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Multimodal prognostic features of seizure freedom in epilepsy surgery

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ABSTRACT

Objective Accurate preoperative predictions of seizure freedom following surgery for focal drug resistant epilepsy remain elusive. Our objective was to systematically evaluate all meta-analyses of epilepsy surgery with seizure freedom as the primary outcome, to identify clinical features that are consistently prognostic and should be included in the future models.

Methods We searched PubMed and Cochrane using free-text and Medical Subject Heading (MeSH) terms according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses. This study was registered on PROSPERO. We classified features as prognostic, non-prognostic and uncertain and into seven subcategories: 'clinical', 'imaging', 'neurophysiology', 'multimodal concordance', 'genetic', 'surgical technique' and 'pathology'. We propose a structural causal model based on these features.

Results We found 46 features from 38 meta-analyses over 22 years. The following were consistently prognostic across meta-analyses: febrile convulsions, hippocampal sclerosis, focal abnormal MRI, Single-Photon Emission Computed Tomography (SPECT) coregistered to MRI, focal ictal/interictal EEG, EEG-MRI concordance, temporal lobe resections, complete excision, histopathological lesions, tumours and focal cortical dysplasia type IIb. Severe learning disability was predictive of poor prognosis. Others, including sex and side of resection, were non-prognostic. There were limited meta-analyses investigating genetic contributions, structural connectivity or multimodal concordance and few adjusted for known confounders or performed corrections for multiple comparisons.

Significance Seizure-free outcomes have not improved over decades of epilepsy surgery and despite a multitude of models, none prognosticate accurately. Our list of multimodal population-invariant prognostic features and proposed structural causal model may serve as an objective foundation for statistical adjustments of plausible confounders for use in high-dimensional models.

PROSPERO registration number CRD42021185232.

Key messages

What is already known on this topic

► Surgery can be curative for some individuals with focal drug-resistant epilepsy but not others. Although various clinical prognostic features - such as unifocal temporal lobe lesions carrying a favourable prognosis - are well-known, there are discrepancies in the scientific literature with regards to whether other features have prognostic value or not. Additionally, we have no accurate method to prognosticate. Therefore, this study reviewed meta-analyses that evaluated prognostic features of postsurgical seizure freedom.

What this study adds

► This study defines a list of 'Essential Prognostic Features' that were consistently prognostic across 38 evaluated meta-analyses of epilepsy surgery that had seizure-freedom as the primary outcome. We outline a structural causal model for statistical adjustments of plausible confounders and use in high-dimensional models. We propose a five-step plan for personalised seizure-freedom predictions, including collaborative multi-variable modelling.

How this study might affect research, practice or policy

► Our list of essential prognostic features might be especially useful in machine learning models of big-data on postsurgical seizure freedom. The proposed structrual causal model could be used in future research to adjust for known confounders. Instead of more meta-analyses, an international collaboration pursuing our proposed five-step plan may impel us towards attaining accurate personalised prognostication for epilepsy surgery.

INTRODUCTION

Epilepsy surgery can be curative for focal drug-resistant epilepsy, yet in over half of individuals, seizures eventually relapse.[1 2] Postsurgical outcomes include seizure freedom, discontinuation of antiseizure medications, neuropsychological and psychiatric outcomes or morbidity. Seizure freedom is the strongest predictor of improved health-related quality of life[3] and is classified according to the ILAE or Engel systems.[4] These outcomes can be used as ordinal scales, binarised into seizure-free and not seizure-free categories at specified post-operative time points or binarised at each year following surgery to build proportional Hazards models.[1 2]

Prognostic features can be related to patient characteristics (eg, age, seizure semiology, variability of seizures and genetics), investigation findings (focal lesion on MRI and localising epileptic activity on EEG), surgical factors (resection margins or technique) and combinations of the above (concordance of imaging with neurophysiology). Favourable

clinically relevant prognostic features have been identified from many individual studies, including clearly localising and lateralising semiology, well-circumscribed unilateral, unifocal and temporal lesions, EEG-MRI concordance and complete excision of the evaluated epileptogenic zone.[5 6]

Other features are prognostic in some studies but not in others such as focal to bilateral tonic-clonic seizures (FBTCS)[5–10] and age at seizure onset.[7–9 11] A feature may erroneously appear prognostic in a single-centre study due to publication bias or overfitting from investigating many unadjusted variables. Conversely, a feature may appear falsely non-prognostic in small studies due to low statistical power. Most individual studies are small retrospective observational studies from single centres and are prone to such biases.

Meta-analyses aggregate data while accounting for different levels of heterogeneity among patients and between studies. Their strength lies in combining data to achieve greater statistical power while adjusting for heterogeneity and confounders, and attributing weights to studies resulting in summary effect size estimates with wider CIs than unweighted methods.

Nevertheless, accurately predicting seizure freedom prior to surgery has remained elusive. Machine learning models show promise, but have almost entirely been trained on temporal lobe (TL) surgeries.[12] Other recent developments, such as the Epilepsy Surgery Nomogram and the modified Seizure Freedom score,[10] are not better than clinical heuristics[13] which have not resulted in improved surgical outcomes over recent decades.[14 15] This highlights the need for a review of the evidence in epilepsy surgery, which we present here by evaluating meta-analyses for prognostic features of postsurgical seizure freedom. In the search for clinical features with robust prognostic value, we consider meta-analyses, because they are considered the pinnacle of evidence-based data.

Our objectives are to address these questions:

1. Which features are consistently prognostic, and could be used in models of seizure freedom?
   This list should also preclude the need for further meta-analyses on these features,[16 17] other than to adjust for potential confounders.
2. Which features do not have prognostic value and could be excluded from future machine-learning models and meta-analyses? This would risk the potential loss of only very weak prognostic variables in exchange for better generalisability.
3. What variables have not been evaluated in meta-analyses and how can we improve postsurgical prognostication?

Methods

Search strategy and Criteria

The study was registered on international prospective register of systematic reviews. The search was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines on PubMed, MEDLINE and Cochrane updated 1 December 2020, using a combination of free-text and Medical Subject Heading (MeSH) terms. We screened titles and abstracts for inclusion criteria and full texts for exclusion criteria for individual prognostic features. Full search strategy and exclusions are in online supplemental methods.

Inclusion criteria

We included studies for full-text review that were meta-analyses of prognostic features for seizure freedom in epilepsy surgery. The neurosurgical resections had to have been performed for patients with drug-resistant focal epilepsy with curative intent.

Data collection

Two neurologists and a neurosurgeon independently screened articles for inclusion criteria, then one collected data and checked against exclusion criteria (AA-M) and the other two checked decisions. Disagreements were resolved through discussion.

The following data, where available, were extracted for each meta-analysis: investigated feature(s) (whether prognostic or not), specified population (resected lobe, adults, specified lesion), numbers of patients and individual studies for each feature or their upper bounds, definition and duration of seizure freedom, effect sizes and method used (univariate, multivariate logistic regression, fixed effect, random effects, network analysis, meta-regression or other). Qualitative evaluation of certainty of evidence was performed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines (online supplemental references 11–17).[18] Trial sequence analyses were assessed for bias using an additional checklist.[19] Where possible, we used the current International League against Epilepsy seizure classification.[20]

Data presentation

Features from the same investigation modality were grouped into seven categories (online supplemental table 2).

Features were further split into essential prognostic features (EPF), uncertain prognostic feature (UPF), and non-prognostic feature (NPF) based on consistency of value across meta-analyses such that if all effect sizes were in the same direction (eg, all favoured postsurgical seizure freedom), then this feature was classified as EPF; whereas, UPF included features that in some meta-analyses favoured seizure freedom, while in others showed no effect or worse outcomes. NPFs were non-significant in all meta-analyses.

Statistical analysis

Effect sizes were inverted such that OR and relative risks over 1 indicate better outcomes favoured good outcome. If effect sizes or CIs were not quoted, these were estimated from the raw data (online supplemental methods). When quoting effect sizes across meta-analyses for the same feature, we used range of effect sizes (ROES) for both point estimates and 95% CIs (min, max).

RESULTS

Overview, PRISMA flowchart and meta-analytical methods

From 50 meta-analyses, 12 were excluded on full-text review, leaving 38 from which data were collected (PRISMA flowchart figure 1). Excluded meta-analyses had lower median numbers of individual studies than those from which data were extracted (11 (IQR 7–22) vs 22 (IQR 15–37)), and lower median number of patients (71 (IQR 33–87) vs 1034 (IQR 320–1999)). The largest number of individual studies in any meta-analysis was 258,[21] and the highest number of included patients was 16 855 from the Cochrane review.[22] Two multicentre studies were included, one from eight centres and another from 37.[23 24]

The main meta-analytical methods and upper bounds on numbers of studies and patients are summarised in table 1.

Online supplemental table 1 lists features from each meta-analysis with GRADE scoring, and online supplemental table 2 categorises these under seven modalities.

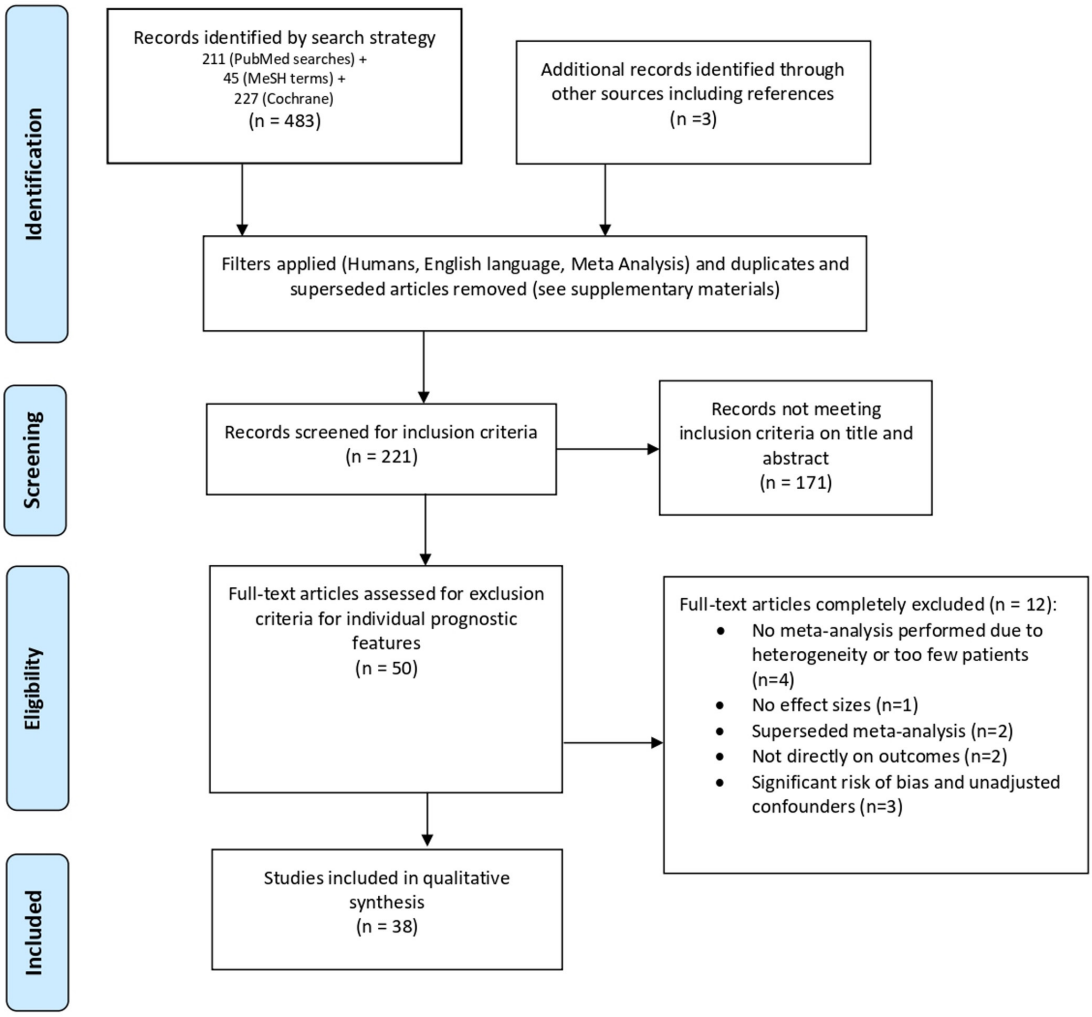

Figure 1 PRISMA flowchart of study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 2 presents EPF that were consistently prognostic in all meta-analyses, and table 3 shows consistently NPF with individual GRADE scores. Online supplemental tables 3,4 provide more details on EPFs, features with UPFs and NPFs.

EPF for epilepsy surgery

Thirteen features were regarded as EPF, as they were consistently prognostic. Three clinical features, from six meta-analyses over 21 years, were severe learning disability including IQ<75, with the largest effect size estimates from the paediatric tuberous sclerosis population (ROES RR 0.26–0.66 (0.14 to 0.94), OR 0.14–0.61 (0.04 to 0.82)), presence of febrile convulsions (RR 1.09 (1.01 to 1.17)) and lack of acute postoperative seizures (OR 4.2 (2.97 to 5.93)) (table 2 and online supplemental table 3).

Prognostic imaging features included the presence of hippocampal sclerosis (RR 1.17 (1.12 to 1.23)) and abnormal Single-Photon Emission Computed Tomography (SPECT) coregistered with MRI (ROES 2.44–3.28 (1.34 to 5.67)). Abnormal MRI was consistently prognostic in 10 meta-analyses with the largest effect sizes from children having hemispherectomies (ROES RR 1.28–1.64 (1.20 to 2.08), OR 1.27–4.6 (1.14 to 16.62)).

Table 1 The main meta-analytical methods for evaluating prognostic features of epilepsy surgery

Type of meta-analysis	Number of meta-analyses	Total number of included individual studies (upper bound)	Total number of patient participants (upper bound)
Univariate (tests of proportions, ANOVA, t-test or crude effect sizes)	9	215	6351
Proportional Hazards models (Cox regression)	1	19	187
Fixed or random (mixed) effects models	17	1122	55 502
Meta-regressions (including logistic regression)	6	372	16 006
(Bayesian) network analyses (NMA)	4	325	6471
Hierarchical/multi-level	0	0	0
Other: partial least squares (projection to latent space)	1	20	186

ANOVA, Analysis of Variance; NMA, Network Meta-Analysis.

Table 2 Essential prognostic features for epilepsy surgery (EPF)

EPF		Prognostic value and supporting evidence base				
Feature	**Population(s) or subgroup(s)**	**Range of effect sizes for seizure freedom**	**Comments**	**Meta-analytical references**	**Publication year (first, last)**	**GRADE score**
Clinical features						
Severe developmental delay and IQ≤75	Children and adults, TLE, structural lesions, tuberous sclerosis, hemispherectomies	RR 0.14–0.66 (0.04, 0.94)	Favours absence of severe learning disability	Chelune, Naugle; Fallah, Guyatt; Hu, Zhang	1998–2019	++ Low
Febrile convulsions (FC)	TL and ET in children and adults	OR 2.08 (1.2, 3.7) RR 1.09(1.01, 1.17)	Favours presence of FC	Tonini, Beghi; West, Nevitt	2004–2019	+ Very low
Without acute postoperative seizures (APOS)	Children and adults, TLE and ET	OR 4.2–5.7 (2.97, 9.8)	Favours absence of APOS within 30 days of surgery	Giridharan, Horn	2016	++ Low
Imaging features						
Hippocampal sclerosis (HS)	Adults and children with TLE	OR 2.13 (1.57, 2.86) RR 1.17(1.12, 1.23)	Favours presence of Mesial Temporal Sclerosis or HS	Tonini, Beghi; West, Nevitt	2004–2019	++ Low
Abnormal or lesional MRI	Adults and children with TLE and ET, FCD, frontal lobe, occipital lobe and posterior quadrant epilepsies, hemispherectomies	RR 1.28–1.64 (1.20, 2.08) OR 1.27–4.6 (1.14, 16.62)	Favours abnormal MRI, see online supplemental table 3) for comments on two borderline meta-analyses	Tonini, Beghi; Téllez-Zenteno, Ronquillo; Yin, Kang; West, Nevitt; Rowland, Englot; Englot, Wang; Englot, Rolston; Harward, Chen; Widjaja, Jain; Cao, Liu	2004–2020	++ Low
SPECT: subtraction SPECT co-registered to MRI (SISCOM)	TL and ET	OR 2.44–3.28 (1.34, 5.67)	Favours ictal and inter-ictal SPECT-SISCOM abnormalities	Chen and Guo	2016	++ Low
Neurophysiological features						
Focal Ictal or interictal or invasive EEG	Adults, children, repeat resections, MRI-negative TLE, tuberous sclerosis, ET	OR 1.55–3.89 (1.24, 9.08) Positive prognostic value on PLS also.	Favours focal EEG changes, for comments on notable exceptions from 2012 to 2013[15 35] see online supplemental table 3	Krucoff, Chan; Wang, Zhang; Fallah, Guyatt; Ibrahim, Morgan; Englot, Breshears	2013–2017	+ Very Low
Multimodal concordance						
EEG-MRI concordance	TL and ET children and adults, tuberous sclerosis, hemispherectomies	RR 1.25 (1.15, 1.37) OR 2.17–4.9 (1.07–13.5) Prognostic value on PLS	Favours EEG and MRI concordance	Tonini, Beghi; West, Nevitt; Fallah, Guyatt; Ibrahim, Morgan; Hu, Zhang	2013–2019	+++ Moderate
Surgical technique or anatomic features						
Temporal lobe (vs ET) resections	Adults and children with FCD, repeat surgery, low grade gliomas	OR 1.35–2 (0.8, 3.45)	Favours surgery for TLE	Rowland, Englot; Chen, Chen; Krucoff, Chan; Widjaja, Jain; Shan, Fan; Lamberink, Otte	2012–2020	+ Very Low
Complete excision (vs subtotal resection)	Adults and children with FCD, FLE, repeat resections, TLE, low grade gliomas	OR 2.6–12.5 (1.3, 20) RR 1.11–1.99 (1.03, 2.84)	Favours complete excision	Rowland, Englot; Chen, Chen; Englot, Wang; Krucoff, Chan; West, Nevitt; Widjaja, Jain; Shan, Fan	2012–2020	+++ Moderate
Pathological features						
Presence of tumours	Children and adults, TLE and ET, gangliogliomas, DNET, neuroepithelial tumours	RR 1.23 (1.14, 1.32) OR 1.27–2.78 (1.12, 3.57)	Favours tumours over multiple other lesions. See comments in online supplemental table 3	Tonini, Beghi; West, Nevitt; Lamberink, Otte	2004–2020	+++ Moderate
Focal cortical dysplasia (FCD)	Adults and children, TLE and ET	FCD: RR 0.90 (0.85, 0.95) FCD type II(b): OR 1.38–1.92 (1.01, 3.57)	Favours the absence of FCD, otherwise favours FCD type IIb	Rowland, Englot; Chen, Chen; West, Nevitt; Lamberink, Otte	2012–2019	++ Low
Lesional pathology vs non-lesional	Adults and children, FLE, TLE, ET, repeat resections, occipital lobe and posterior quadrant.	RR 1.67 (1.36, 28.6) OR 1.08–3.2 (1.02, 5.3)	Favours presence of focal pathological lesion except in MRI neg TLE (see online supplemental table 3) comments)	Englot, Wang; Englot, Rolston; Krucoff, Chan; Wang, Zhang; Harward, Chen; Englot, Breshears; Widjaja, Jain	2012–2017	++ Low

The essential prognostic features (EPFs).
See online supplemental table 3 for more details and full list of references.
ET, extratemporal; FCD, focal cortical dysplasia.; FLE, frontal lobe epilepsy; OR/RR, OR and relative risks over 1 indicate better outcomes; PLS, projection to latent space; TL, temporal lobe; TLE, Temporal Lobe Epilepsy.

Neurophysiological features were ictal and interictal (uni-) focal EEG abnormalities, this effect largely persisted irrespective of whether the MRI was abnormal or if initial epilepsy surgery had failed (ROES OR 1.55–3.89 (1.24 to 9.08)).

Concordant MRI and EEG abnormalities were consistently associated with a good prognosis (ROES OR 2.17–4.9 (1.07 to 13.5)). There were no genetics features in EPF.

Surgical technique EPFs were TL resections (in populations that excluded repeat resections and surgery for low grade gliomas) (ROES OR 1.35–2 (1.06 to 3.45)) and complete excision of lesions (ROES RR 1.11–1.99 (1.03 to 2.84)).

Favourable histopathological features were: (1) presence of tumours (RR 1.23 (1.14 to 1.32)), (2) focal cortical dysplasia type IIb (FCD) (ROES OR 1.38–1.92 (1.01 to 3.57)), (3) presence of any focal pathological lesion (ROES OR 1.08–3.2 (1.02 to 5.3)). One meta-analysis, however, showed non-significance for focal histopathology in MRI-negative temporal lobe epilepsy (TLE),[25] suggesting that the basis of favourable outcomes in individuals with focal imaging abnormalities is a histopathological abnormality (see structural causal model (SCM) in online supplemental materials).

Concordance and complete excision had moderate quality of evidence scores, other results were of low or very low quality.

Uncertain prognostic features

Eighteen features had mixed results with some meta-analyses suggesting prognostic value and others suggesting non-significance: previous head injury, central nervous system (CNS) infections, focal semiology, infantile spasms, seizure frequency, age at onset, age at surgery (investigated by 18 separate

Table 3 Non-prognostic features (NPF)

NPF features		Non-prognostic evidence base					
Feature	**Population(s) or Subgroup(s)**	**Comments**	**Individual patients***	**Individual studies***	**Meta-analytical references**	**Publication years (first, last)**	**GRADE score**
Clinical features							
Sex: male vs female	Adults and children with FLE, TLE, ET, tuberous sclerosis, MRI neg TLE, repeat surgery, hemispherectomies, low grade gliomas	All were non-significant, a large proportion even on weighted univariate tests, which otherwise tend to overestimate significance. Individual unweighted effect sizes ranged from OR 0.83 (0.42, 1.64)[c] in repeat surgery for focal DRE[14] to OR 1.44 (0.86, 2.41) in MRI negative TLE.[25]	5974	148	Englot, Wang; Englot, Rolston; Zhang, Hu; Fallah, Guyatt; Ibrahim, Morgan; Wang, Zhang; Krucoff, Chan; Englot, Breshears; Hu, Zhang; Shan, Fan; Cao, Liu	2012–2018	+++ Moderate
Epilepsia partialis continua (EPC)	Children undergoing hemispherectomies	Not significant on unweighted univariate testing and result is from only one meta-analysis.	127	7	Cao, Liu	2016	++ Low
Imaging features							
Number of cortical tubers	Tuberous sclerosis	Numbers of tubers did not predict outcomes. See online supplemental table 5 for observations on methodology, sample sizes, adjustments and heterogeneity.	286	24	Zhang, Hu; Fallah, Guyatt; Ibrahim, Morgan	2013–2015	++ Low
Magnetic ^{1}H spectroscopy	TLE adults and children	Probably no more valuable than conventional MRI abnormality (online supplemental table 5).	121	22	Willmann, Wennberg	2006	+ Very low
Encephalomalacia	Adults and children	Encephalomalacia was NS in the Cochrane meta-analysis, it was also not significant on subgroup analyses.[22]	317	5	West, Nevitt	2019	+ Very Low
Enhancement, oedema, and/or mass effect	Low grade gliomas in adults	These combined features are not clinically prognostic of low-grade glioma resection for seizure freedom. Although NS, the point estimate and CI are unavailable.	2641	23	Shan, Fan	2018	+ Very low
Vascular lesions	Adults and children with TL and ET	Only one meta-analysis investigated this in 2004, comprising only three individual studies, its pathological counterpart was also NS.[22]	<<3511	3	Tonini, Beghi	2004	+ Very low
Neurophysiological features							
Intraoperative invasive EEG	Children and adults with FLE	Electrico-corticography did not effect outcomes	1024	21	Englot, Wang	2012	+++ Moderate
Video telemetry and long-term monitoring	Children and adults with FLE, lesional and non-lesional TLE and ET	Lesional TLE cases do well, and this was the only subgroup in which long-term monitoring had a point effect size estimate greater than 1.	1738	65	Englot, Wang; Kobulashvili, Kuchukhidze	2012, 2018	+ Very low
Surgical technique or anatomic features							
Mesial vs lateral TL focus	MRI neg TLE	Mesial or lateral TLE, as determined by sEEG, subdural grids, or ATL/SAH vs neocortectomy, are not significant.	92	8	Wang, Zhang	2016	+ Very low
Side of resection (left vs right)	Children and adults, Non-lesional, TLE, FLE, ET, MRI negative TLE, repeat surgery, hemispherectomies	This feature is unlikely to be prognostic—see online supplemental table 5.	6550	188	Tonini, Beghi; West, Nevitt; Willmann, Wennberg; Ansari, Tubbs; Englot, Wang Englot; Rolston; Wang, Zhang; Krucoff, Chan; Englot, Breshears; Hu, Zhang; Ansari, Maher	2004–2019	+++ Moderate
Frontal, central, or posterior resections vs other	ET, adults, non-lesional	Not prognostic	81	?	Ansari, Tubbs	2010	+ Very low

Continued

Table 3 Continued

NPF features		Non-prognostic evidence base					
Feature	Population(s) or Subgroup(s)	Comments	Individual patients*	Individual studies*	Meta-analytical references	Publication years (first, last)	GRADE score
Geographical location of surgery	Tuberous sclerosis in children	Only one meta-analysis investigated North America vs Elsewhere, and the GRADE score is from this meta-analysis alone.	186	20	Ibrahim, Morgan	2015	+++ Moderate
Pathological features							
Neuro-migrational defects	TL and ET children and adults	There was a trend whereby neuromigrational deficits were negative prognostic factors, but the number of participants in this analysis was unclear.	?	6	Tonini, Beghi	2004	+ Very Low
Astrocytoma vs non-astrocytoma	Low grade gliomas in adults	The exact numbers of patients were not provided for this particular analysis.	<2641	<23	Shan, Fan	2018	+ Very Low

See online supplemental table 5 for more details and online supplemental materials for full list of references.
*Upper bound of estimate, not including subgroup analyses.
[m], multivariate; [u], univariate; [c], calculated (usually unweighted) effect size; ET, extratemporal; FLE, frontal lobe epilepsy; MCD, malformations of cortical development; NS, not significant; PLS, projection to latent space; TL, temporal lobe.

meta-analyses), duration of epilepsy (15 meta-analyses), interictal fluorodeoxyglucose positron emission tomography (FDG-PET) focal hypometabolism, preoperative invasive EEG or choice of subdural versus depth electrodes, presence of interictal spikes, lateralising ictal or interictal EEG, extensive surgical resections and vascular pathology (online supplemental table 4).

Non-prognostic features

Fifteen non-prognostic features (table 3 and online supplemental table 5) comprised: sex, epilepsia partialis continua, number of cortical tubers, magnetic spectroscopy abnormality, encephalomalacia, enhancement or mass effect of low grade gliomas, performing intraoperative invasive electrocorticography, use of video-EEG telemetry, mesial versus lateral temporal focus, side of resection, frontal-central or posterior extratemporal lobe resections, geographical location of surgery (North America vs elsewhere), presence of neuronal migration abnormalities on imaging and astrocytoma versus non-astrocytoma.

DISCUSSION

We identified 46 features from 38 meta-analyses on prognostication in epilepsy surgery, only 15 of which were in the 2019 Cochrane review.[22] We categorised features that were consistently prognostic. When investigating other variables for associations with seizure outcomes, EPFs can be used to adjust for confounders.

EPF for epilepsy surgery

EPF is a minimum essential list based on current best-evidence. Our objective was to determine a minimum list of *a priori* features for use in future models, to improve personalised prognosis and outcomes (table 2). We further +propose grouping these features into an *a priori* SCM, to determine if it would be appropriate to adjust for these variables in future studies (see SCM in online supplemental materials, summarised in figure 2).[26]

A 2006 assessment of 3511 patients from 47 articles[27] suggested that the following were associated with a higher chance of seizure remission: prolonged febrile seizures, unilateral EEG epileptiform abnormalities, MRI abnormalities, hippocampal sclerosis, SPECT ictal focal hyperperfusion, PET TL abnormalities and extent of mesial temporal resections. Head trauma, postoperative epileptiform EEG changes, developmental abnormalities with hippocampal sclerosis and acute postoperative seizures were negatively prognostic.[27] Due to unadjusted confounders and heterogeneous definitions of features and seizure freedom, such findings were considered preliminary.[27 28] Another meta-review of 10 reviews and meta-analyses identified lesional, abnormal MRI, focal seizures, complete resection, unifocal ictal EEG abnormality and extensive lobectomy versus tuberectomy, in patients with tuberous sclerosis, as positive predictors. Severe developmental delay, non-localised or bilateral EEG, FCD type 1, abnormal postoperative EEG and tuberectomies were negative predictors.[29]

Lesional and abnormal MRI

A meta-analysis with low study heterogeneity concluded an OR of 2.5 (2.1 to 3.0) in favour of lesional cases with an overall RR of 1.4 ($p<0.001$; 2860 lesional, 697 non-lesional, 40 studies).[30] This trend was maintained for temporal and extratemporal subgroups. Similar results were found in other meta-analyses for occipital lobe epilepsy and in patients undergoing repeat surgery.

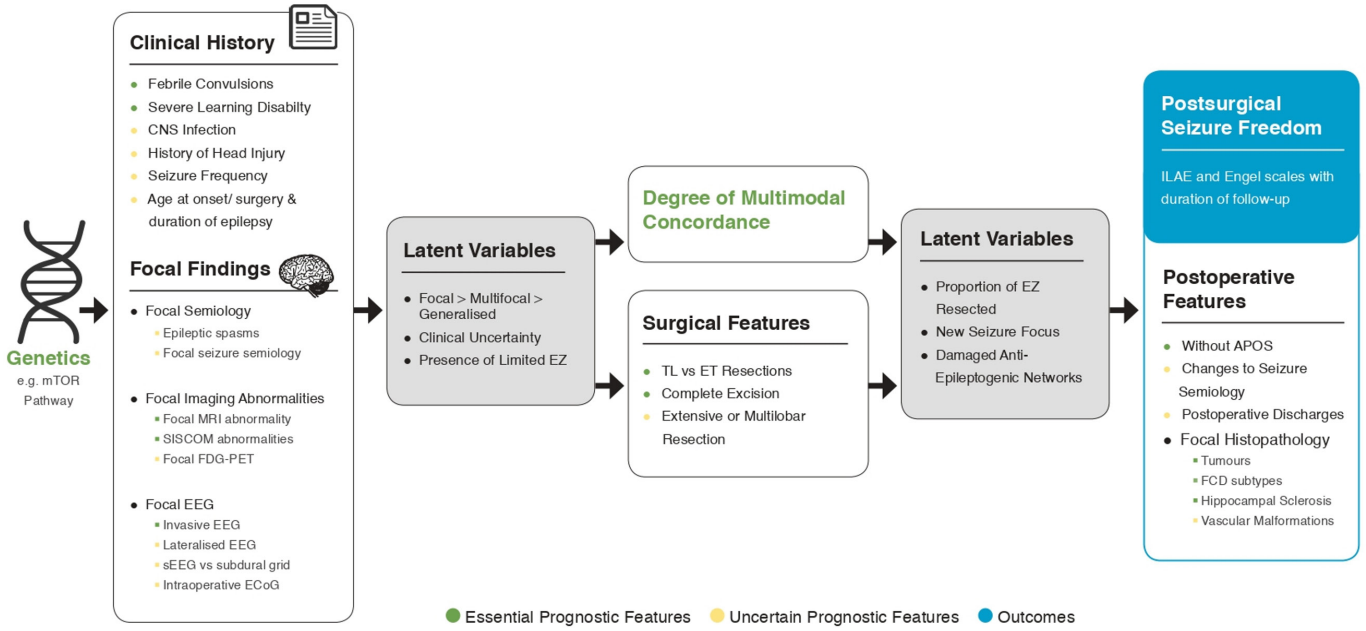

Figure 2 Outline of a structural causal model with latent variables for postsurgical seizure freedom. ET, extratemporal; FCD, focal cortical dysplasia; TL, temporal lobe; ILAE, international league against epilepsy; EZ, epileptogenic zone; FDG-PET, fluorodeoxyglucose positron emission tomography; EEG, electroencephalogram.

When lesions were defined by pathology, MRI abnormalities still had a non-significant trend to higher rates of seizure freedom.[14] Another meta-analysis found a prognostic trend for abnormal pathology even in MRI-negative TLE (p=0.06, OR=1.36 (0.7 to 2.63)).[25] Within lesional-epilepsies, FCD type IIb is further associated with better outcomes.[31]

Although it is well established that lesional epilepsies have better postsurgical outcomes,[14 21 22 25 30 32 33] and that complete lesionectomy is required[15 21 22 31 34 35] the overwhelming majority of studies did not adjust for these.

A meta-analysis of 1999 patients across 35 articles, found outcomes after stereo-electroencephalogram (SEEG), were better than after subdural grids in patients undergoing temporal resections with lesional-MRI (seizure freedom for subdural grid (51.5% to 61.9%) vs SEEG (64.4% to 81.6%)).[36] Such a comparison is limited by ascertainment bias and the differing indications for these methods. Interactions between features have not been formally investigated in meta-analyses, except in specific subpopulations and imaging-EEG concordance.

Multimodal concordance

Five meta-analyses attested the value of concordant MRI and EEG,[22 28 37–39] but none looked at the value of semiological concordance with other modalities. In our SCM, the prominent causal pathway node is multimodal concordance, which should be further studied as a valuable predictor of seizure freedom (figure 2).

Features of uncertain significance

Even meta-analyses may be underpowered, contributing to lack of statistical significance (online supplemental reference 64). PET results were mixed, but when concordant with EEG, PET could predict good seizure outcomes in non-lesional TLE with a positive predictive value of 71% (online supplemental reference 27).

Most meta-analyses reported non-significance of age at seizure onset, age at surgery and duration of epilepsy; however, there is a mixed picture. For every extra year of duration of epilepsy at time of surgery, one metaregression reported overall odds of seizure freedom reduced by a factor of 0.83 and another analysing data from 1545 patients across 12 studies found shorter duration of epilepsy was associated with higher rates of postsurgical seizure freedom with RR ranging from 1.20 to 1.33 (online supplemental reference 57). Conversely, age at surgery and duration of epilepsy before surgery have been documented as having 'no association' with outcomes.[27]

Longer duration of epilepsy may result in worse surgical outcomes due to selection bias (more difficult cases being deferred) or progressive cerebral damage. Strikingly, these three features of age at onset, age at surgery and duration of epilepsy have not been explored for three-way interactions.

Uncertain features can be reclassified into the essential or non-prognostic categories, when future studies that evaluate their value adjust for essential prognostic variables. While such models would clarify to what extent uncertain features may be prognostic over and above the essential features, this may not always be clinically desirable. For example, CNS infections may result in glial scars, and adjusting for imaging lesions may not be clinically desirable. Instead, an SCM could be used (see five-step plan below).

Non-prognostic features

Side of resection and sex were both investigated in 11 meta-analyses but were not prognostic, consistent with a meta-review from 2013.[29] Nevertheless, studies have continued to investigate them. Their use in predictive models risks overfitting and compromising generalisability.

Prognostication: common pitfalls and recommendations

Unmodelled features

As there has not been significant improvement in postoperative outcomes, there are likely to be variables that have not been included .[14 15] This is problematic for two reasons. First, studies

are unable to adjust for unknown confounders. Second, without these features, individualised predictions will not be accurate. It is, therefore, critical to discuss notable missing features.

No meta-analysis has investigated the role of family history or detailed seizure semiology despite the fact that monitoring seizure semiology is integral to presurgical evaluation. Five meta-analyses reviewed MRI-EEG concordance, but none considered semiological concordance; the closest corollaries were FBTCS, epilepsia partialis continua and epileptic spasms. Future studies should evaluate interactions between semiology, epileptogenic zone, imaging and neurophysiology in patients with both favourable and unfavourable surgical outcomes.

The importance of genetics in seizure-free outcomes is belied by relatively few publications. Individuals with mutations affecting synaptic transmission or ion channels (5 articles, 14 patients) were less likely to benefit from epilepsy surgery than those with mutations in the mechanistic target of rapamycin (mTOR) pathway (10 articles, 30 patients). This was despite six of eight patients with SCN1A mutations having concordant semiology and colocalised MRI lesions.[40] This meta-analysis was the only one to investigate genetics but it met our exclusion criteria as a large proportion of the small samples were lesional and no attempt at adjustments had been made (online supplemental tables).[40] High-frequency oscillations and fast ripples were also excluded in our final synthesis (figure 1) due to lack of appropriate effect sizes (online supplemental references 1,6 and online supplemental table 1). This should impel us towards multicentre data sharing in comprehensive models (figure 2).

Other notable factors omitted from meta-analyses include analysis of cerebral structural connectivity (online supplemental reference 65) and resection of the piriform cortex as part of anterior TL resections (online supplemental reference 66).

Towards personalised seizure freedom predictions

Meta-analyses have been widely used for over five decades to quantitatively integrate a collection of studies. They are useful to identify important features based on best-available evidence, but cannot identify new features or provide personalised quantitative prognostication. The majority of studies did not statistically correct for multiple comparisons, potentially introducing false positives.

Machine learning models and nomograms have been proposed to predict outcomes, without prospective validation.[10 12] These models included three features of uncertain significance (duration of epilepsy, frequency of seizures and generalised seizures), one non-prognostic factor (sex) and one EPF (pathological aetiology); it is perhaps unsurprising that the model was not generalisable.[13] We advocate, therefore, that to improve prognostication and outcomes, a five-step plan is adopted:

1. All relevant factors for epilepsy surgery outcome prediction are curated in an agreed international, multicentre endeavour, which include the essential prognostic list curated here. Practically, the preoperative clinical variables should take precedence over postoperative features, for example, *severe developmental delay* should take priority over *acute postoperative seizures* and *FCD type IIb* as the latter two are only known after surgery.
   The final curated features would then form the starting point for building predictive models.
2. An SCM is devised that links outcomes to prognostic factors, to enable adjusting for EPFs when investigating other variables.
3. Identification of the degree to which polygenic risk scores, family history, seizure semiology and concordance may contribute to outcomes as indirect measures of seizure focality within the SCM.
4. Curation of an international multicentre, high-quality, anonymised retrospective and prospective data set of patients who have undergone epilepsy surgery with features and outcomes, similar to the retrospective collaboration on surgical histopathology.[24]
   A challenge in multicentre data collection will be to ensure that clinical and investigatory data are collected in a consistent and standardised manner, the details of which should be finalised in the protocols of the multicentre collaboration.
5. Machine learning models suitable for binary features and outcome classification on the international dataset.

The current study addressed the first two steps including R code to generate and amend SCMs (see online supplemental materials section on SCM for details on R codes for a simplified and complete SCM, and the two online supplemental files: SCM dagitty V.5 super simplified and SCM dagitty V.4). We can verify the value of EPFs and the SCM by building high-dimensional predictive models from international collaborations using SCM to adjust for covariates, subsequently showing that the resulting model predicts outcomes better than current methods.

Limitations

Meta analyses were our unit of analysis, each assuming sufficient homogeneity for estimation of pooled effects.[18] Only English-language articles were searched and we did not check for overlaps between meta-analyses, we, therefore, quote upper limits of numbers of patients and individual studies. We adopted the same definitions of seizure freedom in terms of Engel or ILAE class and duration of follow-up as the meta-analyses, but inconsistent definitions and differing durations meant that we could not adjust for these. Most studies defined seizure freedom as Engel I, potentially compromising results, as this includes patients with ongoing seizures, implying incomplete resection of the epileptogenic zone or multifocal epilepsy.

Meta-analyses improve power, but unless they are hierarchical, lose the granularity of applicability to subgroups. To reduce type I errors, we did not include variables that were significant on unweighted tests, but this can reduce power. Nevertheless, moderate or low-quality evidence from meta-analyses can lead to strong assertions on whether a feature is prognostic (online supplemental reference 13).

Many variables in individual articles of epilepsy surgery outcomes are clinically widely used, contributing to a circular logic, whereby features already considered significant are pooled in meta-analyses. This is why we also discussed unmodelled features.

Whether a feature is of positive or negative prognostic value may be comparable across meta-analyses but due to differing patient populations and seizure-free definitions, diversity of models, unadjusted confounders and unobserved heterogeneity, the magnitude will almost certainly not be, precluding comparisons of effect sizes.[22] Cochrane-Mantel-Haenszel stratification, multinomial logistic regression or projection to latent space[37] attempt to adjust for between-feature correlations; nevertheless, this mitigation is limited if important features are omitted. By not fully adjusting for covariates such as focal MRI abnormality or duration of follow-up, incorrect conclusions may be drawn. This limitation is well known[37] but has not been universally addressed with a definitive set of prognostic features—which was the objective of this study.

As we looked at shared prognostic features across all types of operations and anatomical lobes, our minimum list of EPFs may underidentify variables that may be prognostic for a particular type of operation but not another, such a selective amygdalohippocampectomy as opposed to anterior TL resection. These variables can be identified by further predictive models that adjust for confounders using this list of EPFs. Ultimately interaction terms (deep machine learning models) could adequately stratify seizure freedom.

SUMMARY AND CONCLUSIONS

Personalised prognostication in epilepsy surgery outcomes has remained elusive and outcomes have not improved with time. We curated features into prognostic and uncertain groups and conclude that more meta-analyses on these are not needed; rather, we need predictive models that quantify their relative contributions to outcomes. We proposed a five-step plan towards personalised seizure freedom predictions and addressed the first two steps in this study. EPFs would be particularly useful in machine learning models of a big-data international collaboration to better predict epilepsy surgery outcomes.

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Contributors AA-M conceived the study and conducted the literature search. All three authors screened titles and abstracts for inclusion criteria. AA-M screened for exclusion criteria and VNV and JSD checked decisions independently. AA-M wrote the manuscript, VNV and JSD edited the manuscript. JSD conceived and supervised the study. AA-M acts as guarantor. All authors approved the final manuscript.

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Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. All data pertaining to included studies are available in the main manuscript and supplementary materials. The list of titles and abstracts screened for inclusion criteria are available upon request as excel files.

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Supplementary Materials

Multimodal Prognostic Features of Seizure-Freedom in Epilepsy Surgery: Towards Personalised Seizure-Freedom Predictions

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1 Supplementary Methods

1.1 Search Strategy

The free-text search terms used to search PubMed and MEDLINE were:

"epilep*" AND "surg*" AND ("seizure-free" OR "outcome*") AND "meta analys*"

This returned 202 results. With the Humans filter, this reduced to 174, and with a further English language filter, there were 172 articles, of which 111 were meta-analyses. There were a further nine articles included from a non truncated free text search:

"epilepsy" AND "surgery" AND ("seizure-free" OR "outcome") AND "meta analysis*"*

We also used the following MeSH terms:

"Treatment Outcome"[Mesh] AND "surgery" [Subheading] AND "Epilepsy"[Mesh] AND "Meta-Analysis" [Publication Type]

This returned 45 results. Humans and Meta Analyses filters returned the same 45, English language filter reduced this to 43.

Additionally, the same free-text terms were used to search the Cochrane database

Returning 227 Cochrane reviews, of which 104 remained after using the Neurology topic filter. 4 of these were duplicates from PubMed search, leaving 100 unique Cochrane reviews to be screened for inclusion criteria.

After removing duplicated, the above were screened for inclusion criteria based on title and abstract, and if inclusion criteria met, then full-text reviewed for exclusion criteria and prognostic features to extract.

1.2 Exclusion Criteria

- Generalised epilepsy
- Non-resective interventions such as disconnections, neuromodulation, and ablative therapies
- Resections performed primarily for other indications (not directly on outcomes)
- Superseded meta-analyses (2014 Cochrane review replaced in 2017[1] or another 2015 Cochrane review[2] updated in 2019[3], and 2005 article updated in 2010[4, 5])
- Conference presentations and abstracts
- If there was clear and serious concern about risk of bias and unadjusted confounders for any specific feature e.g., attempting meta-analyses using small number of studies/patients or for a feature which was heavily confounded by known prognostic factors.[1, 6-8]
- No meta-analysis attempted or no effect sizes
- Meta-analysis pooling data from only a single study (e.g. surgical techniques[3]).

- Although we included pooled unweighted crude effect sizes of features from individual participant meta-analyses that were non-significant, we excluded such features if they were significant,[9] as unweighted measures can overestimate true effect sizes (Cochran-Mantel-Haenszel confidence intervals are wider).

We did not exclude hemispherectomies or multicentre meta-analyses.

1.3 GRADE Quality of Evidence Scoring

Baseline GRADE quality of each feature from individual meta-analysis were set at "low" (++ out of ++++) by default due to an overwhelming majority of observational studies, except where the majority of constituent studies were randomised or the pooled number of patients were large (>1000) and analyses to investigate bias and/or heterogeneity were performed through sensitivity or subgroup analyses, in which case the preliminary rating for the feature was "moderate" (+++).

+ = Very Low. ++ = Low. +++ = Moderate. ++++ = High.[10-17]

When performing GRADE scoring, regarding indirectness of evidence, although it may be argued that because of the presumed differences in the maturing brain, paediatric and adult epilepsy surgery populations should be investigated separately or as subgroups, we did not rate down for indirectness of evidence if adult and paediatric populations were mixed (Supplementary Table 1 caption).

1.4 Collection of Effect Sizes

If multiple subgroups were reported, e.g., Engel I and Engel Ia for multiple years of follow-up, then we collected the effect size estimates for the strictest outcome (Engel IA) and for the longest duration of follow-up; but where relevant, did consider all the effect sizes when considering inconsistency on the GRADE scale. Where the Cochrane reviews adjusted effect seizes for outcomes, this was quoted. We considered outcomes worse than Engel I or follow-up durations less than 12 months as indirect evidence of good outcomes.

1.5 Numbers of studies and participants

For calculation of medians and IQR of number of individual studies and participants in the main manuscript results section, there were 2 missing datapoints not reported in the meta-analyses. These were imputed using the medians of the rest of the datapoints for numbers of individual articles and numbers of participants.[18, 19] For this calculation, the 8 multicentre study was considered to be from 8 articles [20].

Where there were no numbers for participants or studies for a specific feature in a meta-analysis, total participants across all features in the meta-analysis were used, this, along with the possibility of individual study overlap across meta-analyses, results in the frequency counts of participants and individual studies in main manuscript Tables 2 through 4 to be upper bound estimates.

For summary Table 1 in the main manuscript, we summed all the total individual studies and participants for each category of meta-analysis, irrespective of overlap of individual studies between meta-analyses, and so these are upper bounds of the number of unique individual studies and participants. If a meta-analysis used more than one method, the total number of studies and patients were duplicated for both methods. This was because some studies did not specify exactly

which method was used for which feature and how many studies/participants that involved. The missing values were not imputed for main manuscript Table 1, and were defaulted to zero.

In the few cases of uncertain statements on specific features without forest plots and without quoting effect sizes or the univariate test(s) used, the features were excluded with comments (in red colour in Supplementary Table 1).

1.6 Estimating Missing Effect Sizes

When calculating odds ratios for raw data and their confidence intervals, where the effect size was not provided but the raw data was, these were calculated according to Altman 1991.[21] These are marked by a [c] to indicate the effect size was calculated from the data provided in the literature, and a * where the confidence interval was also estimated.

1.7 Structural Causal Model

The structural causal model outline was designed using dagitty from daggity.net.[22] We used two different levels of complexity, one encompassing all possible relationships and the other simplified to generate causal pathways that are easier to follow diagrammatically. These codes, attached as text files, can be copy-pasted onto http://www.dagitty.net/dags.html to reproduce the causal pathway figures included in the supplementary results below. The R codes used to generate the figures, for reproducibility and future amendment, can also be obtained from pasting the contents of the attached text files to the above website.

2 Supplementary Results

The Table of 44 meta-analyses and their features with GRADE quality of evidence scores are presented in Supplementary Table 1. Supplementary Table 2 shows the same data after collating and reorganising similar features into seven categories.

2.1 Supplementary Table 1: Individual Meta-Analyses of Prognostic Features for Epilepsy Surgery

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Author, *Year of publication* Years of literature search	*e.g. 12 studies, 100 patients,* *ILAE 1 or 2 outcomes at least 12months post-surgery* *random-effects model*	*Feature 1* *120 patients in the 7 studies from which feature 1 was extracted* *Feature 2* *200 (9)*	*TLE, FLE…* *Age* *Other*	*RR, OR…* *[95% CI]*	*Heterogenous outcome follow-ups* *Exclusion of known prognostic factors and statistical adjustments* *Selective Reporting* *Serious -1* *V. serious -2*	*Widely spread effect sizes as assessed by point estimates, CI, and statistical tests of heterogeneity.* *Serious -1* *V. serious -2*	*Populations, interventions and/or outcomes being studied differ from those of interest:* *e.g.: unseparated paediatric and adult ages, less than 12 months or more than ILAE 2*	*Large and/ or skewed CI* *Serious -1* *V. serious -2*	*"undetected"* *"suspected"* *-1* *"strongly suspected"* *-2*	*at least a two-fold reduction or increase in risk (OR>4 or <0.25)* *+1* *5-fold or more change in RR (OR >10 or <0.1)* *+2*	*Dose response gradient* *+1*	*All plausible residual confounders or biases would reduce a demonstrated effect, or suggest a spurious effect when results show no effect.* *+1*	*High ++++* *+++ Moderate* *++ Low* *+ Very Low*

Meta-analysis *Publication year* Years of individual studies	# included Studies, Patients Outcomes, Follow-up Durations Model(s)	Feature # of total patients with and without (# of studies)	Population: Lobe Age	Effect Sizes (seizure freedom)	Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]								
					Risk of Bias or Internal Validity[1]	Inconsistency of Results[2]	Indirectness of Evidence[3]	Imprecision[4]	Publication bias[5]	Large effect size?[6]	"Dose" response?[6]	All plausible residual confounding?[6]	Quality of the body of evidence (GRADE)

2.1.1 *Chelune, Naugle (20) (1998)

Chelune, Naugle (20) *1998* Baseline Quality: +++	8 centres. 1034 patients Outcome: no more than 2 post-operative seizures excluding auras at 6 months or 1 year. Individual participant one-way ANOVA.	Low IQ total sample 1034 (8) IQ scores were on average 2.3 lower in not seizure-free group (p<0.009)	TLE Age ≥16 yrs With and without structural lesions	NS RR 0.66 [0.54, 0.94*]	presence of structural lesions interaction checked	*Multicentre not meta-analysis*	-2 both duration of follow-up and definition of seizure freedom differ	No CI provided, but could be estimated from data presented	-1 suspected, untested		+1 Higher seizure-freedom rates in higher IQs (their table 3)	+1 Adjusted for lesions	++
		Low presurgical IQ ≤75 in patients with structural lesions other than HS (cf high IQ and lesional) 150 lesional (8)		RR 0.26 [0.14, 0.50]*								Absence of significant interaction with centres, or duration of epilepsy	+

*Found though other sources (see PRISMA flowchart)

2.1.2 Excluded Devous, Thisted (23) (1998)

Excluded as not directly on outcomes, and the data presented on outcomes are proportions of seizure freedom with SPECT, but no other baseline to compare to derive effect sizes. Abstract only.

2.1.3 Tonini, Beghi (24) (2004)

Meta-analysis *Publication year* **Years of individual studies**	**# included Studies, Patients Outcomes, Follow-up Durations Model(s)**	**Feature # of total patients with and without (# of studies)**	**Population: Lobe Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Tonini, Beghi (24) (2004) 1984-2001 Odds ratios inverted so that OR>1 Represents good outcomes +++	47 studies 10 were prospective 2 were both retro and prospective total of 3,511 patients >12 months follow up Fixed-effects and mixed effects	febrile seizures (5)	TL and ET Subgroup analysis showed no change when only TL was considered Children and adults from 1 through to 86 years	OR 2.08 [1.2, 3.7]	sample size of at least 30 patients, MRI performed in at least 90% of cases, English, Italian, French, German, or Spanish	Q=7.9, p=0.093	mixed populations -1 Engel outcomes in 22 studies and other definitions in 25						+
		mesial temporal sclerosis in TLE (15) +++		OR 2.13 [1.57, 2.86]		Q=21.9, p=0.082							++
		Tumours (13) +++		OR 1.74 [1.25, 2.5]		Q=19.3, p=0.08							++

		abnormal MRI (9) +++		OR 2.27 [1.54, 3.45]		One outlier with poor results but wide CI Q=4.9, p=0.768							++
		extensive surgical resection (10) +++		OR 4.27 [2.06, 8.85]		Q=26.9,p=0.001 → used random effects							++
		EEG/MRI concordance (6)		OR 2.36 [1.07, 5.26]		Heterogenous Q=11.4, p=0.044 → used random effects							+
		Post operative discharges (3)		OR 0.28 [0.08, 0.95]		-1 @bias : Only 3 studies Heterogenous Q=6.7, p=0.035 → random effects							+
		Intracranial monitoring (6)		OR 0.37 [0.22, 0.63]		Q=3,p=0.7							+
		Neuro-migrational,defects (6)		NS OR 0.66 [0.42, 1.03]		Q=9.8, p=0.08							+
		CNS infections (2)		NS OR 0.73 [0.29, 1.82]		-1 @Bias: Only 2 studies Q=2.1, p=0.146							+

		Vascular disorders (3)		NS OR 0.66 [0.30, 1.46]		-1 @bias: 3 studies Q=945, p=0.6							+
		interictal spikes (3)		NS OR 1.82 [0.86, 3.88]		-1 @bias: 3 studies		-1 skewed					+
		side of resection (4)		NS OR 0.85 [0.54, 1.34]									+

2.1.4 Excluded as superseded article [4]

See exclusion criteria. This article was superseded by [25]

2.1.5 Willmann, Wennberg (26) (2006)

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Follow-up Durations** **Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Willmann, Wennberg (26) (2006) 1992-2003	22 studies 121 pts Engel 1 Studies exclusively reporting on patients with brain tumors or on children were excluded Engel I Unclear if fixed or mixed effects but likely fixed effects CMH	^{1}H spectroscopy: ipsilateral magnetic spectroscopy abnormality (ipsilateral to lobe of resection)	TLE 3-66 years old	OR 4.9 [1.97–12.17]	Fifteen centers performed chemical shift imaging and seven centers used single-voxel spectroscopy. Most studies were obtained at 1.5 T	Q=2.7	-2 The EZ was mostly defined by EEG data	-1 Large CI		PPV = 82% +1 OR>4			+
		Ipsilateral magnetic spectroscopy	Non-lesional MRI and TLE	NS									+

2.1.6 Willmann, Wennberg (27) (2007)

Meta-analysis *Publication year* **Years of individual studies**	**# included Studies, Patients Outcomes, Follow-up Durations Model(s)**	**Feature # of total patients with and without (# of studies)**	**Population: Lobe Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Willmann, Wennberg (27) (2007) 1992-2006 Studies exclusively reporting on patients with brain tumors or on children were excluded.	46 articles (11 TLE and ET, 35 TLE) 153 patients Follow up >12 months Unweighted crude odds ratios	FDG-PET (46)	TLE and ET Adults	NS Unweighted crude	-1 None of the odds ratios of any test combination was significant The analyses were complicated by significant differences in study design and often by lack of precise patient data. the tracer injection dose from 1 to 15 mCi, and the time for data acquisition after tracer injection from 5 to 60 min		PET does not appear to add value in patients localized by ictal scalp EEG and MRI.						+
		FDG-PET (35)	TLE Adults	NS Unweighted crude									+
		Left vs right temporal	TLE Adults	NS									++

		lobe surgery		Unweighted crude OR 0.569 [0.26, 1.24]									

2.1.7 Téllez-Zenteno, Ronquillo (5) (2010)

Téllez-Zenteno, Ronquillo (5) (2010) 1995-2007 +++	40 studies 3557 (2860 lesional and 697 non-lesional cases) Engel I >1 year follow-up Random-effects	Lesional vs non-lesional TL lesional vs TL non-lesional ET lesion vs ET non lesion	Adults and children	OR 2.5 [2.1, 3.0] RR 1.4 OR 2.7 [2.1, 3.5] OR 2.9 [1.6, 5.1]	-1 Heterogenous SF definitions. But similar results in subgroups: adults, children, TL, ET. Two studies favoured non-lesional epilepsy	Q=35.6, p=0.43	They also investigated whether lesion definition by MRI or histopathology made a difference – it didn't		? non lesional were significantly higher in ET cases (45%) than in TL (24%)				++

2.1.8 Ansari, Tubbs (18) (2010)

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Follow-up Durations** **Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Ansari, Tubbs (18) (2010) >1990 +	? 131 patients Engel classification Outcome at 1 year Fisher's exact and ANOVA	age at onset	adults extratemporal non lesional	NS	-1 Small sample sizes form multiple centres, heterogenous outcome reporting								+
		age at surgery		NS									+
		epilepsy duration		NS									+
		focal vs generalised seizures 62 ()		NS									+
		FCD or gliosis 115 ()		NS									+
		Frontal, central, posterior or		NS									+

		other resections 81 ()											
		Lateralisation		NS									+
		Abnormal MRI 61 ()		NS									+ excluded as ET non lesional population
		Intracranial monitoring 108 ()		NS									+

2.1.9 Ansari, Maher (28) 2010

Meta-analysis *Publication year* **Years of individual studies**	**# included Studies, Patients Outcomes, Follow-up Durations Model(s)**	**Feature # of total patients with and without (# of studies)**	**Population: Lobe Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Ansari, Maher (28) 2010 **1990-2009**	17 studies 95 pts Engel I Univariate ANOVA and Fisher's exact tests	Age at seizure onset <95 (<17)	ET nonlesional children	NS[u]			?outcome duration of follow up		-1 suspected				+
		Mean duration of epilepsy <95 (<17)		NS[u]									+
		At age surgery and outcome <95 (<17)		NS[u]	Report as marginally significant but NS p =0.073								+
		Seizure semiology grouped into complex partial, generalized, infantile spasms and other which included simple partial and mixed types. 65 (?)		Did not perform CMH or meta-analysis besides univariate Fisher's	No direct results between groups								Rejected as significant on univariate tests only
		Histopathology: cortical		As above									As above

		dysplasia, gliosis, other. (included neuronal loss, encephalitis, polymicrogyria, ulegyria, chronic inflammation, and "normal.")											
		Types of surgery (frontal, posterior and other)		NS[u]	Report as marginally significant but NS p =0.059 on univariate, which would not be significant on multivariate / CMH / Bonferronis								+
		Seizure lateralization		NS[u]									+
		Abnormal MRI		NS[u]	High risk of bias due to the selection of non lesional cases (!)								+ rejected as it was ET non lesional…
		Intracranial monitoring		NS[u]									+

2.1.10 Rowland, Englot (29) (2012)

Meta-analysis *Publication year* **Years of individual studies**	**# included Studies, Patients Outcomes, Follow-up Durations Model(s)**	**Feature # of total patients with and without (# of studies)**	**Population: Lobe Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Rowland, Englot (29) (2012) 1971 to 2011 +++	37 studies 2,014 patients Engel outcomes random-effects meta-analysis	Partial (focal) vs generalised seizures (10)	Adults and Children with FCD	OR 1.46 [1.18, 1.82]					-1 No funnel plots/trim fill etc Only 1 forest plot shown for complete resection				++
		Temporal lobe resections (20)		OR 1.35 [1.13, 1.61]									++
		Abnormal MRI (14)		OR 1.67 [1.33, 2.16]									++
		FCD Type II (Palmini) (17)		OR 1.38 [1.22, 1.57]									++

		Complete resection (15)		OR 3.91 [3.03, 5.32]									++
		Age (<18 yrs vs >18yrs) (13)		NS OR 1.14 [0.96, 1.35]									++
		Unilateral EEG vs bilateral ictal EEG (10)		NS OR 1.03 [0.82, 1.31]									++

2.1.11 Englot, Wang (30) (2012)

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Follow-up Durations** **Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Englot, Wang (30) (2012) 1990-2010 Significance set at 0.02 +++	21 studies 1,199 patients Engel I >48 months Chi-squared/t-tests then random-effects model	Lesional 825 (16) ++	FLE Adults and Children	RR 1.67, [1.36, 28.6]	Lesion: tumour, CD, or other lesion vs non-lesional: traumatic, infectious			-1 Wide CI	Funnel plots: undetected (not shown)				+
		abnormal pre-operative MRI 627 (14)		RR 1.64, [1.32, 2.08]									++
		localised frontal resections (vs more extensive frontal +/- extrafrontal resections) 651 (11)		RR 1.71, [1.26, 2.43]									++

		complete lesion excision 345 (7)		RR 1.99, [1.47, 2.84]									++
		Focal vs generalized seizure semiology 269 ()		NS P=0.05 magnitude not provided				-1 Magnitude not provided and p value borderlin					+
		Age <18 yrs vs >18 yrs		NS 43% vs 54% p=0.22									++
		Duration of epilepsy		NS	-1 Limited info								+
		Seizure frequency		NS									+
		side of surgery		NS									+
		gender		NS p0.99 Males 53% females 54%									++
		intracranial EEG performed		NS	-1 Limited info								+
		LTM with video-EEG		NS									+

		localised ictal EEG		NS									+
		lateralised interictal EEG		NS									+
		focal PET abnormality		NS									+
		intraoperative EcOG 1024 ()		NS p=0.14 Pooled ind particicpant OR[c] 1.23 [0.95, 1.62]									+++

2.1.12 Yin, Kang (31) (2013)

Meta-analysis *Publication year* Years of individual studies	# included Studies, Patients Outcomes, Follow-up Durations Model(s)	Feature # of total patients with and without (# of studies)	Population: Lobe Age	Effect Sizes (seizure freedom)	Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]								
					Risk of Bias or Internal Validity[1]	Inconsistency of Results[2]	Indirectness of Evidence[3]	Imprecision[4]	Publication bias[5]	Large effect size?[6]	"Dose" response?[6]	All plausible residual confounding?[6]	Quality of the body of evidence (GRADE)
Yin, Kang (31) (2013) 1995-2012	22 studies 2171 patients >6 months follow up: majority over 1 year, 3 studies <1 year Fixed-effects	lesion on neuroimaging	TL and ET Children and adults	OR 2.03 [1.67, 2.47]	English and Chinese studies	I^2=0%	-1 short follow ups: 3 studies <1 year follow up		undetected				++
	11 studies 1228 pts +++	lesion in temporal resection (11)	TLE Children and adults	OR 1.76 [1.34, 2.32]		I^2=19%, p=0.26 Note that the caption to Fig 3 doesn't fit with the p and I-squared values in the forest plot							++
	5 studies 203 pts	lesion in extratemporal resection (5)	ET Children and adults	OR 2.88 [1.53, 5.43]		I^2=0%							+

2.1.13 Englot, Rolston (32) (2013)

Meta-analysis *Publication year* **Years of individual studies**	**# included Studies, Patients Outcomes, Follow-up Durations Model(s)**	**Feature # of total patients with and without (# of studies)**	**Population: Lobe Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Englot, Rolston (32) (2013) 1993-2012 ++	36 studies 1,318 patients Engel I minimum of 1 year random-effects model after significance on univariate tests.	lesional (FCD, tumour, tuber, vascular malformation) vs non lesional (included HS, trauma, infection) 945 (29)	Paediatric TL	OR 1.08 [1.02, 1.15]			-1 Lesional excludes HS		Funnel plots: undetected				+
		focal seizures (partial) vs generalised 425 (11)		OR 1.36 [1.20, 1.56]									++
		without daily seizures 103 (5)		none given OR[c] individual participant 2.98 [1.24, 7.16]]	-1 small number of studies reported this: no formal CMH Meta-Analysis attempted.								+
		abnormal MRI 802 (26)		OR 1.27 [1.16, 1.40]									++

		Age (17)		NS t-test	Individual participant pooling of data, chi-squared tests or paired t tests failed to show significant and so CMH random effects not performed								+
		Gender/sex: male vs female 553 (14)		NS Pooled individual participant (crude) OR[c] 1.22 [0.90, 1.85]									++
		mean duration of epilepsy (12)		NS t-test									++
		localising ictal EEG 445 (14)		NS Pooled crude individual participant OR[c] 1.23 [0.73, 2.06]									++
		side of surgery 537 (15)		NS OR[c] crude 1.07 [0.72, 1.60]									++
		use of electrocorticography (ECoG) 462 (13)		NS OR[c] crude 1.31 [0.84, 2.04]									++
		Type of surgery: ATL vs lesionectomy vs		"NS"									Excluded as no data looking at

		lesionectomy plus additional vs SAH											the substrata CMH. In the text mentioned and in table p=0.02 but no meta analysis available.

2.1.14 Zhang, Hu (33) (2013)

Meta-analysis *Publication year* **Years of individual studies**	**# included Studies, Patients** **Outcomes, Follow-up Durations** **Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Zhang, Hu (33) (2013) 1990-2012	13 studies 229 patients Engel as reported Mean or median follow up of>12months Random and fixed-effects models	tuberectomy vs lobectomy 189 (10)	tuberous sclerosis	OR 0.51 [0.27, 0.99]		I^2=0% as few numbers	-1 Heterogenous definitions of seizure freedom without sensitivity analyses	-1 CI approaches OR of 1	-1 No funnel plots				+
		seizure onset before 12 months of age 200 (10)		OR 0.47 [0.24, 0.92]		I^2=0% as few numbers							+
		unilateral ictal EEG 159 (8)		OR 2.48 [1.17, 5.24]		I^2=0% as few numbers							+
		unilateral interictal EEG		OR 2.42 [1.11, 5.27]		I^2=0% as few numbers							+

		127 (6)											
		<5yrs vs >5yrs of age (at surgery) 194 (11)		NS OR 1.05 [0.58, 1.88]									+
		Gender: males vs females 186 (10)		NS OR 0.94 [0.52, 1.71]									+
		partial vs generalised 65 (6)		NS OR 1.15 [0.42, 3.11]									+
		Normal vs mental retardation 108 (4)		NS OR 1.36 [0.61, 3.05]		@bias: no definition of "mental retardation"							+
		number of cortical tubers <=4 vs >4 105 (4)		NS OR 1.12 [0.49, 2.57]									+
		intracranial EEG performed vs not preformed 144 (7)		NS OR 1.6 [0.76, 3.37]									+
		Infantile spasms (IS) 157 (7)		OR 0.45 [0.24, 0.85		I^2=45%							+

2.1.15 Josephson, Dykeman (34) (2013)

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Follow-up Durations** **Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Josephson, Dykeman (34) (2013)	11 studies 1,203 patients Engel I outcomes but also Engel I and II fixed-effects	ATLR vs SAH +++	TLE Children and adults	RR 1.32 [1.12, 1.57] Random effects: RR 1.36 [1.09, 1.7]	The result remained significant when 2 studies that contained fewer than 15 participants in at least 1 arm were excluded and in analyses restricted to hippocampal sclerosis and when a study specific to paediatric patients was excluded	(I^2= 29%; df =10, p=0.17	children and adults – but also excluded paediatric only study and results were very similar		undetected	summary risk difference (8%, 95% CI 3%–14%) translates to an NNT of 13 (95% CI 7–33) for 1 additional patient to achieve an Engel Class I outcome following ATL			+++
	10 studies 1092 pts	ATL vs SAH +++	TLE and HS subgroup Children and adults	RR 1.26 [1.05, 1.51].		I^2=0%							+++

2.1.16 Fallah, Guyatt (35) (2013)

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Follow-up Durations** **Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Fallah, Guyatt (35) (2013) Same data as in Ibrahim, Morgan (36)	20 articles 181 pts Engel I Univariate meta-analysis Bivariate logistic regression for each eligible independent variable, adjusting for the maximum length of follow-up.	absence of generalised semiology	Tuberous Sclerosis At least 90% less than 19 years old	OR = 3.1 [1.2, 8.2]	-1 Although a list of biologically plausible predictors was developed a priori; due to the small sample sizes of individual studies (median: 7; range 3–25 patients), and the variable inclusion of predictors across studies, unable to conduct a multivariable analysis or adjust	See publication bias comments on inability to assess hetergoeneity			-1 Suspected but "because of the very small number of participants per study, we could not assess between-study heterogeneity or publication bias."				+
		no or mild developmental delay		OR = 7.3 [2.1–24.7]				-1 Wide CI		+1 OR>4			++
		Unifocal ictal scalp EEG abnormality		OR = 3.21, [1.35–7.58]									+

		MRI/EEG concordance		OR = 4.9, [1.8–13.5]				-1 Wide CI		+1 OR>4			+
													+
		Gender (female)		NS OR 1.09 [0.48, 2.48]									+
		age at seizure onset (Log base 10)		NS OR 1.52 [0.77, 2.99]									+
		Pre-op seizure frequency (Log base 10)		NS OR 2.3 [0.34, 15.51]									+
		infantile spasms		NS OR 0.84 [0.35, 2.03]									+
		age at surgery (Log base 10)		NS OR 1.21 [0.56, 2.62]									+
		preoperative IQ		NS OR 1.01 [0.94, 1.08]									+
		less tuber burden		NS OR 1.01 [0.96, 1.07]									+

		No or unifocal interictal scalp EEG abnormality		NS OR 1.54 [0.73, 3.26]		-1 @Bias: unusual feature dichotomization See publication bias comments on inability to assess hetergoeneity							+

2.1.17 Englot, Breshears (37) (2013)

Meta-analysis *Publication year* **Years of individual studies**	**# included Studies, Patients Outcomes, Follow-up Durations Model(s)**	**Feature # of total patients with and without (# of studies)**	**Population: Lobe Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Englot, Breshears (37) 2013	36 studies 1259 patients Engel I Chi-squared / unpaired t-tests significance correction for multiple comparisons at 0.02. Then fixed effects.	Shorter epilepsy duration (≤ 7 years, the median value in this study) <1259 (8)	Extratemporal paediatric population	OR 1.52 [1.07, 2.14]	-1 suspected as no adjustments reported	Friedman and Kendall's W tests and Cochrane Q statistics			Not detected on funnel plots Although to our eyes figure 2 C shows possible asymmetry for partial vs generalized seizure semiology				+
		Lesional epilepsy (aetiology) 695 (28)		OR 1.34, [1.19, 1.49									+
		absence of generalized seizures 206 (11)		OR 1.61 [1.18, 2.35]									+
		localizing ictal electroencephalographic findings 226 (13)		OR 1.55 [1.24, 1.93]									+
		Mean age at surgery		NS[u] OR									+

		<1259 (17)											
		Gender male vs female 303 (15)		NS[u] OR[c*] 1.16 [0.74, 1.83]									+
		Daily seizures (yes vs no) 158 (4)		NS OR[uc*] 0.54 [0.28, 1.07]									+
		Abnormal preoperative MRI 506 (23)		NS OR[uc*] 1.44 [0.98, 2.12]									+
		Interictal EEG lateralizing Vs non-lateralizing 130 (10)		NS OR[uc*] 2.22 [0.98, 5.05]									+
		Operative variables, surgical lobe (frontal, parietal, Rolandic, occipital, multilobed) 537 (26)		NS[u] See their table 1									+
		Surgery side left vs right 326 (15)		NS OR[uc*] 0.99 [0.64, 1.53]									+

		Extent of lesionectomy: gross-total (complete) vs subtotal 75 (5)		NS[u] OR[uc*] 13.89 [3.30, 58.38] → meta analysis weighted: not shown or reported on the article				-1 few numbers and wide CI					Rejected as significant only on univariate unweighted analysis
		ECoG used vs not used 433 (20)		NS[u] OR[uc*] 0.77 [0.50, 1.19]									+

2.1.18 Kuang, Yang (38) (2013)

Meta-analysis *Publication year* **Years of individual studies**	**# included Studies, Patients Outcomes, Follow-up Durations Model(s)**	**Feature # of total patients with and without (# of studies)**	**Population: Lobe Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Kuang, Yang (38) (2013) 1989 - 2008	6 studies: RCTs 626 patients Engel I 1 year post operatively Fixed effect	ATL vs SAH 626 (6)	TLE	NS RR 1.01 [0.54, 1.09]		No evidence of inconsistency found							

2.1.19 Excluded [39] (2013): Review of Reviews

10 reviews or meta-analyses identified. No formal meta-analysis. Qualitative synthesis.

Table 6 includes common predictors of seizure outcome for

- lesional and non-lesional TLE,
- lesional ET, and
- Tuberous Sclerosis:

Positive Predictors:

- Lesional, abnormal MRI, partial seizures, complete resection
- As above
- No or mild developmental delay, unifocal ictal EEG abnormality, extensive resection (lobotomy)

Negative Predictors:

- Nonlesional epilepsy, poorly localised EEG, bilateral or multifocal MRI lesions, generalized seizures, FCD type 1, need for ictal EEG, incomplete resection, abnormal post-operative EEG
- Generalized seizures and as above
- Severe developmental delay, corpus callosotomy or tuberectomy

Non-Prognostic:

- Age at surgery, sex, duration of epilepsy, ictal EEG, side of surgery
- Seizure frequency and as above
- Infantile spasms, invasive EEG, PET findings, tuber burden

However, no common predictors of seizure outcome were identified in nonlesional ETLE.

2.1.20 Hu, Zhang (40) (2013)

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Follow-up Durations** **Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Hu, Zhang (40) (2013) 1993-2012	13 studies 1397 patients (686 total SAH, 711 total ATL) Engel I Mean or median follow up >1 year Fixed or random effects	SAH vs ATL	TLE	Overall OR 0.65 [0.51, 0.82] Transsylvian SAH OR (4) 0.60 [0.41, 0.87] Transcortical SAH OR (5) 0.68 [0.49, 0.96] Unknown or multiple approaches OR (2) 0.7 [0.25, 1.95]	Also included subgroups of transcortical or transsylvian SAH. Used NOS scale. The sensitivity analysis demonstrated that the significance of seizure outcome was not altered with the exclusion of low-quality studies (OR 0.57 [95% CI 0.43–0.76], p = 0.0001).	Trans-sylvian approach I^2 = 74% and p =0.009 Overall I^2 = 43%, p= 0.06 Otherwise, no significant heterogeneity Insufficient to mark down given the subgroup analysis		Only 2 studies for mixed approaches and hence may lack power with wide CI, whereas the other subgroup analyses show clear benefit for ATL	-1 Mild bias on funnel plot, did not further investigate or use trim and fill				++

2.1.21 Excluded Höller, Kutil (6) (2015)

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Follow-up Durations** **Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Höller, Kutil (6) (2015)	11 studies ILAE 1/Engel Ia Random-effects model	HFO resection ratios (:= proportion of HFO electrodes in the resected lobe, compared to total number of HFO electrodes).	Children and adults	Difference between SF and NSF resection ratios quoted: Ripples 0.18 [0.1, 0.27] Fast ripples 0.17 [0.01, 0.33]	-2 10 studies looked at ripples (80-200Hz) while 7 looked at fast ripples (>200Hz) Diff of HFO ratio quoted, not OR/RR of outcomes. No adjustments.	Q-statistic significant (p=0.025, for ripples and p<0.001 for fast ripples) with I^2 = 53%, 77% respectively.	-1 Difference of resection ratios between SF and NSF groups of 0.184 and 0.167, respectively.	In 9 of 10 studies resection ratio was higher for SF but in 5 of the 9 ripples studies the CI overlapped with zero 5 of 7 fast ripples studies resection ratio > for SF; but in 2 of 5 CI overlapped with zero.	Funnel plots, trim and fill	At best a rather small positive effect The effect sizes found in the meta-analysis are small but significant.			Rejected as no effect size of HFO resection ratio on outcome. Difference in resection ratio quoted.

2.1.22 Ibrahim, Morgan (36) (2015)

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Follow-up Durations** **Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Ibrahim, Morgan (36) (2015) Same data as in [35] ++ 2000 to 2011	20 articles 186 paediatric cases Engel ordinal, median duration of follow up was 2.3yrs [1.3, 4.3] Individual participant meta analysis: Singular value decomposition and partial least squares method used on 11 features. Only 2 were significant. partial least squares (PLS) to model multidimensional variance and study significant patterns in data that are associated with	Concordance EEG-MRI	Paediatric tuberous sclerosis	+ Note no traditional effect sizes as used SVD and PLS (latent variable space)			Only for TS patients		undetected			+1 Permutation testing was performed\to evaluate the significance of the component, and bootstrapping was used to identify significant contributors to the component. PLS accounted for latent structure of data and ordinal Engel outcomes classes	+++

	seizure outcomes												
		Focal ictal EEG		+									+++
		generalised seizure semiology		NS				-1 Fig 1 shows bootstrapping CI just about crosses zero, otherwise significant prognostic value					++
		focal interictal EEG		NS				-1 Skewed bootstrapping CI suggestive of possible positive effect					++
		gender		NS									+++
		tuber burden on MRI		NS									+++
		Epileptic spasms		NS									+++
		age at surgery		NS									+++
		lobe of resection		NS									+++
		age at onset		NS									+++
		Lesionectomy / multilobar resection surgery type		NS									+++

		Geographical location of surgery: N America vs elsewhere		NS									+++

2.1.23 Excluded Bonney, Glenn (41) (2015)

Data not fully extracted as explicitly state due to heterogeneity no formal meta-analysis was performed. Population was for gangliogliomas.

NB Fig 2 shows age at seizure onset to have inverse relationship with seizure freedom proportions, as well as mean or median duration of epilepsy having an inverse relationship with proportion seizure free.

2.1.24 Excluded West, Nolan (2) (2015)

Superseded by Cochrane review in 2019

2.1.25 Ruan, Yu (42) (2015)

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Follow-up Durations** **Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Ruan, Yu (42) 2015 1996 – 2014	10 594 patients Engel I At least 12 months Fixed or random effects based on I^2	Extended excision of surrounding haemosiderin	Mainly Adults with cavernomas (but also few children)	234 of 316 in extended excision (74%) Vs 189 of 278 in limited cavernoma resection (68%) were Engel I OR 1.61 [1.10, 2.38]	-1 missing data in limitations Note using their raw figures from 10 studies: OR 1.32 [uc] [0.94, 1.92] More significant in males than females, in Europe and Asian studies than American studies, and more significant in cohort than case control studies. Also more significant in follow up durations less than 3 years and cavernomas greater than 2cm	I^2 = 28% p=0.16 Did perform sensitivity analyses to removing each of the 13 studies	Some studies used MRI others histology to determine if haemosiderin was resected		Egger's test normal					+

2.1.26 Cao, Liu (43) (2016)

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Follow-up Durations** **Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Cao, Liu (43) (2016) 1995-2015	15 articles 380 sample size Engel I Min mean/median follow up time of 5 years Univariate then fixed or random effects	Seizure onset age ? (13)	Children with epilepsy undergoing hemispheric surgery	SMD = 0.26, [0.03, 0.49] P = 0.028		I square result was 40.2%, and the P value of the heterogeneity test was 0.116			Funnel and Egger				++
		Age at surgery ?(13)		NS[u]									++
		Seizure duration ?(5)		NS[u]									++
		Seizure type focal vs		Invert NS[u] OR[c*] 1.43 [0.58, 3.52]									++

		generalized 212(8)											
		Etiology		NS[u]									++
		epilepsia partialis continua 127 (7)		Invert NS[u] OR[c]* 0.46 [0.19, 1.15]]									++
		Surgical side ?(7)		NS[u]									++
		Gender male vs female 231 (10)		Invert NS[u] OR[c]* 1.15 [0.66, 2.01]									++
		MRI findings: abnormal vs normal ? (8)		OR 4.6 [1.27, 16.62]				-1 wide CI		Note unweighted OR is 1.49			+

2.1.27 Wang, Zhang (44) (2016)

Meta-analysis *Publication year* **Years of individual studies**	**# included Studies, Patients Outcomes, Follow-up Durations Model(s)**	**Feature # of total patients with and without (# of studies)**	**Population: Lobe Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Wang, Zhang (44) (2016)	18 studies 391 patients Mainly Engel I as per constituent studies in Table 1 random-effects model	Shorter epilepsy duration 128 (9)	(MRI neg TLE)	OR = 2.57 [1.21, 5.47]	NOS scores ranged from 4 to 6 stars Newcastle-Ottawa Scale	I^2 = 1%		-1 All have large CI and/or few patient numbers especially per study (imprecision/bias)	Forrest plots				+
		Ictal EEG localised to temporal lobe 125 (6)		OR = 3.89 [1.66, 9.08]	NOS scores ranged from 4 to 6 stars Newcastle-Ottawa Scale	I^2 = 0%							+
		Interictal EEG localised to temporal lobe 149 (7)		OR 3.38 [1.57, 7.25]	NOS scores ranged from 4 to 6 stars Newcastle-Ottawa Scale	I^2 = 0%							+
		PET scan results 127 (5)		NS p=0.06 OR = 2.11	NOS scores ranged from 4 to 6 stars Newcastle-	I^2 = 0%							+

				[0.95, 4.65]	Ottawa Scale								
		Gender: male vs female 146 (11)		NS OR 1.44 [0.86, 2.41] P=0.17	-1 2/11 studies had zero SF cases amongst males and 5 male and 5 females each or 2 males and 5 females – very few numbers with large CI Collected data from even studies with very few cases NOS scores ranged from 4 to 6 stars Newcastle-Ottawa Scale	I^2 = 0%, p=0.51							+
		Age at onset: children < 18 yrs vs >18yrs 69 (6)		NS OR 0.68 [0.22, 2.08]	NOS scores ranged from 4 to 6 stars Newcastle-Ottawa Scale	I^2 = 0%, p=0.79							+

		Age at surgery <18 yrs vs >18yrs 78 (6)		NS OR 1.09 [0.38, 3.07]	NOS scores ranged from 4 to 6 stars Newcastle-Ottawa Scale								+
		Side of surgery 320 (15)		NS Slightly favours Left TL OR 1.33 [0.84, 2.08]	NOS scores ranged from 4 to 6 stars Newcastle-Ottawa Scale	I^2 = 0%,							+
		Positive pathology		NS (p=0.36) OR=1.36 [0.7, 2.63]	NOS scores ranged from 4 to 6 stars Newcastle-Ottawa Scale	I^2 = 6%							+
		Mesial vs lateral TL epileptic focus (as determined on sEEG, subdural grid; or ATL/SAH vs neocortectomy) 92 (8)		NS Sightly favours mTL OR 1.39 [0.61, 3.2]	NOS scores ranged from 4 to 6 stars Newcastle-Ottawa Scale								+

2.1.28 Giridharan, Horn (45) 2016

Giridharan, Horn (45) 2016 1986-2012 Baseline Quality of evidence: +++	17 studies, 2028 patients Engel class I outcome >1 year post-operatively Random-effects model, meta-regressions (logistic regression)	Without APOS within 30 days of surgery Overall: 1983 (17) Paediatric: 730 (6)	TLE and ETE Mixed paediatric and adult. Subgroup analysis for overall APOS persistent in both.	Overall OR 4.2 [2.97, 5.93] (Without APOS 73.5% seizure-free, vs with APOS 39%) Paediatric subgroup OR 5.71 [3.32, 9.8]	-1 64.8% had presurgical lesion, not adjusted Variable APOS definitions (7-30 days) but used meta-regression to explore this for under 24hrs only	Not detected Subgroup analyses for paediatric, time of occurrence, semiology and meta-regressions to explore heterogeneity were performed			-1 Funnel plots and Egger's regression showed no bias. However, we note asymmetry in overall APOS, paediatric APOS and semiology group funnel plots in their Fig e1.	+1 large effect sizes for without APOS			++
		Earlier onset of APOS (within 24hrs) 222 (6)		NS 1.87 [0.89, 3.95]				-1 towards positive Seizure-freedom more likely, but statistically not significant					+
		Postsurgical semiology different from presurgical 109 (3)		NS 4.24 [0.93, 19.25]				-1 towards positive Seizure-freedom more likely, but statistically					+

								not significant					
		Subgroup meta-regression: mean age at surgery		NS									++
		Subgroup meta-regression: mean duration of epilepsy		NS									++
		Subgroup meta-regression: proportion with lesion		No data									No data, rejected

2.1.29 Hu, Zhang (46) 2016

Meta-analysis *Publication year* Years of individual studies	**# included Studies, Patients** Outcomes, Follow-up Durations Model(s)	**Feature** # of total patients with and without (# of studies)	**Population:** Lobe Age	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Hu, Zhang (46) 2016	56 studies 1528 pts mean or median follow-up period ≥ 1 year fixed and random effects	Developmental disorders 1041 (26)	Hemispheric	OR 0.61, 95% CI 0.46–0.82, p = 0.001		I^2 and Q statistics not significant heterogeneity detected			Funnel plots undetected				+++
		Focal vs Generalized seizures 403 (15)		OR 1.84, [1.18, 2.89], p = 0.008									++
		Lateralized findings on interictal EEG 413 (7)		OR 1.66, [1.03, 2.67], p = 0.0									++

		Lateralized findings on ictal EEG 414 (7)		ictal: OR 1.88, [1.15, 3.07], p = 0.01									++
		contralateral MRI abnormalities 332 (6)		OR 0.46, [0.27, 0.77], p = 0.004									++
		Male vs female 575 (24)		NS OR 1.15, 95% CI 0.79–1.67, p = 0.46									++
		Side of resection 539 (29)		NS OR 1.17, [0.79, 1.73], p = 0.43									++

2.1.30 Chen and Guo (47) (2016)

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Follow-up Durations** **Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Chen and Guo (47) (2016) 1995-2015	11 studies 320 patients 275 patients undergoing epilepsy surgery Engel I Univariate then fixed effects and random effects also quoted in Fig 2	subtraction ictal and inter-ictal SPECT co-registered to MRI (SISCOM)	TL and ET	unweighted positive rate of SISCOM was 85.9% (275/320).					-1 Funnel plot was asymmetric and that there was publication bias				Rejected as unsuitable metrics, not an effect size, used non surgical data and unweighted (instead of Trim and Fill)
		concordant lateralized and localized to EZ	TL and ET	unweighted concordant rate of SISCOM was 65.3% (203/311)		I^2 = 61.0%, Q = 0.2938, p = 0.0042	-1 71 pts used presumed EZ, 240 used actual resection		*-1* *p* value of the Egger test was 0.0042				As above
	Fixed effects	Concordance SISCOM with EZ 275 (11)	TL and ET	OR 3.28 [1.90, 5.67]		I^2 = 16.6%, p=0.285)			Egger's and Begg's test not significant				++

	Fixed effects	Concordance SISCOM with EZ 209 (11)	Subgroup ET	OR 2.44 [1.34, 4.43]		I^2 = 10.6%, Q = 10.06, p = 0.345			Egger's and Begg's test not significant				++

2.1.31 Excluded Ampie, Choy (48) (2016)

Meta-analysis *Publication year* **Years of individual studies**	**# included Studies, Patients** **Outcomes, Follow-up Durations** **Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Ampie, Choy (48) 2016 2005-2013	39 articles 88 patients of which 3 had only a biopsy with adjuvant radiotherapy (n=85) "seizure-freedom" no definition, median of 24 months follow up Fisher's exact	Gross total resection (vs subtotal resection)	Angiocentric gliomas Majority of tumour locations was temporal lobe (39%) 2 – 79 years (average = 16 years)	36/37 GTR SF Vs 9/16 STR SF OR 28 [3.04, 258][c]	-2 included individual case reports Did not clearly state what features were being compared for seizure freedom. Did not define seizure freedom.			-2					Excluded as significant risk of bias, unweighted univariate statistics effect sizes overestimate true effect sizes (exclusion criteria)

"Eight patients who presented with seizures (9%) reported seizure recurrence after surgical resection. GTR, when compared to STR, was associated with improved rates of seizure control (**p** = 0.0005). The remaining patients were seizure free post-operatively. In the 37 patients undergoing GTR, only one (2.7%) patient had seizure recurrence, occurring 15 months following surgery. Of the 16 patients undergoing STR, seven (44%) had recurrence of seizures in the post-operative period."

2.1.32 Harward, Chen (49) 2017

Harward, Chen (49) 2017 1990-2015 Baseline Quality: ++	27 series, 584 patients, Engel class I outcome >1 year post-operatively Mixed-effects model.	Age<18 yrs 9+21+13+9+7+36+16 = 111 (7) (at surgery)	Occipital Lobe and posterior quadrant. Mixed adult and paediatric	OR 1.54 [1.13, 2.18]	Attempted to minimise selection bias: variables selected only if at least 80 patients across 5 studies -1 No statistical adjustments "impossible to perform a multivariate analysis looking for interactions across variables" e.g. didn't adjust for lesions	Salanova 1992 study seems to have an outlying large point effect for age, without attempts at subgroup explanation.		Note all 7 studies' CI overlap OR of 1 but that of the overall effect does not	Undetected on funnel plots				+
		Focal pathological lesion 167 (9)		OR 2.08 [1.58, 2.89]									+
		Abnormal pre-operative MRI 132 (7)		OR 3.24 [2.03, 6.55]		Liava 2014 is the only study out of 7 without a CI overlapping OR of 1.							+

2.1.33 Krucoff, Chan (50) (2017)

Krucoff, Chan (50) (2017) 1989-2016 ++	36 studies 782 patients Engel I >12 months Overall Engel I in 47% (n=369) of patients. NB weights attributed to each study data are not shows on their forest plots. Random-effects and pooled univariate	"Congruent" (=focal) electrophysiology (ictal/interictal or invasive EEG) Table 2 & Fig 3: 192 (8)	patients who received repeat resective surgery for refractory focal epilepsy	OR = 3.6, [1.6, 8.2]								++
		Lesional (pathology: tumour, cyst, vascular malformation) Table 2 & Fig 3: 507 (12)		OR = 3.2, [1.9, 5.3]								++
		surgical limitations over disease-related failure of first resection (incomplete resection) vs new emergent seizures or palliative cases Table 2 & Fig 3: 273 (11)		OR = 2.6, [1.3, 5.3]	-1 heterogenous categorisations							+
		invasive monitoring Table 2 & Fig 3: 210 (?)		OR = 0.4, [0.2, 0.9]								++

		trend whereby temporal were more likely to become seizure free than extratemporal resections Table 2 & Fig 3: 943 (1st surgery = 447pts and 2nd resection = 496pts) (12)		NS OR=1.5 [0.8, 3.0]	No clear trend in 1st and 2nd resection subgroups, TL surgeries may have higher rate of redos?			Large CIs of individual studies					++
		Abnormal vs normal preop MRI (cf lesional pathology) Table 2 & Fig 3: 196 (7)		NS OR 1.9 [0.6, 5.4]									++
		Non prognostic factors: c* Gender 140 (?) Epilepsy duration 60 (?) Age at surgeries 1st surgery 194 (?) 2nd/last surgery 164 (?) Time between resections 188 (?)		NS Only univariate estimates can be calculated from the data in table 2 Gender male vs female NS OR c* 0.83 [0.42, 1.64] Side of surgery	Seizure generalisations showed a non-significant trend towards worse outcomes			-1 imprecise and effect sizes and CIs estimated					+ no quantitative data on effect estimates provided, but calculated

		Laterality of resections 1st surgery 218 (?) 2nd/last surgery 209 (?) Seizure generalization 145 (?)		operation #1 OR[c*] 0.73 [0.43, 1.25] Operation #2 OR[c*] 0.77 [0.44, 1.33] Focal vs generalised seizures:									
		Focal onset seizures with impaired awareness vs aware or other seizures 206 (3)		Calculated from Table 2 Non weighted non-CMH univariate pooled [c*] OR 1.61 [0.93, 2.8] p=0.089	-1 no meta-analysis due to paucity of # of semiology studies								+ no quantitative data on effect estimates provided

2.1.34 * Excluded Nevitt, Staba (1) (2017)

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Systematic Review Nevitt, Staba (1) (2017) +	2 studies 11 patients Engel 1 12months follow up	ictal HFOs for epilepsy surgery decision making		NS Found seizure free rates (Engel I) to be 55% - which isn't dissimilar to general seizure-freedom rates	Neither study compared surgical results guided by HFOs versus surgical results guided without HFOs.								+ Rejected as too few patients for formal meta-analysis and no effect sizes

This supersedes [51]

Rejected as 2 papers, 11 patients, no effect sizes.

*Found though other sources

2.1.35 *Excluded Genetic Stevelink, Sanders (7) (2018)

*Found though other sources

Stevelink, Sanders (7) (2018) <2016 24 studies, 82 total patients, 38 patients with positive genetics, 15 different genetic aetiologias grouped into three categories Raw proportions	5 studies 12 patients Engel I Last reported follow-up Raw proportions	Germline Mutations in mTOR > synaptic or ion channel related mutations 38 genetics positive (24)	Genetic Epilepsies Any Lobe	RR[c] = (7/12) / (2/14) = 4.08 [1.04, 16.06]	-2 8 of 12 germline mTOR mutations were lesional		-1 15 different genetic aetiologias grouped into three categories	-1 Very small numbers and large CI					Excluded as few numbers and all lesional without adjustments; and no RR calculations
	6 studies 18 patients Last follow up	Somatic or Mosaic mTOR mutations >synaptic/ion ch mutations	Genetic Epilepsies Any Lobe	RR[c] = 15/18 / 2/14 = 5.833 [1.59, 21.40]	-2 All 18 mosaic mTOR were lesional								Excluded as few numbers and all lesional and no RR calculations
	2 studies 12 patients Last follow up	Other: microdeletions	Majority lesional	Sz free = 10/12 = 75%									Excluded as few numbers and all lesional and no RR calculations
	3 studies 21 patients	Other: NF1	HS or low-grade tumours	12/21 = 57%	-2 majority were lesional								Excluded as few numbers and all lesional and no RR calculations

2.1.36 Excluded Pilipović-Dragović, Ristić (9) (2018)

Pilipović-Dragović, Ristić (9) (2018) 1993-2017	7 studies 253 patients Engel I univariate meta-regression	Localised interictal EEG	Parietal Lobe	No effect sizes given besides a univariate "b". e^b would give the OR, unadjusted e^b=4.80=OR	-2 univariate meta regression without inverse variance weighting for features. No adjustments.	-1 Significant heterogeneity in the meta-analysis (Q p<0.001, I^2=80%	Poor quality, CI of porportions exceed 1 in "Engel Forrest Plot" Figure 1	Excluded as univariate meta regression without adjusting for other factors, "b" coefficient of logistic regression quoted. Although we could calculate the effect size and estimate the CI, their figure 1 showed CI exceeding proportion of 1 for seizure freedom, so we didn't feel we could reliably deduce effect sizes from the rest of the paper. Even then, the results are generally consistent with included meta-analyses. The interesting ones were presence of aura and somatosensory aura not being significant as prognostic features which we didn't find in other meta-analyses. Imaging lesion and localised ictal EEG were even NS in their study , again no effect sizes.					
		Tumour pathology		e^b=1.4=OR									Excluded as above
		Age at onset, duration of epilepsy, age at surgery, mean follow up, imaging done, presence of aura, somatosensory aura, GTCS, imaging lesion, localized ictal EEG, invasive study, MCD, right sided surgery		NS univariate meta-regression	NB: invasive EEG, ictal EEG localization and GTCS are shown in other meta-analyses to be prognostic								Excluded As bove

2.1.37 Jain, Tomlinson (52) 2018

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Follow-up Durations** **Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Jain, Tomlinson (52) 2018 Used GRADE	19 compared ATL vs SAH ?pts Engel Ia or ILAE 1 or Engel 1, 12 months follow up Bayesian random effects NMA	ATL vs SAH (mix of transcortical, transsylvian and subtemporal approaches)	Mainly adults	NS OR 1.14, 95% CI 0.93 to 1.39; p=0.201 NS OR 1.15, 95% credible interval (CrI) 0.84-1.15									++ [52] 2018

2.1.38 Shan, Fan (53) (2018)

Meta-analysis *Publication year* **Years of individual studies**	**# included Studies, Patients Outcomes, Follow-up Durations Model(s)**	**Feature # of total patients with and without (# of studies)**	**Population: Lobe Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Shan, Fan (53) 2018 **1965-2016**	23 studies 2641 patients Engel at last point of follow up 1mo to 17 yrs Fixed-effects	Age >= 45 yrs ++ (at surgery) 1065 (6)	Supratentorial low grade gliomas in adults	RR 1.12 [1.01, 1.23]	NOS scale for individual studies GRADE evidence scale used		-1 Engel I at 1 month post-surgery also included		undetected				+
		Focal seizures +++ 796 (3)		RR 0.76 [0.67, 0.85]	Looked at generalized seizures and focal separately which was seems redundant	Note the caption on Fig 3 is incorrect and confusing.							+
		Prolonged history of seizures >1 yrs		RR 0.82 [0.75, 0.91]									+

		++ <2641 (<23)										
		Gross total resection cf subtotal resesction ++ 1379 (16)		RR 1.47 [1.37, 1.59]								+
		Tumor location TL vs ET ++ <2641 (<23)		NS NA								+
		Sex ++ <2641 (<23)		NS NA								+
		Tumor histology astro vs non astro ++ <2641 (<23)		NS NA								+
		Imaging characteristics (enhancement, oedema, mass effect) No GRADE score provided <2641 (<23)		NS NA								+

2.1.39 Shang-Guan, Wu (54) (2018)

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Follow-up Durations** **Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Shang-Guan, Wu (54) (2018) 1967-2017	7 studies 245 patients Follow up >6 months Fixed/random effects	extended lesionectomy with lesionectomy (:=resection of lesion and surrounding hemosiderin is sufficient) 245 (7)	any	NS OR 1.30 [0.66, 2.56] Removed 1 article with selection bias: OR 0.96 [0.44, 2.08]	NOS>4 only included, English, case reports excluded Sensitivity analysis		-1 f/up 6 months		Eggers and Beggs				+
		Average age <18 yrs excluded as only 1 trial		NS see table 2									Only 1 study
		Average >18yrs vs other at surgery		NS OR 0.95 [0.38, 2.37]									+

		Year of publication <2010 vs >2010		NS OR see table 2									+
		NOS > 6		NS OR 0.51 [0.21, 1.26] see table 2									+
		Seizure duration in years		NS OR see table 2									+
		Follow up in months		NS OR see table 2									+

2.1.40 Kobulashvili, Kuchukhidze (55) (2018)

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Follow-up Durations** **Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
55 2018 1990 – 2015	48 of 94 eligible for meta-analysis (40 for subgroup analysis) 534 patients subgroup analysis Completely seizure free (IA, 1) At least 12 months univariate random-effects meta-analytical models	Long-term monitoring (LTM / VT) localising vs non-localising in subsequent seizure outcome (sensitivity total studies = 44) (specificity total studies = 34)	All Lesional TLE n=406 (33)	Sensitivity 0.7 [0.6, 0.8] Sensitivity higher in tumours for outcomes Specificity 0.4 [0.27, 0.54] Sensitivity 0.85 [0.81, 0.89] highest in MCD/FCD ~0.95 [~0.71, 1] Spec 0.19 [0.13, 0.28] Specificity high for gliosis in	Also looked at covariates: lesional on MRI, TLE vs ETE, pathology including HS, length of follow-up, invasive and non-invasive LTM in their supplementary tables	**Sensitivity:** -1 Very large differences I^2 = 94.9% P<0.0001 **Specificity:** -1 Very large heterogeneity I^2 = 92.6% P<0.0001					With certain sensitivities yes, such as increased specificity with ETE and increased sensitivity with proportion of concordant LTM/MRI	+2 investigated covariates and sensitivity analyses including TLE, ETE, and abnormal MRI etc	+ Very Low

			Nonlesional TLE n=14 (3) Lesional ETE n=108 (16) Nonlesional ETE n=6 (2)	lesional TLE 0.41 [0.18, 0.69] Sens 0.47 [0.36, 0.58] Spec 0.35 [0.21, 0.53]									
		Long-term monitoring (LTM / VT) Odds ratios representing the odds of being seizure-free if the LTM is localizing and concordant with the surgical resection compared to non localizing LTM	Lesional TLE Lesional ETE Nonlesional TLE Nonlesional ETE	OR 1.41 [0.79, 2.53] OR 0.46 [0.2, 1.07] OR 0.6 [0.01, 35.86] 1 [0.06, 17.51]			-1 indirect evidence as their chose of definitions for LTM consists of focal and prognosis (see their discussion)	-1 imprecision for Nonlesional cases as few cases			See above	See above	+ Very Low

2.1.41 Harris, Phillips (56) 2019

Harris, Phillips (56) 2019 1992-2016 Baseline Quality: ++	19 articles, 187 children Engel I outcome at the longest reported follow-up time. Individual participant univariate and multivariate Cox regression analysis.	Younger age at onset	Rasmussen's Paediatric	HR 0.91[u] [0.85, 0.96] NS HR 0.95[m] [0.87, 1.04]	HR 1.10[u] [1.04, 1.18] NS HR 1.05[m] [0.96, 1.15]		-1 Adjusted for the variable length of follow-up, but not lesional or other known factors The NS features were not adjusted for known features in multivariate analyses -1 Reporting bias: 7 out of 19 studies had ≤ 5 patients	Probably not significant			-1 suspected but "unable to measure between-study heterogeneity and publication bias due to the very limited sample size per study"			Note not significant on adjustment for follow up	+
		Younger age at surgery		HR 0.93[u] [0.89, 0.97] NS[m] HR 0.95[m] [0.90, 1.0]	HR 1.08[u] [1.03, 1.12] NS[m] HR 1.05[m] [1.0, 1.11]										+
		Shorter duration of epilepsy		HR 0.92 [0.88, 0.97]	HR 1.09 [1.03, 1.14]										+
		Hemispherectomy (vs resective)		HR 0.28[u] [0.18, 0.45] HR 0.30[m] [0.18, 0.49]	HR 3.57[u] [2.22, 5.56] HR 3.33[m] [2.04, 5.56]									Remained significant on multivariate analysis but it seems only adjusted for length of follow up	+
		General seizure semiology		NS HR 0.8 [0.43, 1.51]	NS HR 1.25 [0.66, 2.33]										+

		Mod-severe developmental delay		NS HR 0.64 [0.31, 1.32]	NS HR 1.56 [0.76, 3.23]										+

2.1.42 Bjellvi, Olsson (57) (2019)

Bjellvi, Olsson (57) (2019) Baseline Certainty: ++ Except for <10 yrs vs >10 yrs +++ as over 1000	12 studies 1,545 patients Engel I >12months (although some exceptions were made) Random-Effects	Shorter duration of epilepsy at different points <2 vs >2yrs 388 (3) <5 vs >5yrs 551 (4) <10 vs >10 1376 (10)+++ <20 vs <20 346 (3) <5 vs >10	Children and adults, all lobes	**RR 1.2-1.33** **(Risk difference 0.15 to 0.21)** RR 1.20 [1.05, 1.39] RR 1.24 [1.08, 1.42] 1.25 [1.09, 1.43] 1.33 [1.08; 1.65] 1.32 [1.19; 1.46]	"Moderate risk of bias" "did not justify downgrading the evidence level"	**-1** 3/12 studies reported no association between duration and outcome 1/12 study was in favour of longer duration I^2 = 9% I^2 = 55% I^2 = 66% (p=0.002) I^2 = 20% I^2 = 0%	"some concerns" "did not justify downgrading the evidence level"		Studies that only reported mean or median duration of epilepsy for patients grouped by seizure outcome were not included.		Evaluated <5 yrs vs >10yrs To investigate if a larger time gap in epilepsy duration resulted in a larger effect – not present		++ GRADE score provided by study

		430 (4)											

2.1.43 *West, Nevitt (3)* 2019

West, Nevitt (3) 2019 1984-2013 Baseline Quality: +++ 182 studies (9 RCTs, 29 multivariate studies) 16855 participants Engel I or Ia, variably between 1 year and 5 years follow-up. Fixed and Mixed-Effects Note this study already includes GRADE scores per features and this is used as the starting	43 studies 3999 patients Combined good outcomes, various follow up Fixed effects	abnormal pre-operative MRI 3999 (43)		RR 1.28 [1.20, 1.37]	-1 †	I^2 = 38.57% p=0.01, no difference between subgroups by outcome							++ Unclear why they didn't use Random effects here
	21 studies 1547 patients Combined good outcomes, various follow up Fixed effects	invasive monitoring 1547 (21)		RR 0.85 [0.78, 0.93]	-1 †	I^2 = 37.28% p=0.04;, no difference between subgroups by outcome							++ Unclear why they didn't use Random effects here
	1 study 70 pts GRADE: ++ Engel Ia at 1 yr Fixed effects	Complete / total vs partial resection 70 (1)	Adults >18yrs	RR 1.82 [1.12, 2.93]	-1 Insufficient information regarding methods of randomization and allocation concealment in the study†								+ Only 1 study

point individually despite overall the study being rated as +++ by us.	46 studies 4430 patients Combined good outcomes, various follow up Fixed	mesial temporal sclerosis 4430 (46)	TLE	RR 1.17 [1.12, 1.23]	-1 †	I^2 = 27.79% p=0.04; no difference between subgroups by outcome (I^2 63% p 0.06) and certainly not by effect estimates							++ Unclear why they didn't use Random effects here
	23 studies 1778 patients Combined good outcomes, various follow up Fixed	MRI and EEG concordance 1778 (23)		RR 1.25 [1.15, 1.37]	-1 †	I^2 = 26%, no difference between subgroups by outcome							++
	15 1368 Combined good outcomes, various follow up Fixed	Febrile seizures 1368 (15)		RR 1.09 [1.01, 1.17]	-1 †	-1 I^2 = 32%, p=0.11; >1 yr SF subgroup had good outcomes with febrile seizures but the other subgroups did not (subgroup I^2 49%, p 0.14)							+
	46 3572 Combined good outcomes, various follow up	presence of FCD 3572 (46)		RR 0.90 [0.85, 0.95]	-1 †	I^2 28%, no significant different between outcome subgroups (I^2 0%, p 0.83)							++

	Fixed												
	41 3357 Combined good outcomes, various follow up Random-Effects	presence of tumour 3357 (41)		RR 1.23 [1.14, 1.32]	-1 †	Mixed effects used as I^2 40.59% p=0; no significant outcome subgroup differences							++
	37 2976	right-sided resection 2976 (37)		NS RR 0.96 [0.91, 1.01]	-1 †	I^2 28.22% p0.06 for total of 47 studies. I^2 0% p0.6 for subgroup heterogeneity. I^2 30% p=0.05 for total of the TLE vs ET subgroup analyses with TLE vs ET subgroups themselves not significant. Unclear why TLE/ET subgroup has fewer studies.		-					++
	Pg. 35 Analysis 4.11 18 studies 1414 pts	unilateral interictal spikes vs bilateral 1414 (18)	Mixed	Pooled RR 1.14 [1.05, 1.24]	CI adjusted for outcome scale Definition was likely to have influenced the analysis, e.g. non-lateralising vs contralateral	-1 I^2 = 67% overall and mixed effects using only Engel outcomes is non-significant: RR [0.88, 2]. Subgroup		-1 small studies with imprecise results. Mixed-effects model RR has no statistical significance.			In best case scenario of pooled effect rather than mixed-effects, the point estimation		+

	Various outcome scales Fixed effects				spikes, focal vs non-focal spikes †	analyses (TLE vs ET) do not explain these differences.					is 14% better. E.g. If bilateral 60% SF, unilateral spokes, 70% SF. This variable only explains one-third of the missing outcome variance, with NNT around 10.		
	40 3013 Various outcome scales Fixed effects	Complete resection (extent of resection) vs incomplete 2930 (39) Temporal 1266 (13) ET 30 (1) Mixed TLE and ET 1634 (25)		RR 1.41 [1.32, 1.50] TL subgroup RR 1.11 [1.03, 1.2] ET RR 2.0 [0.76, 5.29]	-1 †	-1 I^2 77.76% with p <0.0001; outcome subgroup differences also significant I^2 89.51% p<0.0001although the direction of effects are similar. Extratemporal subgroup ommited as only 1 study.							+ Unclear why random effects method was not used ET subgroup Only 1 study
	1 study 47 pts GRADE: ++ randomised	Subtemporal vs transsylvian approach to SAH 47 (1)	TLE Adults>18 yrs	NS RR 0.92 [0.59, 1.46]	Participants not completing one year of follow-up measures were excluded from the study†								+ Only 1 study

	ILAE 1 at 1 year												
	1 study 40 patients GRADE: ++ randomised Engel 1 and IA at 1 and 5 years Fixed effects	ATL vs parahippocampectomy PHC Engel IA 5yrs 28(1)	TLE Adults >18yrs	NS RR 0.57 [0.21, 1.52]	Outcome assessors were not blinded†		Excluded children from the study	-1 Despite the CI overlap, point estimates favour ATL, whether at 1 or 5 yrs or Engel I or IA.					+ Only 1 study
		SAH vs PHC Engel IA at 5 yrs 29 (1)	TLE Adults >18yrs	NS RR 0.54 [0.21, 1.39]	Outcome assessors were not blinded†			-1 Despite the CI overlap, point estimates favour SAH, whether at 1 or 5 yrs or Engel I or IA.					+ Only 1 study
		ATL vs SAH 29 (1)	TLE Adults >18yrs	NS RR 1.07 [0.53, 2.16]	Outcome assessors were not blinded†								+ Only 1 study
	1 study 207 pts GRADE: +++	2.5cm vs 3.5cm ATL resection 207 (4)	TLE Adults >18yrs	NS RR 1.02	†								++

	randomised Engel 1 at 1 yr			[0.86, 1.2]									
	1 study 70 patients GRADE: randomised ILAE 1 at 1yr Fixed effects	Total hippocampectomy > partial 70 (1)	TLE	RR 1.82 [1.12, 2.93]	†								++ Couldn't find a Cochrane GRADE, so rated the study as 3+ as it was randomised. Only 1 study
	1 study 58 patients GRADE: ++ Engel Ib at least, between 25-36months Fixed effects	ATL>stereotactic radiosurgery 58 (1)	TLE Adults >18yrs	RR 1.52 [1.01, 2.22]	Insufficient information regarding methods of randomization and allocation concealment in the study†			Note the limit approaches 1 and not fully adjusted, so could have confounders					+ Only 1 study
	1 study 43 patients GRADE: ++ randomised	Resection ± corpus callosotomy vs resection alone in LGS 43 (1)	LGS Children < 18 yrs	NS for all three 5yrs: RR 1.09 [0.53, 2.21]	Outcomes split into three follow-up groups of 1,3 and 5 years Inadequate method of quasi-randomisation. Unclear if blinded.†								+

	Engel 1 at 1, 3 and 5 years Fixed effects												
	1 study 60 patients GRADE: +++ randomised Engel 1 at 2 years Fixed effects	ATL + CCT vs ATL alone. 60 (1)	TLE Children and Adults	NS RR 1.22 [0.85, 1.76]	Inadequate method of quasi-randomisation. Unclear if blinded.†								++
	7 studies 551 patients Combined good outomces, various follow up Fixed	History of Head injury 551 (7)		NS RR 0.99 [0.86, 1.13]	-1 †	-1 I^2 46%, p 0.08, subgroup analyses by outcome were very different and inconsistent							+
	5 317 Combined good outomces, various follow up Fixed	Encephalomalacia 317 (5)		NS RR 0.78 [0.52, 1.17]	-1 †	No significant difference between outcome subgroups							+

	6 542 Combined good outomces, various follow up Random-effects and Fixed for temporal subgroup	postoperative discharges 542 (6)		NS Adjusted for outcomes RR 0.91 [0.68, 1.22] For TLE subgroup RR 0.81 [0.70, 0.94]	-1 †	Different total results for subgroups TLE/ET vs outcome subgroups, but both NS.							++
	Analysis 4.10 19 studies 1488 pts	vascular malformations 1488 (19)		NS pooled RR 1.07 [0.94, 1.21] adj for outcomes scale	- 1 †	No broad changes to result according to outcomes scales (Engel, Other or seizure freedom for 1 yr).	I^2= 0% for both overall heterogeneity and subgroup differences						++

2.1.44 Chen, Chen (58) (2019)

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Chen, Chen (58) (2019) 1991-2018 +++	48 studies 1580 Engel I and II Combinations of fixed-effects, random-effects and network-analyses (NMA).	FCD type I vs type II 1580 +++ (34)	Patients with focal dysplasia Any lobe Children and adults	OR 0.52 [95%CI 0.41, 0.65]	Trial sequence analysis, sensitivity analyses including removing individual studies Subgroup analyses for geographical locations. Palmini system of FCD (no FCD type III which was developed by IALE in 2011)	I^2=14%, p=0.24 Not in subgroup analyses in asia (OR=1.24 []0.75, 2.04]	-1 Engel II was considered seizure free		Begg rank correlation test and Egger linear regression test with trim and fill as necessary				++
		FCD and **incomplete resection** 567 ++ (16)		OR 0.08 [95%CI 0.05, 0.14]		I^2=0%, p=0.68				+2 large OR<0.1			+++

		FCD and **extratemporal location** 370 (12)		0.52 (95%CI 0.29, 0.94]		I^2=0%, p=0.8							+
		FCD IIb in network meta-analyses of FCD subtypes		OR 1.89 [1.01, 3.57]		P=0.048		-1 CI of OR approached 1					+

2.1.45 Toth, Papp (59) 2019

Toth, Papp (59) 2019 1996-2017	31 studies 1999 patients Engel I, >6 months Random-effects	sEEG > subdural overall: 1999 (31) Nonlesional: 237 (15) Lesional: 665 (21) TL: 470 (17) ET: 420 (14)	TL and ET Adults and Children (but not data from children only)	Overall RR = 64.7% [59.2, 69.8] / 55.9% [50.9, 60.8] NS Nonlesional NS RR = 52% [37.3, 66.3] / 54.4% [40.6, 67.6] Lesional RR = 71.6% [61.6, 79.9] / 57.3% [48.7, 65.6] TL RR = 73.9% [64.4, 81.6] / 56.7% [51.5, 61.9] ET RR = (61% [51, 70.2]) / (46.7%[36.5, 57.2]) = 1.31	-1 average follow up for SEEG was 10 months while for SDG it was nearly 19months. Significant differences overall (p = 0.02), lesional (p = 0.031), and also, temporal sugroups (p = 0.002)	Overall SEEG: I2 = 11.86%;p = 0.318 subdural grid: I2 = 54.47%;p = 0.002	-1 studies <6 months follow-up durations; we are interested in at least 12 months		Funnel plots, Egger's tests: no overall changes or subgroup changes			[Unlcear if ET was significant or not as it mentions lesional in the text whereas it should mention ET]	+

2.1.46 Excluded Pellino, Gencarelli (8) (2020)

Meta-analysis *Publication year* **Years of individual studies**	**# included Studies, Patients** **Outcomes, Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Pellino, Gencarelli (8) (2020)	21 articles 24 patients univariates	Distribution of neurocutaneous melanosis (focal)	Children with parenchymal Neurocutaneous melanosis	Bilateral or isolated amygdala involvement carried the best rates of seizure-freedom 100% cf multiple localisations 58% (>6 months, 24 paediatric cases amongst 21 studies).	Few patients, averaging 1 patient per study								Excluded as no summary effect size, not a meta-analysis and few numbers

2.1.47 Widjaja, Jain (60) 2020

Widjaja, Jain (60) 2020 1990-2017 Baseline Quality: +++	258 studies, 4891 patients "seizure-freedom" ≥12months follow-up, Random-effects, meta-regression and network meta-analysis	Lesional epilepsy (=abnormal MRI) 883 (10)	No mention of distribution by lobe Paediatric	OR 1.85 [1.14, 2.94]	Sensitivity analysis performed by removing the single RCT from results. Newcastle-Ottawa Quality Assessment Scale for observational studies.	2 of 10 studies had a reverse OR point estimate, one of which was a small study, I^2<50%, p=0.01.	-1 SF not clearly defined, some individual studies included Engel Classes I and II		Funnel plots and trim and fill test to impute bias effect estimates: difference between observed and imputed <10% NB the MR for study quality score showed for subgroups of tumour and ETE, higher quality was associated with reduced SF percentages - although not statistically significant, the magnitude of effect was significant (-0.31 and -0.16 respectively)			Age at surgery and age at seizure onset associated with seizure freedom in general and especially for TLE and ETE (age at surgery only) but not for hemisphere-ctomies, tumors or MCD	+
		Pathologies Tumour, HS > Rasmussen > MCD, TS > HH		Proportions only									+
		Complete resections 893 (15)		OR 7.69 [4.76, 12.5]		consistent				+1			++
		Age at seizure onset in general (MR) ? (<30)		SF % coefficient +0.346 [0.21, 0.49]							+1 meta-regression		++
		Age at surgery in general (MR) ? (<30)		SF % -0.19 [-0.27, 0.12]							+1 meta-regression		++
		Surgery Locations hemispheric (NMA) ? (~23)		Vs medical OR 13.1 [4.3, 41]		NMA Surgical locations cf with medical therapy, pairwise comparisons				Large OR only vs medical			+

				But NS for vs ET		similar except for TLE vs ETE							
		Surgery Locations Temporal Lobe (NMA) ? (~23)		OR 9.3 [3.3, 27] vs medical Also significant for vs ET: OR 2 [1.4, 2.9] direct and NMA p=0.025						Large OR only vs medical			+
		Surgery Locations Extratemporal Lobe (NMA) ? (~23)		OR 4.7 [1.7, 14] vs medical But NS except for worse cf TL as above						Large OR only vs medical			+

2.1.48 Excluded Brændholt and Jensen (61) (2020)

6 original studies, 59 patients.

iMSI can reliably localize the EZ in focal epilepsy, but not clearly predictive of outcomes. Sensitivity and specificity are provided for EZ predictions in seizure free and non-seizure free groups, and compared with that of icEEG. The latter which is usually either non-prognostic or has a negative prognostic value. The effect sizes were for EZ prediction rather than outcomes per se.

2.1.49 Lamberink, Otte (62)(2020)

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Follow-up Durations** **Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Lamberink, Otte (62) 2020 Jan 1, 2000, and Dec 31, 2012	37 collaborating tertiary referral centres across 18 European countries Proportions of individuals who were Engel I were reported for 11 categories of histopathological diagnosis at 1, 2 and 5 years of follow-up. 8191 patients for 2 years of follow up data used as ORs available for this and much less missing values than for 5 years follow up. 9147 total patients in study.	low-grade epilepsy associated neuroepithelial tumour (LEAT) 1325 (<37) (similar for LGNET, DNET, ganglioglioma, and others: angiocentric neuroepithelial tumour, pilocytic astrocytoma, gangliocytoma, papillary glio-neuronal tumour, and other low-grade neuroepithelial tumours) – majority were gangliogliomas and DNET Ganglioglioma	Children and Adults	77·5% 80·4%	89·5% of patients had outcomes followed up for 2 years (8191 pts) Missing data were imputed (39% of outcome data at 5yrs and 10% of outcome data at 2 years were missing, as well as 18·5% of	Heterogeneity between centres was modelled through random intercepts.	Reference was LEAT which was a mixture of LGNET, DNET, gangliogliomas and others. Vascular is a mixture of cavernomas and other vascular malformations. Other mixed categories are MCD-other, LEAT, and non-LEAT and Encephalitis. These are rated down. -1		Pooled data from 37 centres. "We acknowledge that not including patients of whom no histopathological data were available, such as those undergoing disconnection surgery, could have introduced a bias when assessing the association between cause and outcome."	Proportion with Engel I around 70% or greater had significant ORs and were concluded to be positively prognostic, whereas in the 50%s were negatively prognostic.		Adjusted for age at surgery and duration of epilepsy and lobe of surgery +1	+++

	retrospective, multicentre, longitudinal, cohort study random-effects logistic regression models all ORs are cf to LEAT	672 DNET 484		74·8%	duration of epilepsy data -1)								
		vascular malformation (cavernomas and others) 443		74·0% NS OR 0.79 [0·60 - 1·06]									++
		Cavernomas 323		77·1%									
		Others 120		65·8%									
		hippocampal sclerosis 2948		71·5% OR 0.79 [0·65 - 0·89]									+++
		FCD type I or MCD 426		Negative 50·0% OR 0.38 [0·28 - 0·49]									+++
		Other MCD (Hypothalamic hamartomas, tubers and others)		Negative 52·3%									++

		405		OR 0.44 [0·29 - 0·63]									
		No histopathological lesion (comprised of gliosis and normal tissue) 740		Negative 53·5% OR 0.36 [0·30 - 0·46]									+++
		FCD type II 796		64·9% NS OR 0.8 [0·61 - 1·09]									+++
		Encephalitis (rasmussen's and limbic, herpes, neurocysticercosis) 124 Encephalitis - Rasmussen's subgroup 72		59·7% OR 0.43 [0·22 - 0·73] 72·2%									++
		Glial scar 261		59·4% OR 0.53 [0·39 - 0·70]									+++
		Non-LEAT (astrocytoma, oligodendroglioma, cysts, ependymoma,		68·4% NS									++

		meningioma, neurocytoma, and pleomorphic xanthoastrocytoma) 310		OR 0.75 [0·54 - 1·02]									
		Year of surgery ? but rated +1 as likely >1000		NS									+++
		Duration in years for LEAT Duration interaction with all other pathologies		0.97 [0·96 – 0·99] NS									+++
		Lobe of surgery TL reference had the highest compared to all other lobes, all significant (multilobar, parietal, occipital, frontal, hypothalamus) ? (rated +1 as likely >1000)		Significant no effect size									+++

Table 1: Individual Meta-Analyses of postsurgical prognostic features, with quality of evidence rating using the GRADE system for each meta-analysis

[1]**Study limitations (risk of bias or internal validity):** Differential surveillance for outcome between studies, failure of accurate measurement of all known prognostic factors and to match for prognostic factors and/or lack of adjustment in statistical analysis. Includes selective reporting bias. [12 14]

[2]**Inconsistency of results:** If some studies suggest substantial prognostic value using relative measures while others suggest no effect or negative prognostic value then it may be appropriate to rate down for quality. Criteria for evaluating consistency include similarity of point estimates, extent of overlap of confidence intervals, and statistical criteria including tests of heterogeneity and I^2. If inconsistent results cannot be explained by differences in subgroups (populations undergoing surgery, surgical intervention, or outcome definitions and follow-up), then the quality of the body of evidence is rated down. [15]

[3]**Indirectness of evidence:** If there are differences in the populations, interventions and/or outcomes being studied compared to what we are interested in, or if interventions are compared without direct head-to-head comparisons, studies can be rated down [16]. We only rate down if there is a compelling reason to believe the populations studied differ from the population of interest that the magnitude of effect would differ significantly. We rate down if there is an outcomes discrepancy, whereby the seizure-freedom duration of follow-up in the inclusion criteria is less than that of interest (at least 12months). We consider ILAE 1 and 2 seizure free, which is equivalent to Engel Ia/Ib (we consider undifferentiated Engel I otherwise not reported to be seizure-free) and only rate down inclusion criteria that specifically include Engel II or ILAE 3.

[4]**Imprecision:** e.g. for a single meta-analysis, effect sizes which overlap the neutral point (for RR and OR, 1) suggesting the feature is not prognostic, but the boundaries of the confidence interval are skewed significantly in one direction such that the largest plausible effect is that the feature is either positively or negatively correlated with outcomes. [11]

[5]**Publication bias:** clinical features that are non-prognostic and smaller effect sizes are less likely to be published and these can be assessed by funnel plots. Cumulative iterative meta-analyses could be indirectly inferred from the publication dates to ascertain time-lag bias. Risk of publication bias is probably larger for small, observational, and industry-funded studies. [14]

[6]**Rating up:** relative risks above 2 (below 0.5) are rated up one level, and above 5 (below 0.2) are rate up two levels unless the CI overlaps significantly with these thresholds. If the baseline proportion of outcomes is low, odds ratios are treated similarly, otherwise a higher threshold is used. Studies were also rated up if a dose response was present or if all plausible residual confounders or biases would reduce a demonstrated effect, or suggest a spurious effect when results show no effect [17]

TLE: Temporal Lobe Epilepsy. ETE: Extratemporal lobe Epilepsy. APOS: Acute Postoperative Seizures. NS: Not Significant. CI: confidence aura. HS: Hippocampal Sclerosis. MCD: Malformations of Cortical Development. HH: Hypothalamic Hamartoma. TS: Tuberous Sclerosis. OR: Odds Ratio. RR: Relative Risk Ratio. SF: Seizure Freedom. NMA: Network Meta-Analysis. ATL: Anterior Temporal Lobectomy. SAH: Selective Amygdalohippocampectomy. NA: Not Available.

*: Our calculated CI from their data. [c]: Effect size derived from article data. [u]: Univariate analyses. [m]: Multivariate analyses. †A weakness of the Cochrane review is that they "did not class any of the pre-operative prognostic factors of interest…as confounders" so in general our GRADE score is one lower.

2.1.50 Remick, Ibrahim (63) (2020)

Meta-analysis ***Publication year*** **Years of individual studies**	**# included Studies, Patients** **Outcomes, Follow-up Durations** **Model(s)**	**Feature** **# of total patients with and without** **(# of studies)**	**Population:** **Lobe** **Age**	**Effect Sizes (seizure freedom)**	**Rating the quality of the meta-analysis evidence using the GRADE guidelines [13]**								
					Risk of Bias or Internal Validity[1]	**Inconsistency of Results[2]**	**Indirectness of Evidence[3]**	**Imprecision[4]**	**Publication bias[5]**	**Large effect size?[6]**	**"Dose" response?[6]**	**All plausible residual confounding?[6]**	**Quality of the body of evidence (GRADE)**
Remick, Ibrahim (63) (2020) 2020 1999 – 2018	33 462 Mixed effects meta analysis PCA and multivariable logistic regression of principle components	SEEG vs SDE SEEG 127/235 (17) SDE 146/227 (18) (33)	All	NS SDE 64.3% [61.1, 67.5] SEEG 54% [50.8, 57.3] It is likely adjusted p value in the text is p = 0.0565 OR^{cu} 0.65 [0.45, 0.95] p=0.025^{cu}	Cox proportional hazards investigated length of follow-up -1 some outcome data unavailable for SEEG and SDE "the difference between seizure freedom rates following SEEG- or SDE-informed resection decreased with long-term follow-up"	-1 "SEEG-informed resections were associated with a lower rate of postresection seizure freedom than SDE-informed resections (p = 0.0247)." But also "Our results demonstrate that while there was no difference in seizure freedom rates regardless of resection (p = 0.0565)"	-2 does not include studies directly comparing SEEG vs SDG						+ Very low

2.2 Supplementary Table 2: Individual Prognostic Features Across All Meta-Analyses

Feature	Population # patients (# studies, #meta-analyses)	Effect Sizes	Rating the quality of the meta-analytic evidence behind the potential prognostic value using GRADE guidelines [13] Risk of Bias or Internal Validity[1]	Inconsistency of Results[2]	Indirectness of Evidence[3]	Imprecision[4]	Publication bias[5]	Large effect size?[6]	"Dose" response?[6]	All plausible residual confounding?[6]	Quality of the body of evidence
Example	*TLE, FLE…* *Age* *Other*	*RR, OR…*	*Heterogenous outcome follow-ups* *Exclusion of known prognostic factors and statistical adjustments* *Selective Reporting*	*Widely spread effect sizes as assessed by point estimates, CI, and statistical tests of heterogeneity.*	*Populations, interventions and/or outcomes being studied differ from those of interest:* *e.g.: unseparated paediatric and adult ages, less than 12 months or more than ILAE 2*	*Large and/ or skewed CI*	*"undetected"* *"suspected"* *-1* *"strongly suspected"* *-2*	*at least a two-fold reduction or increase in risk* *+1* *5-fold or more increase in RR* *+2*	*+1*	*All plausible residual confounders or biases would reduce a demonstrated effect, or suggest a spurious effect when results show no effect.* *+1*	*+ Very Low* *++ Low* *+++ Moderate* *High ++++*
1. Clinical Features											
Low IQ IQ ≤75 "mental retardation"	TLE Age ≥16 yrs With and without structural lesions 1034 (8, 1) non-HS structural lesions in TLE >16 yrs 150 (8, 1) Tuberous sclerosis 108 (4)	RR 0.66 [0.54, 0.94]* IQ on average 2.3 lower in not seizure-free group (p<0.009) RR 0.26 [0.14, 0.50]* NS OR 0.74 [0.33, 1.64]	Adjusted for presence of structural lesions Chelune, Naugle (20) Absence of significant interaction with centres, or duration of epilepsy Chelune, Naugle (20)	Multicentre not meta-analysis Chelune, Naugle (20)	-2 duration of follow-up and definition of seizure freedoms differ Chelune, Naugle (20) -1Heterogenous definitions of seizure freedom without sensitivity analyses. No definition of mental	No CI provided, but could be estimated from data presented Chelune, Naugle (20)	-1 suspected, untested Chelune, Naugle (20) Zhang, Hu (33)		+1 Higher seizure-freedom rates in higher IQs (their table 3)	+1 Adjusted for lesions	+ Chelune, Naugle (20) 1998 +

					retardation. Zhang, Hu (33)						Zhang, Hu (33) (2013)
Severe developmental delay	Tuberous Sclerosis; at least 90% less than 19 years old <181 (<20)	OR 0.14 [0.04, 0.48]						+1 OR< 0.25			++ Fallah, Guyatt (35) (2013)
Pre-operative IQ (note all the others are severe low IQ)	TS in 90% <19yrs	NS OR[u] 1.01 [0.94, 1.08]	-1 Small samples (median 7, IQR[3,25]), could not adjust Fallah, Guyatt (35)			-1 Wide CI Fallah, Guyatt (35)	-1 Small samples, did not assess heterogeneity or bias Fallah, Guyatt (35)				+ Fallah, Guyatt (35) (2013)
Moderate to severe developmental delay	Paedaitric Rasmussen's <187 (<19)	NS HR[u] 0.64 [0.31, 1.32]	-1 Reporting bias: 7 out of 19 studies had ≤ 5 patients				-1 suspected but "unable to measure between-study heterogeneity and publication bias due to the very limited sample size per study"				+ Harris, Phillips (56) 2019
	Children and adults hemispherectomy 1041 (26)	OR 0.61, 95% CI									+++ Hu, Zhang (46) 2016

		0.46–0.82, p = 0.001									
History of Head injury	Adults and children 551 (7)	NS RR 0.99 [0.86, 1.13]	-1 †	-1 I^2 46%, p 0.08, subgroup analyses by outcome were very different and inconsistent							+ West, Nevitt (3) 2019
febrile convulsions	TL and ET Children and adults 1368 (20, 2)	OR 2.08 [1.2, 3.7], RR 1.09 [1.01, 1.17]	-1 †	Q=7.9, p=0.093 Tonini, Beghi (24) -1 I^2 = 32%, p=0.11; >1 yr SF subgroup had good outcomes with febrile seizures but the other subgroups did not (subgroup I^2 49%, p 0.14) West, Nevitt (3) 2019	-1 Engel outcomes in 22 studies and other definitions in 25						+, + Tonini, Beghi (24) (2004), West, Nevitt (3) 2019
CNS infections	TL and ET Children and adults ? (2, 1)	NS OR 0.73 [0.29, 1.82]	-1 Only 2 studies	Q=2.1, p=0.146	-1 Engel outcomes in 22 studies and other definitions in 25						+ Tonini, Beghi (24) (2004)
Focal (partial) seizure semiology (vs generalized)	ET, Adults, Non-lesional 62 (?, 1)	NS[u] (univariate Fisher's)	-1 Small sample sizes form multiple centres, heterogenous outcome reporting Ansari, Tubbs (18)				-1				+ Ansari, Tubbs (18) (2010) ++

	Adults and Children with FCD 2014(10, 1) Adults and Children with FLE 269 (<21, 1) TL in Children 425 (11, 1) Tuberous Sclerosis 65 (6) Tuberous Sclerosis in at least 90% less than 19 years old (~children) 181 (20)	OR 1.46 [1.18, 1.82] NS P=0.05 OR 1.36 [1.20, 1.56] NS OR 1.15 [0.42, 3.11] OR = 3.1 [1.2, 8.2] But same data NS PLS method	-1 Small samples (median 7, IQR[3,25]), could not adjust Fallah, Guyatt (35)		-1 Heterogenous definitions of seizure freedom without sensitivity analyses Zhang, Hu (33) -1 Small samples, did not assess heterogeneity or bias Fallah, Guyatt (35)	-1 Magnitude not provided and p value borderline Englot, Wang (30) -1 Fig 1 shows bootstrapping CI just about crosses zero, otherwise significant prognostic value. Ibrahim, Morgan (36)	No funnel plots/trim fill etc Rowland, Englot (29) Zhang, Hu (33) Fallah, Guyatt (35) Undetected Englot, Rolston (32)			+1 Permutation testing was performed\to evaluate the significance of the component, and bootstrapping was used to identify significant contributors to the component. PLS accounted for latent structure of data and ordinal Engel outcomes classes. Ibrahim, Morgan (36)	Rowland, Englot (29) (2012) + Englot, Wang (30) (2012) ++ Englot, Rolston (32) (2013) + Zhang, Hu (33) (2013) + *Fallah, Guyatt (35) (2013) ++ *Ibrahim, Morgan (36) (2015)

…Focal vs generalized… Focal onset with impaired awareness vs aware or other seizures	Repeat surgery for focal DRE 145 (?) Repeat surgery for focal DRE 206 (?) Paediatric Rasmussen <187 (<19) Paediatric ET 206 (11)	NS[u] OR[c*] 1.84 [0.93, 3.61] NS[u*] OR 1.61 [0.93, 2.8] p=0.089 NS HR 1.125 [0.66, 2.33]	-1 Reporting bias: 7 out of 19 studies had ≤ 5 patients			1 imprecise and effect sizes and CIs estimated. Krucoff, Chan (50) (2017)	-1 suspected but "unable to measure between-study heterogeneity and publication bias due to the very limited sample size per study"				*=same data different methods + Krucoff, Chan (50) (2017) + Krucoff, Chan (50) (2017) + Harris, Phillips (56) 2019 + Englot, Breshears (37) 2013 ++

	Children and adults hemispherectomy 403 (15) Adults with supratentorial low grade gliomas 796 (3) Children hemispherectomy 212(8)	OR 1.61 [1.18, 2.35] OR 1.84, [1.18, 2.89], p = 0.008 RR 0.76 [0.67, 0.85] NS[u]	Note the caption on Fig 3 seems incorrect and confusing.								Hu, Zhang (46) 2016 + Shan, Fan (53) 2018 ++ Cao, Liu (43) (2016)
Infantile/epileptic spasms	Tuberous sclerosis <343 (<27, 2), 90% <19yrs in ref [35]	OR 0.45 [0.24, 0.85, NS OR 0.84 [0.35, 2.03] also NS on PLS	-1 Small samples (median 7, IQR[3,25]), could not adjust Fallah, Guyatt	I^2=45% Zhang, Hu (33) (2013)	-1 Heterogenous definitions of seizure freedom without sensitivity analyses Zhang, Hu (33) (2013)		-1 No funnel plots Zhang, Hu (33) (2013) -1 Small samples, did not assess heterogeneity or bias Fallah, Guyatt			+1 Permutation testing was performed\to evaluate the significance of the component, and bootstrapping was used to identify significant contributors to the component. PLS accounted for latent structure of data and ordinal Engel outcomes classes. Ibrahim, Morgan (36)	+, + Zhang, Hu (33) (2013) *Fallah, Guyatt (35) (2013) +++ *Ibrahim, Morgan (36) (2015)

											* = same data different methods
Gender (male vs female)	Adults and Children with FLE <1199 (<21,1) Children with TLE 553 (14, 1) Tuberous Sclerosis <186 (<30, 2)	NS p=0.99 Males 53% females 54% NS[u] crude OR[c] 1.22 [0.90, 1.85] NS OR 0.94 [0.52, 1.71], NS 0.92 [0.40, 2.08] also NS on PLS	-1 Heterogenous definitions of seizure freedom without sensitivity analyses Zhang, Hu (33) -1 Small samples (median 7, IQR[3,25]), could not adjust Fallah, Guyatt				Funnel plots: undetected Englot, Wang (30) -1 No funnel plots Zhang, Hu (33) -1 Small samples, did not assess heterogeneity or bias Fallah, Guyatt			+1 Permutation testing was performed\to evaluate the significance of the component, and bootstrapping was used to identify significant contributors to the component. PLS accounted for latent structure of data and ordinal Engel outcomes classes	++ Englot, Wang (30) (2012) + Englot, Rolston (32) (2013) +, + Zhang, Hu (33) (2013) *Fallah, Guyatt (35) (2013) +++ *Ibrahim, Morgan (36) (2015) *=same data different methods +

	MRI neg TLE 146 (11) Repeat surgery in focal DRE 140 (?) Paediatric ET 303 (15) Children and adults hemispherecromy 575 (24)	NS OR 1.44 [0.86, 2.41] P=0.17 NS OR[c*] 0.83 [0.42, 1.64] NS[u] OR[c*] 1.16 [0.74, 1.83] NS OR 1.15, 95% CI 0.79–1.67, p = 0.46	-1 2/11 studies had zero SF cases amongst males and 5 male and 5 females each or 2 males and 5 females – very few numbers with large CI. Collected data from even studies with very few cases. NOS scores ranged from 4 to 6 stars Wang, Zhang (44)			-1 imprecise and effect sizes and CIs estimated					Wang, Zhang (44) (2016) + Krucoff, Chan (50) (2017) + Englot, Breshears (37) 2013 ++ Hu, Zhang (46) 2016 + Shan, Fan (53) 2018

	sex in low grade gliomas in adults <2641 (<23) children hemispherectomy 231 (10)	NS NA NS[u] NA									++ Cao, Liu (43) (2016)
Seizure Frequency Without daily seizures	Adults and children with FLE <1199 (<21, 1) TL in Children 103 (5) Paediatric ET 158 (4)	NS[u] OR[c*] individual participant 2.98 [1.24, 7.16]] NS OR[uc*] 1.85 [0.93, 3.57]	-1 Limited info Englot, Wang (30) small number of studies reported this: no formal CMH Meta-Analysis attempted Englot, Rolston (32)								+ Englot, Wang (30) (2012) + Englot, Rolston (32) (2013) + Englot, Breshears (37) 2013
Age at seizure onset	ET, Adults, Non-lesional	NS	-1Small sample sizes form multiple								+

	131 (?, 1)		centres, heterogenous outcome reporting								Ansari, Tubbs (18) (2010)
seizure onset before 12 months of age (dichotomised)	Tuberous sclerosis 200 (10, 1)	OR 0.47 [0.24, 0.92]		I^2=0% Zhang, Hu (33) (2013)	-1 Heterogenous definitions of seizure freedom without sensitivity analyses Zhang, Hu (33) (2013)		-1 No funnel plots Zhang, Hu (33) (2013)			+1 Permutation testing was performed\to evaluate the significance of the component, and bootstrapping was used to identify significant contributors to the component. PLS accounted for latent structure of data and ordinal Engel outcomes classes. Ibrahim, Morgan (16	+ Zhang, Hu (33) (2013)
Log base 10 of age at onset	Tuberous Sclerosis in 90% <19 yrs <181 (<20)	NS OR 1.52 [0.77, 2.99] also NS on PLS	-1 Small samples (median 7, IQR[3,25]), could not adjust Fallah, Guyatt				-1 Small samples, did not assess heterogeneity or bias Fallah, Guyatt				+, +++ *Fallah, Guyatt (35) (2013) *Ibrahim, Morgan (36) (2015) *=same data different methods
<18 yrs vs >18 yrs	MRI neg TLE 78 (6)	NS OR 1.09 [0.38, 3.07]	NOS scores ranged from 4 to 6 stars								+ Wang, Zhang (44) (2016)
Younger age at onset	Paediatric Rasmussen's <187 (<19)	NS HR 0.91[u] [0.85, 0.96] HR 0.95[m] [0.87, 1.04]	-2 Adjusted for the variable length of follow-up, but not lesional or other known factors. Reporting bias: 7 out of 19 studies				-1 suspected but "unable to measure between-study heterogeneity and publication bias due to the very limited				+ Harris, Phillips (56) 2019

	Paediatrics (and paedaitric subgroups: TL, but not ET, hemispherectomy, tumors or MCD) ? (<30) ET non lesional children <95 (<17) Children hemispherectomy <380 (13)	Meta Regression overall = $e^{0.346}$ = OR^c=1.41 (p<0.001) TL $e^{0.144}$= OR^c=1.15 (p=0.023) NS^u SMD = 0.26, [0.03, 0.49] P = 0.028	had ≤ 5 patients		-1 SF not clearly defined, some individual studies included Engel Classes I and II		sample size per study"				++ Widjaja, Jain (60) 2020 + Ansari, Maher (28) 2010 Cao, Liu (43) (2016)
Age at epilepsy surgery Continuous	ET, Adults, Non-lesional 131 (?, 1)	NS (ANOVA)	-1 Small sample sizes form multiple centres, heterogenous outcome reporting								+ Ansari, Tubbs (18) (2010)

<18 yrs vs >18yrs	Adults and Children with FCD <2014 (13, 1)	NS OR 1.14 [0.96, 1.35]					-1 No funnel plots/trim fill Rowland, Englot (29) Zhang, Hu (33)				++ Rowland, Englot (29) (2012)
<18 yrs vs >18yrs	Adults and Children with FLE <1199 (<21, 1)	NS 43% vs 54% p=0.22 (OR[c] ~0.64)					Funnel plots: undetected Englot, Wang (30)				++ Englot, Wang (30) (2012) + Englot, Rolston (32) (2013)
Continuous	Children with TLE <1318 (17, 1)	NS t-test[u]									
<5yrs vs >5yrs Log base 10 age at surgery	Tuberous Sclerosis <375 (<31, 2)	NS OR 1.05 [0.58, 1.88]; NS OR 1.21 [0.56, 2.62] Also NS on PLS	-1 Small samples (median 7, IQR[3,25]), could not adjust Fallah, Guyatt		-1 Heterogenous definitions of seizure freedom without sensitivity analyses Zhang, Hu (33)		-1 Small samples, did not assess heterogeneity or bias Fallah, Guyatt			+1 Permutation testing was performed\to evaluate the significance of the component, and bootstrapping was used to identify significant contributors to the component. PLS accounted for latent structure of data and ordinal Engel outcomes classes. Ibrahim, Morgan (36)	+, + Zhang, Hu (33) (2013), Fallah, Guyatt (35) (2013) +++ Ibrahim, Morgan (36) (2015) +

<18 yrs vs > 18 yrs at surgery	MRI neg TLE 78 (6)	NS OR 1.09 [0.38, 3.07]	NOS scores ranged from 4 to 6 stars Wang, Zhang (44) (2016)	Not detected. Subgroup analyses for paediatric, time of occurrence, semiology and meta-regressions to explore heterogeneity were performed. Giridharan, Horn (45)			-1 Funnel plots and Egger's regression showed no bias. However, we note asymmetry in overall APOS, paediatric APOS and semiology group funnel plots in their Fig e1. Giridharan, Horn (45)				Wang, Zhang (44) (2016)
Subgroup meta-regression: mean age at surgery	TLE and ET children and adults <1983 (<17)	NS		Salanova 1992 study seems to have an outlying large point effect for age, without attempts at subgroup explanation. Harward, Chen (49)							++ Giridharan, Horn (45) 2016
Age<18 yrs	Occipital Lobe and posterior quadrant. Mixed adult and paediatric 111 (7)	OR 1.54 [1.13, 2.18]	Attempted to minimise selection bias: variables selected only if at least 80 patients across 5 studies. -1 No statistical adjustments "impossible to perform a multivariate analysis looking for interactions across variables" e.g. didn't adjust for lesions			-1 imprecise and effect sizes and CIs estimated. Krucoff, Chan (50)					+ Harward, Chen (49) 2017
Age at surgery	Repeat surgery focal DRE 1st surgery 194 (?) 2nd/last surgery 164 (?)	NS[u]									+ Krucoff, Chan (50) (2017)

	Paediatric Rasmussen's <187 (<19) Paediatric Meta Regression ? (<30) Overall TL ET But NS for hemispherectomy, tumors, MCD Paediatric ET <1259 (17)	HR 0.93[u] [0.89, 0.97] NS[m] HR 0.95[m] [0.90, 1.0] Meta regression $e^{-0.189}$ = OR[c] = 0.83 overall p<0.001 $e^{-0.093}$ = OR[c] = 0.91 TL p=0.031 $e^{-0.173}$ = OR[c] = 0.84 ET p 0.004	-2 Adjusted for the variable length of follow-up, but not lesional or other known factors. Reporting bias: 7 out of 19 studies had ≤ 5 patients				-1 suspected but "unable to measure between-study heterogeneity and publication bias due to the very limited sample size per study"		+1 meta-regression		+ Harris, Phillips (56) 2019 ++ Widjaja, Jain (60) 2020 + Englot, Breshears (37) 2013 + Shan, Fan (53) 2018

Age>= 45 yrs	Low grade gliomas in adults 1065 (6) ET non lesional children <95 (<17) Children hemispherectomy <380(13) Cavernomas adults and children >18 vs other <245 (<7)	NS[u] RR 1.12 [1.01, 1.23] NS[u] NS[u] NS 0.95 [0.38, 2.37]									+ Ansari, Maher (28) 2010 ++ Cao, Liu (43) 2016 + Shang-Guan, Wu (54) (2018)
Duration of epilepsy prior to surgery	ET, Adults, Non-lesional 131 (?, 1)	NS NS NA	-1 Small sample sizes form multiple centres, heterogenous outcome reporting -1				Funnel plots: undetected				+ Ansari, Tubbs (18) (2010) +

Mean duration	Adults and Children with FLE <1199 (<21, 1)	NS t-test	Limited information given								Englot, Wang (30) (2012) ++
Shorter epilepsy duration	TLE in Children <1318 (12, 1)	OR = 2.57 [1.21, 5.47]	NOS scores ranged from 4 to 6 stars								Englot, Rolston (32) (2013) +
Subgroup meta-regression: mean duration of epilepsy	MRI neg TLE 128 (9)	NS		Not detected. Subgroup analyses for paediatric, time of occurrence, semiology and meta-regressions to explore heterogeneity were performed. Giridharan, Horn (45)			-1 Funnel plots and Egger's regression showed no bias. However, we note asymmetry in overall APOS, paediatric APOS and semiology group funnel plots in their Fig e1. Giridharan, Horn (45)				Wang, Zhang (44) (2016) ++ Giridharan, Horn (45) 2016
Time between resections	TLE and ET children and adults <1983 (<17)	NS[u] (t-test)									+ Krucoff, Chan (50) (2017)
	Repeat surgery for focal DRE 60 (?)	NS[u] (t-test)									+ Krucoff, Chan (50) (2017)

Shorter duration of epilepsy <2 vs >2yrs 388 (3) <5 vs >5yrs 551 (4) <10 vs >10 1376 (10) <20 vs <20 346 (3)	Repeat surgery for focal DRE 188 (?) Paediatric Rasmussen's <187 (<19) Children and adults all lobes	HR 0.92[u] [0.88, 0.97] (NS likely on adjustment) RR 1.20 [1.05, 1.39] RR 1.24 [1.08, 1.42] 1.25 [1.09, 1.43] 1.33 [1.08; 1.65]	-2 Not even adjusted for the variable length of follow-up, let alone not lesional or other known factors. Reporting bias: 7 out of 19 studies had ≤ 5 patients "Moderate risk of bias" "did not justify downgrading the evidence level"	-1 3/12 studies reported no association between duration and outcome 1/12 study was in favour of longer duration			-1 suspected but "unable to measure between-study heterogeneity and publication bias due to the very limited sample size per study" Studies that only reported mean or median duration of epilepsy for patients grouped by seizure outcome were not included.		Evaluated <5 yrs vs >10yrs To investigate if a larger time gap in epilepsy duration resulted in a larger effect – not present		+ Harris, Phillips (56) 2019 + Bjellvi, Olsson (57) (2019) Except for <10 vs >10 yrs: ++ Bjellvi, Olsson

<5 vs >10 430 (4)		1.32 [1.19; 1.46]										(57) (2019)
Shorter epilepsy duration (≤ 7 years, the median value in this study)	Paediatric ET <1259 (8)	OR 1.52 [1.07, 2.14]										+ Englot, Breshears (37) 2013
More than 1 year history of seizures	Adults with low grade gliomas <2641 (23)	RR 0.82 [0.75, 0.91]										+ Shan, Fan (53) 2018
	ET nonlesional children <95 (<17)	NS[u]										+ Ansari, Maher (28) 2010
												++

	Children hemispherectomy <380 (5) Cavernomas adults and children <245 (<7)	NS[u] NS			-1 f/up 6 months						Cao, Liu (43) (2016) + Shang-Guan, Wu (54) (2018)
Duration in years	Children and Adults with low-grade epilepsy associated neuroepithelial tumour (LEAT) Duration does not interact with any other pathology	0.97 [0·96 – 0·99] NS									+++ Lamberink, Otte (62)
Postsurgical: without acute postoperative seizures (APOS) within 30days after surgery	TLE and ETE Mixed paediatric and adult. 1983 (17) Paediatric: 730 (6) TLE and ET 222 (6)	Overall OR 4.2 [2.97, 5.93] (Without APOS 73.5% seizure-free, vs with APOS 39%) Paediatric subgroup OR 5.71 [3.32, 9.8]	Subgroup analysis for overall APOS persistent in both. -1 64.8% had presurgical lesion, not adjusted Variable APOS definitions (7-30 days) but used meta-regression to explore this for under 24hrs only	Not detected Subgroup analyses for paediatric, time of occurrence, semiology and meta-regressions to explore heterogeneity were performed		-1 towards positive Seizure-freedom more	-1 Funnel plots and Egger's regression showed no bias. However, we note asymmetry in overall APOS, paediatric APOS and semiology group funnel plots in their Fig 1e.	Large effect size +1			++ *Giridharan, Horn (45)* *2016* +

Earlier onset of APOS (within 24hrs)		NS 1.87 [0.89, 3.95]				likely, but statistically not significant					*Giridharan, Horn (45)* *2016*
Postsurgical semiology different from presurgical	TLE and ET adults and children 109 (3)	NS 4.24 [0.93, 19.25]		Not detected Subgroup analyses for paediatric, time of occurrence, semiology and meta-regressions to explore heterogeneity were performed		-1 towards positive Seizure-freedom more likely, but statistically not significant	-1 Funnel plots and Egger's regression showed no bias. However, we note asymmetry in overall APOS, paediatric APOS and semiology group funnel plots in their Fig e1.				+ Giridharan, Horn (45) *2016*
epilepsia partialis continua (EPC)	Children undergoing hemispherectomies 127 (7)	NS[u]									++ Cao, Liu (43) (2016)

2. Imaging Features											
Consistently prognostic											
mesial temporal sclerosis	TLE Children and adults 4430 (61, 2)	OR 2.13 [1.57, 2.86] RR 1.17 [1.12, 1.23]	-1 †	Q=21.9, p=0.082	-1 Engel outcomes in 22 studies and other definitions in 25						++, ++ Tonini, Beghi (24) (2004), West, Nevitt (3) 2019
Abnormal MRI (lesional MRI)	Adults and children, TL and ET <13238 (<114, 4) TL lesion vs TL no lesion <4785 (<51, 2) ET lesion vs ET no lesion <3760 (<45, 2)	OR 2.27 [1.54, 3.45]; OR 2.5 [2.1, 3.0] (RR 1.4); OR 2.03 [1.67, 2.47], RR 1.28 [1.20, 1.37] OR 2.7 [2.1, 3.5]; OR 1.76 [1.34, 2.32] OR 2.9 [1.6, 5.1]; OR 2.88 [1.53, 5.43]	-1 Heterogenous SF definitions. English and Chinese studiesYin, Kang (31); Two studies favoured non-lesional epilepsy Téllez-Zenteno, Ronquillo (5) -1 †	One outlier with poor results but wide CI [24] Q=4.9, p=0.768 Q=35.6, p=0.43	-1 Engel outcomes in 22 studies and other definitions in 25 Tonini, Beghi (24); -1 short follow ups in 3 studies Yin, Kang (31). Téllez-Zenteno, Ronquillo (5) also investigated whether lesion definition by MRI or histopathology made a difference – it didn't.		Non lesional significantly more frequent in ET cases (45%) than in TL (24%)[5]; undetected Yin, Kang (31) -1 No funnel plots/trim fill Téllez-Zenteno, Ronquillo (5),				++, ++, ++, ++ Tonini, Beghi (24) (2004), Téllez-Zenteno, Ronquillo (5), Yin, Kang (31) (2013) *West, Nevitt (3) 2019* ++, ++ Téllez-Zenteno, Ronquillo (5), Yin, Kang (31) (2013) ++, + Téllez-Zenteno, Ronquillo (5), Yin, Kang (31) (2013)

	Adults and Children with FCD <2014 (14, 1) FLE, Adults and Children 627 (14, 1) TL in Children 802 (26, 1) Occipital Lobe and posterior quadrant. Mixed adult and paediatric. 132 (7) Repeat surgery for focal DRE 196 (7)	OR 1.67 [1.33, 2.16] RR 1.64, [1.32, 2.08] OR 1.27 [1.16, 1.40] OR 3.24 [2.03, 6.55] NS OR 1.9 [0.6, 5.4]	-1 No statistical adjustments "impossible to perform a multivariate analysis looking for interactions across variables" e.g. didn't adjust for lesions. Harward, Chen (49)	Liava 2014 is the only study out of 7 without a CI overlapping OR of 1. -1			Funnel plots: undetected (not shown)Rowland, Englot (29)				++ Rowland, Englot (29) (2012) ++ Englot, Wang (30) (2012) ++ Englot, Rolston (32) (2013) + Harward, Chen (49) 2017 ++ Krucoff, Chan (50) (2017)

	Paediatric 883 (10) Paediatric ET 506 (23) Children hemispherectomy <380 (8)	OR 1.85 [1.14, 2.94] NS OR^{uc*} 1.44 [0.98, 2.12] OR 4.6 [1.27, 16.62]	Sensitivity analysis performed by removing the single RCT from results. NOS	SF not clearly defined, some individual studies included Engel Classes I and II		1 wide CI	Funnel and trim and fill: difference between observed and imputed <10%				+ Widjaja, Jain (60) 2020 + Englot, Breshears (37) 2013 + Cao, Liu (43) (2016)
Number of cortical tubers <=4 vs > 4 “less tuber burden”	Tuberous Sclerosis <286 (<24, 2)	NS OR 1.12 [0.49, 2.57]; NS OR 1.01 [0.96, 1.07] also NS on PLS	-1 Small samples (median 7, IQR[3,25]), could not adjust Fallah, Guyatt		-1 Heterogenous definitions of seizure freedom without sensitivity analyses Zhang, Hu (33)		-1 No funnel plots Zhang, Hu (33) -1 Small samples, did not assess heterogeneity or			+1 Permutation testing was performed\to evaluate the significance of the component, and bootstrapping was used to	+, + Zhang, Hu (33) (2013) *Fallah, Guyatt (35) (2013)

							bias Fallah, Guyatt			identify significant contributors to the component. PLS accounted for latent structure of data and ordinal Engel outcomes classes Ibrahim, Morgan (36) (2015)	+++ * Ibrahim, Morgan (36) (2015)
^{1}H spectroscopy: magnetic spectroscopy abnormality ipsilateral to lobe of resection	TLE adults and children TLE, adults and children, normal MRI 121 (22, 1)	OR 4.9 [1.97, 12.17] NS	Fifteen centers performed chemical shift imaging and seven centers used single-voxel spectroscopy. Most studies were obtained at 1.5 T	Q=2.7 Only valuable in lesional MRI cases	-2 The EZ was mostly defined by EEG data (rather than resection)	-1 Large CI		PPV = 82% but no benchmark			+ Willmann, Wennberg (26) (2006) Probably no more valuable than conventional MRI abnormality
Vascular disorders	TL and ET Children and adults ? (3, 1)	NS OR 0.66 [0.30, 1.46]	-1 3 studies	Q=945, p=0.6	-1 Engel outcomes in 22 studies and other definitions in 25						+ Tonini, Beghi (24) (2004)

FDG-PET focal interictal hypometabolism	TLE and ET Adults 153 (46, 1) TLE Adults ? (35, 1) Adults and Children with FLE <1199 (<21,1) MRI negative TLE 127 (5, 1)	NS[u] (unweighted crude) NS[u] (unweighted crude) NS[u] (Chi-squared tests then random effects if significant) NS p=0.06 OR = 2.11 [0.95, 4.65]	-1 The analyses were complicated by significant differences in study design and often by lack of precise patient data. the tracer injection dose from 1 to 15 mCi, and the time for data acquisition after tracer injection from 5 to 60 min NOS scores 4-6 Wang, Zhang (44)				Funnel plots: undetected				+ Willmann, Wennberg (27) (2007) PET does not appear to add value in patients localized by ictal scalp EEG and MRI. + Englot, Wang (30) (2012) + Wang, Zhang (44) (2016)
Encephalomalacia	Adults and children 317 (5)	NS RR 0.78 [0.52, 1.17]	-1 †	No significant difference between outcome subgroups							+ West, Nevitt (3) 2019
Enhancement, oedema, mass effect	Low grade gliomas in adults <2641 (<23)	NS NA									+ Shan, Fan (53) 2018

SPECT: SISCOM concordance with resection area subtraction ictal and inter-ictal SPECT co-registered to MRI (SISCOM)	TL and ET 275 (11) ET subgroup 209 (11)	OR 3.28 [1.90, 5.67] OR 2.44 [1.34, 4.43]		I^2 = 16.6%, p=0.285) I^2 = 10.6%, Q = 10.06, p = 0.345			Egger's and Begg's test not significant				++ Chen and Guo (47) (2016)

3. Neurophysiological Features											
Postoperative discharges	TL and ET Children and adults 1547 (9, 2) TLE subgroup <542 (<6)	OR 0.28 [0.08, 0.95] NS Adjusted for outcomes RR 0.91 [0.68, 1.22] RR 0.81 [0.70, 0.94]	-1 Only 3 studies -1 †	Heterogenous Q=6.7, p=0.035j used random effects	-1 Engel outcomes in 22 studies and other definitions in 25						+, ++ Tonini, Beghi (24) (2004), West, Nevitt (3) 2019
Intracranial / invasive Monitoring / EEG (performed vs not performed)	TL and ET Children and adults 1547 (27, 2) ET, Adults, Non-lesional 108 (?, 1) Children and adults with FLE <1199, <21, 1) Tuberous Sclerosis 144 (7)	OR 0.37 [0.22, 0.63], RR 0.85 [0.78, 0.93] NS NS NS OR 1.6 [0.76, 3.37]	1 † -1 Small sample sizes form multiple centres, heterogenous outcome reporting -1 Limited information provided	Q=3,p=0.7	-1 Engel outcomes in 22 studies and other definitions in 25 -1 Heterogenous definitions of seizure freedom without sensitivity analyses Zhang, Hu (33)		Funnel plots: undetected Englot, Wang (30) Englot, Rolston (32) -1 No funnel plots Zhang, Hu (33)				+, ++ Tonini, Beghi (24) (2004), West, Nevitt (3) 2019 + Ansari, Tubbs (18) (2010) + Englot, Wang (30) (2012) + Zhang, Hu (33) (2013)

ECoG performed Invasive monitoring	Children with TLE 462 (13) Repeat surgery on focal DRE 210 (?) Paediatric ET 433 (20) ET nonlesional children <95 (<17)	NS OR[c] crude 1.31 [0.84, 2.04] OR = 0.4, [0.2, 0.9] NS[u] OR[uc]* 0.77 [0.50, 1.19] NS[u]									++ Englot, Rolston (32) (2013) ++ Krucoff, Chan (50) (2017) + Englot, Breshears (37) 2013 + Ansari, Maher (28) 2010
sEEG vs subdural grid	TL and ET adults and children (but not from children only studies) 1999 (31)	Overall RR = 64.7% [59.2, 69.8] / 55.9% [50.9, 60.8] = 1.16[c]	-1 average follow up for SEEG was 10 months while for SDG it was	Overall SEEG: I^2 = 11.86%; p = 0.318 subdural grid: I^2 = 54.47%; p = 0.002	-1 studies <6 months follow-up durations; we are interested in		Funnel plots, Egger's tests: no overall changes or subgroup changes				+ Toth, Papp (59) 2019

	Nonlesional 237 (15) Lesional 665 (21) TL 470 (17) ET 420 (14) all	Nonlesional NS RR = 52% [37.3, 66.3] / 54.4% [40.6, 67.6] = 0.96 Lesional RR = 71.6% [61.6, 79.9] / 57.3% [48.7, 65.6] = 1.25 TL RR = 73.9% [64.4, 81.6] / 56.7% [51.5, 61.9] = 1.30 ET RR = (61% [51, 70.2]) / (46.7%[36.5, 57.2]) = 1.31 OR[cu] 0.65 [0.45, 0.95] p=0.025[cu] It is likely adjusted p value in the text is p = 0.0565 Therefore NS	nearly 19months. Significant differences overall (p = 0.02), lesional (p = 0.031), and also, temporal sugroups (p = 0.002) See individual paper Remick et al for GRADE scores for this feature		at least 12 months						+ [63] 2020

Intraoperative ECoG	Children and adults with FLE 1024, <21, 1)	NS p=0.14 Pooled ind particicpant OR[c] 1.23 [0.95, 1.62]					Funnel plots: undetected (not shown)				+++ Englot, Wang (30) (2012)
Interictal spikes	TL and ET Children and adults ? (3, 1)	NS OR 1.82 [0.86, 3.88]	-1 Only 3 studies			-1 Skewed					+ Tonini, Beghi (24) (2004)
Lateralised/ unilateral interictal EEG	Children and adults with FLE <1199, <21, 1) Tuberous Sclerosis 127 (6)	NS OR 2.42 [1.11, 5.27]	-1 limited information provided Englot, Wang (30)	I^2=0% Zhang, Hu (33) (2013)	-1 Heterogenous definitions of seizure freedom without sensitivity analyses Zhang, Hu (33) (2013)		Funnel plots: undetected Englot, Wang (30) -1 No funnel plots Zhang, Hu (33) (2013)				+ Englot, Wang (30) (2012) + Zhang, Hu (33) (2013)
Unilateral interictal spikes vs bilateral	Adults and children 1414 (18)	RR 1.14 [1.05, 1.24],	-1 CI adjusted for various outcome scale Definition was likely to have influenced the analysis, e.g. non-lateralising vs contralateral spikes, focal vs non-focal spikes †	-1 I^2 = 67% overall and mixed effects using only Engel outcomes is non-significant: RR [0.88, 2]. Subgroup analyses (TLE vs ET) do not explain these differences.		-1 small studies with imprecise results. Mixed-effects model RR has no statistical significance.			In best case scenario of pooled effect rather than mixed-effects, the point estimation is 14% better. E.g. if bilateral 60% SF, unilateral spokes, 70% SF. This variable only explains one-third of the missing outcome variance, with		+ West, Nevitt (3) 2019

	Paediatric ET 130 (10) Adults and children hemispherectomy 413 (7)	NS OR[uc]* 2.22 [0.98, 5.05] OR 1.66, [1.03, 2.67]							NNT around 10.		+ Englot, Breshears (37) 2013 ++ Hu, Zhang (46) 2016
Unifocal interictal scalp EEG abnormality (or no interictal abnormality) Interictal EEG localised to temporal lobe	Tuberous Sclerosis 90% <19yrs <181 (<20,1) MRI neg TLE 149 (7)	NS OR 1.54 [0.73, 3.26] Also NS on PLS OR 3.38 [1.57, 7.25]	-1 unusual feature dichotomization -1 Small samples (median 7, IQR[3,25]), could not adjust Fallah, Guyatt NOS 4-6		- 1 large CI Wang, Zhang (44)	-1 Skewed bootstrapping CI suggestive of possible positive effect Ibrahim, Morgan (36)	-1 Small samples, did not assess heterogeneity or bias Fallah, Guyatt			+1 Permutation testing was performed\to evaluate the significance of the component, and bootstrapping was used to identify significant contributors to the component. PLS accounted for latent structure of data and ordinal Engel outcomes classes	+ *Fallah, Guyatt (35) (2013) ++ *Ibrahim, Morgan (36) (2015) * = same data different methods +

											Wang, Zhang (44) (2016)
Focal ictal/interictal/invasive EEG	Repeat resective surgery for focal DRE 192 (8)	OR = 3.6, [1.6, 8.2]									++ Krucoff, Chan (50) (2017)
Unilateral vs bilateral ictal EEG (Lateralized ictal EEG)	Adults and Children with FCD <2014 (10, 1) Tuberous Sclerosis 159 (8) Adults and children hemispherectomy 414 (7)	NS OR 1.03 [0.82, 1.31] OR 2.48 [1.17, 5.24] ictal: OR 1.88, [1.15, 3.07], p = 0.01		I^2=0% Zhang, Hu (33)	-1 Heterogenous definitions of seizure freedom without sensitivity analyses Zhang, Hu (33)		-1 No funnel plots/trim fill Rowland, Englot (29) Zhang, Hu (33)				++ Rowland, Englot (29) (2012) + Zhang, Hu (33) (2013) ++ Hu, Zhang (46) 2016

Localized/unifocal ictal (scalp) EEG	Children and adults with FLE <1199, <21, 1) Children with TLE 445 (14, 1) Tuberous Sclerosis; at least 90% less than 19 years old <186 (<20)	NS[u] NS[u] crude OR[c] 1.23 [0.73, 2.06] OR = 3.21, [1.35–7.58] Positive prognostic value (PLS)	-1 limited information provided -1 Small samples (median 7, IQR[3,25]), could not adjust Fallah, Guyatt (15)				Funnel plots: undetected -1 Small samples, did not assess heterogeneity or bias Fallah, Guyatt (15)			+1 Permutation testing was performed\to evaluate the significance of the component, and bootstrapping was used to identify significant contributors to the component. PLS accounted for latent structure of data and ordinal Engel outcomes classes Ibrahim, Morgan (36)	+ Englot, Wang (30) (2012) ++ Englot, Rolston (32) (2013) + *Fallah, Guyatt (35) (2013) +++ *Ibrahim, Morgan (36) (2015) * = same data, different methods
Ictal EEG localized to temporal lobe	MRI neg TLE 125 (6) Paediatric ET 226 (13)	OR = 3.89 [1.66, 9.08] OR 1.55 [1.24, 1.93]	NOS 4-6		- 1 large CI Wang, Zhang (44)						+ Wang, Zhang (44) (2016) + Englot, Breshears (37) 2013

Video-Telemetry (VT)	Children and adults with FLE <1199, <21, 1)	NS (chi-squared tests then random effects if significant)	-1 limited information provided				Funnel plots: undetected				+ Englot, Wang (30) (2012)
(Long Term Monitoring, LTM)	TLE, ETE, lesoinal and nonlesional, (assumed adults and children as not explicitly mentioned) (534, 44)		A high risk of bias was observed in a considerable proportion of included studies; the quality of evidence was assigned as "very low"								+ Very low Kobulashvili, Kuchukhidze (55) (2018)
	Lesional TLE	OR 1.41 [0.79, 2.53]	Note the trend wotwards LTM predicting seizure free outcomes in lesional TLE only, which is a confounder of good outcomes in lesional TLE.								
	Lesional ETE	OR 0.46 [0.2, 1.07]									
	Nonlesional TLE	OR 0.6 [0.01, 35.86]									
	Nonlesional ETE	1 [0.06, 17.51]									

4. Multimodal Concordance											
EEG/MRI Concordance	TL and ET Children and adults 1778 (29, 2)	OR 2.36 [1.07, 5.26] RR 1.25 [1.15, 1.37]	-1 †	Heterogenous Q=11.4, p=0.044 used random effects	-1 Engel outcomes in 22 studies and other definitions in 25					+1 Permutation testing was performed\to evaluate the significance of the component, and bootstrapping was used to identify significant contributors to the component. PLS accounted for latent structure of data and ordinal Engel outcomes classes. Ibrahim, Morgan (36)	+, ++ Tonini, Beghi (24) (2004), West, Nevitt (3) 2019
	Tuberous Sclerosis; at least 90% less than 19 years old <186 (<20, 2)	OR = 4.9, [1.8–13.5] Positive prognostic value (PLS)	-1 Small samples (median 7, IQR[3,25]), could not adjust Fallah, Guyatt			-1 Wide CI Fallah, Guyatt (35)	-1 Small samples, did not assess heterogeneity or bias Fallah, Guyatt undetectedIbrahim, Morgan (36) (2015)	+1 OR>4			++ *Fallah, Guyatt (35) (2013) +++ *Ibrahim, Morgan (36) (2015) * = same data, different methods
Concordance same side	Children and adults hemispherectomy 332 (6)	OR 2.17 [1.30, 3.7]									++ Hu, Zhang (46) 2016

5. Genetics											

6. Surgical Features											
Extensive surgical resection	TL and ET Children and adults <3511 (10, 1)	OR 4.27 [2.06, 8.85]	Result remained significant on multiple sensitivity analyses	Q=26.9,p=0.001 used random effects	-1 Engel outcomes in 22 studies and other definitions in 25	-1 CI approaches OR of 1 Zhang, Hu (33)	Funnel plots: undetected Englot, Wang (30) Josephson, Dykeman (34)	summary risk difference 8 [3%–14%] translates to NNT of 13 [7, 33] for 1 additional patient to achieve an Engel Class I outcome following ATL Josephson, Dykeman (34)			++ Tonini, Beghi (24) (2004)
Extensive frontal +/- extra-frontal vs more localised frontal resections	FLE, adults and children 651 (11, 1)	RR 0.58 [0.41, 0.79]									++ Englot, Wang (30) (2012)
Lobectomy (extensive) vs tuberectomy (focal)	tuberous sclerosis 189 (10, 1)	OR 1.96 [1.01, 3.7]		I^2=0% as few numbers Zhang, Hu (33)	-1 Heterogenous definitions of seizure freedom without sensitivity analyses Zhang, Hu (33)		-1 No funnel plots Zhang, Hu (33)				+ Zhang, Hu (33) (2013)
ATL (extensive) vs SAH (selective)	TLE children and adults 1203 (11, 1)	RR 1.32 [1.12, 1.57] (also quoted a separate random effects figure to the above fixed effects)		I^2= 29%; df =10, p=0.17 Josephson, Dykeman (34)							+++ Josephson, Dykeman (34) (2013)
	TLE and HS subgroup children and adults 1092 (10, 1)	RR 1.26 [1.05, 1.51]		I^2=0% Josephson, Dykeman (34)	children and adults – but also excluded paediatric only study and results were very similar Josephson, Dykeman (34)						
ATL vs SAH (mix of transcortical, transsylvian and subtemporal approaches)	Mainly adults ? (19)	NS OR 1.14, 95% CI 0.93 to 1.39; p=0.201									++ Jain, Tomlinson (52) 2018

ATL vs SAH	TLE 626 (6)	NS RR 1.01 [0.54, 1.09]					-1 Mild bias on funnel plot, did not further investigate or use trim and fill				+++ Kuang, Yang (38) (2013)
	SAH vs ATL in TLE 1397 (13)	Overall OR 0.65 [0.51, 0.82]									++ Hu, Zhang (40) (2013)
Lesionectomy / multilobar resection surgery type <186 (<20)	Tuberous sclerosis children	NS on PLS							+1 Permutation testing was performed\to evaluate the significance of the component, and bootstrapping was used to identify significant contributors to the component. PLS accounted for latent structure of data and ordinal Engel outcomes classes. Ibrahim, Morgan (36)		+++ Ibrahim, Morgan (36) (2015)
Hemispherectomy (vs resective)	Rasmussen's Paediatric <187 (<19)	HR 0.28[u] [0.18, 0.45] HR 0.30[m] [0.18, 0.49]	-2 Adjusted for the variable length of follow-up, but not lesional or other known factors. Reporting bias: 7 out of 19 studies had ≤ 5 patients				-1 suspected but "unable to measure between-study heterogeneity and publication bias due to the very limited sample size per study"v			Remained significant on multivariate analysis but it seems only adjusted for length of follow up	+ Harris, Phillips (56) 2019

3.5cm (extensive) vs 2.5cm (limited) ATL resection	TLE Adults >18yrs 207 (4)	NS RR 0.98 [0.83, 1.16]	†			-1 Despite the CI overlap, point estimates favour SAH, whether at 1 or 5 yrs or Engel I or IA.					+ West, Nevitt (3) 2019
Extended lesionectomy vs limited lesionectomy confined to cavernoma and hemosiderin	Cavernomas in adults and children 245 (7)	NS OR 0.96 [0.44, 2.08]	Removed 1 article with bias		-1 f/up 6 months						+ Shang-Guan, Wu (54) (2018)

Extensive resection of surrounding haemosiderin vs no excision of haemosiderin in cavernomas	Mainly Adults with cavernomas (but also few children)	OR 1.61 [1.10, 2.38]									+ Ruan, Yu (42) 2015
											++ West, Nevitt (3) 2019
Temporal Lobe (vs ET) resections Lobe of resection TL vs ET	Adults and Children with FCD <2384 (32, 2) Tuberous Slceorisis in children <186 (<20, 1) Repeat surgery in focal DRE 943 (12)	OR 1.35 [1.13, 1.61] OR 1.92 [1.06, 3.45] NS on PLS method NS OR=1.5 [0.8, 3.0]	Trial sequence analysis, sensitivity analyses including removing individual studies.Subgroup analyses for geographical locations. Chen, Chen (58) (2019) No clear trend in 1st and 2nd resection subgroups		-1 Engel II was considered seizure free Chen, Chen (58) (2019)		-1 No funnel plots/trim fill etc Rowland, Englot (29) Begg rank correlation test and Egger linear regression test with trim and fill Chen, Chen (58)			+1 Permutation testing was performed\to evaluate the significance of the component, and bootstrapping was used to identify significant contributors to the component. PLS accounted for latent structure of data and ordinal Engel outcomes	++, + Rowland, Englot (29) (2012), Chen, Chen (58) (2019) +++ Ibrahim, Morgan (36) (2015) ++ Krucoff, Chan (50) (2017)

											classes. Ibrahim, Morgan (36)	
TL vs ET	Paediatrics ? (~23)	OR 2 [1.4, 2.9] direct and ~NMA p=0.025										+ Widjaja, Jain (60) 2020
		NS										
ET vs hemispherectomy	Paediatrics ? (~23)											+ Widjaja, Jain (60) 2020
		NS[u]										
surgical lobe	Paediatric ET (frontal, parietal, Rolandic, occipital, multilobed) 537 (26)	See their table 1										+ Englot, Breshears (37) 2013
	Low grade gliomas in adults TL vs ET <2641 (<23)	NS NA										+ Shan, Fan (53) 2018

	Type of surgery (frontal, posterior and other) in ET non lesional children <95 (<17)	NS									+ Ansari, Maher (28) 2010
Lobe of surgery TL reference had the highest compared to all other lobes, all significant (multilobar, parietal, occipital, frontal, hypothalamus) >1000	Children and adults	Significant but no effect size given									+++ Lamberink, Otte (62)
Mesial vs lateral TL epileptic focus (as determined on sEEG, subdural grid; or ATL/SAH vs neocortectomy)	MRI neg TLE 92 (8)	NS OR 1.39 [0.61, 3.2]	NOS scores ranged from 4 to 6 stars								+ Wang, Zhang (44) (2016)
Complete excision (of lesion)	Adults and Children with FCD <2581 (31, 2) Adults and Children with FLE 345 (7, 1)	OR 3.91 [3.03, 5.32] OR 12.5 [7.14, 20] RR 1.99, [1.47, 2.84]	Trial sequence analysis, sensitivity analyses removing individual studies.Subgroup analyses for geographical locations. Chen, Chen (58)		-1 Engel II was considered seizure free Chen, Chen (58)		-1 No funnel plots/trim fill Rowland, Englot (29) Begg rank correlation test and Egger linear regression test with trim and fill as necessary Chen, Chen (58)	+2 large OR<0.1 or OR >10			++, +++ Rowland, Englot (29) (2012), Chen, Chen (58) (2019)

Gross total resection vs subtotal resection	Repeat resective surgery for focal DRE 273 (11)	OR = 2.6, [1.3, 5.3]	-1 heterogenous categorisations				Funnel plots: undetected	+1 large OR >4			++ Englot, Wang (30) (2012)
	Adults and children 2930 (39)	RR 1.41 [1.32, 1.50]	-1 †	-1 I^2 77.76% with p <0.0001; outcome subgroup differences also significant I^2 89.51% p<0.0001although the direction of effects are similar. Extratemporal subgroup ommited as only 1 study.							+ Krucoff, Chan (50) (2017)
	Adults and children TL subgroup 1266 (13)	TL RR 1.11 [1.03, 1.2]									+ West, Nevitt (3) 2019
	Paediatrics 893 (15)	OR 7.69 [4.76, 12.5]		consistent							++ *Widjaja, Jain (60) 2020*
	Low grade gliomas in adults 1379 (16)	RR 1.47 [1.37, 1.59]									+ Shan, Fan (53) 2018

Side of resection (left vs right)	TL and ET Children and adults 2976 (41, 2) TLE adults ? (35) ET, Adults, Non-lesional 131 (?, 1) Adults and children with FLE <1199 (<21, 1) Children with TLE 537 (15, 1) MRI neg TLE 320 (15)	NS OR 0.85 [0.54, 1.34], NS RR 1.04 [0.99, 1.1] NS Unweighted crude OR 0.57 [0.26, 1.24] NS NS NA NS[u] OR[c] crude 1.07 [0.72, 1.60] NS, slightly favours Left TL, OR 1.33 [0.84, 2.08]	-1 † -1 Small sample sizes form multiple centres, heterogenous outcome reporting -1 Limited info NOS 4-6 stars Wang, Zhang (44) (2016)		-1 Engel outcomes in 22 studies and other definitions in 25		undetected				+, ++ Tonini, Beghi (24) (2004), West, Nevitt (3) 2019 ++ Willmann, Wennberg (27) (2007) + Ansari, Tubbs (18) (2010) + Englot, Wang (30) (2012) ++ Englot, Rolston (32) (2013) + Wang, Zhang (44) (2016)

Side of resection L v R	Repeat surgery for focal DRE 1st surgery 218 (?) 2nd/last surgery 209 (?) Paediatric ET 326 (15) Children and adults hemispherectomy 539 (29) ET non lesional children <95 (<17)	NS[u] Surgery #1 OR[c*] 0.73 [0.43, 1.25] NS[u] Surgery #2 OR[c*] 0.77 [0.44, 1.33] NS OR[uc*] 0.99 [0.64, 1.53] NS OR 1.17, [0.79, 1.73], p = 0.43 NS[u]				-1 imprecise and effect sizes and CIs estimated. Krucoff, Chan (50)					+ Krucoff, Chan (50) (2017) + Englot, Breshears (37) 2013 ++ Hu, Zhang (46) 2016 + Ansari, Maher (28) 2010

Frontal, central, posterior vs other resections	ET, Adults, Non-lesional 81 (?, 1)	NS	-1 Small sample sizes form multiple centres, heterogenous outcome reporting								+ Ansari, Tubbs (18) (2010)
Geographical location of surgery N America vs elsewhere	Tuberous Sclerosis in children <186 (<20, 1)	NS on PLS								+1 Permutation testing was performed\to evaluate the significance of the component, and bootstrapping was used to identify significant contributors to the component. PLS accounted for latent structure of data and ordinal Engel outcomes classes	+++ Ibrahim, Morgan (36) (2015)
Year of surgery >1000	Children and adults	NS									+++ Lamberink, Otte (62)

7. Pathology											
Presence of Tumours low-grade epilepsy associated neuroepithelial tumour (LEAT) majority were gangliogliomas and DNET Ganglioglioma 672 DNET 484	TL and ET Children and adults 3357 (54, 2) Children and adults 1325 (<37)	OR 1.74 [1.25, 2.5] RR 1.23 [1.14, 1.32] 77·5% (SF) No OR as used as baseline 80·4% 74·8%	-1 †	Q=19.3, p=0.08	-1 Engel outcomes in 22 studies and other definitions in 25						++ Tonini, Beghi (24) (2004) ++ West, Nevitt (3) 2019 +++ Lamberink, Otte (62)
FCD Type II vs other FCD (Palmini Classification) FCD type 2 vs type 1 Palmini FCD type IIb in network meta-analyses of subtypes (NMA)	Adults and Children with FCD <2014 (17, 1) Children and adults FCD 1580 (34) Adults and children with FCD	OR 1.38 [1.22, 1.57] OR 1.92 [1.54, 2.44] OR 1.89 [1.01, 3.57]	Trial sequence analysis, sensitivity analyses including removing individual studies Subgroup analyses for geographical locations. Chen, Chen (58)	I^2=14%, p=0.24 Not in subgroup analyses in asia (OR=1.24 []0.75, 2.04] Chen, Chen (58)	-1 Engel II was considered seizure free Chen, Chen (58)	-1 CI of OR approached 1	-1 No funnel plots/trim fill Rowland, Englot (29) Begg rank correlation test and Egger linear regression test with trim and fill as necessary Chen, Chen (58)				++ Rowland, Englot (29) (2012) ++ Chen, Chen (58) (2019) + Chen, Chen (58) (2019)

"lesional": tumours, CD, or other lesion (tuber, vascular malformation) i.e. positive pathology vs "non-lesional": traumatic, infectious (Englot, Rolston (32) included HS in non-lesional)	FLE Mixed Adults and Children 825 (16, 1)	RR 1.67, [1.36, 28.6]				1 Wide CI	Funnel plots: undetected (not shown in Englot, Wang (30)) Harward, Chen (49)				+ Englot, Wang (30) (2012) + Englot, Rolston (32)
	TL in Children 945 (29, 1)	OR 1.08, [1.02, 1.15]									++ Krucoff, Chan (50) (2017)
	Repeat resective surgery for focal DRE 507 (12)	OR = 3.2, [1.9, 5.3]									
Focal pathological lesion	MRI neg TLE 167 (7)	NS (p=0.36) OR=1.36 [0.7, 2.63]	NOS 4-6 stars Wang, Zhang (44)								+ Wang, Zhang (44) (2016)
	Occipital Lobe and posterior quadrant. Mixed adult and paediatric 167 (9)	OR 2.08 [1.58, 2.89]	-1 No statistical adjustments "impossible to perform a multivariate analysis looking for interactions across variables" e.g. didn't adjust for lesions. Harward, Chen (49)								+ Harward, Chen (49) 2017

	Paediatric ET 695 (28)	OR 1.34, [1.19, 1.49									++ Englot, Breshears (37) 2013
Neuro-migrational defects	TL and ET Children and adults ? (6, 1)	NS OR 0.66 [0.42, 1.03]		Q=9.8, p=0.08	-1 Engel outcomes in 22 studies and other definitions in 25						+ Tonini, Beghi (24) (2004)
FCD vs gliosis	ET, Adults, Non-lesional 115 (?, 1)	NS	-1 Small sample sizes form multiple centres, heterogenous outcome reporting								+ Ansari, Tubbs (18) (2010)
Presence of FCD (vs absence)	Adults and children TLE and ET 3572 (46)	RR 0.90 [0.85, 0.95]	-1 †								++ West, Nevitt (3) 2019
Vascular malformation	Adults and Children 1488 (19)	NS pooled RR 1.07 [0.94, 1.21] adj for outcomes scale	- 1 † Cavernomas not evaluated separately so uncertain of significance	No broad changes to result according to outcomes scales (Engel, Other or seizure freedom for 1 yr).	I^2= 0% for both overall heterogeneity and subgroup differences						++ West, Nevitt (3) 2019 ++

Vascular malformation (cavernomas and others) vs low grade neuroepithelial Cavernomas Others	Children and Adults 443 (<37) 323 120	NS 74·0% OR 0.79 [0·60 - 1·06] 77·1% 65·8%			Indirect evidence that vascular malformations are as prognostic as LEATs						Lamberink, Otte (62)
Tumour, HS > Rasmussen > MCD, TS > HH	Proportions only				-1 SF not clearly defined, some individual studies included Engel Classes I and II		Funnel plots and trim and fill test to impute bias effect estimates: difference between observed and imputed <10% higher quality was associated with reduced SF percentages - although not statistically significant, the magnitude of effect was significant (-0.31				+ *Widjaja, Jain (60)* *2020*
Astro vs non astrocytoma	Low grade gliomas in adults <2641 (<23)	NS NA									+ Shan, Fan (53) 2018
hippocampal sclerosis 2948 vs Low grade neuroepithelial tumours	Children and adults 2948 (<37)	71·5% OR 0.79 [0·65 - 0·89]									+++ Lamberink, Otte (62)

FCD type I or MCD Vs LEAT 426	Children and adults	Negative 50·0% OR 0.38 [0·28 - 0·49]									+++ Lamberink, Otte (62)
Other MCD (Hypothalamic hamartomas, tubers and others) 405	Children and adults	Negative 52·3% OR 0.44 [0·29 - 0·63]									++ Lamberink, Otte (62)
No histopathological lesion (comprised of gliosis and normal tissue) 740	Children and adults	Negative 53·5% OR 0.36 [0·30 - 0·46]									+++ Lamberink, Otte (62)
FCD type II 796	Children and adults	64·9% NS OR 0.8 [0·61 - 1·09]			Indirectly supports type II as + prognostic feature, as not significantly worse than LEAT						++ Lamberink, Otte (62)
Encephalitis (Rasmussen's and limbic, herpes, neurocysticercosis) 124 Encephalitis - Rasmussen's subgroup 72	Children and adults	59·7% OR 0.43 [0·22 - 0·73] 72·2%									++ Lamberink, Otte (62)

Glial scar 261	Children and adults	59·4% OR 0.53 [0·39 - 0·70]									+++ Lamberink, Otte (62)
Non-LEAT (astrocytoma, oligodendroglioma, cysts, ependymoma, meningioma, neurocytoma, and pleomorphic xanthoastrocytoma) 310	Children and adults	68·4% NS OR 0.75 [0·54 - 1·02]									++ Lamberink, Otte (62)

[1]**Study limitations (risk of bias or internal validity):** Differential surveillance for outcome between studies, failure of accurate measurement of all known prognostic factors and to match for prognostic factors and/or lack of adjustment in statistical analysis. Includes selective reporting bias. [12 14]

[2]**Inconsistency of results:** If some studies suggest substantial prognostic value using relative measures while others suggest no effect or negative prognostic value then it may be appropriate to rate down for quality. Criteria for evaluating consistency include similarity of point estimates, extent of overlap of confidence intervals, and statistical criteria including tests of heterogeneity and I^2. If inconsistent results cannot be explained by differences in subgroups (populations undergoing surgery, surgical intervention, or outcome definitions and follow-up), then the quality of the body of evidence is rated down. [15]

[3]**Indirectness of evidence:** If there are differences in the populations, interventions and/or outcomes being studied compared to what we are interested in, or if interventions are compared without direct head-to-head comparisons, studies can be rated down [16]. We only rate down if there is a compelling reason to believe the populations studied differ from the population of interest that the magnitude of effect would differ significantly e.g. because of the presumed differences in the maturing brain, paediatric and adult epilepsy surgery populations should be investigated separately or as subgroups to avoid reduced population applicability. We also rate down if there is an outcomes discrepancy, whereby the seizure-freedom duration of follow-up is less than that of interest (at least 12months) e.g. in the inclusion criteria. We consider ILAE 1 and 2 seizure free, which is equivalent to Engel Ia/Ib and thus also rate down inclusion criteria that include undifferentiated Engel I.

[4]**Imprecision:** e.g. for a single meta-analysis, effect sizes which overlap the neutral point (for RR and OR, 1) suggesting the feature is not prognostic, but the boundaries of the confidence interval are skewed significantly in one direction such that the largest plausible effect is that the feature is either positively or negatively correlated with outcomes. [11]

[5]**Publication bias:** clinical features that are non-prognostic and smaller effect sizes are less likely to be published and these can be assessed by funnel plots. Cumulative iterative meta-analyses could be indirectly inferred from the publication dates to ascertain time-lag bias. Risk of publication bias is probably larger for small, observational, and industry-funded studies. [14]

[6]**Rating up:** relative risks above 2 (below 0.5) are rated up one level, and above 5 (below 0.2) are rate up two levels unless the CI overlaps significantly with these thresholds. If the baseline proportion of outcomes is low, odds ratios are treated similarly, otherwise a higher threshold is used. Studies were also rated up if a dose response was present or if all plausible residual confounders or biases would reduce a demonstrated effect, or suggest a spurious effect when results show no effect [17]

TL(E): Temporal Lobe (Epilepsy). ETE: Extratemporal lobe Epilepsy. APOS: Acute Postoperative Seizures. NS: Not Significant. CI: confidence aura. HS: Hippocampal Sclerosis. MCD: Malformations of Cortical Development. FCD: Focal Cortical Dysplasia. HH: Hypothalamic Hamartoma. TS: Tuberous Sclerosis. OR: Odds Ratio. RR: Relative Risk Ratio. SF: Seizure Freedom. NMA: Network Meta-Analysis. ATL: Anterior Temporal Lobectomy. SAH: Selective Amygdalohippocampectomy. NA: Not Available. HS: Hippocampal Sclerosis. ECoG: Electrocorticography. PLS: partial least squares. NOS: Newcastle-Ottawa Scale.

*: Our calculated CI from their data. [c]: Effect size derived from article data. [u]: Univariate analyses. [m]: Multivariate analyses. †A weakness of the Cochrane review is that they "did not class any of the pre-operative prognostic factors of interest…as confounders" so in general our GRADE score is one lower.

2.3 Supplementary Table 3: Essential Prognostic Features for Epilepsy Surgery (EPF)

EPF		Prognostic Value and Supporting Evidence Base						
Feature	**Population(s) or Subgroup(s)**	**Range of Effect Sizes for Seizure-Freedom**	**Comments**	**Units of Analysis (Individual Patients*)**	**Individual Studies***	**Meta-Analytical References**	**Publication Year of meta-analysis (first, last)**	**GRADE score**
1. Clinical Features								
***Severe* developmental delay/learning disability and IQ ≤75**	≥16 yrs TLE ≥16 yrs TLE non-HS structural lesions Children TS Children and Adults with hemispherectomy	RR 0.66 [0.54, 0.94] RR 0.26 [0.14, 0.50] OR 0.14 [0.04, 0.48] OR 0.61 [0.46, 0.82]	Five meta-analyses evaluated developmental delay and learning disability as a negative prognostic factor, three of which were significant,[20, 35, 46] while two others were not significant for "*moderate* to severe developmental delay" in paediatric Rasmussen's,[56] *undifferentiated* "mental retardation" in tuberous sclerosis[33] or *continuous* pre-operative IQ scores.[35] The presence of moderate developmental delay in the dichotomised category and continuous IQ scores (on average only 2.3 lower in not seizure-free group, p<0.009)[20] may have masked the subgroup significance for IQ<75.	2256	54	Chelune, Naugle (20) 1998 Fallah, Guyatt (35) 2013 Hu, Zhang (46) 2016	1998 – 2019	++ Low Favours absence of severe learning disability
Febrile Convulsions (FC)	TL and ET in both Children and Adults	OR 2.08 [1.2, 3.7] RR 1.09 [1.01, 1.17]	>1 yr SF subgroup had good outcomes with febrile seizures but the other subgroups did not (subgroup I^2 = 49%, p 0.14).[3] Non-Engel outcomes in more than half of individual studies.[24] It is expected for FC to be favourable in TLE and unfavourable in ET.	4879	20	Tonini, Beghi (24) 2004, West, Nevitt (3) 2019	2004 – 2019	+ Very Low Favours presence of FC

Postsurgical: **Without Acute Postoperative Seizures (APOS) within 30 days**	Children and Adults, TLE and ET Paediatric subgroup	Overall OR 4.2 [2.97, 5.93] OR 5.71 [3.32, 9.8]	There was a rather large effect: without APOS 73.5% seizure-free, vs with APOS 39%. Results of subgroup analyses were similar. A metaregression showed earlier onset of APOS within 24hrs was NS 1.87 [0.89, 3.95]. Note however, like most meta-analyses, although over 64% had presurgical lesions, no adjustment was made. Although they reported no significant bias, we note asymmetry in overall and paediatric APOS funnel plots (their Fig 1e). The clinical significance of the absence APOS is questionable, as it is both postsurgical, and it is logically expected that seizure-free patients would be a subset of those without APOS.	1983	17	Giridharan, Horn (45) 2016	2016	++ Low Favours absence of APOS
2. Imaging Features								
Mesial Temporal Sclerosis (MTS) or Hippocampal Sclerosis (HS)	Adults and Children with TLE	OR 2.13 [1.57, 2.86] RR 1.17 [1.12, 1.23]	12 out of 15 individual studies from Tonini, Beghi (24) had point estimates favouring HS; 5 of the 15 were prospective and a further sixth study was combined retrospective and prospective in design. Amongst those with MTS, 74% were seizure free, compared to 62% of those without MTS. This included patients with MTS on imaging or pathology.[3]	4430	61	Tonini, Beghi (24) 2004 West, Nevitt (3) 2019	2004 – 2019	++ Low Favours presence of HS
Abnormal or Lesional MRI	Adults and Children with TLE and ET TL subgroups ET subgroups Adults and Children with FCD Adults and Children with FLE	OR 2.27 [1.54, 3.45] OR 2.5 [2.1, 3.0] OR 2.03 [1.67, 2.47] RR 1.28 [1.20, 1.37] OR 2.7 [2.1, 3.5] OR 1.76 [1.34, 2.32] OR 2.9 [1.6, 5.1] OR 2.88 [1.53, 5.43] OR 1.67 [1.33, 2.16] RR 1.64 [1.32, 2.08]	An odds ratio of 2.5 for abnormal MRI in a meta-analysis from 2010 of any population translates to a relative risk of RR 1.4,[5] which is comparable to the RR effect size of 1.28 from the 2019 Cochrane review and a RR of 1.64 in patients with FLE.[3, 30] Non lesional cases were significantly more frequent in ET (45%) than in TL (24%),[5] however, when funnel plots and trim and fill were performed, either no publication bias was observed,[29, 31] or the difference between observed and imputed results varied by under 10% (for the paediatric population).[60]	18076	193	Tonini, Beghi (24) 2004 Téllez-Zenteno, Ronquillo (5) 2010 Yin, Kang (31) 2013 West, Nevitt (3) 2019	2004 – 2020	++ Low Favours abnormal MRI, see comments on two borderline meta-analyses.

	Children with TLE Adults and Children with Occipital Lobe and Posterior Quadrant Epilepsy Children Children with hemispherectomy	OR 1.27 [1.16, 1.40] OR 3.24 [2.03, 6.55] OR 1.85 [1.14, 2.94] OR 4.6 [1.27, 16.62]	The only groups for which meta-analyses seemed to be non-significant were in 196 patients with repeat surgery from 7 studies done in 2017, and 506 children with extratemporal resections from 23 studies performed in 2013. Yet in both of these, the effect sizes and skewed confidence intervals still favoured abnormal MRI with odds ratios of 1.9 [0.6, 5.4] and an unweighted OR of 1.44 respectively.[37, 50]			Rowland, Englot (29) 2012 Englot, Wang (30) 2012 Englot, Rolston (32) 2013 Harward, Chen (49) 2017 Widjaja, Jain (60) 2020 Cao, Liu (43) 2016		
SPECT: Subtraction Ictal and Inter-ictal SPECT co-registered to MRI (SISCOM)	TL and ET 275 (11) ET subgroup 209 (11)	OR 3.28 [1.90, 5.67] OR 2.44 [1.34, 4.43]	Odds ratios were favourable for SISCOM abnormalities, for both TL and ET patients across 11 studies. Overall heterogeneity was non-significant (I2 = 16.6%, p=0.29)	275	11	Chen and Guo (47) 2016	2016	++ Low Favours SPECT-SISCOM abnormality
3. Neurophysiological Features								
Focal Ictal or Interictal or Invasive EEG Interictal EEG localised to temporal lobe Localised/unifocal ictal (scalp) EEG	Repeat resective surgery for focal DRE (n=192) MRI neg TLE (n=149)[44] Tuberous Sclerosis in Children MRI neg TLE (n=125)[44]	OR 3.6 [1.6, 8.2] OR 3.38 [1.57, 7.25] OR 3.21 [1.35, 7.58] Positive prognostic value on PLS also. OR 3.89 [1.66, 9.08]	Favours focal EEG changes at any point and via any method with comparable odds ratios between 3 and 4 (lower in paediatric extratemporal epilepsy, OR<1.93). The two earliest meta-analyses from 2012 and 2013 – in children and adults with FLE, and children with TLE – did not find unifocal ictal scalp EEG to be significant for seizure-freedom.[30, 32] The former's GRADE score was "very low" while the latter's was "low" with 445 participants across 14 studies and OR[c] 1.23 [0.73, 2.06]. These discrepancies bring the overall quality of evidence down to very weak.	878	54	Krucoff, Chan (50) 2017 Wang, Zhang (44) 2016 Fallah, Guyatt (35) 2013 Ibrahim, Morgan (36) 2015 Englot, Breshears (37) 2013	2013 – 2017 Notable exceptions from 2012-2013[30, 32]	+ Very Low Favours focal EEG changes, with notable inconsistency

Ictal EEG localised to temporal lobe	Children ET	OR 1.55 [1.24, 1.93]	Other meta-analyses with combined unusual dichotomised features (unifocal interictal scalp EEG abnormality **or** no interictal abnormality at all) were non-significant on both weighted OR 1.54 [0.73, 3.26] and partial least squares.[35, 36]					
4. Multimodal Concordance								
EEG-MRI Concordance **Ipsilateral**	TL and ET Children and adults Children with Tuberous Sclerosis Children and adults hemispherectomy	OR 2.36 [1.07, 5.26][24] RR 1.25 [1.15, 1.37][3] OR 4.9 [1.8–13.5] Positive prognostic value on PLS OR 2.17 [1.30, 3.7]	One of the highest qualities of evidence ratings and most consistent results was for EEG and MRI concordance. However, concordance between other modalities, such as semiology and neurophysiology or imaging have not been investigated in meta-analyses. Note that the largest effect size (OR 4.9) and widest confidence interval belongs to the earliest meta-analysis (2013) with the fewest number of patients.[35] For full limitations and GRADE scores and comments for individual meta-analysis see Supplementary Table 2.	2296	55	Tonini, Beghi (24) 2004 West, Nevitt (3) 2019 Fallah, Guyatt (35) 2013 Ibrahim, Morgan (36) 2015 Hu, Zhang (46) 2016	2013 – 2019	+++ Moderate Favours EEG and MRI concordance
5. Genetics: none								
6. Surgical Technique or Anatomic Features								
Temporal Lobe (vs ET) resections	Adults and children with FCD Repeat surgery in focal DRE (n=943) Children Low grade gliomas in adults (n<2641)	OR 1.35 [1.13, 1.61] OR 1.92 [1.06, 3.45] NS OR 1.5 [0.8, 3.0] OR 2 [1.4, 2.9] NS NA	It is well established from numerous individual studies from many centres that surgery for TLE carries the best prognosis. This is only true as far as the diagnosis is correct, and like other surgical features, is more about patient selection and diagnosis than which lobe is resected. Nevertheless, meta-analyses have confirmed that surgery for TLE carries a favourable prognosis.[29, 58, 60]	15012	127	Rowland, Englot (29) 2012 Chen, Chen (58) 2019 Krucoff, Chan (50) 2017	2012 – 2020	+ Very Low Favours surgery for TLE

			This only applies to TLE, and meta-analyses investigating other lobes or ET vs hemispherectomy did not find significant results.[36, 60 28, 37] Nevertheless, TLE is **not** associated with better outcomes in low grade gliomas in adults, nor in cases where the first surgery for presumed TLE fails, i.e. the second surgery does not carry better prognosis (although the point estimate confirms this trend), presumably due to diagnosis and patient selection rather than the lobe of resection per se.[50]			Widjaja, Jain (60) 2020 Shan, Fan (53) 2018 Lamberink, Otte (62) 2020		
Complete Excision Gross total resection vs subtotal resection	Adults and children with FCD (n<2581) Adults and children with FLE (n=345) Repeat resective surgery for focal DRE (n=273) Adults and children (n=2930)[3] Adults and children TL subgroup[3] (n=1266) Children (n=893) Low grade gliomas in adults (n=1379)	OR 3.91 [3.03, 5.32] OR 12.5 [7.14, 20] RR 1.99 [1.47, 2.84] OR 2.6 [1.3, 5.3] RR 1.41 [1.32, 1.50] TL subgroup RR 1.11 [1.03, 1.2] OR 7.69 [4.76, 12.5] RR 1.47 [1.37, 1.59]	Complete excision of lesions or structural abnormalities are unanimously associated with better outcomes in both adults and children, irrespective of the nature of the lesion, across 7 meta-analyses. The definition of complete excision wasn't always specified, but is usually interpreted through imaging and histology. The largest effect sizes (OR 12.5 and 7.69) belong to two of the latest published in 2019 and 2020, the former also used trial sequential and sensitivity analyses.[58, 60] Trial sequential analysis can prevent over 90% of false positive results in conventional meta-analyses.[64] However, Engel II was also considered SF.[52]	8401	119	Rowland, Englot (29) 2012 Chen, Chen (58) 2019 Englot, Wang (30) 2012 Krucoff, Chan (50) 2017 West, Nevitt (3) 2019 Widjaja, Jain (60) 2020 Shan, Fan (53) 2018	2012 – 2020	+++ Moderate Favours complete excision
7. Pathological Features								

Presence of Tumours Low-grade epilepsy associated neuroepithelial tumours (LEAT) vs HS LEAT vs FCD type I or MCD LEAT vs Hypothalamic hamartomas, tubers and other MCD LEAT vs Encephalitis Vs Glial scars	Children and Adults TLE and ET | | Children and adults (mainly gangliogliomas and DNET) | | | | | | | | |	OR 1.74 [1.25, 2.5] RR 1.23 [1.14, 1.32] OR 2.78 [2.17, 3.33] OR 1.27 [1.12, 1.54] OR 2.63 [2.04, 3.57] OR 2.27 [1.59, 3.45] OR 0.43 [0·22 - 0·73] OR 0.53 [0·39 - 0·70]	Epilepsy surgery for tumours has good outcomes, compared to non-tumour causes, or even compared to HS or multiple other pathologies but not compared to glial scars and encephalitis.[62]	8261	91	Tonini, Beghi (24) 2004 West, Nevitt (3) 2019 Lamberink, Otte (62) 2020	2004 – 2020	+++ Moderate Favours Tumours
FCD Presence of FCD (vs absence) Type II vs Other Type II vs Type I Type IIb in Network Meta-Analysis of Subtypes	Adults and children TLE and ET (n=3572) Adults and Children with FCD (n<2014) Children and adults FCD (n=1580)[58] Adults and children with FCD[58]	RR 0.90 [0.85, 0.95] OR 1.38 [1.22, 1.57] OR 1.92 [1.54, 2.44] OR 1.89 [1.01, 3.57]	FCD Type III was developed by ILAE in 2011, and one study investigated pre-2011 Palmini Classification.[29] Overall there has been better outcomes in the absence of FCD (vs presence) amongst 3572 adults and children in 2019 in the Cochrane review,[3] while in 2010 there was no significant difference between FCD vs gliosis amongst 115 extratemporal adults.[18] When FCD is present, two reports have shown direct evidence that Type II has better prognosis than other subtypes,[29, 58] and another shows indirect evidence as type I is associated with worse outcomes compared to neuroepithelial tumours, whereas type II is not. [62]	Presence or absence of FCD 3572 FCD subtypes 3594	Presence or absence of FCD 46 FCD subtypes 51	Rowland, Englot (29) 2012 Chen, Chen (58) 2019 West, Nevitt (3) 2019 Lamberink, Otte (62) 2020	2012 – 2019	++ Low Favours the absence of FCD, otherwise favours FCD type II(b)

Lesional Pathology vs Non-Lesional	FLE Mixed Adults and Children (n=825) TL in Children (n=945) Repeat resective surgery for focal DRE (n=507) MRI neg TLE (n=167) Occipital Lobe and posterior quadrant. Mixed adult and paediatric (n=167) Paediatric ET (n=695)	RR 1.67 [1.36, 28.6] OR 1.08 [1.02, 1.15] OR 3.2 [1.9, 5.3] NS (p=0.36) OR 1.36 [0.7, 2.63] OR 2.08 [1.58, 2.89] OR 1.34 [1.19, 1.49]	Lesional was defined as positive or focal pathology e.g., tumours, MCD, tubers or vascular malformation vs non-lesional which included traumatic and infectious causes (Englot, Rolston (32) included hippocampal sclerosis in non-lesional). Despite the heterogeneity, all studies except for one favoured positive pathology, and this study was in MRI negative TLE.[44] This suggests the causal prognostic pathway of imaging abnormality and presence of pathological abnormality are shared, and adjusting for one may render the other non-prognostic. Within lesion on pathology in children, tumours and hippocampal sclerosis predict better outcomes than Rasmussen's, which in turn has better postsurgical prognosis than malformations of cortical development and tuberous sclerosis, followed by hypothalamic hamartomas.[60]	3306	101	Englot, Wang (30) 2012 Englot, Rolston (32) 2013 Krucoff, Chan (50) 2017 Wang, Zhang (44) 2016 Harward, Chen (49) 2017 Englot, Breshears (37) 2013 Widjaja, Jain (60) 2020	2012 – 2017	++ Low Favours presence of focal pathological lesion

Supplementary Table 3: The essential prognostic features (EPF). OR/RR=Odds Ratios and Relative Risks over 1 indicate better outcomes. *=upper bound of estimate. NS=Not-significant. [c]=calculated (usually unweighted) effect size. MCD=malformations of cortical development. [u]=univariate. [m]=multivariate. TL=Temporal Lobe. ET=Extratemporal. FLE=Frontal Lobe Epilepsy. PLS=Projection to Latent Space.

2.4 Supplementary Table 4: Uncertain Prognostic Features (UPF)

UPF		Mixed Results Evidence Base						
Feature	**Population(s) or Subgroup(s)**	**Range of Effect Sizes for Seizure-Freedom**	**Comments**	**Individual Patients***	**Individual Studies***	**Meta-Analytical References**	**Publication Year (first, last)**	**GRADE score**
1. Clinical Features								
History of Head Injury	Adults and Children	NS RR 0.99 [0.86, 1.13]	Although there was no overall effect, subgroup analyses by outcome were very different and inconsistent.[3]	551	7	West, Nevitt (3) 2019	2019	+ Very Low Unclear
CNS Infections	TL and ET in Children and Adults	NS OR 0.73 [0.29, 1.82]	Non-Engel outcomes in more than half of individual studies.[24]	<<3511	2	Tonini, Beghi (24) 2004	2004	+ Very Low Unclear

Focal (partial) Seizure Semiology vs Generalised	ET non-lesional Adults, Adults and Children with FCD Adults and Children with FLE TL in Children TS TS in Children Repeat Surgery Children with Rasmussen's ET in Children Adults and Children with hemispherectomy Adults with supratentorial low grade gliomas Children with hemispherectomy	NS OR 1.46 NS (p=0.05) OR 1.36 [1.20, 1.56] NS OR 1.15 [0.42, 3.11] OR = 3.1 [1.2, 8.2] NS NS HR 0.8 [0.43, 1.51] OR 1.61 [1.18, 2.35] OR 1.84, [1.18, 2.89] RR 0.76 [0.67, 0.85] NS	When significant, focal seizures were always a positive predictor of seizure-freedom, except for one study on gliomas in which even TL surgery wasn't associated with better outcomes.[53] One group used two separate techniques in two different studies for the same set of patients. In bivariate logistic regression, OR was 3.1;[35] whereas using partial least squares, the effect was still positive but the bootstrapped CI just crossed point of non-significance; instead, focal ictal EEG was significant on PLS,[36] suggesting a correlation between focal seizure semiology and focal ictal EEG as if observing the same factor from different points in their causal pathway. Those with less than ~250 individual participants were less likely to show significance. On balance, likely to be a positive prognostic feature with low power and in need of adjusting for other confounders.	Total = 4965 Significant studies = 4025 NS studies = 940	Total = 124 Significant = 70 NS = 54	Ansari, Tubbs (18) 2010 Rowland, Englot (29) 2012 Englot, Wang (30) 2012 Englot, Rolston (32) 2013 Zhang, Hu (33) 2013 Fallah, Guyatt (35) 2013 Ibrahim, Morgan (36) 2015 Krucoff, Chan (50) 2017 Harris, Phillips (56) 2019 Englot, Breshears (37) 2013 Hu, Zhang (46) 2016 Shan, Fan (53) 2018 Cao, Liu (43) 2016	2010 – 2019	+ Very Low Possible positive prognostic feature, given the right patient selection and circumstances

Epileptic (Infantile) Spasms	TS TS in Children	OR 0.45 [0.24, 0.85] NS OR 0.84 [0.35, 2.03] NS on PLS	Data for TS patients only. Heterogenous definitions of seizure freedom without sensitivity analyses and no funnel plots to investigate publication bias.[33] Small samples (median 7, IQR [3,25]), did not assess heterogeneity nor bias.[35] One meta-analysis had a moderate GRADE score for spasms.[36]	343	27	Zhang, Hu (33) 2013 Fallah, Guyatt (35) 2013 Ibrahim, Morgan (36) 2015	2013 – 2015	+ Very Low Unclear
Low Seizure Frequency or Without daily seizures	Adults and Children with FLE Paediatric ET TL in Children	NS NS unclear	Although two meta-analyses found seizure frequency to be non-significant, another in TLE in Children included 103 patients from 5 individual studies and the unweighted effect size seemed promising OR[c] 2.98 [1.24, 7.16],[32] but no further attempt at inverse variance weighting was performed and it is unclear if this would have remained significant.	1357	25	Englot, Wang (30) 2012 Englot, Breshears (37) 2013	2012 – 2013	+ Very Low Unclear

Age at Seizure Onset Dichotomised <1yr Log10 age at onset Dichotomised <18yrs Younger age at onset Meta Regression	Adults with non-lesional ET TS TS in Children MRI negative TLE Children with Rasmussen's Children and children with TLE subgroup Children with non lesional ET Children with hemispherectomy	NS OR 0.47 [0.24, 0.92] NS OR 1.52 [0.77, 2.99]; also NS on PLS NS OR 1.09 [0.38, 3.07] HR^u 0.91 [0.85, 0.96] NS HR^m [0.87, 1.04] overall: $OR^c = e^{0.346} = 1.41$ (p<0.001) TLE: $OR^c = e^{0.144} = 1.15$ (p=0.023) NS SMD = 0.26, [0.03, 0.49] P = 0.028	Age at onset was higher in seizure free patients in a metaregression of children with and without TLE but not ET, hemispherectomy, tumours or MCD.[60] Age over 1 year was also associated with better outcomes in TS.[33] However, it was non-significant in at least 5 other meta-analyses. One study had a significant HR of 0.91 (favouring younger age at onset) on univariate, but NS on multivariate testing adjusted for the length of follow-up[56]. Even when results were significant, they weren't too dissimilar e.g., seizure onset age tended to be younger by about 5 months in the Engel Class II to IV group compared with the Engel Class I group (median 3.6 months vs 8.4 months, p=0.006).[43]	1252	115	Ansari, Tubbs (18) 2010 Zhang, Hu (33) 2013 Fallah, Guyatt (35) 2013 Ibrahim, Morgan (36) 2015 Wang, Zhang (44) 2016 Harris, Phillips (56) 2019 Widjaja, Jain (60) 2020 Ansari, Maher (28) 2010 Cao, Liu (43) 2016	2010 – 2020	+ Very Low Unclear
Age at Surgery <18 yrs at surgery <18 yrs at surgery Continuous Log base 10 or <5yrs <18 yrs at surgery Metaregression of mean age and outcomes Age < 18 yrs	Adults non lesional ET Adults and Children FCD Adults and Children FLE Children with TLE TS MRI negative TLE Children and Adults TLE/ET Occipital Lobe and Posterior Adults and Children	NS (ANOVA) NS NS NS (t-test) NS NS OR 1.09 [0.38, 3.07] NS OR 1.54 [1.13, 2.18]	Many results from multiple meta-analyses are non-significant. The only significant results were on unadjusted univariate hazard ratios for children with Rasmussen's,[56] metaregression on paediatric epilepsies where younger age at surgery was associated with better outcomes overall and for TL and ET subgroups (but not for hemispherectomy, tumours or MCD)[60], and older age at surgery for low grade gliomas in adults with a cut-off value of 45 yrs.[53] Two studies looked at hemispherectomy / Rasmussen's in	10798	221	Ansari, Tubbs (18) 2010 Rowland, Englot (29) 2012 Englot, Wang (30) 2012 Englot, Rolston (32) 2013 Zhang, Hu (33) 2013	2010 – 2020	++ Low Probably not prognostic

		NS	children, one was NS[43] and the other had a significant HR of 0.93 on univariate, but NS on multivariate testing adjusted for the length of follow-up[56]; a third study was NS in the hemispherectomy subgroup.[60]			Fallah, Guyatt (35) 2013		
	Repeat Surgery in focal DRE first or last surgery	HR 0.93[u] [0.89, 0.97] NS[m] HR 0.95[m] [0.90, 1.0]				Ibrahim, Morgan (36) 2015		
	Children Rasmussen's							
Metaregression	Children overall TL ET	Overall: OR[c] = $e^{-0.189}$ = 0.83 (p<0.001) TL: OR[c] = $e^{-0.093}$ = 0.91 (p=0.031) ET: OR[c] = $e^{-0.173}$ = 0.84 (p 0.004)	Most other studies were variations on adults or children, TL or ET, lesional or non-lesional and all were non-significant. Two studies looked at TS, although both NS, both also very weak on quality of evidence rating.[33, 35]			Wang, Zhang (44) 2016		
						Giridharan, Horn (45) 2016		
	Children ET	NS	On balance, it is probable that the lack of adjusting for known prognostic factors and heterogeneous follow-up times has resulted in falsely significant results.			Harward, Chen (49) 2017		
Age > 45 yrs	Low grade gliomas in Adults	RR 1.12 [1.01, 1.23]				Krucoff, Chan (50) 2017		
	Children non lesional ET	NS				Harris, Phillips (56) 2019		
	Children hemispherectomy	NS 0.95 [0.38, 2.37]				Widjaja, Jain (60) 2020		
Dichotomised age >18 yrs	Cavernomas Adults and Children					Englot, Breshears (37) 2013		
						Shan, Fan (53) 2018		
						Ansari, Maher (28) 2010		
						Cao, Liu (43) 2016		
						Shang-Guan, Wu (54) 2018		

Duration of Epilepsy Prior to Surgery Mean duration Shorter duration Duration or time between surgeries Shorter duration <2 vs >2yrs <5 vs >5yrs <10 vs >10yrs <20 vs <20yrs <5 vs >10yrs Subgroup Metaregression ≤ 7 years Duration ≥ 1 year	Adults non-lesional ET Adults and Children with FLE TLE in Children MRI neg TLE Repeat surgery for focal DRE Paediatric Rasmussen's | | Children and adults all lobes | | | | | Paediatric ET Adults with low grade gliomas Children and Adults with low-grade epilepsy associated neuroepithelial tumour ET nonlesional children Children hemispherectomy Cavernomas adults and children	NS NS NS (t-test) OR 2.57 [1.21, 5.47] NS (t-test) HR 0.92[u] [0.88, 0.97] RR 1.20 [1.05, 1.39] RR 1.24 [1.08, 1.42] RR 1.25 [1.09, 1.43] RR 1.33 [1.08; 1.65] RR 1.32 [1.19; 1.46] NS OR 1.52 [1.07, 2.14] RR 0.82 [0.75, 0.91] 0.97 [0·96 – 0·99] NS NS NS	Upper bound estimates for participants were nearly half-and-half split between significant and non-significant meta-analyses. All significant studies favoured shorter duration. Studies that favoured shorter duration had relative risk point estimates between 1.2 – 1.32 and odds ratios between 1.52 – 2.57 which are compatible as odds ratios tend to overestimate. Although one study showed possible increases in the effect sizes when longer durations of 10 and 20 years until surgery were considered,[57] another subgroup metaregression was non-significant.[45] Both age at onset and age at surgery from Harris, Phillips (56) lost their significance when adjusted for outcome follow up variability, however, they did not seem to report the same multivariate result for duration of epilepsy. Given the univariate HR approaches 0.97 in children with Rasmussen's, this feature would, we suspect, also become non-significant on adjusting and we therefore include the patients and individual studies in the non-significant category.[56] There were no clear patterns to the populations or ages studied, and no clear adjustments or interactions with TL resections made. Given TL connectivity and involvement in propagation, interaction between duration of epilepsy in TL and ET would be useful. On balance, there may be better prognosis with shorter duration	Overall 18645 NS 5786 Favours Shorter Duration 12859 Favours Longer Duration 0	Overall 185 NS 98 Favours Shorter Duration 87 Favours Longer Duration 0	Ansari, Tubbs (18) 2010 Englot, Wang (30) 2012 Englot, Rolston (32) 2013 Wang, Zhang (44) 2016 Giridharan, Horn (45) 2016 Krucoff, Chan (50) 2017 Krucoff, Chan (50) 2017 Harris, Phillips (56) 2019 Bjellvi, Olsson (57) 2019 Englot, Breshears (37) 2013 Shan, Fan (53) 2018 Lamberink, Otte (62) 2020 Ansari, Maher (28) 2010 Cao, Liu (43) 2016 Shang-Guan, Wu (54) 2018	2010 – 2020	+ Very Low Likely favours shorter duration

			of epilepsy but this is confounded by selection bias of clearer diagnoses of focal epileptogenic zones.					
Postsurgical: **Postoperative Semiology Different to Presurgical Semiology**	Adults and Children, TL and ET	NS 4.24 [0.93, 19.25]	Although results suggest when semiology changes postoperatively there is a higher chance of seizure freedom, this depends on the definition of "seizure-freedom" and with 109 participants across only 3 studies, was not statistically significant.	109	3	Giridharan, Horn (45) 2016	2016	+ Very Low Unclear
2. Imaging Features								
FDG-PET Focal Interictal Hypometabolism	Adults with TLE and ET Adults TLE? (35, 1) Adults and Children with FLE MRI negative TLE	NS NS NS NS OR 2.11 [0.95, 4.65]	PET does not appear to add value in patients localized by ictal scalp EEG and/or MRI. One meta-analysis looked at MRI negative TLE, in which 127 patients across 5 studies was NS, however, the OR was 2.11 and the confidence interval was skewed (p=0.06), favouring a positive prognostic effect.[44]	1479	107	Willmann, Wennberg (27) 2007 Englot, Wang (30) 2012 Wang, Zhang (44) 2016	2007 – 2016	+ Very Low PET may have prognostic value for MRI negative TLE
3. Neurophysiological Features								
Postoperative interictal discharges	TL and ET Children and adults TLE subgroup	OR 0.28 [0.08, 0.95] NS Adjusted for outcomes RR 0.91 [0.68, 1.22] RR 0.81 [0.70, 0.94]	Although we would expect postoperative discharges to be correlated with seizures and poor outcomes, and this is reflected in the overall OR of 0.28, RR <1, and TLE subgroup effect size, when adjusted for outcomes, the overall effect was not statistically significant.[3] 2019	1547	9	Tonini, Beghi (24) 2004 West, Nevitt (3) 2019	2004 – 2019	+ Very Low Probably favours lack of postoperative discharges in at least TLE

Preoperative intracranial (invasive) EEG Monitoring **(EcoG, electrico-corticography, includes subdural grids and stereoEEG – see below for comparison between invasive methods)**	TL and ET Children and adults 1547 (27, 2) ET, Adults, Non-lesional Children and adults with FLE Tuberous Sclerosis Children with TLE Repeat surgery on focal DRE Paediatric ET ET nonlesional children <95 (<17)	OR 0.37 [0.22, 0.63], RR 0.85 [0.78, 0.93] NS NS NS OR 1.6 [0.76, 3.37] NS OR[c] crude 1.31 [0.84, 2.04] OR = 0.4, [0.2, 0.9] NS OR[c] 0.77 [0.50, 1.19] NS	Of the 9 meta-analyses investigating the presence or absence of invasive monitoring, only 2 were of ++ "low" quality on the GRADE score, compared with 7 with + "very low" rating. Both of the higher rated meta-analyses found that performing intracranial EEG was associated with worse outcomes with a relative risk for seizure freedom of 0.85 and odds ratios of 0.4.[3, 50] This may be expected due to selection bias of the most difficult cases. The Cochrane review included the largest number of participants at 1547 across 21 individual studies.[3] The other studies suffered from one or more limitations, including no funnel plots to investigate publication bias,[33] having small sample sizes from multiple centres with heterogenous outcome reporting, [18 24] providing limited information on the actual effect size, [30] and most did not adjust for other variables which could also affect the power to detect significance.	4198	105	Tonini, Beghi (24) 2004 West, Nevitt (3) 2019 Ansari, Tubbs (18) 2010 Englot, Wang (30) 2012 Zhang, Hu (33) (2013) Englot, Rolston (32) 2013 Krucoff, Chan (50) 2017 Englot, Breshears (37) 2013 Ansari, Maher (28) 2010	2004 – 2019	+ Very Low Most likely favours lack of invasive monitoring
sEEG vs Subdural Grid	TL and ET adults and children (but not from children only studies) Nonlesional (n=237) Lesional (n=665) TL (n=470) ET (n=420) Any	Overall RR = 64.7% [59.2, 69.8] / 55.9% [50.9, 60.8] = 1.16[c] NS RR = 52% / 54.4% = 0.96 RR = 71.6% / 57.3% = 1.25 RR = 73.9% / 56.7% = 1.30 RR = 61% / 46.7% = 1.31 SDE 64.3% [61.1, 67.5] SEEG 54% [50.8, 57.3] OR[cu] 0.65 [0.45, 0.95] p=0.025[cu]	While there were significant differences favouring sEEG overall (p = 0.02), in lesional (p = 0.031), and temporal subgroups (p = 0.002), the average follow-up for sEEG was 10 months while for subdural grids was nearly 19months but no adjustment was made for duration of follow up. Furthermore, while there wasn't significant heterogeneity in the sEEG studies (I^2 = 11.86%; p = 0.318), there was in the subdural group (I^2 = 54.47%; p = 0.002) Funnel plots and Egger's tests resulted in no overall or subgroup changes.	2461	64	Toth, Papp (59) 2019 [63] 2020	2019, 2020	+ Very Low Note that this is a complex feature, likely confounded by many others, and interactions with other clinical features have not been investigated. Possibly favours sEEG overall and specifically in

		there was no difference in seizure freedom rates regardless of resection (p = 0.0565)	On balance, although the subdural grid cases were more likely to progress to surgery in both meta analyses, likely to due to more straightforward cases, it's possible that the results favour sEEG specifically for lesional cases when there is considerable uncertainty about the epileptogenic zone localisation.					lesional cases, but uncertain.
Interictal Spikes (presence of)	TL and ET Children and adults	NS OR 1.82 [0.86, 3.88]	The evidence base of this feature is uncertain, although the point estimate supports a positive prognostic feature with a somewhat skewed confidence interval, this is not statistically significant. Tonini, Beghi (24) investigated 3511 patients across 47 studies for 13 features, interictal spikes comprised only 3 individual studies and the exact number of cases was not presented but proportionally would be on the order of ~224.	<<3511	3	Tonini, Beghi (24) 2004	2004	+
Lateralised (Unilateral) Interictal EEG Unilateral vs bilateral interictal spikes	Children and adults with FLE Tuberous Sclerosis (n=127) Adults and children (n=1414) Paediatric ET (n=130) Adults and children hemispherectomy (n=413)	NS OR 2.42 [1.11, 5.27] RR 1.14 [1.05, 1.24], NS OR[c] 2.22 [0.98, 5.05] OR 1.66, [1.03, 2.67]	Two meta-analyses were non-significant, one without further data and the other raw data presented showing a calculated OR of 2.22.[30, 37] Note the lack of TLE subgroup. The largest was the Cochrane review with 1414 patients with RR 1.14 for unilateral vs bilateral interictal spikes. Let's *assume* 70% seizure-freedom for unilateral spikes, if a presurgical patient's interictal EEG shows bilateral spikes – everything else being equal – we should reduce this expectation from 70% down by a factor of 1/1.14 i.e., 61%. (NNT ~11–25 depending on definition of seizure freedom).	3283	62	Englot, Wang (30) 2012 Zhang, Hu (33) 2013 West, Nevitt (3) 2019 Englot, Breshears (37) 2013 Hu, Zhang (46) 2016	2012 – 2019	+ Very Low Likely favours unilateral interictal EEG

Unilateral vs Bilateral Ictal EEG (Lateralized Ictal EEG)	Adults and Children with FCD Tuberous Sclerosis (n=159) Adults and Children hemispherectomy (n=414)	NS OR 1.03 [0.82, 1.31] OR 2.48 [1.17, 5.24] OR 1.88 [1.15, 3.07]	Two meta-analyses estimated odds ratios around 2 for better seizure free outcomes for lateralised ictal EEG in TS and hemispherectomy at any age.Zhang, Hu (33), Hu, Zhang (46) Another found no significance in FCD.Rowland, Englot (29) As with all other features, it must be remembered that even if EEG lateralises, there are other factors such as correct localisation and complete resection of the epileptogenic zone. Therefore, on balance, probably supports favourable outcomes in unilateral ictal EEG abnormalities.	2587	25	Rowland, Englot (29) 2012 Zhang, Hu (33) 2013 Hu, Zhang (46) 2016	2012-2016	+ Very Low Probably favours unilateral ictal EEG
4. Multimodal Concordance: None								
5. Genetics: None								
6. Surgical Technique or Anatomic Features								
Extensive Surgical Resection Extensive frontal vs localised Lobectomy (extensive) vs tuberectomy ATL (extensive) vs SAH (selective) ATL vs SAH ATL vs SAH	TL and ET Children and adults (n<3511) FLE, adults and children (n=651) Tuberous sclerosis (n=189) TLE children and adults (n=1203) TLE and HS subgroup (n=1092) TLE mainly adults (n=?) TLE (n=626) SAH vs ATL in TLE (n=1397)	OR 4.27 [2.06, 8.85] RR 0.58 [0.41, 0.79] OR 1.96 [1.01, 3.7] RR 1.32 [1.12, 1.57] RR 1.26 [1.05, 1.51] NS OR 1.14 [0.93, 1.39] p=0.201 NS RR 1.01 [0.54, 1.09] Overall OR 0.65 [0.51, 0.82]	As a supercategory comprising of ATL (vs SAH), lobectomy or hemispherectomy (vs lesionectomy), or extended lesionectomy vs limited resections, it isn't clear whether extensive surgical resection results in better SF. Meta-analyses supporting extensive resections include those for all patients, [24] tuberous sclerosis,[33] TLE[34–40], and paediatric Rasmussen's [56]. If no significant study favoured limited resections, this would not have been unexpected, given at one end of the extreme spectrum, total brain removal might be expected to result in SF. However, extensive frontal lobe resections resulted in worse outcomes compared to limited resections. [30] This was the only result which favoured limited resections. If taken at face value, non-inferiority or worse SF outcomes for selective procedures, except for frontal lobe	9494	120	Tonini, Beghi (24) 2004 Englot, Wang (30) 2012 Zhang, Hu (33) 2013 Josephson, Dykeman (34) 2013 Jain, Tomlinson (52) 2018 Kuang, Yang (38) 2013 Hu, Zhang (40) 2013	2004 – 2019	

Lesionectomy vs multilobar resection surgery) Hemispherectomy (vs resective) 3.5cm (extensive) vs 2.5cm (limited) ATL resection Extended vs limited lesionectomy	Tuberous sclerosis children (n=186) Rasmussen's Paediatric (n<187) TLE Adults >18yrs (n=207) Cavernomas in adults and children (n=245) Extensive resection of surrounding haemosiderin vs resection of cavernoma only	NS on PLS HR 0.28[u] [0.18, 0.45] HR 0.30[m] [0.18, 0.49] NS RR 0.98 [0.83, 1.16] NS OR 0.96 [0.44, 2.08] OR 1.61 [1.10, 2.38]	patients, may suggest a role for healthy frontal cortex in seizure inhibition (and conversely indicate the role of TL for seizure propagation), or suggest selection bias where large resections are made when there is less clear localisation, the former which warrants further investigation if the effect persists after adjustment. On balance, ATL results in better SF, but has other detrimental outcomes including on cognition, more cortical thinning than SAH especially in the frontal and insular cortices ["Remote effects of epilepsy surgery: long-term morphological changes after surgical resection" Poster, AES 2020] Even for ATL, some studies supported better outcomes, [34 40] whilst other did not. [52 38] There was no clear time or quality of study trend, nor by technique (trans-sylvian, transcortical or subtemporal).			Ibrahim, Morgan (36) 2015 Harris, Phillips (56) 2019 West, Nevitt (3) 2019 Shang-Guan, Wu (54) 2018 Ruan, Yu (41) 2015		
7. Pathological Features								
Vascular Malformations	Adults and Children	NS RR 1.07 [0.94, 1.21] NS OR 0.79 [0·60 - 1·06]	Vascular malformations are non-prognostic when adjusted for different outcomes scales, on pathology or imaging.[24] As a group, they are also not statistically significant when compared to low grade neuroepithelial tumours, and this provides indirect evidence that vascular malformations may be prognostic. Cavernomas especially, are likely prognostic (77.1% Engel I) compared to others (65.8%).[62]	1931	56	West, Nevitt (3) 2019 Lamberink, Otte (62) 2020	2019 – 2020	++ Low Not Prognostic

Supplementary Table 4: Features with inconclusive or conflicting prognostic value for epilepsy surgery. *=upper bound of estimate, not including subgroup analyses. NS=Not-significant. [c]=calculated (unweighted) effect size. MCD=malformations of cortical development. [u]=univariate. [m]=multivariate. TL=Temporal Lobe. ET=Extratemporal. FLE=Frontal Lobe Epilepsy. PLS=Projection to Latent Space.[36]

2.5 Supplementary Table 5: Non-Prognostic Features (NPF)

NPF Features		Non-Prognostic Evidence Base						
Feature	Population(s) or Subgroup(s)	Range of Effect Sizes for Seizure-Freedom	Comments	Individual Patients*	Individual Studies*	Meta-Analytical References	Publication Years of meta-analyses (first, last)	GRADE score
1. Clinical Features								
Sex: male vs female	Adults and Children with FLE Children with TLE, Tuberous Sclerosis, MRI neg TLE, Repeat surgery in focal DRE, Paediatric ET Children and adults hemispherectomy Low grade gliomas in adults Children with hemispherectomy	All NS	All were non-significant, a large proportion even on weighted univariate tests which otherwise tend to overestimate significance. Individual unweighted effect sizes ranged from OR 0.83 [0.42, 1.64][c] in repeat surgery for focal DRE[50] to OR 1.44 [0.86, 2.41] in MRI negative TLE.[44]	5974	148	Englot, Wang (30) 2012 Englot, Rolston (32) 2013 Zhang, Hu (33) 2013 Fallah, Guyatt (35) 2013 Ibrahim, Morgan (36) 2015 Wang, Zhang (44) 2016 Krucoff, Chan (50) 2017 Englot, Breshears (37) 2013 Hu, Zhang (46) 2016 Shan, Fan (53) 2018	2012 – 2018	+++ Moderate Non-Prognostic

						Cao, Liu (43) 2016		
Epilepsia Partialis Continua (EPC)	Children undergoing hemispherectomies	NS	Not significant on unweighted univariate testing which is more likely to make a statistical type I error. Although result is from 1 meta-analysis, the population required to have sufficient numbers with EPC is unlikely to be found in vast numbers elsewhere.	127	7	Cao, Liu (43) (2016)	2016	++ Low Non-Prognostic
2. Imaging Features								
Number of Cortical Tubers **≤ 4 vs > 4 tubers** **"Less tuber burden"**	Tuberous Sclerosis	NS OR 1.12 [0.49, 2.57] NS OR 1.01 [0.96, 1.07] Also NS on PLS.	Note that the patients from two of these meta-analyses were the same patients, albeit in one they were reported to be 186 and in another 181, the main difference was in the methodology, where the 2015 paper used PLS. Overall there were few sample sizes, no adjustment except in PLS, and they either did not perform funnel plots,[33, 35] or did not assess heterogeneity,[35] or used heterogenous seizure-freedom definitions without sensitivity analyses.Zhang, Hu (33)	286	24	Zhang, Hu (33) 2013 Fallah, Guyatt (35) 2013 Ibrahim, Morgan (36) 2015	2013 – 2015	++ Low Non-Prognostic
Magnetic ^{1}H Spectroscopy Abnormality: **Ipsilateral to Resected Lobe**	TLE adults and children TLE, adults and children, normal MRI	OR 4.9 [1.97, 12.17] NS	There was a single meta-analysis that we found and it showed that there was no more value to spectroscopy compared to conventional MRI for patients 3 to 66 years of age. "Fifteen centers performed chemical shift imaging and seven centers used single-voxel spectroscopy. Most studies were obtained at 1.5 T"	121	22	Willmann, Wennberg (26) 2006	2006	+ Very Low Probably no more valuable than conventional MRI abnormality
Encephalomalacia	Adults and children	NS RR 0.78 [0.52, 1.17]	Encephalomalacia was NS in the Cochrane meta-analysis, it was also not significant on subgroup analyses.[3]	317	5	West, Nevitt (3) 2019	2019	+ Very Low Not Prognostic
Enhancement, oedema, and/or mass effect	Low grade gliomas in adults	NS	These combined features are not clinically prognostic of low-grade glioma resection for seizure freedom. Although NS, the point estimate and confidence interval are unavailable.	2641	23	Shan, Fan (53) 2018	2018	+ Very Low Not Prognostic

Vascular Lesions	Adults and Children TL and ET	NS OR 0.66 [0.30, 1.46]	Only 1 meta-analysis investigated this in 2004, comprising only 3 individual studies, its pathological counterpart was also NS.[3]	<<3511	3	Tonini, Beghi (24) 2004	2004	+ Very Low Not Prognostic
3. Neurophysiological Features								
Intraoperative Invasive EEG (EcoG, electrico-corticography)	Children and adults with FLE	NS p=0.14 OR[c] 1.23 [0.95, 1.62]		1024	21	Englot, Wang (30) 2012	2012	+++ Moderate NotPrognostic
Video Telemetry and Long Term Monitoring	Children and adults with FLE Lesional and non-lesional TLE and ET	NS (chi-squared) All confidence intervals overlap with 1, with only a trend for OR>1 in lesional TLE subgroup (confounder)	Limited information on effect size provided. Lesional TLE cases do well, and this was the only subgroup in which long term monitoring had a point effect size estimate greater than 1.	<<1199 539	<21 44	Englot, Wang (30) 2012 Kobulashvili, Kuchukhidze (55) 2018	2012, 2018	+ Very Low Not Prognostic
4. Multimodal Concordance: None								
5. Genetics: None								
6. Surgical Technique or Anatomic Features								
Mesial vs Lateral TL focus	MRI neg TLE 92	NS OR 1.39 [0.61, 3.2]	Mesial or lateral TLE, as determined by sEEG, subdural grids, or ATL/SAH vs neocortectomy, are not significant.	92	8	Wang, Zhang (44) 2016	2016	+ Very Low Not Prognostic

Side of Resection (Left vs Right)	TL and ET Children and adults TLE adults ET, Adults, Non-lesional Adults and children with FLE Children with TLE MRI neg TLE Repeat surgery for focal DRE Surgery #1 Surgery #2 Paediatric ET Children and adults hemispherectomy ET non lesional children	NS OR 0.85 [0.54, 1.34] RR 1.04 [0.99, 1.1] NS[u] OR 0.57 [0.26, 1.24] NS NS NS[u] OR[c] 1.07 [0.72, 1.60] NS OR 1.33 [0.84, 2.08] NS[u] OR[c] 0.73 [0.43, 1.25] NS[u] OR[c] 0.77 [0.44, 1.33] NS OR[uc] 0.99 [0.64, 1.53] NS OR 1.17, [0.79, 1.73], p = 0.43 NS[u]	Although there are some methodological issues which result in the quality of evidence GRADE score for side of resection for each meta-analysis not exceeding ++ "low", such as heterogenous outcome reporting, 11 meta-analysis spanning 15 years were unanimous in not finding significance in side of resection, given a low prior for theoretically considering that there may be better outcomes base on left or right sided surgery, this feature is unlikely to be prognostic irrespective of how many further analyses investigate it.	6550	188	Tonini, Beghi (24) 2004 West, Nevitt (3) 2019 Willmann, Wennberg (27) 2007 Ansari, Tubbs (18) 2010 Englot, Wang (30) 2012 Englot, Rolston (32) 2013 Wang, Zhang (44) 2016 Krucoff, Chan (50) 2017 Englot, Breshears (37) 2013 Hu, Zhang (46) 2016 Ansari, Maher (28) 2010	2004 – 2019	+++ Moderate Not Prognostic
Frontal, Central, or Posterior Resections vs Other	ET, Adults, Non-lesional	NS		81	?	Ansari, Tubbs (18) 2010	2010	+ Very Low Not Prognostic
Geographical Location of Surgery: N America vs Elsewhere	Tuberous Sclerosis in Children	NS on PLS	Only one meta-analysis, and so the GRADE score reflects the quality of the investigated feature from this meta-analysis alone.	186	20	Ibrahim, Morgan (36) 2015	2015	+++ Moderate Not Prognostic

7. Pathological Features								
Neuro-migrational defects	TL and ET Children and adults	NS OR 0.66 [0.42, 1.03]	There was a trend whereby neuromigrational deficits were negative prognostic factors, but the number of participants in this analysis is unclear.	? (<<3511)	6	Tonini, Beghi (24) 2004	2004	+ Very Low Not Prognostic
Astrocytoma vs non-astrocytoma	Low grade gliomas in adults	NS NA	The exact numbers of patients were not provided for this particular analysis.	<2641	<23	Shan, Fan (53) 2018	2018	+ Very Low Not-Prognostic

Supplementary Table 5: Non-prognostic features. *=upper bound of estimate, not including subgroup analyses. NS=Not-significant. [c]=calculated (usually unweighted) effect size. MCD=malformations of cortical development. [u]=univariate. [m]=multivariate. TL=Temporal Lobe. ET=Extratemporal. FLE=Frontal Lobe Epilepsy. PLS=Projection to Latent Space.

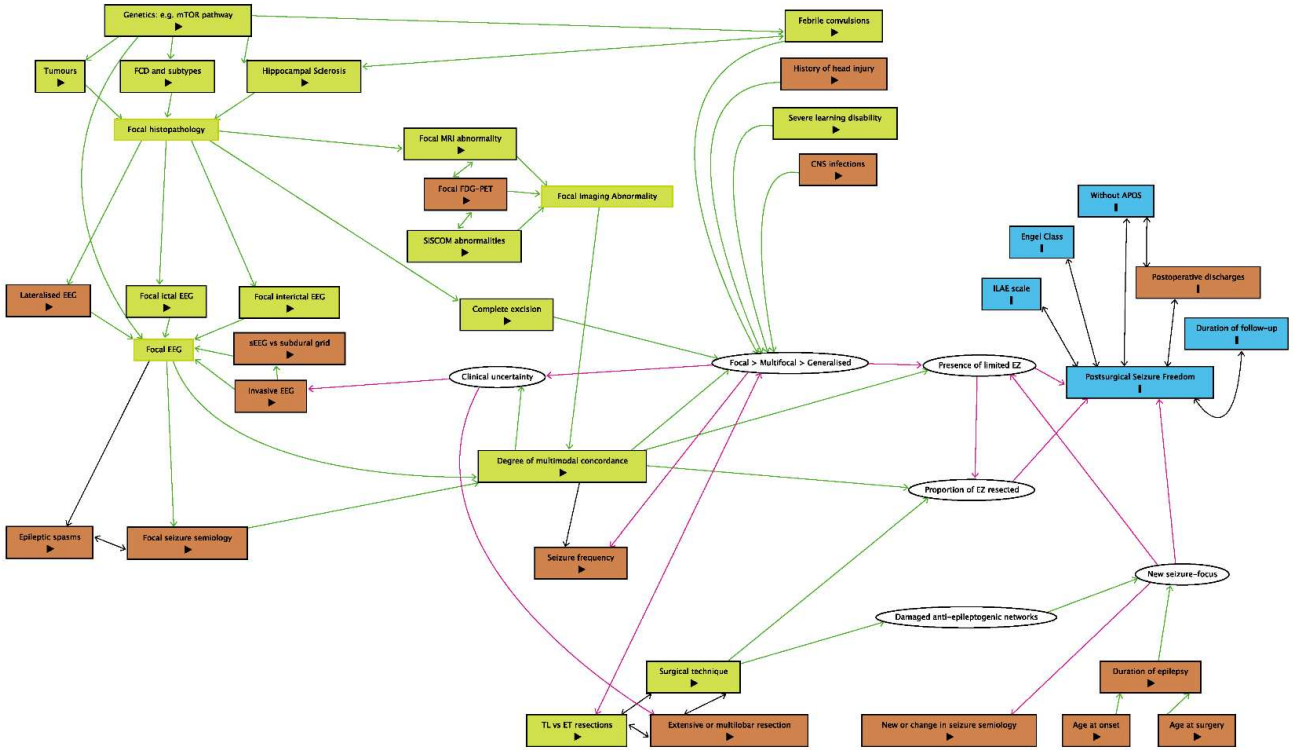
2.6 Structural Causal Models

The attached text file, "SCM dagitty v5 super simplified" generates the simplified SCM when used on http://www.dagitty.net/dags.html (Supplementary Fig. 1, colour coded).

Similarly, "SCM dagitty v4" generates the complete SCM with all of the prognostic, non-prognostic and uncertain features and their relationships (Supplementary Fig. 2, colour coded).

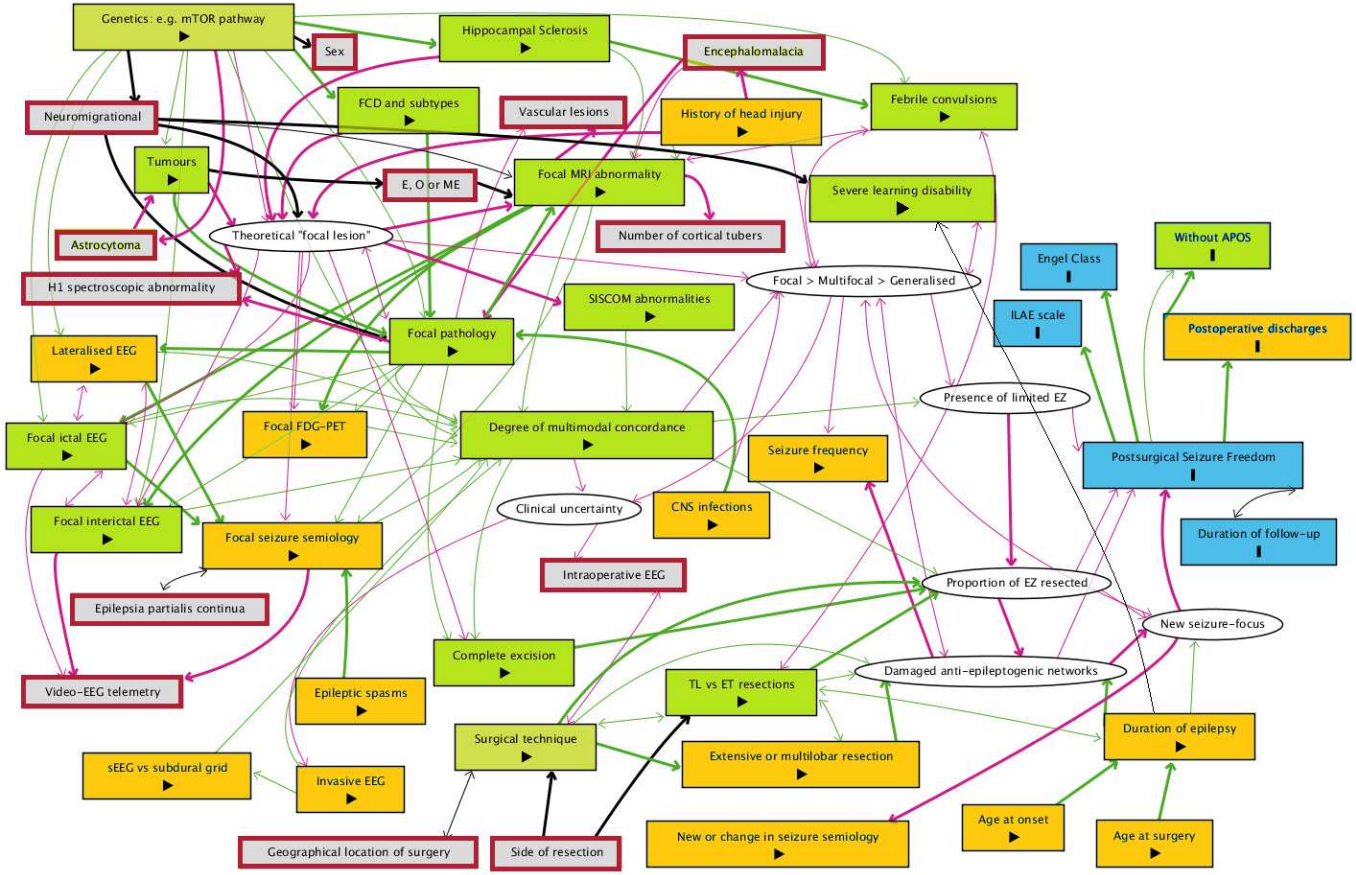
The R codes can also be obtained from dagitty after pasting the contents of the text files. The output of dagitty also states which relationships are direct or biases, and when a specific model is specified, which variables are independent and no adjustment would be necessary.

2.6.1 A Simplified SCM



Supplementary Figure 1: Simplified structural causal model outline for adjusting between variables. In blue are the outcome variables. Latent variables are in oval shapes. Essential prognostic factors are in green and uncertain prognostic factors are in orange. Non-prognostic factors have been omitted for simplicity. Green arrows are causal paths, red arrows are biasing paths. Image created by authors using dagitty v3 (http://www.dagitty.net/dags.html) and can be recreated by pasting the text of supplementary file "SCM dagitty v5 super simplified" onto this website.

2.6.2 A More Complete SCM



Supplementary Figure 2: A more complete structural causal model outline for adjusting between variables. In blue are the outcome variables. Latent variables are in oval shapes. Essential prognostic factors are in green, uncertain prognostic factors in amber, and non-prognostic factors have red borders. Green arrows are causal paths, red arrows are biasing paths. Image created by authors using dagitty v3 (http://www.dagitty.net/dags.html) and can be recreated by pasting the text of supplementary file "SCM dagitty v4" onto this website.

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"Clinical uncertainty" [latent,pos="0.419,0.576"]
"Complete excision" [exposure,pos="0.371,0.740"]
"Damaged anti-epileptogenic networks" [latent,pos="0.730,0.757"]
"Degree of multimodal concordance" [exposure,pos="0.432,0.484"]
"Duration of epilepsy" [exposure,pos="0.869,0.823"]
"Duration of follow-up" [outcome,pos="0.927,0.604"]
"E, O or ME" [adjusted,pos="0.317,0.213"]
"Engel Class" [outcome,pos="0.787,0.296"]
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"Febrile convulsions" [exposure,pos="0.695,0.117"]
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"ILAE scale" [outcome,pos="0.764,0.359"]
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"Lateralised EEG" [exposure,pos="0.069,0.399"]

"New or change in seizure semiology" [exposure,pos="0.573,0.943"]

"New seizure-focus" [latent,pos="0.893,0.705"]

"Number of cortical tubers" [adjusted,pos="0.508,0.270"]

"Postoperative discharges" [outcome,pos="0.926,0.374"]

"Postsurgical Seizure Freedom" [outcome,pos="0.879,0.518"]

"Presence of limited EZ" [latent,pos="0.740,0.452"]

"Proportion of EZ resected" [latent,pos="0.749,0.659"]

"SISCOM abnormalities" [exposure,pos="0.478,0.341"]

"Seizure frequency" [exposure,pos="0.602,0.510"]

"Severe learning disability" [exposure,pos="0.665,0.220"]

"Side of resection" [adjusted,pos="0.410,0.961"]

"Surgical technique" [exposure,pos="0.387,0.834"]

"TL vs ET resections" [exposure,pos="0.546,0.772"]

"Theoretical \"focal lesion\"" [latent,pos="0.222,0.270"]

"Vascular lesions" [adjusted,pos="0.415,0.132"]

"Video-EEG telemetry" [adjusted,pos="0.076,0.781"]

"Without APOS" [outcome,pos="0.893,0.272"]

"sEEG vs subdural grid" [exposure,pos="0.123,0.866"]

Astrocytoma [pos="0.078,0.280"]

Encephalomalacia [pos="0.555,0.064"]

Neuromigrational [adjusted,pos="0.068,0.137"]

Sex [adjusted,pos="0.246,0.063"]

Tumours [exposure,pos="0.126,0.188"]

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"Age at surgery" -> "Duration of epilepsy"

"CNS infections" -> "Focal > Multifocal > Generalised" [pos="0.576,0.374"]

"CNS infections" -> "Focal pathology" [pos="0.576,0.385"]

"Clinical uncertainty" -> "Intraoperative EEG"

"Clinical uncertainty" -> "Invasive EEG" [pos="0.169,0.713"]

"Complete excision" -> "Proportion of EZ resected"

"Damaged anti-epileptogenic networks" -> "New seizure-focus"

"Damaged anti-epileptogenic networks" -> "Postsurgical Seizure Freedom"

"Damaged anti-epileptogenic networks" -> "Seizure frequency"

"Damaged anti-epileptogenic networks" <-> "Focal > Multifocal > Generalised" [pos="0.665,0.562"]

"Degree of multimodal concordance" -> "Clinical uncertainty"

"Degree of multimodal concordance" -> "Complete excision" [pos="0.344,0.598"]

"Degree of multimodal concordance" -> "Focal > Multifocal > Generalised"

"Degree of multimodal concordance" -> "Presence of limited EZ"

"Degree of multimodal concordance" -> "Proportion of EZ resected"

"Duration of epilepsy" -> "Damaged anti-epileptogenic networks"

"Duration of epilepsy" -> "New seizure-focus"

"Duration of epilepsy" -> "Severe learning disability" [pos="0.780,0.591"]

"Duration of epilepsy" <-> "TL vs ET resections" [pos="0.665,0.787"]

"Duration of follow-up" <-> "Postsurgical Seizure Freedom" [pos="0.921,0.556"]

"E, O or ME" -> "Focal MRI abnormality"

"Epilepsia partialis continua" <-> "Focal seizure semiology" [pos="0.124,0.653"]

"Epileptic spasms" -> "Focal seizure semiology" [pos="0.257,0.705"]

"Extensive or multilobar resection" -> "Damaged anti-epileptogenic networks"

"Extensive or multilobar resection" <-> "TL vs ET resections" [pos="0.609,0.797"]

"FCD and subtypes" -> "Focal pathology"

"FCD and subtypes" -> "Theoretical \"focal lesion\"" [pos="0.205,0.169"]

"Febrile convulsions" -> "Focal > Multifocal > Generalised" [pos="0.573,0.171"]

"Febrile convulsions" <-> "Focal MRI abnormality"

"Febrile convulsions" <-> "TL vs ET resections" [pos="0.774,0.366"]

"Focal > Multifocal > Generalised" -> "Clinical uncertainty" [pos="0.583,0.498"]

"Focal > Multifocal > Generalised" -> "Presence of limited EZ"

"Focal > Multifocal > Generalised" -> "Seizure frequency"

"Focal > Multifocal > Generalised" <-> "New seizure-focus" [pos="0.638,0.566"]

"Focal > Multifocal > Generalised" <-> "Severe learning disability" [pos="0.717,0.288"]

"Focal FDG-PET" -> "Degree of multimodal concordance"

"Focal MRI abnormality" -> "Degree of multimodal concordance" [pos="0.390,0.379"]

"Focal MRI abnormality" -> "Focal FDG-PET" [pos="0.269,0.325"]

"Focal MRI abnormality" -> "Focal ictal EEG"

"Focal MRI abnormality" -> "Focal interictal EEG" [pos="0.173,0.414"]

"Focal MRI abnormality" -> "Focal seizure semiology" [pos="0.412,0.402"]

"Focal MRI abnormality" -> "Number of cortical tubers" [pos="0.519,0.203"]

"Focal MRI abnormality" -> "Vascular lesions"

"Focal ictal EEG" -> "Degree of multimodal concordance" [pos="0.194,0.422"]

"Focal ictal EEG" -> "Focal seizure semiology"

"Focal ictal EEG" -> "Video-EEG telemetry" [pos="0.001,0.606"]

"Focal ictal EEG" <-> "Focal interictal EEG"

"Focal ictal EEG" <-> "Lateralised EEG"

"Focal interictal EEG" -> "Degree of multimodal concordance"

"Focal interictal EEG" -> "Video-EEG telemetry" [pos="0.036,0.641"]

"Focal interictal EEG" <-> "Lateralised EEG" [pos="0.110,0.470"]

"Focal pathology" -> "Complete excision" [pos="0.300,0.619"]

"Focal pathology" -> "Degree of multimodal concordance" [pos="0.275,0.434"]

"Focal pathology" -> "Focal FDG-PET"

"Focal pathology" -> "Focal MRI abnormality"

"Focal pathology" -> "Focal ictal EEG"

"Focal pathology" -> "Focal interictal EEG"

"Focal pathology" -> "Focal seizure semiology"

"Focal pathology" -> "H1 spectroscopic abnormality"

"Focal pathology" -> "Lateralised EEG"

"Focal pathology" -> "Vascular lesions" [pos="0.353,0.238"]

"Focal pathology" <-> "Theoretical \"focal lesion\""

"Focal seizure semiology" -> "Degree of multimodal concordance" [pos="0.334,0.548"]

"Focal seizure semiology" -> "Video-EEG telemetry" [pos="0.224,0.729"]

"Genetics: e.g. mTOR pathway" -> "Degree of multimodal concordance" [pos="0.267,0.465"]

"Genetics: e.g. mTOR pathway" -> "FCD and subtypes"

"Genetics: e.g. mTOR pathway" -> "Febrile convulsions" [pos="0.660,0.002"]

"Genetics: e.g. mTOR pathway" -> "Focal ictal EEG" [pos="0.001,0.162"]

"Genetics: e.g. mTOR pathway" -> "Focal interictal EEG" [pos="0.124,0.480"]

"Genetics: e.g. mTOR pathway" -> "Focal pathology" [pos="0.309,0.255"]

"Genetics: e.g. mTOR pathway" -> "Hippocampal Sclerosis"

"Genetics: e.g. mTOR pathway" -> "Lateralised EEG" [pos="0.014,0.199"]

"Genetics: e.g. mTOR pathway" -> "Theoretical \"focal lesion\""

"Genetics: e.g. mTOR pathway" -> Astrocytoma [pos="0.181,0.263"]

"Genetics: e.g. mTOR pathway" -> Neuromigrational

"Genetics: e.g. mTOR pathway" -> Sex

"Genetics: e.g. mTOR pathway" -> Tumours

"Geographical location of surgery" <-> "Surgical technique"

"Hippocampal Sclerosis" -> "Febrile convulsions"

"Hippocampal Sclerosis" -> "Focal MRI abnormality" [pos="0.488,0.082"]

"Hippocampal Sclerosis" -> "Theoretical \"focal lesion\"" [pos="0.170,0.090"]

"History of head injury" -> "Focal > Multifocal > Generalised"

"History of head injury" -> "Focal MRI abnormality"

"History of head injury" -> "Theoretical \"focal lesion\"" [pos="0.234,0.154"]

"History of head injury" -> Encephalomalacia

"Intraoperative EEG" <-> "Surgical technique" [pos="0.477,0.695"]

"Invasive EEG" -> "Degree of multimodal concordance" [pos="0.169,0.770"]

"Invasive EEG" -> "sEEG vs subdural grid"

"Lateralised EEG" -> "Degree of multimodal concordance" [pos="0.206,0.402"]

"Lateralised EEG" -> "Focal seizure semiology"

"New seizure-focus" -> "New or change in seizure semiology" [pos="0.855,0.767"]

"New seizure-focus" -> "Postsurgical Seizure Freedom" [pos="0.850,0.627"]

"Postoperative discharges" -> "Without APOS" [pos="0.867,0.342"]

"Postsurgical Seizure Freedom" -> "Engel Class"

"Postsurgical Seizure Freedom" -> "ILAE scale"

"Postsurgical Seizure Freedom" -> "Postoperative discharges"

"Postsurgical Seizure Freedom" -> "Without APOS" [pos="0.832,0.352"]

"Presence of limited EZ" -> "Postsurgical Seizure Freedom" [pos="0.790,0.480"]

"Presence of limited EZ" -> "Proportion of EZ resected"

"Proportion of EZ resected" -> "Damaged anti-epileptogenic networks"

"Proportion of EZ resected" -> "New seizure-focus"

"Proportion of EZ resected" -> "Postsurgical Seizure Freedom"

"SISCOM abnormalities" -> "Degree of multimodal concordance"

"Side of resection" -> "Surgical technique"

"Side of resection" -> "TL vs ET resections" [pos="0.479,0.850"]

"Surgical technique" -> "Damaged anti-epileptogenic networks" [pos="0.518,0.684"]

"Surgical technique" -> "Extensive or multilobar resection"

"Surgical technique" -> "Proportion of EZ resected" [pos="0.484,0.652"]

"Surgical technique" <-> "TL vs ET resections"

"TL vs ET resections" -> "Damaged anti-epileptogenic networks"

"TL vs ET resections" -> "Proportion of EZ resected"

"Theoretical \"focal lesion\"" -> "Complete excision" [pos="0.299,0.516"]

"Theoretical \"focal lesion\"" -> "Focal > Multifocal > Generalised"

"Theoretical \"focal lesion\"" -> "Focal FDG-PET"

"Theoretical \"focal lesion\"" -> "Focal MRI abnormality"

"Theoretical \"focal lesion\"" -> "Focal ictal EEG" [pos="0.231,0.372"]

"Theoretical \"focal lesion\"" -> "Focal interictal EEG" [pos="0.191,0.324"]

"Theoretical \"focal lesion\"" -> "Focal seizure semiology"

"Theoretical \"focal lesion\"" -> "H1 spectroscopic abnormality"

"Theoretical \"focal lesion\"" -> "SISCOM abnormalities"

"sEEG vs subdural grid" -> "Degree of multimodal concordance" [pos="0.345,0.553"]

Astrocytoma -> Tumours

Encephalomalacia -> "Focal MRI abnormality" [pos="0.486,0.095"]

Encephalomalacia -> "Focal pathology" [pos="0.496,0.074"]

Neuromigrational -> "Focal MRI abnormality" [pos="0.292,0.154"]

Neuromigrational -> "Focal pathology" [pos="0.095,0.297"]

Neuromigrational -> "Severe learning disability" [pos="0.559,0.164"]

Neuromigrational -> "Theoretical \"focal lesion\"" [pos="0.219,0.168"]

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Tumours -> "E, O or ME" [pos="0.193,0.207"]

Tumours -> "Focal pathology" [pos="0.119,0.283"]

Tumours -> "Theoretical \"focal lesion\""

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dag {
bb="0,0,1,1"
"Age at onset" [exposure,pos="0.828,0.888"]
"Age at surgery" [exposure,pos="0.904,0.888"]
"CNS infections" [exposure,pos="0.633,0.208"]
"Clinical uncertainty" [latent,pos="0.376,0.466"]
"Complete excision" [exposure,pos="0.383,0.384"]
"Damaged anti-epileptogenic networks" [latent,pos="0.730,0.757"]
"Degree of multimodal concordance" [exposure,pos="0.425,0.568"]
"Duration of epilepsy" [exposure,pos="0.869,0.823"]
"Duration of follow-up" [outcome,pos="0.934,0.407"]
"Engel Class" [outcome,pos="0.787,0.296"]
"Epileptic spasms" [exposure,pos="0.038,0.660"]
"Extensive or multilobar resection" [exposure,pos="0.551,0.888"]
"FCD and subtypes" [exposure,pos="0.127,0.095"]
"Febrile convulsions" [exposure,pos="0.630,0.034"]
"Focal > Multifocal > Generalised" [latent,pos="0.597,0.449"]
"Focal EEG" [pos="0.124,0.433"]
"Focal FDG-PET" [exposure,pos="0.352,0.238"]
"Focal Imaging Abnormality" [pos="0.459,0.247"]
"Focal MRI abnormality" [exposure,pos="0.348,0.177"]
"Focal histopathology" [pos="0.126,0.166"]
"Focal ictal EEG" [exposure,pos="0.126,0.368"]
"Focal interictal EEG" [exposure,pos="0.219,0.369"]
"Focal seizure semiology" [exposure,pos="0.142,0.661"]
"Genetics: e.g. mTOR pathway" [exposure,pos="0.135,0.027"]
"Hippocampal Sclerosis" [exposure,pos="0.230,0.095"]
"History of head injury" [exposure,pos="0.630,0.092"]
"ILAE scale" [outcome,pos="0.764,0.359"]
"Invasive EEG" [exposure,pos="0.205,0.483"]
"Lateralised EEG" [exposure,pos="0.037,0.367"]
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"New or change in seizure semiology" [exposure,pos="0.717,0.888"]

"New seizure-focus" [latent,pos="0.893,0.705"]

"Postoperative discharges" [outcome,pos="0.905,0.345"]

"Postsurgical Seizure Freedom" [outcome,pos="0.861,0.466"]

"Presence of limited EZ" [latent,pos="0.740,0.452"]

"Proportion of EZ resected" [latent,pos="0.734,0.603"]

"SISCOM abnormalities" [exposure,pos="0.351,0.301"]

"Seizure frequency" [exposure,pos="0.439,0.685"]

"Severe learning disability" [exposure,pos="0.631,0.152"]

"Surgical technique" [exposure,pos="0.524,0.823"]

"TL vs ET resections" [exposure,pos="0.436,0.888"]

"Without APOS" [outcome,pos="0.843,0.246"]

"sEEG vs subdural grid" [exposure,pos="0.219,0.425"]

Tumours [exposure,pos="0.046,0.095"]

"Age at onset" -> "Duration of epilepsy"

"Age at surgery" -> "Duration of epilepsy"

"CNS infections" -> "Focal > Multifocal > Generalised" [pos="0.554,0.201"]

"Clinical uncertainty" -> "Extensive or multilobar resection" [pos="0.292,0.686"]

"Clinical uncertainty" -> "Invasive EEG"

"Complete excision" -> "Focal > Multifocal > Generalised"

"Damaged anti-epileptogenic networks" -> "New seizure-focus"

"Degree of multimodal concordance" -> "Clinical uncertainty"

"Degree of multimodal concordance" -> "Focal > Multifocal > Generalised"

"Degree of multimodal concordance" -> "Presence of limited EZ"

"Degree of multimodal concordance" -> "Proportion of EZ resected"

"Degree of multimodal concordance" -> "Seizure frequency"

"Duration of epilepsy" -> "New seizure-focus"

"Duration of follow-up" <-> "Postsurgical Seizure Freedom" [pos="0.932,0.570"]

"Engel Class" <-> "Postsurgical Seizure Freedom"

"Epileptic spasms" <-> "Focal seizure semiology"

"Extensive or multilobar resection" <-> "Surgical technique"

"Extensive or multilobar resection" <-> "TL vs ET resections"

"FCD and subtypes" -> "Focal histopathology"

"Febrile convulsions" -> "Focal > Multifocal > Generalised" [pos="0.453,0.102"]

"Febrile convulsions" <-> "Hippocampal Sclerosis"

"Focal > Multifocal > Generalised" -> "Clinical uncertainty"

"Focal > Multifocal > Generalised" -> "Presence of limited EZ"

"Focal > Multifocal > Generalised" -> "Seizure frequency"

"Focal > Multifocal > Generalised" <-> "TL vs ET resections"

"Focal EEG" -> "Degree of multimodal concordance" [pos="0.164,0.599"]

"Focal EEG" -> "Epileptic spasms"

"Focal EEG" -> "Focal seizure semiology"

"Focal FDG-PET" -> "Focal Imaging Abnormality"

"Focal FDG-PET" <-> "Focal MRI abnormality"

"Focal FDG-PET" <-> "SISCOM abnormalities"

"Focal Imaging Abnormality" -> "Degree of multimodal concordance"

"Focal MRI abnormality" -> "Focal Imaging Abnormality"

"Focal histopathology" -> "Complete excision"

"Focal histopathology" -> "Focal MRI abnormality"

"Focal histopathology" -> "Focal ictal EEG"

"Focal histopathology" -> "Focal interictal EEG"

"Focal histopathology" -> "Lateralised EEG"

"Focal ictal EEG" -> "Focal EEG"

"Focal interictal EEG" -> "Focal EEG"

"Focal seizure semiology" -> "Degree of multimodal concordance"

"Genetics: e.g. mTOR pathway" -> "FCD and subtypes"

"Genetics: e.g. mTOR pathway" -> "Febrile convulsions"

"Genetics: e.g. mTOR pathway" -> "Focal EEG" [pos="0.007,0.232"]

"Genetics: e.g. mTOR pathway" -> "Hippocampal Sclerosis"

"Genetics: e.g. mTOR pathway" -> Tumours

"Hippocampal Sclerosis" -> "Focal histopathology"

"History of head injury" -> "Focal > Multifocal > Generalised" [pos="0.480,0.109"]

"ILAE scale" <-> "Postsurgical Seizure Freedom"

"Invasive EEG" -> "Focal EEG"

"Invasive EEG" -> "sEEG vs subdural grid"

"Lateralised EEG" -> "Focal EEG"

"New seizure-focus" -> "New or change in seizure semiology"

"New seizure-focus" -> "Postsurgical Seizure Freedom"

"New seizure-focus" -> "Presence of limited EZ"

"Postoperative discharges" <-> "Postsurgical Seizure Freedom"

"Postoperative discharges" <-> "Without APOS" [pos="0.866,0.292"]

"Postsurgical Seizure Freedom" <-> "Without APOS" [pos="0.850,0.338"]

"Presence of limited EZ" -> "Postsurgical Seizure Freedom"

"Presence of limited EZ" -> "Proportion of EZ resected"

"Proportion of EZ resected" -> "Postsurgical Seizure Freedom"

"SISCOM abnormalities" -> "Focal Imaging Abnormality"

"Severe learning disability" -> "Focal > Multifocal > Generalised" [pos="0.519,0.142"]

"Surgical technique" -> "Damaged anti-epileptogenic networks"

"Surgical technique" -> "Proportion of EZ resected"

"Surgical technique" <-> "TL vs ET resections"

"sEEG vs subdural grid" -> "Focal EEG"

Tumours -> "Focal histopathology"

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