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Armstrong, Caren

Marsh, Eric

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REVIEW

Electrophysiological Biomarkers in Genetic Epilepsies

Caren Armstrong[1] · **Eric D. Marsh**[1,2]

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Abstract
Precision treatments for epilepsy targeting the underlying genetic diagnoses are becoming a reality. Historically, the goal of epilepsy treatments was to reduce seizure frequency. In the era of precision medicine, however, outcomes such as prevention of epilepsy progression or even improvements in cognitive functions are both aspirational targets for any intervention. Developing methods, both in clinical trial design and in novel endpoints, will be necessary for measuring, not only seizures, but also the other neurodevelopmental outcomes that are predicted to be targeted by precision treatments. Biomarkers that quantitatively measure disease progression or network level changes are needed to allow for unbiased measurements of the effects of any gene-level treatments. Here, we discuss some of the promising electrophysiological biomarkers that may be of use in clinical trials of precision therapies, as well as the difficulties in implementing them.

Keywords Biomarker · Precision treatment · Developmental encephalopathy

Introduction

The promise of precision medicine—providing treatments for individuals based on specific phenotypes or genetic changes underlying their disease—is a longstanding goal for investigators in many fields. Cancer biology has already seen a massive shift toward treatment based on underlying genetic changes with treatments now targeted at commonly altered pathways such as angiogenesis or cell growth [1, 2]. In neurology, the increasing number of recognized single gene causes for disease along with the recent successes of a few such precision therapies has generated tremendous enthusiasm in developing targeted interventions. As these targeted therapies emerge, a major challenge facing translational/clinical scientists is ensuring that sensitive, rigorous, and specific measures of all important outcomes are developed. The nightmare scenario is failure of a therapy, not due to the agent, but due to bad outcome measurements. This issue is further heightened in rare disorders where the numbers of patients and the cost per patient treated may be very high making failure more consequential. The challenge of accurately measuring outcomes of precision medicine is relevant to all genetic and rare disorders, and strategies are being acutely discussed in the epilepsies as epilepsy precision medicine is beginning.

Seizures are the defining symptom of "the epilepsies" but these disorders are ultimately network disorders, with seizures just one symptom with neurodevelopmental, physical, movement, cognitive, behavioral, social, sleep, and psychological disorders all being equally important concerns for patients. The full gamut of symptoms is ultimately targets for precision medicine, and these non-seizure issues are more difficult to quantify than seizures. Therefore, in the epilepsies, like other genetic neurological disorders, the development of biomarkers to identify meaningful changes in disease status or even disease progression is essential to differentiate variability in disease progression from meaningful modification of disease by precision interventions. Here, we discuss the complexity of the problem by both highlighting examples of biomarkers that are in use and defining the gaps in knowledge that must be addressed to develop more sensitive and specific biomarkers for evaluating precision medicines.

✉ Eric D. Marsh
marshe@chop.edu

[1] Division of Neurology and Pediatric Epilepsy Program, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA

[2] Department of Pediatrics and Neurology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104, USA

The Rise of Precision Treatments for Neurologic Diseases

The potential for targeted therapeutics for genetic diseases to be applied to epilepsy is just beginning to be realized. Targeted therapies include pharmacologic interventions to normalize channel or protein function, protein replacement therapies, RNA-based therapies to alter protein expression, and even replacement, or correction of the genes that are dysfunctional. Despite the theoretical promise of targeted interventions, several examples of precision therapies demonstrate the difficulty of successfully translating precision preclinical studies into clinical practice.

One of the most anticipated precision therapies has been the use of everolimus—a mammalian target of rapamycin (mTOR) inhibitor—for tuberous sclerosis complex (TSC). Everolimus was the subject of numerous preclinical studies suggesting a disease modifying effect on not only the various tumor types seen in TSC, but also on seizures and neurodevelopmental outcomes due to targeting the function of the underlying genetic defect [3, 4]. Everolimus has been found in clinical trials to be modestly effective in the treatment of subependymal giant cell astrocytomas (SEGAs) and for focal seizures, even in younger children [5–11]. However, consistent treatment earlier in the progression may be more effective in disease modification based on preclinical studies, and has yet to be used in that context [3].

The specific impact of any particular pathogenic variant matters: i.e., gain of function variants behave differently from loss of function variants. For example, sodium channels causing a loss of function in the SCN1A sodium channel cause seizures which can be worsened by sodium channel blockers, while seizures caused by gain of function changes in the SCN8A sodium channel gene respond particularly well to sodium channel antagonists [12–14].

Retigabine, an alkyl carbamate anti-seizure medication (ASM) that potentiates $GABA_A$ and acts as an inhibitory M-current enhancing Kv7.2–7.5 potassium channel opener, has been of interest to patients with KCNQ2 related epilepsy, which can cause self-limited familial neonatal epilepsy or a developmental and epileptic encephalopathy (DEE) [15, 16]. The use of a potassium channel opener in patients with defects in potassium channel function seemed to have benefit in patients, especially when started early in the disease course [17]. However, while retigabine was initially approved as adjunct therapy in focal epilepsy, its use was subsequently restricted due to an idiosyncratic adverse effect of blue tissue discoloration and the original manufacturer withdrew the medication from the market [18]. There is now an ongoing phase 3 clinical trial investigating retigabine for seizure control specifically for children with KCNQ2 DEE [19].

One of the more complicated precision medication stories for genetic epilepsy has been quinidine in the treatment of seizures due to potassium channel KCNT1 pathogenic variants, associated with familial focal epilepsy, autosomal dominant nocturnal frontal lobe epilepsy, and malignant migrating focal seizures of infancy. The pathogenic variant typically causes a gain of function in the sodium-activated potassium channel, and in vitro the effects can be reversed by quinidine which is both a broad spectrum potassium channel blocker and a fast inward sodium current antagonist [20, 21]. Despite promising preclinical studies, small clinical trials have been conducted and have not consistently demonstrated seizure reduction by quinidine [21–26]. The variable effect is likely due in part to the variable CNS concentrations of quinidine that can be achieved, thought to be caused by polymorphisms in active transport of quinidine across the blood brain barrier, and also to cardiac side effects of prolonged QT at therapeutic doses [21, 27]. In addition, while some reports have suggested that treatment may only be effective in younger patients [26, 28], other studies in patients diagnosed and treated even in the neonatal period demonstrated no effect of quinidine [29]. Even in patients with KCNT1 who had reduced seizures with quinidine, developmental milestones did not seem to normalize and the patients remained severely affected despite reduced seizures [28].

Pathogenic variants in the NMDA receptor subunit encoded by GRIN2A were predicted in vitro to respond to memantine, an NMDA antangonist [30]. There are now case reports of reduced seizures with memantine in GRIN2A, though there have been no larger clinical studies in this population to date, [30–32]. In addition to memantine, ketamine, another NMDA antagonist along with magnesium, which blocks the NMDA channel, have been used with some success in status epilepticus in case studies of a GRIN2D pathogenic variant as well [33, 34].

Beyond pharmacologic targeted treatments, genetic and protein targets are also being used for precision medicine. Recombinant protein substitution, though limited due to difficulty of delivery to the CNS, has been used in neuronal ceroid lipofuscinosis type 2 (CLN2) with stabilization or slowing of the typical decline associated with this lysosomal neurodegenerative disorder [35]. A newer technology, antisense oligonucleotides (ASOs) are an exciting class of therapy consisting of synthetic short nucleotide sequences that are single stranded and thus bind to and alter mRNA expression in humans [36]. Recently, ASOs have been used clinically to wide acclaim in Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA), and are now in clinical trials for Dravet syndrome for epilepsy and in development in preclinical trials for Rett syndrome, SCN8A, and KCNT1-related epilepsies [37–40]. There is also a potential

for the use of ASOs individualized to specific patients, for example, as done in one notable recent case with CLN7 [41]. In addition to altering protein expression, gene therapy is becoming a real possibility using adeno associated viral (AAV) vectors for SMA and other degenerative disorders [42, 43]. In the coming years, when these precision therapies are trialed for single-gene causes of epilepsy [44], better outcome measures and biomarkers must be available to prevent the disappointing responses seen in the examples above.

Untangling Causation in Developmental and Epileptic Encephalopathies—Will Changing Seizures Change the Comorbidities?

One of the most important questions to consider as we turn to therapies designed to target single gene causes of epilepsy is whether the uncontrolled seizures or the underlying protein dysfunction primarily drive the cognitive and neuropsychological dysfunction often seen in these syndromes. Some 80% of school aged children with active epilepsy are also noted to have behavioral or cognitive impairments which are of significant importance to quality of life for these patients [45]. While we know that poor seizure control can exacerbate cognitive and behavioral difficulties in patients who suffer from epilepsy, the cognitive and behavioral concerns associated with epilepsy often predate the onset of seizures, suggesting that underlying pathophysiology leads to both epilepsy and neurodevelopmental deficits [45]. As targeted therapies for epilepsies emerge, it stands to reason that not only seizure control but also other domains of functioning will be important potential targets for intervention and will need to be evaluated. These comorbidities differ depending on the specific disease being targeted and on the stage of that disease.

Often, caregiver and physician scales are used to monitor therapies, and if not tailored to the specific outcomes of interest, can yield inconsistent or negative trials for precision medications. Insulin like growth factor-1 (IGF-1) analogs underwent several less successful trials in Rett syndrome before a recent phase 2 clinical trial of trofinetide using different scales did eventually show improvements in ambulation and seizures as well as repetitive movements, breathing problems, mood dysfunction, attentiveness, and social interaction [46–50]. Trofinetide also had a positive phase II study in Fragile X, but notably, this trial used a novel assessment tool that incorporated specific key symptoms of Fragile X into the scales [51]. Clinical trials for metabotropic glutamate receptor type 5 (mGluR5) antagonist mavoglurant or negative allosteric modulator basimglurant for behavior symptoms in Fragile X did not show any benefit when measured by a checklist designed for use in autism in patients, while behavior measured on different scales and studies of visual attention during viewing of faces did show changes with mavoglurant [52–56]. And studies of methylation-targeting medication in Rett syndrome did not provide objective evidence of improvements, though parents reported subjective improvements during the study [57]. Failed clinical trials like this, in the face of robust preclinical findings and subjective reports by parents of improvements, raise the question of whether it is the treatment or the outcome measurement which has failed. There is a clear need for better objective biomarkers that can act as more sensitive measure of functioning in domains that are important families but may lie beyond subjective surveys of seizure counts or intermittent measurements of specific behaviors. Are there better measurements to use that can avoid this fate in future therapeutic trials?

To obtain higher quality information in clinical trials, we must first consider which features of DEEs can be measured reliably, and which features we expect to be sensitive to changes in its underlying pathophysiology, even if changes in that physiology may not have an immediate robust seizure reducing effect. Measurement tools that largely consist of subjective scales are susceptible to placebo effects and are not sensitive to small changes that may be overlooked by a close observer over time. What kinds of biomarkers can be used to determine if our interventions are changing the course of disease, and over what time course should we expect to see a change in these biomarkers? Next, we will look at the existing potential biomarkers that may be of use in clinical trials to get at some of these questions for DEEs.

Biomarkers of Brain and Network Functions

A major concern is that precision interventions may not perform well in clinical trials designed for new anti-seizure medications (ASMs) which evaluate seizure reduction in established refractory cases. By using biomarkers designed to query underlying network function, the goal is to identify meaningful changes in a network earlier and with greater sensitivity than behavioral scales. The hope is that focusing our efforts on those biomarkers that are normal or minimally abnormal early on in a particular disease and which typically show progression as the disease progresses may better identify those targeted interventions that halt meaningful clinical disease progression before the onset of severe symptoms. Biomarkers that can provide information about network function across a range of DEEs would be ideal since they might be applicable to several rare diseases. In neurology, assessments often involve imaging-based evaluations such as MRI; function-based measures such as nerve conduction, auditory, visual, or sensory evoked potentials, and EEG; or a combination of imaging and functional modalities

such as fMRI, PET, and magnetoencephalography (MEG). Other biosensors may also add to the overall assessment in meaningful ways [58]. An intriguing in vitro predictive biomarker of sorts has been in development using patient-derived human-induced pluripotent stem cells (iPSCs) to evaluate the nature of specific mutations in certain patients and predict responses to possible precision treatments, but these studies also raise questions of neuronal cell type, brain regional effects, maturity, and network role that must be addressed in order to bring the information back to the treatment of specific patients [59, 60]. Nevertheless, specific biomarkers like this that may be able to detect successful target engagement and functional improvement with therapy early in treatment would be helpful in quickly identifying precision treatments of use in specific patients.

Some modalities such as fMRI or MEG are out of reach without sedation in DEEs, degrading the quality of the information that can be obtained. However, neurophysiological techniques can often be performed in patients without need for sedation or cooperation. Here we review examples of the use of standard neurophysiological techniques as biomarkers in DEEs that might be of use as we develop more targeted therapies.

Evoked Potentials

A few studies have demonstrated that auditory evoked potentials (AEPs) can track disease progression in certain syndromes. In Rett syndrome, a recent multicenter study reported on a clear association of P1-N1 amplitudes with severity as measured by the Rett specific clinical severity scale or motor behavioral assessment [61]. Additionally, in subjects recorded 1 year later, both the waveforms and the association with severity were reproducible [61]. This was the first multicenter study to show the promise of evoked potentials in the DEEs. Previous to this study, a number of single-site studies in Rett syndrome reported similar results using responses to basic tones and responses to "oddball" stimulus delivery paradigms, with increasing central abnormalities seen with disease progression [62, 63]. Increases in gamma frequency are seen in Rett patients when exposed to familiar voices and event-related potentials (ERPs) to their own name are increased in magnitude, while interestingly in MeCP2 duplication syndrome, the increases in gamma are seen when exposed to unfamiliar voices, and ERP amplitude increased to others' names rather than the patient's own [64, 65]. More negative left hemisphere amplitudes in response to words as compared with non-words are correlated with better receptive language skills and adaptive behavior in girls with Rett syndrome and may be a measurement that could serve as a biomarker of disease severity [66]. Evoked potentials can also be detected using MEG, and delays in the M100 response in the right hemisphere seem to be correlated with autism [67]. Gamma frequency modulation differences are also seen in other DEs; for example, gamma modulation is not seen in response to frequency-varying stimulation in patients with Dravet syndrome [68]. In patients with Fragile X syndrome exposed to minocycline, ERPs to a passive odd-ball paradigm demonstrated reduced amplitudes compared to patients exposed to placebo, demonstrating that the differences in AEPs seen in DEEs are sensitive to medication effects [69]. In patients with Angleman syndrome, auditory evoked potentials using an odd-ball paradigm were correlated (but not statistically significantly) with adaptive behavior scale [70]. Besides the recent study in Rett, these were all single site—small numbers of subjects, but each gives promise for auditory evoked potentials in the DEEs.

Visual evoked potentials (VEPs), though apparently normal in some studies of DEEs such as FOXG1, but with very small sample size, have been noted to have smaller amplitude, varied latencies correlating with disease severity, and exhibit decreased visual spatial acuity in Rett syndrome [61, 71–73]. Relatively fewer studies have been completed using VEPs compared with AEPs [61].

Somatosensory evoked potentials (SEPs) in girls with Rett syndrome were noted to have increased central latencies, similar to findings in auditory and visual evoked potentials [74, 75]. In addition, they demonstrate delayed giant SEPs which are associated with cortical reflex myoclonus [75, 76]. Several studies in younger girls under age 9 with Rett syndrome did not demonstrate differences from typically developing girls, and thus, SEPs may represent good biomarkers for disease progression [77, 78].

EEG

A longitudinal study in TSC seeking a biomarker for impending infantile seizures demonstrated that epileptiform discharges in TSC infants (identified by other features- such as cardiac rhabdomyomas) prior to developing epilepsy preceded clinical seizure onset by an average of 3.6 months, and thus, a routine EEG could indeed be used as a biomarker for seizure development in this population [79, 80]. In addition, background abnormalities and dysmaturity in newborns and infants with TSC also correlate with neurodevelopmental comorbidities at later time points [81]. Vigabatrin, another medication known to have specific clinical utility in TSC, was selected as another specific candidate for disease modifying treatment, with initial open label studies suggesting that treatment at the onset of discharges on EEG, but prior to onset of clinical seizures, could improve outcome in terms of both seizures and neurocognitive scores compared with historical controls [82, 83]. Recently, published results of the EPISTOP trial in the EU demonstrated that infants who were treated with Vigabatrin prophylactically at onset of EEG abnormalities compared with children treated at

clinical seizure onset had longer time to first seizure (364 vs 124 days), as well as decreased risk of clinical seizures (OR 0.21), drug-resistant epilepsy (OR 0.23), and infantile spasms (OR 0.0) [84, 85]. A similar trial in the USA called PREVeNT assigned infants with TSC to receive preventive or standard treatment with vigabatrin and is in progress at this time [86].

In patients with history of perinatal stroke, mean spike frequency diverges in patients who go on to develop electrical status epilepticus in sleep (ESES) from those who do not approximately 3 years before diagnosis of ESES [87]. EEG in Rett syndrome follows a characteristic developmental pattern, in which EEG is largely normal before regression starts, then spike and sharp waves arise over the centrotemporal regions before becoming more generalized [88, 89]. As the disorder progresses further, epileptiform abnormalities subside and a slow background with frontocentral theta remains. EEG in Angelman syndrome develops interictal epileptiform discharges, rhythmic delta and theta, and posterior slowing which differ qualitatively depending on the genetic change [90, 91]. These all demonstrate that the EEG follows disease-specific trajectories that can potentially be used as an outcome measure in these disorders.

Beyond the visual inspection of EEG, resting state quantitative EEG can identify even more subtle differences in EEG using the spectral power, interelectrode coherence, and other features like amplitude, kurtosis, skewness, and variability in the signal. Analysis of resting state and sleep EEG has been performed for several disorders including autism, anxiety and depression, several DEEs, and in normal child development [92–95]. The relative delta power and rhythmicity corrected for age and genotype in Angelman syndrome predict cognitive scores [96, 97]. Delta power is higher in post-perinatal stroke patients who go on to develop ESES than those who do not, higher in Rett syndrome patients in the post regression state compared with during, and higher in Angelman syndrome during both wakefulness and sleep [87, 98]. Power in the delta bands is also increased in sleep in Rett syndrome compared with neurotypical controls, and unlike in controls, that delta power does not decline overnight [99]. Coherence measures are also noted to be increased during sleep in children with Angelman syndrome [100]. Beta power is decreased in Angelman syndrome, while in duplication 15q syndrome, which includes the same region deleted in Angelman syndrome, beta power is increased, mimicking the observed effect on EEG of the addition of a benzodiazepine on adult neurotypical control patients [101].

Within similar phenotypic disorders, differences in quantitative EEG can be seen on the basis of genotype. For example, in occipital and temporal regions, differences in the pattern of interelectrode coherence have been noted both between Rett syndrome caused by MeCP2 deletion and CDKL5 deficiency disorder (CDD), as well as within different genotypes of Angelman syndrome [91]. At the same time, phenotypically different subtypes of Rett syndrome caused by alterations of the same gene (either with or without epilepsy or with classic or preserved speech variant) display differences in patterns of interelectrode coherence [102].

Quantitative EEG measures also change with interventions. Even brief periods of cognitive training in Rett syndrome seem to increase beta and decrease theta power, suggesting that changes in power may be very sensitive to interventions [103]. And although mecasermin did not show clear improvements in subjective scales in Rett syndrome as discussed above, asymmetry in frontal alpha, a finding that typically correlates with anxiety and depression symptoms, was decreased with mecasermin use, suggesting this is a more sensitive biomarker than scales to evaluate medication effects in Rett syndrome [49, 93, 104]. In Angelman syndrome, power spectra were found to have decreased delta power after treatment with minocycline [105].

Beyond evaluating changes in EEG with interventions, attention has also been turned toward attempting to identify baseline quantitative EEG characteristics that will predict responses to therapy. For example, differences in network organization, synchronicity, and connectivity, often measured using EEG, evoked potentials, or functional imaging modalities, and heart rate variability seem to have better predictive validity in identifying patients who will benefit from vagal nerve stimulators (VNS) compared with structural differences or laboratory values such as inflammatory markers [106–112]. In a recent study, patients with temporal lobe epilepsy with lower connectivity values on quantitative EEG measurements were noted to be more likely to experience seizure freedom on monotherapy with levetiracetam [113].

Taken together, the evidence for use of evoked potentials and EEG as biomarkers for progression of disease or response to precision therapies looks promising, but with a significant number of hurdles to be tackled.

Pitfalls and Considerations

Before we can implement into clinical trials or in real-world practice, these research results of neurophysiologic or other functional biomarkers for monitoring therapeutic treatments, larger studies including a battery of different tests in people with varying genetic and phenotypic syndromes in different stages of disease will need to be performed. As these previous studies have documented (Table 1), there are differences not only over time within one disease, but between different diseases or even between phenotypic subsets of patients with the same

Table 1 Summary of study types, disorders, and medications described in the text

Measurement	Disorders with clinical data	Interventions tested with this modality	References
Clinical surveys: seizure counts	TSC, SCN8A, KCNQ2, KCNT1, GRIN2A, GRIN2D	Everolimus, sodium channel antagonists, retigabine, quinidine, memantine, ketamine	[3–14, 17–26, 30–34]
Clinical surveys: behavior and other symptoms	CLN2, Rett Syndrome, Fragile X syndrome	Recombinant proteins, trofinetide, mavoglurant, basimglurant, methylation modulation	[35, 46–57]
Evoked potentials	Autism, Rett, MeCP2 duplication, Fragile X, Angelman, and Dravet syndromes	minocycline (Fragile X)	[61–78]
EEG abnormalities: qualitative	TSC, post perinatal stroke, Rett syndrome, Angelman syndrome	Vigabatrin (TSC)	[79–91]
EEG: quantitative	Rett syndrome, Angelman syndrome, duplication 15q syndrome, post perinatal stroke, CDD	Mecasermin (Rett), minocycline (Angelman), cognitive training (Rett)	[49, 87, 91, 93, 96–105]

TSC tuberous sclerosis complex, *CLN2* neuronal ceroid lipofuscinosis type 2, *CDD* CDKL5 deficiency disorder

disease. Concomitant medications, age, state, and temporal relationships to seizures can alter the network function in ways that may affect neurophysiologic biomarkers and so attention will need to be paid to all these factors when taking measurements.

The measures which are most robust and most sensitive to small changes in neurologic status must be identified, adjusted, and validated in specific populations before these potential biomarkers can be implemented in clinical trials. With the small patient populations being studied in the DEEs, good proof of reliability and reproducibility needs to occur before implementing these measures, as with small numbers the likely variability of any given study is greater than originally believed. As described above, many of the exploratory studies for EEG and EP biomarkers have performed multiple tests on different features of the EEG/EP. Ensuring that sound statistical methods, including correcting for multiple comparisons and ensuring reproducibility in different cohorts is needed before these tests are used as primary outcome measures in any clinical trial. Biomarkers which have an easily translatable counterpart in animals will also be ideal in allowing for more seamless translation of preclinical research into the clinical realm.

Predictive biomarkers of response to intervention are highly sought, since having a measure of the likelihood of a response to treatment before it is initiated would be ideal in selecting medications in clinical use or choosing subjects for prospective interventions. However, it is possible that the best biomarkers may ultimately be derived from identifying specific changes in network function after initiation of an intervention. While this may seem counterintuitive, having an early predictive biomarker that is calculated using data from a physiological study before initiation of a treatment then again after a brief trial of therapy without having to wait for sufficient time to evaluate for seizure reduction or change in behavior could allow us to more quickly find individual solutions that will work best for a particular patient without lengthy trials.

Timing of clinical trials within a disease course is also critical to consider when engaging in therapeutic treatments that might alter the course of a disease. Studies that are designed to focus on changing specific targets in older patients might fail to find even a robust treatment effect that could be evident if initiated prior to the onset of refractory epilepsy and neurodevelopmental deficits. For example, an ASO designed to facilitate functional Nav1.1 channel formation in patients with pathogentic SCN1A variants has been tested in preclinical models and is now in a clinical trial [40]. While this is a very exciting trial with high hopes for use in patients with Dravet syndrome, patients cannot enroll prior to onset of refractory seizures. Therefore, the question of whether intervening before significant epilepsy and developmental consequences have already appeared cannot be answered using this trial design. As biomarkers are identified earlier in disease, these early symptomatic or presymptomatic biomarkers may become the most important targets for future studies.

Conclusions

As we develop new precision therapies, clinical trials will need to shift focus from altering seizures in patients with already refractory disease to allow for the early or even presymptomatic treatment of individuals prior to their developing refractory epilepsy or other neurodevelopmental effects. This shift will require a substantial investment in the development of biomarkers for different genetic and phenotypic

patient populations that can identify patient groups who will benefit from novel therapies earlier. Neurophysiologic and other brain-based functional neurologic measurements are well positioned to fill this need, with a number of studies pointing toward the sensitivity of these measurements to even small interventions. Candidate biomarkers will need to be validated by age, disease genotype and phenotype, and stage of disease, and priority should be given to measures that correlate with the comorbidities that most influence the quality of life of patients and their caregivers.

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