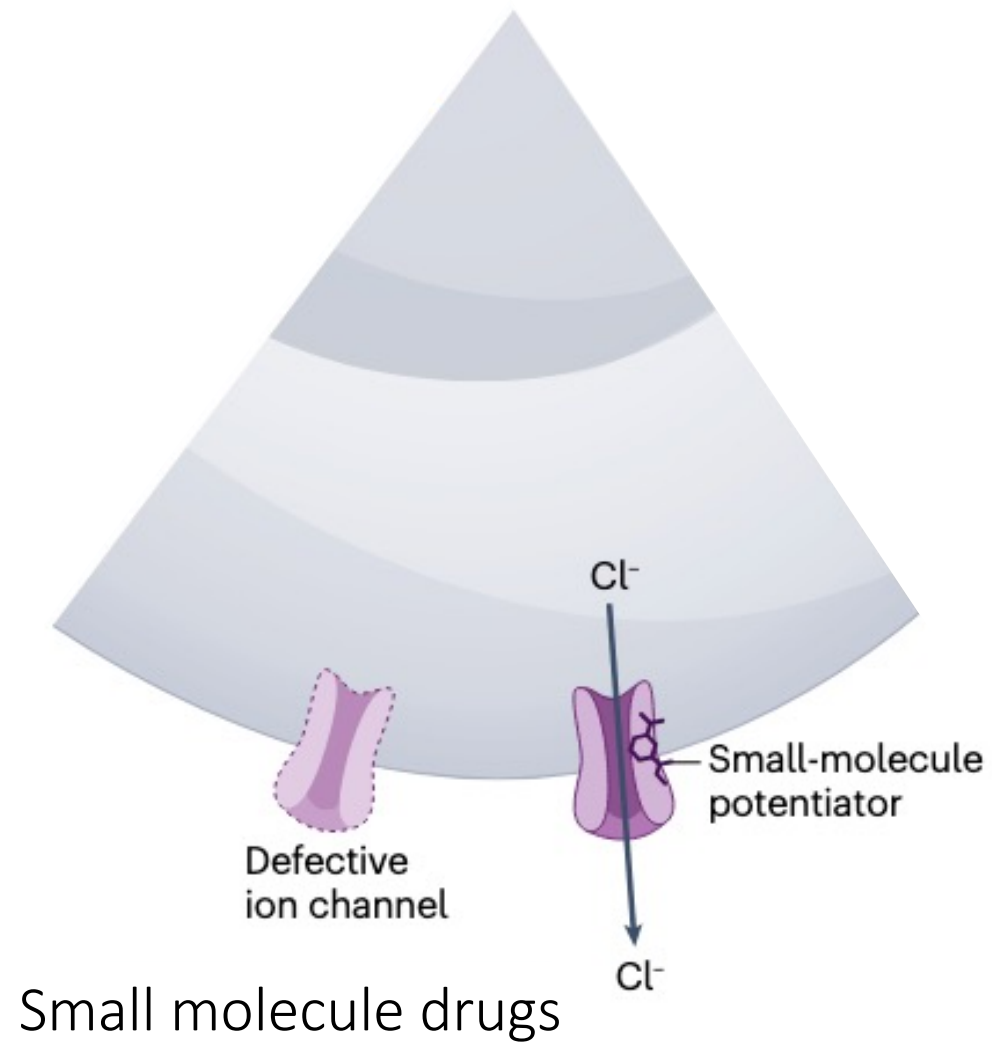
**Cohort size considered across the POLARIS program

© 2026 ENCODED THERAPEUTICS | ETX101 is an investigational gene regulation therapy. Its safety and efficacy have not yet been established.

MCSF, monthly countable seizure frequency; POC, proof of concept



Precision therapy approaches



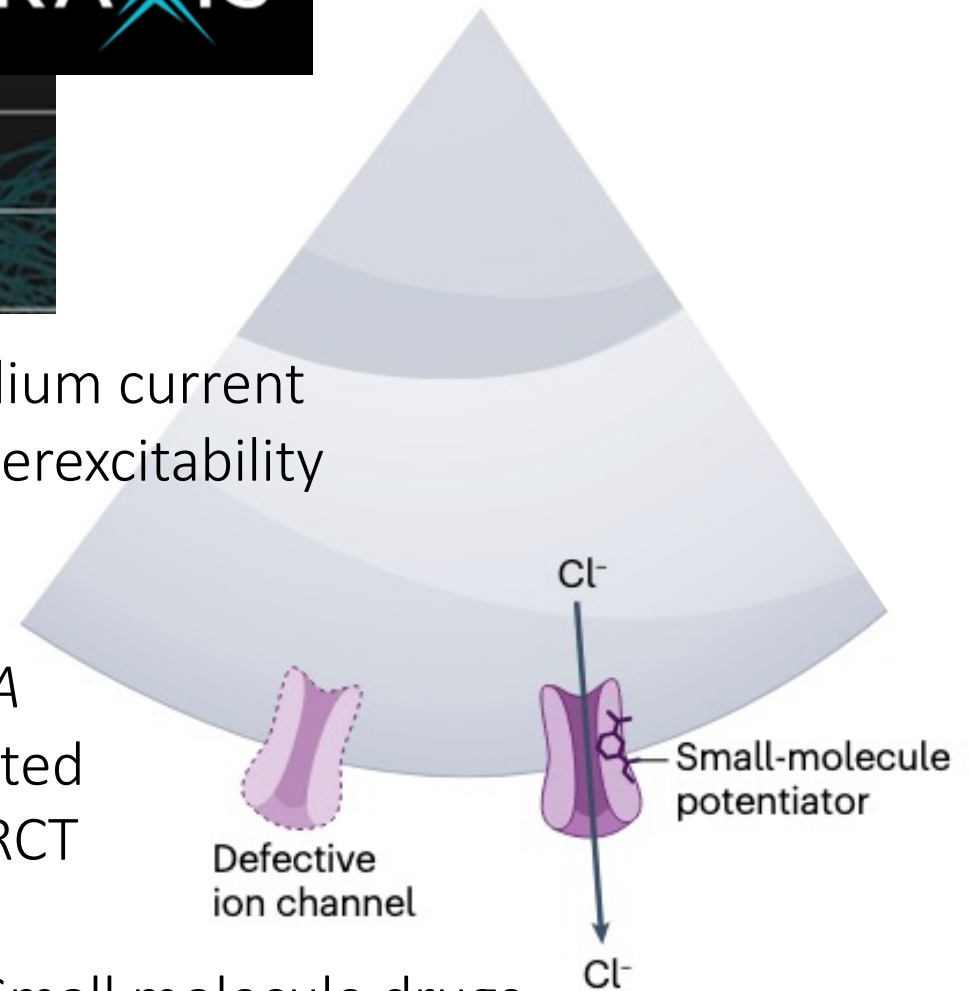
Relutrigine DEEs

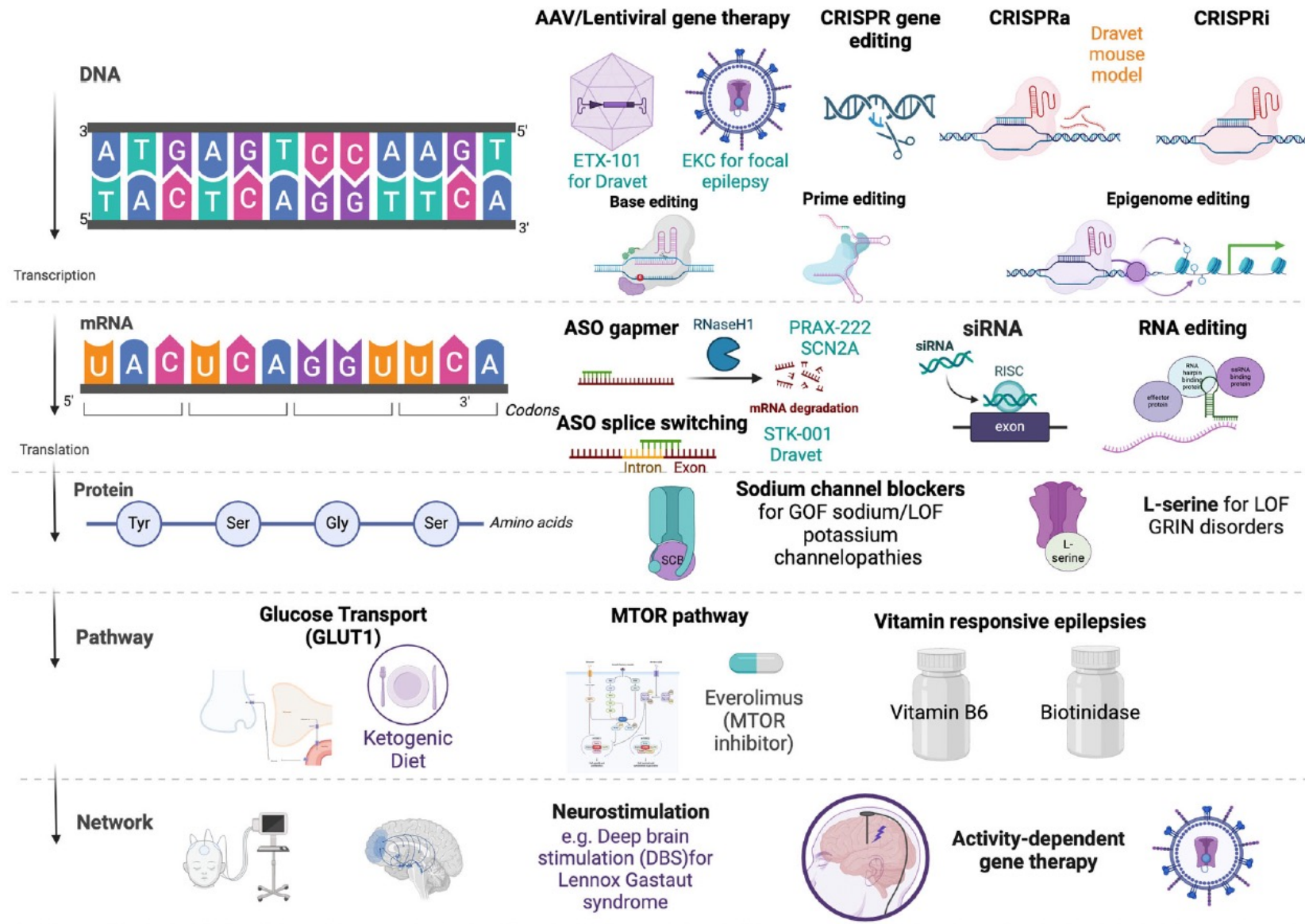
EMBOLD Cohort 2 SCN2A GoF and SCN8A

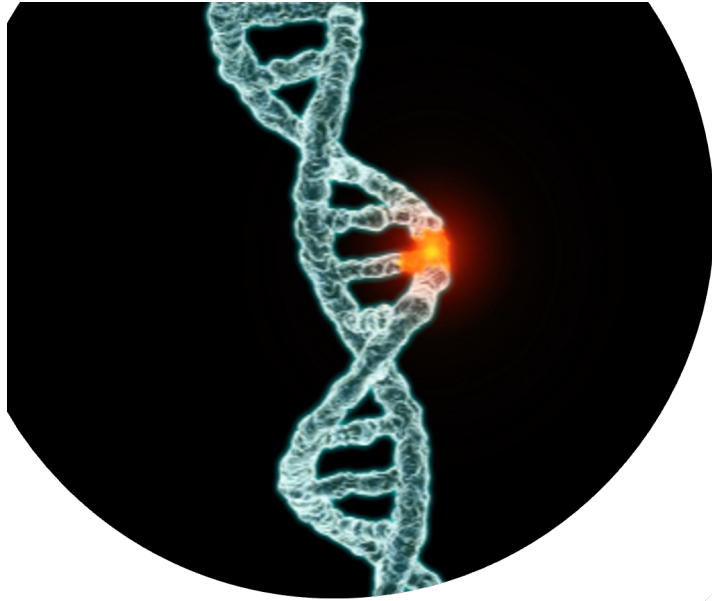
EMERALD Broad DEEs

- Preferential inhibitor of persistent sodium current
- Superior selectivity of Na channel hyperexcitability
- Dose-dependent block of seizures
- Trials
 - Gain-of-function *SCN2A* and *SCN8A*
 - 16 children: 46% placebo-adjusted reduction in motor seizures in RCT
 - 5 seizure-free at 16 weeks
 - DEEs - underway

Small molecule drugs







Precision diagnosis

→ Precision therapy

- Many approaches
 - Early results promising but not likely to be a cure
 - May need > 1 approach
 - Set appropriate expectations for patients and families
 - Many unresolved questions
eg. access, cost
risk versus benefit
- Exciting times!

