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REVIEW

Genetic Testing for Epilepsy: A User Guide

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Abstract

Purpose of Review About 30% of epilepsy cases have an underlying genetic etiology. Despite rapid progress with understanding the genetic underpinnings of epilepsy and with gene-specific treatments for epilepsy, many barriers for clinicians to send genetic testing remain. This review aims to provide clinicians with a practical approach to genetic testing for epilepsy.

Recent Findings Incorporation of genetic counselors into neurology practices is a useful model for supporting providers to implement proper recommendations. Selecting the appropriate genetic test for epilepsy involves prioritizing patients' informed consent and evaluating diagnostic yield, cost-effectiveness, and turnaround time following certain algorithms, with exome/genome sequencing as first-tier options, and multigene epilepsy panel as a more accessible alternate for resource-limited situations. Result interpretation should be conducted on a case-by-case basis, and should include interpretation of the results, changes in clinical management, inheritance risks, testing of family members, and discussion of additional testing if needed.

Summary We provide a comparative assessment of the yield of genetic tests for epilepsy, with possible test outcomes and practical considerations for the clinical decision-making process. Continued research and integration of cutting-edge approaches will expand our understanding of genetics in epilepsy and improve clinical outcomes for individuals with epilepsy.

Keywords Genetic testing · Epilepsy · Whole genome sequencing · Genetic counseling · Whole exome sequencing

Introduction

Epilepsy, characterized by recurrent unprovoked seizures, is a common neurologic disorder estimated to affect approximately 50 million people worldwide, or 0.6–0.8% of the general population [1, 2]. Epilepsy can be the result of a variety of factors, including structural brain abnormalities, infection, metabolic disorders, immune disorders, and genetic etiologies [3]. Improvements in genetic testing over time have led to the identification of over 500 genes associated with epilepsy [4]. Currently, approximately 30% of cases of epilepsy are thought to have an underlying genetic etiology [4, 5]. Some of the most common monogenic causes of epilepsy include variants in: *SCN1A, KCNQ2, CDKL5, SCN2A, PRRT2, PCDH19, STXBP1, SLC2A1, GABRG2, SCN8A, UBE3A, MECP2, GRIN2A, TSC2*, and *FOXG1* [6].

Why Should I Send Genetic Testing for Epilepsy?

Knowing the genetic etiology behind a patient's epilepsy can be crucial in guiding management decisions [7]. For example, early initiation of the ketogenic diet for patients with pathogenic *SLC2A1* variants or use of sodium channel blockers for patients with pathogenic *SCN2A* and *SCN8A* variants have been shown to lead to improved seizure control and outcomes (reviewed in [8]). Even in the absence of such direct treatment implications, a clear diagnosis can provide important information for families regarding prognosis, risks to family members, and recurrence risks for future children [5, 8]. An early genetic diagnosis can also save healthcare-related costs by decreased utilization of other potentially non-diagnostic tests [9]. While genetic testing does not always have direct treatment or management implications,

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diagnostic clarity may still provide relief for families and prevent unnecessary testing. Further, a clear diagnosis may give patients and their families the opportunity to connect with communities with shared experiences, providing support and the opportunity to better advocate for the patient. Because of these reasons, clinical guidelines support genetic testing for all patients with unexplained epilepsy [10]. In particular, genetic testing has the highest diagnostic yield in patients with neonatal or infantile-onset seizures, developmental and epileptic encephalopathies, other neurodevelopmental comorbidities, or drug-resistant epilepsy [10], as shown in Table 1.

How do I Choose Which Test(s) to Send for First-Tier Testing?

Multiple genetic tests are available to send from the clinic (Table 2). There has been significant debate regarding the best first-line test for a patient with unexplained epilepsy, especially given new and emerging technologies, both in testing and in therapeutics. Recent papers have recommended specific testing strategies with this new information in mind [10–12]. The goal of genetic testing should be to identify a genetic etiology quickly and cost-effectively. That said, one of the most important aspects to choosing the correct test is having a discussion with the patient regarding their goals. Some patients will want all the information that can be found, while others may prefer not to pursue wide-based testing. Having open and honest conversations regarding their preferences allows for autonomy of the patient and helps to build trust. Multiple factors, including the patient's clinical presentation, their preferences and goals, insurance, costs, and availability of clinic resources, should all be considered in the choice of genetic testing.

Recent recommendations are to use exome sequencing (ES) or genome sequencing (GS) as the best first line test for patients with unexplained epilepsy [10, 11]. ES/GS have been found to have high clinical yield for patients with epilepsy, most likely due to their comprehensive assessment of the genome as well as the inclusion of biological parents or other family members, allowing for variant segregation and improving interpretation [13–15]. ES/GS is best for patients who not only have epilepsy of an unknown etiology, but who also have additional comorbidities such as multiple congenital anomalies, autism spectrum disorder, developmental concerns, or other features. Another benefit of ES/GS is identification of dual diagnoses [16]. It is becoming more common to find patients with multiple genetic diagnoses, and thus, ordering testing that assesses for changes in all genes decreases the chance of missing conditions. Currently, ES is more easily accessible to clinicians than GS due to costs of GS to patients and hospital systems. However, GS overall tends to be the superior test as it can assess for deep intronic and intergenic variants, repeat expansions disorders, structural rearrangements, and copy number variants (CNVs).

If ES/GS is not available, multi-gene epilepsy panels with good CNV coverage have been shown to have the next highest yield. Epilepsy panels are more easily available to clinicians with fewer resources, such as those who lack access to a genetic counselor. Many labs will complete insurance authorization of testing themselves, decreasing the need for additional clinic staff and minimizing wait times for patients who otherwise would not have testing completed prior to being seen in a medical genetics clinic. Epilepsy panels in general have a faster turnaround than ES/GS. Most panels yield results within 3–4 weeks, versus ES/GS which, if not performed using a rapid method, tend to take closer to 8–10 weeks. An additional benefit of multi-gene

Table 1 Indications for genetic testing with high diagnostic yield in epilepsy patients

Indication	Examples
Neonatal/infantile-onset DEEs	Early-infantile developmental and epileptic encephalopathy
	Epilepsy of infancy with migrating focal seizures
	Dravet syndrome
	Infantile spasms syndrome (West syndrome)
Childhood-onset DEEs	Lennox-Gastaut syndrome
	Developmental and/or epileptic encephalopathy with spike-and-wave activation in sleep
Progressive epilepsies	Progressive myoclonic epilepsies
Epilepsy plus	Intellectual disability
	Autism
	Dysmorphic features
	Multiple congenital anomalies
Drug-resistant epilepsy of unknown etiology	-

DEEs Developmental and epileptic encephalopathies

Table 2 Characteristics of clinically available genetic tests

	Definition	Use cases	Advantages	Limitations
Karyotype	Staining of condensed chromosomes and counted/analyzed visually	• Examine for ring chromosomes, aneuploidy, balanced translocations	• Only test that can reliably detect ring chromosomes	• Only able to identify large deletions/duplications and structural differences, which account for only a small portion of genetic epilepsies
Chromosomal microarray (CMA)	Analysis of DNA copy number variants and regions of homozygosity	• Copy number variants causing developmental delays	• Identifies submicroscopic DNA deletions or duplications	• Unable to detect balanced rearrangements, single nucleotide variants. Does not consistently detect uniparental disomy
Multigene panel	Simultaneous sequencing of a selected set of genes associated with a disease	• First line testing for epilepsy if ES/GS not available	• Useful for disorders with genetic heterogeneity • Can identify smaller genetic variants (e.g. single nucleotide variants) • Time-efficient	• Testing is limited to a subset of genes • Cannot assess for larger copy number variants
Exome Sequencing (ES)	Sequencing of almost all protein-coding regions of the genome, including intron/exon boundaries for splice sites	• First line testing for epilepsy	• Captures ~ 1% of the human genome and ~ 85% of variants with large effects on disease-related traits [5] • Able to identify single-nucleotide variants and most copy number variants • Can identify more than one genetic condition • Cost-effective	• Some genes may not be covered by exome sequencing • Pathogenic variants may need to be confirmed by Sanger sequencing • Difficult to sequence areas of GC-rich nucleotides may lead to false negatives and false positives
Genome Sequencing (GS)	Sequencing of entire genome: all exons, introns, and intergenic regions	• First line testing for epilepsy if covered by insurance and available	• Similar to ES, but captures entire human genome, including variants outside of exons that can be pathogenic • More likely than ES to provide complete coverage of the entire coding region of the genome [45]	• More time-consuming analysis • Variants often need to be confirmed by Sanger sequencing • Intronic and intergenic variants are not yet as well characterized, and this may complicate interpretation
Repeat Expansion Detection	PCR- or Southern blot-based assay to detect expansions of trinucleotide repeats	• FMR1 CGG repeat testing for Fragile X	• Use in a suspected clinical diagnosis, disorders with clinical anticipation and complex pattern of inheritance	• Expensive, time-consuming, not always conclusive • No comprehensive panel exists to simultaneously test for all known repeat expansions • Newer methods to interrogate for repeat expansions in short-read sequencing data (ES or GS) have been described [46]
Methylation Testing	Profiling technique recognizing syndrome-specific DNA methylation epi-signatures	• Test for Prader-Willi/Angelman Syndrome (Chromosome 15q11.2)	• First-line for diseases affected by imprinting • Only test to examine epigenetics (heritable, physical changes that affect gene expression without affecting the genetic code)	• Clinically available methylation tests for epilepsy examine a single genetic locus • Genome-wide methylation studies are not yet clinically available

panels is that they cover most of the conditions that have implications for changing medical management. One thing to keep in mind when selecting a panel is how many genes are included, as the larger panels often include less clinically relevant conditions or genes that may not be associated with a known epilepsy. Less commonly, ordering a larger panel may lead to the identification of an incidental finding which may be unwanted and surprising information for the patient. Notably, some commercially-available epilepsy panels use ES combined with a directed analysis limited to the epilepsy-associated genes. In these cases, reflex testing to ES can be performed after a negative panel.

Other tests that generally have a lower diagnostic yield for patients with epilepsy include chromosomal microarray (CMA), karyotype, repeat expansion tests, methylation tests, and tests for single gene disorders. While GS should be able to identify most CNVs, exome sequencing from many labs is not guaranteed to find all clinically relevant CNV disorders. There are multiple well-known genetic disorders caused by CNVs that lead to epilepsy, as well as more novel CNVs that may be pathogenic but missed on ES [17]. For these reasons, CMA should be pursued if ES and multi-gene panel testing are non-diagnostic. Karyotype testing is important for the identification of epilepsy caused by ring chromosome conditions. Ring chromosomes are not consistently identified on chromosomal microarray, therefore karyotype may be considered should the above testing be non-diagnostic and the patient has developmental delay or congenital anomalies in addition to epilepsy. While GS can detect repeat expansion disorders, not all labs that offer GS offer analysis of repeat expansions and those that do may offer only a subset of the clinically relevant conditions. Thus, if there is a concern for a repeat expansion disorder, testing specifically for those conditions should be ordered.

In some cases, there may be concern for a specific genetic disorder based on electroencephalogram (EEG) findings, physical exam, or family history. If there is a known genetic disorder in the patient's family, with previous confirmatory testing and plausible inheritance to the patient, it is best to start with single gene testing. However, given that panels have about the same turnaround time as single gene testing, it may still be beneficial to still begin with a panel even if there is suspicion for a particular condition.

What do I Discuss with my Patient Before Sending Testing?

Prior to ordering genetic testing, it is important that patients and their families understand the process and possible results of the recommended tests. Genetic counseling prior to a genetic test being ordered, known as pre-test counseling, is a crucial part of obtaining informed consent for testing to be completed [12]. Pre-test counseling encompasses a review of the testing process and time frame of results, possible results of testing, clinical implications of those results, recurrence risks (the likelihood that a hereditary disorder will occur again in other family members), costs, and insurance coverage [18–20].

The timing of results is discussed further in this review, along with recurrence risks. Here we provide a brief overview of possible test outcomes along with their implications: positive, negative, variants of uncertain significance (VUS), and incidental. Pathogenic/likely pathogenic, or positive, results refer to the identification of a genetic variation associated with a known human disease. Medical management recommendations are made based on the known associations with the gene, and additional family members may be recommended to complete testing.

Negative results, that is, finding only benign/likely benign variants, do not provide a diagnosis and do not identify any genetic variants known to be associated with genetic conditions. The specific benign/likely benign variants are not typically reported on the results. Typically, no medical management recommendations are made, and no additional family members are tested. Negative results can provide physicians with an understanding of what a patient does *not* have, allowing for specific medications to be utilized that were not options previously. For example, negative *POLG* testing may prompt consideration of valproic acid therapy [21]. That said, a negative test result does not rule out a genetic diagnosis, given the inherent limitations in genetic testing.

The third possible outcome, VUS, can be difficult to interpret and often require review by genetic experts [10]. A variant of uncertain significance is defined as a variant that does not meet the American College of Medical Genetics (ACMG) criteria for pathogenic or benign due to lack of available evidence [22–24]. This is often confusing to patients and providers alike and exemplifies why post-test genetic counseling is necessary [10]. A full review of a variant, including its potential gene and disease associations and segregation within a family, can help determine relevance to a patient's health. Notably, variant classification is dependent on the current body of knowledge. As more is learned about genetic variation, variants may be reclassified, and VUS's that are reclassified are more often changed to benign than to pathogenic [25, 26].

Finally, individuals may receive an incidental finding on genetic test results, particularly with ES and GS. This encompasses unexpected and unanticipated results for a genetic condition, secondary findings (variants in genes related to conditions that have medical management guidelines and health impacts on an individual), and additional non-medical factors such as nonpaternity. Depending on the testing ordered, it may identify genetic conditions not associated with the symptoms being evaluated [27]. For

example, ES may identify maturity-onset diabetes of the young (MODY) in a child being assessed based on a history of focal epilepsy. Discussion of possible incidental findings is a crucial aspect of pre-test counseling as it allows patients to prepare for these unexpected findings and ensure they do in fact wish to proceed with testing.

Not only is obtaining informed consent for genetic testing the standard of care, in many US states it is also the law [28, 29]. Michigan, for example, enacted the law of informed consent (MCL § 333.17020), requiring written informed consent for all presymptomatic or predictive genetic testing. Florida has enacted a law to prohibit life insurance companies from penalizing individuals with a predictive genetic test (FL § 627.4301). Federally, the Genetic Information Nondiscrimination Act was enacted in 2008 to restrict the ability of health insurance companies and employers to use genetic information in cost or employment decisions (29 C.F.R. § 1635). Patients should be aware of these laws prior to undergoing genetic testing to ensure their comfort level and understanding of risks.

What do I Discuss with my Patient After Receiving Genetic Testing Results?

An important part of disclosing genetic testing results is how the results are communicated. This should be reviewed in pre-test counseling, to ensure the clinician and patient agree how final test results will be shared. Coming up with a plan for a phone call, in-person discussion, electronic medical record portal message, or letter is needed as a part of the informed consent process. Positive results should be discussed on the phone, or in-person to allow the patient and family to ask questions.

Despite pre-test counseling, many patients may be confused regarding testing results. In post-test counseling, the clinician should review what type of testing was ordered, why the testing was ordered, and the types of results that can come from this testing before reviewing the patient's specific results. With positive results, management changes, inheritance, and testing of other family members are important to review. For negative results, clinicians should remind patients that this does not necessarily mean there is not a genetic cause for their symptoms, but that this specific test was not able to find one. The clinician should also discuss additional recommended testing at this time. Uncertain results are often the most difficult to explain; the clinician should review the result prior to a discussion with the patient to determine the likelihood that the variant is causative of their features, and whether testing of additional family members (such as parents) could be helpful for VUS resolution. Overall, having a plan regarding the test results is the most important part of post-test counseling, whether that is a referral to medical genetics for further discussion or testing, a recommendation for additional genetic testing either now or in the future (such as ES/GS reanalysis), an office visit to review results, or other diagnostic tests (e.g. an EKG in someone with a VUS in a gene related to heart arrhythmia).

How Much Does this Cost?

The cost of genetic tests has dramatically decreased with improvements in technology, and ES and multigene panels are superior to CMA in cost effectiveness [30]. The out-of-pocket cost for the patient/family depends on many factors, including but not limited to: insurance, income of the patient/patient's family, setting of testing (inpatient vs. outpatient), and the performing lab. Insurance authorization is often needed for testing to proceed. This can be difficult if the clinic does not have access to an insurance team/specialist. Some labs will run insurance authorizations and benefits investigations for the patients. This is helpful but can be misleading as they are not always accurate. Often, there is no specific policy that determines if a test will be covered for a patient [31].

Many labs will offer self-pay options for testing which tend to be around $250–300. If this is not affordable for the patient, financial support and payment plans are typically available as well. If testing is not possible for families, there are often multiple laboratories offering similar gene panels that can be evaluated for different insurance and cost policies. These options are best for the patients to discuss directly with the labs, as this decreases the need for clinic support and allows the patient to receive the information directly from the testing companies. Currently, there are certain labs that do not charge patients for most testing if they have a Medicaid insurance product (either primary or secondary). These and other lab policies are subject to change, making it difficult to fully understand what cost the patient will incur.

Some labs offer testing via sponsored programs, at no cost to patients. This may seem like a great option; however, many companies are unclear on storage and use of patient data for these programs. Sponsored testing may be the only option for some patients from a financial standpoint. If using these, it is vital to discuss the implications of data sharing and fully review the panel-specific consent form so patients know how their data may be used.

Research studies can also be used to obtain testing. One should note that this can be very beneficial in continuing research and participating in studies, but at times the research study will not provide patients with genetic test results. Additionally, any genetic test results suggesting changes in medical management are recommended to be confirmed by a clinical genetic laboratory.

What is the Role of Genetic Counselors?

Genetic counselors (GCs) are clinical professionals who have expertise specifically in medical genetics and genetic testing [32]. There are 55 (as of May 2021) genetic counseling training programs in the United States. These programs are about two years in length and offer master's degrees in genetic counseling to graduates. Genetic counseling programs are not specialty-specific, and thus GCs are trained to work in all aspects of genetic medicine. Neurology has been a growing field for GCs as a greater number of neurological conditions are found to have genetic explanations, and as neurotherapeutics have evolved and become more dependent on genetic diagnoses.

GCs have expertise in explaining why genetic testing may be helpful, the technology behind genetic testing, assessing risk in family and medical histories, explaining testing results, and helping patients cope both with genetic disorders and lack of clear answers. They can be a vital resource for clinics given their knowledge base includes medical genetics, counseling patients, research, and resource identification.

Quick Start Guide to Genetic Testing

Setting Up the Team

Many different practice models exist for performing genetic testing in the clinical setting. Testing can be sent from a general neurology, epilepsy, epilepsy genetics, neurogenetics, or medical genetics clinic, or in the inpatient setting. Team members may include physicians (neurologists, epileptologists, neurogeneticists, medical geneticists), nurses, GCs, GC assistants (GCAs), administrative staff, and other medical personnel. Depending on the composition of the team, pre-test counseling, test choice and ordering, post-test counseling, and follow-up may be divided among different team members. The level of resources and team members may also affect what testing is available. For example, a neurologist with limited knowledge of genetics and without access to a GC may be comfortable with sending multigene panels, but not ES. Notably, many laboratories employ GCs that can work with providers and patients to deliver genetic counseling and can also help to review genetic testing results with the ordering provider. Criteria for what patients may be seen in the neurology clinic and what tests may be sent should be established, as certain patients may be better served by referral to a clinic with a higher level of expertise, whether that be a medical genetics, epilepsy genetics, or neurogenetics clinic. Other logistical considerations include state, national, and institutional policies that dictate who can send genetic testing, and insurance company policies that restrict coverage of testing depending on who the ordering provider is.

Choosing a Lab

Determining what test to send on a patient is equally as important as determining the laboratory to send the testing to. Clinical Laboratory Improvement Amendments (CLIA) and College of American Pathologists (CAP) (https://www.cap.org/laboratory-improvement/accreditation/laboratory-accreditation-program) certified laboratories are the gold standard for genetic testing. Other factors of importance include turnaround time, variant interpretation capabilities, call rate of different variants, what genes are tested (for multi gene panels), whether orthogonal confirmatory testing (such as Sanger sequencing) is used for pathogenic variants, read depth of coverage (how many sequencing reads are represented at each sequenced base), accepted insurances, and out of pocket costs for patients [33]. Each laboratory utilizes a slightly different variant interpretation pipeline to aid in determining which variants are of importance and how to classify them utilizing the ACMG criteria [22–24]. Not all are identical and variant databases such as ClinVar exist to aid in comparing variant classifications at different laboratories. Discordance between variant calling can lead to different medical management recommendations for patients [34]. Additionally, some laboratories report more variants of uncertain significance than others, dependent on their variant pipeline and reporting policies.

Ordering Processes

The majority of genetic testing laboratories have paper test requisitions and online portals. A clinic creates an account and has providers and support staff sign up for portal access through their clinic. This streamlines the ability to order testing and determine insurance coverage and allows support staff to place orders on behalf of neurologists, geneticists, and genetic counselors. Support staff varies from clinic to clinic, with a well-supported clinic having multiple GCAs to aid in these administrative tasks. GCAs are trained in similar ways as administrative assistants, with additional background and training in genetics and genetic testing [35].

Troubleshooting Guide

Testing is Negative – What Now?

If first and second-tier testing (multi gene panel, ES/GS, CMA) is negative, this does not necessarily mean that the etiology is not genetic. A referral to a geneticist

can be beneficial to determine if there are any additional imaging or laboratory screenings that would aid in determining a genetic etiology. If a patient is identified to have a VUS, metabolic or other functional testing may be beneficial in determining the potential impact of the variant on the patient.

There are genetic epilepsies that are not evaluated on the testing reviewed above. Many epilepsies have complex/polygenic inheritance such as the genetic generalized epilepsies. In this case, multiple gene variants contribute a small effect that results in epilepsy. Current methodologies detect monogenic causes and CNVs that predispose an individual to epilepsy but will not detect polygenic causes. Additionally, new genetic etiologies of epilepsy are being identified by ongoing research, so the patient's specific variants may not be known to be associated with epilepsy yet. Reanalysis of genetic testing is recommended on an annual or two-year basis when nondiagnostic to detect any newly identified genetic conditions [36]. Finally, the patient simply may not have a genetic etiology for their epilepsy.

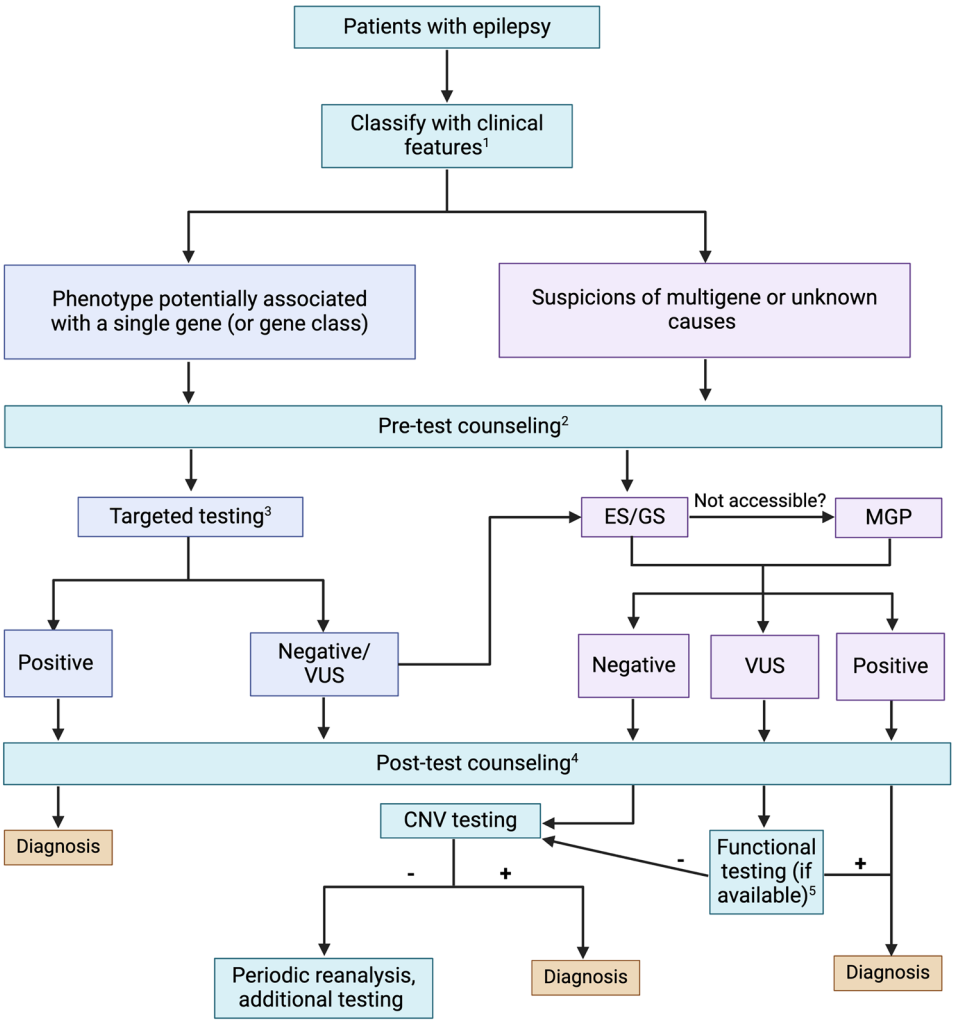

Fig. 1 Recommended genetic testing algorithm, adapted from Smith et al. [10]. In general, ES/GS is preferable to MGP due to higher yield. [1]Indications for genetic testing are initially evaluated according to clinical features of the individuals with epilepsy, including symptoms/signs, comorbidities, imaging/EEG/metabolic investigation (if needed), and family history.[2]Pre-test counseling should incorporate the following: a comprehensive introduction to the testing process, timeframe, all possible results with clinical implications, costs/insurance, and recurrence risks. [3]Targeted testing includes any single gene testing, specific phenotype-driven gene panel, or repeat expansion analysis. [4]The post-test counseling typically incorporates explanations of findings and implications for management, familial testing, and referral to additional resources if neede4d. [5]If the testing results come back with variants with uncertain significance, there may be additional tests that can functionally characterize the variants (e.g., metabolic panels) to determine their pathogenicity. Also, periodic reanalysis and/or reinterpretation of any variants of uncertain significance is recommended, particularly in cases where testing is negative. Generated with *BioRender*. *Notes:* ES, exome sequencing. GS, genome sequencing. MGP, multi-gene panel. VUS, variants with uncertain significance. CNV, copy number variant

Patient/Family Declines Testing

Not all patients/families are interested in genetic testing, for many valid reasons (and at times from misinformation), and not all patients require genetic testing. If a patient or family declines genetic testing when a genetic condition is likely, it is important to have an open, honest conversation about the risks and benefits of testing [37–39]. If the patient or family's underlying concern can be identified and addressed directly, they may be more comfortable proceeding with testing.

GCs specialize in discussing genetic testing with families, especially when families are unsure about proceeding with testing or not. GCs can provide additional counseling for a family to thoroughly review their reasoning and thoughts on moving forward with testing or not [37, 40]. After a detailed discussion, families may still decline testing. This is a valid and available option, whether medically recommended or not.

Conclusions

In summary, genetic testing plays a pivotal role in guiding diagnosis, prognosis, and medical management for patients with epilepsy and can provide information on reproductive risks. Physicians can work with GCs to provide an enhanced level of care in a specialized epilepsy genetics program that can triage which patients may benefit the most from genetic testing, choose the appropriate testing strategy (Fig. 1), and counsel the patients before the testing and after the results. For most cases, based on diagnostic yield, cost-effectiveness, and turnaround time, we recommend comprehensive genome testing (i.e. ES or GS) as the first-tier test or panel testing if the clinic does not have the capacity for ES/GS. If first-line testing is inconclusive, CMA, repeat expansion analysis, karyotype, or other specialized testing can be considered as well as referrals to genetics clinics as appropriate. Additional testing (which is beyond the scope of this review) includes pharmacogenomics, in which testing for specific gene variants can uncover information on an individual's response to drugs. This can be particularly important in epilepsy given the wide range of anti-seizure medications and a high degree of variability in pharmacokinetics in the population.

The rapid advances in genetic testing for epilepsy are driven by the growing understanding of genetic and epigenetic contributions to the disease, from both scientific and clinical perspectives. For example, a polygenic risk score (PRS) can aggregate the effects of multiple gene variants from Genome-Wide Association Studies (GWAS) to estimate an individual's susceptibility to epilepsy [41]. Additionally, improved understanding of epigenetic changes related to epilepsy and epileptogenesis [42, 43] have resulted in genome-wide methylation studies that can serve as a potential predictive factor for disease progression and efficacy of anti-epileptic therapies [44]. By integrating these cutting-edge approaches, we can move towards more precise and personalized interventions, ultimately improving clinical outcomes for individuals with epilepsy.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

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References

1. Forsgren L, Beghi E, Oun A, Sillanpää M. The epidemiology of epilepsy in Europe - a systematic review. Eur J Neurol. 2005;12:245–53.
2. Hauser WA, Annegers JF, Rocca WA. Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester. Minnesota Mayo Clin Proc. 1996;71:576–86.
3. Scheffer I, Berkovic S, Capovilla G, Connolly M, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE commission for classification and terminology. Epilepsia. 2017;58(512):521.
4. Weber YG, Biskup S, Helbig KL, Von Spiczak S, Lerche H. The role of genetic testing in epilepsy diagnosis and management. Expert Rev Mol Diagn. 2017;17:739–50.
5. Sands TT, Choi H. Genetic testing in pediatric epilepsy. Curr Neurol Neurosci Rep. 2017;17:45–45.
6. Lindy AS, Stosser MB, Butler E, Downtain-Pickersgill C, Shanmugham A, Retterer K, et al. Diagnostic outcomes for genetic testing of 70 genes in 8565 patients with epilepsy and neurodevelopmental disorders. Epilepsia. 2018;59:1062–71.
7. McKnight D, Morales A, Hatchell KE, Bristow SL, Bonkowsky JL, Perry MS, et al. Genetic testing to inform epilepsy treatment management from an international study of clinical practice. JAMA Neurol. 2022;79:1267–76.
8. Poduri A. When should genetic testing be performed in epilepsy patients? Epilepsy Currents. 2017;17:16–22.
9. Swartwood SM, Morales A, Hatchell KE, Moretz C, McKnight D, Demmer L, et al. Early genetic testing in pediatric epilepsy: Diagnostic and cost implications. Epilepsia Open. 2023;9:439–44.
10. Smith L, Malinowski J, Ceulemans S, Peck K, Walton N, Sheidley BR, et al. Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors. J Genet Couns. 2023;32:266–80.
11. Karlin A, Ruggiero S, Fitzgerald M. Genetic testing for unexplained epilepsy: A review of diagnostic approach, benefits,

and referral algorithm. Curr Probl Pediatr Adolesc Health Care. 2024;101579.
12. Krey I, Platzer K, Esterhuizen A, Berkovic SF, Helbig I, Hildebrand MS, et al. Current practice in diagnostic genetic testing of the epilepsies. Epileptic Disord. 2022;24:765–86.
13. Helbig KL, Farwell Hagman KD, Shinde DN, Mroske C, Powis Z, Li S, et al. Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. Genet Med. 2016;18:898–905.
14. Stefanski A, Calle-López Y, Leu C, Pérez-Palma E, Pestana-Knight E, Lal D. Clinical sequencing yield in epilepsy, autism spectrum disorder, and intellectual disability: A systematic review and meta-analysis. Epilepsia. 2021;62:143–51.
15. Sheidley BR, Malinowski J, Bergner AL, Bier L, Gloss DS, Mu W, et al. Genetic testing for the epilepsies: A systematic review. Epilepsia. 2022;63(2):375–87.
16. Spedicati B, Morgan A, Pianigiani G, Musante L, Rubinato E, Santin A, et al. Challenging Occam's Razor: Dual molecular diagnoses explain entangled clinical pictures. Genes (Basel). 2022;13:2023.
17. Montanucci L, Lewis-Smith D, Collins RL, Niestroj L-M, Parthasarathy S, Xian J, et al. Genome-wide identification and phenotypic characterization of seizure-associated copy number variations in 741,075 individuals. Nat Commun. 2023;14:4392.
18. Meiser B, Irle J, Lobb E, Barlow-Stewart K. Assessment of the content and process of genetic counseling: A critical review of empirical studies. J Genet Couns. 2008;17:434–51.
19. Ying CS. The effects of decision aids for genetic counselling among people considering genetic testing: A systematic review. J Clin Nurs. 2023;32:6796–810.
20. Rink B, Kuller J. What are the required components of pre- and post-test counseling? Semin Perinatol. 2018;42:287–9.
21. Guo HL, Jing X, Sun JY, Hu YH, Xu ZJ, Ni MM, et al. Valproic Acid and the Liver Injury in Patients with Epilepsy: An Update. Curr Pharm Des. 2019;25:343–51.
22. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24.
23. McCormick EM, Lott MT, Dulik MC, Shen L, Attimonelli M, Vitale O, et al. Specifications of the ACMG/AMP standards and guidelines for mitochondrial DNA variant interpretation. Hum Mutat. 2020;41:2028–57.
24. Riggs ER, Andersen EF, Cherry AM, Kantarci S, Kearney H, Patel A, et al. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). Genet Med. 2020;22:245–57.
25. Slavin TP, Manjarrez S, Pritchard CC, Gray S, Weitzel JN. The effects of genomic germline variant reclassification on clinical cancer care. Oncotarget. 2019;10:417–23.
26. Wright M, Menon V, Taylor L, Shashidharan M, Westercamp T, Ternent CA. Factors predicting reclassification of variants of unknown significance. Am J Surg. 2018;216:1148–54.
27. Miller DT, Lee K, Gordon AS, Amendola LM, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23:1391–8.
28. Rothstein MA. Can genetic nondiscrimination laws save lives? Hastings Cent Rep. 2021;51:6–7.
29. Joly Y, Dupras C, Pinkesz M, Tovino SA, Rothstein MA. Looking Beyond GINA: Policy approaches to address genetic discrimination. Annu Rev Genomics Hum Genet. 2020;21:491–507.
30. Sánchez Fernández I, Loddenkemper T, Gaínza-Lein M, Sheidley BR, Poduri A. Diagnostic yield of genetic tests in epilepsy: A meta-analysis and cost-effectiveness study. Neurology. 2019;92:e418–28.
31. Zion TN, Berrios CD, Cohen ASA, Bartik L, Cross LA, Engleman KL, et al. Insurance denials and diagnostic rates in a pediatric genomic research cohort. Genet Med. 2023;25: 100020.
32. Biesecker B. Genetic counseling and the central tenets of practice. Cold Spring Harb Perspect Med. 2020;10: a038968.
33. Franceschini N, Frick A, Kopp JB. Genetic testing in clinical settings. Am J Kidney Dis. 2018;72:569–81.
34. Amendola LM, Muenzen K, Biesecker LG, Bowling KM, Cooper GM, Dorschner MO, et al. Variant classification concordance using the ACMG-AMP variant interpretation guidelines across nine genomic implementation research studies. Am J Hum Genet. 2020;107:932–41.
35. Hnatiuk MJ, Noss R, Mitchell AL, Matthews AL. The current state of genetic counseling assistants in the United States. J Genet Couns. 2019;28:962–73.
36. Wojcik MH, Reuter CM, Marwaha S, Mahmoud M, Duyzend MH, Barseghyan H, et al. Beyond the exome: What's next in diagnostic testing for Mendelian conditions. Am J Hum Genet. 2023;110:1229–48.
37. Lesperance MM, Winkler E, Melendez TL, Yashar BM. "My Plate is Full": Reasons for declining a genetic evaluation of hearing loss. J Genet Couns. 2018;27:597–607.
38. Brett GR, Martyn M, Lynch F, de Silva MG, Ayres S, Gallacher L, et al. Parental experiences of ultrarapid genomic testing for their critically unwell infants and children. Genet Med. 2020;22:1976–85.
39. Heiniger L, Butow PN, Price MA, Charles M. Distress in unaffected individuals who decline, delay or remain ineligible for genetic testing for hereditary diseases: a systematic review. Psychooncology. 2013;22:1930–45.
40. Pereira S, Gutierrez AM, Robinson JO, Christensen KD, Genetti CA, Blout Zawatsky CL, et al. Parents' decision-making regarding whether to receive adult-onset only genetic findings for their children: Findings from the BabySeq Project. Genet Med. 2023;25: 100002.
41. Heyne HO, Pajuste F-D, Wanner J, Onwuchekwa JID, Mägi R, Palotie A, et al. Polygenic risk scores as a marker for epilepsy risk across lifetime and after unspecified seizure events [Internet]. medRxiv; 2023. Available from: https://www.medrxiv.org/content/10.1101/2023.11.27.23297542v1
42. Rooney K, van der Laan L, Trajkova S, Haghshenas S, Relator R, Lauffer P, et al. DNA methylation episignature and comparative epigenomic profiling of *HNRNPU*-related neurodevelopmental disorder. Genet Med. 2023;25: 100871.
43. Kobow K, Blümcke I. The methylation hypothesis: Do epigenetic chromatin modifications play a role in epileptogenesis? Epilepsia. 2011;52:15–9.
44. Pedersen S, Kverneland M, Nakken KO, Rudi K, Iversen PO, Gervin K, et al. Genome-wide decrease in DNA methylation in adults with epilepsy treated with modified ketogenic diet: A prospective study. Epilepsia. 2022;63:2413–26.
45. Meienberg J, Bruggmann R, Oexle K, Matyas G. Clinical sequencing: is WGS the better WES? Hum Genet. 2016;135:359–62.
46. Bahlo M, Bennett MF, Degorski P, Tankard RM, Delatycki MB, Lockhart PJ. Recent advances in the detection of repeat expansions with short-read next-generation sequencing. F1000Res. 2018;7:F1000 Faculty Rev-736.