Azienda ospedaliero-universitaria Senese

LA GESTIONE DELL'EPILESSIA FARMACORESISTENTE

Sabina Bartalini & Giampaolo Vatti

UOC Neurologia e Neurofisiologia Clinica

AOU Siena

Epidemiology

- Epilepsy affects 0.8-1.0 % of population worldwide

  50 million people worldwide

  third most frequent neurological disease

  (Haedache and CVD)

- Italy
  - 5-600.000 epileptic patients
  - 150-200.000 drug resistant
- Tuscany
  - 36.000 **epileptic patients**
  - >10.000 **drug resistant**

- **Around 70% of patients have seizures controlled by drugs**

- **30% are Drug Resistant Epilepsy:**
  - **30% of all epilepsies**
  - > 50% of focal epilepsies

Prevalenza strato-specifica stimata dell'epilessia (31 dicembre 2015)

Genere/Età	Numero	Prevalenza grezza (x 1.000)
F: 0-15 anni	842	3,4
F: 16-44 anni	4.456	7,2
F: 45-64 anni	5.776	10,5
F: 65-84 anni	6.768	15,8
F: 85+ anni	1.553	15,2
M: 0-15 anni	1.082	4,1
M: 16-44 anni	4.839	7,8
M: 45-64 anni	4.844	9,3
M: 65-84 anni	5.001	14,2
M: 85+ anni	789	16,7
TOTALE	35.950	9,6

ARS TOSCANA agenzia regionale di sanità

Drug-resistant epilepsy is a severe health problem, associated with increased mortality, morbidity, and reduced HRQOL for patients and their caregivers.
It is associated with high unmet needs, especially regarding the availability of treatment alternatives that provide added efficacy over existing therapeutic alternatives.

DRE ***"failure of adequate trials of two tolerated, appropriately chosen and used ASM schedules (in monotherapy or in combination) to achieve sustained seizure freedom*** for 12 months or three times the preintervention interseizure interval, whichever is longer ***(ILAE -Kwan et al., 2010)."***

Predictive factors of DRE

- early age at onset of the disease
- presence of interictal epileptiform activity
- history of status epilepticus
- febrile seizures
- symptomatic etiology
- multiple seizure types
- comorbidity of neuropsychiatric or neurological disorders
- retardation in the neurodevelopment process

FULL-LENGTH ORIGINAL RESEARCH

The epidemiology of drug-resistant epilepsy: A systematic review and meta-analysis

Linda Kalilani, Xuezheng Sun, Barbara Pelgrims, Matthias Noack-Rink, Vicente Villanueva

First published: 13 November 2018 | https://doi.org/10.1111/epi.14596 | Citations: 140

Voll 2015, Yldiz 2018; Nogueira 2017, Wang Xue-Ping 2019

Possible interplay between the theories of DRE

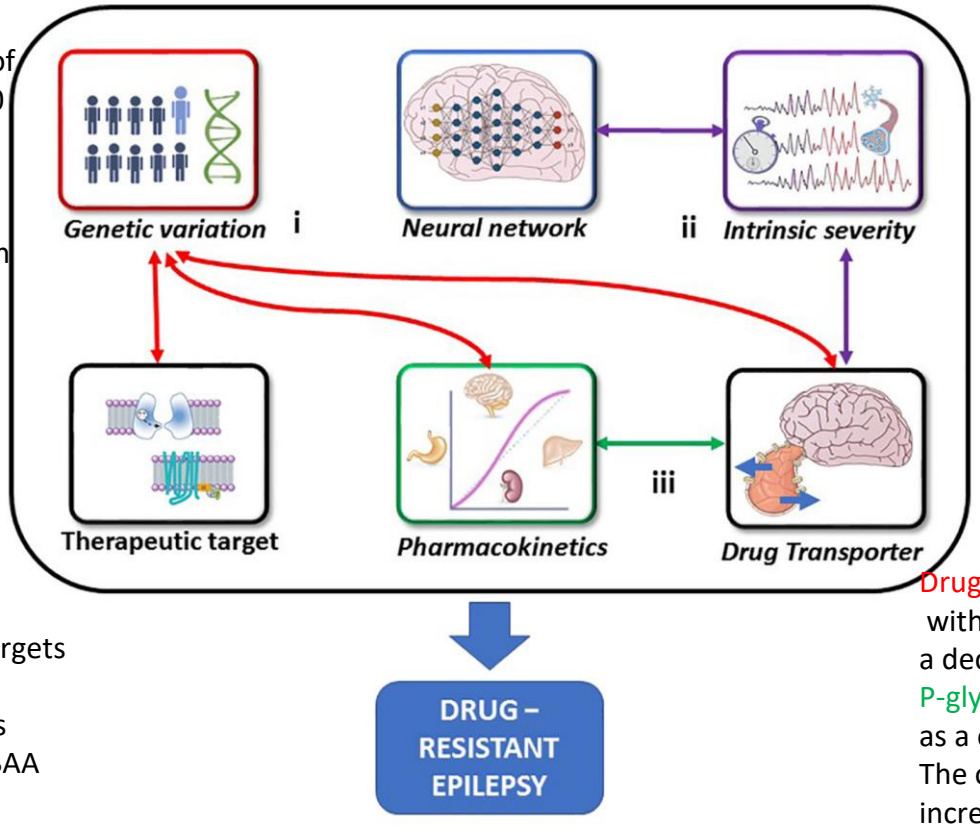
Contents lists available at ScienceDirect
Epilepsy & Behavior
journal homepage: www.elsevier.com/locate/yebeh
Review

Drug-resistant epilepsy: From multiple hypotheses to an integral explanation using preclinical resources

Daniel Pérez-Pérez [a,1], Christian L. Frías-Soria [b,1], Luisa Rocha [b,*]

Neural network: recurrent epileptic seizures in DRE generate neural death and the formation of aberrant and excitatory circuits. (MRI PET: identifying both poor anatomical and functional connectivity during epileptic activity as well as during brain activity at rest)

Genetic variation:
-Gene variants associated with the protein expression of GABAA, ion channels, enzymes of the cytochrome P450 family and drug transporters
-Epigenetic changes alter gene expression through chromatin modifications without altering the DNA
→ activation or silencing of gene expression



Intrinsic severity: is associated with a high release of glutamate
(detected in the epileptic focus of patients with drug-resistant
TLE during the ictal and interictal activity) induces excitotoxicity and the formation of aberrant neuronal circuits
(a condition associated with the neural network hypothesis)
Glutamate favors the overexpression of P-glycoprotein

Therapeutic target: molecular changes in therapeutic targets with lack of efficacy of AED
. i.e changes in the voltage-dependent sodium channels
or Alterations in the distribution and expression of GABAA

Drug transporter: elevated expression of drug transporters in BBB with low concentrations of AED at the brain parenchyma and a decrease in their effectiveness .
P-glycoprotein is overexpressed in neurons, astrocytes,cardiomyocytes as a consequence of repeated seizures or status epilepticus.
The overexpression of P-glycoprotein is associated with an increase in the membrane depolarization potential and increased neuronal excitability
(in cardiomyocytes can relates with SUDEP)

Pharmacokinetic: DRE as a consequence of alterations in the cytochromes and drug transporters involved in the metabolism and elimination of antiepileptic drugs.
Polymorphisms in the CYP3A isozyme are related to drug-resistant epilepsy because they are associated with decreased plasma levels of several antiepileptic drugs and a poor therapeutic response

EPILEPSY FOUNDATION
END EPILEPSY TOGETHER

NO SIDE EFFECTS

In controlled epilepsy, normal quality of life

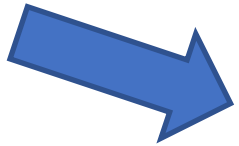
In DRE the quality of life is poor, associated, among the others, with the occurrence of ASD-related adverse events (especially those affecting mood, cognition and coordination.)

Clinical Outcome in DRE

DRE higher frequency of

- comorbidities
- behavioral, motor and cognitive deficits
- higher suicidal tendency (Lhatoo and Sander, 2005; Mesraoua et al., 2020)
- ASD-induced side effects (such as dizziness, weight gain, and sexual dysfunction) (Hermann et al., 2006; Alexopoulos et al., 2007; McCagh et al., 2009; Atif et al., 2016).
- higher mortality rates (2–10- times) compared with the general population (Chapell et al., 2003; Gaitatzis et al., 2012; Trinka et al., 2013)

"sudden unexpected death in epilepsy" (SUDEP) a principal cause of high mortality rates (Tomson et al., 2008; DeGiorgio et al., 2017).



- 1/150 PWE dies from SUDEP
- Leading epilepsy related cause of death
- Issue rarely addressed (18%)

Psycho-Social Outcome in DRE

- Lack of access to or change in employment or education
- Loss of a driving licence
- Marital and social problems
- Physical inactivity
- Experience of stigma and discrimination
- Psychological comorbidities such as anxiety, depression and sleep disturbance
- Cognitive disturbances (learning disabilities, memory, attention)

Hackett *et al. BMC Neurology* 2011, **11**:3
http://www.biomedcentral.com/1471-2377/11/3

BMC Neurology

STUDY PROTOCOL Open Access

Sydney epilepsy incidence study to measure illness consequences: the SESIMIC observational epilepsy study protocol

Maree L Hackett[1*], Nicholas S Glozier[2], Alexandra L Martiniuk[3], Stephen Jan[4], Craig S Anderson[1]

Original Article

CLINICAL REHABILITATION

Clinical Rehabilitation
2021, Vol. 35(5) 629–638

DOI: 10.1177/0269215520975327
journals.sagepub.com/home/cre
SAGE

ZMILE, a multicomponent self-management intervention for adults with epilepsy: Rationale and description of the intervention

Hoi Yau Chan[1], Loes AM Leenen[2], Ben FM Wijnen[3,4], Ingeborg M van der Putten[1], Silvia MAA Evers[1,3], Marian HJM Majoie[2,5,6,7] and Caroline M van Heugten[5,8]

Abstract

Objective: In this paper, we aim to provide a comprehensive description of the multicomponent self-management intervention for adults with epilepsy, ZMILE.

Rationale or theory: Acquiring self-management skills has been shown to play a vital role in enabling patients with epilepsy overcoming (health-related) struggles in daily life and coping with limitations their condition poses on them. ZMILE is a course consisting of education (to increase concordance to treatment), goal-setting (proactive coping), and self-monitoring.

Resources needed: The course is guided by two nurse practitioners and each patient is allowed to bring one family member or friend. Self-monitoring plays an important role and can be done through e-Health tools or written diaries.

Processes involved: During and after the course, patients are required to work toward a personally defined goal using a five-step approach by means of pro-active coping. Moreover, patients are expected to use self-monitoring tools to reflect on their own behavior and identify ways to optimize medication intake when required.

Quantification: ZMILE is provided in an outpatient setting over five weekly group sessions and one booster session. From the start, patients are encouraged to set individual goals. Each group session will have a different theme but part of every session is reflecting on personal goals and to learn from eachother.

Conclusions: The ZMILE-intervention has been evaluated and may be a promising intervention in terms of effectiveness and feasibility for adults with epilepsy, relatives, and professionals. We present the adapted version which can be implemented in clinical practice.

EPILEPSY SELF-MANAGEMENT IS A

Partnership.

Self-management does not mean that people manage their health alone. Self-management *requires an active partnership between a person with epilepsy, their family or friends, and their health care provider.* Each one plays an important role in epilepsy self-management.

Epilepsy self-management encompasses three broad areas:

- **Treatment Management.** Medication schedules, keeping clinic appointments, and communicating with health care professionals.
- **Seizure Management.** Recognizing and avoiding seizure triggers whenever possible and keeping track of seizures.
- **Lifestyle Management.** Getting adequate sleep, reducing stress, and maintaining social support networks.

Coordinating Centers:
Dartmouth-Hitchcock Medical Center, Lebanon, NH
Emory Prevention Research Center, Atlanta, GA

CDC Prevention Research Centers
CDC Epilepsy Program

SELF-MANAGEMENT TIPS FROM THE EPILEPSY FOUNDATION:

Take medicines as prescribed.

It is important to take your anti-seizure medicine exactly as prescribed by your healthcare provider. If you are having trouble taking your medicines or are experiencing side effects, contact your healthcare team.

Learn more.

Understand your diagnosis.

Understand what your epilepsy or seizure diagnosis means for you.

Learn more.

Keep a seizure diary.

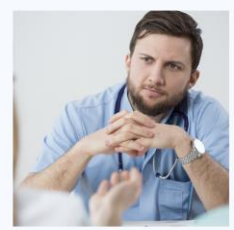
Keep a record of your seizures and look for patterns so that you can talk about them with your healthcare team.

Explore Epilepsy Foundation's **My Seizure Diary**.

Manage triggers.

Understand and monitor your seizure patterns to avoid or limit exposure to triggers.

Learn more.



Talk to your providers.

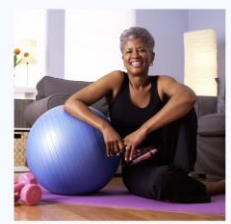
Learn how to talk to your healthcare team.

Communication Tools can help.

Get enough sleep.

Sleep and seizures can be closely connected.

Learn more.



Exercise safely.

Learn ways to exercise safely as part of a healthy lifestyle. Start with small changes.

Learn more.

Reduce stress.

Understand the role stress plays in your life and how it affects your epilepsy. Develop ways of reducing and coping with stress.

Learn more.

Eat well.

Understand the importance of diet in seizure control, including regular eating and dietary therapies.

Learn more.

Unmet Needs

Epilepsy & Behavior 122 (2021) 108222

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Identifying key unmet needs and value drivers in the treatment of focal-onset seizures (FOS) in patients with drug-resistant epilepsy (DRE) in Spain through Multi-Criteria Decision Analysis (MCDA)

Vicente Villanueva [a], Mar Carreño [b], Antonio Gil-Nagel [c], Pedro Jesús Serrano-Castro [d], José María Serratosa [e], Manuel Toledo [f], Elena Álvarez-Barón [g], Alicia Gil [h], Silvia Subías-Labazuy [h,*]

- Insufficient number of referrals to specialized epilepsy units ⟹ misdiagnosis, late detection, and delayed instauration of effective therapies

- Lack of effective pharmacological treatments.
- Availability of resources at regional level

- Dependence on family : High unemployment rates and occupational incapacity

- Negative impact of DRE in healthrelated quality of life (HRQOL) in patients and caregivers

More than one-third of patients need a caregiver for day life activities

Unmet Needs

- The costs associated with the treatment of DRE consumes a high percentage of healthcare resources
- DRE results in a considerable budgetary impact for patients and their families/caregivers, particularly in rural and remote regions where equity of access to necessary resources and skilled medical care can be difficult

Key Skills in Managing DRE

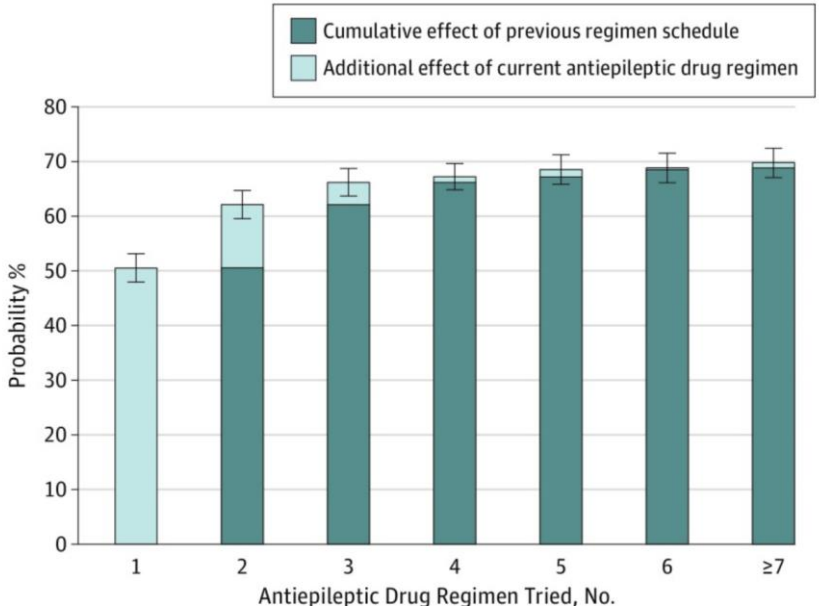
Knwoledge of anti seizure medications

Knowledge of electroclinical features - Precision Therapy

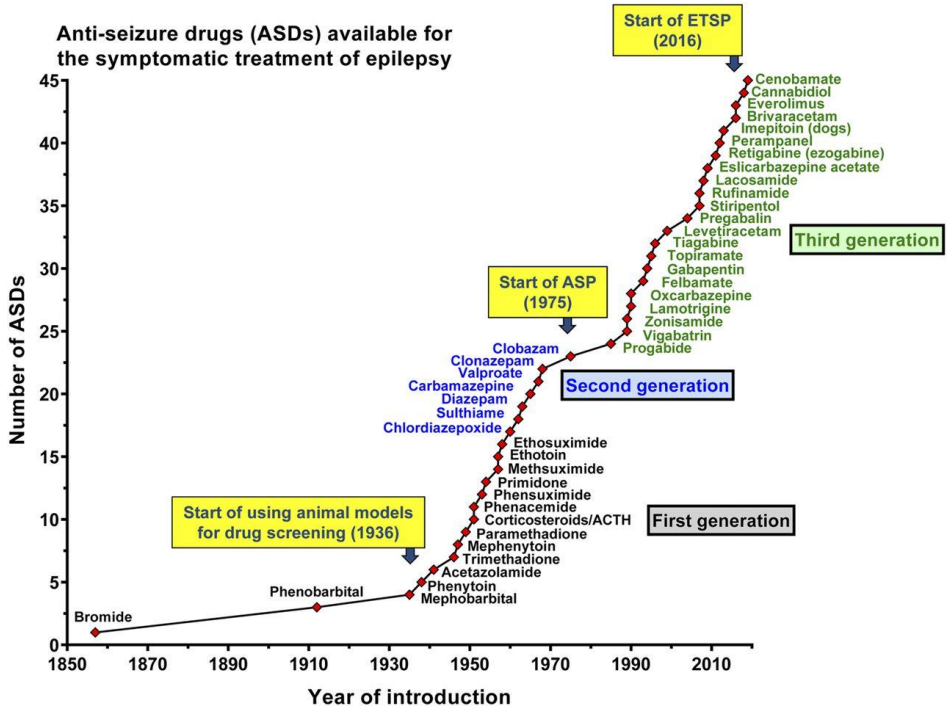
Taylored therapy (surgery)

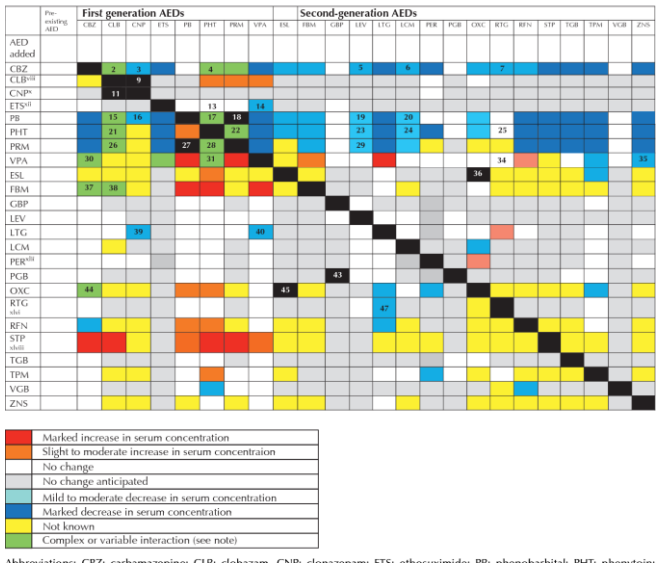
I-Alternative Monotherapy or Adjunctive Therapy?

a second ASD could render 11% additional patients seizure-free
Third AED or more provided less than 5% additional probability of seizure freedom



II-Use ASDs adapted to the patient's epilepsy syndrome.

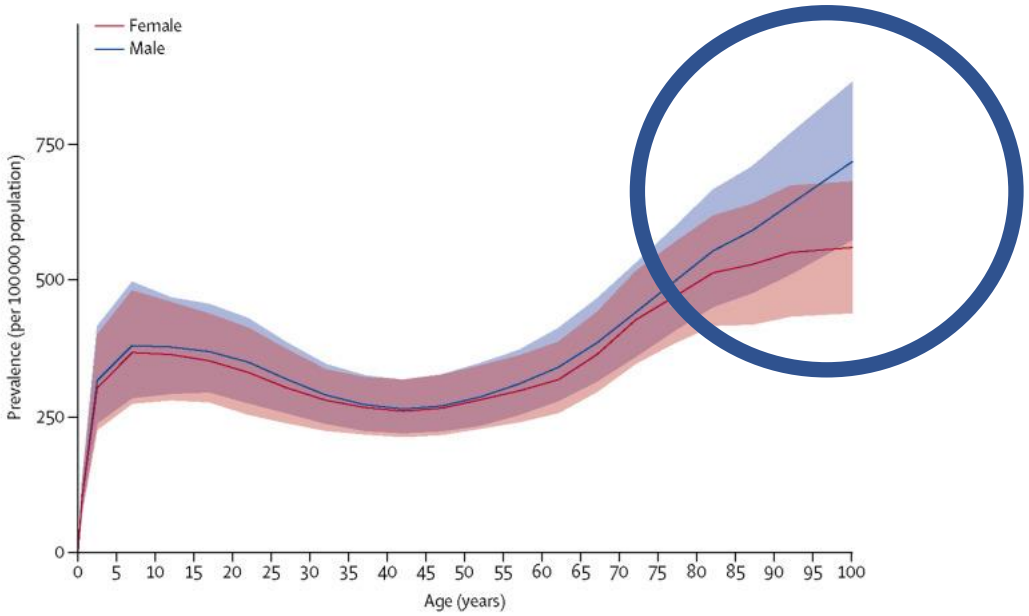


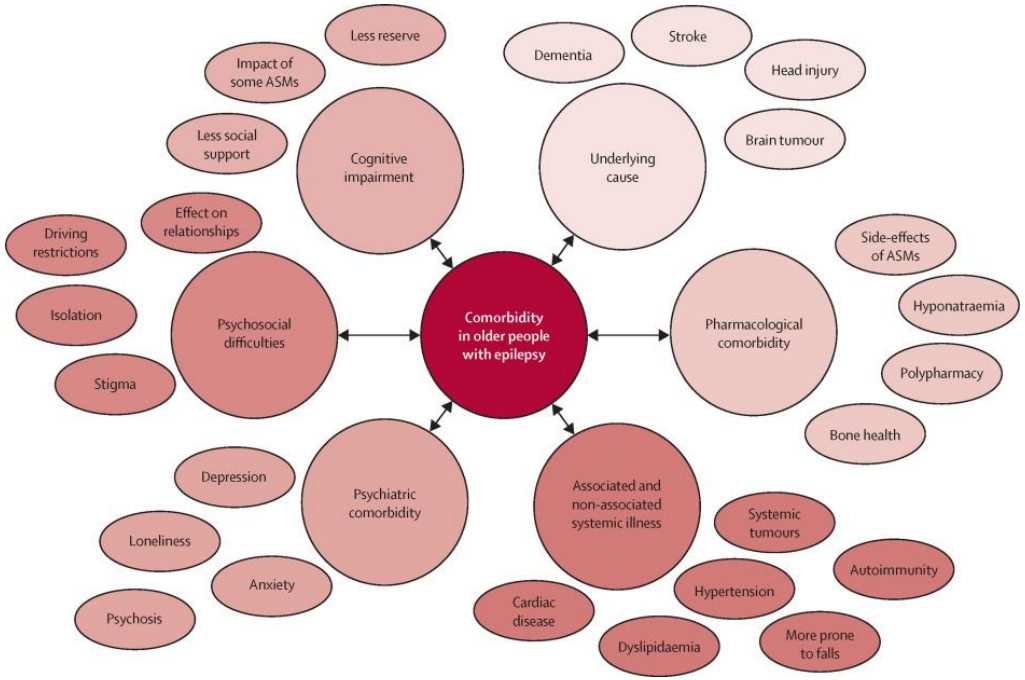


(Chen, 2018)

Choosing ASD Upon Their Safety Profile

Lifetime Prevalence of Epilepsy





- PATIENT'S AGE: impact of ASD on cognitive functioning (VPA in children) risk of imbalance (sodiumchannel blockers), impaired alertness (BDZ)
- PATIENT'S GENDER: risk of malformations and/or cognitive deficit in children after inutero exposition to ASD
- RISK OF DRUG–DRUG INTERACTIONS (between ASDs and/or with non-ASD molecules)
- PATIENTS' COMORBIDITIES

III- Drugs acting on Disease-Specific Pharmacological targets? Precision Therapy

→ a personalization of treatments that ideally should be targeted towards the precise molecular pathogenesis of disease

Neurotherapeutics (2020) 17:609–615
https://doi.org/10.1007/s13311-020-00835-4

CURRENT PERSPECTIVES

From Genetic Testing to Precision Medicine in Epilepsy

Pasquale Striano[1,2] · Berge A. Minassian[3]

Published online: 24 January 2020

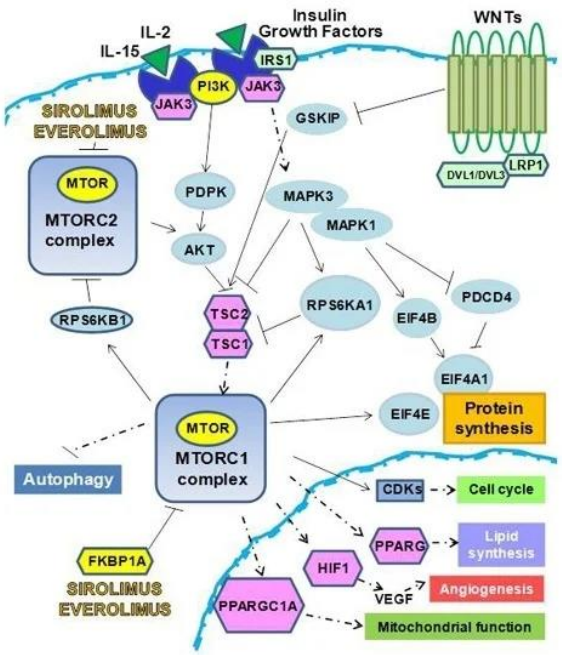
- Genetic abnormalities cause 70% of epileptic syndromes
  - Multigene panel
  - Clinical exome testing
  - Clinical genome testing
  - Chromosomal Microarray
  - Next generation sequencing

Table 1 Examples of precision medicine applied to epilepsy

Epilepsy syndrome (# OMIM)	Gene(s)	Protein function	Possible targeted treatments
Pyridoxin-dependent epilepsy (#266100)	*ALDH7A1*	Aldehyde dehydrogenase	Pyridoxine (B6 vitamin)
Focal epilepsy with speech disorder, with/without mental retardation (#245570)/EIEE 27 (# 616139)	*GRIN2A, GRIN2B*	NMDAR subunits	NMDAR antagonists (memantine) and dextromethorphan, potentially useful (GOF variants)
EIEE 32 (# 616366)	*KCNA2*	Voltage-gated potassium channel	Potential efficacy of 4-aminopyridine (4-AP, Kv1 channels inhibitor) for GOF variants
EIEE 7 (#613720); BFNS1 (#121200)	*KCNQ2*	Voltage-gated potassium channel	Potassium channel openers (Retigabine and Ezogabine for LOF variants), potential efficacy of sodium channel blockers (CBZ)
EIEE 14 (#614959); Nocturnal frontal lobe epilepsy (#615005)	*KCNT1*	Sodium-activated potassium channel	Potassium channel openers (Quinidine for GOF variants)
PNP oxidase deficiency (#610090)	*PNPO*	PNP oxidase	Pyridoxal-5-phosphate
Familial infantile convulsions with paroxysmal choreoatetosis (#602066); BFIS 2 (#605751)	*PRRT2*	Coregulator of synaptic transmission	sodium channel blocker (carbamazepine)
Dravet syndrome (#607208)	*SCN1A*	Voltage-gated sodium channel subunit	Avoid sodium channel blockers (carbamazepine, phenytoin)
EIEE 11 (#613721)/BFIS 3 (#607745)	*SCN2A*	Voltage-gated sodium channel subunit	Sodium channel blockers for GOF variants; avoid sodium channel blockers for LOF variants
EIEE 13 (#614558); BFIS 5 (#617080)	*SCN8A*	Voltage-gated sodium channel subunit	Favor sodium channel blockers for GOF variants
GLUT1 deficiency (#606777; #612126)	*SLC2A1*	Glucose transporter	Ketogenic diet
FCD type II (#607341)	*mTOR, TSC1, TSC2*	mTOR pathway effectors/regulators	Everolimus and other mTOR inhibitors

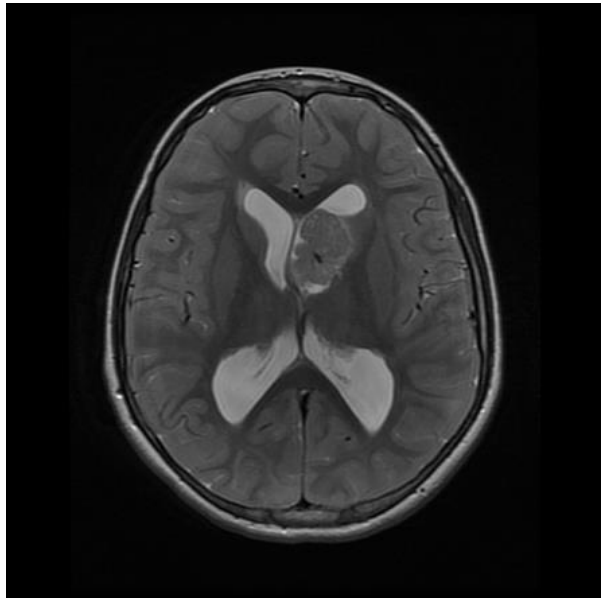
BFIS (benign familial infantile seizures); *BFNS* (benign familial neonatal seizures); *CBZ* (carbamazepine); *EIEE* (early infantile epileptic encephalopathy); *FCD* (focal cortical dysplasia); *GOF* (gain-of-function); *LOF* (loss-of-function); *LTG* (lamotrigine); *NMDAR* (*N*-methyl-D-aspartate receptor); *PHT* (phenytoin); *PNP* (pyridoxine 5-prime-phosphate)

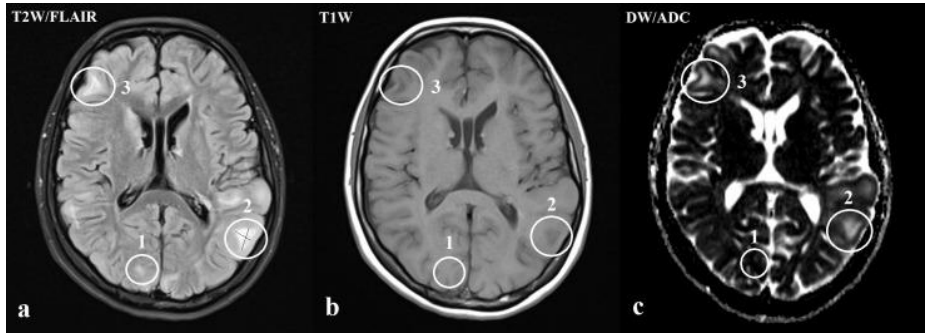
Need for genetic counseling



Tuberous Sclerosis Complex

- Mental retardation
- Multiorgan lesions
- Brain tumor
- Encephalopathy
- Drug resistant epilepsy





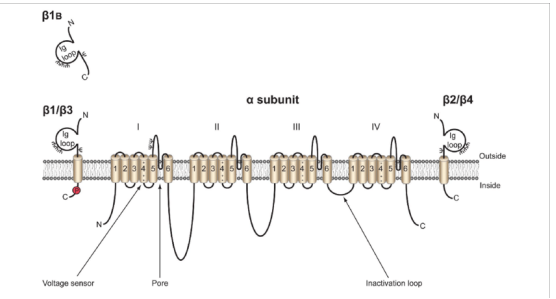
Mutations of TSC1 or TSC2 genes (95% of patients) cause suppression of mTOR (mechanistic target of rapamycin) inhibition

Everolimus, a drug inhibiting the mTOR pathway, significantly reduces seizure frequency in patients with TSC

- **Dravet Syndrome**

loss of function in the SCN1A gene encoding the α1 subunit of the sodium channel gene SCN1A

→ avoided treatment with sodium channel blockers (CBZ, PHT)



- **Developmental epileptic encephalopathy**

gain of function in the SCN2A and SCN8A genes encoding subunits of the neuronal voltage-gated sodium channel

→ main therapeutic strategy use of sodium channel blocking

Retigabine a potassium channel opener drug restoring normal channel function (**KCNQ2 -encephalopathy associated with loss-of-function mutations)** (adverse effects including skin and retinal pigmentation potentially leading to visual loss)

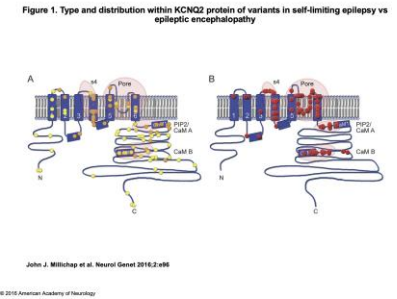


Figure 1. Type and distribution within KCNQ2 protein of variants in self-limiting epilepsy vs epileptic encephalopathy

John J. Millichap et al. Neurol Genet 2016;2:e96

ketogenic diet –standard choice-
it provides ketone bodies for brain energy metabolism and thus compensates the brain energy failure syndrome caused by impaired glucose transport across brain tissue barriers.

Epilepsy Surgery

Resective

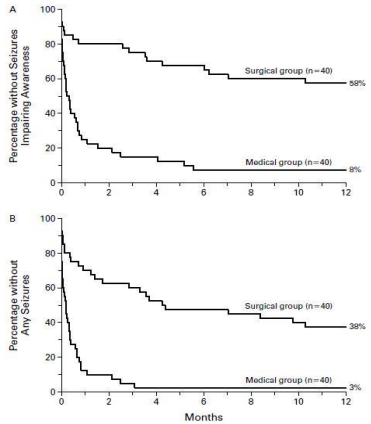
Palliative

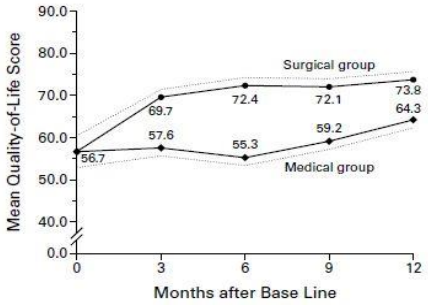
- VNS
- DBS
- Callosotomy
- Others

Surgical utilization and referrals	Epilepsy surgery is underutilized worldwide.[8,9]
Cost of epilepsy	Successful epilepsy surgery is more cost-effective than medical therapy, and greater savings accrue with earlier surgery.[10,11]
Indications for surgery	The most common criteria used to define surgical candidacy are seizure frequency (>1 per month) and failure of ≥2 antiepileptic drugs.[12] In cases of lesional epilepsy, surgery can be considered even earlier.
Seizure outcome after surgery	Approximately 60–65% of patients are seizure free after temporal lobe resection, compared with 40% of patients after extratemporal resection.[13]
Use of antiepileptic drugs after surgery	There is uncertainty about the proportion of patients who discontinue antiepileptic drugs after surgery.
Neuropsychological outcomes after surgery	Epilepsy surgery is associated with specific cognitive decline (most often involving verbal memory and naming after dominant lobe resections), but cognition may also improve in some patients.[14]
Psychiatric outcomes after surgery	There is either improvement or no change in psychiatric outcomes after surgery.[15]
Quality of life after surgery	Quality of life improves after surgery and is strongly influenced by seizure freedom.[16]
Social outcome after surgery	After surgery, improvement is seen in patients' employment, driving, and relationships.[17]
Complications after surgery	Surgical complications are usually minor or transient; major and minor neurologic complications were reported in 4.7% and 10.9% of patients, respectively, with resective surgery, with the most common being minor visual field deficits (affecting one quadrant or less).[18]
Mortality after surgery	Mortality appears to be lower if patients are rendered seizure free after epilepsy surgery.[19]


The New England Journal of Medicine

A RANDOMIZED, CONTROLLED TRIAL OF SURGERY FOR TEMPORAL-LOBE EPILEPSY





The Effectiveness of Medical and Surgical Treatment for Children With Refractory Epilepsy

BACKGROUND: Pediatric refractory epilepsy affects quality of life, clinical disability, and healthcare costs for patients and families.
OBJECTIVE: To show the impact of surgical treatment for pediatric epilepsy on healthcare utilization compared to medically treated pediatric epilepsy over 5 yr.
METHODS: The Pediatric Health Information System database was used to conduct a cohort study using 5 published algorithms. Refractory epilepsy patients treated with antiepileptic medications (AEDs) only or AEDs plus epilepsy surgery between 1/1/2008 and 12/31/2014 were included. Healthcare utilization following the index date at 2 and 5 yr including inpatient, emergency department (ED), and all epilepsy-related visits were evaluated. The propensity scores (PS) method was used to match surgically and medically treated patients. PS. SAS® 9.4 and Stata 14.0 were used for data management and statistical analysis.
RESULTS: A total of 2106 (17.1%) and 10186 (82.9%) were surgically and medically treated. A total of 4050 matched cases, 2025 per each treated group, were included. Compared to medically treated patients, utilization was reduced in the surgical group: at 2 and 5 yr postindex date, there was a reduction of 36% to 37% of inpatient visits and 47% to 50% of ED visits. The total number (inpatient, ED, ambulatory visits) of epilepsy-associated visits were reduced by 39% to 43% in the surgical group compared to the medically treated group. In those who had surgery, the average reduction in AEDs was 16% at 2 and 5 yr after treatment.
CONCLUSION: Patients with refractory epilepsy treated with surgery had significant reductions in healthcare utilization compared with patients treated only with medications.

KEY WORDS: Drug-resistant epilepsy, Effectiveness, Epilepsy surgery, Healthcare utilization, Pediatric epilepsy, Refractory epilepsy

Neurosurgery 0:1–10, 2020 DOI:10.1093/neuros/nyaa307 www.neurosurgery-online.com

Cost-effectiveness of surgery for drug-resistant temporal lobe epilepsy in the US

Shehryar R. Sheikh, MD, MPH, Michael W. Kattan, PhD, Michael Steinmetz, MD, Mendel E. Singer, PhD, Belinda L. Udeh, PhD, and Lara Jehi, MD, MHCDS

Neurology® 2020;95:e1404-e1416. doi:10.1212/WNL.0000000000010185

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Abstract

Objective
Surgery is an effective but costly treatment for many patients with drug-resistant temporal lobe epilepsy (DR-TLE). We aim to evaluate whether, in the United States, surgery is cost-effective compared to medical management for patients deemed surgical candidates and whether surgical evaluation is cost-effective for patients with DR-TLE in general.

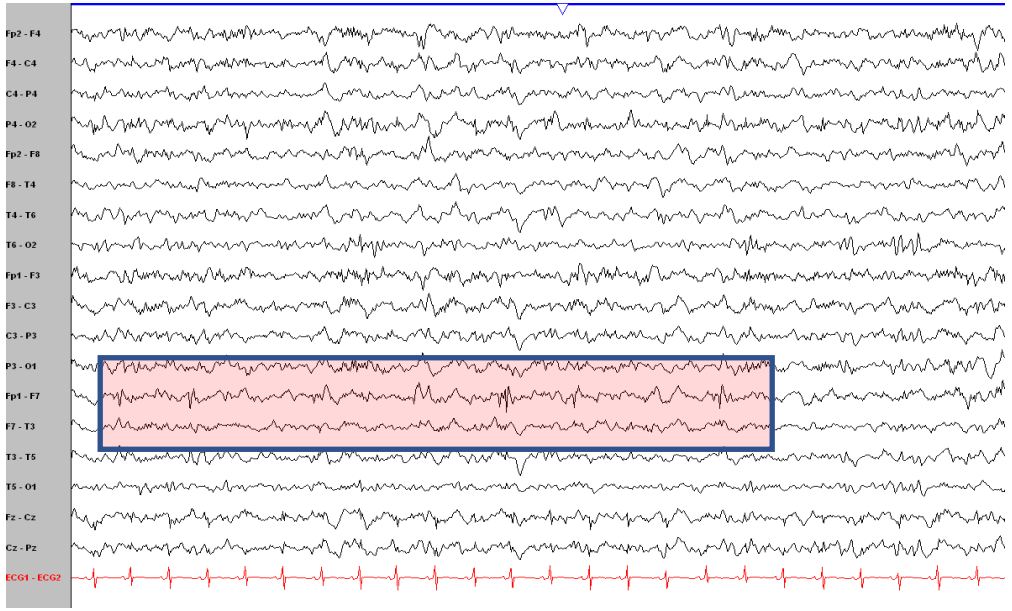
Methods
We use a semi-Markov model to assess the cost-effectiveness of surgery and surgical evaluation over a lifetime horizon. We use second-order Monte Carlo simulations to conduct probabilistic sensitivity analyses to estimate variation in model output. We adopt both health care and societal perspectives, including direct health care costs (e.g., surgery, antiepileptic drugs) and indirect costs (e.g., lost earnings by patients and care providers.) We compare the incremental cost-effectiveness ratio to societal willingness to pay (~$100,000 per quality-adjusted life-year [QALY]) to determine whether surgery is cost-effective.

Results
Epilepsy surgery is cost-effective compared to medical management in surgically eligible patients by virtue of being cost-saving ($328,000 vs $423,000) and more effective (16.6 vs 13.6 QALY) than medical management in the long run. Surgical evaluation is cost-effective in patients with DR-TLE even if the probability of being deemed a surgical candidate is only 5%. From a societal perspective, surgery becomes cost-effective within 3 years, and 89% of simulations favor surgery over the lifetime horizon.

Conclusion
For surgically eligible patients with DR-TLE, surgery is cost-effective. For patients with DR-TLE in general, referral for surgical evaluation (and possible subsequent surgery) is cost-effective. Patients with DR-TLE should be referred for surgical evaluation without hesitation on cost-effectiveness grounds.

RELATED ARTICLE
Editorial
Epilepsy surgery: Expensive, but worth the "price" of admission
Page 417

MORE ONLINE
Podcast
Dr. Jason Crowell talks with Dr. Lara Jehi about her paper discussing surgery costs in temporal lobe epilepsy.
NPub.org/wtj0x0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F4 - C4
C4 - P4
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T6 - O2
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F3 - C3
C3 - P3
P3 - O1
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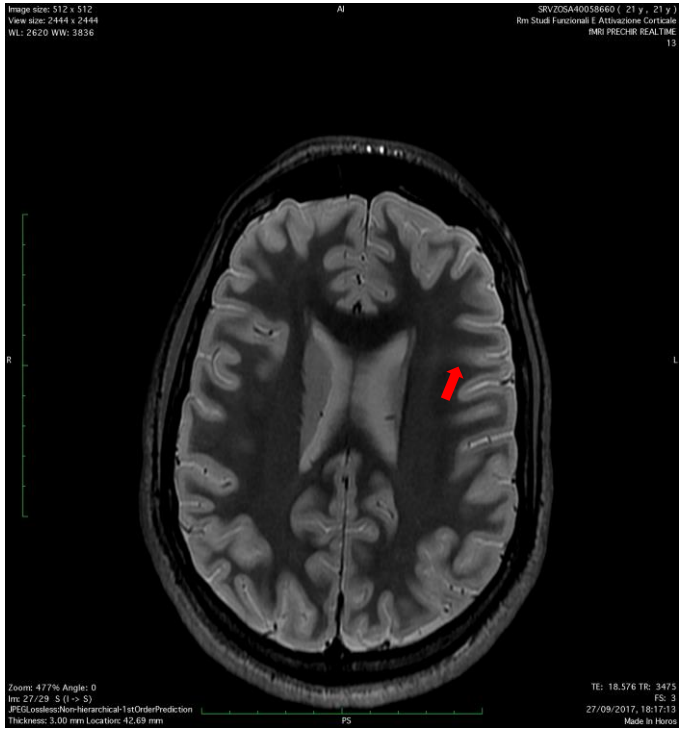
F7 - T3
T3 - T5
T5 - O1
Fz - Cz
Cz - Pz
ECG1 - ECG2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JPEGLossless:Non-hierarchical-1stOrderPrediction
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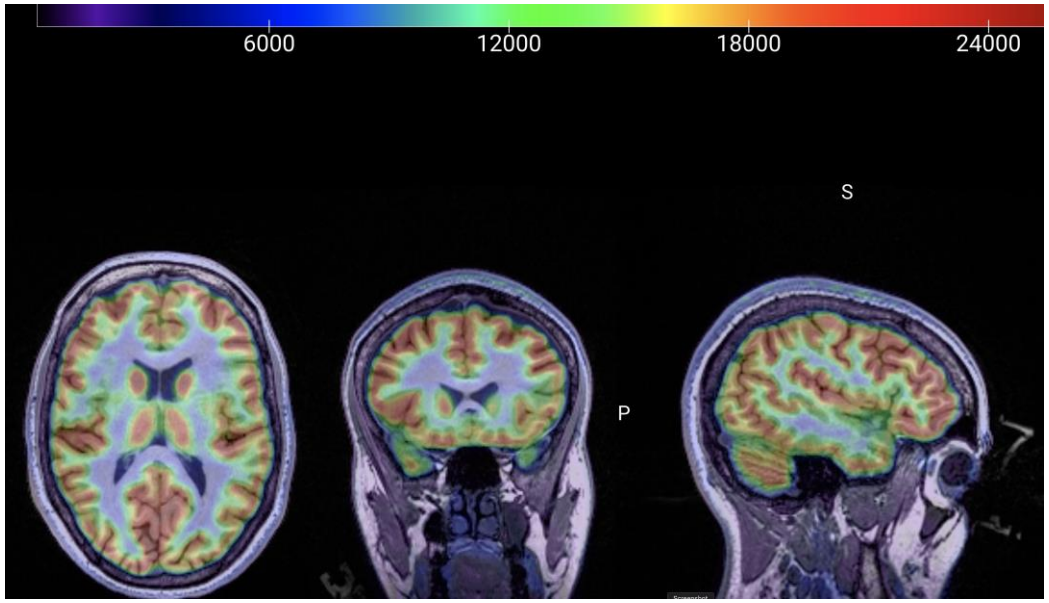
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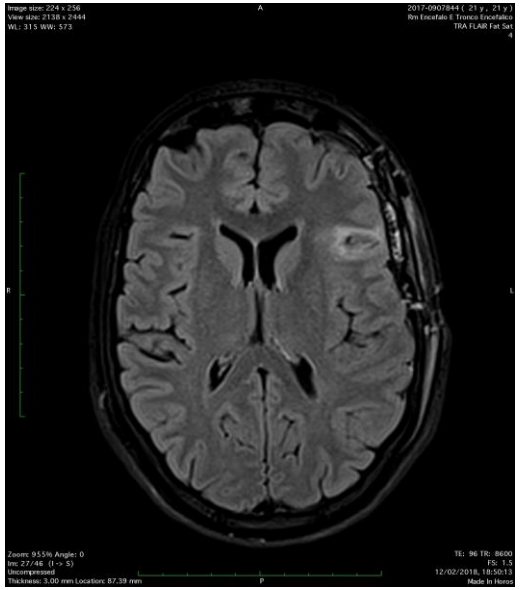
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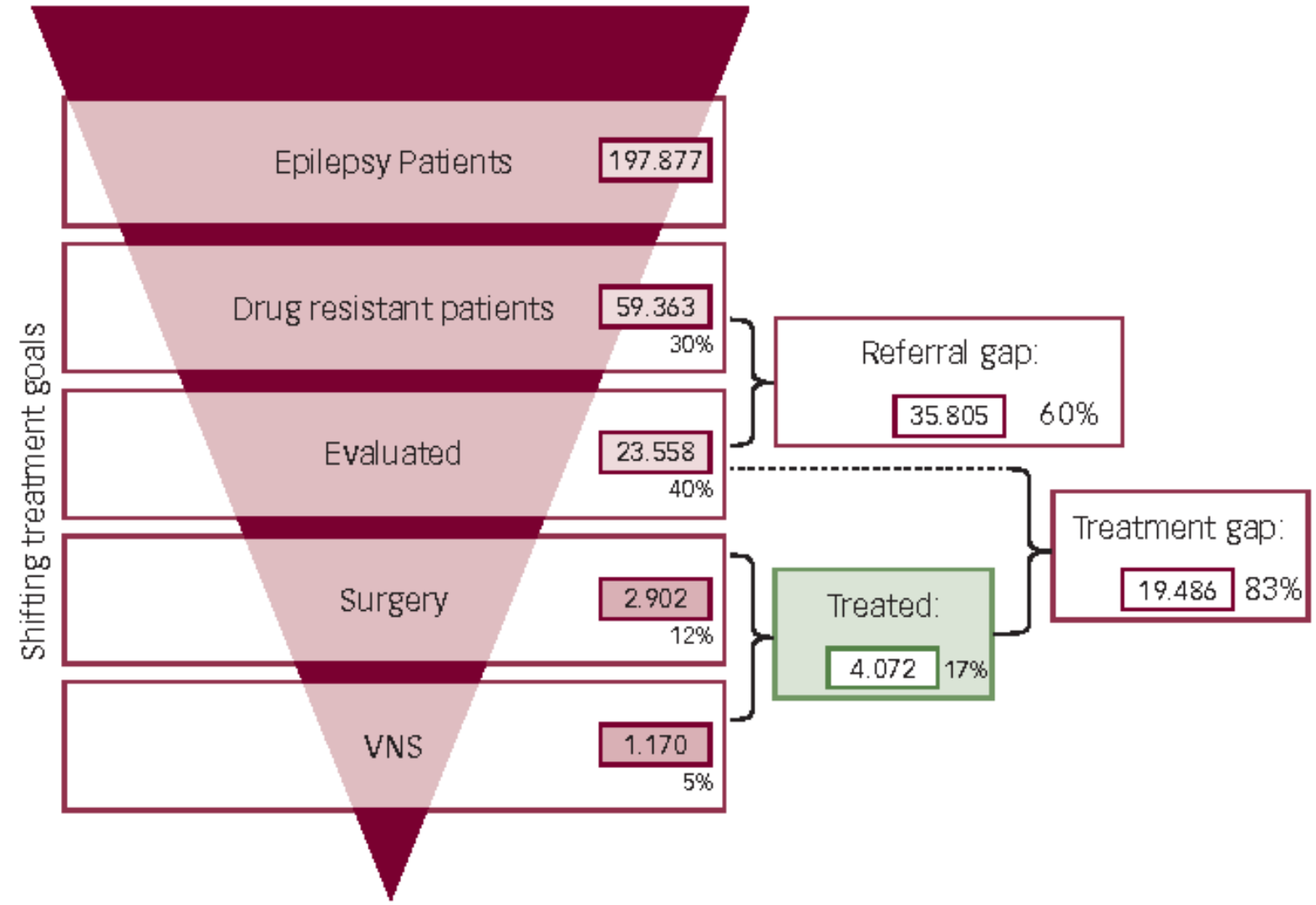
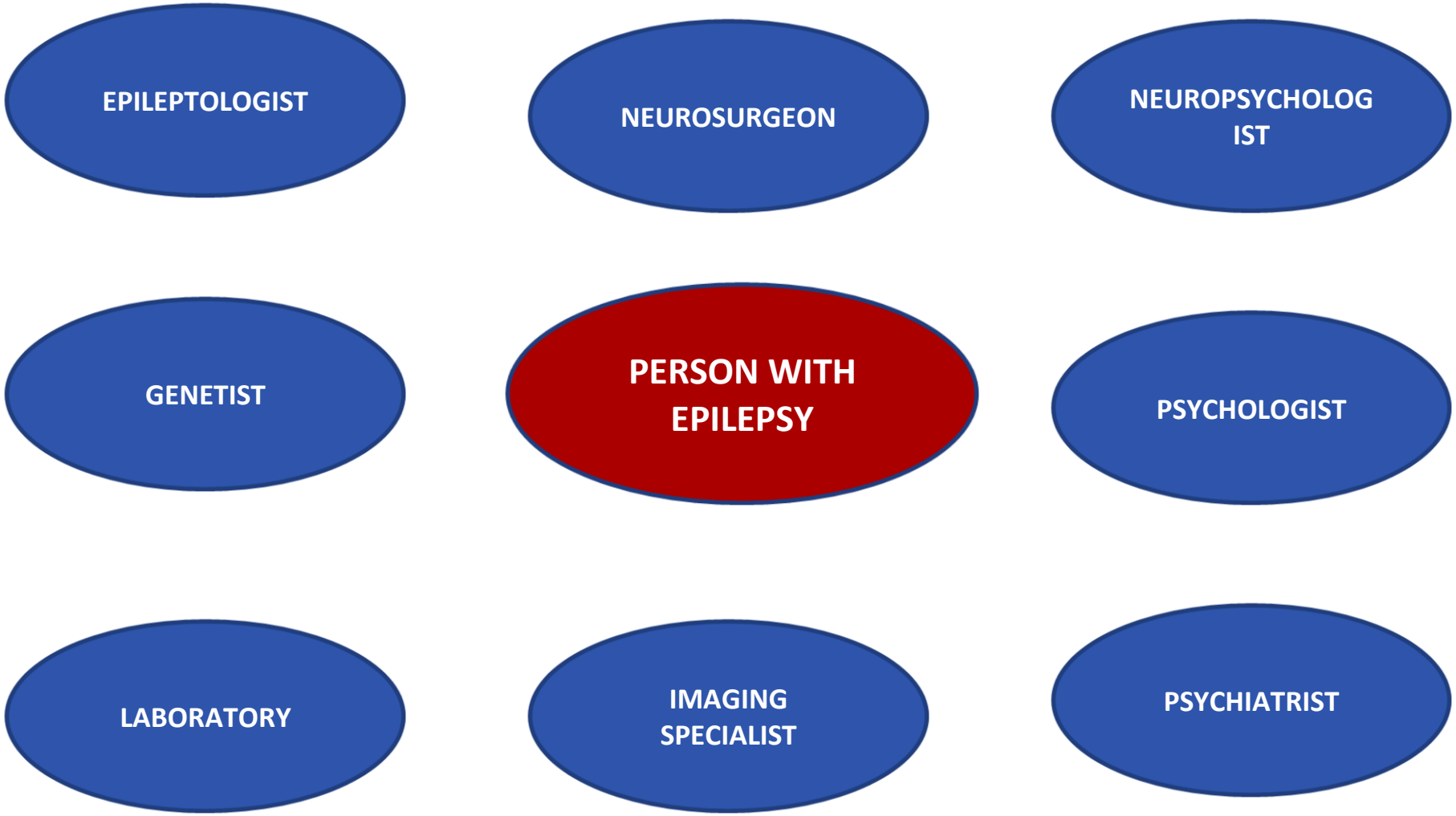


VNS = vagus nerve stimulation.

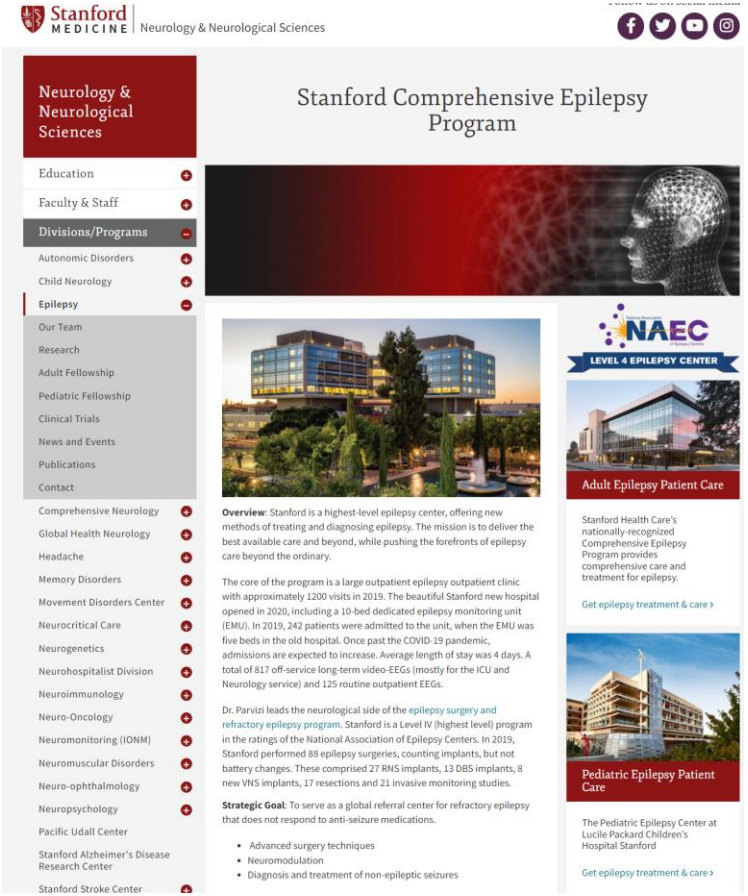
TREATMENT DELAY 18 YEARS

Multidisciplinary Approach to Drug Resistant Epileptic Patient



NAEC defines four levels of epilepsy care:

- Level 1 epilepsy care typically occurs at an **emergency room or a primary care physician's office** with an epilepsy evaluation.
- Level 2 epilepsy care involves a consultation with a **general neurologist**. This consultation may occur at a specialized epilepsy center.
- Levels 3 epilepsy centers provide basic neurodiagnostic evaluations (medical, neuropsychological, and psychosocial treatment). Some level 3 centers offer noninvasive evaluation for epilepsy surgery, straight-forward resective epilepsy surgery, and implantation of the vagus nerve stimulator. These centers do not perform intracranial evaluations or other more complex epilepsy surgery.
- Level 4 center provides the more complex forms of intensive neurodiagnostic monitoring, as well as more extensive medical, neuropsychological, and psychosocial treatment. Level 4 centers also offer a complete evaluation for epilepsy surgery, including intracranial electrodes and a broad range of surgical procedures for epilepsy.



Centri riconosciuti dalla LICE ad indirizzo medico o chirurgico,
classificati in diversi livelli in base alla tipologia organizzativa e alle prestazioni strumentali e terapeutiche che possono essere erogate presso le diverse strutture

Tabella sinottica 1: requisiti tecnico-organizzativi CE-LICE Medico di I, II e III livello

Specifiche	I Livello	II Livello	III livello
Personale medico	1 specialista	2 specialisti	3 specialisti
PcE in carico	300	500	700
Ambulatori/Settimana	2	3	4
TNFP	Disponibile entro Azienda	Disponibile entro Azienda	Disponibili entro il centro
EEG standard	Disponibile entro Azienda	Disponibile entro Azienda	Necessario nel Centro
EEG dinamico	Collaborazioni anche Esterne	Collaborazioni anche Esterne	Collaborazioni anche Esterne
PSG diurna	Collaborazioni anche Esterne	Disponibile entro Azienda	Necessario
VEEG	Collaborazioni anche Esterne	Collaborazioni anche Esterne	Necessario
Trial Farmacologici	Non Necessario	Non Necessario	Necessario
Collaborazioni multidisciplinari	Necessarie	Necessarie	Indispensabili e strutturate
Attività formativa	Non Necessario	Non Necessario	Necessario
Attività di Ricerca	Non Necessario	Non Necessario	Necessario

Legenda
PcE Persone con Epilessia in carico: almeno una visita negli ultimi due anni
TNFP: Tecnico di Neurofisiopatologia
PSG: polisonnografia in ambiente dedicato mirata a registrazione di un periodo di sonno
VEEG: registrazione Video-EEG di almeno 1 ora in ambiente dedicato

Tabella sinottica 2: requisiti tecnico-organizzativi CE-LICE chirurgico

Specifiche	II Livello	III livello
Epilettologo	2 specialisti	3 specialisti
Neurochirurgo	1 specialista	2 specialisti
PcE in carico	300	500
Ambulatori/Settimana	2	3
TNFP	2	3
VEEG in RO	Necessario	Necessario
Registrazioni invasive	Non Necessario	Necessario
Interventi chirurgici	>10 e <25	>25
Collaborazioni multidisciplinari	Necessario	Necessario e strutturato
Attività formativa	Non Necessario	Necessario
Attività di Ricerca	Non Necessario	Necessario

Legenda:
PcE Persone con Epilessia in carico: almeno una visita negli ultimi due anni
TNFP tecnico di Neurofisiopatologia
VEEG: registrazioni Video-EEG di lunga durata con registrazione di crisi
RO: ricovero ospedaliero

Nel 2019:

Piemonte, Toscana ed Emilia Romagna risultano le uniche tre Regioni italiane ad avere un Piano Diagnostico Terapeutico Assistenziale (PDTA) dedicato alla patologia.

Nel Lazio e in Abruzzo è in corso di elaborazione.

Emilia Romagna, Toscana e Lombardia, inoltre, le sole Regioni ad avere proprie Linee Guida Terapeutiche dell'epilessia.

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**PERCORSO ASSISTENZIALE
PER LA PRESA IN CARICO
DELLE PERSONE CON EPILESSIA**

Allegato A

Decisione Comitato Tecnico Scientifico n. 12 del 04/06/2019

Regione Toscana

SST Servizio Sanitario della Toscana

PEDIATRICO

> I pazienti che rispondono alla prima terapia farmacologica, e quelli che sono controllati da una prima terapia di combinazione, possono essere seguiti in regime ambulatoriale nelle strutture regionali in cui operano neuropsichiatri infantili o neurologi pediatri con esperienza in ambito epilettologico. Le visite di controllo dovrebbero essere effettuate con tempistica che dipende dalla evoluzione clinica e nel corso di queste, oltre che l'efficacia della terapia, dovrebbero essere valutati con attenzione la regolarità dell'acquisizione delle tappe di sviluppo psicomotorio e la evoluzione delle capacità cognitive, gli effetti collaterali dose dipendenti di un farmaco e gli effetti collaterali cronici. Inoltre, un tempo adeguato dovrà essere dedicato a fornire informazioni ai familiari sulla malattia, sulle conseguenze del trattamento e su quali procedure adottare nel caso si verifichino particolari evenienze.

Tutti i pazienti pediatrici affetti da epilessie farmacoresistenti dovrebbero essere valutati da specialisti esperti presenti nelle strutture di terzo livello della Regione (AOU Meyer, AOU Siena, AOU Pisa, IRCCS Stella Maris). In queste strutture tutti i pazienti dovrebbero essere valutati regolarmente in regime di ricovero o ambulatoriale, con una frequenza che dipende dall'evoluzione clinica. Idealmente, personale infermieristico specializzato dovrebbe essere in contatto con i familiari dei pazienti più gravi per poter programmare contatti telefonici o accessi ambulatoriali rapidi nel caso di un peggioramento clinico o dell'emergenza legata a effetti avversi importanti del trattamento.

ADULTO

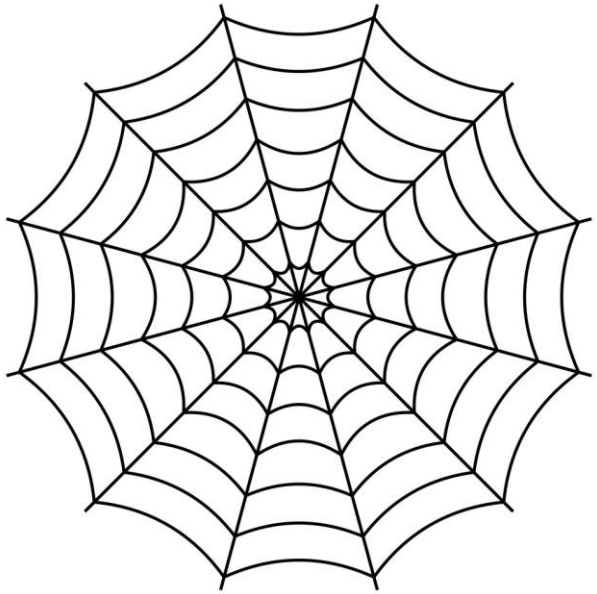
La decisione di iniziare un trattamento farmacologico deve essere presa in linea di massima da un neurologo.
La modalità del consulto neurologico varia in rapporto alla situazione clinica e può avvenire nei locali del DEA in situazioni di urgenza, in ospedale se il paziente resta ricoverato, oppure ambulatorialmente mediante accesso richiesto dal medico del DEA o dal MMG con criterio di priorità urgente (entro 72 ore) o breve (entro 10 giorni).
Nei casi più complessi per inquadramento diagnostico e scelta terapeutica, il paziente dovrebbe essere inviato a visita da un epilettologo.

I pazienti affetti da epilessia devono essere seguiti da un neurologo.
Quei pazienti che rispondono alla prima terapia farmacologica oppure quelli che sono controllati da una prima terapia di combinazione possono essere seguiti presso un ambulatorio di neurologia generale.
Le visite di controllo neurologiche dovrebbero essere effettuate in linea di massima una volta l'anno e comunque almeno ogni due anni. Nel corso di queste, oltre che l'efficacia della terapia, dovrebbero essere valutati con attenzione gli effetti collaterali dose dipendenti che si osservano presto dopo l'introduzione di un farmaco, e soprattutto gli effetti collaterali cronici (esempio l'insorgenza di osteoporosi o di disturbi cognitivi). Inoltre un tempo adeguato dovrà essere dedicato a fornire informazioni sulla malattia, sulle conseguenze del trattamento e su quali procedure adottare nel caso si verifichino particolari evenienze (effetti collaterali gravi, malattie intercorrenti, assunzione di altri farmaci, dimenticanza di una dose, diete particolari, ecc) e dovrà essere controllata l'aderenza al trattamento.
Una diversa risposta organizzativa dovrebbe essere invece adottata per i pazienti farmacoresistenti (secondo la definizione di farmacoresistenza della lega internazionale contro l'epilessia sono farmacoresistenti quei pazienti le cui crisi non sono state controllate dopo aver provato almeno due trattamenti farmacologici indicati nella forma di epilessia in di cui il paziente è affetto, usati a dosaggi adeguati e per un tempo sufficientemente

prolungato). Questi pazienti dovrebbero essere valutati da specialisti esperti nel trattamento delle epilessie (vedere capitolo introduttivo).
Altrettanto dovrebbe essere fatto per pazienti che sperimentano effetti avversi gravi ai farmaci antiepilettici, pazienti con epilessie sintomatiche che necessitano di attenta sorveglianza, quando ci sono importanti comorbidità psichiatriche, quando la diagnosi sindromica non è chiara.
Nei presidi ospedalieri più importanti (ospedali di secondo livello) della Regione sono allestiti ambulatori dedicati per i pazienti affetti dalle forme di epilessia più difficili da trattare. Queste strutture dovrebbero disporre di tutti i mezzi per trattare pazienti con epilessie complesse. Dovrebbero quindi avere la possibilità di effettuare ricoveri diagnostici anche per video-registrazione delle crisi, dovrebbero avere la possibilità di contattare rapidamente altri specialisti come neurochirurghi, radiologi, ecc, per il trattamento di tutte le eventuali complicanze.
Oltre alle procedure diagnostiche e terapeutiche già descritte, in questi ambulatori tutti i pazienti dovrebbero essere visitati con una frequenza di almeno una visita ogni sei mesi. Idealmente, infermieri specializzati dovrebbero essere in contatto con i pazienti più gravi e dovrebbero poter programmare contatti telefonici o accessi ambulatoriali rapidi nel caso di un peggioramento clinico o dell'emergenza di effetti avversi importanti.

In progress….in collaboration with LICE Tuscany coordinators (E. Rosati & R. Galli)

Update Mapping of Epilepsy Care facilities in Tuscany to allow an easier accessibility to the best possible care related to each individual person with Epilepsy needs



Without the need of super abilities

Complexity levels

- Epileptic patients well controlled → General Neurologist
  - Epileptic patients controlled but «special patients»

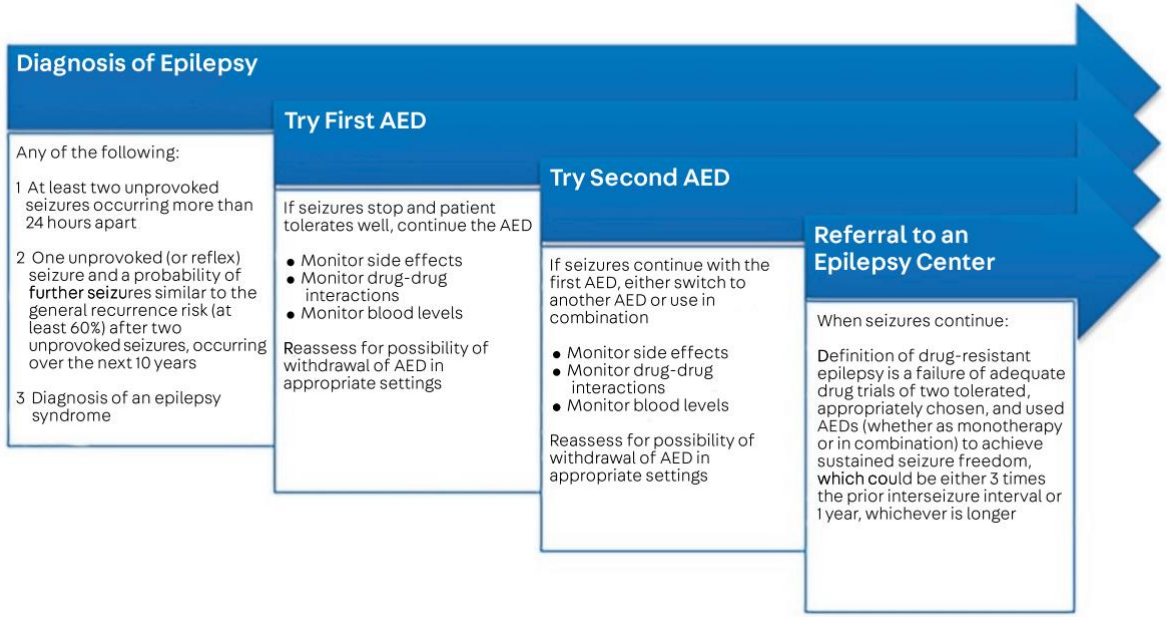
    polytherapy

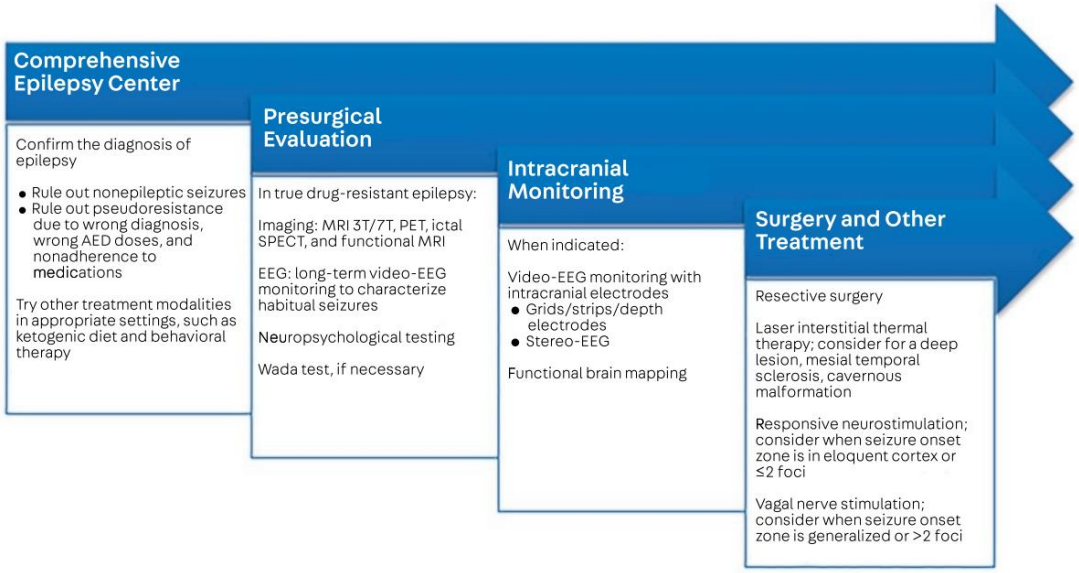
    elderly → General Neurologist ↔ Epilepsy Center

    pregnancy

- Drug Resistant Epileptic patients → Medical/Surgical Epilepsy Center

Decision tree





(Yoo and Panov, 2019)

Need to be underscored

- The minimum duration required to evaluate the response to an ASD might vary across patients
- The threshold of two ASD may look arbitrary
- Only half of patients with uncontrolled seizures might meet the ILAE criteria of DRE (divergences related to ASD dosage and/or adverse events e/or the choice of the previously failed ASD.)
- Distinguishing drug-resistance from “pseudoresistance”:

  -Treatment compliance needs to be systematically evaluated

  -Psychogenic non-epileptic seizures (up to 20 to 25% of pseudo-resistance)

  - Inefficacious, or even worsening, ASD for a dedicated epilepsy syndrome (i.e carbamazepine, phenytoin or gabapentin, can aggravate seizure frequency or precipitate status epilepticus in IGE)