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Candidate Biomarkers in Pediatric Epilepsy: A Narrative Review of Clinical Applications and Translational Challenges

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ABSTRACT

Background: Pediatric epilepsy is a complex and varied group of conditions with different etiologies, seizure types, developmental trajectories, and treatment responses. Potential biomarkers have been investigated to improve etiologic classification, prognostic assessment, disease monitoring, seizure forecasting, and presurgical evaluation. *Objectives*: To narratively synthesize current evidence on biomarkers with potential clinical applications in pediatric epilepsy, focusing on biological rationale, clinical applications, methodological limitations, and translational status. *Methods*: A narrative review of English-language articles published from January 2016 to June 15, 2026 was conducted using PubMed. Earlier publications were included when fundamental to biomarker definitions, diagnostic criteria, or methodological concepts. Studies were selected according to their relevance to the review objectives. Findings were synthesized narratively because of heterogeneity in populations, biomarker definitions, analytical methods, and outcomes. *Results*: Candidate fluid biomarkers included neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), neuron-specific enolase (NSE), and S100B. MicroRNAs, pathogenic genetic variants, and epigenetic signatures were identified as candidate molecular biomarkers, while quantitative neuroimaging and electrophysiological features may represent candidate neurodiagnostic biomarkers. Potential applications included assessment of seizure activity, neuronal or glial injury, epilepsy etiology, drug-resistant epilepsy, prognosis, and presurgical evaluation. However, evidence remains limited by small and heterogeneous cohorts, methodological variability, inconsistent definitions, and lack of external validation. *Conclusions*: Genetic testing has reached the most advanced stage of clinical implementation, particularly in selected pediatric epilepsy syndromes. Most other biomarkers remain under investigation. Further research is needed to establish clinical validity and utility.

Keywords: pediatric epilepsy; biomarkers; neurofilament light chain; microRNA; neuroimaging; electroencephalography; precision medicine; narrative review

1. INTRODUCTION

One of the most common chronic neurological disorders occurring in childhood is epilepsy. It is a major cause of neurological dysfunction and affects approximately 0.5%-1% of children (Aaberg et al., 2017; Olusanya et al., 2020). It is an extensive group of neurological disorders that vary in age at onset, etiology, seizure type, developmental course, treatment response, and risk of neurological impairment (Scheffer et al., 2017; Wirrell et al., 2017). Given this heterogeneity, objective biological markers may complement clinical assessment by facilitating more accurate classification, prognostic assessment, and treatment selection (Pitkänen et al., 2016). While the classification of epilepsy has improved by developments in molecular genetics, neuroimaging, and electrophysiology, in many cases proper diagnosis, prognosis assessment, and treatment selection remain a challenge.

Even with the availability of numerous antiseizure medications, about one-third of children eventually fulfill the International League Against Epilepsy's (ILAE) definition of drug-resistant epilepsy as they continue to experience persistent seizures while receiving proper pharmacological treatment (Aaberg et al., 2018; Kwan et al., 2010). Early identification of patients at high risk of poor treatment outcomes is crucial, since it is linked to increased risks of neurodevelopmental impairment, cognitive dysfunction, psychiatric comorbidity, reduced quality of life, and premature mortality (Aaberg et al., 2018; Wirrell et al., 2017).

Epilepsy evaluation is based mainly on the clinical history, electroencephalography (EEG), and magnetic resonance imaging (MRI) when indicated (Bernasconi et al., 2019; Smith, 2005). EEG performed after an initial seizure has limited sensitivity and may not register discharges even in clinically confirmed epilepsy (Smith, 2005). Similarly, subtle epileptogenic lesions may remain undetected when MRI is not performed using an epilepsy-specific protocol or when abnormalities are difficult to recognize. What is more, neuroimaging and EEG interpretation are influenced by reader expertise and methodological factors (Bernasconi et al., 2019). Due to these limitations, interest in objective biomarkers that may supplement current diagnostic approaches has grown (Pitkänen et al., 2016).

According to the Biomarkers, EndpointS, and other Tools (BEST) Resource developed by the U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH), a biomarker is defined as a measurable characteristic that indicates normal biological processes, pathogenic processes, or responses to treatment (FDA-NIH Biomarker Working Group, 2016). In the case of childhood epilepsy, research has concentrated on multimodal biomarkers such as molecular profiles, neuroimaging, and electrophysiological features (Pitkänen et al., 2016). The intended use of a biomarker—diagnostic, prognostic, predictive, monitoring, or presurgical—determines the clinical question it must answer and thus requires distinct validation approaches.

The potential clinical role of these biomarkers extends beyond diagnosis. Investigations have looked at candidate biomarkers as means of aiding etiologic classification, for identifying children at increased risk of developing drug-resistant epilepsy, for measuring seizure-related neuronal injury, for predicting treatment response, for improving presurgical assessment, and for helping to develop precision medicine approaches (Pitkänen et al., 2016; Wirrell et al., 2017). In the case of seizure-forecasting studies, the insufficient reporting of false-positive rates is an additional significant limitation (Esparza et al., 2026; Pitkänen et al., 2016).

This narrative review intends to critically synthesize existing evidence on possible biomarkers investigated in pediatric epilepsy. Significant attention was paid to their biological rationale, possible clinical use, methodological limitations, and translational readiness. Rather than equating statistical association with clinical usefulness, this review evaluates the available evidence by analytical validity, clinical validity, and evidence of clinical utility.

2. REVIEW METHODS

A narrative review was conducted searching PubMed for relevant publications. Only publications written in English and published between January 2016 and June 15, 2026 were considered for the review, with updates conducted on several occasions until June 15, 2026. In conducting the search, combinations of terms relating to biomarkers, epilepsy, pediatric populations, children, and seizures were used. In addition to these most recent publications, earlier publications containing fundamental definitions and/or diagnostic criteria, as well as key methodological concepts that were relevant to the current review, were also considered.

Because this was a narrative rather than a systematic review, publications were selected according to their relevance to the objectives of the review rather than through a formal systematic screening process. The reference lists of relevant publications were also examined to identify additional studies. Pediatric studies were prioritized, while selected adult studies were included only when they provided important mechanistic, methodological, or contextual evidence relevant to biomarker research in pediatric epilepsy.

For each biomarker domain, the reviewed studies were considered with respect to the investigated population, specimen or modality, biomarker measurement methods, potential clinical role, and principal limitations. Attention was also given to sample size, study design, timing of biomarker assessment, methodological heterogeneity, reported diagnostic or prognostic associations, external

validation, and potential clinical applicability. The findings were synthesized narratively because of heterogeneity in study populations, biomarker definitions, specimens and modalities, analytical methods, and reported outcomes. The literature identification and selection process is summarized in Figure 1.

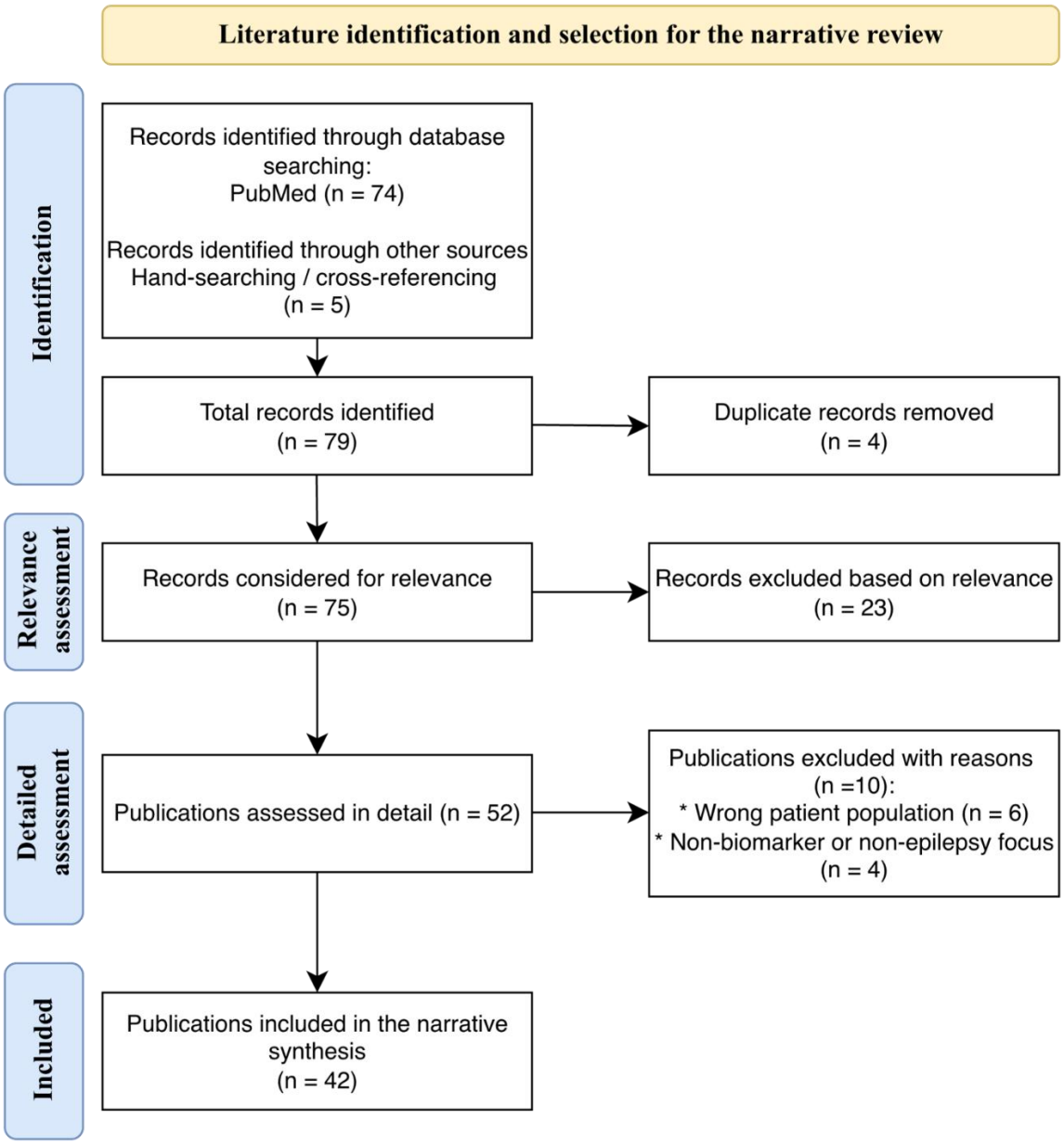

Figure 1. Literature identification and selection process for the narrative review.

3. RESULTS AND DISCUSSION

Structural and Glial Fluid Biomarkers

In pediatric epilepsy, structural and glial fluid biomarkers have been investigated as potential indicators of neuronal injury and astroglial activation associated with seizures. Candidate fluid biomarkers investigated in pediatric epilepsy include neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), S100 calcium-binding protein B (S100B), and neuron-specific enolase (NSE) (Pitkänen et al., 2016). Even though these biomarkers may provide information about brain injury linked to seizures and the severity of the disease, none of them has yet been validated for use in clinical practice in pediatric epilepsy.

Neurofilament Light Chain (NfL)

Neurofilament light chain (NfL) is a structural protein found in myelinated axons and passes into cerebrospinal fluid and blood as a result of neuroaxonal damage. Owing to advances in ultrasensitive immunoassays, in particular the single-molecule array (Simoa), it is now possible to measure circulating NfL accurately. It has thus become one of the most well-characterized fluid markers of neuroaxonal damage (Khalil et al., 2024).

NfL has long been considered an indicator of neuroaxonal damage resulting from seizures in people with epilepsy. In children, though, the evidence for an acute increase in serum NfL following seizures is limited and inconsistent. In a prospective study with young children, Evers et al. found that there was no significant increase in serum NfL after either febrile or epileptic seizures. Neither the length of the seizure nor the time that passed between the onset of the seizure and the moment the blood sample was taken had any significant influence on NfL levels (Evers et al., 2020). Abdelhak et al., (2023) also found no significant differences in serum NfL among children who had epileptic seizures, children who had febrile seizures, and the control group, even though the number of children in the subgroup with epileptic seizures was very small (n=6). On the other hand, a previous multicentre study looking at pediatric CSF biomarkers found that NfL levels in the CSF were higher in some children with neurological disorders, with especially high concentrations noted in some children with status epilepticus, indicating that prolonged seizures may be associated with greater neuroaxonal injury (Shahim et al., 2013). In contrast, in adult patients with status epilepticus, both serum and CSF NfL concentrations are increased, and serum NfL seems to rise as the duration of status epilepticus increases (Margraf et al., 2023; Schlabitz et al., 2026). Importantly, circulating NfL levels depend strongly on age in childhood, and age-adjusted reference values for children have therefore been developed (Abdelhak et al., 2023). NfL thus remains a promising biomarker of neuroaxonal injury, but its relevance in relation to seizures and its prognostic value in pediatric epilepsy are still not sufficiently established.

Glial Fibrillary Acidic Protein (GFAP)

Glial fibrillary acidic protein (GFAP) is an intermediate filament protein that is mainly produced by astrocytes and is released after there has been astroglial activation or injury. It has come to be considered a possible biomarker of seizure-related damage to astrocytes since astrocytes play a role in neuronal excitability, in the integrity of the blood–brain barrier, and in neuroinflammation (Banote et al., 2022).

In a pediatric case-control study, the levels of circulating GFAP were found to be significantly higher in children who had epilepsy as compared to the healthy control group, especially in children who had active or generalized seizures, and there was an association between GFAP levels and the severity of the seizures (Elhady et al., 2021). Many of the studies involved relatively small numbers of participants, limiting the precision and generalizability of between-group comparisons. Above all, raised GFAP levels are not specific to epilepsy since they can also be found in cases of brain injury, stroke, tumors, and a variety of other neurological disorders (Banote et al., 2022). As a result, GFAP may offer insights into astroglial cell responses to seizures, but its clinical usefulness in pediatric epilepsy has not yet been established (Khalil et al., 2024).

S100 Calcium-Binding Protein B (S100B)

S100 calcium-binding protein B (S100B) is mainly produced by astrocytes and has been used as a marker of astroglial activation and blood–brain barrier dysfunction. In the case of pediatric epilepsy, increased levels of serum S100B have been observed in children who have recently developed epilepsy (Zhu et al., 2018). Yet the results vary among different groups of children with seizures. For example, children with simple febrile seizures did not have significantly higher serum S100B levels than either febrile or healthy controls. Similarly, a subsequent meta-analysis found no significant difference between children with febrile seizures and those with fever but no seizures as controls, indicating that factors other than seizure activity may be responsible for the rise in S100B (Atici et al., 2012; Huang et al., 2021). Even though S100B might indicate astroglial or blood–brain barrier reactions associated with epilepsy, its lack of specificity regarding the disease and its dependence on the clinical context as well as the time at which the sample is taken limit its usefulness as a routine biomarker in pediatric epilepsy. S100B levels can likewise be raised in other neurological disorders, for example, traumatic brain injury, stroke, and infections of the central nervous system, thereby decreasing its diagnostic specificity (Marchi et al., 2004). Moreover, the association between S100B levels and seizure characteristics or clinical severity has not been consistent across different studies. When interpreting S100B levels, it is necessary to consider the time at which the sample was taken in relation to the seizure. To conclude, the existing evidence does not support the routine use of S100B as a biomarker in children with epilepsy.

Neuron-Specific Enolase (NSE)

Neuron-specific enolase (NSE) is a glycolytic enzyme primarily found in neurons and neuroendocrine cells (Isgrò et al., 2015). After neuronal injury, NSE can be released into both the cerebrospinal fluid and the blood, thus making it a possible indicator of neuronal injury.

In the case of pediatric epilepsy, the evidence concerning NSE is varied. An early study involving 49 children showed that there was no general difference in CSF NSE levels between children who had seizures and those who did not; yet, very high NSE levels were seen in a small group of children with medically intractable status epilepticus whose condition had a metabolic or genetic cause (Wong et al., 2002). More recent evidence indicates that NSE might have a prognostic value in cases of pediatric status epilepticus.

A retrospective study of 132 children with convulsive status epilepticus found that serum NSE measured within 48 hours of admission was independently associated with poor neurological outcome and showed good discrimination for in-hospital mortality in this single-center cohort. However, the study was single-center and retrospective, and the incremental prognostic value of NSE beyond established clinical severity measures requires further validation (Yavuz and Bingol, 2026). There was a great deal of variability between the studies (I^2 = 96.7%), which hampers the interpretation of the pooled estimates (Mu et al., 2020). NSE is not specific to epilepsy, and its levels can also be increased in other conditions involving neuronal injury, while sample hemolysis can lead to artificially high serum concentrations (Isgrò et al., 2015). As a result, even though NSE is a possible marker of neuronal injury and may have prognostic potential in pediatric status epilepticus, the current evidence is still not adequate to recommend its regular use in the clinical management of pediatric epilepsy.

Molecular and Systemic Biomarkers

Molecular biomarkers have emerged as promising tools for investigating the pathophysiology of epilepsy and identifying potential markers of disease activity and prognosis. Among molecular biomarkers, microRNAs and inflammatory mediators have received considerable attention because of their potential roles in neuronal excitability, neuroinflammation, and epileptogenesis (Henshall et al., 2016; Pitkänen et al., 2016; Vezzani et al., 2019). Although alterations in these biomarkers have been reported in pediatric epilepsy, their clinical usefulness remains under investigation because of methodological variability and limited external validation.

MicroRNAs

MicroRNAs are small noncoding RNA molecules that regulate post-transcriptional gene expression by modulating mRNA translation and degradation. They participate in numerous biological processes, including neuronal development, synaptic plasticity, neuroinflammation, and apoptosis, all of which have been involved in epileptogenesis (Henshall et al., 2016; Pitkänen et al., 2016).

Several circulating microRNAs have been looked at as possible biomarkers in pediatric epilepsy. In a pediatric study of children with idiopathic generalized epilepsy, serum miR-155 and miR-223 were elevated in children with epilepsy compared with controls, while miR-146a, miR-155, and miR-223 were higher in children with drug-resistant than drug-responsive epilepsy (Çarman et al., 2023).

More recent evidence indicates that circulating miR-134-3p and miR-155-5p may be associated with seizure control in children with epilepsy (Yang et al., 2025). In a prospective longitudinal cohort, Salimbene et al., (2026) found that miR-15a-5p, miR-106b-5p, miR-146a-5p and miR-152-3p were significantly upregulated in children with epilepsy when compared to healthy controls. There is now evidence showing that the expression of miR-15a-5p and miR-106b-5p is linked to seizure frequency. The variability observed in the miRNA profiles reported in different studies can be attributed to differences in the patient groups, the causes of epilepsy, the biological samples used, the normalization procedures, the analytical methods, and sampling times. Although these findings are promising, circulating microRNAs have not yet been sufficiently externally validated for routine clinical use in pediatric epilepsy (Henshall et al., 2016; Salimbene et al., 2026).

Inflammatory Markers

Increasing evidence suggests that neuroinflammation contributes to seizure generation and epileptogenesis through activation of innate immune pathways, disruption of the blood–brain barrier, and modulation of neuronal excitability. Accordingly, numerous inflammatory mediators have been investigated as candidate biomarkers of seizure-related inflammatory activation (Vezzani et al., 2019).

In children with seizure disorders and epilepsy, there have been reports of increased inflammatory mediators, but the findings differ depending on the type of seizure, the severity of the disease, when the sample was taken, and the extent of treatment exposure.

In children who have recently developed epilepsy, the levels of serum HMGB1, IL-1β, S100B, and GFAP were found to be significantly higher than those in healthy controls when measured within 24 hours of the seizure, and HMGB1 and IL-1β were associated with subsequent seizure frequency and showed prognostic potential (Zhu et al., 2018). In children with febrile seizures, HMGB1 and IL-1β were also increased compared with fever-only controls, while IL-6 was elevated in children with typical febrile seizures (Choi et al., 2011). Moreover, children with severe epilepsy, defined in one study as having at least one seizure per week despite treatment with three or more antiseizure medications, had higher serum HMGB1, TLR4, TNF-α, and IL-1β concentrations than children with milder epilepsy and healthy controls (Kamaşak et al., 2020).

Even though these results have been obtained, inflammatory biomarkers are not specific to epilepsy, and changes in their concentrations might be affected by the timing of sampling, infection, treatment, and other systemic inflammatory processes. Furthermore, differences in the groups of patients studied, the intervals at which samples were taken, and the analytical techniques used make it difficult to compare the studies. As a result, even though inflammatory biomarkers offer useful information regarding the mechanisms of epileptogenesis, their value as diagnostic and prognostic tools in pediatric epilepsy has not been sufficiently validated.

Metabolomics

Metabolomics involves comprehensive profiling of small molecules involved in cellular metabolism and can provide a functional overview of cellular physiology. Since seizures are linked to changes in energy metabolism, in the neurotransmitter pathways, and in other metabolic processes, metabolomic profiling has become a promising method for finding potential biomarkers in epilepsy (Johnson et al., 2016; Lai et al., 2022). Studies using metabolomics in children have found alterations in metabolic pathways that involve amino acids, energy metabolism, and other small molecules, but the particular metabolites detected have differed between cohorts and biological samples. A study used metabolomics to identify and relate CSF metabolites in children with status epilepticus to their subsequent neurological status. A model combining these two metabolites for predicting neurological outcome achieved an AUC of 0.976. However, the study had limitations due to the small number of participants and the absence of external validation (Wang et al., 2023).

In a multicentre prospective study involving children with newly developed epilepsy who had not been treated, only taurine was found to be reduced in the epilepsy group in both GC/MS/MS and LC/MS/MS analyses. Absolute quantification of the amino acids did in fact confirm the decrease in taurine, but because of the small number of subjects, the strength of this conclusion is limited (Akiyama et al., 2024). A more recent small case-control study that used plasma metabolomics has identified changes in tryptophan metabolism and several metabolites derived from the gut microbiota in children with epilepsy, further supporting the potential of metabolomics for biomarker discovery (Chojnowski et al., 2025).

Although the findings are promising, metabolomic biomarkers are still mainly in the investigational phase. Differences in analytical platforms, biological specimens, patient populations, age, diet, antiseizure medication exposure, and sampling time may contribute to variability between studies. Consequently, large-scale studies in multiple centers using the same tools for sample measurement and external validation are required to make use of metabolomic data for clinical purposes.

Genetic and Epigenetic Biomarkers

Genetic and epigenetic approaches have greatly improved our understanding of pediatric epilepsy by offering insights into disease mechanisms, aiding diagnosis, supporting prognostic assessment, and indicating possible therapeutic targets. Although genetic testing is now an essential part of the diagnostic evaluation of various forms of childhood epilepsy, especially those involving developmental and epileptic encephalopathies, epigenetic biomarkers are still mainly in the investigational stage (Krey et al., 2022; Scheffer et al., 2017).

In a number of pediatric epilepsy syndromes, pathogenic variants have been found in the genes that code for ion channels, synaptic proteins, and regulators of neuronal development. Examples include SCN1A, SCN2A, KCNQ2, STXBP1, and CDKL5. Genetic testing is able to aid in an early diagnosis, enhance the etiologic classification, provide information for prognostic assessment, and, in certain cases, help direct precision therapies, for example, treatment selection in Dravet syndrome may be influenced by the identification of pathogenic SCN1A variants, with avoidance of seizure-aggravating sodium-channel blockers being an important consideration (Krey et al., 2022; Symonds and McTague, 2020). Thus, genetic testing has already achieved clinical implementation in selected epilepsy syndromes.

Epigenetic mechanisms—such as DNA methylation, histone modifications, and noncoding RNAs—play a role in the regulation of gene expression without changing the DNA sequence and have been linked to epileptogenesis (Kobow and Blümcke, 2018). In epilepsy, altered DNA methylation patterns and dysregulated microRNA expression have been found, indicating that they may be involved in the disease mechanisms and could have potential applications in biomarker development. Yet these findings are still in their early stages and are hampered by considerable methodological variability, which limits the reproducibility of the results across different studies. More research is required to find out whether epigenetic biomarkers can offer clinically useful information in addition to that provided by existing genetic testing.

Neuroimaging and Electrophysiology

The use of neuroimaging and electrophysiological techniques is central to the diagnosis and evaluation of epilepsy and has also enabled the identification of quantitative features that are being investigated as candidate neurodiagnostic biomarkers. Progress in magnetic resonance imaging, electroencephalography, and computational analysis has broadened the study of the structural and functional abnormalities linked with epileptogenesis and seizure propagation (Frauscher et al., 2017; Pitkänen et al., 2016).

More advanced techniques, including diffusion tensor imaging (DTI) and functional MRI (fMRI), are able to give information about microstructural and functional network abnormalities which might not be obvious from conventional structural imaging (Bernasconi et al., 2019). Quantitative EEG analyses have looked at features such as high-frequency oscillations and functional connectivity, and machine-learning methods have in recent years been applied to these data in order to improve seizure localization and the characterization of epileptogenic networks as well as to assist in the presurgical assessment (Frauscher et al., 2017). More recent evidence from children has also investigated non-invasive electrophysiological markers of an excitation–inhibition imbalance. Children with epilepsy, as studied by Rijal et al., (2025), displayed altered visually evoked and induced beta- and gamma-band oscillations using high-density EEG and magnetoencephalography. It is important to note that children with epilepsy exhibited reduced amplitudes and longer latencies in these oscillatory responses as compared to neurotypical controls. Nevertheless, these features need to be validated before they can be used clinically, and their connection to the underlying excitation–inhibition imbalance should also be established. Although the findings are promising, many quantitative electrophysiological biomarkers are still mainly limited to research settings or to specialized epilepsy centers and must undergo independent validation, as well as the establishment of standardized procedures for data acquisition and analysis, together with evaluation among diverse groups of children, before they can be widely adopted in a clinical context.

Biomarkers used in neuroimaging and electrophysiological studies have great potential to supplement the clinical evaluation of the individual patient with epilepsy. Beyond neural signals and imaging, non-invasive physiological measures have also been investigated as complementary biomarkers for seizure forecasting. One potential application of these biomarkers is seizure forecasting. In children with epilepsy, cardiovascular variables (such as heart rate and heart-rate variability), electrodermal activity, and body temperature have all been looked at as possible predictors of seizures. A systematic review of the research into seizure forecasting in children with epilepsy was carried out Esparza et al., (2026). Furthermore, a great many of the studies did not give sufficient details regarding false-positive rates, a piece of information that is important when assessing systems that predict seizures. Hence, there is a need for large-scale studies involving children with epilepsy and using standardized monitoring over extended periods to determine their potential clinical utility for seizure forecasting.

Future multicenter studies that combine imaging, electrophysiological, physiological, and molecular biomarkers could help to achieve more accurate diagnosis, better prognostic stratification, and more personalized treatment approaches. A summary of the main biomarker domains, including their suggested clinical applications, translational status, and existing limitations, is given in Table 1.

Table 1. Candidate biomarker domains studied in pediatric epilepsy.

*Translational status reflects the level of evidence available in pediatric epilepsy and does not imply established clinical validity or clinical utility. Neuroimaging and electrophysiological entries refer to quantitative features being investigated as candidate neurodiagnostic biomarkers rather than universally validated biomarkers. Table compiled and adapted by the authors from the studies cited in the corresponding sections of the manuscript.

Biomarker domain	Representative biomarkers	Specimen / modality	Proposed clinical application	Translational status*	Main limitations
Genetic	Pathogenic variants in *SCN1A, SCN2A, KCNQ2, STXBP1,*	Blood (DNA)	Etiologic diagnosis, prognostic assessment, treatment selection,	Established in selected epilepsy syndromes	Variant interpretation, limited genotype–phenotype correlation

	CDKL5		precision medicine		
Epigenetic	DNA methylation, histone modifications, noncoding RNAs	Blood, brain tissue	Disease classification, treatment-response research, epileptogenesis research	Investigational	Tissue specificity, methodological variability, limited validation
Axonal injury	NfL	Serum, plasma, CSF	Assessment of neuroaxonal injury, disease monitoring	Investigational	Low disease specificity, age dependence
Glial injury	GFAP, S100B	Serum, plasma, CSF	Assessment of astroglial injury/activation and blood–brain barrier responses	Investigational	Low disease specificity, timing of sampling, clinical heterogeneity
Neuronal injury	NSE	Serum, CSF	Assessment of seizure-related neuronal injury, prognostic assessment in status epilepticus	Investigational	Hemolysis, limited specificity
Inflammatory	IL-1β, IL-6, TNF-α, HMGB1	Blood, CSF	Assessment of neuroinflammatory activity, prognostic research	Investigational	Temporal variability, systemic inflammation, limited disease specificity
Transcriptomic	miR-146a, miR-155, miR-223, miR-134-3p, miR-15a-5p, miR-106b-5p	Serum, plasma	Diagnosis, assessment of seizure burden, drug-resistant epilepsy	Investigational	Lack of assay standardization, heterogeneous expression patterns, inconsistent replication
Metabolomic	Taurine, glutamyl-glutamine, 3-iodothyronamine, tryptophan-related metabolites	Plasma, urine, CSF	Metabolic phenotyping, biomarker discovery, prognostic research	Investigational	Biological and analytical variability, diet- and age-dependent effects, antiseizure medication exposure, limited external validation
Neuroimaging	Quantitative MRI features, DTI measures, fMRI network measures	MRI	Lesion detection, network characterization, presurgical evaluation	Specialized or investigational	Technical and methodological variability, specialized expertise, limited availability, lack of standardized quantitative thresholds
Electrophysiologic	High-frequency oscillations, EEG connectivity, quantitative EEG, beta/gamma oscillatory features	EEG/MEG	Seizure localization, prognostic assessment, seizure forecasting, assessment of excitation–inhibition imbalance	Specialized or investigational	Lack of standardized acquisition and interpretation, methodological variability, limited external validation, specialized expertise

Clinical Applications

Biomarkers have been investigated for a wide range of clinical purposes, including etiologic classification, prognostic assessment, disease monitoring, the evaluation of treatment response, the prediction of seizures, and presurgical assessments. Evidence obtained for one clinical application does not automatically extend to another. Although there has been significant progress in biomarker research, only a small number of candidate biomarkers have so far been adopted into routine clinical practice in the case of pediatric epilepsy. The possible applications of these biomarkers include assisting diagnosis, providing prognostic assessment, enabling disease monitoring, aiding treatment selection, identifying cases of drug-resistant epilepsy, and supporting precision medicine. However, most

current evidence shows only biological associations, not proven clinical usefulness. It is important to note that the detection of a measurable association with epilepsy does not in itself mean that a clinically useful biomarker has been established. Candidate biomarkers must go through a series of stages involving analytical validation, clinical validation, assessment of clinical utility, and finally their implementation into routine practice. Consequently, any quantitative abnormalities detected by MRI, EEG, or other electrophysiological techniques should be considered as candidate neurodiagnostic biomarkers unless their reproducibility, diagnostic or prognostic performance, and clinical utility have been independently verified.

Genetic testing represents the most advanced biomarker-based approach in terms of clinical application. Genetic testing is now recommended or strongly considered in many children with developmental and epileptic encephalopathies, since this helps to establish the cause of their condition, allows for a prognosis to be assessed, enables genetic counseling, and in some cases can guide the choice of treatment. When pathogenic variants are identified in genes such as SCN1A, SCN2A, or KCNQ2, the molecular diagnosis can in some cases influence therapeutic decisions and contribute to precision medicine (Scheffer et al., 2017; Wirrell et al., 2017).

Biomarkers that are fluid in nature—such as NfL, GFAP, S100B, NSE, inflammatory cytokines, and circulating microRNA—have not yet been established as routine clinical biomarkers in pediatric epilepsy. Even though some studies have found associations between these biomarkers and seizure burden, neuronal injury, drug-resistant epilepsy, or the severity of the disease, their regular use in a clinical context is still limited due to the lack of disease specificity, methodological heterogeneity, and the fact that there are no standardized pediatric reference ranges or validated diagnostic thresholds (Khalil et al., 2024; Pitkänen et al., 2016).

Just as quantitative neuroimaging and electrophysiological biomarkers hold considerable promise for improving seizure localization, prognostic assessment, and presurgical evaluation, advanced MRI techniques, quantitative EEG analyses, and machine learning methods could offer information that goes beyond what is available through conventional imaging and visual EEG interpretation. However, these methods do require specialized expertise, standardized acquisition and analysis protocols, and prospective multicentre validation before they can be used in routine pediatric epilepsy care (Bernasconi et al., 2019; Frauscher et al., 2017).

Clinical practice in the future might come to depend more and more on multimodal biomarker approaches that combine molecular, genetic, neuroimaging, and electrophysiologic data to enhance diagnostic accuracy, prognostic stratification, and the ability to plan individualized treatment. Yet it is necessary to have large prospective studies showing analytical validity, clinical validity, and clinical utility before most of the candidate biomarkers can be introduced into routine use.

Limitations

The review has several limitations. To begin with, since it is a narrative review, it is prone to selection bias and does not use the systematic approach that is employed in a formal systematic review or meta-analysis. Even though a structured literature search was carried out, studies not indexed in PubMed or not identified within the predefined search period may have been missed, although earlier publications were included when they provided relevant foundational or methodological evidence.

Moreover, the existing evidence concerning biomarkers in pediatric epilepsy is hindered by small study populations, heterogeneity in epilepsy syndromes and clinical phenotypes, variability in the biological samples and analytical techniques used, and the use of inconsistent outcome measures. Many potential biomarkers have been assessed in single-center studies without external validation, which reduces the generalizability and reproducibility of the reported results. Age-related physiological changes represent an additional challenge when interpreting biomarker data in children, while further heterogeneity arises from differences in age and developmental stage, epilepsy etiology and syndrome, seizure characteristics, antiseizure medication exposure, and timing of biomarker sampling.

As a result, although many biomarkers have shown biological relevance and hold potential for clinical use, most are still in the investigational stage. Before they can be incorporated into routine pediatric epilepsy care, further large-scale, multicenter studies are needed. Lastly, a biological association should not be taken as proof of clinical usefulness; statistically significant differences in biomarker levels do not by themselves demonstrate that biomarker-guided assessment improves diagnosis, prognostic evaluation, treatment selection, or patient outcomes.

Future Directions

Future research should determine age-specific reference values, carry out independent external validation, examine the calibration of predictive models, use standardized or harmonized analytical methods, and provide transparent reporting of the performance of both

diagnostic and prognostic tests. Prospective longitudinal studies should also evaluate how biomarker levels change over time and, when biomarkers are used to assess treatment response, evaluate them before, during, and after treatment.

A key area for future research is to combine molecular, genetic, neuroimaging, electrophysiological, and physiological biomarkers into multimodal models that integrate complementary data types. Artificial intelligence and machine-learning methods may facilitate the integration and analysis of multimodal biomarker data, but their clinical implementation will likewise require adequately powered multicenter validation and assessment of generalizability. Such approaches may ultimately improve diagnostic accuracy, prognostic stratification, and treatment individualization if their clinical utility is demonstrated. Ultimately, translation of candidate biomarkers into routine clinical care will require not only analytical and clinical validation but also evidence of clinical utility, including demonstration that biomarker-guided use improves patient outcomes or clinical decision-making.

4. CONCLUSION

Research into biomarkers in children with epilepsy has found a large number of candidate biomarkers that could be used for diagnosis, prognosis assessment, disease monitoring, seizure forecasting, and treatment selection. Among the biomarker approaches reviewed, genetic testing has reached the most advanced level of clinical application, particularly in selected pediatric epilepsy syndromes. Other biomarkers, including fluid, molecular, neuroimaging, electrophysiological, and physiological measurements, are still mainly in the investigational stage, and their incorporation into clinical practice is limited due to methodological heterogeneity, inadequate external validation, and, in some cases, the absence of standardized reference values for children.

Multidisciplinary research combining genomics, neuroimaging, electrophysiology, and computational analysis could accelerate the development of precise methods for managing pediatric epilepsy. Yet in order for possible biomarkers to be incorporated into standard care for children with epilepsy, there will need to be solid evidence of their analytical validity, clinical validity, and clinical utility, including proof that using the biomarkers leads to meaningful benefits for patients or for clinical decision-making.

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Informed consent

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Ethical approval

Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

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Conflict of interest

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on the reasonable request to the corresponding author.

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