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SPECIAL REPORT

Timing of referral to evaluate for epilepsy surgery: Expert Consensus Recommendations from the Surgical Therapies Commission of the International League Against Epilepsy

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Abstract

Epilepsy surgery is the treatment of choice for patients with drug-resistant seizures. A timely evaluation for surgical candidacy can be life-saving for patients who are identified as appropriate surgical candidates, and may also enhance the care of nonsurgical candidates through improvement in diagnosis, optimization of therapy, and treatment of comorbidities. Yet, referral for surgical evaluations is often delayed while palliative options are pursued, with significant adverse consequences due to increased morbidity and mortality associated with intractable epilepsy. The Surgical Therapies Commission of the International League Against Epilepsy (ILAE) sought to address these clinical gaps and clarify when to initiate a surgical evaluation. We conducted a Delphi consensus process with 61 epileptologists, epilepsy neurosurgeons, neurologists, neuropsychiatrists, and neuropsychologists with a median of 22 years in practice, from 28 countries in all six ILAE world regions. After three rounds of Delphi surveys, evaluating 51 unique scenarios, we reached the following Expert Consensus Recommendations: (1) Referral for a surgical evaluation should be offered to every patient with drug-resistant epilepsy (up to 70 years of age), as soon as drug resistance is ascertained, regardless of epilepsy duration, sex, socioeconomic status, seizure type, epilepsy type (including epileptic encephalopathies), localization, and comorbidities (including severe psychiatric comorbidity like psychogenic nonepileptic seizures [PNES] or substance abuse) if patients are cooperative with management; (2) A surgical referral should be considered for older patients with drug-resistant epilepsy who have no surgical contraindication, and for patients (adults and children) who are seizure-free on 1–2 antiseizure medications (ASMs) but have a brain lesion in noneloquent cortex; and (3) referral for surgery should not be offered to patients with active substance abuse who are noncooperative with management. We present the Delphi consensus results leading up to these Expert Consensus Recommendations and discuss the data supporting our conclusions. High level evidence will be required to permit creation of clinical practice guidelines.

KEYWORDS

drug-resistant epilepsy, epilepsy surgery, health care delivery, neuromodulation, public health, treatment

1 | INTRODUCTION

In 2003, the American Academy of Neurology published guidelines stating that patients who continue to have disabling focal seizures with impaired awareness after appropriate antiseizure medication (ASM) trials should be considered for referral to undergo an evaluation for epilepsy surgery, but acknowledged the caveat that "criteria for failure of drug treatment have not been definitely established."[1] In 2010, a taskforce of the International League Against Epilepsy (ILAE) addressed this uncertainty and defined drug resistance as "failure of adequate trials of two tolerated and appropriately chosen antiseizure medication (ASM) schedules (whether as monotherapies or in combination) to achieve seizure freedom."[2] Resective surgery can improve quality-of-life and cognitive outcomes and is the only treatment demonstrated to improve survival and reverse excess mortality attributed to drug-resistant epilepsy (DRE).[3–6] Surgical evaluation is the most cost-effective approach to treating drug-resistant epilepsy, even when the likelihood of subsequent resection is less than 5%.[7] Despite this evidence, referral for consideration of surgical therapy continues to be delayed as epilepsy duration still approximates two decades on average before initiation of a surgical workup in adults, and the neurology community remains ambivalent due to ongoing barriers and misconceptions about epilepsy surgery. In parallel, the

Key points

- We present Expert Consensus Recommendations generated through a Delphi process designed by the Surgical Therapies Commission of the International League Against Epilepsy (ILAE)
- Referral for a surgical evaluation should be offered to every patient with epilepsy (up to 70 years of age) as soon as drug-resistance is ascertained
- A surgical referral should be considered for older patients with drug-resistant epilepsy who have no surgical contraindication
- A surgical referral should be considered for patients who are seizure-free on 1–2 antiseizure medications but have a brain lesion in noneloquent cortex
- Referral for surgery should not be offered to patients with active substance abuse who are noncooperative with management

epilepsy surgery landscape is evolving to include therapeutic options such as laser interstitial thermal therapy (LiTT) with potentially less morbidity than resective surgery, and neuromodulation to treat patients not suitable for resective surgery. Identifying candidacy for any of these approaches starts with a surgical referral, so a timely evaluation is key.

The Surgical Therapies Commission of the ILAE set out to provide Expert Consensus Recommendations for the timing of pre-surgical evaluation, based on a rigorous Delphi process to achieve consensus involving subject-matter experts from all six ILAE world regions. Our goal was to provide clear, evidence-informed, objective, and clinically meaningful recommendations to guide any clinician involved in the care of people with epilepsy on when to refer patients of any age for evaluation of candidacy for epilepsy surgery.

2 | CRITICAL DEFINITIONS AND CONCEPTS

2.1 | Distinction between guidelines and expert consensus statement

The recommendations generated as part of this report are based on expert consensus opinion, which differ from a clinical practice guideline. Clinical practice guidelines provide evidence-based recommendations that are generated following a rigorous process including a systematic review, appraising the quality of the evidence and linking the evidence to the recommendations. Consensus recommendations are based on expert opinion and are used when there is limited evidence on a particular topic or where controversies exist, but where recommendations are needed.

2.2 | Definition of drug-resistant epilepsy

Rates of medication failure have been explored extensively to identify patients with DRE. In a seminal study by Kwan and Brodie in 2000, investigators examined ASM response in 470 patients with previously untreated epilepsy.[8] They found that of the entire cohort—47%, 13%, and 4% of individuals—became seizure-free after the first, second, and third or subsequent ASM, respectively. Thus 36% of the original clinic-based cohort had ongoing disabling seizures despite maximal medical therapy. Considering these and other findings in adults[9] and children,[10,11] the ILAE Commission on Therapeutic Strategies proposed a definition of drug resistance as failure to achieve sustained seizure freedom after adequate and well-tolerated trials of two ASMs.[2]

In the last two decades, several new ASMs have been introduced, many with novel mechanisms of action and improved side-effect profiles, but this definition of drug resistance still stands.[12] In 2018, an investigation of 1795 people with newly diagnosed epilepsy found that 51%, 12%, and 4% of individuals achieved seizure freedom of 1 year or longer after a first, second, and third ASM regimen, respectively.[13] Only 2% of the entire cohort became seizure-free with subsequent ASMs, and 36% of individuals suffered from persistent drug-resistant seizures. These findings emphasize that the likelihood of seizure freedom with medical therapy alone is small in patients with documented DRE.[13] In contrast, in a controlled trial of drug-resistant patients with temporal lobe epilepsy randomized to surgery or ASMs alone, no individuals who received maximal medical therapy achieved seizure freedom at 2 years, compared to 73% who underwent surgical resection.[14] A randomized controlled trial (RCT) of children randomized to immediate surgical treatment vs continuation of medical treatment for 12 months (and later surgery) showed seizure freedom in 77% of the immediate surgery group after 12 months compared to only 7% of the medical group.[15]

2.3 | Value of referral to a tertiary epilepsy center beyond presurgical evaluation

A referral for an epilepsy surgical evaluation is not equivalent to a commitment to undergo brain surgery. People

with epilepsy have a lifelong brain disorder with localized or diffuse dysfunctional neuronal networks that result in seizures and other comorbidities. Specialized epilepsy care strives to promote the best possible quality-of-life through a comprehensive approach beyond trial-and-error choices of ASMs. Epilepsy centers offer a wide range of specialized diagnostic and therapeutic approaches with key benefits to our patients with uncontrolled seizures, even when surgical resection is not eventually pursued.[16] In fact, most patients with DRE do not end up undergoing surgery after referral,[17] but still benefit from comprehensive epilepsy care improving quality-of-life and lowering mortality.[18] A better characterization of the epilepsy can also help optimize medical therapy and address somatic, cognitive, behavioral, and psychiatric comorbidities.

An additional basic benefit of referral is to verify diagnosis. One third of patients with presumed DRE referred to epilepsy centers do not have epilepsy,[19] but are instead diagnosed after video-EEG (electroencephalography) with psychogenic nonepileptic seizures (PNES), which are associated with significant morbidity and mortality.[20] An early and accurate diagnosis of PNES can facilitate implementation of psychotherapy, lead to elimination of ASM, and improve outcomes. In parallel, for patients who do have epilepsy, recording their seizures in an epilepsy monitoring unit can be invaluable to help them understand their behavior during the event.[19]

Other key outcomes of a specialized evaluation are defining the etiology and type of epilepsy.[21] For example, the yield of an epilepsy magnetic resonance imaging (MRI) is directly related to hardware quality and imaging sequences but may be doubled by knowledge of the suspected epilepsy localization and experience of the neuroradiologist.[22] Lesions such as hippocampal sclerosis, cavernous malformation, or glioneuronal tumors may warrant early surgical intervention.[14,23] Complex or multifocal lesions or patients with nonlesional focal epilepsy, on the other hand, require additional testing and may have a lower chance of seizure freedom. In general, resective surgical options are far more common and successful in focal epilepsy syndromes, particularly in individuals with an identified lesion.[24] Neuromodulation approaches are used more commonly in patients whose seizures originate in eloquent cortex, precluding resective surgery, those with poorly localized focal epilepsies or in those with generalized epilepsy syndromes.[25]

2.4 | Surgical resective procedures, neuromodulation, and ablative approaches

The landscape of nonpharmacological interventions to treat drug-resistant epilepsy continues to expand. A referral for a "surgical evaluation" can actually lead to a variety of interventions, and a specialized epilepsy program can identify the best options for any given patient. Traditional surgical procedures aiming for seizure freedom include focal resections, multilobar resections, and hemispherotomies, depending on the etiology and the localization of the epileptogenic zone (EZ) that must be removed/disconnected to achieve seizure freedom.[26] The definition of the EZ is reached with the integration of seizure semiology, EEG, neuropsychological evaluation, and multimodal imaging. When a surgical resection is not possible due to bilateral, generalized, or nonlocalized EZ, or an EZ located in eloquent cortex, palliative procedures can be used, such as subpial transection of focal abnormalities, corpus callosotomy for disabling drop attacks, or neuromodulation including vagus nerve stimulation, deep brain stimulation, and responsive neurostimulation. These procedures rarely bring seizure freedom but can reduce seizure frequency and severity.[25]

Newer techniques, considered minimally invasive, include the stereotactic ablation of epileptogenic lesions or disconnection procedures.[27,28] The two basic physical mechanisms of action currently in use are stereotactic radiosurgery (gamma knife, linear accelerators) and thermocoagulation (also known as thermotherapy or thermal ablation), where focused and controlled heat is applied to ablate tissue. The heating of the tissue can be achieved in three ways: focused ultrasound, stereotactic radiofrequency thermocoagulation (RF-TC), and LiTT.[27,28] RF-TC is a less resource-intensive alternative to LiTT. Focused ultrasound also has a potential use for neuromodulation in epilepsies.[29] There is compelling evidence of efficacy for these emerging minimally invasive approaches,[30,31] but recent meta-analyses suggest waning seizure freedom over time across all types of epilepsy surgery, most noticeable in minimally invasive approaches.[32,33] Overall, rigorous research is still needed to adequately resolve controversies regarding the long-term risks and benefits.

3 | CURRENT STATE OF REFERRALS FOR EPILEPSY SURGERY

3.1 | Current data on the timing of initiation of presurgical evaluations

Despite the emphasis placed on early intervention in focal epilepsy in the last decades, referral paths for presurgical evaluation have remained long, arduous, and underutilized,[34] as epilepsy surgery is still considered by some pediatric and adult neurologists as a treatment of last

resort.[35] Several studies have found a considerable delay in the referral of patients with focal epilepsy for presurgical evaluation,[36] with the mean latency between seizure onset and surgery amounting to 20 years in adults and 5 years in children.[37] The situation is more dramatic in the pediatric age group, where timely surgery can prevent otherwise irreversible neurocognitive decline[38] and lead to long-term cognitive improvement.[39,40] Two-thirds of children who had epilepsy surgery in the 2004 ILAE survey were younger than 3 years at epilepsy onset, but only a few of these children received surgery within 2 years.[41] Fortunately, considerable decrease in epilepsy duration to surgery has been noted over the last decades, as shown in a multicenter European epilepsy surgery study[42] but early referral for presurgical evaluation is essential to support this encouraging trend.

3.2 | Underutilization of surgery

In a Swedish study focusing on epileptogenic tumors and cavernomas,[5] adults had a mean epilepsy duration of 13 years and children of 5 years, amounting to over a third of their lives, although all but one patient had an MRI-detectable lesion, which eventually proved to be epileptogenic. Despite the results of two randomized controlled trials showing that surgery for temporal lobe epilepsy in adults,[14,43] and resective surgery in children,[15] is superior to continued ASMs both in terms of seizure freedom and improved quality-of-life, the mean epilepsy duration to temporal lobe resection has persisted at over 20 years.[44] Although drug resistance is reached with a mean latency of 9 years in epilepsy surgery candidates,[45] these patients have experienced a decade of unabating seizures with detrimental effects including cognitive and psychiatric comorbidities, poor psychosocial outcomes, potential injuries, and risk of death.

Pediatric epilepsy surgery studies have shown trends for shorter epilepsy duration over time among surgical candidates,[46,47] in line with the expansion and increasing utilization of pediatric epilepsy surgery in the last decades.[48]

3.3 | Barriers and facilitators

Delayed referral may be attributed partly to temporary seizure remissions with new ASM trials, overestimation of surgical risks, underestimation of morbidity and mortality associated with ongoing seizures, and lack of access to appropriate health care.[49] Barriers to epilepsy surgery include lack of knowledge or misconceptions about surgical risks, negative behaviors, or cultural issues and access issues. These barriers vary by region and setting and can originate from patients, their caregivers, clinicians, or health care systems.[50,51] Table 1 provides examples of possible solutions to typical barriers.

4 | METHODS

4.1 | Working groups and participants

The Surgical Therapies Commission of the ILAE decided to pursue a systematic, inclusive, and rigorous process to generate Expert Consensus Recommendations for referral for an epilepsy surgical evaluation. First, the Commission created a *Recommendations Writing Group*, which included members from all the relevant professional groups including the Commission's leadership, chairs of the Commission's five taskforces (Pediatric Surgery Taskforce, Education Taskforce, Evidence Based Surgery Taskforce, Outcomes Taskforce, and Resource-Limited Countries Surgery Taskforce), and two members with epilepsy surgery expertise from each ILAE region nominated by that region's Chair (Africa, Asia-Oceania, Eastern Mediterranean, Europe, Latin America, and North America), except in Africa where only one member participated. We then created a *Delphi Working Group* to develop the initial Delphi questionnaire. Participants included the Chair of the ILAE Surgical Therapies Commission, a representative of the ILAE Executive Committee, a Delphi expert and the Chair of the ILAE Standards and Best Practice Council, an epileptologist with epidemiological and statistical expertise and a Young Epilepsy Section (YES) representative (neurosurgeon with health services research expertise).

4.2 | Survey development, testing, and revisions

The *Expert Consensus Recommendations Writing Group* and the *Delphi Working Group* members participated in several online meetings to discuss the initial core elements for the questionnaire. The *Delphi Working Group* then generated the first Delphi questionnaire including criteria that may influence the decision to refer for an epilepsy surgery evaluation (e.g., sociodemographic, clinical history, therapies, EEG, imaging findings). The initial questionnaire was sent to the *Writing Group* members. Revisions were made based on their feedback. When answering questions, participants were asked to assume that potential surgical candidates had no surgical contraindications unless specified. They were asked

TABLE 1 Summary of barriers and facilitators of seeking epilepsy surgery evaluations

	Barrier	Facilitator (solutions)
Physician	Lack of knowledge about: • Definition of drug-resistant epilepsy (DRE) • Role of epilepsy surgery • Indications for possible epilepsy surgery	• Online tools to facilitate identification of possible candidates: e.g. www.toolsforepilepsy.com • EMR tools: ◦ Machine learning techniques to identify DRE patients in electronic medical records (EMR) ◦ Decision analysis tool, nomograms, etc. embedded in EMR ◦ Computerized clinical practice guidelines ◦ EMR prompts • Peer reviewed publications • Guidelines • Pay-per-performance models
	Misconceptions about epilepsy surgery • Negative or ambivalent attitudes and perceptions about epilepsy surgery. • Deficient communication practices with patients regarding risk–benefit analysis of epilepsy surgery	• Online educational tools • Self-management programs: e.g., Managing Epilepsy Well Network • Webinars and podcasts • Patient testimonial videos • Social media • Treatment of comorbidity (e.g., depression)
Person with epilepsy	Access and cost issues	• Mobile clinics • Telehealth • Multidisciplinary team including social worker to assist with identification of supportive services (e.g., transportation, health insurance) • Work with epilepsy organization (nonprofit, academic) to advocate for improved policies nationally to facilitate health coverage for epilepsy surgery
Health system and health resources	Team expertise – clinicians (epileptologists, epilepsy surgeons, neuropsychologists, intensivists, anesthesiologists), EEG technologists	• Building a multidisciplinary team • Maintaining/tracking volume and complexity of cases
	Equipment – e.g., neuroimaging, neurophysiology	• Utilizing advanced diagnostics tools • Considering minimally invasive surgical techniques • Some epilepsy surgery interventions can be completed without needing invasive monitoring
	Challenging coordination issues with referral center and epilepsy program	• Promote communication and collaboration between referring providers (e.g. community physician) and epilepsy specialists
	Cost	Improve access to epilepsy surgery via policy changes • Anti-discrimination policy • Exemption of transportation cost • Telehealth reimbursement policy • Patient-centered epilepsy care models • Affordability and access to insurance
	LMICs – overwhelmed by existing burden of disease.	• Collaboration with high resource settings (e.g., visiting professorships, cross appointment of faculty experts interested in global health) • Cross region/country multidisciplinary rounds

Abbreviations: EEG, Electroencephalography; LMIC, Low and Middle Income Countries.

to not base their answer on the resources available in their health care system, but rather assume that surgical resources were available. Each criterion was rated on a 5-point Likert scale (Table 2). The pilot questionnaire was then revised by implementing additional suggestions from the *Writing Group* to generate a final questionnaire for the Delphi process. The survey was hosted on Survey Monkey.

TABLE 2 Response options for Delphi questionnaire rounds 2–3

Irrespective of all other patient characteristics:
1. I would never refer the patient for epilepsy surgery evaluation if this characteristic is present
2. I am unlikely to refer the patient for epilepsy surgery evaluation if this characteristic is present
3. I am not sure if this characteristic would influence my decision to refer the patient for epilepsy surgery evaluation
4. It is likely I would refer the patient for epilepsy surgery evaluation if this characteristic is present
5. I would always refer the patient for epilepsy surgery evaluation if this characteristic is present (This option also applies if this characteristic is irrelevant)
If you choose options 2–4, please explain your choice and comment. For example, if you are uncertain about the relevance of age (answer 3), or you would likely not refer or refer (answer 2 or 4) based on certain age ranges (the very young or older adults) please state this.

4.3 | Delphi process

Delphi panel members were selected to achieve broad representation of relevant clinical disciplines (adult and pediatric epileptologists, epilepsy neurosurgeons, neurologists, neuropsychiatrists, and neuropsychologists) and all world regions. Thus participants included all members of the *ILAE Surgical Therapies Commission*, plus the additional participants identified by the ILAE Regional Chairs (Total $N = 73$ participants). For each of the three Delphi rounds, results were categorized as follows: (1) always/likely to refer (ratings #4–5) or irrelevant (i.e., would refer regardless of this criterion), (2) unsure (rating #3), and (3) unlikely to refer or would never refer (ratings #1–2). Consensus was defined as having at least 66% of respondents in one of these categories (i.e., refer, unsure, or never refer). Criteria without consensus were included in a subsequent round with revisions made according to the comments received from participants. The process was repeated (three rounds) until consensus was optimized.

4.4 | Statistical methods

We used parametric and nonparametric descriptive statistics to describe baseline participant demographics, including comparisons between those who would refer and those who would not. The results of the Delphi process were dichotomized into referral categories ("always/likely" and "never/unlikely") and demographic characteristics were compared across these two groups using Kruskal-Wallis and Fisher's exact tests for continuous and categorical variables, respectively, to investigate relationships between responder characteristics and their preferences.

4.5 | Formulating the Expert Consensus Recommendations

The survey responses were converted into Expert Consensus Recommendations as follows:

1. Consensus reached in the category of "always/likely to refer" = referral for a surgical evaluation "should be offered."
2. Consensus reached in the category of "unlikely or never to refer" = referral for surgical evaluation "should not be offered."
3. Consensus not reached but ≥50% answered "always" or "very likely" to refer = referral for surgical evaluation "should be considered."
4. Consensus not reached and < 50% agreement = "further research is needed."

An initial draft of the Expert Consensus Recommendations was created by the *Delphi Working Group* after the final Delphi round, which was then reviewed by the *Writing Group* and revised after further discussions.

5 | RESULTS

5.1 | Participants and response rate

A total of 61 participants provided responses in at least one round of the Delphi process. Participants were comprised of epileptologists ($n = 23$; 38%), epilepsy neurosurgeons ($n = 21$; 34%), neurologists ($n = 14$; 23%), neuropsychiatrists ($n = 1$; 2%), and neuropsychologists ($n = 2$; 3%) with a median of 22 years (interquartile range [IQR] 12–28) in practice. There was equal representation between those focusing on adult ($n = 24$; 39%) or both adult and pediatric ($n = 25$; 41%), with a minority whose practice was dedicated solely to pediatric epilepsy ($n = 12$; 20%). Participants were from North America ($n = 18$; 30%), Europe ($n = 17$; 28%), Asia/Oceania ($n = 11$; 18%), Latin America ($n = 8$; 13%), the Eastern Mediterranean ($n = 4$; 7%), and Africa ($n = 3$; 4%). The majority of participants worked in a dedicated epilepsy center that offered surgery ($n = 54$; 88%).

5.2 | Delphi results

A total of 57 participants (93%) contributed to round 1 of the Delphi, 39 (64%) to round 2, and 38 (62%) to round 3. Consensus was reached in 30 of 38 scenarios in round 1 (79%). Criteria for which there was a lack of consensus were revised for clarity and included in the next round. Likewise, additional scenarios suggested by participants

were included in the subsequent round. This resulted in 20 scenarios in round 2 (in which consensus was reached in 17; 85%) and 7 scenarios in round 3 (in which consensus was reached in 3; 43%). The final number of unique scenarios was 51, among which 45 (88.2%) had agreement. Of the 45 scenarios with agreements, 44 recommended a referral for an epilepsy surgery evaluation. Figure 1 shows the level of agreement for each scenario. Table S1 lists in more details all scenarios with % agreement for each.

5.2.1 | Consensus reached in the category of "Always/Likely to refer"

>66% responded that they would always/likely refer patients with:

- Drug resistance: Once drug resistance is established (failure to achieve sustained seizure remission despite two ASMs, as defined by the ILAE), consensus was reached on referral regardless of age (up to 70-years-old), sex, socioeconomic status, seizure type, epilepsy type (including epileptic encephalopathy), epilepsy duration, and epilepsy-associated comorbidities including severe psychiatric comorbidities or substance use, if cooperative with management, and co-morbid PNES.

Consensus for referral in DRE was maintained regardless of epilepsy localization or the likelihood of candidacy for resective epilepsy surgery. In addition, our criteria for consensus to refer were still met accounting for:

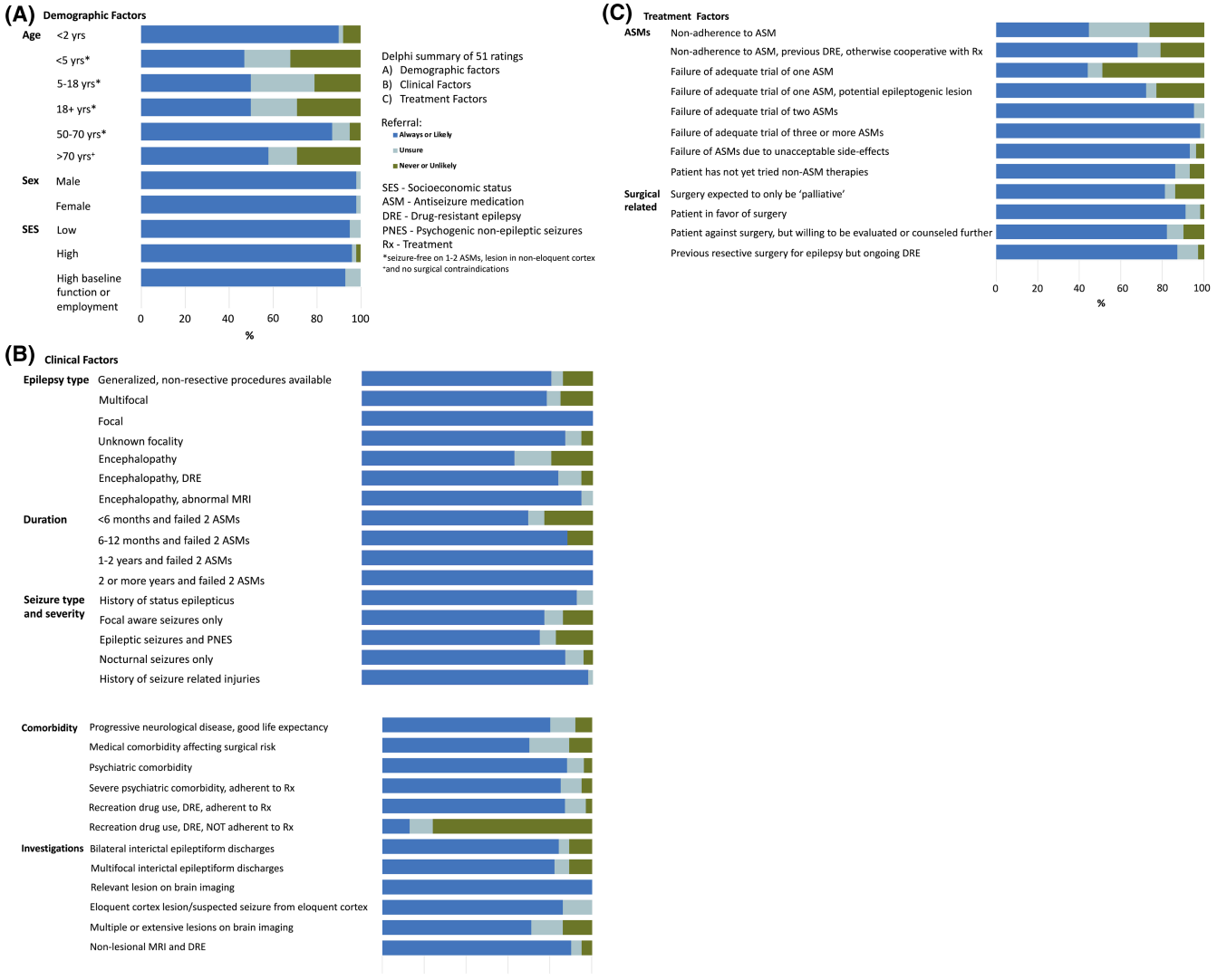

FIGURE 1 Delphi summary of 51 ratings based on (A) demographic factors, (B) clinical factors, and (C) treatment factors. Dark blue shades are for proportions where response was to always or likely refer for presurgical evaluation; light blue for unsure, and green for never or unlikely. ASM, antiseizure medication; DRE, drug-resistant epilepsy; PNES, psychogenic nonepileptic seizures; Rx, treatment; SES, socioeconomic status. *Seizure free on 1–2 ASMs, lesion in noneloquent cortex, +and no surgical contraindications.

- Patient preference: 82% would always/likely refer a patient who is against surgery but willing to be evaluated and/or counseled further.
- Therapies: 86% would always/likely refer patients with DRE even if they have not tried nontraditional therapies (e.g., ketogenic diet, cannabidiol). Similarly, more than 80% would still always/likely refer patients with DRE even if resective surgery is expected to only be "palliative," or if patients had prior surgical resection but have ongoing drug-resistant seizures.
- Number of ASMs: Survey responses re-enforced the general principle of surgical referral once drug resistance is established. Consensus to refer was achieved in patients who failed an adequate trial of ≥2 ASMs, failed an adequate ASM trial due to side effects, or if they were nonadherent to ASMs but otherwise had documented DRE and were cooperative with management.
- Of note, demonstrating drug resistance was not a prerequisite for surgical referral in lesional cases: 72% would always/likely refer patients who failed an adequate trial of one ASM (i.e., technically not meeting the definition of DRE) if they have a potentially epileptogenic lesion.

5.2.2 | Consensus reached in the category to "not refer for a surgical evaluation"

The only situation where a consensus was reached to withhold a surgical referral was the use/abuse of alcohol and/or recreational substances in patients with DRE who are not cooperative with management (76% unlikely/never refer; 11% unsure/no judgment; 13% always/likely refer).

5.2.3 | No agreement reached, but a higher proportion of experts recommended to refer

Although consensus as defined by >66% agreement was not reached in the following situations, a higher proportion would still always/likely refer:

1. Children of all age groups, and adults who are seizure-free on 1–2 ASMs, with a lesion in noneloquent cortex (*47% were always/likely to refer for children younger than 5 years*, whereas *50% reported that they would always/likely refer for surgical evaluation in children 5 years or older, and in adults*)
2. Patients of older age (>70 years) with no surgical contraindications (29% unlikely/never refer; 13% unsure/no judgment; *58% always/likely refer)*
3. Patients who are non-adherent to ASM (29% unlikely/never refer; 32% unsure/no judgment; *49% always/likely refer)*

5.2.4 | No agreement reached, but a higher proportion of experts recommended not to refer

Forty-nine percent of responders were unlikely or would never refer patients in whom an adequate trial of **one** tolerated and appropriately chosen and used ASM schedule failed to achieve sustained seizure freedom (49% unlikely/never refer; 7% unsure/no judgment; 44% always/likely refer).

Table 3 presents the final Expert Consensus Recommendations derived from these results.

6 | DISCUSSION

The Expert Consensus Recommendations presented in this document reflect the experience of medical and surgical epileptologists, neurosurgeons, and neuropsychologists/psychiatrists from around the world, as enabled by the Surgical Therapies Commission of the ILAE. Beyond expert opinions, our team followed a methodical Delphi process to optimize rigor, diversity, and inclusiveness.

The overarching theme is that patients need to be referred for a surgical evaluation as soon as drug resistance is ascertained (Recommendation 1). The only scenario in which referral of patients with DRE was withheld was ongoing substance abuse with poor adherence with management (Recommendation 2). Several factors likely influenced these recommendations:

6.1 | Although many therapies offer seizure remission, epilepsy surgery offers seizure freedom

Epilepsy surgery (whether through resection or ablation) is the only available potentially curative option, offering immediate and sustained seizure freedom. In the context of resection, this is documented in three randomized clinical trials comparing resective surgery to medical therapy,[14,15,43] whereas troves of observational studies and meta-analyses show sustained seizure-freedom rates ranging from 40%–50% a decade after extratemporal procedures to 50%–60% a decade after temporal lobe resections.[52–55] In the context of neuro-ablation, sustained seizure-freedom rates of 50%–60% are observed 1–2 years after the procedure, and long-term data seem encouraging.[56] For patients with DRE, these odds of seizure

TABLE 3 Final Expert Consensus Recommendations of the Surgical Therapies Commission of the ILAE on the timing of referral for an evaluation of candidacy for epilepsy surgery

1. Referral for a surgical evaluation should be offered to every patient with drug-resistant epilepsy (up to 70 years) regardless of epilepsy duration, sex, socioeconomic status, seizure type, epilepsy type (including epileptic encephalopathies), comorbidities (including severe psychiatric comorbidity or substance abuse, if cooperative with management, and patients with both seizures and psychogenic nonepileptic seizures (PNES), and/or epilepsy localization). Specifically,
   a. Patients with DRE who may not appear to be appropriate candidates for resective surgery should be referred as other options may be offered.
   b. A patient's reluctance to surgery should not preclude a referral if willing to be evaluated and/or counseled further.
   c. A surgical referral should not be delayed:
      (i) If therapies other than seizure medications have not yet been tried;
      (ii) if surgery is expected to be "palliative";
      (iii) if patient already had prior surgical resection but has ongoing drug-resistant seizures as either additional resection or other options might be offered;
      (iv) if failure of adequate ASM trials was due to unacceptable side effects,
      (v) if a patient with nonadherence to medical therapy previously demonstrated drug-resistance and is now otherwise cooperative with management.
2. Referral for a surgical evaluation should not be offered for patients with drug-resistant epilepsy who use/abuse alcohol and/or recreational substances and are not cooperative with management.
3. Referral for a surgical evaluation should be considered in:
   a. Patients 70 years or older with no surgical contraindications.
   b. Children and adults who are seizure-free on 1–2 ASMs, with a lesion in noneloquent cortex.
4. Further research is needed to clarify risk vs benefit balance of epilepsy surgery for patients with ongoing seizures in the context of nonadherence to ASM without previously documented drug-resistance

freedom after surgery need to be compared with the odds of seizure freedom with ongoing medical therapy alone. In the seminal studies of response to medical therapy in newly diagnosed epilepsy,[8,13] the percentage of responders to the third or more ASM was 2%–4% if we use the percentage of the total cohort vs 15% if we use the percentage of those who actually try the next medication (meaning the pool of nonresponders to the first and second medications). Either way, these numbers reflect the same drug-resistant cohort, only seen from different perspectives, and therefore should not alter the decision to refer, as they remain significantly inferior to the odds of seizure freedom with surgery. "Honeymoon" periods of intermittent remission do not modify the long-term outlook of this population. In one study of drug-resistant patients, the estimated cumulative probability of 12-month seizure remission was 33% at 7 years with adjustments of medical therapy, emphasizing the importance of expert management in ASMs offered in comprehensive epilepsy care programs. However, the risk for subsequent relapse was 71% at 5 years, highlighting the importance of surgery for definitive seizure freedom.[57]

It is key to note that our Delphi expert panelists recommended a referral for surgical evaluation in those with DRE even if a patient was considered to be an unlikely candidate for resective surgery. This is because a specialized evaluation can further identify surgical candidates or other options for palliation in this challenging patient category. Uncontrolled open-label extension studies demonstrated a 28% chance of achieving a 6-month remission at 9 years after initiation of responsive neurostimulation (RNS),[58] and 18% achieved 6-month remission 7 years after anterior nucleus of the thalamus stimulation.[59] In the open-label extension studies for RNS, the median seizure reduction was 53%, 66%, and 75% at 2, 5, and 9 years of follow-up, respectively, highlighting the potential value of these palliative therapies to aid in long-term management of nonsurgical patients and improving their quality-of-life. Altogether, these data support the 2010 ILAE definition of drug-resistant epilepsy and suggest that although transient periods of seizure remission may occur, immediate and sustained seizure freedom with medical therapy or neuromodulation is unlikely after the failure of two ASMs. Initiating surgical evaluation as soon as drug resistance is ascertained is key.

6.2 | Delaying complete seizure freedom by delaying surgery comes with consequences

6.2.1 | Cognitive consequences of delaying surgery

Delayed surgery can result in suboptimal cognitive outcomes for people with epilepsy via several mechanisms. First, delayed surgery fails to capitalize on the superior reorganization and compensatory capacities of the developing brain. The relocation of language abilities is just one characteristic of brain plasticity in young children; however, multiple windows of opportunity exist that allow the reorganization of specific cognitive functions as they mature at different timepoints through childhood and adolescence. These windows invariably narrow with age. In very young children, early surgery can prevent, halt, or even reverse developmental arrest and regression of cognitive function.[40]

Second, delayed surgery fails to mitigate the impact of growing up with epilepsy. Seizures, subclinical EEG discharges, and ASMs all adversely impact neurodevelopment.[38,60] Growing up with a poorly understood and stigmatizing condition such as epilepsy also has an impact on educational and social development. People who grow up with epilepsy are set on a different trajectory for life. Surgery in adulthood does not reverse this trajectory, and difficulties adjusting to the "burden of normality" following even successful surgery are common.[61] Surgery is the only intervention proven to be disease modifying, with seizure-free children attaining psychosocial developmental milestones similar to their healthy peers.[62] Recent studies provide evidence of progressive atrophy that is reversible after successful surgery, changes that are not seen when seizures are controlled with medication.[63] These data likely underlie the recommendation to consider surgery in children who have a resectable lesion at low risk from surgery, even when they are seizure-free (Recommendation 3b).

Although not contraindicated, surgery in later life is associated with lower cognitive reserves due to normal age-related declines in function and higher risk for postoperative cognitive decline, particularly among individuals with nonlesional epilepsy whose seizures arise from eloquent areas within the language-dominant hemisphere.[64] Accelerated cognitive decline in some may also significantly increase the cognitive morbidity associated with surgery in adulthood. Sometimes it is too late to offer surgery, as cognitive risks become too great, which would not have been the case earlier in the disease. Limited data exist on the cognitive outcomes of surgery in the elderly, likely underlying the lower degree of consensus in our recommendation of surgery for patients older than 70 years (Recommendation 3a).

A comprehensive evaluation for epilepsy surgery in individuals with DRE includes neuropsychological evaluation to characterize cognitive and behavioral functioning and estimate the potential risks/benefits of surgery on cognitive and emotional functioning.[65] In children, cognitive risk depends on a range of factors including age at seizure onset and evaluation, seizure freedom, antiseizure medication load, and the extent of preoperative damage more so than its lateralization or localization.[66,67] Cognitive functioning, in turn, has been shown to predict a child's achievement of developmental milestones and longer-term psychosocial trajectory, which can be improved by surgery.[68] All of these factors must be carefully considered in the preoperative neuropsychological evaluation in conjunction with the medical risks/benefits[69] to determine the optimal treatment approach (e.g., resective surgery, LiTT, neuromodulation) for any given patient. The complexity of such an informed assessment needs to be done by experts in epilepsy surgery and further underscores why a referral for a surgical evaluation is critical.

6.2.2 | Mortality

Epilepsy surgery has the potential to reverse the most serious complication of epilepsy, that of excess mortality.[3,5,6] Compelling evidence indicates that uncontrolled epilepsy is associated with increased mortality rates, and equally compelling data demonstrate that surgery is associated with a reduction in excess mortality. The largest published series contrasted mortality in 1006 surgically treated patients with 104 nonsurgically treated patients. Those who had surgery had a lower mortality rate (8.6 per 1000 person-years (95% confidence interval [CI] 6.58–11.15) than nonsurgical patients (25.3 per 1000 person-years (95% CI 14.50–41.17) ($p < .001$). Seizure-free patients had a mortality rate indistinguishable from that of the general population, and postoperative tonic-clonic seizure frequency was associated with increased mortality. Patients with persistent focal impaired awareness seizures had lower mortality than nonsurgical patients ($p = .005$); they showed a trend toward an increased mortality risk compared with seizure-free patients ($p = .08$).[6] A recent study reporting the results in 590 surgical patients and a comparison group of 122 nonsurgical patients confirmed the reduction in mortality in surgical patients with lower all-cause and sudden unexplained death in epilepsy (SUDEP)–related mortality. Time to SUDEP was longer in surgical patients, and 10 of 14 cases occurred more than 10 years after surgery.[3]

6.2.3 | Seizure outcome implications of delayed surgery

Worse outcomes with late surgery (frontal, temporal)

In the last two decades, several observational studies, both in pediatric and adult cohorts, have suggested that longer epilepsy duration is associated with worse seizure outcomes after resective epilepsy surgery.[40,54,70,71] This association has been reported in epilepsies related to epileptogenic lesions and epilepsies arising from the frontal, temporal, or posterior cortex, thus rendering unlikely the possible confounding effects of referral patterns favoring the presence of a lesion or a specific lobar localization. A positive correlation between longer epilepsy duration and lower rates of postsurgical seizure freedom has also been established independently of age at surgery in pediatric cohorts.[54,72] In addition, delayed surgery has been shown recently to entail reduced chances of seizure and ASM freedom for all lesions, with the sole exception of hippocampal

sclerosis, in a multicentric pediatric and adult cohort.[24] Furthermore, two meta-analyses showed significant positive effects of early surgery on seizure freedom, including both epilepsy durations as short as 2 years and very long durations of up to 20 years,[73] and an average delay to surgery of 2.8 years less for seizure-free patients compared to those with a less-favorable outcome.[74] These data suggest that epileptogenic processes presenting with longer epilepsy duration decrease the chances of surgical success, independently of other predictors. Based on this assumption, recent studies suggest recommending surgery very early in the course of the disease, even for non–drug-resistant patients. For example, in certain lesional scenarios, such as epilepsy associated with cavernous malformations, surgery following two or fewer seizures has been associated with 95% seizure- and 79% ASM-freedom rates compared to 63% and 25% in patients with more than two seizures before surgery.[75] These observations likely contributed to our Delphi findings leading to Recommendation 3b.

6.2.4 | Expected risk vs benefit analysis does not favor surgery in patients with active substance abuse

Although there is some evidence that seizure outcomes are no different in individuals with active substance use disorder who have epilepsy surgery,[76] the literature suggests increased perioperative surgical and anesthetic risk in this cohort.[77] Patients with active substance abuse are more likely to be nonadherent with their seizure medications,[78] and to leave the hospital against medical advice.[79] This would further complicate already complex presurgical evaluations that require multiple inpatient tests and outpatient appointments, particularly in the subgroup of active substance users with documented nonadherence, thus our recommendation to delay surgical work-up until substance abuse is controlled and adherence with medical management is established (Recommendation 2).

6.2.5 | Areas of further research and conclusion

We were able to generate Expert Consensus Recommendations in most scenarios; yet, we identified several scenarios where consensus could not be reached (Table 3), highlighting opportunities for future research, including situations where no consensus was reached, or situations where the strength of consensus did not reach 50% (e.g., surgical referral in very young children who are seizure-free on ASM but have a lesion in noneloquent cortex).

The primary limitation of these recommendations is that they are based on the Delphi process for expert consensus generation, rather than evidence-based guidelines, which require a high grade of evidence that is not available at present. Of note, the existing American Academy of Neurology (AAN) guidelines now state that patients with drug-resistant epilepsy should be referred for consideration of epilepsy surgery. As such, the Expert Consensus Recommendations presented here reinforce and dissect the experts' interpretation of the existing guidelines in specific clinical scenarios. Randomized clinical trials could theoretically investigate the risks vs benefits of epilepsy surgery for each of our >50 clinical scenarios to strengthen the credibility of our recommendations, but this is neither possible nor ethical given the overwhelming evidence and data presented in our discussion and underlying our recommendations. We hope this expert consensus report will reduce misconceptions and fill the knowledge gap about epilepsy surgery and, as a result, decrease time to surgery for persons living with epilepsy who have ongoing seizures.

AUTHOR CONTRIBUTIONS

LJ and SW led the overall project. NJ, CSK, and CBJ led the Delphi survey design and execution. JGB, FC, MRS, SB, and RB led the author teams for specific sections in the article. All remaining co-authors contributed to initial drafts. All authors reviewed and edited the final recommendations draft.

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CONFLICT OF INTEREST

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DISCLAIMER

This report was written by experts selected by the International League Against Epilepsy (ILAE) and was approved for publication by the ILAE. Opinions expressed by the authors, however, do not necessarily represent the policy or position of the ILAE.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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