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SPECIAL REPORT

Classification of the epilepsies: New concepts for discussion and debate—Special report of the ILAE Classification Task Force of the Commission for Classification and Terminology[1]

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Summary

The ILAE Task Force on Classification presents a road map for the development of an updated, relevant classification of the epilepsies. Our objective is to explain the process to date and the plan moving forward as well as to invite further discussion about the newly proposed terms and concepts. Here, we present our response to feedback about the 2010 Organization of the Epilepsies and clarify the reintroduction of the word "classification" to map out a framework for epilepsy diagnosis. We introduce some new concepts and suggest four diagnostic levels: seizure type, epilepsy category, epilepsy syndrome, and epilepsy with (specific) etiology to denote specific levels of diagnosis. We expand the etiological categories to six, focusing on those with treatment implications. Finally, we discuss the changes in terminology originally suggested and modifications in response to comments from the epilepsy community. We welcome feedback and discussion from the global epilepsy community, particularly for the new suggested terms, so that we can cement a classification that both reflects current thinking and scientific understanding and provides a dynamic, evolving framework.

KEY WORDS: Classification, Epilepsy syndromes, Terminology, Etiology.

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Key Points

- A road map for the development of a revised classification of the epilepsies is presented.
- Your comments are invited online; due by 30th August 2016.
- This paper presents a framework for overall epilepsy classification and is complementary to the revision of the classification of seizure types currently underway.

The purpose of this article in *Epilepsia Open* is to update the community on the work being done by the Task Force on the Classification of the Epilepsies and to solicit comments and criticism from readers. Please send your comments to the ILAE website, http://www.ilae.org/Visitors/Centre/Class-Roadmap.cfm, where all comments are posted. —The president of the ILAE and the editors in chief of *Epilepsia Open*, the new open access journal of the ILAE.

Classification in epilepsy is primarily for clinical purposes. It influences every clinical consultation, yet its impact stretches far beyond the clinical domain to clinical and basic epilepsy research and to the development of novel therapies. The need for an updated classification of the epilepsies that reflects current clinical practice has been recognized for many years because many clinicians still use the 1989 classification of epilepsies and epilepsy syndromes.[1] With the advent of significant advances in understanding the neurobiology of seizures and epileptic diseases, there have been major paradigm shifts in the concepts underpinning classification. If not updated to mirror current understanding, the classification will become irrelevant to clinical practice rather than the preeminent tool for communication in the clinical and research domains.

The aim of this paper is to describe the process involved in developing an updated classification, to map out the way forward, and to invite further thoughts from the epilepsy community regarding the new suggested concepts and terms. In addition to this task force focusing on the overall framework for classification, a second seizure task force is developing a new structure and lexicon for seizures. We will ask for comments online regarding the proposals in this paper and arrange discussion pieces in *Epilepsia* and educational settings to further refine the classification.

When is a Classification of the Epilepsies Accepted and Ready for Implementation?

The classification of the epilepsies is the mandate of the ILAE Commission for Classification and Terminology. The work of many commissions over the last 25 years has driven thinking forward since the last formal classification in 1989.[1] The process for the adoption of an official classification of the epilepsies has been somewhat unclear, with commission publications often using the term "proposal" or "recommendation." This has meant that members of the epilepsy community have been unsure *when* they should adopt a new classification into their daily practice, teaching, research, and overall lexicon.

Classification is inherently dynamic and will never be set in stone. In an ideal world, a classification should have a solid scientific basis. Where there are gaps in knowledge, a classification is formulated on well-accepted concepts based on robust scientific evidence. Where our classification framework proves incompatible with new findings, we need flexibility to modify or essentially reconstruct the framework in light of new insights into this complex group of diseases. Importantly, however, concepts today considered as innovative may one day be regarded as outdated and, in some instances, even proven incorrect. We also recognize that it is challenging to change practice in terms of the use of novel nomenclature. We are comfortable using words that we have employed for many years and have a natural reluctance to change.

Procedure for ILAE Position Papers

The ILAE has recently developed a policy for League position papers.[2] Such papers address topics that provide a common language or definitions for the international epilepsy community, and the classification of the epilepsies clearly falls within this remit. The Commission for Classification and Terminology 2009–2013 followed the policy and submitted a proposal to refine the 2010 Organization of the Epilepsies[3] largely in response to the feedback received over the intervening 3 years. After intense review, a document was submitted to *Epilepsia* and posted online (Data S1). Comments from the global community were invited. There was a vigorous response, with more than 120 pages of commentary, and the journal received six reviews. It was clear that there was a lack of clarity about a number of issues.

The next stage in the process was the assignment of a new task force, with the membership determined by the ILAE executive, comprising members from the previous commission and the current 2013–2017 commission, together with members of the executive committee, an *Epilepsia* editor, and a few additional invited participants. The task force met and believes that a road map should be presented outlining the way forward. The road map should discuss key concepts rather than present a definitive classification because presenting a classification requires further deliberation and discussion. Presenting a road map is the purpose of this paper.

Return to Epilepsy Classification

The Berg et al.[3] report suggested that the term "organization of the epilepsies" be used, rather than "classification of the epilepsies," to emphasize that the fundamental basis of the epilepsies is not well understood and cannot be scientifically classified, in contrast to many areas of biology. This approach was also designed to promote flexibility in classification so that one could classify according to any domain or property (for example, one could classify by myoclonic seizures, electroencephalogram [EEG] trait, or a host of other features).[4]

There was dissatisfaction with, and misunderstanding of, the term "organization." The argument has subsequently been made that, in many areas of medicine, the term "classification" is employed for disorders based on clinical features and without the benefit of a fundamental scientific understanding. For this reason, the word "classification" was again brought into favor because it is commonly employed in clinical practice and clinicians understand that it provides a framework for diagnosis without being the final definitive scientific answer. The flexibility underpinning the concept of an organization can still be applied to the classification and is strongly encouraged. Therefore, a decision was made to retain the word "classification" to describe the epilepsies.

Proposal for a Framework for Epilepsy Classification and Diagnosis

An overarching framework for classification of the epilepsies has been developed (Fig. 1). This is designed to allow diagnosis at multiple levels depending on the information and resources available. In the first instance, clinicians have to determine whether a paroxysmal event is an epileptic seizure. Once they have established clinically (or

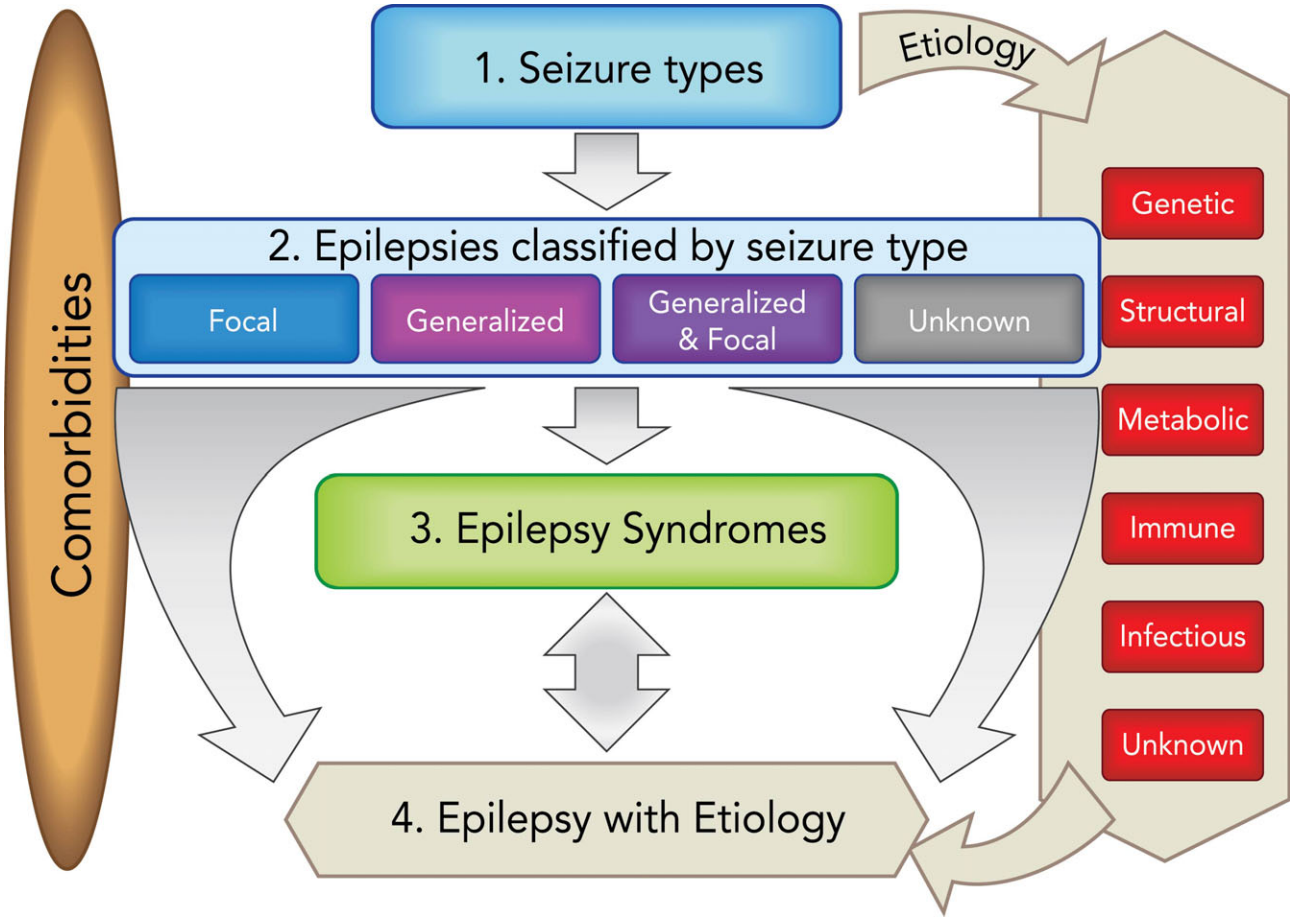

Figure 1.
Framework for epilepsy classification. The etiological framework can also be used for acute seizures. The term "genetic" refers to the etiology in an individual if there is an epilepsy syndrome that is known to be primarily genetic based on evidence from family and twin studies. Although the underlying gene may be identified for some individuals, in most cases, the underlying genetic mutation will not be known.
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with support from video, EEG studies, or both) that a patient is having epileptic seizures, they can make a level 1 diagnosis of the patient's seizure types. A revised classification of seizure types has been recently developed for further discussion by the epilepsy community.[5] In some settings, clinicians may not have the resources to take the diagnosis further, and then classification according to seizure type may be the maximum level of diagnosis possible. In other cases, clinicians may simply have too little available information to be able to make a higher-level diagnosis, such as when a patient has had only a single event.

Often, however, a diagnosis regarding the type of epilepsy can be made (level 2: epilepsy classified by seizure type), and clinicians should strive to make a diagnosis at this level whenever possible. For many years we have used the concept of focal and generalized epilepsies in daily practice. In the 2010 commission publication, it was suggested that the terms "focal" and "generalized" be reserved for seizure types rather than for epilepsies per se.[3] Following our own experience and considerable feedback regarding the utility of the terms "focal epilepsies" and "generalized epilepsies" in clinical practice, we reinstated these terms with the caveat that generalized and focal epilepsies do not provide a dichotomous classification into which all epilepsies can be squeezed.[4] We have therefore added the categories of "generalized *and* focal epilepsy" and "unknown if generalized or focal epilepsy" (Fig. 1).

At the next level (level 3), we aim to make an epilepsy syndrome diagnosis in our patients. Epilepsy syndromes are determined by a distinctive clinical pattern and EEG features. They may have associated imaging, etiological, prognostic, and treatment implications. Well-recognized examples include childhood absence epilepsy, juvenile myoclonic epilepsy, and benign epilepsy with centrotemporal spikes.[3] The recently released educational ILAE website, epilepsydiagnosis.org, provides an excellent resource to aid in understanding the parameters for diagnosis, to review videos of seizure types, and to assess the EEG features of many established syndromes, and it can be used as a teaching tool around the world by the epilepsy community.

Although Fig. 1 highlights the critical issue of considering etiology at *all* levels of epilepsy diagnosis (right-hand vertical bar), the fourth level of diagnosis establishes that the primary etiology and epilepsy diagnosis have been determined. The task force had some debate as to the preferred term for this level of diagnosis, and suggestions included "epilepsy with etiology," "epilepsy with specific etiology," and "epilepsy with known etiology." We welcome views regarding this terminology and alternative suggestions. This level of diagnosis opens the gateway to a precision-medicine approach that reflects current scientific efforts. Our ability to make an etiological diagnosis is rapidly increasing with the revolution in genetics and other fields such as neuroimaging. This means that the definitive etiology is known, although factors influencing phenotypic variability are usually not yet understood, such as modifier genes or the influence of environmental factors. Many new etiological diagnoses are emerging such as *CHD2* encephalopathy, *KCNQ2* encephalopathy, and *STXBP1* encephalopathy, to name a few.[6–9] One of the best-known examples is an individual with Dravet syndrome, who has a known mutation of the sodium channel gene *SCN1A*.[10]

In some instances, the epilepsy syndrome may not be known even though the etiology is established and a level 4 classification can be made. Importantly, an epilepsy syndrome does not have a one-to-one correlation with an etiological diagnosis and serves a different purpose, such as guiding management. For example, *SCN1A* mutations are also seen in the milder familial epilepsy syndrome of GEFS+ (genetic epilepsy with febrile seizures plus). The GEFS+ spectrum includes the phenotype of febrile seizures plus, where medication is often not necessary in contradistinction to a patient with Dravet syndrome and an *SCN1A* mutation.[11,12] Another example is the metabolic condition of glucose transporter 1 deficiency, for which the ketogenic diet is the usual therapeutic approach. This can be regarded as an etiology that causes epilepsy syndromes as diverse as juvenile absence epilepsy and epilepsy with myoclonic-atonic seizures in addition to the well-known GLUT1 encephalopathy.[13–15] Thus, one genetic cause may be associated with several epilepsy syndromes. By making an epilepsy syndrome or an etiological diagnosis, a targeted therapeutic approach may be possible now or in the future.

An excellent example of precision medicine using the paradigm of an etiological diagnosis is the finding of a de novo mutation of the potassium channel gene *KCNT1* in up to 50% of children with the syndrome of epilepsy of infancy with migrating focal seizures.[16] These mutations are associated with a gain of function of the mutant ion channel.[16] This gain of function can be reversed in vitro by an "old" drug, quinidine, which targets the KCNT1 potassium channel.[17] Quinidine is both an antiarrhythmic agent and antimalarial treatment. Open-label trials of quinidine in three children with *KCNT1* mutations and devastating epilepsies provide the first glimmer of hope for precision medicine, with improvement in seizure frequency observed in the two children whose mutations showed the greatest gain of function in vitro and were associated with the most severe phenotype, epilepsy of infancy with migrating focal seizures.[18,19] Although promising, randomized double-blind placebo-controlled trials are necessary to prove unequivocal efficacy as a precision medicine.

At *all* levels of diagnosis, we should consider more broadly the etiology of the patient's epilepsy. In some patients, the etiology will not be known. In others, more than one known etiology will apply. A range of etiological groups has been recognized, with emphasis on those that have implications for treatment. This has been expanded to include six groups, with room for further expansion as

knowledge evolves. The groups are genetic, structural, metabolic, immune, infectious, and unknown (Fig. 1). In many instances, multiple etiologies apply and can be used because they are not meant to be mutually exclusive groups. For example, tuberous sclerosis complex has both a genetic and a structural etiology. Both etiological groups provide support for different, relatively diverse treatment paths: tuberectomy[20] and mammalian target of rapamycin (mTOR) inhibitors.[21]

Similarly, patients may have a range of comorbidities associated with any level of the diagnostic framework (Fig. 1, left-hand vertical oval). Although long known, a recent increase in awareness of comorbidities by the epilepsy community means that learning, psychological, and behavioral features are identified and appropriately managed. In addition, the description of specific comorbidities with known etiologies allows earlier recognition, diagnosis, and treatment. For example, girls with *PCDH19* mutations are at risk of severe behavioral and autistic features that may be far more challenging in terms of management than are seizures in adolescents and adult women.[22]

Road Map

The approach planned is to engage the epilepsy community in further discussion about the more controversial concepts. This will take place through educational forums in epilepsy conferences, commentaries and online polls in *Epilepsia Open*, and online discussions through the ILAE website. Commentaries will focus on the major points of debate. Some examples are provided to stimulate further discussion.

The term "genetic"

The term "genetic" was also the subject of intense debate. Although most agree that the term "idiopathic" is outdated and that many facets of medicine no longer use it, epilepsy clinicians are comfortable with its use. There was considerable misunderstanding of the suggested replacement term "genetic" because many thought that this meant that the underlying genetic mutation was known or inherited.

"Genetic" encompasses several concepts, of which one or all may apply to a specific patient. The most straightforward is where the causative genetic mutation is known. Specific genetic mutations are known in only a small minority of patients with epilepsy. Increasingly, de novo mutations are found. This explains the absence of a family history of seizure disorders and often the family's reluctance to accept that genes could play an etiological role. This finding emphasizes the distinction between genetic and inherited, because "genetic" does not mean "inherited."

On the other hand, a genetic mutation may be inherited, but not fully penetrant, so that some individuals carrying the mutation are unaffected. In other settings, complex inheritance may be present where several genes contribute to risk. Thus, a mutation of one gene may not be sufficient to result in epilepsy in an individual.

In *most* instances, the term "genetic" is used to denote that twin and family studies provide strong evidence for a genetic basis.[23–25] Here, the genes are usually *not* known, and the scientific support is based on clinical genetic research.

The idiopathic generalized epilepsies map to either generalized genetic epilepsies or generalized epilepsy of unknown etiology

For the generalized epilepsies specifically, the broad epilepsy syndrome group of the idiopathic generalized epilepsies is well established, with the original term "idiopathic" essentially meaning genetic.[1] This group accounts for a quarter of all epilepsies.[26] The collective name "idiopathic generalized epilepsies" (IGE) encompasses the syndromes of childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and epilepsy with generalized tonic-clonic seizures alone (EGTCS) as well as some cases that do not fit into one of these clearly defined syndromes. Strong evidence from family studies and twin studies shows that genetic factors (typically not known at present) play a predominant etiological role. In individuals in whom the generalized epilepsy cannot be classified as one of these syndromes or when evidence is lacking for a genetic basis, the epilepsy may be classified as having an unknown etiology. This means that a generalized epilepsy can be classified as a generalized genetic epilepsy when sufficient information is present to indicate a genetic basis. When there is insufficient information, the epilepsy is classified as generalized epilepsy of unknown etiology. One example is an individual with a clinical diagnosis of a specific generalized epilepsy syndrome, such as juvenile myoclonic epilepsy, for which there is no family history of seizures. There is debate as to whether the JME should be classified as generalized epilepsy of unknown etiology or as generalized genetic epilepsy based on evidence of a genetic background in other patients with the same syndrome. The task force welcomes feedback on this issue and specifically whether the collective term IGE should be replaced by the term "generalized genetic epilepsy" (GGE) or the mixed term "generalized epilepsy of genetic or unknown etiology."

Unfortunately, the term "genetic" carries significant cultural concerns in some countries and leads to additional stigma for the person with epilepsy. This is an important point, and we need to find solutions with education about the meaning of the word "genetic" in the context of etiology. Epilepsy has a long history of stigma and inappropriate attribution of causation over the last 5,000 years, and we need to understand that genetic does not mean inherited and is a common cause of many human diseases. At this time, in certain countries the label "genetic" creates major problems in terms of marriage and stigma for affected individuals. The

classification exists to assist people with epilepsy rather than to make life more challenging. So, in these settings, it is suggested that the clinician may elect to classify the patient as having generalized epilepsy of unknown etiology if the collective term IGE were to be replaced by the term "generalized genetic epilepsy" (GGE) rather than by the mixed term "generalized epilepsy of genetic or unknown etiology."

Developmental and epileptic encephalopathies

"Epileptic encephalopathy" was carefully defined in the Berg et al.[3] report as the notion that the epileptic activity itself contributes to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (e.g., cortical malformation). Global or selective impairments can be seen along a spectrum of severity and across all epilepsies and can worsen over time.[3]

The term "epileptic encephalopathy" for an overarching group of epilepsies has appropriately gained widespread use, particularly with regard to the severe epilepsies of infancy and childhood.[27] This term encompasses many of the well-recognized syndromes such as West syndrome and Lennox-Gastaut syndrome but, equally, can be applied to many more recently recognized disorders such as *CDKL5* encephalopathy and *CHD2* encephalopathy.[6,7,28] It implies that abundant epileptiform activity interferes with development, with cognitive slowing and often regression, and sometimes has psychiatric and behavioral consequences. Conversely, an important part of the concept is that amelioration of epileptiform activity has the potential to improve the developmental consequences of the disorder.[29,30] The epileptiform activity can cause regression in a child with previously normal development or in one who has always been delayed and then shows developmental plateauing or regression. This is a critical issue from a clinical perspective and one often mirrored in the observations of parents.

However, many, if not most, of these disorders are not solely associated with developmental or behavioral deterioration due to epileptiform activity. For example, in the relatively common encephalopathy of Dravet syndrome, developmental slowing or regression occurs between 1 and 2 years of age at a time when epileptiform activity is typically not yet frequent. This suggests a developmental component in addition to an epileptic component, with both aspects likely occurring secondary to the underlying sodium channel subunit gene (*SCN1A*) mutation in >80% of cases. This observation, pertinent to many of the genetic encephalopathies, suggests that a broadening of the terminology, when appropriate, to include the word "developmental" acknowledges that both aspects may be playing a role in the observed clinical presentation. These concepts are critical for families and clinicians to understand the disease process.

When patients manifest features of both delayed development and very active epileptiform abnormalities, they could be considered to have a "developmental epileptic encephalopathy" to emphasize that both features play a role in their disease. In many instances, when a genetic mutation of major effect is identified, the patient may have an etiology of a *gene name* encephalopathy, such as "*STXBP1* encephalopathy." When genes are associated with both severe and self-limited pharmacoresponsive epilepsies, such as *KCNQ2* or *SCN2A*, then the term "encephalopathy" can be used to denote the severe form.[8,31,32]

It is suggested that, moving forward, we can use the terms "developmental encephalopathy" and "epileptic encephalopathy" either independently or together, as in "developmental epileptic encephalopathy," selecting whichever most aptly describes the patient.

Symptomatic generalized epilepsy often maps to epileptic encephalopathy

The term "symptomatic generalized epilepsy" has gained widespread use to denote epilepsy with bilateral network involvement that is symptomatic of the underlying cause. It has also been used synonymously with secondary generalized epilepsy; both typically are associated with intellectual disability. These terms have also met with considerable confusion, partly because the words are similar to "secondarily generalized epilepsy," which refers to seizures that begin in one part of the brain and then spread to involved generalized networks. We propose these terms should no longer be used. Many patients who would have previously been diagnosed with symptomatic generalized epilepsy would now map to a (developmental) epileptic encephalopathy with generalized, focal, or generalized and focal epilepsy if there is evidence of worsening of cognition over time. In some cases, refractory epilepsy can occur in the setting of intellectual disability without worsening, in which case the patient would have intellectual disability, rather than an epileptic encephalopathy, with generalized, focal, or focal and generalized epilepsy, depending on their seizure types.

The term "benign"

There is increasing awareness of the comorbidities that accompany many, if not most, epilepsies. These range from subtle learning difficulties to intellectual disability, to psychiatric features such as autism spectrum disorders and depression, to psychosocial concerns. There has been considerable concern that the term "benign" underestimates these issues in the milder epilepsy syndromes such as benign epilepsy with centrotemporal spikes (BECTS) and childhood absence epilepsy (CAE). Despite the gestalt of a benign syndrome, BECTS may be associated with transient or long-lasting cognitive effects[33,34] and CAE with significant psychosocial consequences such as increased risk of early pregnancy.[35] The Berg et al.[3] report suggested new

terms to distill the elements implied in the term "benign." These are "self-limited," to denote the likely spontaneous resolution of a syndrome such as BECTS, and "pharmacoresponsive," to show that it is expected that this syndrome will be controlled with the appropriate antiepileptic drugs.[3]

Here, we have highlighted critical issues that have elicited much discussion and merited the development of new concepts or terms, including the introduction of an etiological level of diagnosis and the question of the most appropriate term or terms to replace IGE. We now need to consider whether we should apply these new terms to our epilepsy practice, and we encourage feedback and thoughts from our global epilepsy community. It is sometimes helpful to start to employ new terms in practice to see how they work in the real world, so it would be helpful to hear of your experience. With further discussion and careful consideration of feedback, we will frame a definitive outline of classification with the support of the ILAE. We very much look forward to hearing more from the epilepsy community as we continue to move classification forward.

Conflict of Interest

Ingrid Scheffer received support from and/or has served as a paid consultant for UCB, Eisai, Athena Diagnostics, GlaxoSmithKline, Transgenomics, and Biocodex. She is on the editorial board of *Neurology* and *Epileptic Disorders*. She has received grants from the NHRMC, ARC, NIH, HRC, CURE, US Department of Defense, and March of Dimes. The Epilepsy Study Consortium pays Jacqueline French's university employer for her consultant time related to Acorda, Anavex, Brabant Pharma, Bio-Pharm Solutions, Eisai Medical Research, GlaxoSmithKline, GW Pharma, Impax, Johnson and Johnson, Marinus, Neusentis, Novartis, Pfizer, Roivant, Sage, SK Life Science, Sunovion, Supernus Pharmaceuticals, Takeda, UCB, Ultragenyx, Upsher-Smith, Vertex, Zogenix, and Zynerba; she is on the scientific advisory board for Anavex and UCB; she has received grants and research from Acorda, Alexza, Eisai Medical Research, LCGH, Lundbeck, Pfizer, SK Life Science, UCB, Upsher-Smith, and Vertex and grants from NINDS, Epilepsy Therapy Project, Epilepsy Research Foundation, Epilepsy Study Consortium; she is on the editorial board of *Lancet Neurology*, *Neurology Today*, and *Epileptic Disorders*; and she is an associate editor of *Epilepsia*, for which she receives a fee. Edouard Hirsch has received support from UCB and/or has served as a paid consultant for UCB, ESAI, and BIAL. Gary Mathern is partially supported by the Davies/Crandall Chair for Epilepsy Research at UCLA and is coeditor in chief for *Epilepsia* and *Epilepsia Open*. Solomon L. Moshé is the Charles Frost Chair in Neurosurgery and Neurology and is funded by grants from NIH NS43209, CURE, US Department of Defense, UCB, the Heffer Family and Segal Family Foundations, and the Abbe Goldstein/Joshua Lurie and Laurie Marsh/ Dan Levitz families. He serves as Associate Editor of *Neurobiology of Disease* and is on the editorial board of *Brain and Development*, *Pediatric Neurology*, and *Physiological Research*. He receives from Elsevier an annual compensation for his work as Associate Editor of *Neurobiology of Disease* and royalties from two books he coedited. He received a consultant's fee from Lundbeck and UCB. Emilio Perucca has received speaker's or consultancy fees and/or research grants from the following pharmaceutical companies: Eisai, Biopharm Solutions, GW Pharma, Sanofi, SK Life Science, Sun Pharma, Takeda, and UCB Pharma. Torbjörn Tomson has received research grants and/or speaker honoraria to his institution from the following pharmaceutical companies: Eisai, GlaxoSmithKline, Novartis, Bial, and UCB. He has also received research grants from CURE, Stockholm County Council, and EU (DG Sante). Sameer Zuberi has received research support and or speaker honoraria/consultancy fees from Epilepsy Research United Kingdom, Dravet Syndrome United Kingdom, UCB Pharma, Yorkhill Children's Charity, GW Pharma, Brabant Pharma, and Zogenix. He is Editor in Chief of the *European Journal of Paediatric Neurology*. The remaining authors have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Report of the ILAE Commission on Classification and Terminology posted on the ILAE website in November 2013.

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