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PRACTICE GUIDELINE

Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors

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Abstract

Epilepsy, defined by the occurrence of two or more unprovoked seizures or one unprovoked seizure with a propensity for others, affects 0.64% of the population and can lead to significant morbidity and mortality. A majority of unexplained epilepsy (seizures not attributed to an acquired etiology, such as trauma or infection) is estimated to have an underlying genetic etiology. Despite rapid progress in understanding of the genetic underpinnings of the epilepsies, there are no recent evidence-based guidelines for genetic testing and counseling for this population. This practice guideline provides evidence-based recommendations for approaching genetic testing in the epilepsies using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision framework. We used evidence from a recent systematic evidence review and meta-analysis of diagnostic yield of genetic tests in patients with epilepsy. We also compiled data from other sources, including recently submitted conference abstracts and peer-reviewed journal articles. We identified and prioritized outcomes of genetic testing as critical, important or not important and based our recommendations on outcomes deemed critical and important. We considered the desirable and undesirable effects, value and acceptability to relevant stakeholders, impact on health equity, cost-effectiveness, certainty of evidence, and feasibility of the interventions in individuals with epilepsy. Taken together, we generated two clinical recommendations: (1) Genetic testing is strongly recommended for all individuals with unexplained epilepsy, without limitation of age, with exome/genome sequencing and/or a multi-gene panel (>25 genes) as first-tier testing followed by chromosomal microarray, with exome/genome sequencing conditionally recommended over multi-gene panel. (2) It is strongly recommended that genetic tests be selected, ordered, and interpreted by a qualified healthcare provider in the setting of appropriate pre-test and post-test genetic counseling. Incorporation of genetic counselors into neurology practices and/or referral to genetics specialists are both useful models for supporting providers without genetics expertise to implement these recommendations.

[Correction added on November 09, 2022, after first online publication. Endorsement information is added in this version.]

KEYWORDS
epilepsy, genetic counseling, genetic testing, practice guideline

1 | INTRODUCTION

Epilepsy is a common condition defined as the occurrence of two or more unprovoked seizures, one unprovoked seizure with a risk of developing additional seizures or the diagnosis of an epilepsy syndrome (Fisher et al., 2014). It has a prevalence of 0.64% worldwide (Fiest et al., 2017). At least one-third of individuals with epilepsy do not achieve seizure control with available anti-seizure medications (ASM) (Loscher, 2016). Many individuals with epilepsy, particularly those with early onset epilepsy, have neurodevelopmental comorbidities, including intellectual disability (ID) and autism spectrum disorder (ASD). Many genetic epilepsy syndromes have been described (Hebbar & Mefford, 2020; McTague et al., 2016; Thakran et al., 2020), and a majority of otherwise unexplained epilepsy, that which cannot be attributed to an acquired etiology such as trauma, infection or stroke, is now assumed to have an underlying genetic etiology (Helbig & Lowenstein, 2013; McTague et al., 2016; Thomas & Berkovic, 2014). A genetic diagnosis for an individual with epilepsy may have direct clinical implications by informing choice of ASM, reducing additional invasive tests or procedures, establishing eligibility for clinical trials, and informing reproductive decision-making and/or cascade testing for the patient or their at-risk relatives.

The advent of next-generation sequencing (NGS) technology has led to an exponential increase in the discovery of novel genetic etiologies as well as the expansion of phenotypic spectra of established genetic epilepsy syndromes (McTague et al., 2016). The epilepsies are genetically and phenotypically heterogeneous, often with broad and overlapping phenotypes, which can complicate the diagnostic process (McTague et al., 2016). Technological advances in genetic testing have allowed for enhanced interrogation of the genome. The testing repertoire has expanded from genome-wide comparative genomic hybridization/chromosome microarray (CGH/CMA) and single gene tests to multi-gene panels (MGP), exome sequencing (ES), and genome sequencing (GS). Each modality has specific benefits and limitations which require consideration when approaching clinical testing in this population. GS has the greatest potential to address many of the limitations of CGH/CMA, MGP, and ES.

Despite recent progress in epilepsy genetics research, there are limited consensus- and evidence-based clinical practice guidelines for genetic testing and counseling for individuals with epilepsy. The most recent evidence-based review was completed in 2015 by the International League Against Epilepsy (ILAE) Commission of Pediatrics, which endorsed genetic evaluation for patients suspected to carry a diagnosis of Dravet syndrome and other developmental and epileptic encephalopathies (DEEs), in the setting of appropriate counseling and ability to interpret results (Wilmshurst et al., 2015). Consensus-based recommendations have included the provision of genetic testing in general (Andrade et al., 2017; Brodie et al., 1997; Devinsky et al., 2015; Guideline Development Group, 2009), genetic counseling and discussion of reproductive recurrence risk (Guideline Development Group, 2009; Hesdorffer et al., 2011; National Clinical Guideline Centre (UK), 2012) and testing of *SCN1A* variants for individuals with Dravet syndrome (Burgunder et al., 2010). However, these consensus-based and early evidence-based practice guidelines have been limited in scope or were developed prior to widespread adoption of NGS technologies. Most recommendations for genetic testing have been incorporated into more comprehensive guidelines for the clinical evaluation of individuals with epilepsy, with little guidance on testing strategy. Although there are no published data, our working group has observed that the lack of current guidelines leads to inconsistency in patient care, with some patients receiving disparate, incomplete or in some cases, no genetic evaluation. Overall, there is a clear need for an updated evidence-based practice guideline addressing genetic testing and counseling for individuals with epilepsy to support clinical decision-making, access to genetic counseling, and reimbursement for genetics services. A recent systematic evidence review (SER) and meta-analysis was published evaluating the yield and non-yield outcomes of genetic testing in the unexplained epilepsies (Sheidley et al., 2022). Here, we used this SER and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision framework to create an evidence-based clinical practice guideline for genetic testing and counseling in the epilepsies.

What is known about this topic

A significant proportion of unexplained epilepsies have underlying genetic etiologies. There are no current evidence-based guidelines for genetic testing and counseling for individuals with unexplained epilepsy, leading to inconsistency in patient care.

What this paper adds to the topic

This is the first evidence-based guideline that outlines recommendations for genetic testing and genetic counseling for all individuals with unexplained epilepsy.

2 | METHODS

2.1 | Workgroup selection and composition

In 2016, the National Society of Genetic Counselors (NSGC) solicited proposals for evidence-based clinical practice guidelines. A proposal for an epilepsy genetics clinical practice guideline was written

and submitted to NSGC in 2016 on behalf of a professional group of genetic counselors specializing in epilepsy (EpiGC; https://www.epigc.net/). Once accepted, NSGC recruited genetic counselors (LS, SC, KP, BRS, and NL) and a medical geneticist (NW) with expertise in epilepsy for this practice guideline. A methodologist (JM) was added to the guideline author group as a non-voting member to provide methodological guidance for the Evidence to Decision process in 2020. In March 2021, one author withdrew from participating in the remainder of the GRADE process and drafting the recommendations due to time commitment.

Applicants were reviewed by NSGC's Board of Directors, and the Practice Guidelines and Conflict of Interest (COI) Committees. NSGC requires practice guideline authors to complete a COI disclosure survey annually, starting at the formation of the author group. Authors must also report interim COI changes to the NSGC Practice Guideline Committee (PGC) within 30 days. The PGC categorizes COI into two tiers. Tier 1 COI includes any direct, personal financial benefit that is ongoing or within the previous 12 months from a commercial entity that may benefit from the document. Tier 1 COI includes research funding from a commercial entity for 25 percent or greater of an author's salary. Tier 2 COI includes limited consultant roles, paid stipends/travel, and ongoing consultancy roles with companies that are involved in health care, but may not directly benefit from the document. The PGC assesses the overall balance of COI for the author group and requires that no more than 40 percent of authors have Tier 1 COI and no more than 80 percent have either Tier 1 or Tier 2 COI. Lead authors must be free of Tier 1 COI for the entirety of the development of the document and can only have Tier 2 COI if serving alongside a co-lead author with no Tier 1 or Tier 2 COI.

2.2 | Systematic evidence review process

The primary basis of evidence for the guideline was an NSGC-supported SER. Genetic counselors interested in participating in a SER were recruited by NSGC in 2016. A methodologist and a pediatric epileptologist with extensive expertise in genetics were also added to the author group. One genetic counselor was appointed by NSGC as the chair of the SER author group and also as a guideline panelist (BRS) to improve coordination between the groups. The practice guideline panelists met with the SER authors to identify the clinical question, population, intervention, comparators, outcomes, timing and setting (PICOTS) of interest (Table 1).

The SER was conducted following standard methods which were reported in Sheidley et al. (2022). Briefly, the SER authors developed a search strategy, inclusion and exclusion criteria based on the input from the guideline panel to align to the PICOTS. SER authors screened the peer-reviewed literature published up to 18 December 2020 and reviewed potentially relevant articles in full according to the a priori-developed inclusion and exclusion criteria. Included studies were in English language, otherwise were not limited by population or study location. Data were extracted and the risk of bias assessed for the included articles as described in Sheidley et al. (2022). All SER stages were performed in duplicate, by reviewers blinded to the other's decision, with conflicts adjudicated through discussion or, if necessary, with the aid of a third reviewer.

TABLE 1 Population, intervention, comparator, outcomes, timing and setting (PICOTS) utilized in the epilepsy systematic evidence review (adapted from Sheidley et al., 2022, with permission).

Population	Individuals of any age with a diagnosis of any type of epilepsy
Intervention	Genetic/genomic testing relevant to epilepsy limited to GS, ES, MGP, GCH/CMA
Comparator	No genetic testing
Outcomes	Prognosis, Changes to treatment/medical management; Reproductive recurrence risk counseling, Psychosocial well-being, Test yield
Timing	Unspecified
Setting	Any clinical or research setting

Abbreviations: CGH/CMA, genome-wide comparative genomic hybridization/chromosome microarray; ES, exome sequencing; GS, genome sequencing; MGP, multi-gene panel.

2.3 | Data synthesis and assessing the certainty of the evidence

From 5985 articles screened, 154 were included in random-effects meta-analyses of diagnostic yield, and 43 further provided evidence of clinical utility and were narratively synthesized (Sheidley et al., 2022). The evidence from the SER was provided to the guideline workgroup for review. For each outcome, certainty of the evidence was based on the overall risk of bias of included studies, heterogeneity (inconsistency), indirectness, and imprecision of the results and reported as either high, moderate, low or very low.

2.4 | Evidence to recommendation process

The guideline workgroup used the GRADE Evidence to Decision framework to arrive at a recommendation. In addition to the desirable (benefits) and undesirable (harms) effects of the interventions, the panel considered the certainty of the evidence, patient values, the

impacts on health equity of genetic testing and genetic counseling, the acceptability of the interventions to relevant stakeholders, feasibility of implementation and cost-effectiveness to inform the strength and direction of the recommendation (Files S1 and S2). For domains where no peer-reviewed literature was identified in the SER by Sheidley et al. (2022), additional searches for peer-reviewed articles, recent (2020) conference abstracts or proceedings, and economic analyses were undertaken. We executed targeted searches for data pertaining to equity, acceptability, feasibility, and cost-effectiveness (Files S3 and S4). Additionally, given the rapid advancements in genetics knowledge in the epilepsies, we included relevant new evidence that was published after the last search date of the SER (December 2020).

Summaries of the evidence (peer-reviewed) and additional considerations (non-peer-reviewed evidence and clinical evidence) for each domain were documented in a table in a shared Google Drive folder that each guideline workgroup member had access to at all times (See File S5).

Judgments for each domain assessed in the Evidence to Decision framework were made during conference calls with the authors. Votes were obtained verbally or written as needed. Consensus (≥80% agreement) was required to finalize a judgment; dissent of any working group member unable to be resolved through discussion was documented with their rationale. Recommendation strengths were applied as defined by GRADE. A "strong" recommendation is one in which the working group concludes that the desirable effects of adhering to the recommendation outweigh the undesirable effects. A "conditional" recommendation is one for which the desirable effects of adherence likely outweigh the undesirable effects, but the working group is not confident of the trade-offs (Andrews et al., 2013; Guyatt et al., 2008).

2.5 | Draft recommendation

The draft recommendations were reviewed and revised by the entire guideline working group. Unanimous agreement was obtained for the final recommendation statements (File S6). A drafted guideline manuscript was prepared by working group members (LS, NL) and methodologist (JM), which was iteratively revised by the entirety of the guideline working group.

2.6 | External peer-review process

The guideline manuscript underwent external peer review through the standard peer-review process at the Journal of Genetic Counseling. Additionally, a draft of the manuscript was reviewed and critically appraised by NSGC membership, the NSGC Practice Guideline Committee, the NSGC Ethics Advisory Group, NSGC Legal, and the NSGC Board of Directors. The PG workgroup's co-lead authors and the methodologist revised the manuscript in response to external peer-review comments and those from the above NSGC reviews. Changes to the recommendation statement were required to be unanimously accepted by the full PG workgroup.

3 | RECOMMENDATIONS

These recommendations are relevant to genetic testing and counseling for individuals with unexplained epilepsies. Epilepsy is considered unexplained when—according to history, physical examination, imaging and other standard evaluations—the cause of seizures cannot be attributed to a structural, metabolic, infectious, immunological, or other acquired etiology such as trauma or stroke. Notably, metabolic or structural etiologies may be acquired or genetic, the latter of which may indicate targeted germline or somatic genetic testing (Scheffer et al., 2017). Specific recommendations relevant to the clinical evaluation of an individual presenting with new onset seizures, such as metabolic, mitochondrial, and immunological evaluations, are beyond the scope of this guideline. Such evaluations are under the direction of current guidelines pertaining to routine neurological care. If seizures are suspected to be part of a multi-system presentation in which there are extra-neurological features, or the constellation of features suggests a specific syndrome or genetic etiology, targeted testing most appropriate for that clinical indication should be considered and pursued separately (e.g., methylation studies for Angelman syndrome or triplet repeat expansion for fragile X syndrome). A referral to a medical geneticist may be necessary for a full evaluation and recommendations for testing.

Recommendation 1: We strongly recommend that individuals with unexplained epilepsy be offered genetic testing, without limitation of age.

a. We strongly recommend comprehensive, multi-gene testing, such as ES/GS or MGP as a first-tier test. We conditionally recommend ES/GS over MGP as the first-tier test.
b. The MGP panel should have a minimum of 25 genes and include copy number analysis.

4 | RATIONALE

Genetic testing for individuals with unexplained epilepsy is strongly recommended, as a combination of evidence from the SER (Sheidley et al., 2022) and clinical experiences of the working group support that the benefits of adhering to this recommendation would outweigh potential harms or undesirable effects. The SER included patients of any age (Table 1), however did not stratify yield based on age. A position paper by the International League Against Epilepsy (ILAE) (Riney et al., 2022) describes variable ages of onset for a number of genetic epilepsy syndromes from the neonatal period to adulthood (McTague et al., 2016). As such, we recommend that the

provision of genetic testing should not be limited by age. The potential benefits and harms of the following outcomes as reported by the SER were considered by the working group: change in treatment and management, establishment of disease prognosis, and change in reproductive recurrence risk estimation.

4.1 | Treatment and management

Identifying a genetic etiology may inform ASM selection, direct initiation of the ketogenic diet (KD), alter plans for epilepsy surgery, and allow patients to be referred for gene-specific clinical trials in 12%–80% of individuals with a genetic diagnosis (Sheidley et al., 2022). Beyond targeted treatments, a diagnosis may inform decisions to continue ASM, wean ASM in cases of self-resolving epilepsies, or initiate palliative care in life-limiting conditions (O'Quinn & Giambra, 2014). Due to the individually rare nature of each diagnosis, some interventions have been used in the absence of clinical trials (i.e., off-label medication use) and adverse events have been reported (Bearden et al., 2014; McGraw et al., 2021; Mullen et al., 2018; Pierson et al., 2014). This highlights the need for genetically stratified clinical trials in epilepsy and is an active area of research within the community (Epi, 2015; Thakran et al., 2020). One must also consider the psychological impact of families expecting to receive a genetic diagnosis that would lead to a precision treatment or change in management, only to learn in many instances that, as of yet, no such benefit exists. Both pre-and post-test counseling regarding potential benefits and limitations of testing are critically important to the testing process.

4.2 | Prognosis

A genetic diagnosis may provide enhanced information beyond what would have been prognosticated based on the epilepsy phenotype alone. Examples include expectations regarding developmental outcomes and the identification of elevated risk for sudden unexpected death in epilepsy (SUDEP) risk (Sheidley et al., 2022). This type of information may help families obtain support services or influence decisions to procure a seizure monitoring device. While not captured in the literature, it has been the clinical experience of the working group that in addition to recurrence risk estimates, the prognosis of a child's epilepsy factors into parental reproductive decision-making. For example, an individual or a parent of a child with non-refractory epilepsy and typical development may choose to have additional children without prenatal testing, even if the recurrence risk is relatively high (i.e., *PRRT2*). Conversely, the parent of a child with a DEE due to a de novo variant may use prognosis information in reproductive planning due to the challenges of caring for a child with complex medical needs. Potential harms may include the psychological impact of receiving a diagnosis of a newly described condition for which there is limited prognostic data or a neurodegenerative condition with a poor prognosis.

4.3 | Reproductive recurrence risk

Among the studies included in the SER (Sheidley et al., 2022), very little systematically collected or reported data exist regarding potential benefits or harms of reproductive recurrence risk counseling in the epilepsies. Several studies included in the SER revealed anecdotal reports of families that used a genetic diagnosis for prenatal testing in subsequent pregnancies (Palmer et al., 2018; Papuc et al., 2019; Sheidley et al., 2022). A genetic diagnosis enables individuals to pursue prenatal testing through amniocentesis or chorionic villus sampling (CVS), and in some instances preimplantation genetic testing (PGT). We highlight an important distinction between the ability to provide reproductive recurrence risk counseling and an individual's use of this information for reproductive management, acknowledging the importance of nondirective, client-centered counseling, further limiting the scope of what is available in published data. Individuals and families may also use recurrence risk estimates to prepare emotionally or financially to have a subsequent child and/or to prepare for the onset of seizures in future children. Potential harms concerning reproductive recurrence risk estimates from obtaining a genetic diagnosis may include newfound awareness of recurrence and ensuing distress to families not previously aware that risk for developing epilepsy could be inherited.

4.4 | Approach to testing

We strongly recommend comprehensive, multi-gene testing (such as ES/GS or MGP) as a first-tier test, with ES/GS recommended conditionally over MGP. Recommended tiered testing strategy is outlined in Figure 1 and described below. While providing general guidance, determination of testing approach should be left to the clinical judgment of the ordering practitioner.

The working group strongly considered diagnostic yield in adjudicating the recommended testing strategy. The diagnostic yield of genetic testing in the epilepsies differed significantly based on the type of genetic test utilized (Sheidley et al., 2022). GS had the highest diagnostic yield (48%), while CGH/CMA had the lowest yield (9%; Sheidley et al., 2022). Diagnostic yields from ES and MGP appeared to be comparable (24% and 19%, respectively; Sheidley et al., 2022). However, one limitation reported in the SER (Sheidley et al., 2022) is that many studies included cohorts where subjects had previous negative genetic testing (e.g., MGP) and then went on to have ES. In many instances, it was not possible to determine whether prior genetic testing had been done and/or ES yield published was not delineated between those with or without previous genetic testing. Overall, this could suggest that the diagnostic yield of ES as a first-tier test may be higher than what was reported.

The working group conditionally recommends ES/GS over MGP as the first-tier test. The working group notes that ES/GS has many advantages over MGP in terms of diagnostic yield, attributable to the genetic heterogeneity and rapid rate of gene discovery in the

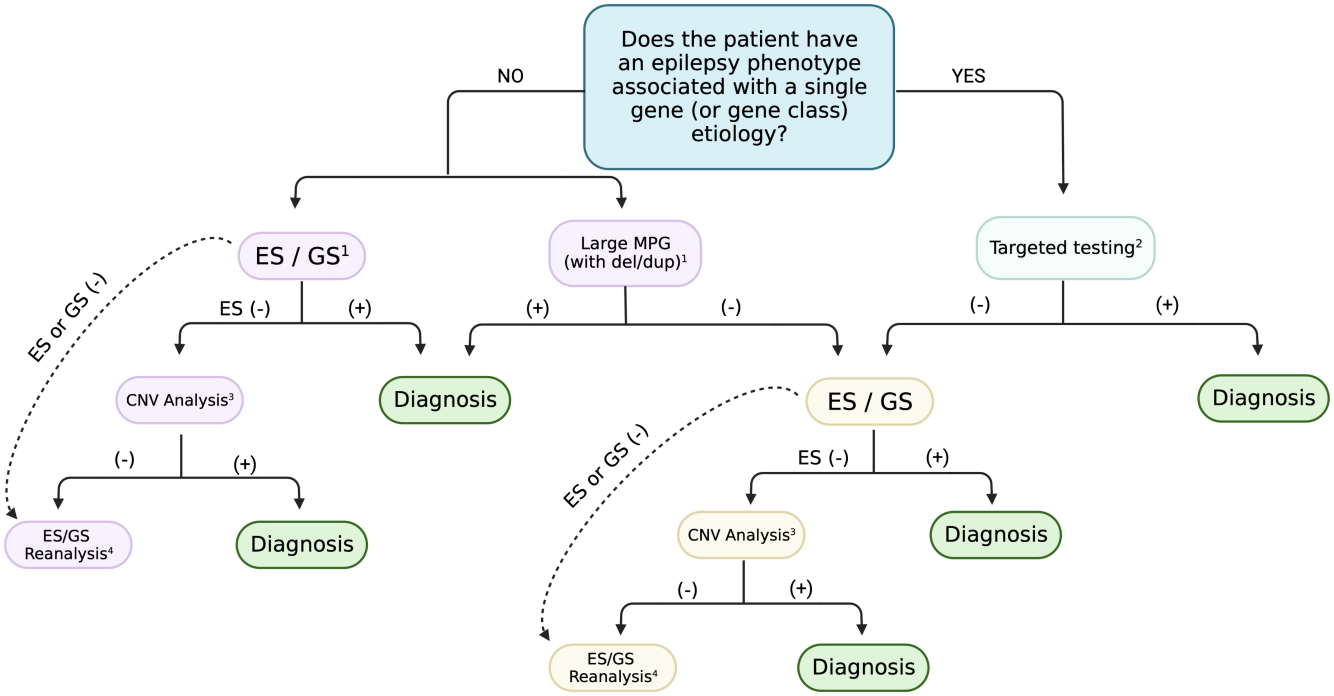

FIGURE 1 Recommended genetic testing strategy. ES: exome sequencing. GS: genome sequencing. MGP: multi-gene panel. (+): positive result. (–): Negative or non-diagnostic result. CNV: copy number variant. [1]ES/GS conditionally recommended over MGP due to higher yield. MGP may be used under certain clinical scenarios, or if ES/GS is not accessible. [2]Targeted testing includes any single gene testing, phenotype-driven panel, and/or repeat expansion analysis in genes for which that may be common. [3]CNV analysis may be indicated following negative ES if adequate CNV analysis was not included. This may include chromosomal microarray, or gene-specific exon-level deletion/duplication analysis if not previously done. [4]Reanalysis: If, upon completion of the genetic workup, a diagnosis is not achieved, reanalysis of ES/GS data over time and/or reinterpretation of any variants of uncertain significance identified is recommended. *Note*: While providing general guidance, determination of testing approach should be left to the clinical judgment of the ordering provider.

epilepsies. The recommendation of ES/GS as a first-tier test in the epilepsies mirrors that for other neurodevelopmental disorders, such as ID and ASD (Srivastava et al., 2019) and recent guidelines developed for genetic testing in individuals presenting with DD and ID (Manickam et al., 2021). However, for specific clinical scenarios outlined below, MGP may be indicated as the first test.

The benefits and limitations of all testing modalities are shown in Table 2. These are not specific to the epilepsies, and this table serves as general guidance only. Testing methodology is laboratory dependent, and genetic testing technologies continue to evolve (Amarasinghe et al., 2020; Yuan et al., 2020). ES/GS allows for synchronized analysis of all known epilepsy genes, in addition to newly identified and candidate genes. ES/GS also incorporates informative relatives, such as biological parents, when available in concurrent, trio-based analysis, to aid in variant interpretation (i.e., determining de novo status for autosomal dominant conditions or allelic segregation of variants for autosomal recessive conditions). GS is a single, comprehensive genetic test with more uniform coverage and the ability to detect structural variants, intronic variants that may create cryptic splice sites, and some repeat expansions. The ability to detect all repeat expansions is continuing to evolve, so ordering providers should discuss with the laboratory regarding coverage if there is a region of interest and follow-up as advised. If GS is negative, we recommend continual reanalysis over time. ES can also be used as a first test, as GS continues to become more widely accessible. ES can detect coding sequence variants, as well as flanking intronic variants that may impact splicing. NGS technology in ES has begun to detect copy number variants (CNVs) and some laboratories report these out, but CNV detection remains limited in ES (Zhao et al., 2020). Detection of single-exon-level deletions and duplications remains unreliable currently, and larger, multi-gene CNVs may be missed by ES. Repeat expansions are also not detectable via ES. If ES is negative, we recommend that healthcare providers consider pursuing other genetic tests such as (1) exon-level deletion/duplication analysis via a targeted array or other designated deletion/duplication-based MGP, if single gene etiologies are highly suspected, (2) CGH/CMA and (3) ES reanalysis over time. While yield of ES/GS reanalysis could not be identified in the SER, this recommendation is based on literature showing that NGS reanalysis can provide new diagnoses specifically within the epilepsy population (Epilepsy Genetics Initiative, 2019; Rochtus et al., 2020).

MGPs are valuable clinical tools that can be employed in a number of clinical scenarios, for example, when an individual presents with a defined epilepsy syndrome for which a subset of genes should be interrogated more robustly than through ES when GS is unavailable. Additionally, if urgent results are required and rapid ES/GS is unavailable, a targeted MGP may be considered. MGPs may also be utilized as a first-tier test when access to ES/GS, or the additional genetic counseling required to implement such testing, may be limited. When

TABLE 2 Standard scope and limitations of testing modalities.

	Genetic test			
	CGH/CMA	MGP	ES	GS
Variant detection				
Single nucleotide variants (coding region)	−	+	+	+
Single vucleotide variants (non-coding region)	−	(−)	(−)	+
Nucleotide Repeats	−	Δ	−	Δ
Single Exon CNV	Δ	(+)	−	+
Multi Exon CNV	+	(+)	Δ	+
Full Gene CNV	+	(+)	Δ	+
Multi Gene CNV	+	−	Δ	+
Structural Rearrangements	−	−	−	+
Methodology				
Targeted gene list	−	+	−	−
Potential for variants in novel/candidate genes	+	+	+	+
Concurrent, trio-based analysis standard	−	−	+	+

Note: For CGH/CMA's, single-exon CNV detection is laboratory and gene dependent. For MGPs, laboratories may include analysis for recurrent intronic variants for specific genes, and/or repeat expansions for genes in which those are common. Most MGP's include concurrent CNV analysis; however, some MGP's may only include next-generation sequencing technology and not a secondary methodology for robust CNV detection, so clinicians should inquire with the laboratory. For ES, laboratories may include targeted analysis for select intronic variants. CNV analysis is an emerging technology and the size of CNV detection is variable. For GS, detection of repeat expansions is currently limited and laboratory dependent, often to the presence of an expansion but repeat size may require follow-up testing.

Technologies are continuously evolving. The information represented above may not reflect all possible nuances of testing, and/or the most recent advances in testing technology. This information is meant to provide points to consider when selecting a testing modality; however, the platforms used may vary widely among different laboratories and healthcare providers may inquire with the laboratory to determine coverage of genes, variant types, and regions of interest, specifically.

Abbreviations: CGH/CMA, comparative genomic hybridization/chromosomal microarray analysis; ES, exome sequencing; GS, genome sequencing; MGP, multi-gene panel; Δ, variable or limited; may be laboratory or gene/region dependent or an emerging technology; −, not routinely offered; +, routinely offered; (+) or (−), caveats, as described.

pursued, we recommend the use of MGPs that incorporate deletion/duplication analysis. Currently, the use of NGS with deletion/duplication analysis is laboratory dependent. The SER included all MGPs but did not delineate how deletion/duplication analysis was utilized or impacted yield. However, 9%–11% of pathogenic variants reported to date within the epilepsy population have been exon-level deletions and duplications (Lindy et al., 2018; Rim et al., 2018), making this analysis clinically relevant for inclusion in these guidelines. Other benefits of MGPs in designated laboratories include the availability of additional methodologies to detect repeat expansions for genes in which this mechanism is common (e.g., *CSTB*, *ARX*), which may be included with the order and cost of some panels or need to be added on separately. However, as some laboratories move toward the utilization of a genome backbone, detection of exon-level deletions and duplications and repeat expansions may improve. MGPs may have higher depth of coverage over some genes compared with ES/GS, which could increase the likelihood of detecting post-zygotic or somatic mosaicism. Given these nuances, the ordering provider must have expertise in the specific, possible variant type(s) based on phenotype and gene(s) of interest and must inquire with the laboratory when formulating testing approach. One could consider choosing a specific laboratory based on the inclusion of additional testing modalities based on a patient's specific presenting phenotype.

When epilepsy MGPs are utilized, we recommend the use of larger panels (>25 genes). The diagnostic yield was found to differ significantly based on the size of the panel, as MGPs with more than 25 genes had a consistently higher yield (20%–25%) than MGPs with fewer than 25 genes (7%; Sheidley et al., 2022). While the SER did not provide data on gene content, the working group notes its importance. Providers should ensure genes of interest are included, while also considering the genetic heterogeneity of the epilepsies and phenotypic overlap among genes as to not limit gene selection. Most standard, clinically available epilepsy MGPs include a prevailing list of established and commonly implicated epilepsy genes, while substantially larger panels may include newer epilepsy-associated genes or genes with preliminary evidence. Smaller, epilepsy syndrome-based MGPs should only be considered for individuals with very specific phenotypic profiles for which a defined set of genes have been identified (such as neuronal ceroid lipofuscinoses or progressive myoclonic epilepsies). However, care should be taken given the phenotypic overlap of some of the epilepsy syndromes when approaching such targeted testing.

If ES and MGP are negative, we recommend CGH/CMA testing, which has a lower, but still significant, overall diagnostic yield (9%) in the epilepsies (Sheidley et al., 2022). CGH/CMA are used to detect larger CNVs, such as multi-exon, single gene or microdeletions/microduplications. This test may not detect single-exon deletions or duplications in all genes. Some laboratories have established tests that may include exon-level coverage of some genes but may not include all genes or all exons in epilepsy-relevant genes.

4.5 | Indications for testing

When considering *whom* to test, providers should exercise clinical judgment based on the outcomes outlined above. Individuals with neonatal or infantile-onset seizures, those with DEE or epilepsy plus other neurodevelopmental comorbidities have the highest diagnostic yield to date (Costain et al., 2019; Sheidley et al., 2022; Stefanski et al., 2021; Symonds et al., 2019; Wang et al., 2021). Diagnostic yields remain significant among other age groups (Helbig et al., 2016; Stefanski et al., 2021), and among individuals with generalized and

focal epilepsies in the absence of other reported clinical features (Sheidley et al., 2022). Therefore, later ages of onset or absence of comorbidities should not preclude genetic testing. Furthermore, reported outcome data on changes in treatment and management, ability to establish prognosis, and recurrence risk counseling have not been stratified based on phenotype (Sheidley et al., 2022). While individuals with DEE are currently more likely to obtain a genetic diagnosis, there are no data to suggest that a molecular diagnosis for this patient population is more or less likely to be impactful than a molecular diagnosis for individuals/families impacted by other epilepsy subtypes. In the clinical experiences of the working group, all individuals with epilepsy, regardless of phenotype, have the potential to benefit from a genetic diagnosis. As testing increases across all phenotypic groups, our understanding of the genetic architecture of the epilepsies is likely to expand, thus increasing diagnostic yield across all categories of the epilepsies. This has already been demonstrated with gene variants that were originally described in patients with DEE and later identified in patients with less severe phenotypes, suggesting variable expressivity (Anand et al., 2016).

4.6 | Balance of effects

Overall, the balance between the desirable and undesirable effects favors genetic testing in individuals with epilepsy. Many individuals would receive a genetic diagnosis, the proportion of which will likely increase as knowledge increases with wider utilization of testing. A diagnosis clarifies prognosis, provides recurrence risk estimation, and informs management in a subset of individuals with a diagnosis. Potential harms were deemed trivial and were largely psychological in nature, which could be managed with appropriate pre- and post-test counseling.

4.7 | Certainty of evidence

Using the GRADE framework, the panel deemed that the evidence pertaining to yield-based outcomes is of *moderate certainty*. The meta-analysis did not identify randomized control trials; however, a large number of studies were included (n = 154), reporting on 174 distinct cohorts, encompassing more than 30,000 patients (Sheidley et al., 2022). The risk of bias for the included studies was moderate or severe. Despite this high risk of bias, the preponderance of evidence leads to high confidence that the data are accurate. Although not a primary aim of many of the included studies, non-yield outcome data regarding treatment/management, prognosis, and reproductive counseling are consistent among studies in which they were reported.

The psychosocial impact of a genetic diagnosis on a patient and the patient's family is an additional factor that warrants consideration. Identifying an underlying genetic etiology may end the diagnostic odyssey and provide an alternative explanation for parents who have experienced guilt or self-blame for "causing" their child's epilepsy. Conversely, parents who discovered that they have passed on a dominant genetic epilepsy may experience newfound feelings of guilt and shame. Although, for individuals and families with non-revealing ('negative') genetic findings or genetic results that do not immediately impact management, they may find comfort in knowing that they did everything possible and that treatable epilepsies have been investigated and not identified.

Recommendation 2: We strongly recommend that genetic tests be selected, ordered, and interpreted by a qualified healthcare provider in the setting of appropriate pre-test and post-test genetic counseling.

5 | RATIONALE

Genetic testing by a qualified healthcare provider is strongly recommended, as a combination of evidence from the SER (Sheidley et al., 2022), reports of non-yield outcomes of genetic testing in other clinical settings, and clinical evidence of the working group indicate benefits of adhering to this recommendation.

Here, we define a qualified healthcare provider as an individual with specialized training and/or knowledge in genetics who can adequately discuss the scope, benefits, limitations, and psychological implications of genetic testing and has the ability to evaluate and interpret genetic test results in the context of an individual's presenting phenotype. We define genetic counseling as described in part by the NSGC, "Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease" (Resta et al., 2006). Genetic tests for the epilepsies are currently ordered by a wide variety of healthcare providers, some of whom have limited formal training in genetics. In some situations, it may be appropriate for a genetic counselor to work with a non-genetics provider to select and order genetic tests and provide genetic counseling. However, the working group recognizes that this may not be possible in every clinical setting. We emphasize that non-genetics healthcare providers who order genetic tests without support from genetic counselors or geneticists should have a strong grounding in genetics with extensive knowledge and experience to appropriately interpret and discuss results with individuals and families. Conversely, medical geneticists who have proficiency in interpreting and communicating genetics information may have less extensive formal training in epilepsy and the genetics of the epilepsies, specifically. Such providers may benefit from consulting with neurology colleagues on the clinical correlation of the findings and ensure that patients have appropriate neurology follow-up care to incorporate the genetic findings into epilepsy management.

To our knowledge, the benefits and risks of genetic counseling specifically within the epilepsy population have not been systematically studied; however, individual elements of genetic counseling, such as reproductive recurrence risk counseling and psychosocial implications, have been reported (Sheidley et al., 2022). A recent review evaluated outcomes of genetic counseling across a variety of medical

specialties, the findings of which could translate to individuals with unexplained epilepsy. Results indicated that individuals who receive genetic counseling have increased knowledge, decreased anxiety, elevated perceived personal control, increased positive health behaviors, and improved risk perception accuracy (Madlensky et al., 2017). These findings mirror the critical outcomes as prioritized by our working group, such as establishing disease prognosis and change in reproductive recurrence risk estimation. Genetic counseling within the epilepsies should include a discussion of how genetic testing and a genetic diagnosis may help refine disease prognosis and inform reproductive recurrence risk. Discussion of testing strategies should include reasonable expectations of yield based on the presenting phenotype and family history. Other consensus and expert opinion-based epilepsy guidelines have recommended genetic counseling by trained healthcare providers for individuals pursuing genetic testing (Devinsky et al., 2015; National Clinical Guideline Centre (UK), 2012; Wilmshurst et al., 2015). Additionally, professional societies within other specialties, such as cancer and cardiology, have recommended genetic counseling when individuals undergo genetic testing (Forbes et al., 2019; Musunuru et al., 2020).

The inclusion of a healthcare provider with proficiency in genetics is extrapolated from non-epilepsy genetics literature and grounded in our working group's clinical experience. Genetic testing and counseling through a provider with limited genetics knowledge and experience has been shown to lead to incorrect recurrence risk assessment, inaccurate test selection, and misinterpretation of results (Farmer et al., 2019). These risks may be amplified in the event a variant of uncertain significance (VUS) is identified. The interpretation and communication of a VUS result is a critical and complex skill. Interpretation requires consideration of additional information that may not be included in the genetic test report (e.g., pathomechanism of disease and types of variants that are typically pathogenic for a given gene). Returning results requires placing appropriate weight on the level of certainty of the diagnosis based on available data. While difficult to capture in the literature and thus not reported systematically, our working group members have identified missed diagnoses due to incorrect interpretation of a VUS result (e.g., dismissing a VUS entirely or not following up with segregation analysis to confirm de novo status of variant). Panel members have also encountered situations in which VUS results were assumed to be diagnostic, and precision treatment approaches were pursued, despite the fact that many VUS findings are later downgraded to benign variants.

6 | IMPLEMENTATION OF RECOMMENDATIONS

6.1 | Feasibility

We recommend genetic testing and genetic counseling be offered to all patients with unexplained epilepsy. Our recommendations are evidence-based, and we discuss how the benefits of these recommendations outweigh potential harms or undesirable effects. We consider these recommendations to be generally feasible as genetic testing for epilepsy is already common practice in both genetics and neurology practices. These recommendations would likely only affect current practice in terms of scale. Managing a larger number of genetic tests and performing the necessary counseling around these tests may require a genetic counselor, a genetic counseling assistant, and/or other additional support staff to be integrated into neurology practice settings. In particular, ES and GS require a more extensive informed consent process and may necessitate referral to a medical geneticist or other specialist for discussion of results that implicate non-neurological phenotypic features or secondary findings. Optimally, a neurologist should have available genetic counseling support with a referral pathway to a medical geneticist if additional assistance is needed. Genetic counselor support ideally extends beyond pre- and post-test counseling and may include test selection and ordering, result follow-up, and interpretation of findings as part of a multi-disciplinary healthcare team. Additionally, genetic counselors who become specialized in epilepsy develop content expertise, which optimizes result interpretation and counseling (Smith et al., 2017).

6.2 | Acceptability

Genetic testing and counseling have been shown to be acceptable among relevant stakeholders, including patients, healthcare systems/clinicians, and insurance providers. Evidence supports the idea that individuals are interested in pursuing genetic testing, particularly for diagnostic purposes. The SER (Sheidley et al., 2022) included genetic testing in over 30,000 individuals in 174 distinct cohorts, indicating that genetic testing is being offered by providers and being pursued by individuals and families. In another study that examined the perspective of caregivers of children across indications who underwent ES, most participants had neutral or positive reactions to the results. Three participants noted feeling empowered with only one participant having a negative attitude toward the testing (Li et al., 2019). In a survey of both pediatric and adult neurologists regarding current practices and attitudes toward genetic testing, 95% of pediatric neurologists and 78% of adult neurologists had ordered genetic tests within the past 2 years (Ferraro, Pollard, & Helbig, 2016). In addition, 75% of pediatric and 51% of adult neurologists reported that their patients specifically request genetic testing. Furthermore, integrated care systems may find these recommendations helpful in demonstrating benefits to genetic testing that may be seen many years after initial testing (e.g., by the avoidance of other diagnostic tests if genetic test is positive) and could extend to family members. While individual payors have established independent criteria for reimbursement of genetic testing, these criteria vary widely and changes in coverage may lag behind recent technological advances and new findings in the literature. Overall, these above studies demonstrate that providers are ordering genetic testing and patients are agreeing to receive genetic testing, suggesting that genetic testing is acceptable to individuals and families, healthcare providers, and healthcare systems.

6.3 | Values and outcomes

Individuals with epilepsy and their families reportedly value similar outcomes of genetic testing and counseling. Studies indicate that interest in diagnostic genetic testing is high among parents of individuals with epilepsy in families with multiple affected individuals, especially when there is a potential for clinical utility (Caminiti et al., 2016; Okeke et al., 2014). A recent systematic review (LePoire et al., 2019) found that individuals who encountered genetics in the clinical setting had increased knowledge of disease etiology, how genetic information can be used in health care, and a greater perception of risk than the general population. From the provider perspective, ES quickly and efficiently provides a diagnosis, benefitting the healthcare team, patient, and family (O'Donnell-Luria & Miller, 2016). Taken together, the literature suggests providers, parents/caregivers, and individuals affected by epilepsy value the outcomes of genetic testing and genetic counseling.

6.4 | Cost-effectiveness

Data examining the cost-effectiveness of genetic testing in the epilepsies have been limited to ES, MGP, and CGH/CMA (Howell et al., 2018; Palmer et al., 2018; Sanchez Fernandez et al., 2019; Varesio et al., 2021). These studies have shown that early use of a phenotype-driven ES in the diagnostic pathway yielded a higher diagnostic yield at a lower cost (Howell et al., 2018), and that ES is more cost-effective than the standard diagnostic pathway (i.e., CMA, smaller MGP and/or metabolic studies; Palmer et al., 2018). Varesio et al. (2021) showed that, on a research basis, data generated on an exome backbone can be analyzed sequentially utilizing larger phenotype-driven "panels." However, if ordered as separate tests, as is done clinically, then ES would be more cost-effective to reach a diagnosis. Though these studies examined epilepsy patient populations in different countries where what is considered the standard diagnostic pathway may differ, the evidence suggests that NGS sequencing technologies (MGP and ES) are more cost-effective as a first-tier tests, with ES or phenotype-driven ES (large MGPs) being more effective. Importantly, it should be noted that common outcome measures in cost-effectiveness analyses have been limited to diagnostic yield, to date. Other outcome measures, such as long-term clinical utility of a genetic diagnosis or associated impact on healthcare costs per diagnosis, would be of interest.

Studies have begun to examine the costs associated with GS, particularly in neurodevelopmental disorders. One study compared microcosts of GS, ES, and CMA and found that the difference in cost between GS and CMA+ES in a proband-only analysis was not significant (Jegathisawaran et al., 2020). However, trio ES+CMA was less expensive than trio GS analysis. Notably, there are variants identified through GS that could be undetectable on ES+CMA (Palmer et al., 2021), so an informative cost-effectiveness analysis would need to compare GS to multiple tests beyond just ES+CMA in order to incorporate the full diagnostic potential of GS. Overall, additional studies focusing specifically on cost-effectiveness of GS in the epilepsies are needed.

6.5 | Resources required

The resources required to implement these recommendations vary and include costs associated with the genetic test as well as salaries for clinicians and support staff required to facilitate testing. From the perspective of individuals and families, the cost of genetic testing and genetic counseling varies depending on health insurance coverage and in some instances contracted rates between healthcare institutions and genetic laboratories. In a hospital setting, billing mechanisms for genetic testing may differ depending upon whether testing takes place during an inpatient admission or an outpatient visit. A genetic counselor, a genetic counseling assistant, and/or billing professional may all be required to provide adequate counseling, interpretation of results, clinic workflow management, and insurance prior authorizations. Incorporating a laboratory genetic counselor into the clinical setting can also reduce costs by ensuring proper test selection (Conta, 2019; Haidle et al., 2017). The salary of these professionals varies depending on location, years of experience, and work environment (National Society of Genetic Counselors, 2021).

6.6 | Impact on health equity

Our hope is that the implementation of a consistent genetic testing approach for all individuals with unexplained epilepsy will lead to more uniform diagnosis and treatment across the population of individuals with epilepsy. While studies pertaining to healthcare disparities in genetic testing in the epilepsies are limited, data relevant to healthcare disparities in terms of epilepsy management and genetic testing in other populations can be generalized. Data have shown that uninsured or publicly insured individuals and those who are unemployed or have low income were more likely to visit the emergency room, to have uncontrolled seizures, and to have drug-related side effects (Groover et al., 2020). Outside of the epilepsy population, Odgis et al. (2021) have shown that individuals from underserved communities are less likely to receive genetic testing, suggesting this might be due to the lack of provider awareness of when genetic testing may be indicated or the process for procurement. Fraiman and Wojcik (2021) suggested that biases may exist for some providers, who may be more likely to suspect environmental causes or adverse childhood events rather than genetic causes for neurodevelopmental disorders for children in underserved populations. In the past, individuals from underserved populations are reportedly less likely to be referred for genetic testing even when indicated based on established guidelines (Nikolaidis et al., 2019; Peterson et al., 2020). Moving forward, our hope is that these recommendations would lead to an increase in genetic testing and genetic counseling, including

among individuals with epilepsy who historically have been underrepresented in biomedical research. Expanding access to genetic testing would ideally lead to a decrease in existing health disparities and allow the benefit of genetic testing to reach more of the epilepsy population. However, we do acknowledge that guidelines alone may be insufficient to standardize access to genetic testing across all populations. Studies have shown that individuals from underserved populations may be less likely to utilize genetic services once referred. This may be due to high out-of-pocket costs and increased appointments to procure counseling, testing, and results (Jones et al., 2016). If genetic testing is completed within the neurology setting, and/or if genetic counselors are embedded within the neurology practices and incorporated into the outpatient visit, additional appointments may not be required. We will need to continue to identify and address access challenges to genetic testing to support efforts to increase health equity. Telehealth and remote genetic counseling sessions and sample collection have become common in the context of the COVID-19 pandemic (Shannon et al., 2021). These alternative genetic counseling approaches may increase access to genetic counseling services for all individuals and families and may help reduce barriers to access.

6.7 | Potential barriers

One potential barrier to the full implementation of these recommendations relates to the lack of insurance provider reimbursement of genetic testing for individuals with epilepsy. Another is limited availability of genetic counselors (Bamshad et al., 2018). Genetic counseling assistants may help ease the administrative burden on genetic counselors, thereby increasing the ability of genetic counselors to serve more individuals and families. Additionally, increased training of neurologists and other healthcare providers in test selection, result interpretation, and the psychological considerations of testing will help to ensure an optimal and equitable experience for all individuals receiving genetic testing. Billing professionals in clinical practices may help ease the burden on individuals and families by determining out-of-pocket costs for genetic testing. Insurance provider reimbursement of genetic testing will likely reflect the cost of genetic testing, which is expected to decrease over time. Indeed, over the last 10 years, the cost of sequencing a human genome has substantially decreased (NHGRI, 2020). However, it may take time for this to impact the overall cost of clinical testing which reflects the additional efforts required in analysis and interpretation.

7 | LIMITATIONS

This practice guideline was based largely on the data collected in the recently published SER (Sheidley et al., 2022). As the authors of the SER note, there were limitations to the systematic evidence review including the exclusion of studies that did not utilize either ES, GS, MGP, or CGH/CMA and so our guideline does not comment on other genetic testing technologies/strategies (i.e., single gene testing) and the ability to ascertain detailed methodologies and tiered testing approaches which would more accurately inform our recommendations. Additionally, the content of the specific genes within MGPs could not be extracted from many journal articles and so our guideline could only comment on the number of genes rather than the specific gene content included in a panel. Our guideline was developed for patients with a diagnosis of unexplained epilepsy. These guidelines are not intended for individuals with a specific, syndromic presentation. The SER outcome data were based on studies where at least 80% of the cohort were required to have epilepsy and ascertainment was based upon epilepsy (either solely, or in conjunction with another condition, e.g., ID). Therefore, it is possible that the some of the data included in the SER did come from subjects who had syndromic presentations.

8 | RESEARCH RECOMMENDATIONS

Future research should focus on long-term prospective studies to better understand the clinical utility of a genetic diagnosis in the epilepsies. As discussed in the SER (Sheidley et al., 2022), long-term prospective studies are needed to systematically determine whether a genetic diagnosis led to a change in management, such as choice of ASM, frequency of EEGs or MRIs, and the impact on other diagnostic procedures. Further knowledge of clinical utility could inform cost-effectiveness analyses and insurance provider reimbursement for different testing strategies. Additionally, further elucidation of the diagnostic yield and clinical utility of GS in this population would be of interest.

9 | PLANNED REVIEW/REVISION

Given the evolving landscape in genetics and genomic testing, the working group recommends that this guideline be updated every 3–5 years or if additional evidence emerges that may alter the strength or direction of these recommendations or the overall certainty of the evidence. This is of particular importance, as GS will continue to be studied and potentially more widely adopted in the clinical space. We look forward to the opportunity to collaborate with epileptologists in future revisions of this guideline.

10 | CONCLUSIONS

We recommend genetic testing for individuals with unexplained epilepsy. This evidence-based guideline is based on literature demonstrating the high diagnostic yields of GS, ES, MGP, and CMA, as well as the clinical utility of genetic testing to guide treatment/medical management, revise, or establish prognosis and/or provide reproductive risk counseling. Additionally, we recommend that the

genetic testing in the unexplained epilepsy population be implemented by a qualified healthcare provider with appropriate pre-test and post-test genetic counseling and interpretation of results.

AUTHOR CONTRIBUTIONS

Lacey Smith: Conceptualization; data curation; formal analysis; investigation; visualization; writing – review and editing. **Jennifer Malinowski:** Conceptualization; data curation; investigation; methodology; validation; visualization; writing – review and editing. **Sophia Ceulemans:** Conceptualization; data curation; formal analysis; investigation; visualization; writing – review and editing. **Katlin Peck:** Conceptualization; data curation; formal analysis; investigation; visualization; writing – review and editing. **Nephi Walton:** Conceptualization; data curation; formal analysis; investigation; visualization; writing – review and editing. **Beth Rosen Sheidley:** Conceptualization; data curation; formal analysis; investigation; visualization; writing – review and editing. **Natalie Lippa:** Conceptualization; data curation; formal analysis; investigation; visualization; writing – review and editing. All authors participated in the GRADE Evidence to Decision process for prioritizing outcomes and voting on judgments. All authors contributed to the research evidence needed for the judgments. Lacey Smith and Natalie Lippa drafted the manuscript and all authors edited and approved the final manuscript.

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CONFLICT OF INTEREST

The authors LS, SC, KP, NW, BRS, and NL declare that they have no conflict of interest. JM serves as the contract methodologist for NSGC and has no other conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

No original data have been used for this practice guideline manuscript.

HUMAN STUDIES AND INFORMED CONSENT

This practice guideline did not include human subject research.

ANIMAL STUDIES

No animal studies were carried out by the authors for this article.

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SUPPORTING INFORMATION

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