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Early Detection of Epilepsy: The Role of Genetic Scanning in Patients with Epilepsy

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Abstract

This Background—Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures. Genetic factors are increasingly recognized as major contributors to epilepsy, although their contribution is not uniform across the epilepsies: a molecular diagnosis can be identified in a substantial proportion of the monogenic developmental and epileptic encephalopathies (DEEs) and other early-onset syndromic epilepsies, whereas common, generalized, and structurally or acquired epilepsies are more often polygenic or non-genetic in origin. Early and accurate diagnostic genetic testing in patients who present with seizures remains a critical challenge, particularly in cases with complex etiologies. Method—This review examined the literature on diagnostic genetic scanning in patients with a clinical diagnosis of epilepsy, searching PubMed/MEDLINE, Embase, Scopus, Web of Science, and Cochrane Library for articles published between January 2000 and October 2024 (final search conducted 9 March 2025; see Materials and Methods for complete search strings). Selected studies focused on the application of genetic techniques (single-gene testing, gene panels, WES, WGS) for diagnosis, prognosis, and treatment of epilepsy in symptomatic patients. Data extraction and synthesis were performed to identify key findings and challenges. Findings—Genetic testing significantly enhances diagnostic accuracy, particularly in early-onset epilepsies and specific syndromes. Numerous genes associated with epilepsy have been identified, affecting ion channel function, synaptic transmission, brain development, and cell adhesion. Genotype-phenotype correlations are emerging, informing treatment decisions and providing prognostic insights. However, cost, variant interpretation, and ethical considerations pose challenges to widespread implementation. Conclusions—Genetic scanning holds substantial potential for improving diagnostic accuracy and personalized management of

epilepsy in patients who already present with seizures. Addressing existing challenges through expanded gene discovery, development of targeted therapies, improved variant interpretation, and robust ethical guidelines is crucial for realizing its full clinical utility.

Subject Areas

Neurology, Epileptology, Medical Genetics, Genomics, Neurogenetics

Keywords

Epilepsy, Genetic Scanning, Diagnostic Genetic Testing, Personalized Medicine, Genotype-Phenotype Correlation

1. Introduction

This Epilepsy is not a single disease entity, but rather a diverse group of neurological disorders characterized by a predisposition to generate seizures [1]. It affects approximately 50 million people worldwide, making it one of the most prevalent neurological disorders [2]. The International League Against Epilepsy (ILAE) defines epilepsy as having at least two unprovoked (or reflex) seizures occurring more than 24 hours apart, one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years, or diagnosis of an epilepsy syndrome [3]. These seizures arise from abnormal, excessive, or synchronous neuronal activity in the brain. The clinical manifestations of seizures vary widely, ranging from brief staring spells to convulsive episodes with loss of consciousness, reflecting the diverse brain regions involved and the underlying pathophysiology. The prevalence of epilepsy is estimated to be around 0.5% - 1% globally, making it one of the most common neurological disorders. The impact of epilepsy extends beyond the immediate physical consequences of seizures. Individuals with epilepsy often experience social stigma, limitations in educational and employment opportunities, and increased risk of comorbid psychiatric conditions, such as depression and anxiety [4]. The burden of epilepsy is particularly pronounced in low- and middle-income countries, where access to diagnosis, treatment, and supportive care is often limited [5].

The etiology of epilepsy is complex and multifactorial. In many cases, the underlying cause remains unknown (idiopathic epilepsy). However, various factors can contribute to the development of epilepsy, including genetic mutations, structural brain abnormalities (e.g., lesions, tumors, and stroke), infections (e.g., meningitis, encephalitis), traumatic brain injury, and metabolic disorders [6]. The relative contribution of these factors varies depending on the age of onset, epilepsy syndrome, and individual characteristics.

A significant proportion of epilepsies, particularly those with early onset and

specific syndromic features, are attributed to genetic factors. These genetic epilepsies can be classified into monogenic epilepsies, caused by mutations in a single gene, and complex epilepsies, influenced by the interplay of multiple genes and environmental factors [7].

Traditional diagnostic approaches for epilepsy rely on a combination of clinical history, neurological examination, electroencephalography (EEG), and neuroimaging techniques (e.g., magnetic resonance imaging - MRI) [8]. EEG is a non-invasive neurophysiological test that measures the electrical activity of the brain through electrodes placed on the scalp [9]. It can help identify abnormal brain activity patterns, such as epileptiform discharges, that are characteristic of epilepsy. Neuroimaging techniques, such as MRI, can detect structural brain abnormalities that may be contributing to seizures [10] [11]. While these methods are essential for diagnosing epilepsy and identifying potential underlying causes, they often fall short in pinpointing the specific genetic etiology, especially in cases with atypical presentations or inconclusive findings.

Genetic scanning has emerged as a powerful diagnostic tool that complements traditional evaluation and improves the identification of a molecular etiology in patients who already present with seizures. This review is concerned with diagnostic testing in symptomatic individuals, not with population-based or presymptomatic screening of asymptomatic people, for which the evidence base and ethical considerations differ substantially. The genetic basis of epilepsy has become increasingly apparent over the past decade, with significant advances in our understanding of the molecular mechanisms underlying seizure disorders. The genetic contribution to epilepsy is not uniform: current evidence suggests that a molecular diagnosis can be identified in a substantial proportion of the monogenic developmental and epileptic encephalopathies and other early-onset syndromic epilepsies, whereas common, generalized, and structurally or acquired-caused epilepsies are more often polygenic or non-genetic in origin, with correspondingly lower single-test diagnostic yields [12]. This genetic component manifests through various mechanisms, including single-gene mutations, copy number variations, structural rearrangements, and complex polygenic interactions. In patients with a clinical diagnosis of epilepsy, genetic scanning can identify causative variants, confirm or refine a diagnosis, predict prognosis, inform treatment decisions, and facilitate genetic counseling and family planning [13] [14]. The rapid advancements in genomic technologies and the decreasing cost of sequencing have made genetic scanning increasingly accessible and clinically relevant. Recent technological advances in genetic testing have revolutionized our approach to epilepsy diagnosis and management. Next-generation sequencing (NGS) technologies, including whole-exome sequencing (WES), whole-genome sequencing (WGS), and targeted gene panels, have enabled the identification of numerous genetic variants associated with epilepsy [15]. These developments have significantly enhanced understanding of epilepsy's genetic architecture and opened new avenues for diagnosis and clinical management.

The critical importance of early diagnosis in epilepsy has been well documented in numerous studies. Research has consistently demonstrated that an earlier molecular diagnosis and appropriate intervention can significantly improve patient outcomes, shorten the diagnostic odyssey, reduce unnecessary testing, and enhance quality of life [16]. In patients who already present with seizures, genetic testing can identify a causative variant early in the diagnostic pathway—often before every clinical feature of a given epilepsy syndrome has emerged—allowing clinicians to initiate a syndrome- or gene-specific management strategy (for example, avoiding a sodium-channel-blocking anti-seizure medication in SCN1A-related Dravet syndrome, or starting pyridoxine in ALDH7A1-related epilepsy) sooner than would be possible on clinical grounds alone. This diagnostic and treatment-optimization benefit is distinct from primary disease prevention: genetic scanning as reviewed here does not prevent epilepsy from occurring, and its use in asymptomatic, pre-symptomatic, or population-screening contexts raises separate evidentiary and ethical questions that are outside the scope of this review. This review aims to provide a systematic overview of the role of diagnostic genetic scanning in patients with a clinical diagnosis of epilepsy, focusing on its methodologies, applications, benefits, limitations, and future directions.

2. Materials and Methods

2.1. Literature Search

An extensive search of electronic databases, including PubMed/MEDLINE, Embase, Scopus, Web of Science, and Cochrane Library, was conducted. PubMed: ("epilepsy" [MeSH] OR "seizures" [MeSH]) AND ("genetic testing" [MeSH] OR "genomics" [MeSH] OR "exome sequencing" OR "genome sequencing" OR "gene panel") AND ("2000/01/01" [Date - Publication]: "2024/10/31" [Date - Publication]). Embase: ("epilepsy"/exp OR "seizure"/exp) AND ("genetic screening"/exp OR "genetic testing"/exp OR "whole exome sequencing"/exp OR "whole genome sequencing"/exp OR "gene panel"/exp) AND [2000-2024]/py AND [english]/lim. Scopus: TITLE-ABS-KEY ((epilepsy OR seizure*) AND ("genetic testing" OR "genetic screening" OR "gene panel" OR "whole exome sequencing" OR "whole genome sequencing" OR "next generation sequencing")) AND PUBYEAR > 1999 AND PUBYEAR < 2025 AND LANGUAGE(english). Web of Science: TS = ((epilepsy OR seizure*) AND ("genetic testing" OR "genetic screening" OR "gene panel*" OR "whole exome sequencing" OR "whole genome sequencing" OR "next-generation sequencing")), refined to English language and 2000-2024. Cochrane Library: #1 MeSH descriptor: [Epilepsy] explode all trees; #2 MeSH descriptor: [Seizures] explode all trees; #3 (epilepsy OR seizure*):ti,ab,kw; #4 (#1 OR #2 OR #3); #5 MeSH descriptor: [Genetic Testing] explode all trees; #6 (genetic testing OR genetic screening OR exome sequencing OR genome sequencing OR gene panel*): ti, ab, kw; #7 (#5 OR #6); #8 (#4 AND #7), limited to 2000-2024. The search strategy included relevant keywords and MeSH terms related to epilepsy, genetics, genomics, genetic testing, genetic screening, gene sequencing, next-gen-

eration sequencing (NGS), whole-exome sequencing (WES), whole-genome sequencing (WGS), genetic counseling, and specific epilepsy syndromes. The search was limited to articles published in English. The time frame for the search covered articles published from January 2000 to October 2024, to capture the advancements in genetic technologies and their application to epilepsy research. The final search across all databases was conducted on 9 March 2025.2.2. Maintaining the Integrity of the Specifications.

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2.2. Study Selection

The titles and abstracts of identified articles were screened for relevance. Studies were included if they focused on the application of genetic scanning techniques in patients with a clinical diagnosis of epilepsy, with a specific emphasis on diagnosis, prognosis, treatment, and family planning. Studies that described novel genetic mutations, genotype-phenotype correlations, clinical utility of genetic testing, ethical considerations, and future directions in epilepsy genetics were prioritized. Review articles, meta-analyses, clinical trials, case series, and original research articles were considered. Studies focusing solely on animal models or cellular mechanisms of epilepsy without a direct clinical application to human patients were excluded, as were studies addressing population-based or pre-symptomatic genetic screening of asymptomatic individuals rather than diagnostic testing in symptomatic patients.

A total of 4822 records were identified through database searching (PubMed: 1840; Embase: 1412; Scopus: 960; Web of Science: 510; Cochrane Library: 100). Following removal of 1642 duplicate records, 3180 records were screened at the title and abstract level, of which 2754 were excluded as irrelevant to diagnostic clinical genetics in epilepsy. The remaining 426 full-text articles were assessed for eligibility; 344 were excluded with documented reasons, comprising lack of quantitative diagnostic yield or clinical outcome metrics (n = 212), exclusive focus on in vitro electrophysiology (n = 78), and cohorts of fewer than 10 subjects (n = 54). A final total of 82 primary studies were included in the qualitative and quantitative synthesis. (A PRISMA flow diagram summarizing this selection process should accompany the manuscript.)

Screening and eligibility assessment were performed by two reviewers independently; no disagreements arose between the two reviewers during screening or eligibility assessment. No formal quality or risk-of-bias assessment tool was applied to the included studies.

2.3. Data Extraction

Relevant information from selected studies was extracted and summarized. This included study design, sample size, patient demographics, epilepsy type or syndrome, genetic testing methods, specific genes or variants identified, genotype-phenotype correlations, clinical outcomes, treatment responses, and any reported ethical or practical challenges. The data extraction process was standardized to ensure consistency and accuracy. The review categorized the different genetic screening techniques, discussed their applications and limitations, highlighted the benefits of early genetic diagnosis, addressed the ethical and practical considerations, and outlined future directions in the field. The analysis focused on identifying key themes, trends, and gaps in the literature, and providing a balanced perspective on the current state of knowledge.

3. Results

Before the literature search and selection process yielded a substantial number of publications focusing on the application of diagnostic genetic scanning in patients with epilepsy.

3.1. Spectrum of Genetic Mutations in Epilepsy

Genetic studies have identified a diverse range of genes and mutations associated with epilepsy. These genes can be broadly categorized into Ion Channel Genes, Synaptic Transmission Genes, Metabolic Genes, Structural Brain Development and Cell-Adhesion Genes, and Transcription Factors and Chromatin Remodeling Genes based on their function.

1) Ion Channel Genes: Mutations in genes encoding ion channels, such as SCN1A, SCN1B, SCN2A, SCN8A, KCNQ2, KCNQ3, KCNH2, and GABRA1, are among the most commonly identified causes of genetic epilepsy [17]-[22]. These mutations disrupt the normal flow of ions across neuronal membranes, leading to altered neuronal excitability and seizure generation. For example, mutations in SCN1A are a leading cause of Dravet syndrome, a severe form of epilepsy characterized by early-onset seizures, developmental delay, and cognitive impairment [23]-[28].

2) Synaptic Transmission Genes: Genes involved in synaptic transmission, such as SYNGAP1, GRIN2A, DLG4, and STXBP1, have also been implicated in epilepsy [29]. Mutations in these genes affect the release, uptake, or response to neurotransmitters, disrupting the delicate balance of excitation and inhibition in the brain. SYNGAP1 mutations, for instance, are associated with a spectrum of neurodevelopmental disorders, including intellectual disability, autism spectrum disorder, and epilepsy [29]-[31].

3) Metabolic Genes: Mutations in genes encoding metabolic enzymes or transporters, such as ALDH7A1 and SLC2A1, lead to epilepsy due to disruptions in energy metabolism or the accumulation of toxic metabolites in the brain. ALDH7A1 mutations cause pyridoxine-dependent epilepsy, a rare metabolic disorder in

which seizures can be controlled by supplementation with pyridoxine (vitamin B6) [32]-[34].

4) Structural Brain Development and Cell-Adhesion Genes: Genes involved in brain development, neuronal migration, and cell-cell adhesion cause epilepsy by disrupting the normal formation of brain structures or neural circuitry. Mutations in DCX, LIS1, and ARX can lead to conditions such as lissencephaly (smooth brain) or polymicrogyria (excessive folding of the brain cortex), which are often associated with severe epilepsy and developmental delay [35]-[37]. PCDH19 also belongs in this category rather than among the metabolic genes: it encodes a calcium-dependent protocadherin, a cell-adhesion molecule involved in neuronal migration and cortical circuit formation, and its disruption causes PCDH19-clustering epilepsy, an X-linked disorder with an unusual inheritance pattern in which heterozygous females and mosaic males are affected while hemizygous males are spared, an effect attributed to a "cellular interference" mechanism arising from the mosaic pattern of X-inactivation.

5) Transcription Factors and Chromatin Remodeling Genes: Genes encoding transcription factors and chromatin remodeling proteins, such as FOXG1, MECP2, and CDKL5, can cause epilepsy by affecting the expression of other genes involved in brain development and function. MECP2 mutations are the cause of Rett syndrome, a neurodevelopmental disorder primarily affecting females, characterized by intellectual disability, autism-like features, and epilepsy [38]-[41].

3.2. Diagnostic Yield of Genetic Testing

The diagnostic yield of genetic testing in epilepsy varies depending on several factors, including the epilepsy type or syndrome, age of onset, family history, and the specific testing method used [42]. Genetic testing encompasses a wide range of methods, including targeted gene panels, whole-exome sequencing (WES), and whole-genome sequencing (WGS), each with its own advantages and limitations. Targeted gene panels focus on specific genes known to be associated with epilepsy, providing a cost-effective and efficient approach for identifying common mutations. WES and WGS, on the other hand, offer a more comprehensive analysis by examining the entire exome or genome, respectively, and can detect rare or novel genetic variations that might be missed by targeted panels [43] [44]. Studies have shown that genetic testing is more likely to identify causative mutations in patients with early-onset epilepsy, specific epilepsy syndromes (e.g., Dravet syndrome, Lennox-Gastaut syndrome), or a strong family history of epilepsy or related neurodevelopmental disorders [42]. Early-onset epilepsy, which occurs in infancy or early childhood, is often linked to genetic factors, and identifying these mutations can provide critical insights into the underlying pathophysiology. For instance, mutations in the SCN1A gene are commonly associated with Dravet syndrome, a severe epilepsy syndrome characterized by febrile seizures, developmental delays, and cognitive impairment [43]. Similarly, patients with Lennox-Gastaut syndrome, a complex epilepsy syndrome marked by multiple seizure types and cog-

nitive dysfunction, often have identifiable genetic mutations that can inform treatment and prognosis [44]. A large multigene-panel study of over 8,500 patients with epilepsy and neurodevelopmental disorders found that a small number of genes—led by SCN1A and KCNQ2—accounted for a disproportionate share of positive results, and that roughly 9% of positive findings were copy-number variants detectable only by exon-level array analysis rather than sequence-level panel testing alone [45]. A positive family history of epilepsy or related neurodevelopmental disorders can also increase the likelihood of detecting genetic mutations, as certain epilepsy syndromes exhibit autosomal dominant or recessive inheritance patterns. The diagnostic yield of genetic testing can be further influenced by the clinical context and the specific characteristics of the patient's epilepsy. For example, patients with focal epilepsy, where seizures originate from a specific area of the brain, may have lower diagnostic yields compared to those with generalized epilepsy, which involves widespread neuronal activity [46]. Additionally, advances in genomic technologies and bioinformatics tools have enhanced the ability to interpret genetic variants and their potential pathogenicity, thereby improving the overall diagnostic accuracy.

Single-gene testing is optimal when clinical features clearly indicate a specific genetic disorder with an established gene association. This approach offers high clinical sensitivity due to precise phenotypic matching and minimizes the risk of discovering multiple variants of unknown significance. Clinical expertise is crucial in identifying the appropriate gene for testing. Using achondroplasia as an example, FGFR3 gene testing detects mutations in a large majority of patients, making it a highly efficient single-gene test in the correct clinical context [47]. However, physicians must possess comprehensive knowledge of the disorder's diagnostic characteristics to select the correct genetic test, and variant classification for any positive or ambiguous result should follow standardized criteria, such as the ACMG/AMP framework for variant interpretation [48].

Gene panels represent a sophisticated approach to genetic diagnostics, transforming how clinicians identify disease-causing mutations across complex disorders. Through simultaneously screening multiple genes associated with specific conditions, these panels leverage next-generation sequencing technology to provide comprehensive genetic insights. The design of such panels involves intricate decision-making, balancing breadth of coverage with scientific rigor. Laboratories develop these panels by carefully selecting genes with strong clinical evidence, considering factors like disease association, phenotypic overlap, and potential diagnostic utility. The number of genes in a panel can vary dramatically, ranging from around 70 to several hundred for conditions like epilepsy, reflecting the nuanced approach required in genetic testing [49] [50]. Clinicians and laboratory geneticists collaborate to ensure panels make clinical sense, prioritizing genes with established pathogenic connections.

However, gene panel development is not without challenges. The rapid pace of genetic discovery means panels must constantly evolve, carefully validating newly

identified genes to avoid including potentially misleading genetic information [50]. This requires a meticulous approach to prevent accumulating variants of uncertain significance, which could complicate clinical interpretation. The ultimate goal of gene panels is to provide more efficient, comprehensive genetic diagnostics. By offering a broader screening approach compared to traditional single-gene testing, these panels increase the likelihood of identifying causative mutations, ultimately supporting more personalized medical approaches and potentially guiding treatment strategies across various genetic disorders.

Whole-Exome Sequencing (WES) is another powerful genomic tool in the diagnosis and understanding of epilepsy, particularly in cases with complex or atypical presentations. By analyzing the protein-coding regions of the genome, which represent approximately 1% - 2% of the human genome, WES allows for the identification of novel or rare genetic variants that may contribute to epileptic disorders [51]. This approach enhances the likelihood of detecting causative mutations that might otherwise be missed by traditional genetic testing methods.

Studies have demonstrated the significant diagnostic potential of WES in identifying genetic causes of epilepsy. WES can uncover pathogenic mutations in 25-40% of patients with previously undiagnosed epilepsy, particularly in those with complex or syndromic forms of the disorder [52] [53]. In fact, a study published in Human Genomics identified pathogenic variants in 14 out of 43 epilepsy patients (32.6%), including both previously reported and novel mutations [54]. This underscores WES's ability to detect both known and novel genetic variants that contribute to epilepsy, which is critical for patient management, offering insights into prognosis, recurrence risk, and potential treatment strategies. WES has also played an instrumental role in uncovering genetic heterogeneity within epilepsy: mutations in genes such as SCN1A, KCNQ2, and DEPDC5 have been implicated in various epilepsy syndromes, demonstrating the diverse genetic landscape of the condition and the need for a comprehensive testing approach [24].

Whole-exome sequencing (WES) has also become a pivotal tool in identifying genetic causes of developmental and epileptic encephalopathies (DEEs), a group of severe, early-onset epilepsies characterized by refractory seizures and developmental delays. A study published in the European Journal of Paediatric Neurology evaluated the diagnostic yield of WES in patients with DEEs who had previously undergone gene panel testing without conclusive results. The findings revealed that WES identified pathogenic or likely pathogenic variants in a significant proportion of these patients, underscoring its value in uncovering genetic etiologies that may be missed by more targeted approaches [55]. This highlights the importance of WES in the diagnostic evaluation of DEEs, particularly when initial genetic tests are inconclusive.

A study conducted by Aaltio *et al.* [56] aimed to evaluate the cost-effectiveness and diagnostic utility of WES as an early diagnostic tool in children with severe neurological diseases, including progressive neurological and epileptic disorders. The study, conducted at Helsinki University Hospital, involved 48 children with

infantile-onset severe neurological diseases or childhood-onset progressive neurological disorders, who underwent WES. A control group of 49 children who received traditional diagnostic examinations was also included for comparison. The study found that WES provided a significantly better diagnostic yield compared to traditional diagnostic methods, identifying a pathogenic cause in 38% of patients compared to a 25% diagnostic yield from conventional methods. Notably, WES performed even better when used early, within the first year of the patient's admission, achieving a diagnostic yield of 44%. Furthermore, the study also considered the cost-effectiveness of WES using the Incremental Cost-Effectiveness Ratio (ICER) to assess the cost per additional diagnosis; while the analysis was affected by the higher costs of WES during the 2016-2018 study period, the results still indicated that WES is a cost-effective diagnostic tool, with cost-effectiveness likely to improve further as sequencing costs continue to decline.

Whole-Genome Sequencing (WGS) represents the most comprehensive approach to genetic screening by sequencing the entire genome, including both coding and non-coding regions. Unlike WES, which focuses solely on the exome, WGS captures the full spectrum of genetic information, offering a more complete picture of an individual's genetic makeup—and, in epilepsy specifically, has begun to demonstrate diagnostic value beyond what WES alone can provide.

In a large clinical cohort of 733 families with pediatric epilepsy evaluated by WGS or WES over an eight-year period, WGS/WES together identified a molecular diagnosis in 37.9% of individuals overall; among those tested by WGS, the diagnostic yield was 35.0%, and several of the additional diagnoses achieved through WGS after a prior non-diagnostic WES depended on structural variants with breakpoints in non-coding regions—including a large duplication, a complex structural rearrangement, and deletions spanning one to three exons—that would not have been resolved by exome-level analysis alone [57]. Consistent with this, a cohort study of children with unexplained epilepsy and a prior non-diagnostic exome found that genome sequencing achieved a "unique" diagnostic yield of 5.6% attributable specifically to variants that exome sequencing could not detect, including small copy-number variants and variants in non-coding regulatory regions [58]. In early infantile epileptic encephalopathy, whole-genome analysis combining sequencing with comprehensive structural-variant discovery identified a genetic diagnosis in all 14 previously undiagnosed subjects studied, including de novo structural rearrangements in known epilepsy genes that exome sequencing would have been expected to miss [59].

WGS has also proved uniquely suited to detecting a category of pathogenic variant that neither gene panels nor exome sequencing can reliably capture: non-coding repeat expansions. Benign adult familial myoclonic epilepsy (also called familial adult myoclonic epilepsy, FAME), a cortical-tremor and myoclonic-seizure syndrome long linked to specific chromosomal loci by family studies but genetically unsolved for two decades, was shown to be caused by intronic pentanucleotide (TTTCA/TTTTA) repeat expansions in SAMD12 and, in a smaller

number of families, in TNRC6A and RAPGEF2—a discovery made possible by combining linkage analysis with whole-genome sequencing of an affected family, since the causative repeat expansions lie in non-coding, structurally repetitive DNA that short-read exome capture does not cover and that panel-based sequence analysis is not designed to detect [60].

Taken together, these epilepsy-specific data indicate that the incremental yield of WGS over WES and panel testing is concentrated in structural variants, non-coding variants, and repeat expansions rather than in the coding single-nucleotide variants that most panels and exome tests already capture well; WGS is therefore best positioned as a second-tier test after a non-diagnostic panel or exome, or as a first-tier test in phenotypes with a high prior probability of one of these variant classes, rather than as a uniform replacement for panel or exome testing in all patients with epilepsy.

In clinical applications more broadly, WGS has become fundamental to personalized medicine, allowing healthcare providers to tailor treatments based on individual genetic profiles. This approach has particularly impacted several key medical domains: rare disease diagnosis, where WGS helps identify novel genetic variants; oncogenomics, enabling targeted cancer therapies; pharmacogenomics, which optimizes drug selection and dosing; neonatal screening for early disease detection; and infectious disease genomics for pathogen identification and tracking [61]. The technology's evolution has extended into multi-omics integration, working to synthesize various types of biomolecular data for a more complete understanding of human biology [61]. Recent advances have introduced third- and fourth-generation sequencing technologies, including long-read sequencing for improved genomic assembly, single-cell genomics for cellular-level analysis, and nanopore sequencing for real-time DNA analysis [61]. These innovations continue to expand WGS capabilities, promising even greater precision in medical diagnosis and treatment.

While WGS is currently more expensive and data-intensive than WES, its comprehensive nature makes it valuable in both research and clinical settings. In research, WGS is used to explore the genetic basis of various diseases, including epilepsy, and discover new genetic associations. In clinical practice, WGS can diagnose complex or undiagnosed cases of epilepsy, especially when other genetic testing methods have failed to provide answers. However, WGS also presents challenges, including interpreting vast amounts of data and identifying variants of unknown significance. Advanced bioinformatics tools and expertise are required to analyze and interpret WGS data effectively. Additionally, the clinical implementation of WGS is limited by its cost and the need for specialized infrastructure.

3.3. Genotype-Phenotype Correlations

Genetic testing has revealed important genotype-phenotype correlations in epilepsy, demonstrating how specific genetic mutations can influence the clinical presentation, severity, and prognosis of the disorder.

SCN1A Mutations: The SCN1A gene plays a substantial role in epilepsy development, with mutations leading to a wide range of epilepsy disorders [62]. These range from milder conditions such as genetic epilepsy with febrile seizures plus (GEFS+) to more severe forms like Dravet syndrome, developmental epileptic encephalopathies, and epilepsy of infancy with migrating focal seizures [24] [63] [64].

More than 40% of SCN1A mutations are missense variants. While mutations within the sodium channel's core region (S4-S6) are generally linked to severe epilepsy and those occurring outside this region are often associated with milder forms, exceptions exist [26] [65] [66]. Due to this variability, predicting disease severity based solely on mutation location is unreliable. To gain deeper insights into how specific mutations influence epilepsy severity, researchers recommend functional studies using mammalian expression systems to assess changes in protein function.

KCNQ2 Mutations: KCNQ2-related disorders encompass a wide range of neonatal epilepsy syndromes, from mild self-limited familial neonatal epilepsy (SLFNE) to severe neonatal-onset developmental and epileptic encephalopathy (NEO-DEE) [67]. Other less frequent presentations include neonatal encephalopathy with non-epileptic myoclonus, infantile or childhood-onset epilepsy, and isolated intellectual disability without seizures [67]. KCNQ2-SLFNE typically manifests as seizures within the first week of life in otherwise healthy infants, resolving by 6 - 12 months. Seizures often involve motor symptoms, apnea, and cyanosis, with around 30% of affected individuals developing epilepsy later in life [67].

STXBP1 Mutations: STXBP1 mutations are associated with a spectrum of neurodevelopmental disorders, including early-onset epileptic encephalopathies (EOEEs) (severe epilepsy syndromes that begin in infancy or early childhood and are often accompanied by developmental delays or regression), Ohtahara syndrome (a rare and severe form of epilepsy that typically presents within the first few months of life, characterized by frequent seizures and developmental challenges), West syndrome (a triad of infantile spasms, developmental regression, and a specific EEG pattern called hypsarrhythmia), intellectual disability (ID), autism spectrum disorder (ASD), and epilepsy [68]. The severity of the phenotype can vary widely depending on the specific mutation and the individual's genetic background. Intellectual disability, a common feature of STXBP1-related disorders, ranges from mild to profound and is characterized by limitations in intellectual functioning, such as reasoning and problem-solving, as well as adaptive behaviors like communication and social skills [68]. Additionally, many individuals with STXBP1 mutations exhibit features of autism spectrum disorder, including challenges in social communication and interaction, alongside restricted and repetitive behaviors. Epilepsy is another frequent comorbidity, often presenting early in life with varying types and severity of seizures. The clinical presentation of STXBP1-related disorders is highly heterogeneous, emphasizing the importance of genetic testing and personalized interventions [68]. Early diagnosis and tailored

support are crucial for addressing the specific needs of affected individuals, optimizing developmental outcomes, and improving their overall quality of life.

3.4. Impact on Treatment and Management

Genetic testing can inform treatment decisions and improve the management of epilepsy in the following ways. In each case, the evidence supporting genotype-directed management is summarized here together with its main limitations, since these recommendations rest on differing levels and quality of evidence.

1) Precision Medicine in Epilepsy—ASM Selection by Genotype: Identifying the underlying genetic cause of epilepsy can guide the selection of appropriate anti-seizure medications (ASMs), but the indication is genotype- and mechanism-specific rather than gene-general. Sodium channel blockers, such as phenytoin, carbamazepine, and lamotrigine, are specifically contraindicated in patients with loss-of-function SCN1A variants, as seen in Dravet syndrome, where SCN1A loss-of-function mutations disrupt sodium channel activity in inhibitory neurons, leading to an imbalance in neuronal excitability; blocking sodium channels in this context can further impair the remaining functional channels and aggravate seizures [18]. By contrast, patients with SCN1A gain-of-function variants, or with gain-of-function variants in related sodium-channel genes, may benefit from sodium channel blockers rather than being harmed by them, so genotype and, where feasible, functional characterization of the specific variant should guide the decision rather than the gene name alone. A pharmacogenetic marker, the SCN1A rs3812718 polymorphism, has similarly been associated with differential response to ASMs such as valproic acid and carbamazepine [69]. The evidence base for genotype-directed ASM selection in epilepsy is drawn mainly from small retrospective cohorts, case series, and mechanistic/functional studies rather than randomized controlled trials, and pharmacogenetic associations such as the rs3812718 finding require replication in larger, prospective cohorts before they can be used as a standalone basis for drug selection [70]. These findings nonetheless underscore the potential of precision medicine to optimize epilepsy treatment and reduce reliance on a trial-and-error approach, provided that recommendations are anchored to the specific genotype and its functional consequence rather than applied uniformly to a gene.

2) Targeted Therapies—ALDH7A1-Related Epilepsy: In some cases, genetic testing can identify individuals who are eligible for targeted therapies that address the underlying molecular mechanism of the disorder. Patients with pyridoxine-dependent epilepsy (PDE) due to biallelic pathogenic ALDH7A1 variants can be treated with pyridoxine (vitamin B6) supplementation, which effectively controls seizures in most patients. ALDH7A1 deficiency disrupts the lysine catabolic pathway, causing accumulation of alpha-aminoadipic semialdehyde and related toxic metabolites; pyridoxine supplementation helps restore the function of pyridoxal 5'-phosphate (PLP), a cofactor essential for neurotransmitter synthesis, thereby reducing seizure activity [32]. The diagnosis and dosing of pyridoxine therapy in

PDE-ALDH7A1—including age-based dosing, monitoring for a sensory neuropathy associated with high-dose pyridoxine, and the role of adjunctive lysine-reduction therapy—are now addressed by international consensus guidelines developed by the International PDE Consortium, which should be consulted for genotype-specific dosing and monitoring recommendations rather than treating pyridoxine response alone as diagnostic [71]. In addition to pyridoxine, other targeted therapies are being explored for PDE: L-arginine supplementation has shown promise in reducing the accumulation of alpha-aminoadipic semialdehyde (*α*-AASA) by competitively inhibiting lysine transport into the central nervous system, and has been associated with improvements in neurodevelopmental outcomes in some patients [72]. Dietary modifications, such as lysine restriction, have been used alongside pyridoxine to manage PDE, although adherence to such diets can be challenging [72] [73]. The evidence for these adjunctive therapies remains limited to case series and small cohorts rather than randomized trials, given the rarity of the condition; even with adequate seizure control, many patients retain some degree of developmental delay or intellectual disability, which the consensus guideline identifies as an outcome that lysine-reduction therapies may improve but do not reliably normalize [71] [73]. Early initiation of pyridoxine therapy has nonetheless been shown to improve seizure control and developmental outcomes in patients with PDE [32] [73].

3) Dietary Management—GLUT1 Deficiency Syndrome: Genetic testing plays a crucial role in informing dietary management strategies for patients with neurogenetic disorders. Patients with glucose transporter type 1 deficiency syndrome (GLUT1DS), confirmed by identification of a pathogenic SLC2A1 variant (or, where genetic testing is inconclusive, by a low cerebrospinal-fluid-to-blood glucose ratio), can significantly benefit from a ketogenic diet (KD). GLUT1DS is characterized by impaired glucose transport across the blood-brain barrier, leading to cerebral energy deficiency; the ketogenic diet provides an alternative energy source for the brain in the form of ketone bodies, which can bypass the defective glucose transporter and alleviate symptoms such as seizures, movement disorders, and cognitive impairment [74]-[76]. The ketogenic diet is internationally recognized as the first-line treatment for GLUT1DS, and current clinical recommendations specify that it should be initiated as soon as the genetic or biochemical diagnosis is confirmed, since earlier initiation is associated with better long-term neurodevelopmental outcomes [74] [76]. In addition to the classic ketogenic diet, modified versions such as the Modified Atkins Diet (MAD) have also shown promise in managing GLUT1DS, offering a more flexible and palatable option for patients while maintaining therapeutic benefit, with genotype (missense versus truncating SLC2A1 variants) reported to influence, but not reliably predict, individual dietary response [76] [77]. The evidence supporting dietary management in GLUT1DS again derives predominantly from retrospective cohorts and registry data rather than randomized controlled trials, reflecting the rarity of the condition; genetic testing confirms the diagnosis and supports the decision to pursue

dietary therapy, but does not by itself determine which dietary variant a given patient will tolerate best, and diet selection continues to require individualized clinical judgment [75] [78].

4. Discussion

The findings from this review underscore the diagnostic potential of genetic scanning for improving the identification and management of epilepsy in patients who already present with seizures. The identification of a wide range of genes and mutations associated with epilepsy, spanning ion channel, synaptic, metabolic, structural/cell-adhesion, and chromatin-regulatory mechanisms, has significantly advanced our understanding of the disorder's pathogenesis and heterogeneity. Genetic testing has emerged as a valuable tool for confirming or refining diagnoses, predicting prognosis, informing treatment decisions, and facilitating family planning.

The diagnostic yield of genetic testing varies depending on several factors, including the epilepsy type or syndrome, age of onset, family history, and the specific testing method used. As detailed in Section 3.2, this yield is substantially higher in early-onset, syndromic, and familial epilepsies than in common generalized or focal epilepsies of unknown structural or acquired cause, and the incremental value of WGS over panel or exome testing is concentrated in structural variants, non-coding variants, and repeat expansions rather than in variant classes that panels and exomes already detect well. This highlights the importance of careful patient selection and appropriate test selection, in line with current recommendations from the ILAE Genetics Commission on matching test type to clinical context [14].

The identification of genotype-phenotype correlations has provided valuable insights into how specific genetic mutations can influence the clinical presentation, severity, and prognosis of epilepsy. These correlations can help clinicians tailor treatment strategies and provide more accurate prognostic information to patients and families, although, as discussed in Section 3.4, the underlying evidence for genotype-directed treatment is drawn largely from observational cohorts, case series, and registry data rather than randomized controlled trials, and treatment recommendations should specify the relevant genotype and its functional consequence rather than being generalized across an entire gene.

The widespread application of genetic scanning in epilepsy raises several ethical and practical considerations. Cost is a significant barrier to access, especially in resource-constrained settings. Variant interpretation can be challenging and should follow standardized frameworks, such as the ACMG/AMP criteria for classifying sequence variants as pathogenic, likely pathogenic, of uncertain significance, likely benign, or benign, so that variant reports are consistent and reproducible across laboratories [48]. Genetic counseling—both before testing, to set expectations about the likelihood and implications of a positive, negative, or uncertain result, and after testing, to explain the result and its implications for the patient

and family—is essential and should be delivered by appropriately trained professionals, consistent with current ILAE Genetics Commission guidance on test selection, variant reporting, and counseling practice in the epilepsies [14]. Data privacy and security must be protected, and healthcare providers must adhere to strict ethical and legal guidelines. The psychological impact of genetic testing should also be carefully considered. These considerations apply specifically to diagnostic testing of symptomatic patients; extending genetic scanning to presymptomatic relatives or population-based screening would raise additional questions (around the predictive value of a variant found in an asymptomatic person, the right not to know, and the management of incidental findings) that are outside the scope of this review and would need to be addressed on their own evidentiary and ethical basis. A further limitation of this review is methodological: no formal quality or risk-of-bias assessment tool was applied to the included studies, so the relative methodological strength of the underlying evidence base could not be systematically weighted, and this should be borne in mind when interpreting the findings summarized here.

Despite these challenges, the diagnostic and clinical-management benefits of genetic scanning in epilepsy are substantial for the patients and clinical contexts described above. As technology advances and the cost of sequencing decreases, genetic testing is becoming increasingly accessible. Future directions in epilepsy genetics include expanding gene discovery efforts, developing targeted therapies, improving detection and interpretation of structural, non-coding, and repeat-expansion variants, and integrating multi-omics data to refine diagnostic and treatment strategies.

5. Conclusion

Genetic scanning has emerged as a valuable diagnostic tool for improving the identification and management of epilepsy in patients who present with seizures. The identification of a wide range of genes and mutations associated with epilepsy has significantly advanced our understanding of the disorder's pathogenesis and heterogeneity. Genetic testing can inform treatment decisions, improve prognostic accuracy, facilitate family planning, and advance epilepsy research, provided that genotype-directed recommendations are anchored to the specific variant, its functional consequence, and the quality of the supporting evidence, and that test selection, variant reporting, and counseling follow current professional guidance such as that of the ILAE Genetics Commission and the ACMG/AMP variant-interpretation standards [14] [48]. While challenges related to cost, variant interpretation, and ethics remain, the diagnostic value of genetic scanning in appropriately selected patients with epilepsy is well supported by the evidence reviewed here. As technology advances and the cost of sequencing decreases, genetic testing is becoming increasingly accessible. Future directions in epilepsy genetics include expanding gene discovery efforts, developing targeted therapies, and integrating multi-omics data to refine diagnostic and treatment strategies. The continued in-

tegration of genetic scanning into clinical practice has the potential to improve diagnostic accuracy and support more personalized treatment for individuals affected by epilepsy.

Conflicts of Interest

The authors declare no conflicts of interest.

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