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RECENT ADVANCEMENTS IN THE DIAGNOSIS AND TREATMENT OF EPILEPSY

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Abstract. Epilepsy represents one of the most prevalent neurological disorders globally, affecting over fifty million individuals with significant morbidity, mortality, and socioeconomic burden. The past three years have witnessed transformative advances across the epilepsy care continuum, fundamentally reshaping diagnostic paradigms and therapeutic possibilities. This comprehensive scientific review synthesizes breakthrough developments in epilepsy diagnosis and treatment from 2024 through early 2026. In diagnostic innovation, the validation of blood-based DNA methylation biomarkers capable of distinguishing focal cortical dysplasia subtypes IIa and IIb with exceptional accuracy represents a seminal advance, offering noninvasive presurgical diagnosis for previously MRI-negative cases. Concurrently, neuroimaging has evolved from lesion-centric localization toward sophisticated network-based connectomic approaches integrating ultra-high-field magnetic resonance, functional connectivity analyses, and quantitative positron emission tomography. Therapeutic advancements span multiple domains: precision sodium channel modulators including relutrigine and vormatrigine have demonstrated unprecedented efficacy in developmental and epileptic encephalopathies and focal epilepsy respectively, with regulatory filings underway; antisense oligonucleotide therapy targeting SCN2A gene expression offers the first disease-modifying strategy for genetic epilepsies; interleukin blockade with anakinra and tocilizumab has achieved consensus recommendation status for new onset refractory status epilepticus and febrile infection-related epilepsy syndrome; and electromagnetic neuromodulation technologies encompassing responsive neurostimulation, deep brain stimulation, transcranial magnetic stimulation, transcranial direct current stimulation, and emerging transcranial ultrasound stimulation provide expanding options for pharmacoresistant populations. Computational neuroscience contributions include neural mass modeling demonstrating that sleep electroencephalography can reveal synaptic hyperexcitability parameters predictive of imminent seizure risk. This review concludes that epilepsy care is undergoing fundamental paradigm shifts from symptomatic seizure control toward etiologic, precision therapeutics and from invasive intracranial evaluation toward minimally invasive and noninvasive diagnostic methodologies.

Key words: epilepsy; precision medicine; biomarkers; DNA methylation; focal cortical dysplasia; neuromodulation; neurostimulation; antisense oligonucleotide; developmental and epileptic encephalopathy; new onset refractory status epilepticus

INTRODUCTION

Epilepsy is a severe, chronic, and multifactorial neurological disorder characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition . Contemporary epidemiological

estimates indicate that more than fifty million individuals worldwide live with active epilepsy, with approximately five million new diagnoses annually and a lifetime prevalence approaching one in twenty-six persons . Despite significant therapeutic advances over recent decades, the proportion of patients developing pharmacoresistance has remained stubbornly fixed at approximately thirty percent for more than thirty years, and many individuals with controlled seizures continue to experience significant medication-related adverse effects that compromise quality of life . The past three years, spanning 2024 through early 2026, have witnessed an unprecedented acceleration in epilepsy research translation, yielding transformative advances across the entire spectrum from fundamental pathophysiological understanding to clinical diagnostic methodology and therapeutic intervention. These developments have been catalyzed by several converging factors: maturation of genomic and epigenomic technologies enabling molecular characterization of epileptogenic lesions; expansion of precision medicine frameworks from oncology to neurogenetics; regulatory incentives for rare pediatric epilepsy therapies; and sophisticated computational approaches for extracting pathological signatures from routine clinical electrophysiology. This review examines the most significant recent advancements in epilepsy diagnosis and treatment. The diagnostic section analyzes developments in molecular biomarkers, particularly the validation of blood-based epigenetic signatures for focal cortical dysplasia subtyping; advanced neuroimaging methodologies emphasizing network-based connectomic approaches and ultra-high-field magnetic resonance; and computational electroencephalography analyses utilizing neural mass modeling. The therapeutic section comprehensively examines precision pharmacotherapy including next-generation sodium channel modulators and antisense oligonucleotide therapy; immunomodulatory strategies for catastrophic epileptic encephalopathies; and the rapidly expanding neuromodulation armamentarium encompassing both invasive and noninvasive brain stimulation technologies.

The primary objectives are to synthesize evidence from peer-reviewed studies published between 2024 and 2026 with emphasis on clinical translation potential, to critically evaluate the strength of current evidence supporting emerging diagnostic and therapeutic modalities, and to identify remaining knowledge gaps and future research imperatives. By integrating molecular, electrophysiological, imaging, and therapeutic advances within a unified framework, this review aims to provide clinicians and investigators with a comprehensive understanding of the contemporary epilepsy landscape and its trajectory toward increasingly precise, personalized, and minimally invasive care.

LITERATURE REVIEW

Diagnostic Innovations

Molecular Biomarkers and Epigenetic Diagnostics - the most transformative recent advance in epilepsy diagnostics emerges from the intersection of epigenomics and surgical epilepsy. Focal cortical dysplasia represents the most common cause of drug-resistant focal epilepsy in both children and adults, yet its detection and classification have historically depended upon invasive intracranial electroencephalography and postoperative histopathological examination. Even with high-resolution magnetic resonance imaging, a substantial proportion of focal cortical dysplasia lesions remain radiographically occult, precluding surgical consideration or complicating operative planning . Investigators from Cleveland Clinic and the Baker Heart and Diabetes Institute have fundamentally altered this diagnostic landscape through identification and validation of blood-based DNA methylation biomarkers capable of distinguishing focal cortical dysplasia subtypes IIa and IIb . In a rigorous investigation employing genome-wide methylation profiling of paired brain tissue and peripheral blood samples, the research team identified three specific gene loci—Interleukin-1 receptor accessory protein, Homeodomain-

interacting protein kinase 2, and Chondromodulin—demonstrating differential methylation patterns that reliably differentiated focal cortical dysplasia IIb from IIa. The diagnostic performance was exceptional: combination of clinical factors with these three methylation biomarkers achieved an area under the receiver operating characteristic curve of 1.0 in the discovery cohort, validated with areas under the curve of 0.96 and 0.98 in independent replication cohorts . The mechanistic and clinical implications are profound. Epigenetic alterations detectable in peripheral blood reflect brain tissue pathology, establishing proof-of-principle that noninvasive liquid biopsy approaches are feasible for epileptogenic lesion characterization. For patients with medically intractable epilepsy and negative high-resolution magnetic resonance imaging in whom focal cortical dysplasia is suspected, a blood-based epigenetic test could enable presurgical diagnosis, specific subtype determination, and optimized surgical planning without intracranial electrode implantation. This advance simultaneously addresses diagnostic accuracy, patient safety, healthcare resource utilization, and timeliness of surgical intervention .

Advanced Neuroimaging and Connectomic Paradigms

Contemporary epilepsy neuroimaging has undergone fundamental reconceptualization, transitioning from a focal, lesional-centric model to a network-based disorder paradigm with profound implications for image acquisition, interpretation, and clinical application . This conceptual shift recognizes that epileptogenesis and seizure generation involve distributed neural circuits rather than isolated cortical patches, and that successful surgical intervention requires disruption of pathological networks rather than mere lesional resection. Current clinical neuroimaging practice in epilepsy encompasses multiple complementary modalities. Structural magnetic resonance imaging remains the cornerstone examination, with established consensus guidelines from the International League Against Epilepsy specifying optimal acquisition protocols including three-dimensional T1-weighted, T2-weighted, and fluid-attenuated inversion recovery sequences with thin slices and isotropic voxels . Ultra-high-field magnetic resonance at 7 Tesla provides superior signal-to-noise ratio and spatial resolution, enabling detection of subtle cortical dysplasias, hippocampal subfield abnormalities, and architectural disorganization invisible at conventional field strengths. Diffusion tensor imaging and diffusion kurtosis imaging interrogate white matter microstructural integrity, revealing tractography alterations that delineate epileptogenic network involvement and predict postoperative deficits. Resting-state functional magnetic resonance imaging examines intrinsic connectivity networks, with recent studies demonstrating increased network segregation in bilateral temporal lobe epilepsy and characteristic subcortical functional connectivity gradients . Magnetoencephalography combines millisecond temporal resolution with reasonable spatial localization, identifying irritative zones through equivalent current dipole modeling of interictal epileptiform discharges. Nuclear medicine techniques maintain essential roles in pharmacoresistant epilepsy evaluation. Fluorodeoxyglucose positron emission tomography reveals interictal hypometabolism that frequently exceeds magnetic resonance-visible lesion boundaries, providing complementary localization information and prognostic stratification. Ictal single-photon emission computed tomography, though logistically demanding, identifies hyperperfused seizure onset zones when radiotracer injection occurs rapidly after electrographic onset. The emerging integration of positron emission tomography-magnetic resonance hybrid systems enables simultaneous acquisition of metabolic and structural-functional data with precise coregistration and reduced radiation exposure .

Computational Electroencephalography and Neural Mass Modeling

The electroencephalography-computer interface has advanced substantially through application

of sophisticated computational modeling approaches to routine clinical recordings. Dunstan and colleagues employed neural mass modeling to replicate sleep electroencephalography recorded from children with focal lesional epilepsies and healthy age-matched controls, revealing that sleep electroencephalography differences are driven by enhanced firing rates in neuronal populations arising predominantly from enhanced excitatory synaptic currents . Critically, these model-derived parameters demonstrated clinical predictive validity: synaptic hyperexcitability abnormalities were significantly more pronounced in patients who experienced seizures within seventy-two hours following the sleep recording, and model parameters inferred from individual patients resided closer to parameter spaces associated with simulated seizure activity . This investigation establishes proof-of-concept that routine interictal electroencephalography contains latent information regarding dynamic seizure risk that can be extracted through biologically informed computational models, potentially enabling individualized seizure forecasting and temporally targeted therapeutic interventions.

First Seizure Diagnostic Frameworks Contemporary approaches to first seizure evaluation emphasize systematic diagnostic frameworks distinguishing epileptic seizures from syncopal events and psychogenic nonepileptic attacks, with emphasis on meticulous history acquisition from eyewitnesses . Essential investigations include comprehensive metabolic panel, electrocardiogram with QT interval measurement, and urgent neuroimaging when intracranial pathology is suspected. Notably, clinical guidance continues to emphasize that elevated white blood cell count is common postictally and does not necessarily indicate infection, and that simple febrile seizure phenomenology does not occur in adult populations .

Therapeutic Innovations

Precision Pharmacotherapy: Sodium Channel Modulation The therapeutic landscape for genetic epilepsies has been transformed by the development of precision small molecules targeting disease-specific biophysical abnormalities. Relutrigine represents a first-in-class preferential inhibitor of persistent sodium current, designed to selectively mitigate the pathological hyperexcitability characterizing developmental and epileptic encephalopathies associated with SCN2A and SCN8A gain-of-function mutations .

Preclinical investigations demonstrated dose-dependent seizure inhibition with complete seizure control achieved in SCN2A and SCN8A mouse models. The Phase 2 EMBOLD study subsequently demonstrated robust, sustained reduction in motor seizures among heavily pretreated pediatric patients, with maintained seizure freedom in selected individuals. Relutrigine has received Orphan Drug Designation, Rare Pediatric Disease Designation, and Breakthrough Therapy Designation from the United States Food and Drug Administration, with New Drug Application submission planned for early 2026 . Vormatrigine is a next-generation, functionally selective sodium channel modulator targeting the hyperexcitable state of voltage-gated sodium channels in the brain. Preclinical characterization revealed unprecedented potency in the maximal electroshock seizure model, a highly predictive translational assay for focal epilepsy efficacy, with superior selectivity for disease-state channel hyperexcitability compared to existing antiseizure medications. The RADIANT study demonstrated robust seizure reduction in adults with treatment-resistant focal epilepsy and a favorable safety profile, supporting continued development as a once-daily oral therapy .

Antisense Oligonucleotide Therapy

Elsunersen exemplifies the translation of genetic insights into etiologic therapeutics. This antisense oligonucleotide is designed to selectively decrease SCN2A gene expression, directly targeting the fundamental molecular pathology underlying early-seizure-onset SCN2A

developmental and epileptic encephalopathy resulting from gain-of-function mutations . In vitro studies demonstrated reduction in both SCN2A gene expression and Nav1.2 protein levels. In vivo investigations in SCN2A mouse models revealed significant, dose-dependent seizure reduction, improved behavioral and locomotor activity, and increased survival. Elsunersen has received Orphan Drug Designation, Rare Pediatric Disease Designation, and Priority Medicines designation, with ongoing clinical evaluation in the EMBRAVE study. Unlike conventional antiseizure medications that provide symptomatic seizure control, antisense oligonucleotide therapy offers the potential for disease modification by addressing the primary genetic driver .

Immunomodulatory Therapy for Refractory Status Epilepticus

New onset refractory status epilepticus and febrile infection-related epilepsy syndrome represent catastrophic epileptic encephalopathies characterized by super-refractory status epilepticus in previously healthy individuals, associated with prolonged intensive care hospitalization, high mortality, and devastating neurocognitive outcomes . While the definitive pathogenesis remains incompletely elucidated, hypothesized mechanisms involve fulminant neuroinflammation mediated through the interleukin-1 beta-interleukin-1 receptor type 1 axis and excitotoxic concentrations of interleukin-6. The International NORSE Consensus Group and international FIRES workshop have established clinical management guidelines recommending prompt immunologic diagnostic workup and expeditious immunomodulatory therapy initiation. First-line agents include plasma exchange, intravenous methylprednisolone, and intravenous immunoglobulin. Second-line recommendations designate anakinra, an interleukin-1 receptor antagonist, and tocilizumab, an interleukin-6 receptor antagonist, as safe and effective immunotherapeutic options . Despite escalation to interleukin blockade, many patients continue to experience refractory status epilepticus. Emerging evidence from case series and cohort studies supports consideration of additional adjunctive therapies including vagal nerve stimulation, deep brain stimulation, electroconvulsive therapy, surgical resection, intrathecal dexamethasone, intravenous rituximab, cyclophosphamide, magnesium infusion, and sevoflurane anesthesia. While the evidence base remains limited to case reports and small series due to disease rarity, these interventions demonstrate therapeutic value for extinguishing the persistent epileptogenic activity described as smoldering embers .

Neuromodulation Technologies

Electromagnetic stimulation-mediated neuromodulation therapy has emerged as a rapidly expanding domain for pharmacoresistant epilepsy management. These approaches fundamentally differ from pharmacotherapy by modulating pathological network activity through targeted electrical or magnetic field application . Invasive neuromodulation modalities include vagus nerve stimulation, deep brain stimulation, and responsive neurostimulation. Vagus nerve stimulation, approved for pharmacoresistant focal epilepsy, delivers intermittent electrical stimulation to the left cervical vagus nerve with cumulative efficacy improving over years of therapy. Deep brain stimulation targeting the anterior nucleus of the thalamus received regulatory approval based on the SANTÉ trial demonstrating sustained seizure reduction through ten-year follow-up . Responsive neurostimulation represents a closed-loop paradigm wherein chronically implanted intracranial electrodes detect electrocorticographic seizure onsets and deliver targeted electrical stimulation to abort clinical events, with nine-year prospective efficacy and safety data now available . Non-invasive brain stimulation techniques offer the advantages of avoidance of intracranial surgery, absence of implantation-related complications, and suitability for patients ineligible for or declining invasive procedures . Transcranial magnetic stimulation delivers focused magnetic pulses inducing cortical depolarization; repetitive transcranial magnetic stimulation can produce lasting excitability modifications. Transcranial

direct current stimulation applies low-amplitude direct current via scalp electrodes, with cathodal stimulation reducing cortical excitability. Transcranial ultrasound stimulation represents an emerging modality employing focused mechanical energy to modulate neuronal membrane function noninvasively with superior spatial resolution compared to electromagnetic techniques . Current evidence indicates that electromagnetic stimulation-mediated neuromodulation can markedly improve neurological function and reduce epileptic seizure frequency. However, clinical application remains constrained by variability in stimulation protocols, limited standardization, heterogeneous patient responsiveness, and incomplete understanding of underlying mechanisms. Future research priorities include protocol optimization, predictive biomarker identification, and rigorous comparative effectiveness evaluation .

DISCUSSION

Synthesis of Diagnostic Advances - The diagnostic innovations reviewed herein collectively demonstrate that epilepsy diagnostics are transitioning from a historically syndromic, electroclinical discipline toward a molecularly precise, mechanistically informed specialty. The validation of blood-based epigenetic biomarkers for focal cortical dysplasia subtyping represents a particularly seminal contribution . This advance addresses a long-standing clinical conundrum: patients with drug-resistant focal epilepsy and negative magnetic resonance imaging who are presumed to have occult focal cortical dysplasia but cannot access curative surgical resection without invasive intracranial electroencephalography confirmation. The availability of a noninvasive blood test providing both diagnostic confirmation and specific histological subtype classification would fundamentally restructure the presurgical evaluation pathway, potentially expanding surgical candidacy, accelerating time to operation, and improving seizure freedom outcomes.

The simultaneous demonstration that focal cortical dysplasia subtype-specific methylation signatures are detectable in peripheral blood and mirror brain tissue pathology establishes proof-of-principle that extends beyond this specific condition. Similar epigenetic biomarker approaches may prove applicable to other epileptogenic lesions including tuberous sclerosis complex, hypothalamic hamartoma, and Rasmussen encephalitis. Moreover, DNA methylation patterns reflect both underlying genetic drivers and environmental exposures, potentially capturing dynamic disease-modifying influences inaccessible through static genomic sequencing. The reconceptualization of epilepsy as a network disorder with corresponding evolution in neuroimaging methodology carries profound implications for both diagnostic interpretation and therapeutic targeting. Traditional lesion-focused radiology sought to identify a singular epileptogenic zone corresponding to the seizure onset area. Contemporary connectomic approaches recognize that epileptogenicity distributes across structurally and functionally connected networks, that surgical disruption of critical network nodes may achieve seizure freedom without complete lesional resection, and that network topology predicts postoperative outcomes and neuropsychological morbidity. This paradigm shift necessitates corresponding evolution in radiology training, neuroradiology-neurophysiology collaboration, and surgical planning infrastructure. The application of neural mass modeling to routine sleep electroencephalography exemplifies a broader trend toward computational neurophysiology. Rather than relying exclusively on visual identification of interictal epileptiform discharges, contemporary analytical approaches extract latent pathological signatures from background electroencephalography dynamics. The demonstration that model-derived synaptic excitability parameters correlate with imminent seizure risk suggests that electroencephalography contains substantially more clinically actionable information than currently utilized. Implementation barriers include computational expertise requirements, algorithm validation across diverse

populations and recording systems, and integration into clinical workflow.

Synthesis of Therapeutic Advances - The therapeutic innovations reviewed herein demonstrate that epilepsy pharmacotherapy is finally entering the precision medicine era decades after oncology. The development of precision sodium channel modulators targeting disease-specific biophysical states rather than indiscriminately blocking channel function represents a fundamental advance in therapeutic selectivity. Traditional sodium channel blocking antiseizure medications exhibit little discrimination between physiologic and pathologic channel activity, producing dose-limiting central nervous system adverse effects that constrain efficacy. Relutrigine's preferential inhibition of persistent sodium current—a pathologic conductance characteristic of epileptogenic mutations—enables greater therapeutic effect with improved tolerability.

The emergence of antisense oligonucleotide therapy for genetic epilepsy signals the transition from symptomatic seizure suppression toward etiologic, disease-modifying intervention. Rather than mitigating consequences of SCN2A gain-of-function mutations, elsunersen directly reduces mutant allele expression at the transcriptional level. This mechanistic approach offers potential for comprehensive amelioration of the developmental and epileptic encephalopathy phenotype beyond seizure control, including improvement in cognitive function, behavioral abnormalities, and survival. The oligonucleotide therapeutic platform is readily adaptable to other monogenic epilepsies with documented pathogenic mechanisms. The establishment of evidence-based immunomodulatory protocols for new onset refractory status epilepticus and febrile infection-related epilepsy syndrome addresses previously untreatable catastrophic epileptic encephalopathies with historically near-uniform poor outcomes. While interleukin-1 and interleukin-6 blockade represent significant advances, the continued occurrence of treatment-refractory cases despite second-line immunotherapy highlights persistent knowledge gaps regarding optimal agent selection, treatment timing, combination strategies, and duration. The rarity of these conditions constrains prospective randomized trial feasibility, necessitating continued reliance on rigorously conducted observational studies and registry-based investigations. The expanding neuromodulation armamentarium provides essential alternatives for the thirty percent pharmacoresistant population. The availability of multiple invasive (vagus nerve stimulation, deep brain stimulation, responsive neurostimulation) and noninvasive (transcranial magnetic stimulation, transcranial direct current stimulation, transcranial ultrasound stimulation) modalities enables individualized selection based on epilepsy type, comorbidity profile, patient preference, and healthcare system resources. However, substantial evidence gaps persist including limited comparative effectiveness data, uncertainty regarding optimal stimulation parameters, incomplete characterization of long-term efficacy durability, and inadequate predictive biomarkers for patient selection.

Integration and Synergy - The most promising contemporary developments emerge at the intersection of diagnostic and therapeutic innovation. Blood-based epigenetic biomarkers identifying focal cortical dysplasia subtype IIb may eventually guide selection of mTOR inhibitor therapy, which demonstrates particular efficacy in tuberous sclerosis complex and candidate applicability to focal cortical dysplasia IIb sharing mechanistic mTOR pathway hyperactivation. Neural mass modeling parameters indicating imminent seizure risk could trigger responsive neurostimulation parameter adjustments or temporally targeted benzodiazepine administration. Antisense oligonucleotide therapy requires precise genetic diagnosis, creating essential linkage between molecular diagnostics and molecular therapeutics.

RESULTS

Synthesis of current evidence from 2024 through early 2026 yields the following definitive findings regarding recent advances in epilepsy diagnosis and treatment.

First, blood-based DNA methylation biomarkers have been validated for noninvasive diagnosis and subtyping of focal cortical dysplasia. Three specific gene loci—IL1RAP, HIPK2, and CNMD—demonstrate differential methylation patterns distinguishing focal cortical dysplasia IIb from IIa with exceptional diagnostic accuracy (area under the curve 1.0 in discovery cohort, 0.96-0.98 in validation cohorts). This represents the first validated molecular biomarker panel enabling presurgical epilepsy diagnosis from peripheral blood .

Second, epilepsy neuroimaging has fundamentally shifted from lesion-centric to network-based paradigms. Current clinical practice encompasses structural magnetic resonance with International League Against Epilepsy consensus protocols, diffusion imaging for white matter tractography, resting-state functional magnetic resonance for connectivity analysis, magnetoencephalography for irritative zone localization, and fluorodeoxyglucose positron emission tomography for metabolic mapping. Ultra-high-field 7 Tesla magnetic resonance and positron emission tomography-magnetic resonance hybrid systems represent emerging advanced modalities .

Third, computational neural mass modeling of routine sleep electroencephalography reveals latent synaptic excitability parameters correlating with imminent seizure risk. Children with epilepsy demonstrate enhanced neuronal firing rates and excitatory synaptic currents compared to controls, with abnormalities significantly more pronounced in patients experiencing seizures within seventy-two hours post-recording. This establishes proof-of-concept for electroencephalography-derived dynamic seizure forecasting biomarkers .

Fourth, precision sodium channel modulators have demonstrated transformative efficacy in developmental and epileptic encephalopathies and pharmacoresistant focal epilepsy. Relutrigine, a preferential persistent sodium current inhibitor, produced robust, sustained motor seizure reduction in heavily pretreated SCN2A and SCN8A developmental and epileptic encephalopathy patients with regulatory filing underway. Vormatrigine, a next-generation functionally selective sodium channel modulator, demonstrated unprecedented potency in predictive preclinical models and significant seizure reduction in treatment-resistant focal epilepsy .

Fifth, antisense oligonucleotide therapy has achieved clinical translation for genetic epilepsy. Elsunersen selectively decreases SCN2A gene expression, directly targeting the molecular etiology of early-seizure-onset SCN2A developmental and epileptic encephalopathy. Preclinical studies demonstrated dose-dependent seizure reduction, behavioral improvement, and increased survival in mouse models, with ongoing clinical evaluation representing the first disease-modifying strategy for this condition .

Sixth, interleukin blockade with anakinra and tocilizumab has achieved consensus recommendation status as second-line immunotherapeutic agents for new onset refractory status epilepticus and febrile infection-related epilepsy syndrome. Despite these advances, many patients remain refractory, with emerging evidence supporting adjunctive therapies including vagal nerve stimulation, deep brain stimulation, electroconvulsive therapy, surgical resection, intrathecal dexamethasone, magnesium infusion, and sevoflurane anesthesia .

Seventh, electromagnetic stimulation-mediated neuromodulation therapies have expanded substantially. Invasive modalities including vagus nerve stimulation, deep brain stimulation, and responsive neurostimulation have accumulated long-term efficacy and safety data. Noninvasive techniques including transcranial magnetic stimulation, transcranial direct current stimulation,

and transcranial ultrasound stimulation offer promising alternatives for pharmacoresistant epilepsy with fewer adverse effects, though clinical application remains limited by protocol variability and incomplete mechanistic understanding .

CONCLUSION

Epilepsy care in 2026 stands at an unprecedented inflection point. The convergence of molecular diagnostics, computational neurophysiology, advanced neuroimaging, precision pharmacotherapy, genetic therapeutics, immunomodulation, and neuromodulation technologies has created therapeutic possibilities unimaginable a decade ago. The trajectory of epilepsy research has shifted fundamentally from empirical antiseizure medication development toward mechanistically informed, etiologically targeted, and individually tailored interventions. Several overarching principles emerge from this comprehensive review. First, the binary classification of epilepsy as either genetic or acquired, lesional or nonlesional, surgically amenable or pharmacologically managed has become obsolete. Contemporary understanding recognizes that genetic susceptibility influences response to acquired insults, that radiographically occult lesions harbor detectable molecular signatures, and that optimal management frequently integrates pharmacologic, immunologic, neuromodulatory, and surgical approaches in individualized combinations. Second, the diagnostic-therapeutic divide is progressively dissolving. Molecular diagnostics increasingly identify specific therapeutic targets rather than merely assigning syndromic labels. Computational electroencephalography biomarkers may soon guide real-time treatment adjustments. Neuroimaging identifies not only epileptogenic zones for surgical resection but also network nodes for neuromodulation targeting. Third, the population of patients with truly untreatable epilepsy is progressively contracting. Patients with catastrophic developmental and epileptic encephalopathies previously offered only palliative care now access precision therapies targeting specific channelopathies. Patients with new onset refractory status epilepticus previously experiencing near-uniform mortality or devastating disability now benefit from rapidly administered immunomodulatory protocols. Patients with pharmacoresistant focal epilepsy and MRI-negative focal cortical dysplasia previously excluded from surgical consideration face imminent availability of noninvasive epigenetic diagnostics. Critical knowledge gaps demanding urgent investigation include: validation of focal cortical dysplasia epigenetic biomarkers in larger, diverse, prospective cohorts; development of analogous blood-based diagnostic panels for additional epileptogenic lesion types; identification of predictive biomarkers for neuromodulation patient selection and parameter optimization; rigorous comparative effectiveness research across expanding therapeutic modalities; characterization of long-term outcomes for precision therapies including antisense oligonucleotides; elucidation of mechanisms underlying incomplete response to interleukin blockade in new onset refractory status epilepticus and febrile infection-related epilepsy syndrome; and translation of computational electroencephalography seizure forecasting biomarkers from research settings to clinical implementation. The pace of epilepsy therapeutic innovation has accelerated dramatically, yet translation from breakthrough discovery to routine clinical availability remains protracted. Regulatory mechanisms facilitating expeditious approval while ensuring adequate safety characterization, healthcare reimbursement policies recognizing the value of precision diagnostics and high-cost genetic therapies, and continuing medical education ensuring practicing clinicians maintain current knowledge represent essential enabling infrastructure. The fifty million individuals worldwide living with epilepsy, including the one-third whose seizures remain uncontrolled despite optimal conventional therapy, deserve nothing less than the full and rapid deployment of these transformative advances. The foundational investments in epilepsy research spanning decades, from Penry and colleagues' establishment of video-electroencephalography gold standards to Sato and Dreifuss's prognostic factor elucidation to

Glauser and the Childhood Absence Epilepsy Study Group's definitive comparative effectiveness trials , have created the scientific substrate upon which current breakthroughs are built. The translation of this accumulated knowledge into tangible improvements in seizure control, cognitive function, quality of life, and survival for patients with epilepsy represents the imperative and the opportunity for the neuroscience community in the years ahead.

References.

1. Fine AL. Foundational Work in Absence Epilepsy: Laying the Groundwork and Establishing the Gold-Standard. Epilepsy Currents. 2026 Feb 4:15357597251403278.
2. Bansal CS, Kim HJ, Luo J, Vogel RT, Kothare SV. Beyond Anakinra and Tocilizumab: Additional Adjunctive Therapies in Pediatric New Onset Refractory Status Epilepticus and Febrile Infection-Related Epilepsy Syndrome – A Narrative Review. Pediatric Neurology. 2026;175:27-39.
3. NHS Scotland. Suspected seizure: ED / AMAU (Guidelines). Right Decisions Scotland; June 2025.
4. Praxis Precision Medicines. Praxis Precision Medicines Announces Plans to File an NDA for Relutrigine in SCN2A and SCN8A Developmental and Epileptic Encephalopathies in Early 2026. Press Release; December 11, 2025.
5. Cleveland Clinic. Blood-Based Epigenetic Biomarkers Differentiate FCD Subtypes. Consult QD; October 10, 2025.
6. Praxis Precision Medicines. Praxis to present latest preclinical and clinical advancements across leading epilepsy portfolio at the 2025 American Epilepsy Society (AES) Annual Meeting. Press Release; November 24, 2025.
7. Jiao D, Xu L, Gu L, Liu X, Xu Z, Ren C, Jiang Z, Chen S, Li M, Guo W, Wang W. Pathogenesis, diagnosis, and treatment of epilepsy: electromagnetic stimulation-mediated neuromodulation therapy and new technologies. Neural Regeneration Research. 2025 Apr 1;20(4):917-935.
8. Dunstan DM, Chan SYS, Goodfellow M. Neural mass modeling reveals that hyperexcitability underpins slow-wave sleep changes in children with epilepsy. Epilepsia. 2025;66(5):1652-1664.
9. Afshari M, Ganj S, Nasr S, et al. Dual strategies for epilepsy management employing pharmacological and non-invasive brain stimulation approaches. Frontiers in Neurology. 2025 Aug 15;16:1541064.
10. Cole AJ. Imaging in Epilepsy: Current Clinical Practice and Future Directions. Seminars in Neurology. 2026; published online January 7.