Impact of predictive, preventive and precision medicine strategies in epilepsy

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Abstract | Over the last decade, advances in genetics, neuroimaging and EEG have enabled the aetiology of epilepsy to be identified earlier in the disease course than ever before. At the same time, progress in the study of experimental models of epilepsy has provided a better understanding of the mechanisms underlying the condition and has enabled the identification of therapies that target specific aetiologies. We are now witnessing the impact of these advances in our daily clinical practice. Thus, now is the time for a paradigm shift in epilepsy treatment from a reactive attitude, treating patients after the onset of epilepsy and the initiation of seizures, to a proactive attitude that is more broadly integrated into a 'P4 medicine' approach. This P4 approach, which is personalized, predictive, preventive and participatory, puts patients at the centre of their own care and, ultimately, aims to prevent the onset of epilepsy. This aim will be achieved by adapting epilepsy treatments not only to a given syndrome but also to a given patient and moving from the usual anti-seizure treatments to personalized treatments designed to target specific aetiologies. In this Review, we present the current state of this ongoing revolution, emphasizing the impact on clinical practice.

Electro-clinical syndromes
Clusters of common clinical and EEG characteristics that enable the grouping of patients with epilepsy into more homogenous patient groups in terms of outcome and response to anti-seizure medicines.

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Epilepsy is defined as a long-lasting predisposition to generate epileptic seizures, resulting from hyperexcitability and hypersynchrony of brain networks, with subsequent neurobiological, cognitive, psychological and social consequences[1]. In 2019, a report by the WHO estimated that 50 million individuals were living with epilepsy worldwide[2], making epilepsy one of the most common chronic neurological disorders. The incidence of epilepsy is estimated to be 49 per 100,000 people per year in high-income countries and 139 per 100,000 people per year in low-income and middle-income countries[2]. However, despite the development of 20 novel anti-seizure medicines since the 1990s[3], the proportion of epilepsy patients with drug-resistant epilepsies has remained stable, at 30%–40%, for the last 30 years[4–7]. In addition, 80% of patients with epilepsy report experiencing adverse events related to their anti-seizure medicine and 30–40% will have adverse effects that substantially impair their quality of life or result in medication cessation or non-adherence[8].

The classification of epilepsy aims to determine the seizure type (focal, generalized or unknown), the type of epilepsy (focal, generalized, combined focal and generalized, or unknown) and the type of epileptic syndrome for each individual patient[9]. An epileptic syndrome is defined as "a cluster of features incorporating seizure types, EEG, and imaging features that tend to occur together"[9]. This classification of epilepsy should be considered parallel to the classification of aetiologies that cause epilepsy. Considerable effort has been directed towards the development of biomarkers based on molecular biology, multimodal imaging and electrophysiology with the aim of accelerating and increasing the accuracy of epilepsy diagnosis. For an individual patient, the classification of epilepsy and the identification of epilepsy aetiology are two major steps towards accessing the most appropriate therapy and care pathway.

In this Review, we illustrate, from a clinical point of view, the evolution of our knowledge from the identification of epilepsy types and electro-clinical syndromes, to the identification of epilepsies with specific aetiologies. Indeed, this process has paved the way for a shift in the therapeutic management of patients from a population approach, which is based on epilepsy types and syndromes, to an individualized approach. This individualized approach considers a combination of characteristics specific to the individual patient, for example, age, race, sex and physiological parameters, in addition to the epilepsy type or syndrome. This shift towards precision, or personalized, medicine will enable health practitioners to treat patients in a more targeted manner in order to improve outcome. The ultimate goal of this approach is

Key points

- Advances in genetics, biochemistry, neurophysiology and imaging have led to the development of diagnostic biomarkers for epilepsy and the redefinition of some epileptic syndromes to incorporate aetiology.
- Three new types of targeted therapies have been applied to the treatment of epilepsies: substitutive therapy, therapies that block signalling pathways and therapies that normalize ion channel conductance.
- Targeted therapies and gene therapy are components of personalized medicine, which belongs to 'P4' medicine, a new proactive approach that puts the patient at the centre of care.
- Primary and secondary prevention of epilepsy is becoming a reality in humans, particularly in the case of monogenic epilepsy, where certain therapies seem to have an anti-epileptogenic effect.

to prevent the development of abnormal epileptic networks in at-risk individuals to avoid seizure genesis and recurrence. We focus mainly on paediatric-onset epilepsies, where the identification of multiple aetiologies and the potential for early intervention provides the ideal environment for the implementation of a preventive precision medicine approach.

Diagnosis and biomarkers

Seizure semiology and EEG characteristics are used to determine seizure and epilepsy type and, in some patients, to identify an epilepsy syndrome. This classification can guide the therapeutic management and provide information on prognosis, risk of comorbidities and mortality — notably, the risk of sudden unexpected death in epilepsy[9]. Epilepsy classification can also provide useful information for the development of clinical trials[9,10]. The identification of multiple genetic, metabolic and immune aetiologies of epilepsy as well as advances in brain imaging techniques have furthered our understanding of the pathophysiological mechanisms of epilepsy and led to calls for the identification of aetiology to be incorporated into epilepsy classification[9,11]. Indeed, in 2017, the International League Against Epilepsy proposed a multilevel framework for the classification of epilepsies[9]. This framework first uses clinical characteristics to classify epileptic seizures and then uses the seizure types observed in an individual to determine epilepsy type. Epileptic syndromes can then be defined in some patients[9]. This framework also places comorbidities and aetiological identification at the centre of all stages of classification, from the diagnosis of the epileptic seizure to the identification of the epilepsy type and syndrome. Comorbidities include psychiatric (autism spectrum disorders, depression, anxiety), cognitive (intellectual and learning disabilities) and motor (abnormal movement, motor deficits) disorders[9]. The framework divides epilepsy aetiologies into six broad and possibly overlapping categories: structural, genetic, infectious, metabolic, immune and unknown. The identification of specific epilepsy aetiologies has led to an improved understanding of the underlying pathophysiological mechanisms of the condition and to the identification of specific biomarkers that are modulated during the various stages of the disorder. The development of diagnostic biomarkers for these aetiologies will be crucial for the study of the early stages of the disorder, which could enable the identification of novel therapeutic targets.

A biomarker is defined as "an objectively measured characteristic of a normal or pathologic process"[12,13]. Biomarkers can be divided into eight broad categories (FIG. 1): susceptibility and/or risk, diagnostic, monitoring, prognostic, predictive, pharmacodynamic and/or response, and safety[12]. In epilepsy, biomarkers can be used for classification, prognosis evaluation, measurement of response to medication and overall outcome assessment. In this Review, we focus on susceptibility and diagnostic biomarkers from the electro-clinical, genetic, metabolic, electrophysiology and imaging fields.

Electro-clinical syndromes. As described above, the classification of epilepsies is based on seizure semiology and on EEG features[14]. Some electro-clinical presentations are quasi-pathognomonic of a specific epileptic syndrome. For example, childhood absence epilepsy was diagnosed on the discovery of 2.5–3.5 Hz generalized spike-and-wave sequences in a previously healthy 4-year-old child with abrupt daily episodes of altered consciousness[15]. This clinical description of seizure semiology and EEG pattern confirms the diagnosis without any further investigation. Similarly, the identification of continuous 1.5–2 Hz slow spike-and-wave sequences during non-rapid eye movement sleep in a previously healthy 5-year-old child with progressive cognitive, behavioural and psychiatric decline led to a diagnosis of epileptic encephalopathy with continuous spike-and-wave during sleep[16,17]. Some electro-clinical characteristics need to be particularly accurately and extensively evaluated. For example, the presence of asymmetrical or focal clinical or EEG patterns in patients with infantile spasms can guide the clinician towards the identification of a structural brain lesion and could support the need for epilepsy surgery assessement[18–21]. In this case, brain MRI and functional brain imaging (PET) can be used to identify the brain lesion and guide the identification of aetiology and further therapy. However, in some epilepsy syndromes, EEG findings might be non-specific or even normal at the onset of epilepsy; thus, additional biomarkers are needed.

Non-genetic molecular biomarkers. Non-genetic molecular biomarkers, such as autoantibodies, organic acids, neurotransmitters and amino acids, are mainly used to diagnose autoimmune epilepsies and epilepsies related to metabolic diseases but can also be used for prognosis, monitoring and prediction of disease course. Limbic encephalitis is a common type of autoimmune encephalitis that should be considered as a possible diagnosis in individuals with rapid progression (within 3 months of onset) of cognitive decline (particularly short-term memory loss) combined with psychiatric symptoms and onset of seizures[22]. Although performing autoantibody tests should not delay immunotherapy, the identification of autoantibodies in a patient with suspected limbic encephalitis usually changes the diagnostic status from possible to definite. This antibody testing also helps determine the subtype of limbic encephalitis, look for paraneoplastic origin (in the case of some subtypes)

Seizure semiology
Clinical symptoms linked to epileptic seizures.

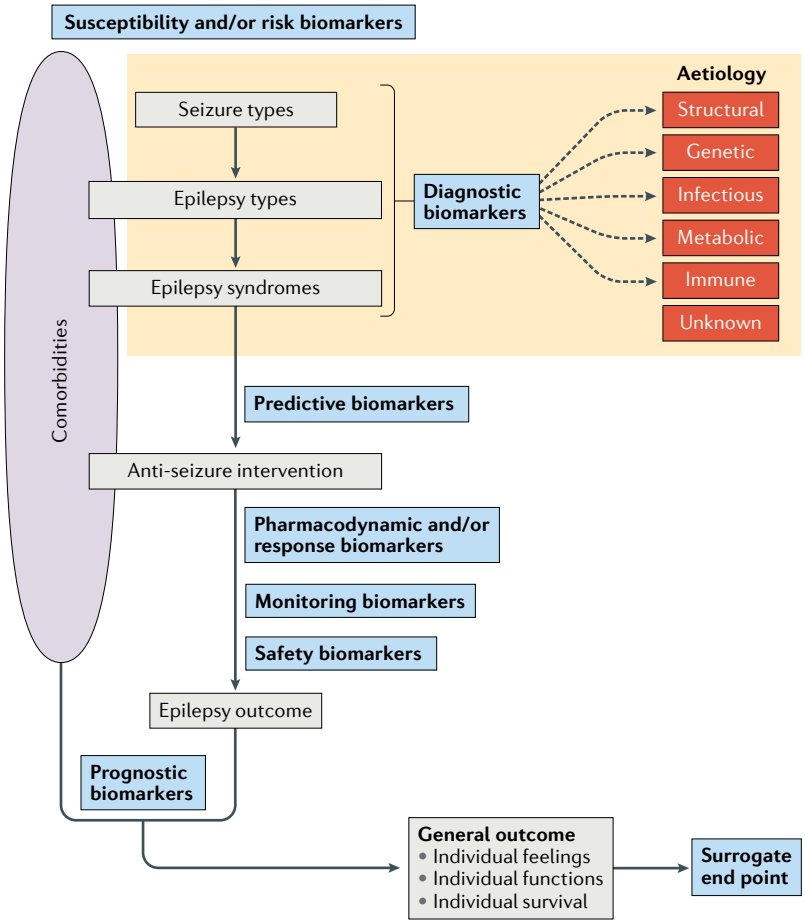

Fig. 1 | **Use of biomarkers in the management of epilepsy.** Representation of the different types of biomarkers plotted on the multi-level classification framework for the classification of epilepsy of the International League Against Epilepsy[9]. Susceptibility and risk biomarkers are upstream of the classification framework. Diagnosis biomarkers provide information for the classification of epileptic syndromes and are an integral part of the epilepsy classification framework. Predictive, pharmacodynamic, response, monitoring and safety biomarkers are used to assess the effects of anti-seizure interventions. Prognosis biomarkers determine the likelihood of favourable or unfavourable outcomes in epilepsy and the associated comorbidities. A surrogate end point is generally a biomarker that is predictive of the final result of an intervention. Adapted with permission from REF.[9], Wiley.

and identify the most appropriate therapy for the individual patient[22]. In some patients, data on autoantibodies can also inform the choice of second line therapies and subsequent follow-up[22–24]. The proportion of patients with limbic encephalitis who have a good long-term outcome ranges from 40% in patients with intracellular antibodies to 67–83% in patients with extracellular antibodies[25]. However, in 4–16% of patients with a diagnosis of limbic encephalitis, no autoantibodies are identified and, conversely, autoantibodies can be identified at low levels in the CSF of healthy individuals[23,26,27].

One of the archetypal metabolic disease-related epilepsies is pyridoxine-dependent epilepsy, which is a treatable cause of epilepsy and intellectual disability[15]. This epilepsy is caused by a deficiency of antiquitin (encoded by *ALDH7A1*), which results in reduced lysine metabolism and the accumulation of α-amino-adipic semialdehyde (AASA) and piperidine-6-carboxylate[28]. Clinically, pyridoxine-dependent epilepsy encompasses a wide spectrum of prenatal and neonatal onset epilepsies and some atypical presentations start later, usually in childhood[29–31]. Seizures are drug resistant and polymorphic, including focal, generalized, clonic, tonic, and myoclonic seizures and epileptic spasms[30]. Pyridoxine substitutive therapy should be initiated as soon as this epileptic syndrome is suspected and until biomarker tests rule out this diagnosis. The most commonly used biomarker of this syndrome is the elevation of the AASA to creatine ratio in blood and urine[29]. However, this ratio can also be elevated in molybdenum cofactor and sulfite oxidase deficiencies; therefore, a diagnosis of pyridoxine-dependent epilepsy is confirmed when an *ALDH7A1* pathogenic variant is identified. The diagnosis of many other epilepsies, such as those resulting from GLUT1 deficiency, urea disorders, organic acidaemia, glycine disorders and mitochondrial disorders[32,33], has greatly benefited from technological advances in biochemistry, which have increased the number of testing facilities and reduced the cost of analysis.

Genetic biomarkers. Genetic biomarkers are a quantitative, binary form of data that enables the identification of the aetiology of various epileptic syndromes. Indeed, the proportion of heritability that can be attributed to single-nucleotide polymorphisms has been estimated to be 32–36% for genetic generalized epilepsy and 9–23% for focal epilepsy[34,35]. For example, a previously healthy young infant presenting with unilateral hemiclonic seizures occurring during a febrile illness might be considered to have focal epilepsy. However, in >90% of these infants, pathogenic variants in *SCN1A* can be identified with genetic testing, confirming the diagnosis of Dravet syndrome before the full clinical criteria of this syndrome become apparent[36].

For other epilepsy syndromes that begin in infancy and childhood, relatively discrete but well-established clinical features can indicate a potential genetic diagnosis. For example, pathogenic variants in *PCDH19* are strongly suspected in girls presenting with clusters of febrile focal seizures with motor and non-motor features, accompanied by affective symptoms, particularly fear[37,38]. Similarly, patients with mutations in *CDKL5* have a normal background EEG despite early-onset encephalopathy with tonic or tonic–clonic, focal or generalized seizures with epileptic spasms[39]. Patients with pathogenic variants in *SYNGAP1* present with reflex seizures triggered by chewing, fixation-off sensitivity with irregular peak wave discharges of 3 Hz, and bilateral eyelid myoclonia[40].

In one-third of children with epilepsy, there are no clear clinical, EEG, MRI or non-genetic molecular biomarker findings that enable the identification of a given aetiology[41]. Therefore, investigating genetic biomarkers in these individuals is essential for aetiological diagnosis. In routine clinical practice, this investigation includes chromosomal microarray testing (which has a diagnostic yield of 6–12% in the population of children with presumed genetic epilepsy), epilepsy gene panel testing (with a diagnostic yield of 15–25%) and whole exome sequencing (with a diagnostic yield of 35–60%)[42–45]. The high yield of epilepsy gene panels and whole

exome sequencing, both of which are forms of next-generation sequencing, has led most clinical research centres to use these techniques as the first-line genetic tests for unexplained epilepsy despite the high cost[42,46], which has remained relatively stable at around US$1,000 per test since 2015 (REFS[44,47]).

The impact of these new sequencing techniques on the diagnosis of neonatal epilepsies has been particularly interesting[48]. One study in this patient population reported a >98% reduction in average time to diagnosis (from 3.4 years to 21 days) and a 70% reduction in cost when epilepsy gene panels were used as the first-line investigation instead of the classical strategy, which is based on metabolic investigations in blood, urine and CSF samples followed by array comparative genomic hybridization and single gene testing[48]. Despite this progress, more than 98% of the human genome is made up of 'non-coding' DNA[49], which is not covered by exome sequencing. Furthermore, somatic mutations can be missed by the molecular biology approaches used in gene panels and whole-exome sequencing[50]. Various techniques, which we discuss in detail in the next section, are being developed to fill these gaps and should increase the proportion of patients in whom a genetic epilepsy aetiology can be identified.

The central tenet of pathogenic genetic variants as biomarkers for epilepsy diagnosis can be challenged. Indeed, the specificity and sensitivity of this approach might be excellent in certain monogenic epilepsies with a strong phenotype–genotype correlation as in the case of epilepsy caused by pathogenic variants in *PCDH19* or *CDKL5* (REFS[37–39,51]). However, some genes can be causal in multiple epilepsy syndromes and, similarly, some epilepsy syndromes have a large number of causative genes. For example, pathogenic variants in *KCNT1*, the major cause of epilepsy in infancy with migrating focal seizures (EIMFS), are also observed in >7 other epileptic syndromes[52] and at least 23 different genes have been identified as causal in EIMFS[53].

Future direction of biomarkers. Many molecular, electrophysiological, imaging, cognitive and behavioural biomarkers for epileptic syndromes are under development[54–58]. In focal epilepsies, existing EEG approaches identify the zone of seizure onset by determining the areas involved in ictal activity onset. However, as the failure rate of epilepsy surgery is around 35%[59], additional markers present during the interictal period, including high-frequency oscillations (HFOs; 80–500 Hz), could help refine the identification of the trigger zone[60]. Some researchers have proposed HFOs as a diagnostic and prognostic biomarker that can also be used to monitor the response to therapeutic interventions[61–64]. However, studies have found that analysis of HFOs can identify seizure onset zone and predict post-surgical outcome with a sensitivity of >85%, but a specificity of just ~50%[65,66], which is not satisfactory. However, studies aimed at improving the specificity of HFOs have been performed, including one study that assessed the response of HFOs to stimulation during stereo-EEG and another that used an improved method of identifying pathological HFOs[67,68].

HFOs are not the only innovative EEG biomarkers of epilepsy under development. In patients with EIMFS, which is a severe epilepsy with infantile onset and frequent migrating seizures, we quantified ictal activity characteristics and determined that seizure migration followed a particular pattern of propagation and was not a random phenomenon[69]. In addition, we identified two EEG biomarkers — time delay index and phase coherence index — that enabled us to distinguish *KCNT1*-related EIMFS from other early-onset infantile epilepsies with a sensitivity of 91.2% and a specificity of 84.4%. We expect that further development of these two biomarkers could enable the earlier diagnosis of individuals with this early-onset infantile epilepsy.

New genetic biomarkers are also being sought with the aim of detecting pathogenic variants in individuals with presumed genetic epilepsy but without a specific genetic diagnosis. In these cases, genetic studies are performed mainly by whole-exome sequencing and, in few cases, by whole-genome sequencing, which enables the identification of non-coding mutations and the analysis of intronic variants[70]. Non-coding regions of the genome are not explored by gene panels or whole-exome sequencing; however, these regions could influence gene expression by altering chromatin states, promoter-associated activity, or enhancer-associated activity and some evidence suggests that these regions do encode part of the human proteome[71,72], highlighting the value of whole-genome sequencing. In addition, advances have been made in the detection of pathogenic variants that affect only a small proportion of cells or tissues, that is, pathogenic variants derived from somatic mutations and two-hit mutations. Potential strategies for this type of genetic biomarker involve the study of DNA from neuro-epithelium (nasal biopsy), brain tissue (biopsy or neurosurgical operative sample), CSF (cell-free DNA) or peripheral blood[50]. In a recent study, deep sequencing of resected brain tissue from 232 participants with intractable epilepsy identified a somatic pathogenic variant in 22% of participants, two-hit mutations in 0.9% of participants and germline mutations in 9.1% of participants[73].

Composite scores that enable the integration of information from different diagnostic biomarkers should improve aetiological disease identification and guide clinical strategies. For example, an 18-point scale based on clinical symptoms, non-genetic molecular biomarkers (including CSF protein level and white blood cell counts) and MRI criteria was developed with the aim of diagnosing autoimmune epilepsies[74,75]. The scale did not include autoantibody tests but was validated using measurements from individuals with autoantibody-positive autoimmune encephalitis. A score of >7 predicted a diagnosis of autoimmune encephalitis with 100% specificity and a score of 4–6 indicated possible autoimmune encephalitis[76]. A clinical guideline based on this scale has been proposed with the aim of defining possible and probable diagnostic status in autoantibody-negative individuals. Overall, we expect that the development of new diagnostic biomarkers, in combination with traditional assessment of seizure semiology, will allow the rapid identification of a specific epilepsy, thus reducing

Ictal
The period of time during an epileptic seizure.

the time and cost involved in reaching a diagnosis and enabling a precision medicine-type approach to epilepsy management.

Precision medicine in practice

Precision medicine, also known as personalized medicine, has been described by the US President's Council of Advisors on Science and Technology as the "tailoring of medical treatment to the individual characteristics of each patient"[77]. The Council also explained that this approach involves the classification of individuals into subpopulations on the basis of susceptibility to a particular disease or response to a specific treatment, thus enabling the targeting of preventive or therapeutic interventions to the individuals who are most likely to benefit. This approach is expected to reduce treatment costs and the number of individuals who experience the adverse effects of treatment without the benefits[77]. Through the Precision Medicine Initiative in the USA, announced in 2015, and the International Consortium for Personalized Medicine in the EU, launched in 2016, public health policy is promoting this revolution in care[78,79]. The move towards precision medicine has been facilitated by a combination of 'big data' from the widespread digitization of patients' medical records, progress in genetic, imaging, electrophysiological and biochemical tests, increased access to these tests, and advances in information and communication technologies for health, known as eHealth[80]. This new paradigm is in contrast to the classic 'one-size-fits-all' approach and is already gradually changing clinical care in epilepsy[81,82].

First, do no harm. The phase "First, do no harm", attributed to Hippocrates in the fifth century BC, is now more relevant than ever and can be considered the first recommendation in the area of personalized medicine. Early diagnosis can avoid many adverse situations — from unnecessary treatment to treatment that worsens the condition. Of patients undergoing EEG evaluation for intractable epilepsy, 20–30% show paroxysmal non-epileptic events[83–86] and distinguishing these events from epileptic seizures can be challenging. For example, in one study, 14% of patients admitted to the intensive care unit following incorrect diagnosis of seizures were receiving anti-seizure medicines inappropriately[87]. Depending on the epileptic syndrome, some anti-seizure medicines can be associated with increased frequency and duration of seizures as well as with worse long-term epilepsy and cognitive outcomes[88,89]. In a study using a mouse model of absence epilepsy, a group of animals that received inappropriate initial carbamazepine treatment for 2 weeks, followed by appropriate treatment for 6 weeks, had more seizures at the end of the 8 weeks than a control group treated only with saline[90]. Similarly, in individuals with Dravet syndrome, treatment with lamotrigine was associated with an increase in seizure frequency and duration[91]. In addition to this worsening effect on seizures, treatment with lamotrigine and other sodium channel blockers during the first 5 years after seizure onset has been associated with a negative effect on cognitive outcome in patients with Dravet syndrome[92]. To our knowledge, these two studies are among the first to identify a negative disease-modifying effect linked to inappropriate epilepsy therapies[90,92].

Do not fall behind. The diagnosis of epilepsy and the initiation of appropriate therapy should not be delayed. The clinical definition of epilepsy published in 1991 required two unprovoked seizures to occur >24 hours apart[93]. This definition was changed in 2014 to better consider the consequences of repeated seizures on patient outcomes[94]. Indeed, the duration of epilepsy and the number of pre-treatment seizures have been identified as risk factors for seizure recurrence[95–97]. In one study, the risk of seizure recurrence was higher in patients who had previously experienced two symptomatic seizures than in patients who had experienced just one symptomatic seizure[98]. The new clinical definition of epilepsy is based on the definition from 1991 but includes two additional conditions: "one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years" and "diagnosis of an epilepsy syndrome"[94]. If either of these conditions are met, an individual is considered to have epilepsy. Delays in initiating therapy have been associated with a negative impact on patient outcome in numerous epilepsies and epilepsy syndromes, including epileptic spasms[99–101], pyridoxine-responsive epilepsy[102,103], autoimmune epilepsy[25] and focal epilepsies[104–106].

In studies of infantile spasms syndrome, the median delay between the identification of fits by the parents and the diagnosis of epileptic spasms was 10–24 days and parents consulted a median of three physicians before achieving a definite diagnosis[100,107]. The identification of this syndrome and the underlying aetiology has major implications for the approach to treatment. First, this diagnosis requires treatment with vigabatrin and/or hormonal treatment (prednisolone or adrenocorticotropic hormone)[108,109]. These drugs are not a first-line treatment for other epileptic syndromes in infancy and are unlikely to be prescribed unless a diagnosis of infantile spasms syndrome has been made. Second, the identification of a focal lesion responsible for infantile spasms syndrome can enable surgical management. Indeed, 60–80% patients who undergo surgical treatment for epileptic spasms achieve seizure freedom with minimal adverse effects on motor function and, often, an improvement in cognitive function[110–112]. Moreover, one study found that a longer duration of epilepsy before surgical management was associated with a lower likelihood of achieving a favourable seizure outcome, highlighting the importance of early diagnosis and intervention[113].

Early diagnosis is also important for the treatment of epilepsy caused by neurodegenerative diseases such as neuronal ceroid lipofuscinosis type 2 (CLN2). The long-term outcome of patients with CLN2 has dramatically improved since the introduction of targeted therapy with recombinant human tripeptidyl peptidase[114]. This treatment has been associated with a slowing or even stabilization of the deterioration in gait and language ability[114]. Participants receiving this treatment have been followed-up for 3 years and this effect seems to be

Table 1 | **Targeted, substitutive therapies for genetic epilepsies**

Gene containing pathogenic variant	Specific target	Related syndromes	Targeted therapies	Contraindicated therapies	Refs
SLC2A1	Glucose transporter type 1	GLUT1 deficiency[a]	Ketogenic diet	PB, VPA or BZD: to inhibit GLUT1	192–195,[b]
ALDH7A	Pyridoxine metabolic pathway	Pyridoxine-responsive epilepsy	Pyridoxine	Data not available	196
PNPO	Pyridoxamine 5′-phosphate oxidase	Pyridoxamine 5'-phosphate oxidase deficiency	Pyridoxal-5-phosphate	Data not available	197
TPP1	Tripeptidyl peptidase 1	Neuronal ceroid lipofuscinosis type 2	Cerliponase alfa	Data not available	114
SLC6A8	Solute carrier family 6 member 8	Cerebral creatine deficiency syndrome 1	Creatine combined with L-arginine and L-glycine	Data not available	198
GAMT	Guanidinoacetate methyltransferase	Cerebral creatine deficiency syndrome 2	Creatine	Data not available	199
AGAT	Glycine amidinotransferase	Creatine deficiency syndrome 3	Creatine	Data not available	200
TRPM6	Transient receptor potential melastatin 6	Hypomagnesemia 1	Magnesium sulfate	Data not available	201
POLG	DNA polymerase gamma	Mitochondrial disease	Data not available	VPA	202–206
MOCS1	Molybdenum cofactor	Molybdenum cofactor deficiency	Cyclic pyranopterin monophosphate	Data not available	207
FOLR1	Cerebral folate transport	Folinic acid-responsive seizures	Folinic acid	Data not available	208
SLC35A2	Endoplasmic reticulum and Golgi UDP-galactose transporter	Glycosylation disorder	Galactose supplementation	Data not available	209

BZD, benzodiazepine; PB, phenobarbital; VPA, valproate acid. [a]GLUT1 deficiency was classified as a substitutive therapy because a ketogenic diet will provide the substitution of glucose as brain fuel via ketone bodies. [b]Indicates preclinical studies that reported no human data.

maintained over time[115]; however, the approach relies on the early, accurate diagnosis of CLN2.

Evidence-based individual strategies. Advances in the identification of the underlying causes of epilepsies have made it possible to use an evidence-based approach to determine the optimal treatment for an individual patient. This approach, which targets the underlying aetiology of the epilepsy, could achieve a better outcome than the 'one-size-fits-all' approach on seizure severity and frequency as well as on epilepsy-related comorbidities. Three different categories of therapy are used in these individual treatment strategies: substitutive therapies (TABLE 1), therapies that modify cell-signalling pathways (TABLE 2) and function-based therapies (TABLE 3).

Substitutive therapies are currently used to treat epilepsies that are related to hereditary metabolic diseases, for example, vitamin-responsive epilepsies, epilepsy caused by GLUT1 deficiency syndrome and epilepsy caused by CLN2 disease[114,116,117]. Therapies that modify signalling pathways are used to treat autoimmune epilepsy and epilepsies related to the mTOR pathway[118,119]. Finally, therapies that modify the function of voltage-gated or ligand-gated ion channels can be used to treat epilepsies caused by pathogenic variants that result in a gain or loss of function of these channels. The phenotype caused by these variants can be related to the effect on the channel function, for example, gain of NMDA receptor function linked to a pathogenic variant of *GRIN2A* is associated with severe developmental and epileptic encephalopathy but individuals with loss-of-function variants in the same gene display a milder epileptic and developmental phenotype[120]. Similarly, pathogenic gain-of-function variants in *SCN2A*, which encodes the voltage-gated sodium channel Nav1.2, are associated with early epileptic phenotypes, that is, encephalopathies and benign (familial) neonatal or infantile seizures, whereas loss-of-function variants in the same gene are associated with autism spectrum disorder or intellectual disability, sometimes with epilepsy beginning in childhood[121,122]. The severity of these phenotypes correlates with the severity of impairment of channel function[123]. Currently, precision therapies aim to increase channel conductance in individuals with loss-of-function variants and decrease channel conductance in individuals with gain-of-function variants. However, this binary, loss-of-function versus gain-of-function approach is simplistic. For example, pathogenic variants in *KCNB1*, which encodes the voltage-gated potassium channel Kv2.1, can cause a loss of potassium selectivity and changes in voltage sensitivity, gating (resulting in a constitutively open channel), or channel localization[124]. Better characterization of the functional impact of pathogenic variants on ion channels and the pathophysiological pathways involved in generating the resulting phenotype is required for the identification of specific therapeutic targets.

Finally, the personalized medicine concept goes beyond targeted therapy and should also consider other information such as pharmacogenomic, metabolomic or proteomic data, race, sex, age, comorbidities, and other therapies that the patient is receiving[81,125,126]. Indeed, any of these factors could affect the safety and efficacy of a drug, for example, carriers of the *HLA-B*15:02* or *HLA-A*31:01* alleles are at risk of developing carbamazepine-induced

Antisense oligonucleotides (ASOs). Synthetic oligonucleotides that have a sequence that is complementary to a target messenger RNA resulting in binding of the messenger RNA and inhibition of the synthesis of the target protein.

Stevens–Johnson syndrome[127,128]. Similarly, African American individuals require a higher dosage of the anti-seizure medicine lacosamide than white individuals[125] and individuals with *CYP2C9* polymorphisms can have altered metabolism of the anti-seizure medicine phenytoin[129].

Overall, the results of applying precision medicine to the treatment of epilepsy have been encouraging. More than 70% of patients with anti-NMDAR and anti-VGKC encephalitis treated with targeted therapies are left with no disability or mild disability that allows independent living[25]. Individuals with CLN2 disease treated with the substitutive therapy recombinant human tripeptidyl peptidase 1 showed a slower rate of decline in motor and language domains than was observed in a cohort of historical controls[114,115], indicating that the treatment can modify disease course.

Gene therapy. In gene-related epilepsy, the ultimate goal for precision medicine is either to correct the pathogenic variant within the gene itself or to modulate the expression of the mutated gene in order to compensate for the impact of the pathogenic variant on transcription. This kind of correction or modulation should stop the pathophysiological cascades responsible for epilepsy seizures and associated comorbidities.

The FDA defines gene therapies as "products that mediate their effects by transcription or translation of transferred genetic material or by specifically altering host (human) genetic sequences"[130,131]. Despite 3,000 clinical trials of potential gene therapies, only 16 gene therapy products are approved worldwide and two-thirds of these approvals have been given since 2015 (REF.[132]). Seven of the approved gene therapy products are for the management of cancer and three are for neurological diseases with neuromuscular involvement, that is, spinal muscular atrophy (Zolgensma (Novartis) and Spinraza (Biogen)) and hereditary transthyretin amyloidosis (Onpattro (Alnylam))[133].

Currently, 53 clinical trials of gene therapies for neurological disorders (mainly Parkinson disease, multiple sclerosis and amyotrophic lateral sclerosis) are ongoing[134]. One of these trials is investigating a treatment for temporal epilepsy that targets the expression of neuropeptide Y, an inhibitory neuropeptide[135–137]. Indeed, in rat models of mesial temporal lobe epilepsy, a gene therapy-mediated increase in the expression of neuropeptide Y was associated with a decrease in seizure frequency[138,139]. An anti-seizure effect of neuropeptide Y on human epileptic brain tissue has also been reported[136]. Although none of the 350 ongoing clinical trials of gene therapies for monogenic diseases specifically focus on monogenic epilepsy, epilepsy is a major feature in nine of the inherited metabolic diseases targeted by these trials, including four forms of neuronal ceroid lipofuscinosis[132].

Despite the lack of relevant clinical trials, preclinical data on gene therapies for monogenic epilepsies seem promising. In 2015, a study in a mouse model of *MECP2* duplication syndrome, which displays a phenotype of seizures and behavioural disorders, found that treatment with *MECP2* antisense oligonucleotides (ASOs) was associated with a lowering of MECP2 levels and a behavioural, molecular and electrophysiological phenotype that was close to that of wild-type mice[140]. Similarly, in a mouse model of epilepsy related to a gain-of-function mutation in *SCN8A*, treatment with *SCN8A* ASOs was associated with delayed seizure onset and reduced ataxia and muscle wasting[141]. Additional positive results of ASO treatment were reported in a mouse model of *KCNT1* gain of function, a major cause of epilepsy in infancy with migrating focal seizures[142].

ASOs have also been used to upregulate gene expression in epilepsy caused by loss-of-function pathogenic variants. Initially, this approach was used

Table 2 | **Targeted epilepsy therapies that modify signalling pathways**

Gene containing pathogenic variant	Specific target	Related syndromes	Targeted therapies	Refs
mTOR signalling pathways				
DEPDC5	GATOR1 complex subunit	FFEVF; familial mesial temporal lobe epilepsy; West syndrome	Rapamycin and rapamycin derivatives (e.g. everolimus, sirolimus, temsirolimus and ridaforolimus)	210,211,a
NPRL2	GATOR1 complex subunit	FFEVF		212,a
NPRL3	GATOR1 complex subunit	FFEVF		213
TSC1	TSC1	Tuberous sclerosis; focal dysplasia		214
TSC2	TSC2	Tuberous sclerosis; focal dysplasia		214,215
Immunity pathways				
NA	Onconeural antigen; autoimmunity	Autoimmune epilepsy	Corticosteroid therapy; plasmapheresis; IVIG; immunosuppressive therapies; tumour ablation	216–219
NA	IL-1β	FIRES	Recombinant IL-1 receptor antagonist	220

No contraindicated therapies reported. FFEVF, familial focal epilepsy with variable foci; FIRES, febrile infection-related epilepsy syndrome; IVIG, intravenous immunoglobulin; NA, not applicable. [a]Indicates preclinical studies that reported no human data.

Table 3 | **Targeted epilepsy therapies that modify ion channel function**

Gene containing pathogenic variant	Specific target	Related syndromes	Targeted therapies	Contraindicated therapies	Refs
Sodium channels					
SCN1A	Nav1.1 LoF in fast spiking GABAergic neurons	Dravet syndrome; GEFS+; febrile seizure; MAE; EIMFS	Data not available	CBZ, OXC, PHT or LTG to block sodium channels; RUF to prolong the inactive state of voltage-gated sodium channels; possibly VGB	91,92, 221–225
	Nav1.1 GoF	DEE	CBZ, OXC, PHT or LTG to block sodium channels	Data not available	226
SCN2A	GoF in Nav1.2	Benign familial neonatal–infantile epilepsy; DEE; EIMFS; symptom onset <3 months of age	CBZ, OXC, PHT or LTG to block sodium channels	Data not available	227–230
	LoF of Nav1.2	Seizures associated with autism spectrum disorder; onset >3 months of age	Data not available	CBZ, OXC, PHT or LTG to block sodium channels	227,228
SCN8A	Nav1.6 LoF	DEE; familial myoclonic epilepsy; BFNE; EIMFS	Data not available	Data not available	231
	Nav1.6 GoF		CBZ, OXC or PHT to block sodium channels	Data not available	232–235
Potassium channels					
KCNT1	SLACK GoF	EIMFS; NFLE	Quinidine	Data not available	236–239
	SLACK LoF	DEE	NA	Data not available	240
KCNT2	SLICK GoF	EIMFS; DEE	Quinidine	Data not available	241
	SLICK LoF	EIMFS; DEE	NA	Data not available	242
KCNQ2	Kv7.2 LoF	DEE; BFNE	RET to open Kv7.2 channel	Data not available	243–245
	Kv7.2 GoF		Data not available	RET to open Kv7.2 channel	246
KCNQ3	Kv7.3 LoF	DEE; BFNE	RET to open Kv7.3 channel	Data not available	245
	Kv7.3 GoF		Data not available	Data not available	247
Calcium channels					
CACNA1A	Cav2.1 GoF	West syndrome; DEE; idiopathic generalized epilepsy	ETX or LMT to block T-type calcium channels	Data not available	248–250,a
	Cav2.1 LoF	DEE	Data not available	Data not available	251
Hyperpolarization-activated cyclic nucleotide gate channels					
HCN1	HCN1 LoF	GEFS+; DEE	LMT or GBP to enhance HCN1 current	Data not available	252,253,a
	HCN1 GoF		Ketamine or propofol to inhibit HCN1 channels	Data not available	254,255,a
NMDA receptor					
GRIN2A	NMDA receptor subunit 2A; mild phenotype is NMDA LoF	Atypical SELECTS; CSWS; Landau–Kleffner syndrome; DEE	Data not available	Data not available	256
	NMDA receptor subunit 2A; severe phenotype is NMDA GoF		Memantine, an NMDA receptor antagonist	Data not available	257
GRIN2B	NMDA receptor subunit 2B; NMDA LoF	West syndrome; LGS; DEE	Data not available	Data not available	258
	NMDA receptor subunit 2B; NMDA GoF		Memantine or radiprodil, both NMDA receptor antagonists	Data not available	259,a
GRIN2D	NMDA receptor subunit 2D; NMDA GoF	DEE	Ketamine to block NMDA channels; memantine, an NMDA receptor antagonist	Data not available	260
nAChR					
CHRNA2c, *CHRNB2* or *CHRNA4*	nAChR LoF	NFLE	Transdermal nicotine	Data not available	261,262

BFNE, benign familial neonatal epilepsy; CBZ, carbamazepine; CSWS, epilepsy with continuous spike-wave during sleep; DEE, developmental and epileptic encephalopathy; EIMFS, epilepsy in infancy with migrating focal seizures; ETX, ethosuximide; GBP, gabapentin; GEFS+, generalized epilepsy with febrile seizures plus; GoF, gain of function; LGS, Lennox–Gastaut syndrome; LMT, lamotrigine; LoF, loss of function; LTG, lamotrigine; MAE, myoclonic astatic epilepsy; NA, not applicable; NFLE, nocturnal frontal lobe epilepsy; OXC, oxcarbamazepine; PHT, phenytoin; RET, retigabine; RUF, rufinamide; SELECTS, self-limited epilepsy with centro-temporal spikes; VGB, vigabatrin. [a]Indicates preclinical studies that reported no human data.

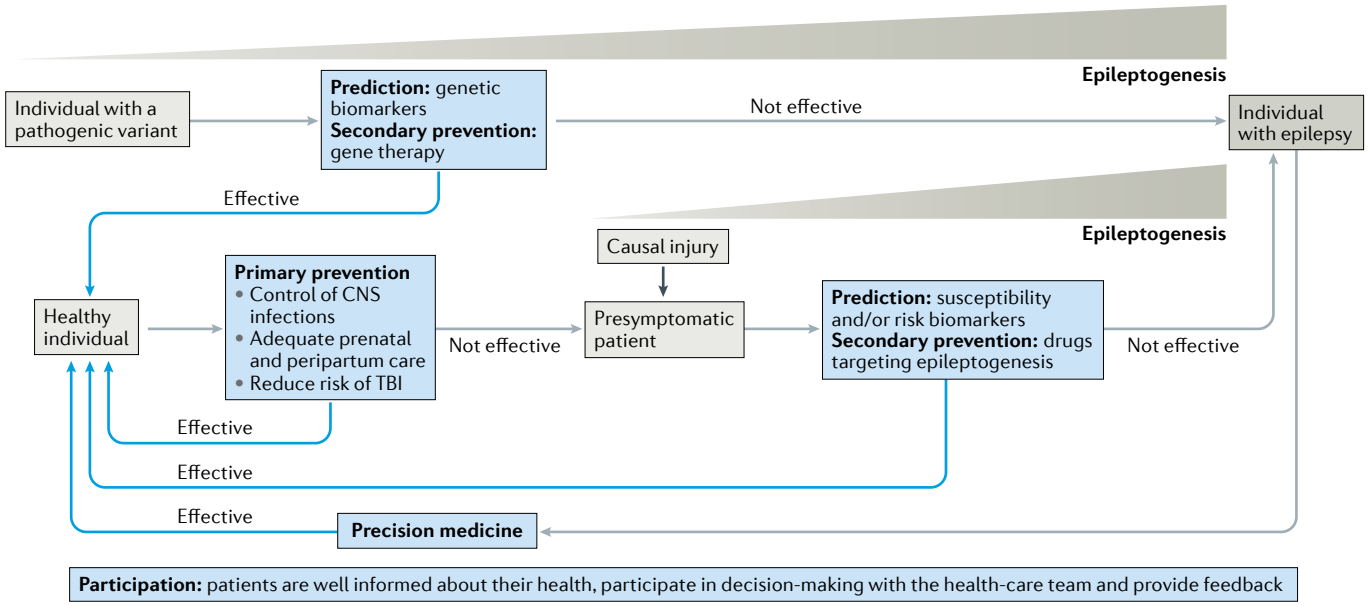

Fig. 2 | **A P4 medicine-type approach applied to the management of epilepsy.** 'P4' medicine is an individual-centred approach to medicine that is personalized, preventive, predictive and participatory. This method involves the assessment of the personal profile of an individual, including information on their genome, proteasome, physiological parameters, age and sex, in order to propose a personalized treatment approach. The preventive aspect of this approach aims to reduce the risk of the individual developing a pathology (primary prevention) and to achieve early management of illness (secondary prevention). This preventive strategy is a direct result of the ability to predict the risk of epilepsy using, among other factors, susceptibility and risk biomarkers. The participatory element of this approach involves the participation of the patient in the decision-making process. TBI, traumatic brain injury.

to target the natural antisense non-coding RNA SCN1ANAT, which controls *SCN1A* expression. In a mouse model of Dravet syndrome, which is caused by a heterozygous loss-of-function mutation in *SCN1A*, and in healthy non-human primates, the administration of oligonucleotide-based compounds targeting SCN1ANAT was associated with an increase in the expression of *SCN1A*[143]. An ASO that targets *SCN1A* pre-messenger RNA to increase the proportion of productive mRNA has also been developed. In a mouse model of Dravet syndrome, administration of this ASO was associated with increased survival rate and a reduction in the number of generalized seizures[144,145]. Furthermore, in non-human primates, the treatment showed a favourable safety profile and was associated with an increase in brain *SCN1A* expression[146].

Recently, a tailored ASO treatment was developed for a specific patient with Batten disease, which is a form of neuronal ceroid lipofuscinosis with drug-resistant seizures and is caused by mutations in *CLN7*. The ASO, called Milasen, was customized to the patient's specific *CLN7* mutation[147]. After almost 1 year of treatment with Milasen, the frequency and duration of seizures in the patient decreased by >50% and their neuropsychological test scores remained stable[147]. Although this approach raises economic, ethical and pharmacological questions[148], it is the quintessence of precision medicine.

Another approach is to deliver gene therapy via viral vectors. In one study, a transcription factor engineered to upregulate endogenous *SCN1A* expression in inhibitory interneurons was packaged in an adeno-associated viral vector[149,150]. In a mouse model of Dravet syndrome, treatment with this gene therapy was associated with a dramatic decrease in febrile and unprovoked seizures and a significant increase in survival rate. A CRISPR–Cas9 technique using a nuclease-dead Cas9 and a single guide RNA targeting the proximal promoter of *SCN1A* was also tested in a mouse model of Dravet syndrome and was associated with enhanced *SCN1A* gene expression[151].

From early to 'preventive' therapies

Precision medicine is one element of the proactive 'P4' medicine approach, which also includes predictive, preventive and participatory medicine[152]. The preventive element of this approach aims to avoid epilepsy development and should therefore be the ultimate objective of therapy (FIG. 2). Preventive medicine represents a paradigm shift from a reactive treatment strategy, where therapy is started as soon as a disease is diagnosed, to a proactive preventive treatment strategy that aims to anticipate and prevent the onset of diseases[153]. Epileptogenesis is defined as the period during which cascades of molecular, structural and functional alterations progressively facilitate the emergence and development of neuronal networks that are capable of generating epileptic seizures. These alterations can initiate epilepsy (primary epileptogenesis) and/or enhance the progression of the epilepsy after it is established (secondary epileptogenesis)[154]. Considerable evidence from animal models indicates that the prevention of epileptogenesis is possible but the translation of these results into humans has not yet been fully achieved, as we discuss in the following sections.

Data from animal models. Epileptogenesis has been studied in animal models (predominantly mouse models) of traumatic injury, status epilepticus and genetic epilepsies. Several candidate drugs targeting one or more epileptogenic mechanisms have been tested. Targeted mechanisms include glutamate-mediated excitotoxicity, inflammation, oxidative stress, energy deficiency, glial cell responses, expression of neurotransmitters and composition of ionic transmembrane channels[154–156]. The drugs tested included rapamycin and analogues, specific anti-inflammatory drugs (IL-1-converting enzyme inhibitors, IL-1β receptor antagonists and cyclooxygenase 2 (COX2) inhibitors), immunosuppressors (fingolimod), hormones (melatonin, neurosteroids, progesterone and erythropoietin), antioxidants (vitamin E, N-acetyl cysteine), adenosine, some anti-seizure medicines (vigabatrin, levetiracetam, lamotrigine, zonisamide, gabapentin, topiramate), anaesthetic drugs (isoflurane, ketamine), antibiotics (ceftriaxone) and statins (atorvastatin)[154–161]. Studies have also tested stem cell therapy, brain-derived neurotrophic factor (BDNF) and tropomyosin-related kinase B (TRKB) inhibitors, low frequency deep brain stimulation, and a ketogenic diet as potential preventive epilepsy treatments[157,158].

Although the majority of these drugs seem to be anti-epileptogenic in animal models[154,157], translating these proof-of-concept findings into humans remains challenging. Indeed, the design of these preclinical animal experiments is not always directly transferrable to clinical trials in humans. For example, the drug doses used in some preclinical studies would cause serious adverse effects if administered to humans. In addition, some of the preclinical studies administered the antiepileptogenic intervention before injury, which is unlikely to be possible in a clinical setting[162]. Increased collaboration between preclinical and clinical researchers is needed to ensure that animal studies of antiepileptogenic drugs are designed in a way that provides appropriate information for clinical investigators.

Data from clinical studies. Epilepsy can develop following brain insults, including CNS infections, head injuries and strokes; according to the WHO, ~25% of epilepsy is preventable[2]. Measures designed to avoid the occurrence of these insults constitute primary prevention. For example, improved access to the antiparasitic therapy ivermectin in low-income countries has reduced the annual incidence of epilepsy associated with onchocerciasis[163–165].

Secondary prevention strategies aim to reduce the impact of these insults on brain networks to limit epileptogenesis. For example, the early identification of the underlying cause of status epilepticus and the limitation of its duration could prevent epileptogenesis and subsequent cognitive impairment[166–168]. The results of 25 clinical trials on the prevention of epilepsy with anti-seizure medicines (phenytoin, phenobarbital, valproic acid, levetiracetam and zonisamide) in individuals with traumatic brain injury, brain tumour or craniectomy have been reported. These studies include >2,300 individuals with traumatic brain injury, 400 individuals with brain tumours and 1,800 individuals with craniectomy[169–171]; however, none of the studies identified a statistically significant effect of the preventive treatments on epileptogenesis and many trials reported a high rate of adverse events. It seems to us that the most likely reasons for the failure of these trials include the use of traditional anti-seizure medicines that might not have antiepileptogenic action, in addition to the very short epileptogenic latency period in the conditions studied[162,172].

In order to use secondary prevention measures in a clinical setting, biomarkers of epilepsy susceptibility are required to enable the identification of patients who are likely to benefit from such therapies (FIG. 1). However, the potential adverse effects must be considered in order to balance the possible benefit of treatment against the risks. The two main epilepsy-related conditions that have been targeted with secondary preventive therapies so far are Sturge–Weber syndrome and tuberous sclerosis complex, both of which have an identifiable epilepsy latency period. In these two patient populations, the prevalence of epilepsy is particularly high, which enables the evaluation of the efficacy of secondary preventive therapies[173,174].

Sturge–Weber syndrome is a neurocutaneous disorder related to somatic mosaic pathogenic variants in *GNAQ*[175]. Clinically, this syndrome is associated with a facial angioma in the ophthalmic distribution of the trigeminal nerve, with ipsilateral glaucoma and leptomeningeal angioma[176]. Epilepsy develops in 80% of individuals with Sturge–Weber syndrome, usually before 1 year of age, and ~50% of individuals with the syndrome have cognitive impairment, one of the risk factors of which seems to be the severity of epilepsy[177]. The first study to evaluate the effect of prophylactic drugs in genetic epilepsy was performed by Ville et al. in 2002 (REF.[178]). In this study, 16 participants with Sturge–Weber syndrome without seizures were prospectively treated with phenobarbital and their outcome was compared with that of 21 participants with Sturge–Weber syndrome who were treated with phenobarbital only after their first seizure. Of the participants that received prophylactic treatment, 69% experienced epilepsy during the follow-up period, which was of >2 years (participant ages at the end of the follow-up period were from 2 years 9 months to 28 years), whereas 100% of participants not receiving prophylactic treatment developed epilepsy during that time period. Additionally, a retrospective study of 55 individuals with Sturge–Weber syndrome not receiving prophylactic treatment found that >80% developed epilepsy, usually before 2 years of age[179]. In the Ville et al. study[178], participants who received prophylactic treatment and subsequently developed epilepsy had a later mean age of epilepsy onset and the epilepsy features were less severe than in participants who received treatment after their first seizure. The rate of intellectual disability was 44% in the group of participants that received prophylactic treatment and 76% in the group of participants receiving treatment after their first seizure[178]. A more recent study in children with Sturge–Weber syndrome reported similar results. In this study, seizure onset in the first year of age occurred in 25% of participants receiving the preventive anti-seizure medicine and in 94% of participants not receiving the preventive anti-seizure medicine[180].

Tuberous sclerosis complex is a multisystemic disease caused by the presence of a pathogenic variant in *TSC1* or *TSC2* (REF.[181]). Seizures are the main neurological symptom and are present in 80–90% of patients, usually (in >80% of patients) beginning before the age of 2 years; ~50% of patients have epileptic spasms[182]. Most individuals with tuberous sclerosis complex also have intellectual disability, which seems to be more severe in individuals with epileptic spasms and drug-resistant, early-onset epilepsy[182]. In three studies, the occurrence of epileptic abnormalities, in particular interictal epileptiform discharges, in individuals with tuberous sclerosis complex was identified as a predictive biomarker for the onset of seizures in the short term (days to months)[183–185]. The presence of interictal epileptiform discharges predicted future epilepsy with a sensitivity of 85% and a specificity of 58.3%[184]. The identification of this predictive biomarker has enabled trials of preventive therapies to be performed. In an open-label study by Jóźwiak et al.[185], infants with tuberous sclerosis complex received either standard or preventive therapy. In the standard group, antiepileptic treatment was initiated after the onset of seizures whereas, in infants in the preventive group, antiepileptic treatment was initiated when active epileptic discharges were seen on EEG but before the onset of seizures. At 24 months of age, 93% of infants receiving preventive therapy were seizure-free compared with just 35% of infants receiving standard therapy. Preventive treatment was also associated with a higher rate of drug-responsive epilepsy and a higher average IQ score[185]. At 5 years after initiation of preventive therapy (treatment was withdrawn after 3 years of age in 5 of the 11 participants), average IQ score and the proportion of infants that were free of seizures were still higher in the group of infants receiving preventive therapy than in the group of infants receiving standard therapy[186]. Two prospective studies — EPISTOP[187] and PREVENT[188] — randomly assigned participants with tuberous sclerosis complex to receive preventive (before seizure onset in case of EEG abnormalities) or standard treatment (after seizure onset). The PREVENT study is still ongoing, but the first results from EPISTOP indicate that preventive treatment was associated with a reduced risk of epilepsy at 24 months of age[189].

A case report describing the treatment of two patients from families with well-known pyridoxine-responsive epilepsies provides another example of successful preventive therapy. The mothers of these patients were treated with pyridoxine during pregnancy. Birth and pregnancy were normal for both infants but the second infant experienced seizures at 7 days of age owing to the cessation of pyridoxine supplementation at birth. These seizures responded quickly to pyridoxine supplementation[190]. These two infants had a better long-term cognitive outcome than their siblings, who were treated with pyridoxine only after birth[102,190].

The evidence discussed in this section shows that targeting epileptogenesis in order to prevent epilepsy (seizures and comorbidities) might be achievable in genetic epilepsies, especially in epilepsies with a fairly long latency period[157,162,191].

Conclusions and future prospects

Despite the development of a dozen new anti-seizure medicines during the last two decades, the proportion of individuals with drug-resistant epilepsy has not substantially changed since the 1980s[7]. However, the field of epilepsy has advanced within the last decade and is now entering the era of targeted and precision medicine. Our increased understanding of epilepsy aetiologies, including immune, genetic and structural causes, has now made it possible, in some patients, to identify specific targets for therapies that go beyond anti-seizure medicines and that enable treatment of the cause of epilepsy. This advance is the beginning of a major shift in our paradigm of epilepsy treatment as we are now entering the era of therapies that target the underlying cause and mechanisms of epilepsy.

We have no doubt that gene therapy, an example of personalized medicine, will change our therapeutic approach to monogenic epilepsies. Gene editing in particular seems to be a very promising tool to correct the pathophysiological impact of pathogenic variants. Gene therapy is likely to be most effective when administered during the early stages of disease or even preventively. Therefore, the future challenge for epileptologists will be to identify the causes of epilepsy early, especially using susceptibility biomarkers, in order to promote preventive therapies and to avoid the occurrence of epilepsy, including seizures and comorbidities.

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