Epilepsy Syndromes with Onset in Neonates & Infants

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Disclosures relevant to this presentation

Chair ILAE Commission on Classification & Terminology 2013-17

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Member ILAE Task Force on Nosology & Definitions 2017-21

Member ILAE Task Force on Etiology Specific Syndromes 2021-25

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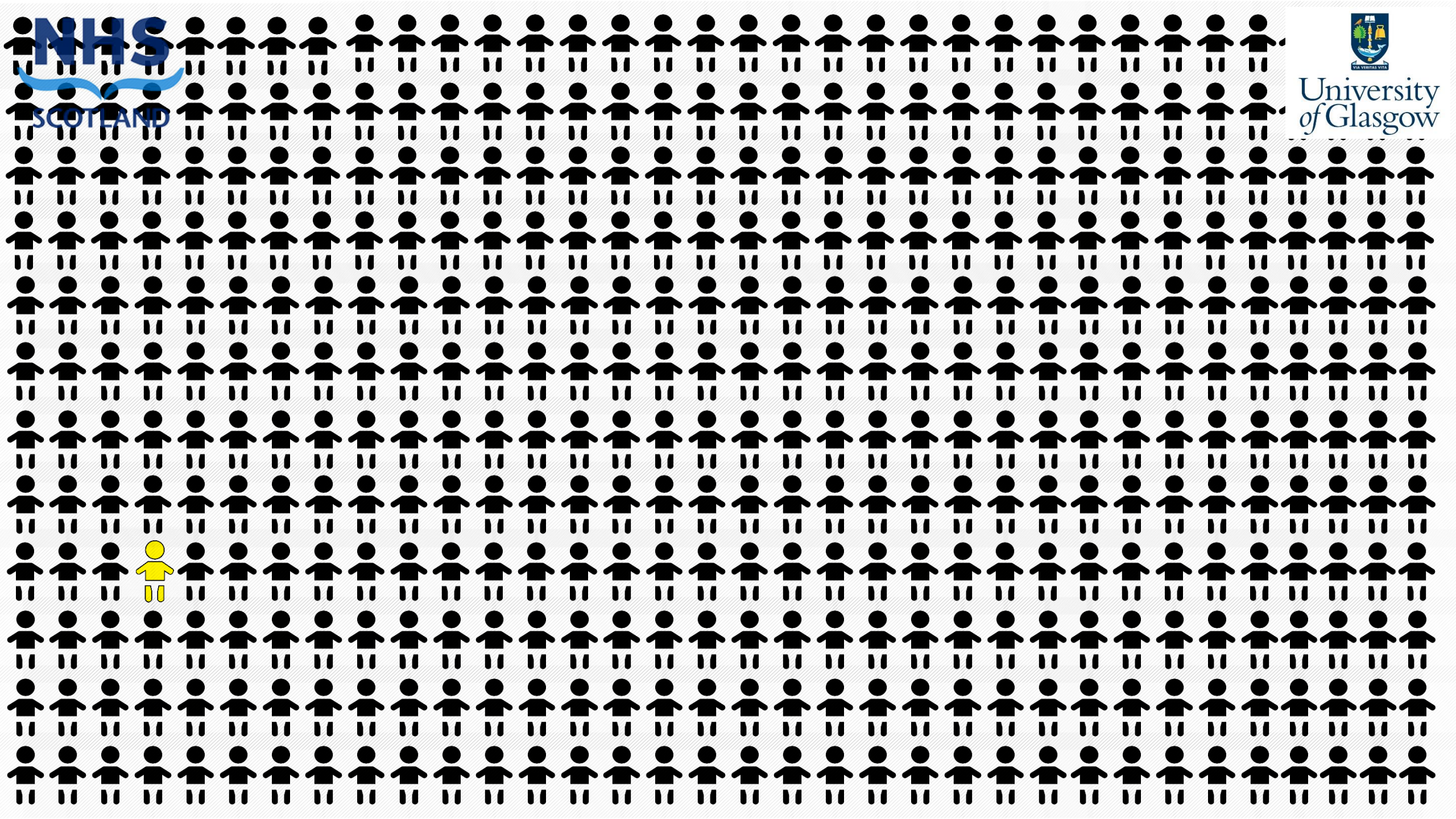
SPECIAL REPORT

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

Sameer M. Zuberi[1] | Elaine Wirrell[2] | Elissa Yozawitz[3] | Jo M. Wilmshurst[4] | Nicola Specchio[5] | Kate Riney[6,7] | Ronit Pressler[8,9] | Stephane Auvin[10] | Pauline Samia[11] | Edouard Hirsch[12] | Santiago Galicchio[13] | Chahnez Triki[14] | O. Carter Snead[15] | Samuel Wiebe[16] | J. Helen Cross[17,18] | Paolo Tinuper[19,20] | Ingrid E. Scheffer[21] | Emilio Perucca[22,23] | Solomon L. Moshé[24,25,26] | Rima Nabbout[27]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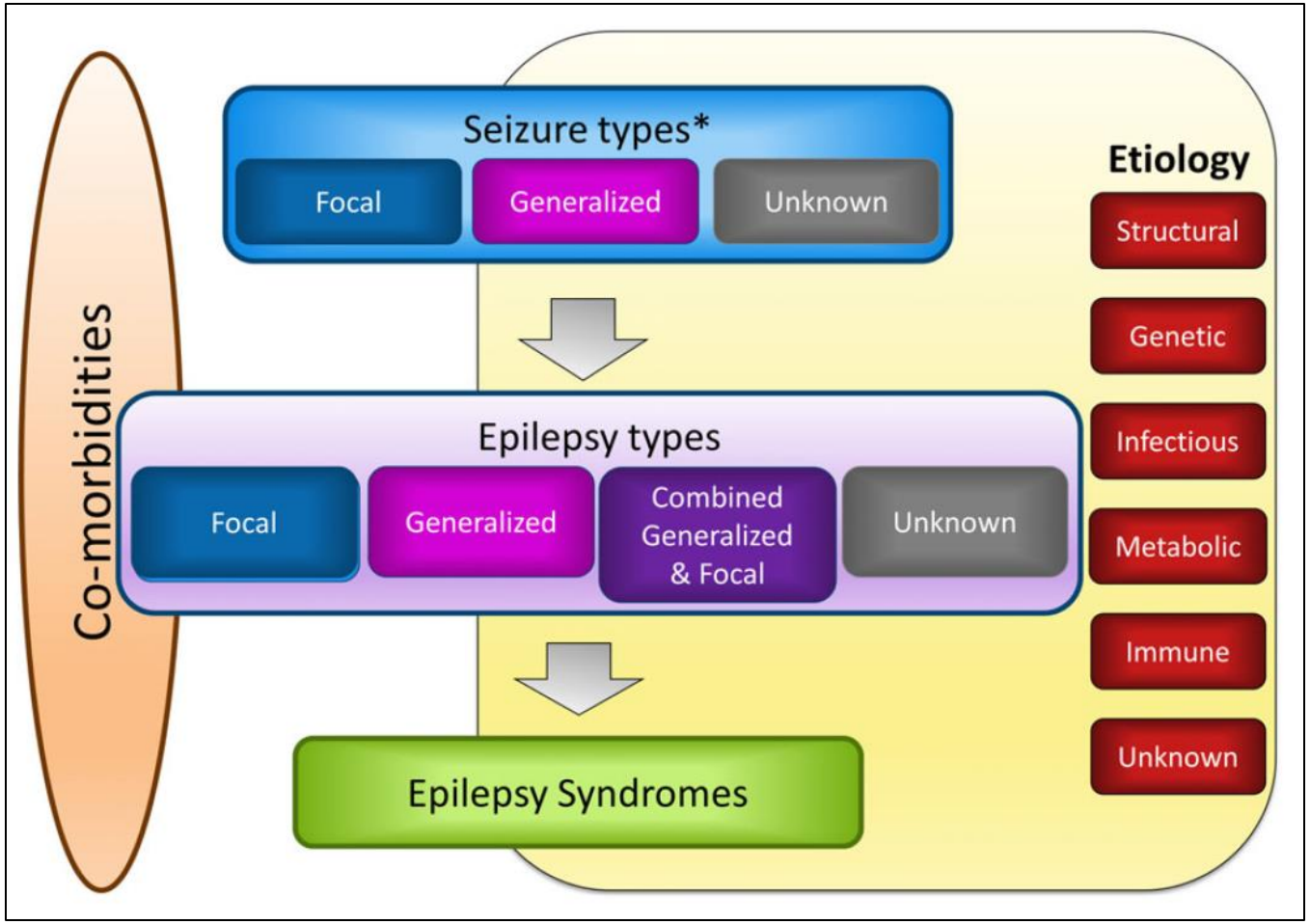

ILAE POSITION PAPER

ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology

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An epilepsy syndrome is a characteristic cluster of clinical and EEG features often supported by specific etiological findings (structural, genetic, immune and infectious

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The ILAE classification of seizures and the epilepsies: Modification for seizures in the neonate. Position paper by the ILAE Task Force on Neonatal Seizures

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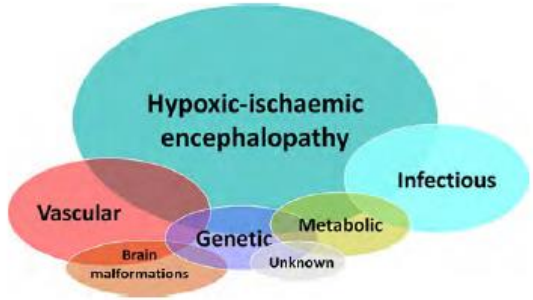
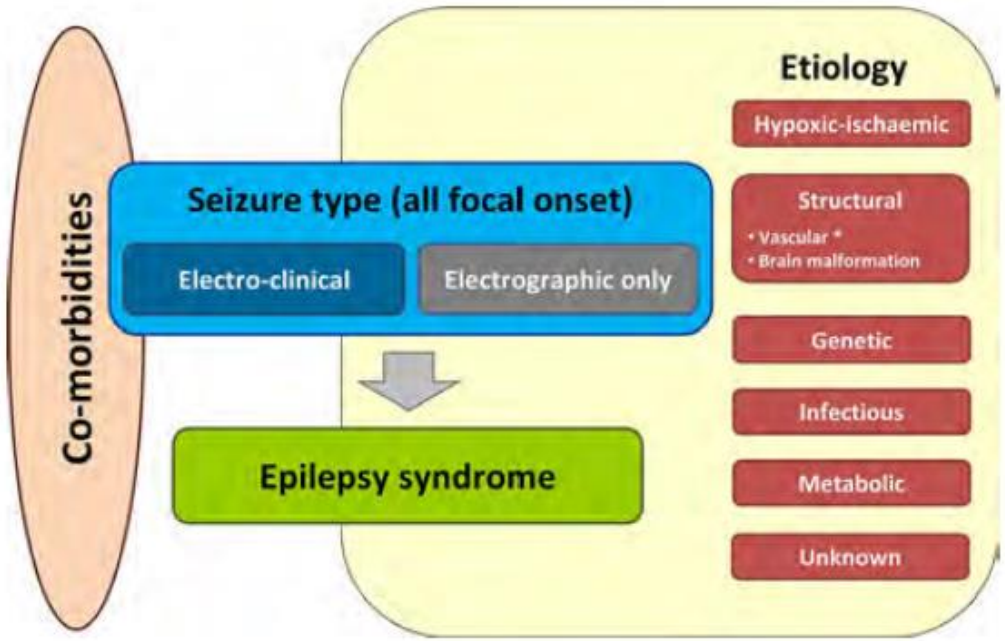
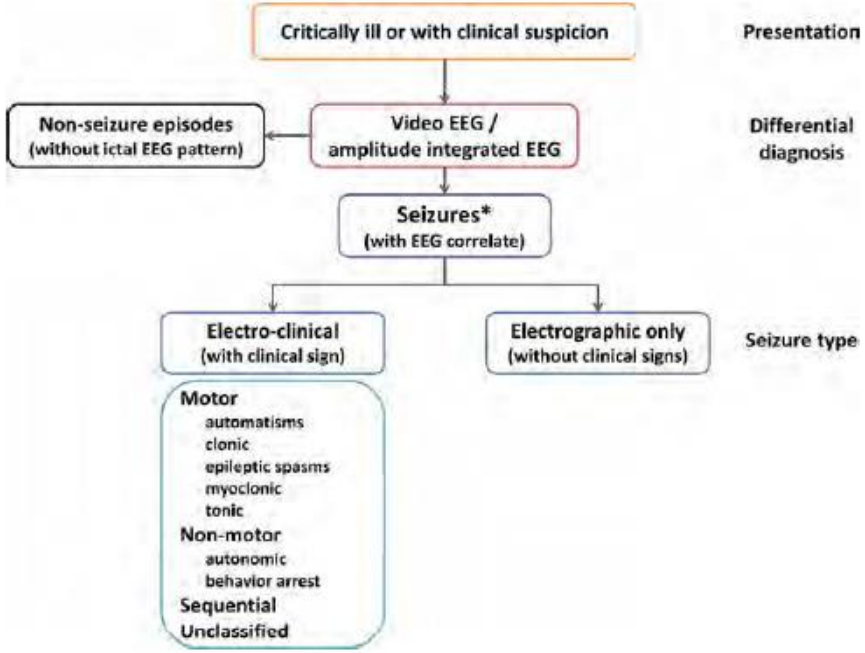


FIGURE 1 Relative occurrences of common etiologies of neonatal seizures in term infants. Adapted from [3–5,8,81,82]





Classification should guide clinical management

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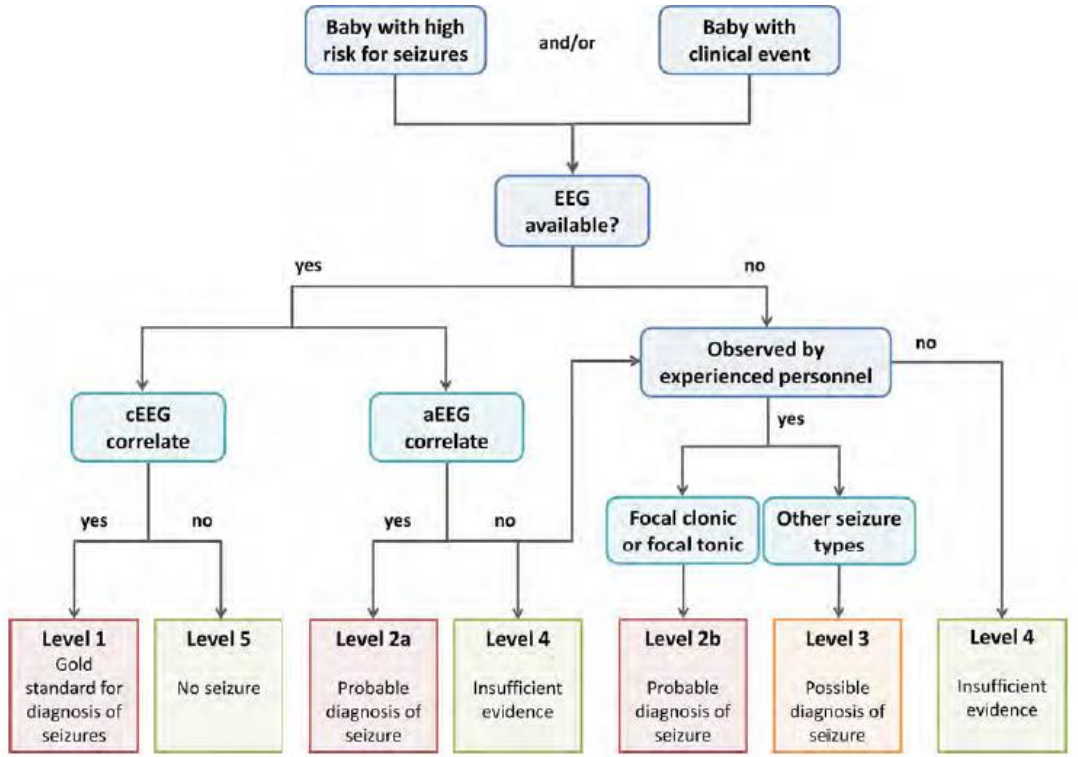

FIGURE 5 Algorithm to determine degrees of diagnostic certainties for neonatal seizures. This flow chart will help to determine the diagnostic certainty of neonatal seizures depending on the available diagnostic method (EEG, aEEG or observation by experienced personnel) and seizure type. Developed by the Brighton collaboration (adapted from[4]). cEEG conventional EEG; aEEG; amplitude-integrated EEG

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Self-limited epilepsies

- Self-limited neonatal epilepsy (SeLNE)
- Self-limited familial neonatal-infantile epilepsy (SeLFNIE)
- Self-limited infantile epilepsy (SeLIE)
- Genetic epilepsy with febrile seizures plus (GEFS+)
- Myoclonic epilepsy in infancy (MEI)

Developmental and epileptic encephalopathies (DEE)

- Ealy infantile developmental and epileptic encephalopathy (EIDEE)
- Epilepsy in infancy with migrating focal seizures (EIMFS)
- Infantile epileptic spasms syndrome (IESS)
- Dravet syndrome (DS)

Etiology-specific syndromes

- *KCNQ2*-DEE
- Pyridoxine-dependent (*ALDH7A1*)-DEE (PD-DEE)
- Pyridox(am)ine 5'-Phosphate Deficiency (PNPO)-DEE (P5PD-DEE)
- *CDKL5*-DEE
- *PCDH19* clustering epilepsy
- Glucose Transporter 1 Deficiency Syndrome (GLUT1DS)
- Sturge Weber syndrome (SWS)
- Gelastic seizures with hypothalamic hamartoma (GS-HH)

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Epilepsies where there is likely to be spontaneous remission

Developmental and epileptic encephalopathies (DEE)

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- Infantile epileptic spasms syndrome (IESS)
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Epilepsies where developmental impairment is related to both the underlying etiology independent of epileptiform activity and the epileptic encephalopathy

Etiology-specific syndromes

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Syndromes due to specific genetic, structural, immune and infectious etiologies where there are consistent electroclinical features, management and prognostic implications

Self-limited neonatal epilepsy

TABLE 1 Diagnostic criteria for self-limited (familial) neonatal epilepsy

	Mandatory	Alerts	Exclusionary
Seizures	Seizures are characterized by focal tonic features at onset, affecting the head, face, and limbs. Focal clonic or tonic seizures may alternate sides from seizure to seizure, and may evolve to bilateral tonic or clonic seizures	Clinical history suggestive of in utero seizures	Epileptic spasms Myoclonic seizures Generalized tonic seizures Generalized tonic-clonic seizures
EEG		Interictal: Mild background slowing	Interictal: Persistent focal slowing or moderate or greater background slowing not limited to the postictal period Burst suppression pattern Hypsarrhythmia Ictal: Lack of EEG correlate with clinical symptoms
Age at onset			Onset after first month of age
Development at onset			Any degree of encephalopathy
Neurological exam		Significant neurological examination abnormalities, excluding incidental findings	
Imaging			Neuroimaging documenting a causal lesion for seizures
Other studies – genetics		Lack of pathogenic variant in gene associated with this syndrome, most commonly *KCNQ2* or *KCNQ3* OR Lack of family history suggesting AD inheritance with incomplete penetrance	Other acute symptomatic cause of seizures including intracranial infection, ischemic or hemorrhagic stroke, hypoxic-ischemic brain injury, significant metabolic disturbances
Course of illness		Mild neurodevelopmental delay long-term Lack of remission of epilepsy after 6 months of age Drug-resistant epilepsy	Moderate to severe neurodevelopmental disability
Are MRI or ictal EEG required for diagnosis? A nonlesional MRI is required to diagnose this syndrome An ictal EEG is not required for diagnosis			
Syndrome without laboratory confirmation: In resource-limited regions, SeLNE can be diagnosed without EEG and MRI in a neonate with a family history suggestive of familial SeLNE who meets all other mandatory and exclusionary clinical criteria and has no Alerts. However, the clinical history of affected family members should be consistent with the expected course for SeLNE, and careful follow-up of the patient is required to ensure their course is also consistent with this syndrome			

Abbreviations: EEG, electroencephalogram; MRI, magnetic resonance imaging; SelNE, self-limited neonatal epilepsy.

Early Infantile Developmental &Epileptic Encephalopathy replaces the terms Ohtahara syndrome and Early Myoclonic Encephalopathy

TABLE 5 Diagnostic criteria for early infantile developmental and epileptic encephalopathy

	Mandatory	Alerts	Exclusionary
Seizures	Tonic and/or myoclonic seizures		
EEG	Interictal: Either burst suppression or multifocal discharges Diffuse slowing		
Age at onset	Birth to 3 months (adjusted for prematurity)		
Development at onset		Normal development at onset, although it is acknowledged that this can be challenging to accurately assess historically	
Neurological exam at onset		Normal neurological examination, although it is acknowledged that this can be challenging to assess historically or in an infant who has had very frequent seizures and/or received ASMs that may alter their exam	
Early Comorbidities	Developmental impairment is present prior to or shortly after seizure onset		
Course of illness	Abnormal neurodevelopment including intellectual disability		
Are MRI or ictal EEG required for diagnosis? An MRI is not required for diagnosis but is strongly recommended to exclude structural causes An ictal EEG is not required in an infant with characteristic clinical features where the interictal EEG shows burst-suppression, multi-focal discharges with diffuse slowing			
Syndrome without laboratory confirmation: In resource-limited regions, this syndrome cannot be diagnosed without an interictal EEG			

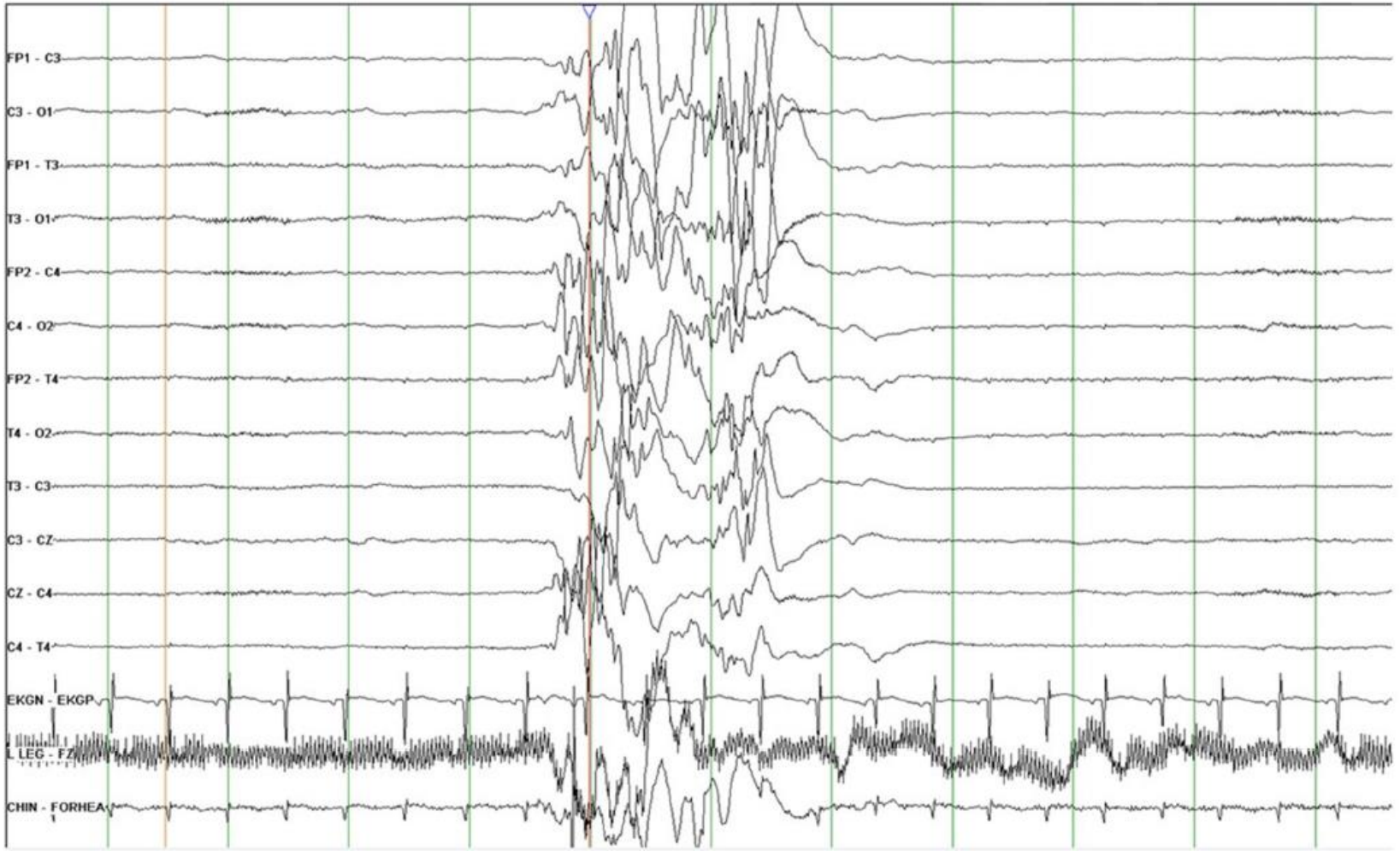

FIGURE 5 A 4-week-old boy with Early Infantile DEE. He presented on day 2 of life with sequential seizures with a prominent tonic component and severe encephalopathy. The EEG (20 microvolt/mm, 30 mm/s) shows a burst-suppression pattern. Genetic testing showed a *KCNQ2* pathogenic variant. The patient showed a marked reduction in seizures with carbamazepine but remained profoundly delayed

Dravet syndrome

TABLE 8 Diagnostic criteria for Dravet syndrome

	Mandatory	Alerts	Exclusionary
Seizures	Recurrent focal clonic (hemiclonic) febrile and afebrile seizures (which often alternate sides from seizure to seizure), focal to bilateral tonic-clonic, and/or generalized clonic seizures	No history of prolonged seizures (>10 min) Lack of fever sensitivity as a seizure trigger	Epileptic spasms Early infantile *SCN1A* DEE
EEG		Normal EEG background without interictal discharges after age 2 years	
Age at onset	1–20 months	1–2 months or 15–20 months	
Development at onset		Developmental delay at seizure onset	
Neurological exam		Focal neurological findings (other than Todd's paresis)	
Imaging			MRI showing a causal focal lesion
Other testing: ie, genetics, and so on		Lack of pathogenic *SCN1A* or other causal variant	
Course of illness	Drug-resistant epilepsy Intellectual disability	Good efficacy with prophylactic sodium-channel agents including carbamazepine, oxcarbazepine, and phenytoin	
Is MRI or ictal EEG required for diagnosis? An MRI is not required for diagnosis but is highly recommended to exclude other causes. An ictal EEG is not required for diagnosis			
Possible evolving syndrome: In a child <12 months who presents with a prolonged hemiclonic or bilateral tonic-clonic seizure with fever, and no other underlying cause, the possibility of Dravet syndrome should be considered. Further convulsive seizures (often with fever, and if prolonged or hemiclonic) would allow more definitive diagnosis of Dravet syndrome. A diagnosis would be further supported by the finding of a pathogenic *SCN1A* variant			
Syndrome without laboratory confirmation: In resource-limited regions, Dravet syndrome can be diagnosed in children without Alerts who meet all other clinical mandatory and exclusionary criteria, without EEG, MRI, and genetic testing			

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Epilepsia

FULL-LENGTH ORIGINAL RESEARCH

Defining Dravet syndrome: An essential pre-requisite for precision medicine trials

Wenhui Li[1,2] | Amy L. Schneider[2] | Ingrid E. Scheffer[2,3,4]

Syndrome papers provide overviews. Review the literature for finer details of each syndrome

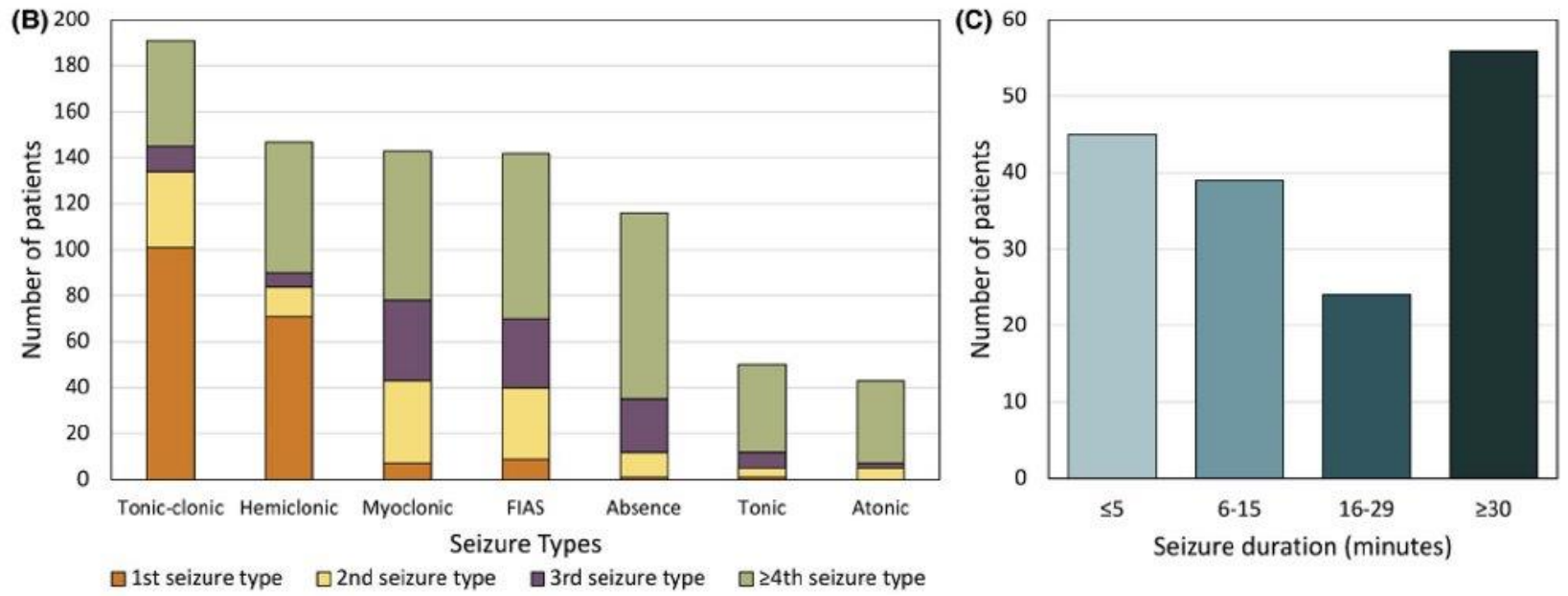


FIGURE 1 (A) Age at seizure onset in our cohort of 205 patients with *SCN1A*-Dravet syndrome together with published patients with onset after 12 months or with pathogenic mosaic *SCN1A* variants. (B) First, second, third, and fourth or more seizure type to develop in patients. (C) Duration of first seizure in 164 patients with *SCN1A*-Dravet syndrome

Infantile epileptic spasms syndrome

TABLE 7 Diagnostic criteria for infantile epileptic spasms syndrome

	Mandatory	Alerts	Exclusionary
Seizures	Flexor, extensor or mixed epileptic spasms which often occur in clusters		
EEG	Interictal: Hypsarrhythmia, multifocal or focal epileptiform discharges (that might be seen quickly after the spasms onset)	Interictal: Normal EEG Suppression-burst pattern	Ictal: Normal EEG during recorded clinical events of suspected spasms
Age at onset	1–24 months (while epileptic spasms may begin later, this would not be ISS)	Age at onset 1–2 months	
Comorbidities	Developmental slowing after spasms onset but may be absent early in the course (difficult to determine in a child with existing significant developmental disorders)		

Is MRI or ictal EEG required for diagnosis?

An MRI is not required for diagnosis but is highly recommended to evaluate for underlying cause.

An ictal EEG is not required for diagnosis provided the interictal study shows hypsarrhythmia or epileptiform abnormalities or developmental delay. In the absence of hypsarrhythmia or epileptiform anomalies, an ictal recording is required

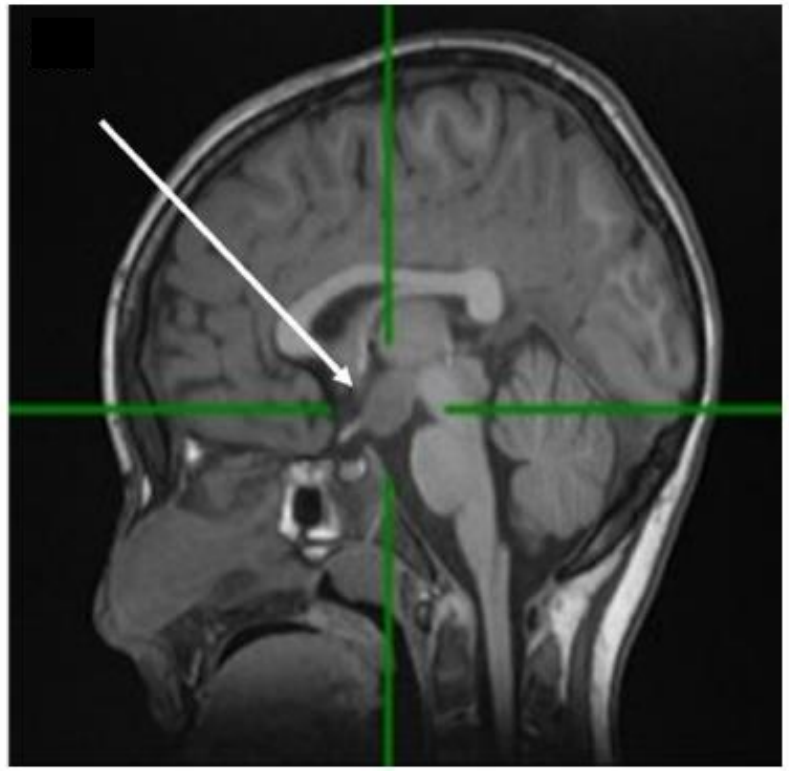
Possible evolving syndrome: Infants with preceding brain injury, developmental brain malformations, or specific genetic conditions, including early-infantile DEE, who show significant interictal EEG abnormalities (high amplitude, background slowing, and/or multifocal discharges) should be watched carefully for the development of clinical epileptic spasms. However, the syndrome of ISS cannot be diagnosed prior to onset of the mandatory seizure type

Syndrome without laboratory confirmation: In resource-limited regions, an interictal EEG is highly recommended. However, if EEG is unavailable, if clear clusters of typical epileptic spasms are witnessed by an experienced clinician (in person or on video recording), with the other clinical mandatory and exclusionary criteria, ISS can be diagnosed

Etiology specific syndrome - Gelastic seizures with hypothalamic hamartoma

TABLE 15 Diagnostic criteria for gelastic seizures with hypothalamic hamartoma

	Mandatory	Alerts	Exclusionary
Seizures	Gelastic seizures with mechanical, mirthless laughter, inappropriate to context	Seizure frequency less than daily	
EEG		Interictal: Generalized or focal background slowing (excluding immediate postictal period) Ictal: Gelastic seizures may lack ictal EEG correlate	
Age at onset		Onset >5 years of age	
Development at onset		Clear developmental delay at seizure onset	
Neurological exam		Focal neurological findings (other than Todd's paresis) or generalized hypotonia	
Imaging	Hypothalamic hamartoma (may require thin slices through the hypothalamic region to confirm)		
Course of illness	Drug-resistant epilepsy	Lack of behavioral problems including aggression, impulsivity, and hyperactivity	
Is MRI or ictal EEG required for diagnosis? An MRI is required for diagnosis An ictal EEG is not required for diagnosis. Furthermore, gelastic seizures may lack ictal correlate on EEG			
Syndrome without laboratory confirmation: In resource-limited regions, HH-GS cannot be diagnosed in the absence of an MRI, as gelastic seizures may arise from other brain regions			



Precision medicine drives classification in the epilepsies

"A treatment approach in which disease treatment and prevention is tailored to individual variability in genes, environment and lifestyle for each person"

Medical therapy, surgical treatment, metabolic therapy, gene related therapy

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