National Institute for Health and Care Excellence

Draft for consultation

Epilepsies in children, young people and adults: diagnosis and management

[03] Evidence review: Diagnosis of epilepsies

NICE guideline <number>

Evidence review underpinning recommendations 1.2.1 – 1.2.10 in the NICE guideline

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Developed by the National Guideline Centre, hosted by the Royal College of Physicians]

1

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Contents

1

1 Diagnosis of epilepsy

1.1 Introduction

Epilepsy is diagnosed in people who have had two unprovoked seizures or in those who have had one seizure, but there are features to suggest a high risk of recurrence. Confirming and diagnosing epilepsy can be difficult and relies heavily on the description of seizures. Many different conditions can cause epilepsy, although often, an underlying cause is not identified. Conditions associated with epilepsy include brain infections, brain injury, brain malformations, metabolic disorders, stroke, dementia and underlying genetic abnormalities. This evidence review evaluates the accuracy of a range of diagnostic strategies to optimise diagnosis and assessment in people who may have epilepsy.

1.2 Review question: What is the most accurate approach for 1) diagnosis of epilepsy and 2) differentiation between types of epilepsy?

1.2.1 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: Strata: - Children and adults with suspected epilepsy. - Children and adults with epilepsy, where uncertainty remains as to the type of epilepsy Exclusion: New-born babies with acute symptomatic seizures
Target condition	Epilepsies, or type of epilepsy
Index test(s)	Any diagnostic strategies used in papers to detect 1) epilepsy, 2) type of epilepsy. These may include (for example) symptoms/signs, imaging, EEG, ECG, serum measures, either singly or in combination.
Reference standard(s)	Any gold standard used in the studies.
Outcomes	Diagnostic accuracy – sensitivity and specificity
Study design	Observational

1.2.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[138] Methods specific to this review question are described in the review protocol in Appendix A.

1.2.3 Effectiveness evidence

1.2.3.1 Included studies

77 studies were included in this diagnostic accuracy review[6, 7, 10, 11, 16, 20, 25, 26, 28, 39, 43, 56, 58, 60-62, 64, 65, 68, 69, 73-75, 81, 82, 84, 86, 87, 90, 92, 94, 96, 97, 99, 100, 102, 107, 109, 111, 114, 116, 124, 125, 131, 132, 136, 137, 143-146, 158-161, 163, 166, 171, 176, 177, 179-181, 184, 186, 191, 193, 194, 196, 199, 200, 203, 205, 209, 213, 215, 216]. The characteristics of

these studies are summarised in **Table 2**, and evidence from these studies are summarised in the clinical evidence summaries (**Table 3** to **Table 16**). Further details are available in the study selection flow chart in Appendix C.1, sensitivity and specificity forest plots and receiver operating characteristics (ROC) curves in Appendix E, and study evidence tables in Appendix D.

Analysis was stratified by the population requiring diagnostic attention: 1) children and adults with suspected epilepsy, or 2) children and adults with definite epilepsy, where uncertainty remains as to the type of epilepsy. The aim of most studies was not to differentiate between different types of epilepsy but to differentiate epilepsy from no epilepsy, and only two studies [64, 132] fitted into the latter stratum. Some studies [6, 7, 58, 68, 82, 86, 100, 114, 124, 136, 159, 163, 186, 200, 205] evaluated an index test in an epilepsy population that was restricted to a certain type (such as temporal lobe epilepsy). However, the findings from these were evaluated in the first stratum because the ability of the index test to differentiate between the specific type and *no epilepsy* was being assessed; that is, these studies were not differentiating between different types of epilepsy. The sub-types of epilepsy included status epilepticus (SE), non-convulsive status epilepticus (NCSE), temporal lobe epilepsy (TLE), frontal lobe epilepsy (FLE), partial epilepsy, focal epilepsy, generalised epilepsy, generalised genetic epilepsy, autoimmune epilepsy, and absence seizures. These categories overlap but reflected the classification systems of the included papers. The types of epilepsy are highlighted in the results tables where appropriate.

For each of the above strata, pre-hoc sub-grouping strategies (conditional on observed heterogeneity) were:

1. Age: <2, 2-11, 11-18, 18-55, >55
2. Learning disability / no learning disability
3. Head injury / no head injury
4. Gender
5. Type of epilepsy
6. Person carrying out the index tests

Sub-grouping was only considered for the two meta-analyses concerning interictal routine EEG and postictal stertorious breathing, as these were the only analyses where heterogeneity was evident. However, none of the protocol sub-grouping strategies were able to 'explain' heterogeneity (by yielding homogenous results within each sub-group) in either meta-analysis. Only 5 diagnostic meta-analyses were possible because at least 3 studies are required for a valid pooling of results, and for most index tests, only one or two studies were available.

Several studies did not recruit consecutively from the population under clinical suspicion but instead employed a case-control strategy where they recruited people with gold-standard confirmed epilepsy, as well as others with specific differential diagnoses that were also confirmed by a gold-standard method. In the majority of cases, the differential diagnosis was psychogenic non-epileptic seizures (PNES). These studies have been highlighted in the analysis because this approach has an important impact on the interpretation of specificity results. Specificity measures may have been affected because the propensity towards false positives may be associated with the characteristics of the non-epilepsy group. For example, a group of people with PNES may be more likely (or less likely) to yield false-positive results than a more random group of people who were initially suspected of epilepsy. However, the sensitivity of the index test will not be affected by this approach, as sensitivity will depend solely on the response of the group who have gold-standard confirmed epilepsy. It should also be mentioned that in some papers, the target condition for diagnosis was not epilepsy but PNES (for example, the paper expressed the accuracy for detecting PNES, rather than epilepsy). These studies were still included because it was possible to convert the results to those that would have been observed had epilepsy been the target condition. This was achieved in most cases by simply exchanging the sensitivity and specificity measures.

However, this could only occur if the study was restricted to epilepsy and PNES. If the non-PNES group comprised groups additional to those with epilepsy, then it was not possible to extrapolate the sensitivity and specificity for the detection of epilepsy.

Gold standards varied between studies, but the protocol had allowed for a variety of approaches. For inclusion, a study needed to have a sufficient description of the gold standard to permit the assumption that it was the best method available to the researchers when doing the study. If a study gave no indication of the methods used to decide on the gold standard diagnosis, it was excluded.

For the purposes of decision-making, sensitivity and specificity were given equal priority. For a test to be able to be recommended as a diagnostic strategy, it would normally need to exceed 0.9 for both sensitivity and specificity, and values below 0.6 would be regarded as clinically useless. Poor sensitivity indicates that an unacceptably large number of patients with epilepsy would not be diagnosed as having epilepsy (false negatives), and might remain untreated. Poor specificity means that an unacceptable proportion of those without epilepsy would be misdiagnosed as having epilepsy (false positives), leading to unnecessary and potentially harmful treatments, as well as unwarranted anxiety.

Because of the large numbers of included studies and results, it was necessary to categorise the index tests in the results tables. This categorisation is arbitrary, is not based on a pre-defined system, and has no impact on the strength of results. The 12 categories of index test are: symptoms/signs/semiology; serum measures; ECG testing; Imaging tests; EEG tests; MEG/TMS tests; psychological measures; linguistic tests; EMG tests; accelerometer testing; clinical impression at admission based on a variety of data; and miscellaneous methods.

Finally, it is important to point out that this review question covers the 6 questions previously in the scope:

1.2 Diagnostic accuracy of signs and symptoms

1.3 What is the role of electrocardiograph (ECG) in distinguishing between seizures and non-seizure events after a first seizure or seizure like episode?

1.4 What is the diagnostic accuracy of electroencephalogram (EEG) (including specific EEG techniques) in distinguishing between seizures and non-seizure events?

1.5 What is the diagnostic accuracy of EEG (including specific EEG techniques) in identifying specific seizure types and epilepsy syndromes?

1.6 What is the diagnostic accuracy of EEG (including specific EEG techniques) in assessing the likelihood of seizure recurrence after a first seizure

These questions were combined to ensure that we could capture testing strategies that combined elements from more than one of the original questions. For example, a testing strategy utilising signs and symptoms combined with EEG might not have fitted into either question 1.2 or 1.4. A combined question with a more open scope also allowed a greater range of index-test types to be included. Previously, using the 6 separate questions, the index test categories of imaging, magnetoencephalography, psychological tests, serum tests, EMG and accelerometer testing would not have been included, whereas they are now being considered in the review.

1.2.3.2 Excluded studies

Please see the excluded studies list in Appendix I.

1.2.4 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review for detection of epilepsy

Study	Population	Index test(s)	Reference standard
Albadareen, 2016[6]	N=78; USA; Mean age 34.8 GCS (generalised convulsive seizure), 35.2 PNES-C (psychogenic nonepileptic seizures with convulsion, 40.1 FS (focal seizures); 57% female. Inclusion: Adult patients (≥18 years of age) admitted to the epilepsy monitoring unit for event characterization, seizure focus localization, or treatment optimization Exclusion: Factors known to be associated with hyperammonaemia: pre-existing liver disease/cirrhosis, current use of valproic acid or 5- fluorouracil, history of gastrointestinal bleeding, hematologic malignancies, and end-stage renal disease; no event during study. Non-epilepsy population: any suspected of epilepsy	baseline serum ammonia at cut-off >=80 micromol/L	VIDEO EEG
Alving, 1998[7]	N=58; Denmark; median age 28; 46/58 female Inclusion: People with diagnosed epilepsy or pseudo-epileptic seizures Exclusion: Uncertain diagnoses; insufficient seizure description; uncertainty about time elapsed from previous seizure to index seizure; neuroleptic drugs; pregnancy Non-epilepsy population: PNES	Postictal paired serum prolactin measurements at 3 different thresholds	Clinical and video EEG
Arnold, 1996[10]	N= 41; USA; mean age 34 years; 53.6% female Inclusion: Patients admitted to the inpatient 24-hour video/EEG monitoring unit for people with intractable seizures; aged >18 Exclusion: not reported Non-epilepsy population: PNES	Interviews to ascertain the following test data: Lifetime Axis I Current Axis I Current Axis II Trauma history	VIDEO EEG

Study	Population	Index test(s)	Reference standard
Asadi-Pooya, 2016[11]	N=60; mean age 28.6 years; 70% female Inclusion: Patients admitted to the Epilepsy Centre with a video-EEG confirmed diagnosis of epilepsy or PNES Exclusion: Patients with concomitant PNES and epilepsy Non-epilepsy population: PNES	Review of systems (ROS) questionnaire, which was in the medical records. This covered the following 10 systems, where each was graded as normal or abnormal: skin; head & ear, nose and throat (HENT); musculoskeletal; pulmonary; cardiovascular; gastrointestinal; genitourinary; hematologic; psychiatry; cognition and memory. The questionnaire was completed by the HCP according to the patient's history. Scores were generated by any abnormality yielding a score of 1.	VIDEO EEG
Azar, 2008[16]	N=40; USA; mean age 34.4 years; 47.5% female Inclusion: Adult patients with epilepsy and generalised tonic-clonic seizures; patients with non-epileptic psychogenic seizures; people with hyper motor seizures from frontal lobe epilepsy Exclusion: Not reported Non-epilepsy population: PNES	Ictal and post ictal physical characteristics, recorded by video	VIDEO EEG
Bayly, 2013[20]	N=35; Australia; mean age epilepsy/PNES: 33/38; 23/34 female Inclusion: Patients being offered video EEG for the diagnosis of seizure-like events; patients having a convulsive seizure (>10s, with rhythmic movements affecting at least 1 limb) detected by accelerometery during video EEG Exclusion: None reported Non-epilepsy population: PNES	Wrist accelerometer data	Consensus agreement based on clinical and EEG data

Study	Population	Index test(s)	Reference standard
Benbadis, 1995[25]	N=108; USA; mean age 43 years; 56% female Inclusion: All patients admitted to a Epilepsy Monitoring Unit for the diagnosis of spells or presurgical evaluation of epilepsy over a 6-month period. Patients selected whose episodes are characterised by bilateral motor phenomena, LOC, or both. Exclusion: Typical complex partial seizures, with altered awareness but no LOC Non-epilepsy population: syncope	Existence of tongue biting	VIDEO EEG
Benge, 2012[26]	N=120; USA; Age and gender not reported Inclusion: Case files from patients at a large Veteran's Affairs hospital's continuous video-EEG long term monitoring (LTM) programme Exclusion: No SIMS data; missing LTM data; unclear LTM results Non-epilepsy population: PNES	SIMS questionnaire	VIDEO EEG
Bernardo, 2018[28]	N=11; USA; mean age 21.3 months; 36% female. Inclusion: Infants with active medically refractive epilepsy related to tuberous sclerosis; all video EEGs recorded on Nihon Kohden systems; vEEG sampled at 3000Hz; vEEG recorded at 2 h or more from the most recent seizure; human visual identification of interictal scalp FR; at least 1 brain MRI previously obtained. Controls were children with no brain-related diagnoses including epilepsy, autism and developmental delay; underwent a normal overnight scalp vEEG for clinical reasons with normal results Exclusion: none reported Non-epilepsy population: healthy controls	Existence of interictal fast-ripple events	VIDEO EEG
Chen, 2008[39]	N=43; USA; mean age 33.6; 29/43 female Inclusion: Patients had seizures with behavioural semiology suggestive of partial seizures, with or without	Ictal video evidence alone Ictal EEG evidence alone	Diagnosis of epilepsy or PNES was considered established by response to surgery, confirmation by invasive

Study	Population	Index test(s)	Reference standard
	secondary generalisation; EEGs from patients with epilepsy all showed recognisable changes though this was not known to blinded readers. Exclusion: Patients with known mixed epilepsy and PNES Non-epilepsy population: PNES	Selected ictal semiological features	recording, response to psychiatric therapy, or surface video-EEG confirmation followed by serial observations for at least a year
Choi, 2020[43]	N=160; South Korea; mean age 14.6 years; 59.4% female Inclusion: Under 18 years of age who had been admitted to the Department of Paediatrics or had visited the outpatient clinic or emergency department at Kyung Hee University Hospital (Seoul, South Korea) for TLOC between June 2013 and May 2018. Patients were initially identified who were assigned International Classification of Disease, 10th Revision (ICD-10) billing codes for “syncope and collapse” at the time of the first visit. The medical charts of patients with TLOC as the chief complaint were retrospectively analysed. Exclusion: Patients who had visited the hospital previously due to TLOC and were diagnosed with any disease; patients who had previously undergone any diagnostic tests; patients who had been diagnosed with acute systemic illness on visiting the hospital due to TLOC; patients who were taking medications that can lead to arrhythmia or orthostasis. Non-epilepsy population: any suspected of epilepsy	ECG Brain CT Brain MRI EEG Echocardiogram Head up tilt test	Clinical impression based on all data over prolonged follow up period.
Deli, 2021[56]	N=69; mean age 36.2 years (PNES only); 59% female (PNES only) Inclusion: People with epilepsy or PNES admitted for V-EEG. Exclusion: None reported Non-epilepsy population: PNES	Reports of physical symptoms: Light headedness/dizziness Sensory disturbances/dysesthesias Hot flushes Palpitations	VIDEO EEG
Derry, 2006[58]	N=62; Australia; mean age 27.9 years; 27.4% female Inclusion: Patients who had been referred to a sleep physician or neurologist with a history of nocturnal events of uncertain cause. Individuals with NFLE were eligible for	FLEP scale	Expert interview and, when necessary, recording of events using video-EEG monitoring

Study	Population	Index test(s)	Reference standard
	the study if they had a history consistent with NFLE and at least 1 of the following: video-EEG monitoring with clinical or electrographic evidence of nocturnal frontal lobe seizures or a genetic mutation consistent with ADNFLE. Patients with parasomnias were recruited in 2 sub-groups. The first group consisted of subjects who were referred to a sleep clinic for diagnosis of their nocturnal events but in whom a definite diagnosis of "typical" parasomnia was made by the specialist without recourse to video-EEG monitoring. In this group, the diagnosis was made on the basis of the history independently by 3 clinicians (a consultant adult epileptologist, a consultant paediatric epileptologist, and a consultant sleep paediatrician), none of whom were involved in the validation of the FLEP scale. The second group comprised cases in which there was diagnostic uncertainty on the basis of the history alone and in which the diagnosis was established by video-EEG or PSG monitoring. These cases were designated "atypical" parasomnias. Exclusion: not reported Non-epilepsy population: arousal parasomnia and sleep disorder		
Dixit, 2013[60]	N= 280; USA; mean age not reported; 62.5% female Inclusion: People evaluated in EMU with video EEG Exclusion: Unclear diagnosis on vEEG; dual diagnosis of epilepsy/PNES; learning disability; first language not English Non-epilepsy population: PNES	Existence of >1 co-morbidities from medical records	VIDEO EEG
Dogan, 2017[61]	N=270; Turkey; age range 19-92; 42% female Inclusion: >=18 years; normal serum pH levels; final definitive diagnosis of generalised tonic-clonic seizures, psychogenic nonepileptic seizures or syncope. Needed to have CT/MRI, EEG and ECG data with observable clinical signs and symptoms. Exclusion: None reported	Serum lactate	Final definitive diagnosis of generalised tonic-clonic seizures, psychogenic nonepileptic seizures or syncope. Needed to have CT/MRI, EEG and ECG data with observable clinical signs and symptoms

Study	Population	Index test(s)	Reference standard
	Non-epilepsy population: psychogenic nonepileptic seizures and syncope		
Douw, 2010[62]	N=161; Holland; mean age 52 years; 51% female Inclusion: 18 years old; evaluated with a standard EEG because of suspected epilepsy after a first possible seizure. Exclusion: not reported Non-epilepsy population: healthy controls	Degree of synchronisation of EEG in time domain, quantified by theta SL	Medical chart review was conducted for all patients to determine whether a clinical diagnosis of epilepsy was reached within a follow-up of one year.
Dubey, 2017[64]	N= 387; USA; mean age 53/44 years; 47.7%/57.4% female Inclusion: Patients in whom autoimmune encephalopathy, autoimmune epilepsy or autoimmune dementia evaluations of serum, CSF, or both were requested; patients with ICD classification of epilepsy or recurrent seizures Exclusion: not reported Non-epilepsy population: any suspected of epilepsy	Antibody prevalence in epilepsy score (APE)	CNS-specific antibodies (neural antibody positive) in presence of confirmed diagnosis based on 2 unprovoked seizures at least 24hrs apart or one unprovoked seizure with additional clinical features suggesting a high probability of recurrence
Duez, 2016[65]	N= 52; Denmark; median age 29 years; 69.2% female Inclusion: Paroxysmal clinical episodes, suggesting epileptic seizures; at least 3 normal EEG recordings, 2 of which included provocation methods of hyperventilation and photo stimulation and 1 of which was sleep-EEG Exclusion: not reported Non-epilepsy population: any suspected of epilepsy but with no interictal findings on provoked EEG	Magnetoencephalography	Diagnostic reference standard was inferred from the diagnosis obtained from the medical chart, after at least one year follow-up after MEG. This was based on all available clinical and para-clinical data for each patient, including description of witnessed seizures, home video recordings of seizures, neuroimaging, laboratory and neurophysiological data.
Egawa, 2020 #1740[68]	N= 50; Japan median age 72 years; 34% female Inclusion: Altered Mental Status (AMS) with unknown aetiology Exclusion: Patients with consciousness recovered completely between HS-cv EEG and C-cEEG monitoring; if C-cEEG monitoring was not performed due to unavailability, or if the HS-cv EEG data were not clear	Headset-type continuous video EEG monitoring (HS-cv EEG monitoring).	Researchers performed definitive diagnosis of abnormal EEG patterns and NCSE by employing conventional continuous EEG [C-cEEG] monitoring with 21 collodion-type electrodes from the international 10–20 with video camera monitoring. All cEEG records were reviewed by at least two trained

Study	Population	Index test(s)	Reference standard
	enough due to artefact interruption. Those with do not attempt resuscitation (DNAR) declarations were also excluded, considering that earlier initiation of HS-cv EEG was not performed. Non-epilepsy population: any suspected of epilepsy		neurophysiologists or epileptologists. If any of the EEG findings were equivocal, consensus was used.
Ehsan, 1996[69]	N= 50; USA; mean age 33 years; 60% female Inclusion: Patients admitted to epilepsy monitoring unit for video-EEG monitoring for a history of refractory seizures or non-epileptic events; first clinical event only analysed Exclusion: not reported Non-epilepsy population: any suspected of epilepsy	Paired capillary prolactin measures	VIDEO EEG or audio EEG
Erba, 2016[73]	N= 21; Italy/USA; mean age >18 years; gender not reported Inclusion: Aged >18 years; admitted to epilepsy centre Exclusion: Lacked intellectual capacity to answer questionnaires Non-epilepsy population: any suspected of epilepsy	Video without EEG or other data	The GS diagnosis was that established by the clinical team after a comprehensive evaluation of the patient's risk factors, comorbidities, psychosocial status, results of neurologic examination and neuroimaging, video semiology, EEG findings including purely electrical seizures, and the results of monitoring other physiologic parameters (ECG [electrocardiography], blood pressure, orthostatic testing, blood sugar, and so on) as appropriate.
Ettinger, 1998[75]	N=22; USA; age range 10-46; 77.2% female Inclusion: Patients undergoing continuous video EEG monitoring on EMU; diagnostic testing carried out; episodes associated with impaired consciousness Exclusion: No altered awareness; pregnancy; use of neuroleptic agents; unobtainable PRL results; SPECT scans compromised by movement artefact; unacquired SPECT because of failure to inject radioisotope at correct time Non-epilepsy population: PNES	Postictal and interictal single photon emission computed tomography (SPECT).	VIDEO EEG

Study	Population	Index test(s)	Reference standard
Ettinger, 1999[74]	N=39; USA; mean age 41.4 years; 76.9% female Inclusion: Adult patients evaluated at the Epilepsy Management site between 1996-98; epilepsy patients were 1) focal with secondary generalisation, or 2) generalised tonic clonic; documented epilepsy on video-EEG for epilepsy group, and patients with episodes characterised by bilateral motor activity and altered responsiveness, but without video-EEG evidence of seizures or without significant post-ictal prolactin elevation Exclusion: Learning disability; mixed epileptic/NES; patients with interictal headaches Non-epilepsy population: PNES	Symptom questionnaire. The responses to the question, 'what symptoms do you have after a seizure?' were reviewed	VIDEO EEG
Geut, 2017[81]	N= 104; Holland; mean age 47 years; 35.6% female Inclusion: Patients with unprovoked focal or generalized seizures who were admitted to the Clinical Neurophysiology department. Unprovoked seizures were defined as convulsive episodes occurring in the absence of precipitating factors. This included seizures of unknown aetiology as well as seizures in relation to a demonstrated pre-existing brain lesion (remote symptomatic seizure). Patients were subsequently selected in whom the routine EEG (including hyperventilation and photic simulation) was normal or did not show convincing IEDs, and either a sdEEG or an aEEG was requested. Finally, both groups were matched for age and gender. Exclusion: Patients younger than 6 years, patients with known epilepsy and patients with provoked seizures. Non-epilepsy population: any suspected of epilepsy	Ambulatory EEG Sleep deprived EEG	The patients' clinical record was evaluated for age, sex, first seizure, start of anti-epileptic drugs, MRI or CT results and whether or not diagnosis of epilepsy was made with a follow up of one year. The diagnosis of epilepsy was based on the new ILAE criteria published in 2014
Geyer, 2000[82]	N= 261; USA; mean age 33.75 years; 39.8% female Inclusion: Patients with TLE, FLE, generalised epilepsy or PNES undergoing video EEG Exclusion: not reported Non-epilepsy population: PNES	Existence of ictal pelvic thrusts	VIDEO EEG

Study	Population	Index test(s)	Reference standard
Giorgi, 2013[84]	N=210; Italy; mean age 41 years; 45% female Inclusion: Sleep deprived EEG (SD EEG) requested as a prospective evaluation for suspected epileptic seizures; previous standard waking EEG not showing any interictal abnormalities (IIAs); not under antiepileptic drugs until at least date of SD EEG; previous 1.5T MRI; minimum 1 year follow up; final diagnosis performed in the centre and defined as 'non-epilepsy', 'focal epilepsy' or 'generalised epilepsy'. Exclusion: juvenile myoclonic epilepsy Non-epilepsy population: any suspected of epilepsy	Sleep deprived EEG	Final diagnosis obtained after collegial discussion by epileptologists in the centre with at least 5 years' experience in clinical epilepsy. Diagnosis confirmed based on recurrence of clear epileptic unprovoked seizures. Single seizures not included. Most patients also given video EEG or 24 hour dynamic EEGs. Clinical records also evaluated
Gonzalez-Cuevas, 2019[86]	N= 29; Spain; mean age 64.75years; 48.3% female Inclusion: >=18 years old; PCT acquired immediately following diagnosis; clinical or EEG diagnosis of status epilepticus (SE) established in ER or hospitalisation Exclusion: Patients with delayed PCT acquisition; allergy to iodinated contrast material; other contraindications for PCT Non-epilepsy population: any suspected of epilepsy	Perfusion computed tomography	Diagnosis by ictal EEG and clinical semiology
Goselink, 2019[87]	N= 187; Holland; age and gender not reported Inclusion: All consecutive EEG recordings from both adult and pediatric patients with a clinical suspicion of non-convulsive status epilepticus (NCSE); all consecutive EEG recordings without a clinical suspicion but with an abnormal EEG were included in the clinically 'not suspected for NCSE' group. Exclusion: Patients with technically insufficient EEG recordings and EEG recordings lasting <30 minutes Non-epilepsy population: any suspected of epilepsy	EEG review using SalzburgSalzburg criteria	Expert opinion of another four neurophysiologists who had access to all clinical information, including laboratory tests, imaging studies, response to treatment, follow-up and outcome, as well as all EEG recordings. The consensus view held as the final diagnosis.
Hanrahan, 2018[90]	N=12; mean age 40.6 years; 33% female Inclusion: Patients admitted to the Epilepsy Monitoring Unit for 'spell classification' who had videos taken of their events during the evaluation Exclusion: not reported	Clinical history. Videos of the seizure event captured during EMU evaluation.	The paper describes EMU diagnosis as entailing video-EEG, clinical history and witnessed semiology. The reported EMU-confirmed diagnosis was

Study	Population	Index test(s)	Reference standard
	Non-epilepsy population: any suspected of epilepsy		considered final. The diagnosis was also described as 'established'.
Hendrickson, 2014[92]	N= 354; USA; mean age not reported; 64.4% female Inclusion: Patients undergoing vEEG monitoring; participated in either neuropsychological or psychological testing; interviewed for panic attack criteria Exclusion: Unclear diagnosis; episodes secondary to another primary disorder; diagnosis of both PNES and epilepsy Non-epilepsy population: PNES	Number of panic attack symptoms	VIDEO EEG
Hoefnagels, 1991[94]	N= 119; USA; mean age not reported; 47% female Inclusion: All consecutive patients (> 15 years of age) referred to the neurological department because of one or more episodes of transient loss of consciousness. Transient loss of consciousness was defined as an episode of less than one hour with inability to maintain posture and to recall events during the episode. Exclusion: Patients with loss of consciousness due to trauma or subarachnoid haemorrhage and patients with pre-diagnosis of epilepsy. Non-epilepsy population: any suspected of epilepsy	Routine interictal EEG. If patient <65years, had an additional hyperventilation test (40 breaths per minute for 3 minutes. End tidal CO2 level had to be <2.5% after hyperventilation. Blood gases measured. Hyperventilation test considered negative if end tidal CO2 did not restore to >90% baseline value after 3 minutes recovery. Standard ECG given and assessed as normal or abnormal according to the QT-interval. Laboratory examination of serum sodium, potassium, calcium, phosphate, glucose, urea, ESR, liver function and FBC.	A definitive diagnosis of seizure was given by: movements during loss of consciousness and identified clonic movements from a range of movements imitated by the interviewer; if an eyewitness observed automatisms, such as chewing or lip smacking, during loss of consciousness; if the patient reported an unequivocal aura, such as a strange smell, preceding the event; if the patient felt confused immediately after the event (inability to recognise familiar persons or environment);if the patient had tongue biting. Unclear if needed just one of these or all of these to trigger a diagnosis.
Huang, 2019[96]	N=12; China; mean age 16 months; gender unclear Inclusion: Infants with paroxysmal events that had been videoed; resolution was high enough to ensure facial features were visible; all possible body movements were	Medical record only Medical record plus 1 minute video of event	All corresponding descriptions, home videos, and VEEG reports were presented to two senior epileptologists

Study	Population	Index test(s)	Reference standard
	recorded; sound in videos is clear, and excessive ventilation sounds can be distinguished. Exclusion: No consent from caregivers; video >1 minute long (may impair public playback) Non-epilepsy population: any suspected of epilepsy		blind to the study purpose, and they made diagnoses accordingly
Husain, 2020[97]	N=17; USA; mean age 49.1 years; 21.1% female Inclusion: Patients with a history of ES or PNES admitted to one of 3 EMUs for routine seizure characterisation Exclusion: Any patients on whom intracranial EEG monitoring was used Non-epilepsy population: PNES	sEMG classification of seizure events by expert review. Single channel surface EMG (sEMG) attached unilaterally on the belly of the biceps. Graphical user interface allowed expert review Automated sEMG classification. As above, but using an automated decision tool. This generated a 'seizure score from 0-25 with a threshold of 8 or above (= epilepsy)	VIDEO EEG
Jackson, 2016[99]	N=219; Australia; median age 45 years; 40% female Inclusion: Patients referred by the ED to the adult first seizure clinic at Monash medical centre Exclusion: not reported Non-epilepsy population: any suspected of epilepsy	ED initial assessment by ED doctors	Final diagnosis: Index test data, PLUS MRI brain scans and EEG data that had been collected after ED discharge, with decision made by study authors (epilepsy specialists).
Jaraba, 2019[100]	N=55; Spain; mean age 62.1 years; 38.1% female Inclusion: All patients undergoing 99mTc-hexamethyl propyleneamine oxime [HMPAO] single photo emission computed tomography [SPECT] [HMPAO-SPECT] as part of their diagnostic workup in the centre; clinical suspicion of NCSE Exclusion: Patients with sub-optimal EEG recordings; patients with NCSE because of hypoxic-anoxic aetiology;	Ictal HMPAO SPECT scans (visual) Ictal HMPAO SPECT scans (quantitative) Ictal EEG using Salzburg criteria	Patients were classified as NCSE or non-NCSE following a consensus decision based on all clinical and paraclinical data, including EEG readings, laboratory data, therapeutic response, follow up and final outcome. Two clinicians evaluated these data independently blinded to HMPAPO-SPECT results. A third clinician was used to resolve conflicts.

Study	Population	Index test(s)	Reference standard
	no consensus on diagnosis; where EEG and HMPAO-SPECT were not done simultaneously Non-epilepsy population: any suspected of epilepsy		
Keezer, 2016[102]	N=72; Canada; mean age 35 years; 61% female Inclusion: All patients undergoing a prolonged ambulatory EEG (paEEG); medical record at the MNI to allow expert to ascertain clinical diagnosis of epilepsy or not Exclusion: not reported Non-epilepsy population: any suspected of epilepsy	Routine EEG. Prolonged ambulatory EEG (paEEG).	One neurologist, a fellow of the Royal College of Physicians of Canada, reviewed medical records to identify those individuals with epilepsy. To minimize verification bias (i.e., constructing the reference standard with prior knowledge of the index test results), the assessor relied on the documented medical history and event semiology. Additional data collected were subject age, sex, epilepsy aetiology, the use of antiepileptic drug(s), and reason for referral by the treating physician
Khan, 2009[107]	N=50; USA; mean age not reported; 57% female Inclusion: Patients being evaluated for a medically refractory seizure disorder; aged 18 or older; able to undergo hypnosis (able to hear and see) Exclusion: Pregnancy; learning disability; psychosis; under the influence of illicit substances Non-epilepsy population: any suspected of epilepsy	Patients underwent the Hypnotic Induction Profile	VIDEO EEG
Kimiskidis, 2017[109]	N= 31; Greece; mean age 28 years; 54.8% female Inclusion: Patient group: Patients with GGE; passed TASS questionnaire except epilepsy-related questions; both clinical and EEG features consistent with GGE; at least 2 seizures and on AEDs Exclusion: Other CNS disorders; comorbid conditions; EEG evidence of focal abnormalities; slow spike and wave discharges or triphasic patterns; centrally acting drugs other than AEDs; past or present substance/ETOH abuse Non-epilepsy population: healthy controls	Paired pulsed transcranial magnetic stimulation	Diagnosis by 2 experienced epileptologists who reached consensus based on clinical and laboratory data.

Study	Population	Index test(s)	Reference standard
Knox, 2018[111]	N=340; USA; mean age 3.9 years; gender not reported Inclusion: First time vEEG without capturing a habitual event; at least 1 year of FU; on hospital database Exclusion: Neonates; diagnosis of epilepsy that predated the initial vEEG study by >1 month; no history of paroxysmal events Non-epilepsy population: any suspected of epilepsy	No event video EEG	Final definitive diagnosis based on full medical records and a minimum of 1 clinic visit in 1 year of follow up. Often unblinded to EEG results
Koren, 2018[114]	N=85; Austria; mean age 58.9 years; 51.8% female Inclusion: Neurological critical care patients with clinically suspected NCSE [unexplained deterioration or fluctuation of consciousness, subtle motor activity (persistent or fluctuating muscle twitching of the face or extremities, manual and oral automatisms) as well as pupillary and ocular movement abnormalities (nystagmus, hippus, mydriasis, or sustained eye deviation). Exclusion: not reported Non-epilepsy population: any suspected of epilepsy	Several early findings (first 30 minutes of EEG recordings) were tested: Early sporadic epileptiform discharges (SED) Early rhythmic and periodic EEG patterns of 'ictal-interictal uncertainty' (RPPIIIU) Early SED or RPPIIU Clinical signs of non-convulsive seizures (NCS) Early SED or RPPIIU and clinical signs of NCS Early SED, RPPIIU, or clinical signs of NCS	Critical care continuous EEG (for detection of NCSE). Used 21 electrodes according to the 10-20 system. Recordings performed as soon as possible following clinical suspicion of NCSE (all within 12 hours). EEG data classified according to the ACNS SCCET. Mean recording time was 72 (67) hours [range 5-388 hours]
Kusmakar, 2019[116]	N=79; Australia; mean age 31.6 years; 60% female Inclusion: Patients undergoing VIDEO EEG; history of events that mimicked generalised seizures or events characterised by the presence of bilateral convulsions Exclusion: Patients having intracranial monitoring or with a psychiatric disorder Non-epilepsy population: PNES	Wrist accelerometer	Decided by consensus between 2-6 epileptologists, where a decision was made based on clinical history, neuropsychiatric evaluation, neuroimaging, Video EEG for 3 days and observed seizure semiology
Leitinger, 2016[124]	N= 120; Denmark/Austria; median age 65 years; 47% female Inclusion: Aged 4 months or older (if from tertiary centre); 18 years or older (if from the 2 secondary care centres); clinical suspicion of non-convulsive status epilepticus,	Routine EEG using Salzburg criteria	The reference standard was inferred from all clinical and para-clinical data, including EEG readings (but not the results of Salzburg criteria), laboratory data, neuroimaging data, therapeutic

Study	Population	Index test(s)	Reference standard
	having a history of decreased cognition/consciousness for at least 10 minutes. Exclusion: Participants with technically insufficient EEG recordings; EEG recordings lasting <20 minutes. Non-epilepsy population: any suspected of epilepsy		response, follow-up, and final outcome. For all patients and recordings, two authors evaluated these data independently, while blinded to the Salzburg criteria scorings
Li, 2017[125]	N=54; USA; age and gender not reported Inclusion: ED discharge diagnosis of 'generalised seizures' or 'generalised shaking episodes'; aged >=18 years; well documented spell onset within 24 hours of a basic metabolic panel drawn in the ED Exclusion: Other documented active medical problems that could cause acidosis and confound the analysis, such as sepsis, alcohol or medicine toxicity Non-epilepsy population: PNES	Anion gap	Abnormal interictal EEG showing epileptiform discharges, plus with a documented semiology of their event consistent with a generalised convulsive seizure. Subjects diagnosed as PNES if video EEG confirmed this.
Manni, 2008[131]	N= 71; Italy; mean age 54years; 15.5% female Inclusion: Patients with undefined (epileptic or parasomnia) nocturnal paroxysmal motor-behavioural episodes attending the Sleep Medicine and Epilepsy Unit (an outpatient facility) at the IRCCS "C. Mondino Institute of Neurology" Foundation in Pavia, Italy; final diagnosis of arousal parasomnias, NFLE or idiopathic RBD. Exclusion: not reported Non-epilepsy population: parasomnias or idiopathic RBD	FLEP scale	VIDEO EEG
McGinty, 2021[132]	N= 219; UK; mean age 49 years; 49.8% female Inclusion: Consecutive adult patients with a diagnosis of new-onset focal epilepsy and their first seizure within the previous 12 months Exclusion: not reported Non-epilepsy population: any suspected of new onset focal epilepsy	ACE attention domain APE2 score	Detection of Neuronal surface-directed antibodies (NSAb)
Mueller, 2013[136]	N=80; USA; mean age 35.9 years; 65% female Inclusion: Not reported, though all patients were reported to be seizure free for at least 24 hours before the MRI study.	4T MRI	Seizure semiology and prolonged ictal and interictal Video/EEG/Telemetry (VET)

Study	Population	Index test(s)	Reference standard
	Exclusion: not reported Non-epilepsy population: healthy controls		
Naganur, 2019[137]	N=11; Australia; mean age (seizures/PNES) 20/24years; 58.3% female Inclusion: Patients admitted for VEM for the investigation of possible epilepsy were eligible for inclusion. Patients were eligible for inclusion if they experienced one of their typical clinical events of at least 20 seconds (s) in duration in which there was sustained, rhythmic or arrhythmic movements affecting at least one limb. This included patients with purely tonic or hyper motor movements. Exclusion: Patients experiencing solely non-convulsive seizures were excluded. Non-epilepsy population: PNES	Wrist accelerometer data	VIDEO EEG
Noe, 2012[143]	N=439; USA; mean age 47.9 years; 64% female Inclusion: Patients admitted to EMU for spell classification Exclusion: Subjects with a known diagnosis of epilepsy admitted to EMU for pre-surgical evaluation, medication adjustment, status epilepticus, or seizure quantification. Non-epilepsy population: any suspected of epilepsy	Impression of the admitting epidemiologist, based on review of history, physical and available diagnostic testing as documented in the medical record prior to vEEG.	VIDEO EEG
Okazaki, 2018[144]	N= 57; USA; mean age 42 years; 52.6% female Inclusion: People aged >18 admitted to having scalp continuous vEEG monitoring for episode classification Exclusion: People whose monitoring session was inconclusive because of the lack of recorded events Non-epilepsy population: any suspected of epilepsy	Epifinder application – a clinical decision support tool.	VIDEO EEG
Oliva, 2008[145]	N=84; Australia; mean age 38.0 years; 50% female Inclusion: Patients admitted to Royal Melbourne Hospital for inpatient video monitoring, in whom at least 1 convulsive event was captured Exclusion: not reported Non-epilepsy population: any suspected of epilepsy	Existence of oral lacerations and incontinence. Information collected by medical scientists via direct questioning and examination of the patient after a convulsive event.	VIDEO EEG

Study	Population	Index test(s)	Reference standard
Ottman, 2010[146]	N=342; USA; mean age 54 years; 61% female Inclusion: All residents of the city of Rochester, MN, U.S.A., who were born in 1920 or later and had incidence of either epilepsy (two or more unprovoked seizures) or an isolated unprovoked seizure between 1935 and 1994. Exclusion: not reported Non-epilepsy population: healthy controls	General screening interview for epilepsy	A comprehensive review of the medical records of each case or control was carried out. Abstraction involved initial review by trained nurse abstractors followed by expert review by the study epileptologists and provided detailed information for the duration of each subject's residence in the Rochester area, including all outpatient examinations, home and emergency room visits, hospitalization records, laboratory tests, and neurologic and other special examinations.
Rawlings, 2017[158]	N= 293; UK; mean age 43.8 years; 73.0% female Inclusion: Patients with epilepsy or PNES supported by video EEG recordings of typical seizures involving TLOC identified from patient databases; patients with a diagnosis of recurrent syncope supported by pathophysiological evidence Exclusion: Patients unable to complete the questionnaire without help (learning disability) Non-epilepsy population: PNES or syncope	Panic measures. This was captured by the Paroxysmal Event Profile – this consists of 86 Likert style questions about symptoms, 7 of which were focussed on panic symptoms.	VIDEO EEG
Renzel, 2016[159]	N= 237; Switzerland; mean age 38 years; 39.2% female Inclusion: Age >16; at least one routine EEG because of suspected epilepsy and been subsequently examined with an EEG SD (24 hours); full documentation of history, EEG and diagnosis available; no diagnosis made before SD EEG; no specific epileptiform changes in the EEG before SD-EEG; documented cerebral imaging via MRI within 2 years of EEG recordings Exclusion: Patients declined use of their data; no final diagnosis available; no adequate documentation of the medication taken; use of highly potent neuroleptic drugs Non-epilepsy population: any suspected of epilepsy	Sleep deprived EEG	Established after collegial discussion for each case by the study investigators according to the ILAE guidelines
Reuber, 2009[161]	N=20; UK; mean age 36.9 years; 65% female	Linguistic aqnalysis	VIDEO EEG

Study	Population	Index test(s)	Reference standard
	Inclusion: Refractory seizure disorders; referred for Video EEG; uncertainty between epilepsy and PNES; seizure captured by video; ictal EEG allowed unequivocal diagnosis of epilepsy or PNES Exclusion: Combined epilepsy and PNES; admitted for epilepsy surgery evaluation; non-fluent English; unable to complete self-report measures Non-epilepsy population: PNES		
Reuber, 2016[160]	N=300; UK; mean age 43.5years; 73% female Inclusion: Patients with epilepsy or PNES supported by video EEG recordings of typical seizures involving TLOC identified from patient databases; patients with a diagnosis of recurrent syncope supported by pathophysiological evidence Exclusion: not reported Non-epilepsy population: PNES or syncope	Paroxysmal Event Profile Questionnaire – 86 items focussing on TLOC manifestations, plus 7 further questions related to demographic and clinical features.	VIDEO EEG
Rosenow, 1998[163]	N=40; Germany; mean age 103.4 months; gender not reported Inclusion: Children presenting with a chief complaint of staring spells Exclusion: not reported Non-epilepsy population: any suspected of epilepsy	Symptom questionnaire.	VIDEO EEG
Rowberry, 2020[166]	N=101; UK; median age 4 years; 47.5% female Inclusion: Patients under 18 years identified by PICU clinicians to be at risk of epileptic seizures and commenced on Quantitative EEG (qEEG) Exclusion: Patients with decompressive craniectomy and allergy to collodion glue Non-epilepsy population: any suspected of epilepsy	Quantitative EEG interpreted in real time by PICU clinicians	A clinical neurophysiologist retrospectively reviewed each qEEG recording to identify epilepsy seizures. The neurophysiologist had access to the same electrophysiology information available to the PICU clinicians. This included the raw EEG.
Schmidt, 2016[171]	N=68; UK; age 16-59 years; gender not reported Inclusion: IGE individuals were drug naïve Exclusion: not reported Non-epilepsy population: any suspected of epilepsy	Computational biomarker based on extent of synchrony between EEG channels and the normalised power	This was a 'case-control' design where 38 healthy controls and 30 people with a diagnosis of Idiopathic Generalised Epilepsy (IGE) were recruited. A diagnosis of epilepsy was confirmed in

Study	Population	Index test(s)	Reference standard
		spectrum from a short resting state interictal EEG	each IGE case by an experienced epilepsy specialist through observation of typical generalized spike-wave (GSW) activity on EEG either spontaneously or following hyperventilation or photic stimulation. For 10 of these people, the diagnosis was confirmed following an initial routine EEG. For the remaining 20, diagnosis was confirmed following sleep-deprived or longer-term EEG monitoring (including sleep). Similar healthy control EEG was collected at King's College Hospital EEG department.
Sen, 2007[176]	N = 36; UK; age and gender unclear Inclusion: Epilepsy or PNES Exclusion: not reported Non-epilepsy population: PNES	Existence of postictal stertorous breathing	Full use of all clinical data collected over 18 months
Seneviratne, 2017[177]	N= 138; Australia; mean age 43 years; 52.2% female Inclusion: All patients undergoing monitoring at the EMU of Monash Medical Centre; adults aged >=18; diagnosed with PNES or ES Exclusion: Events with subjective symptoms or without obvious semiological features; electrographic epileptic seizures without clinical semiology Non-epilepsy population: PNES	Ictal duration	VIDEO EEG
Sierra-Marcos, 2011[179]	N= 131; Spain; mean age 52.4years; 45% female Inclusion: Adult patients who consulted consecutively for a new onset seizure to the ER; stereotyped paroxysmal spell highly suggested an epileptic seizure Exclusion: Patients with previous seizures Non-epilepsy population: any suspected of epilepsy	Early EEG Follow up routine EEG Sleep deprived EEG CT	Full clinical, EEG, CT, video EEG AND 12 months follow up

Study	Population	Index test(s)	Reference standard
Simani, 2018[180]	N=82; Iran; mean age 30.9 years; 53.6% female Inclusion: Patients with a history of recurrent seizures, admitted to EMU for further evaluation; control group comprised healthy volunteers with no history of seizure. Exclusion: Patients with other medical, neurologic or psychiatric diseases, or history of recent head trauma; medications other than AEDs or psychoactive drugs Non-epilepsy population: any suspected of epilepsy	Post-seizure serum glial fibrillary astrocytic protein (GFAP) serum levels	VIDEO EEG
Slater, 1995[181]	N=49; USA; age and gender not reported Inclusion: Age >=18; patients admitted to EEG video telemetry unit. Exclusion: not reported Non-epilepsy population: PNES	Wilkus classification guideline: A patients has pseudo seizures if any of the following are true: a) hysteria or hypochondriasis score >=70 and one of the two highest points in the profile (disregarding the masculinity-femininity and social introversion scales, b) hysteria or hypochondriasis score >=80 and not necessarily among the two highest points, c) hysteria and hypochondriasis both >59 and both 10 points higher than the depression scale.	VIDEO EEG
Stroink, 2003[184]	N= 760; Holland; ages 1 month to 16 years; gender not reported Inclusion: All children aged 1 month to 16 years referred by GP or paediatrician at participating hospital for a single seizure or suspected epilepsy Exclusion: Children with only neonatal, febrile or other acute symptomatic seizures; children referred from other hospitals for a second opinion Non-epilepsy population: any suspected of epilepsy	Clinical diagnosis: Attending paediatric neurologist completed an extensive questionnaire on description of events, including postictal signs, possible provoking factors, medical and family history. Standard EEG performed in each child. If no epileptiform discharges a recording after	Use of original data plus information gained over 5 years of follow up (if epilepsy originally diagnosed), 2 years of follow up (if single seizure) or 1 year of follow up (if no epilepsy diagnosis or single event at baseline).

Study	Population	Index test(s)	Reference standard
		partial sleep deprivation was made, or in small children during a daytime nap.	
Swartz, 2002[186]	N=462; USA; age and gender not reported Inclusion: Patients referred to PET facility Exclusion: No seizures within 72 hours Non-epilepsy population: any suspected of epilepsy	Positron Emission Tomography with 2-deoxy-2[18F] fluro-D-glucose (FDG-PET)	VIDEO EEG
Syed, 2011[191]	N=35; USA; mean age 37.0 years; 60% female Inclusion: Seizure patients scheduled for vEEG; VEEG recorded epilepsy or PNES during stay Exclusion: not reported Non-epilepsy population: PNES	Epileptologist blinded and independent review of seizure videos in terms of the following semiological signs: 1) eye-opening or widening at onset of seizure, 2) abrupt onset, 3) post-ictal confusion/sleep Eye-witness accounts of seizure in terms of the following semiological signs: 1) eye-opening or widening at onset of seizure, 2) abrupt onset, 3) post-ictal confusion/sleep	VIDEO EEG
Tatum, 2020[193]	N=44; USA; mean age 45.1 years; 70% female Inclusion: 18 years or older; voluntary consent; had completed a history assessment and physical examination; outpatients referred with events that could be epilepsy; submitted an outpatient smartphone video of their primary ictal event; underwent gold standard test of video-EEG; >95% of each survey completed by reviewers; had a final diagnosis Exclusion: <18 years; pregnant; incomplete or absent history/physical examination; no smartphone video; did not undergo gold standard; confirmed history of mixed epileptic and non-epileptic events; declined study participation; no informed consent	Patients provided a witness-generated outpatient smartphone video. History and physical examination done by 3 experts, lasting an average of 60 minutes	VIDEO EEG

Study	Population	Index test(s)	Reference standard
	Non-epilepsy population: any suspected of epilepsy		
Tews, 2015[194]	N= 248; Germany; mean age 6.2 years; 45.2% female Inclusion: first afebrile seizure; aged 1 mo. to 18 yrs. not suffering from pre-existing neurological disorders Exclusion: situation-related or acute symptomatic seizures resulting from toxic, metabolic, infectious or traumatic reasons were excluded. Non-epilepsy population: any suspected of epilepsy	EEG MRI	Seizure recurrence at 48 months, with use of the International League Against Epilepsy definitions to clinically classify patients as having epilepsy
Thompson, 2010[196]	N= 184; USA; mean age 37 years; 67.4% female Inclusion: Patients completing the Personality Assessment Inventory (PAI) and video EEG at the regional epilepsy centre. Exclusion: Not diagnosed by video EEG as either epilepsy or PNES Non-epilepsy population: PNES	Psychological indices PNES (Psychogenic nonepileptic seizures); threshold for PNES >=1 SOM-C (conversion); threshold for PNES >=70 SOM (somatic complaints); threshold for PNES >=70 SOM-S (somatisation); threshold for PNES >=70 DEP (Depression); threshold for PNES >=60 DEP-P (Depression-physiological); threshold for PNES >=70 ANX-P (Anxiety-Physiological); threshold for PNES >=60	VIDEO EEG
Tyson, 2018[199]	N=105; USA; mean age 36.9 years; 54.3% female Inclusion: Patients with neuropsychological assessments, and data on psychometric testing Exclusion: not reported Non-epilepsy population: PNES	Multivariate model of psychometric testing, using 4 measures of cognitive ability – vocabulary, information, Boston naming test and letter fluency)	EEG evidence of ES, with neurological exam, seizure semiology and neuroradiological findings. Video EEG used to exclude PNES so likely that video EEG was used for all, although not directly stated.

Study	Population	Index test(s)	Reference standard
van Diessen, 2013[200]	N=70; Holland; mean age 10 years; 31.4% female Inclusion: One or more suspected epileptic event(s) were eligible for our study. Children included who were eventually diagnosed with new onset partial epilepsy. Exclusion: Children with neurological or psychiatric comorbidities, including developmental delay Non-epilepsy population: control group not suspected of epilepsy	Routine interictal EEG recording, using international 10-20 system. Functional network approach: Periods of resting-state EEG, free of abnormal slowing or epileptiform activity, were selected to construct functional networks of correlated activity.	The clinical diagnosis of epilepsy was defined by at least two unprovoked seizures within one year, judged by two neurologists to be of epileptic origin.
Varma, 1996[203]	N= 20; UK; mean age 35.3years; 50% female Inclusion: Patients referred to neurosurgery unit and diagnoses with NES or epilepsy; diagnosis based on video EEG findings Exclusion: People with dual epilepsy/PNES; brain lesions on CT/MRI Non-epilepsy population: PNES	Hexamethyl propylene amine oxime single photon emission tomography (HMPAO SPECT) brain imaging	VIDEO EEG
Verhoeven, 2018[205]	N=75; Switzerland, Belgium and Austria; mean age 31.7 years; 52.5% female Inclusion: drug resistant TLE, or 'healthy' Exclusion: not reported Non-epilepsy population: any suspected of epilepsy	Resting-state high-density EEG recording data was used. Epochs without interictal spikes were selected. The cortical source activity was obtained for 82 regions of interest and whole brain directed functional connectivity was estimated in the theta, alpha and beta frequency bands. These connectivity values were then used to build a classification system based on two two-class Random Forests classifiers: TLE vs healthy controls and left vs right TLE.	Drug resistant TLE was definitively diagnosed as follows: unilateral anteromedial localization of the epileptogenic zone confirmed by good surgical outcome (Engel's class I or II, after at least 12 months post-operative follow-up), intracranial EEG or concordant presurgical evaluation methods and the existence of at least a 10–15 min resting state eyes-closed high-density EEG recording (96–256 channels).
Vukmir, 2004[209]	N=200; USA; age and gender not reported	Serum prolactin level	A hospital discharge diagnosis of seizure either initially or at the end of

Study	Population	Index test(s)	Reference standard
	Inclusion: Patients who presented to the emergency department with a clinical symptom complex consistent with seizure, manifested as near or total loss of consciousness, accompanied by abnormal motor activity and/or a post-ictal phase. Exclusion: <18 years Non-epilepsy population: any suspected of epilepsy		the stay. The diagnosis was recorded from ED records if discharged or inpatient discharge record if admitted. The presence of an abnormal electroencephalogram indicated by abrupt onset and termination of repetitive rhythmic activity usually consisting of a sharp or spike wave pattern, during the hospital stay if performed was included as well.
Watson, 2012[213]	N= 630; UK; mean age 49.5 years; gender not reported Inclusion: People with EEGs done in the department between July 2006 to December 2009 Exclusion: not reported Non-epilepsy population: any suspected of epilepsy	Routine EEG	Final diagnosis of epilepsy/ no epilepsy, based on all information, including laboratory results, MRI/CT/X ray imaging.
Wilkus, 1984[215]	N=20; USA mean age 28.2 years; gender unknown Inclusion: Patients referred for inpatient EEG/CCTV monitoring Exclusion: not reported Non-epilepsy population: PNES	See Wilkus classification guideline (Slater, 1995)	VIDEO EEG
Willert, 2004[216]	N=52; Germany; mean age 34.7years; 41.6% female Inclusion: Single seizures with an interval of at least 24 hours before and after the seizure; normal levels of NSE, PRL and CK at baseline Exclusion: Acute disorders of the CNS or endocrinological diseases; pregnancy; medication other than anticonvulsants Non-epilepsy population: PNES	Serum neuron-specific enolase (NSE) Serum prolactin (PRL) Serum creatine kinase (CK)	VIDEO EEG

1.2.5 Quality assessment of clinical studies included in the evidence review

For measurement of imprecision, clinical decision thresholds were set at 0.90 [above which may be willing to recommend] and 0.60 [below which is clinically unhelpful (for both sensitivity and specificity).

STRATUM 1: Detection of any epilepsy (differentiation from no epilepsy)

Table 3: Clinical evidence summary: diagnostic test accuracy of different symptoms/signs/semiology for detection of epilepsy. Where detection is of a specific type of epilepsy, rather than epilepsy overall, this is stated clearly in the first column. Each index test is positive if the described symptom is present.

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Tongue biting / oral lacerations during seizure	2 [25] [145]	194	NR/ medical scientist	Video EEG Non-epilepsy group: syncope / population suspected of epilepsy	0.22 [0.10, 0.39] 0.26 [0.16, 0.38]	0.99 [0.93, 1.00] 1.00 [0.81, 1.00]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	None[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	None[c]	VERY LOW
Incontinence during seizure	1 [145]	84	Medical scientist	Video EEG Population suspected of epilepsy but no definite differential diagnoses	0.23 [0.13, 0.35]	0.94 [0.73, 1.00]	**Sensitivity**				
							serious[a]	none	NA	None[c]	MOD
							Specificity				
							serious[a]	none	NA	serious[c]	LOW
Urine loss during seizure *DETECTING ABSENCE SEIZURES IN INFANTS*	1 [163]	40	Physician	Video EEG Non-epilepsy group: population suspected of epilepsy	0.12 [0.01, 0.36]	1.00 [0.85, 1.00]	**Sensitivity**				
							serious[a]	none	NA	None[c]	MOD
							Specificity				
							serious[a]	none	NA	serious[c]	LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Oral lacerations AND incontinence during seizure	1 [145]	84	Medical scientist	Video EEG Population suspected of epilepsy but no definite differential diagnoses	0.08(0.03-0.18)	1.0(0.78-1.0)	**Sensitivity**				
							serious[a]	none	NA	None[c]	MOD
							Specificity				
							serious[a]	none	NA	serious[c]	LOW
Sign observed by epileptologist on video during seizure - eye opening or widening at onset	1 [191]	36	epileptologist	Video EEG Non-epilepsy group: PNES	1.00 [0.79, 1.00]	0.85 [0.62, 0.97]	**Sensitivity**				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure - abrupt onset	2 [39, 191]	79	epileptologist	Video EEG Non-epilepsy group: PNES	0.94 [0.70, 1.00] 1.00 [0.87, 1.00]	0.55 [0.32, 0.77] 0.13 [0.02, 0.38]	**Sensitivity**				
							serious[a]	serious[b]	none	serious[c]	VERY LOW
							Specificity				
							serious[a]	serious[b]	none	serious[c]	VERY LOW
Sign observed by epileptologist on	1 [191]	36	epileptologist	Video EEG	0.81 [0.54, 0.96]	0.70 [0.46, 0.88]	**Sensitivity**				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
video during seizure – postictal confusion/sleep				Non-epilepsy group: PNES			serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – eyes fixed	1 [191]	36	epileptologist	Video EEG Non-epilepsy group: PNES	0.57 [0.34, 0.77]	0.92 [0.62, 1.00]	**Sensitivity**				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – unilateral head turning	1 [191]	36	epileptologist	Video EEG Non-epilepsy group: PNES	0.30 [0.13, 0.53]	1.00 [0.74, 1.00]	**Sensitivity**				
							serious[a]	serious[b]	NA	None[c]	LOW
							Specificity				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – non-sensical speech	1 [191]	36	epileptologist	Video EEG Non-epilepsy group: PNES	0.00 [0.00, 0.15]	0.92 [0.62, 1.00]	**Sensitivity**				
							serious[a]	serious[b]	NA	None[c]	LOW
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – clenched mouth	1 [191]	36	epileptologist	Video EEG Non-epilepsy group: PNES	0.09 [0.01, 0.28]	0.25 [0.05, 0.57]	**Sensitivity**				
							serious[a]	serious[b]	NA	None[c]	LOW
							Specificity				
							serious[a]	serious[b]	NA	None[c]	LOW
Sign observed by epileptologist on video during seizure – hand automatisms	2 [39, 191]	79	epileptologist	Video EEG / surgical or long term follow up Non-epilepsy group: PNES	0.26 [0.10, 0.48] 0.52 [0.32, 0.71]	1.00 [0.74, 1.00] 0.94 [0.70, 1.00]	**Sensitivity**				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – ictal scream	1 [191]	36	epileptologist	Video EEG Non-epilepsy group: PNES	0.22 [0.07, 0.44]	1.00 [0.74, 1.00]	**Sensitivity**				
							serious[a]	serious[b]	NA	None[c]	LOW
							Specificity				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure - grasping	1 [191]	36	epileptologist	Video EEG Non-epilepsy group: PNES	0.09 [0.01, 0.28]	1.00 [0.74, 1.00]	**Sensitivity**				
							serious[a]	serious[b]	NA	None[c]	LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
							Specificity				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – post-ictal nosewiping	1 [191]	36	epileptologist	Video EEG Non-epilepsy group: PNES	0.09 [0.01, 0.28]	1.00 [0.74, 1.00]	**Sensitivity**				
							serious[a]	serious[b]	NA	None[c]	LOW
							Specificity				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure - epostical aphasia	1 [191]	36	epileptologist	Video EEG Non-epilepsy group: PNES	0.09 [0.01, 0.28]	1.00 [0.74, 1.00]	**Sensitivity**				
							serious[a]	serious[b]	NA	None[c]	LOW
							Specificity				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – postictal snoring	2 [16, 191]	104	epileptologist	Video EEG Non-epilepsy group: PNES	0.35 [0.16, 0.57] 0.34 [0.20, 0.50]	1.00 [0.74, 1.00] 1.0 [00.86, 1.00]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	None[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
Sign observed by epileptologist on	1 [39, 191]	79	epileptologist	Video EEG	0.75[e] 0.74 [0.54, 0.89]	0.7[e] 0.31 [0.11, 0.59]	**Sensitivity**				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
video during seizure – abrupt offset				Non-epilepsy group: PNES			serious[a]	serious[b]	NA	Serious[c]	VERY LOW
							Specificity				
							serious[a]	serious[b]	NA	none[c]	LOW
Sign observed by epileptologist on video during seizure – continuous movements	1 [191]	36	epileptologist	Video EEG Non-epilepsy group: PNES	0.57 [0.34, 0.77]	0.67 [0.35, 0.90]	**Sensitivity**				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – eyes rolled back into head	1 [191]	36	epileptologist	Video EEG Non-epilepsy group: PNES	0.52 [0.31, 0.73]	0.67 [0.35, 0.90]	**Sensitivity**				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
Upward eye movements	1 [163]	40	Physician	Video EEG	0.35 [0.14, 0.62]	0.91 [0.72, 0.99]	**Sensitivity**				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
DETECTING ABSENCE SEIZURES IN INFANTS				Non-epilepsy group: population suspected of epilepsy			serious[a]	none	NA	serious[c]	LOW
							Specificity				
							serious[a]	none	NA	serious[c]	LOW
Sign observed by epileptologist on video during seizure – postictal exhaustion	1 [191]	36	epileptologist	Video EEG Non-epilepsy group: PNES	0.52 [0.31, 0.73]	0.42 [0.15, 0.72]	**Sensitivity**				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – postictal stertorous/loud/deep breathing	4 [16, 39, 176, 191]	183	epileptologist	Video EEG, or overall clinical findings over prolonged follow up Non-epilepsy group: PNES	0.43 [0.23, 0.66] 0.22 [0.09, 0.42] 0.52 [0.37, 0.68] 0.96[0.80, 1.0] **Pooled (95% CrIs): 0.57(0.14 – 0.93)**	0.50 [0.21, 0.79] 1.00 [0.79, 1.00] 0.79[0.58, 0.93] 1.0 [0.90,1.0] **Pooled (95% CrIs): 0.89 (0.46 – 0.99)**	**Sensitivity**				
							Very serious[a]	serious[b]	none	Very serious[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	none	Very serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – looking around	1 [191]	36	epileptologist	Video EEG Non-epilepsy group: PNES	0.48 [0.27, 0.69]	0.25 [0.05, 0.57]	**Sensitivity**				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
							serious[a]	serious[b]	NA	None[c]	LOW
Sign observed by epileptologist on video during seizure – epileptic aura	1 [191]	36	epileptologist	Video EEG Non-epilepsy group: PNES	0.5[e]	0.17[e]	**Sensitivity**				
							serious[a]	serious[b]	NA	NA[c]	LOW
							Specificity				
							serious[a]	serious[b]	NA	NA[c]	LOW
Sign observed by epileptologist on video during seizure - gradual behavioural build-up to peak intensity, but within 70 seconds	1 [39]	43	epileptologist	Surgical or long term follow up Non-epilepsy group: PNES	0.81 [0.62, 0.94]	0.94 [0.70, 1.00]	**Sensitivity**				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – eyes closed at peak	1 [39]	43	epileptologist	Surgical or long term follow up Non-epilepsy group: PNES	0.00 [0.00, 0.14]	0.20 [0.04, 0.48]	**Sensitivity**				
							serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	none	LOW
Sign observed by epileptologist on	1 [39]	43	epileptologist	Surgical or long term follow up	0.04 [0.00, 0.19]	0.31 [0.11, 0.59]	**Sensitivity**				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
video during seizure – waxing / waning event tempo				Non-epilepsy group: PNES			serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	none	LOW
Sign observed by epileptologist on video during seizure – non-synchronous movements	1 [39]	43	epileptologist	Surgical or long term follow up Non-epilepsy group: PNES	0.07 [0.01, 0.24]	0.56 [0.30, 0.80]	**Sensitivity**				
							serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – side to side head movements	1 [39]	43	epileptologist	Surgical or long term follow up Non-epilepsy group: PNES	0.00 [0.00, 0.13]	0.75 [0.48, 0.93]	**Sensitivity**				
							serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	Very serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – pelvic thrusting	4 [16, 39, 82]	594	Epileptologist/neurologist	Surgical or long term follow up / Video EEG Non-epilepsy group: PNES and other Epi types	0.04 [0.00, 0.19] 0.11 [0.07, 0.17] 0.02 [0.00, 0.12] **Pooled (95%CrIs): 0.055(0.0066-0.227)**	0.69 [0.41, 0.89] 0.83 [0.74, 0.90] 0.92 [0.73, 0.99] **Pooled (95%CrIs): 0.834(0.520-0.961)**	**Sensitivity**				
							Very serious[a]	serious[b]	none	none	VERY LOW
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
							Very serious[a]	serious[b]	none	serious[c]	VERY LOW
Pelvic thrusting during seizure DETECTING RIGHT TLE *(not included in above meta-analysis because the data already included in the overall epilepsy data)*	1 [82]	261	neurologists	Critical care continuous EEG Non-epilepsy group: PNES / other epilepsy types	0.08 [0.02, 0.19]	0.85 [0.80, 0.90]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	none[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	none[c]	VERY LOW
Pelvic thrusting during seizure DETECTING LEFT TLE *(not included in above meta-analysis because the data already included in the overall epilepsy data)*	1 [82]	261	neurologists	Critical care continuous EEG Non-epilepsy group: PNES / other epilepsy types	0.04 [0.00, 0.14]	0.84 [0.79, 0.89]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	none[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	none[c]	VERY LOW
Pelvic thrusting DETECTING FLE	1 [82]	261	neurologists	Critical care continuous EEG	0.24 [0.13, 0.38]	0.89 [0.84, 0.93]	**Sensitivity**				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
(not included in above meta-analysis because the data already included in the overall epilepsy data)				Non-epilepsy group: PNES / other epilepsy types			Very serious[a]	serious[b]	NA	none[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – expression of pain	1 [39]	43	epileptologist	Surgical or long term follow up Non-epilepsy group: PNES	0.00 [0.00, 0.13]	0.75 [0.48, 0.93]	**Sensitivity**				
							serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	Very serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – motor behavioural onset	1 [39]	43	epileptologist	Surgical or long term follow up Non-epilepsy group: PNES	0.22 [0.09, 0.42]	0.81 [0.54, 0.96]	**Sensitivity**				
							serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	Very serious[c]	VERY LOW
Sign observed by epileptologist on	1 [39]	43	epileptologist	Surgical or long term follow up	0.22 [0.09, 0.42]	0.94 [0.70, 1.00]	**Sensitivity**				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
video during seizure – head version				Non-epilepsy group: PNES			serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	Serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – eye deviation	1 [39]	43	epileptologist	Surgical or long term follow up Non-epilepsy group: PNES	0.20 [0.07, 0.41]	1.00 [0.78, 1.00]	**Sensitivity**				
							serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	Serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – repetitive eye blinks	1 [39]	43	epileptologist	Surgical or long term follow up Non-epilepsy group: PNES	0.04 [0.00, 0.20]	0.80 [0.52, 0.96]	**Sensitivity**				
							serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	Very serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – facial grimacing	1 [39]	43	epileptologist	Surgical or long term follow up Non-epilepsy group: PNES	0.11 [0.02, 0.29]	0.88 [0.62, 0.98]	**Sensitivity**				
							serious[a]	serious[b]	NA	none	LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
							Specificity				
							serious[a]	serious[b]	NA	Serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – abnormal posturing	1 [39]	43	epileptologist	Surgical or long term follow up Non-epilepsy group: PNES	0.37 [0.19, 0.58]	0.63 [0.35, 0.85]	**Sensitivity**				
							serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	Serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – clonic activities	1 [39]	43	epileptologist	Surgical or long term follow up Non-epilepsy group: PNES	0.30 [0.14, 0.50]	0.81 [0.54, 0.96]	**Sensitivity**				
							serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	Very serious[c]	VERY LOW
Sign observed by epileptologist on video during seizure – vocalisation/speech	1 [39]	43	epileptologist	Surgical or long term follow up Non-epilepsy group: PNES	0.37 [0.19, 0.58]	0.69 [0.41, 0.89]	**Sensitivity**				
							serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	Serious[c]	VERY LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Sign observed by epileptologist on video during seizure – thrashing/writhing	1 [39]	43	epileptologist	Surgical or long term follow up Non-epilepsy group: PNES	0.15 [0.04, 0.34]	0.69 [0.41, 0.89]	**Sensitivity**				
							serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	Serious[c]	VERY LOW
Neurologist observation of video: eyes open during seizure	1 [16]	68	neurologist	Video EEG Non-epilepsy group: PNES	1.00 [0.92, 1.00]	0.88 [0.68, 0.97]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	none	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
Neurologist observation of video: Ictal vocalisation	1 [16]	68	neurologist	Video EEG Non-epilepsy group: PNES	0.64 [0.48, 0.78]	0.88 [0.68, 0.97]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
Neurologist observation of	1 [16]	68	neurologist	Video EEG	0.39 [0.24, 0.55]	0.38 [0.19, 0.59]	**Sensitivity**				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
video: Ictal side to side head and body turning				Non-epilepsy group: PNES			Very serious[a]	serious[b]	NA	none	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	none	VERY LOW
Neurologist observation of video: Ictal asynchronous extremity motion	1 [16]	68	neurologist	Video EEG Non-epilepsy group: PNES	0.48 [0.32, 0.63]	0.04 [0.00, 0.21]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	none	VERY LOW
Neurologist observation of video: Post ictal breathing regularity	1 [16]	68	neurologist	Video EEG Non-epilepsy group: PNES	0.50 [0.35, 0.65]	0.79 [0.58, 0.93]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
Neurologist observation of video: Post ictal agitation	1 [16]	68	neurologist	Video EEG Non-epilepsy group: PNES	0.34 [0.20, 0.50]	0.88 [0.68, 0.97]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	none	VERY LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
							Specificity				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
Neurologist observation of video: Post ictal confusion	1 [16]	68	neurologist	Video EEG Non-epilepsy group: PNES	0.76 [0.56, 0.90]	0.88 [0.68, 0.97]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
Twitching arms or legs during seizure DETECTING ABSENCE SEIZURES IN INFANTS	1 [163]	40	Physician	Video EEG Non-epilepsy group: population suspected of epilepsy	0.24 [0.07, 0.50]	1.00 [0.85, 1.00]	**Sensitivity**				
							serious[a]	none	NA	None[c]	MOD
							Specificity				
							serious[a]	none	NA	serious[c]	LOW
Occurrence of seizure when tired DETECTING ABSENCE SEIZURES IN INFANTS	1 [163]	40	Physician	Video EEG Non-epilepsy group: population suspected of epilepsy	0.59 [0.33, 0.82]	0.74 [0.52, 0.90]	**Sensitivity**				
							serious[a]	none	NA	serious[c]	LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
							Specificity				
							serious[a]	none	NA	serious[c]	LOW
Twitching arms or legs OR urine loss during seizure DETECTING ABSENCE SEIZURES IN INFANTS	1 [163]	40	Physician	Video EEG Non-epilepsy group: population suspected of epilepsy	0.35 [0.14, 0.62]	1.00 [0.85, 1.00]	**Sensitivity**				
							serious[a]	none	NA	serious[c]	LOW
							Specificity				
							serious[a]	none	NA	serious[c]	LOW
Upward eye movement during seizures and occurrence of seizures when tired DETECTING ABSENCE SEIZURES IN INFANTS	1 [163]	40	Physician	Video EEG Non-epilepsy group: population suspected of epilepsy	0.29 [0.10, 0.56]	0.96 [0.78, 1.00]	**Sensitivity**				
							serious[a]	none	NA	None[c]	MOD
							Specificity				
							serious[a]	none	NA	serious[c]	LOW
Eye witness (family/relative) account of eye opening or	1 [191]	36	epileptologist	Video EEG Non-epilepsy group: PNES	0.83 [0.61, 0.95]	0.25 [0.05, 0.57]	**Sensitivity**				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							serious[a]	serious[b]	NA	None[c]	LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
widening at onset during seizure											
Eye witness (family/relative) account of abrupt onset during seizure	1 [191]	36	epileptologist	Video EEG Non-epilepsy group: PNES	0.48 [0.27, 0.69]	0.25 [0.05, 0.57]	**Sensitivity**				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							serious[a]	serious[b]	NA	None[c]	LOW
Eye witness (family/relative) account of post-ictal confusion/sleep	1 [191]	36	epileptologist	Video EEG Non-epilepsy group: PNES	0.78 [0.56, 0.93]	0.00 [0.00, 0.26]	**Sensitivity**				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							serious[a]	serious[b]	NA	None[c]	LOW
Symptom questionnaire for patients – existence of headache after seizure?	1 [74]	39	NR	Video EEG Non-epilepsy group: PNES	0.38 [0.15, 0.65]	0.96 [0.78, 1.00]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
Symptom questionnaire for patients – existence of fatigue or lethargy?	1 [74]	39	NR	Video EEG Non-epilepsy group: PNES	0.56 [0.30, 0.80]	0.87 [0.66, 0.97]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
Symptom questionnaire for patients – existence of confusion alone?	1 [74]	39	NR	Video EEG Non-epilepsy group: PNES	0.13 [0.02, 0.38]	0.88 [0.69, 0.97]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	none	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
Symptom questionnaire for patients – existence of no symptoms?	1 [74]	39	NR	Video EEG Non-epilepsy group: PNES	0.00 [0.00, 0.21]	0.52 [0.31, 0.72]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	none	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
Reports of physical symptoms: light-	1 [56]	69	NR	Video EEG	0.10 [0.02, 0.27]	0.21 [0.09, 0.36]	**Sensitivity**				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
headedness				Non-epilepsy group: PNES			serious[a]	Serious[b]	NA	none	LOW
							Specificity				
							serious[a]	Serious[b]	NA	none	LOW
Reports of physical symptoms: sensory disturbances/dysaesthesias	1 [56]	69	NR	Video EEG Non-epilepsy group: PNES	0.17 [0.06, 0.35]	0.38 [0.23, 0.55]	**Sensitivity**				
							serious[a]	Serious[b]	NA	none	LOW
							Specificity				
							serious[a]	Serious[b]	NA	none	LOW
Reports of physical symptoms: hot flushes	1 [56]	69	NR	Video EEG Non-epilepsy group: PNES	0.00 [0.00, 0.12]	0.74 [0.58, 0.87]	**Sensitivity**				
							serious[a]	Serious[b]	NA	none	LOW
							Specificity				
							serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
Reports of physical symptoms: palpitations	1 [56]	69	NR	Video EEG Non-epilepsy group: PNES	0.03 [0.00, 0.17]	0.79 [0.64, 0.91]	**Sensitivity**				
							serious[a]	Serious[b]	NA	none	LOW
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
							serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
Clinical signs of non-convulsive seizures (unexplained deterioration of consciousness, subtle motor activity, pupillary and ocular movement abnormalities) DETECTING NCSE	1 [114]	NC	neurologists	Critical care continuous EEG Non-epilepsy group: population suspected of epilepsy	0.929 [e]	0.631 [e]	**Sensitivity**				
							serious[a]	none	NA	NA[c]	MOD
							Specificity				
							serious[a]	none	NA	NA[c]	LOW
Clinical signs of non-convulsive seizures (unexplained deterioration of consciousness, subtle motor activity, pupillary and ocular movement abnormalities) AND early sporadic epileptiform discharges OR Early rhythmic and periodic EEG	1 [114]	NC	neurologists	Critical care continuous EEG Non-epilepsy group: population suspected of epilepsy	0.786 [e]	0.892 [e]	**Sensitivity**				
							serious[a]	none	NA	NA[c]	MOD
							Specificity				
							serious[a]	none	NA	NA[c]	LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
patterns of 'ictal-interictal uncertainty' *DETECTING NCSE*											
Clinical signs of non-convulsive seizures (unexplained deterioration of consciousness, subtle motor activity, pupillary and ocular movement abnormalities) OR early sporadic epileptiform discharges OR Early rhythmic and periodic EEG patterns of 'ictal-interictal uncertainty' *DETECTING NCSE*	1 [114]	NC	neurologists	Critical care continuous EEG Non-epilepsy group: population suspected of epilepsy	1.0 [e]	0.492 [e]	**Sensitivity**				
							serious[a]	none	NA	NA[c]	MOD
							Specificity				
							serious[a]	none	NA	NA[c]	LOW
Ictal duration >60s (measured by epileptologist using video)	1 [177]	782	epiletologist	Video EEG Non-epilepsy group: PNES	0.35 [0.30, 0.40]	0.29 [0.24, 0.34]	**Sensitivity**				
							serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	none	LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Ictal duration >120s (measured by epileptologist using video)	1 [177]	782	epiletologist	Video EEG Non-epilepsy group: PNES	0.07 [0.05, 0.10]	0.48 [0.43, 0.54]	**Sensitivity**				
							serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	none	LOW
Ictal duration >180s (measured by epileptologist using video)	1 [177]	782	epiletologist	Video EEG Non-epilepsy group: PNES	0.02 [0.01, 0.04]	0.63 [0.58, 0.68]	**Sensitivity**				
							serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
Ictal duration >240s (measured	1 [177]	782	epiletologist	Video EEG	0.01 [0.01, 0.03]	0.71 [0.66, 0.75]	**Sensitivity**				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
by epileptologist using video)				Non-epilepsy group: PNES			serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	none	LOW
Ictal duration >300s (measured by epileptologist using video)	1 [177]	782	epiletologist	Video EEG Non-epilepsy group: PNES	0.01 [0.00, 0.03]	0.79 [0.74, 0.83]	**Sensitivity**				
							serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	none	LOW
Paroxysmal Event Profile Questionnaire – 'factor scores' (PNES as non-epilepsy group). No details of	1 [160]	200	NR	Video EEG Non-epilepsy group: PNES	0.72 [0.62, 0.81]	0.78 [0.69, 0.86]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	none	VERY LOW
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
scoring or thresholds used.							Very serious[a]	serious[b]	NA	none	VERY LOW
Paroxysmal Event Profile questionnaire – 'patient information' (PNES as non-epilepsy group). No details of scoring or thresholds used.	1 [160]	200	NR	Video EEG Non-epilepsy group: PNES	0.46 [0.36, 0.56]	0.74 [0.64, 0.82]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	none	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	none	VERY LOW
Paroxysmal Event Profile questionnaire – 'combined'(PNES as non-epilepsy group). No details of scoring or thresholds used.	1 [160]	200	NR	Video EEG Non-epilepsy group: PNES	0.74 [0.64, 0.82]	0.80 [0.71, 0.87]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	none	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	none	VERY LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Paroxysmal Event Profile questionnaire – 'factor scores' (syncope as non-epilepsy group). No details of scoring or thresholds used.	1 [160]	200	NR	Video EEG Non-epilepsy group: syncope	0.83 [0.74, 0.90]	0.87 [0.79, 0.93]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	none	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
Paroxysmal Event Profile questionnaire- 'patient info' (syncope as non-epilepsy group). No details of scoring or thresholds used.	1 [160]	200	NR	Video EEG Non-epilepsy group: syncope	0.68 [0.58, 0.77]	0.88 [0.80, 0.94]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
Paroxysmal Event Profile – 'combined' (syncope as non-epilepsy group). No details of scoring or	1 [160]	200	NR	Video EEG Non-epilepsy group: syncope	0.91 [0.84, 0.96]	0.92 [0.85, 0.96]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
thresholds used.							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
>1 comorbidity on medical records	1 [60]	280	NR	Video EEG Non-epilepsy group: PNES	0.27 [0.19, 0.36]	0.34 [0.27, 0.42]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	none	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	none	VERY LOW
Use of video information alone during seizure (from Video EEG) without other data to form 'diagnosis'.	3 [39, 73, 90]	170	Epileptologist/neurologist	Surgery or long term observation / Video EEG Non-epilepsy group: PNES / suspected of epilepsy but no differential diagnoses	0.93 [0.76, 0.99] 0.75 [0.59, 0.87] 1.00 [0.48, 1.00] **Pooled (95% CrIs): 0.892(0.534-0.996)**	0.94 [0.70, 1.00] 0.95 [0.87, 0.99] 0.71 [0.29, 0.96] **Pooled (95% CrIs): 0.917(0.603-0.987)**	**Sensitivity**				
							serious[a]	none	none	serious[c]	LOW
							Specificity				
							serious[a]	none	none	serious[c]	LOW
Use of Clinical history / interview to form 'diagnosis'	2 [146] [90]	354	NR/neurologist	Medical record review / Video EEG Non-epilepsy group: healthy controls /	0.96 [0.92, 0.98] 0.80 [0.28, 0.99]	0.93 [0.88, 0.96] 0.86 [0.42, 1.00]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
				suspected of epilepsy but no differential diagnoses			Very serious[a]	serious[b]	NA	serious[c]	LOW
Use of history and physical examination only to form 'diagnosis'	1 [193]	530	expert	Medical record review / Video EEG Non-epilepsy group: suspected of epilepsy but no differential diagnoses	1.00 [0.97, 1.00]	0.89 [0.85, 0.92]	**Sensitivity**				
							serious[a]	none	NA	none	MOD
							Specificity				
							serious[a]	none	NA	serious[c]	LOW
Use of medical record only to form diagnosis INFANTS	1 [96]	NC	expert	Medical record review / Video EEG Non-epilepsy group: suspected of epilepsy but no differential diagnoses	0.849[e]	0.399[e]	**Sensitivity**				
							serious[a]	none	NA	NA	MOD
							Specificity				
							serious[a]	none	NA	NA	MOD
Use of medical record and 1 minute video of event to form 'diagnosis' INFANTS	1 [96]	NC	expert	Medical record review / Video EEG Non-epilepsy group: suspected of epilepsy but	0.888[e]	0.514[e]	**Sensitivity**				
							serious[a]	none	NA	NA	MOD
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
				no differential diagnoses			serious[a]	none	NA	NA	MOD
Use of smartphone video taken by witness to form 'diagnosis' (by experts and residents)	1 [193]	530	Experts and residents (ALL)	Medical record review / Video EEG Non-epilepsy group: suspected of epilepsy but no differential diagnoses	0.60 [0.51, 0.68]	0.91 [0.88, 0.94]	**Sensitivity**				
							serious[a]	none	NA	serious[c]	LOW
							Specificity				
							serious[a]	none	NA	serious[c]	LOW
Use of smartphone video taken by witness to form 'diagnosis' (by experts only)	1 [193]	530	Experts only	Medical record review / Video EEG Non-epilepsy group: suspected of epilepsy but	0.77 [0.69, 0.83]	0.93 [0.90, 0.96]	**Sensitivity**				
							serious[a]	none	NA	none	MOD
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
				no differential diagnoses			serious[a]	none	NA	none	MOD
Use of smartphone video taken by witness to form 'diagnosis' (by residents only)	1 [193]	NC	Residents only	Medical record review / Video EEG Non-epilepsy group: suspected of epilepsy but no differential diagnoses	0.42 [0.33, 0.50]	0.88 [0.85, 0.91]	**Sensitivity**				
							serious[a]	none	NA	none	MOD
							Specificity				
							serious[a]	none	NA	serious[c]	LOW

(a) *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*
(b) *Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect*
(c) *Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed one of the clinical thresholds (0.90 or 0.60), and downgraded by 2 increments when the confidence interval around the point estimate crossed both of the clinical thresholds. The upper clinical threshold marked the point above which recommendations would be possible, and the lower clinical threshold marked the point below which the tool would be regarded as of little clinical use.*
(d) *Inconsistency was assessed by visual inspection of the sensitivity/specificity plots, or data (if 2 studies). The evidence was downgraded by 1 increment if there was no overlap of 95% confidence intervals. For single studies no evaluation was made and 'not applicable' was recorded.*
(e) *No confidence intervals were presented because there was insufficient information available or there was a mismatch between the raw data and the accuracy results.*

Table 4: Clinical evidence summary: diagnostic test accuracy of different serum measurements for detection of epilepsy. Where detection is of a specific type of epilepsy, rather than epilepsy overall, this is stated clearly in the first column.

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
serum prolactin level at threshold >29.9 mg/dl (indicating epilepsy). This was measured in the ED for patients presenting with recent seizure	1 [209]	200	NR	Discharge diagnosis. Non-epilepsy group: range of people without epilepsy initially suspected of epilepsy (not restricted to one differential diagnosis)	0.42 [0.33, 0.52]	0.82 [0.73, 0.90]	**Sensitivity**				
							Serious[a]	None[b]	NA	None[c]	MOD
							Specificity				
							Serious[a]	None[b]	NA	Serious[c]	LOW
Paired serum prolactin >1025 microU/ml (indicating epilepsy) in immediate post-seizure period	1 [7]	58	NR	Video EEG Non-epilepsy group: PNES	0.34 [0.20, 0.51]	1.00 [0.83, 1.00]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	None[c]	LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
Paired serum prolactin RI > 5.5 in post seizure period (5.5 x increase in serum prolactin between 15 mins post-seizure and	1 [7]	58	NR	Video EEG Non-epilepsy group: PNES	0.21 [0.10, 0.37]	1.00 [0.83, 1.00]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	None[c]	LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
2 hours after baseline sample)											
Paired serum prolactin RI > 2 in post seizure period (2 x increase in serum prolactin between 15 mins post-seizure and 2 hours after baseline sample)	1 [7]	58	NR	Video EEG Non-epilepsy group: PNES	0.68 [0.51, 0.82]	0.75 [0.51, 0.91]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Very serious[c]	VERY LOW
Paired serum prolactin >1025 microU/ml (indicating epilepsy) in immediate post-seizure period *DETECTING COMPLEX PARTIAL SEIZURES*	1 [7]	40	NR	Video EEG Non-PC epilepsy group: PNES	0.35 [0.15, 0.59]	1.00 [0.83, 1.00]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	None[c]	LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
Paired serum prolactin RI > 5.5 in post seizure period (5.5 x increase in serum prolactin between 15 mins post-seizure and 2 hours after baseline sample) *DETECTING COMPLEX PARTIAL SEIZURES*	1 [7]	40	NR	Video EEG Non-PC epilepsy group: PNES	0.28[e]	1 [e]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	NA[c]	LOW
							Specificity				
							Serious[a]	Serious[b]	NA	NA[c]	LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Paired serum prolactin RI > 2 in post seizure period (2 x increase in serum prolactin between 15 mins post-seizure and 2 hours after baseline sample) *DETECTING PARTIAL COMPLEX SEIZURES*	1 [7]	40	NR	Video EEG Non-PC epilepsy group: PNES	0.61 [e]	0.74 [e]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	NA[c]	LOW
							Specificity				
							Serious[a]	Serious[b]	NA	NA	LOW
Paired serum prolactin >1025 microU/ml (indicating epilepsy) in immediate post-seizure period *DETECTING GENERALISED CLOINIC TONIC SEIZURES*	1 [7]	36	NR	Video EEG Non-GCS epilepsy group: PNES	0.38 [0.15, 0.65]	1.00 [0.83, 1.00]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
Paired serum prolactin RI > 5.5 in post seizure period (5.5 x increase in serum prolactin between 15 mins post-seizure and 2 hours after baseline sample) *DETECTING GENERALISED*	1 [7]	36	NR	Video EEG Non-GCS epilepsy group: PNES	0.2	1	**Sensitivity**				
							Serious[a]	Serious[b]	NA	NA[c]	LOW
							Specificity				
							Serious[a]	Serious[b]	NA	NA[c]	LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
CLOINIC TONIC SEIZURES											
Paired serum prolactin RI > 2 in post seizure period (2 x increase in serum prolactin between 15 mins post-seizure and 2 hours after baseline sample) *DETECTING GENERALISED CLONIC TONIC SEIZURES*	1 [7]	36	NR	Video EEG Non-GCS epilepsy group: PNES	0.94 [0.70, 1.00]	0.75 [0.51, 0.91]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Very serious[c]	VERY LOW
Capillary prolactin level above 6.7 ng/ml at 15 minutes post-seizure	1[69]	50	Nursing staff	Video EEG Non-epilepsy group: PNES	0.69 [0.52, 0.84]	0.93 [0.66, 1.00]	**Sensitivity**				
							Serious[a]	None[b]	NA	Serious[c]	LOW
							Specificity				
							Serious[a]	None[b]	NA	Serious[c]	LOW
2 fold decrease in capillary prolactin level, between 15 min sample and sample obtained 1 hr later	1[69]	50	Nursing staff	Video EEG Non-epilepsy group: PNES	0.69 [0.52, 0.84]	0.86 [0.57, 0.98]	**Sensitivity**				
							Serious[a]	None[b]	NA	Serious[c]	LOW
							Specificity				
							Serious[a]	None[b]	NA	Very serious[c]	VERY LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
15 min cap prolactin level above 6.7 ng/ml AND a 2 fold decrease between 15 mins and 1 hour post-seizure	1[69]	50	Nursing staff	Video EEG Non-epilepsy group: PNES	0.56 [0.38, 0.72]	1.00 [0.77, 1.00]	**Sensitivity**				
							Serious[a]	None[b]	NA	Serious[c]	LOW
							Specificity				
							Serious[a]	None[b]	NA	Serious[c]	LOW
Serum prolactin >23 microg [women]/>16.5 [men] at 10mins post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.88 [0.71, 0.96]	0.58 [0.28, 0.85]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
serum prolactin >23 microg [women]/>16.5 [men] at 20mins post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.88 [0.71, 0.96]	0.67 [0.35, 0.90]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
Serum prolactin >23 microg [women]/>16.5 [men] at 30mins post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.84 [0.67, 0.95]	0.75 [0.43, 0.95]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Very serious[c]	VERY LOW
Serum prolactin >23 microg [women]/>16.5 [men] at 60mins post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.63 [0.44, 0.79]	0.92 [0.62, 1.00]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
							Specificity				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
Serum prolactin >23 microg [women]/>16.5 [men] at 6 hours post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.22 [0.09, 0.40]	0.83 [0.52, 0.98]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	none[c]	LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Very serious[c]	VERY LOW
Serum prolactin >23 microg [women]/>16.5 [men] at 12 hours post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.19 [0.07, 0.36]	0.83 [0.52, 0.98]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	none[c]	LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Very serious[c]	VERY LOW
Serum prolactin >23 microg [women]/>16.5 [men] at 24 hours post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.13 [0.04, 0.29]	0.92 [0.62, 1.00]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	None[c]	LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
Serum neuron-specific enolase >12 microg/L at 10 minutes post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.06 [0.01, 0.21]	1.00 [0.74, 1.00]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	None[c]	LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Serum neuron-specific enolase >12 microg/L at 20 minutes post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.06 [0.01, 0.21]	1.00 [0.74, 1.00]	**Sensitivity**				
							Serious[a]	None[b]	NA	None[c]	MOD
							Specificity				
							Serious[a]	None[b]	NA	Serious[c]	LOW
Serum neuron-specific enolase >12 microg/L at 30 minutes post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.06 [0.01, 0.21]	1.00 [0.74, 1.00]	**Sensitivity**				
							Serious[a]	None[b]	NA	None[c]	MOD
							Specificity				
							Serious[a]	None[b]	NA	Serious[c]	LOW
Serum neuron-specific enolase >12 microg/L at 60 minutes post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.03 [0.00, 0.16]	1.00 [0.74, 1.00]	**Sensitivity**				
							Serious[a]	None[b]	NA	None[c]	MOD
							Specificity				
							Serious[a]	None[b]	NA	Serious[c]	LOW
Serum neuron-specific enolase >12 microg/L at 6 hours post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.13 [0.04, 0.29]	1.00 [0.74, 1.00]	**Sensitivity**				
							Serious[a]	None[b]	NA	None[c]	MOD
							Specificity				
							Serious[a]	None[b]	NA	Serious[c]	LOW
	1 [216]	44	NR	Video EEG	0.09 [0.02, 0.25]	1.00 [0.74, 1.00]	**Sensitivity**				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Serum neuron-specific enolase >12 microg/L at 12 hours post seizure				Non-epilepsy group: PNES			Serious[a]	None[b]	NA	None[c]	MOD
							Specificity				
							Serious[a]	None[b]	NA	Serious[c]	LOW
Serum neuron-specific enolase >12 microg/L at 24 hours post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.00 [0.00, 0.11]	1.00 [0.74, 1.00]	**Sensitivity**				
							Serious[a]	None[b]	NA	None[c]	MOD
							Specificity				
							Serious[a]	None[b]	NA	Serious[c]	LOW
Serum creatine kinase >2.8 [women]/>3.25 [men] at 10 minutes post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.00 [0.00, 0.11]	1.00 [0.74, 1.00]	**Sensitivity**				
							Serious[a]	None[b]	NA	None[c]	MOD
							Specificity				
							Serious[a]	None[b]	NA	Serious[c]	LOW
Serum creatine kinase >2.8 [women]/>3.25 [men] at 20 minutes post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.00 [0.00, 0.11]	1.00 [0.74, 1.00]	**Sensitivity**				
							Serious[a]	None[b]	NA	None[c]	MOD
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
							Serious[a]	None[b]	NA	Serious[c]	LOW
Serum creatine kinase >2.8 [women]/>3.25 [men] at 30 minutes post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.00 [0.00, 0.11]	1.00 [0.74, 1.00]	**Sensitivity**				
							Serious[a]	None[b]	NA	None[c]	MOD
							Specificity				
							Serious[a]	None[b]	NA	Serious[c]	LOW
Serum creatine kinase >2.8 [women]/>3.25 [men] at 60 minutes post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.00 [0.00, 0.11]	1.00 [0.74, 1.00]	**Sensitivity**				
							Serious[a]	None[b]	NA	None[c]	MOD
							Specificity				
							Serious[a]	None[b]	NA	Serious[c]	LOW
Serum creatine kinase >2.8 [women]/>3.25 [men] at 6 hours post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.09 [0.02, 0.25]	1.00 [0.74, 1.00]	**Sensitivity**				
							Serious[a]	None[b]	NA	None[c]	MOD
							Specificity				
							Serious[a]	None[b]	NA	Serious[c]	LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Serum creatine kinase >2.8 [women]/>3.25 [men] at 12 hours post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.16 [0.05, 0.33]	1.00 [0.74, 1.00]	**Sensitivity**				
							Serious[a]	None[b]	NA	None[c]	MOD
							Specificity				
							Serious[a]	None[b]	NA	Serious[c]	LOW
Serum creatine kinase >2.8 [women]/>3.25 [men] at 24 hours post seizure	1 [216]	44	NR	Video EEG Non-epilepsy group: PNES	0.19 [0.07, 0.36]	1.00 [0.74, 1.00]	**Sensitivity**				
							Serious[a]	None[b]	NA	None[c]	MOD
							Specificity				
							serious[a]	Serious[b]	NA	Serious[c]	LOW
Anion gap in first 2 hrs after seizure event (threshold at >10 mEq/L)	1 [125]	54	NR	Video EEG Non-epilepsy group: PNES	0.81 [0.62, 0.94]	1.00 [0.87, 1.00]	**Sensitivity**				
							Serious[a]	None[b]	NA	Serious[c]	LOW
							Specificity				
							Serious[a]	None[b]	NA	Serious[c]	LOW
serum lactate 2 hrs post ictal (threshold >=2.2 mmol/L)	1 [61]	270	NR	Final definitive diagnosis with CT/MRI, EEG and ECG data with observable clinical signs and symptoms Non-epilepsy group: PNES and syncope	0.85 [0.78, 0.90]	0.82 [0.74, 0.89]	**Sensitivity**				
							Very serious[a]	None[b]	NA	None[c]	MOD
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
							Very serious[a]	None[b]	NA	None[c]	LOW
Post-seizure (within 6 hours) serum glial fibrillary astrocytic protein levels at threshold of >=2.71 ng/ml	1 [180]	63	NR	Video EEG Non-epilepsy group: PNES	0.72 [0.56, 0.85]	0.60 [0.36, 0.81]	**Sensitivity**				
							Serious[a]	None[b]	NA	serious[c]	LOW
							Specificity				
							Serious[a]	None[b]	NA	serious[c]	LOW
baseline serum ammonia at cut-off of >=80 micromol/L *DETECTING GENERALISED CLONIC TONIC SEIZURES*	1 [6]	26	NR	Video EEG Non- GCS epilepsy group: people initially suspected of epilepsy but with no definite differential diagnoses	0.53 [0.28, 0.77]	1.00 [0.66, 1.00]	**Sensitivity**				
							Very serious[a]	none[b]	NA	Serious[c]	VERY LOW
							Specificity				
							Very serious[a]	none[b]	NA	Serious[c]	VERY LOW

(a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.
(b) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect
(c) Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed one of the clinical thresholds (0.90 or 0.60), and downgraded by 2 increments when the confidence interval around the point estimate crossed both of the clinical thresholds. The upper clinical threshold marked the point above which recommendations would be possible, and the lower clinical threshold marked the point below which the tool would be regarded as of little clinical use.
(d) Inconsistency was assessed by visual inspection of the sensitivity/specificity plots, or data (if 2 studies). The evidence was downgraded by 1 increment if there was no overlap of 95% confidence intervals. For single studies no evaluation was made and 'not applicable' was recorded.
(e) No confidence intervals were presented because there was insufficient information available or there was a mismatch between the raw data and the accuracy results.

Table 5: Clinical evidence summary: diagnostic test accuracy of ECG tests for detection of epilepsy. Where detection is of a specific type of epilepsy, rather than epilepsy overall, this is stated clearly in the first column.

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
ECG. Interictal. No details of measures or thresholds used.	1 [43]	142	NR	EEG plus clinical findings, over prolonged follow up. Non-epilepsy group: range of people without epilepsy initially suspected of epilepsy (not restricted to one differential diagnosis)	0.14 [0.02, 0.43]	0.73 [0.65, 0.81]	**Sensitivity**				
							serious[a]	none[b]	NA	none	MOD
							Specificity				
							serious[a]	none[b]	NA	none	MOD

(a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.
(b) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect
(c) Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed one of the clinical thresholds (0.90 or 0.60), and downgraded by 2 increments when the confidence interval around the point estimate crossed both of the clinical thresholds. The upper clinical threshold marked the point above which recommendations would be possible, and the lower clinical threshold marked the point below which the tool would be regarded as of little clinical use.
(d) Inconsistency was assessed by visual inspection of the sensitivity/specificity plots, or data (if 2 studies). The evidence was downgraded by 1 increment if there was no overlap of 95% confidence intervals. For single studies no evaluation was made and 'not applicable' was recorded.
(e) No confidence intervals were presented because there was insufficient information available or there was a mismatch between the raw data and the accuracy results.

Table 6: Clinical evidence summary: diagnostic test accuracy of different imaging tests for detection of epilepsy. Where detection is of a specific type of epilepsy, rather than epilepsy overall, this is stated clearly in the first column.

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Echocardiogram. Interictal. No details of measures or threshold available.	1 [43]	63	NR	EEG plus clinical findings, over prolonged follow up Non-epilepsy group: those initially suspected of epilepsy but with no differential diagnoses	0.00 [0.00, 0.46]	0.96 [0.88, 1.00]	**Sensitivity**				
							Serious[a]	None	NA	none	MOD
							Specificity				
							Serious[a]	None	NA	serious[c]	LOW
Brain CT. Interictal. No details of measures or threshold available.	1 [43]	33	NR	EEG plus clinical findings, over prolonged follow up Non-epilepsy group: those initially suspected of epilepsy but with no differential diagnoses	0.20 [0.01, 0.72]	0.79 [0.59, 0.92]	**Sensitivity**				
							Serious[a]	None	NA	serious[c]	LOW
							Specificity				
							Serious[a]	None	NA	Very serious[c]	VERY LOW
Single photon emission computed tomography (SPECT) - post-	1 [75]	22	nuclear medicine specialists	Video-EEG Non-epilepsy group: PNES	0.64 [0.31, 0.89]	0.73 [0.39, 0.94]	**Sensitivity**				
							None	Serious[b]	NA	serious[c]	LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
ictal abnormal measure							**Specificity**				
							None	Serious[b]	NA	Very serious[c]	VERY LOW
Single photon emission computed tomography (SPECT) - inter-ictal abnormal measure	1 [75]	22	nuclear medicine specialists	Video-EEG Non-epilepsy group: PNES	0.36 [0.11, 0.69]	0.73 [0.39, 0.94]	**Sensitivity**				
							None	Serious[b]	NA	serious[c]	LOW
							Specificity				
							None	Serious[b]	NA	Very serious[c]	VERY LOW
Hexamethyl propylene amine oxime single photon emission tomography (HMPAO SPECT) brain imaging. Interictal. (positive=hypoperfusion not including equivocal hypoperfusion)	1 [203]	20	nuclear medicine specialists	Video-EEG Non-epilepsy group: PNES	0.80 [0.44, 0.97]	0.80 [0.44, 0.97]	**Sensitivity**				
							Very serious[a]	Serious[b]	NA	Very serious[c]	VERY LOW
							Specificity				
							Very serious[a]	Serious[b]	NA	Very serious[c]	VERY LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Hexamethyl propylene amine oxime single photon emission tomography (HMPAO SPECT) brain imaging. Interictal. (positive=hypoperfusion including equivocal hypoperfusion)	1 [203]	20	nuclear medicine specialists	Video-EEG Non-epilepsy group: PNES	1.00 [0.69, 1.00]	0.70 [0.35, 0.93]	**Sensitivity**				
							Very serious[a]	Serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Very seriousa	Serious[b]	NA	Very serious[c]	VERY LOW
HMPAO-SPECT using visual analysis: SPECTS considered positive for status Epilepticus when there was at least one area of Focal Uptake compared to the adjacent or contralateral areas of the brain. ICTAL *DETECTING NCSE*	1 [100]	55	3 experts in nuclear medicine	consensus based on all data, inc EEG Non-epilepsy group: those initially suspected of epilepsy but with no differential diagnoses	0.81 [0.64, 0.92]	0.89 [0.67, 0.99]	**Sensitivity**				
							none	none	NA	serious[c]	MOD
							Specificity				
							none	none	NA	serious[c]	MOD
HMPAO-SPECT - QtSPECTCOM using quantitative analysis: Results were compared	1 [100]	55	3 experts in nuclear	consensus based on all data, inc EEG Non-epilepsy group: those	0.83 [0.67, 0.94]	0.79 [0.54, 0.94]	**Sensitivity**				
							none	none	NA	serious[c]	MOD

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
to a normal database and the difference in terms of the Z score was quantified. ICTAL *DETECTING NCSE*			medicine	initially suspected of epilepsy but with no differential diagnoses			**Specificity**				
							none	none	NA	Very serious[c]	LOW
Perfusion computed tomography using hyperperfusion detection. ICTAL. *DETECTING STATUS EPILEPTICUS*	1 [86]	29	Experienced neuroradiologist	Ictal EEG and clinical semiology Non-epilepsy group: those initially suspected of epilepsy but with no differential diagnoses	0.79 [0.54, 0.94]	0.90 [0.55, 1.00]	**Sensitivity**				
							serious[a]	None	NA	Very serious[c]	VERY LOW
							Specificity				
							serious[a]	None	NA	Very serious[c]	VERY LOW
Brain MRI. Interictal. No details of measures or threshold available.	1 [43]	13	NR	EEG plus clinical findings, over prolonged follow up Non-epilepsy group: those	0.20 [0.01, 0.72]	0.88 [0.47, 1.00]	**Sensitivity**				
							Serious[a]	None	NA	serious[c]	LOW
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
				initially suspected of epilepsy but with no differential diagnoses			Serious[a]	None	NA	Very serious[c]	VERY LOW
MRI (IN CHILDREN). No details of measures or threshold available.	1 [194]	NC	NR	49 month follow up Non-epilepsy group: those initially suspected of epilepsy but with no differential diagnoses	0.36[e]	0.74[e]	**Sensitivity**				
							Serious[a]	None	NA	serious[c]	LOW
							Specificity				
							Serious[a]	None	NA	Very serious[c]	VERY LOW
4T MRI: the presence/absence of MTS in TLE was based on hippocampal subfield volumetry. Appears to be interictal. *DETECTING TLE with MTS*	1 [136]	80	NR	Video EEG Non-epilepsy group: healthy controls and other types of epilepsy	0.84 [0.60, 0.97]	0.87 [0.76, 0.94]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
4T MRI: the presence/absenc	1 [136]	80	NR	Video EEG	0.73 [0.50, 0.89]	0.86 [0.75, 0.94]	**Sensitivity**				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
e of MTS in TLE was based on hippocampal subfield volumetry. Appears to be interictal. *DETECTING TLE without MTS*				Non-epilepsy group: healthy controls and other types of epilepsy			Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
4T MRI. Appears to be interictal. *DETECTING FLE*	1 [136]	80	NR	Video EEG Non-epilepsy group: healthy controls and other types of epilepsy	0.64 [0.35, 0.87]	0.86 [0.76, 0.94]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
Positron Emission Tomography with 2-deoxy-2[18F] fluro-D-glucose (FDG-PET). Interictal.	1 [186]	NC	board certified neuroradiologists	Video EEG Non-epilepsy group: those initially suspected of epilepsy but with	0.7 [e]	0.56 [e]	**Sensitivity**				
							Very serious[a]	None	NA	NA	LOW
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
DETECTING TLE				no differential diagnoses			Very serious[a]	None	NA	NA	LOW
Positron Emission Tomography with 2-deoxy-2[18F] fluro-D-glucose (FDG-PET). Interictal. *DETECTING FLE*	1 [186]	NC	board certified neuroradiologists	Video EEG Non-epilepsy group: those initially suspected of epilepsy but with no differential diagnoses	0.57 [e]	0.45 [e]	**Sensitivity**				
							Very serious[a]	None	NA	NA	LOW
							Specificity				
							Very serious[a]	None	NA	NA	LOW
Positron Emission Tomography with 2-deoxy-2[18F] fluro-D-glucose (FDG-PET). Interictal. *DETECTING parietal – occipital lobe epilepsy*	1 [186]	NC	board certified neuroradiologists	Video EEG Non-epilepsy group: those initially suspected of epilepsy but with no differential diagnoses	0.59 [e]	0.6 [e]	**Sensitivity**				
							Very serious[a]	None	NA	NA	LOW
							Specificity				
							Very serious[a]	None	NA	NA	LOW

(a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

(b) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect

(c) Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed one of the clinical thresholds (0.90 or 0.60), and downgraded by 2 increments when the confidence interval around the point estimate crossed both of the clinical thresholds. The upper clinical threshold marked the point above which recommendations would be possible, and the lower clinical threshold marked the point below which the tool would be regarded as of little clinical use.

(d) Inconsistency was assessed by visual inspection of the sensitivity/specificity plots, or data (if 2 studies). The evidence was downgraded by 1 increment if there was no overlap of 95% confidence intervals. For single studies no evaluation was made and 'not applicable' was recorded.

(e) No confidence intervals were presented because there was insufficient information available or there was a mismatch between the raw data and the accuracy results.

Table 7: Clinical evidence summary: diagnostic test accuracy of EEG methods for detection of epilepsy. Where detection is of a specific type of epilepsy, rather than epilepsy overall, this is stated clearly in the first column.

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Routine Interictal EEG – abnormal (i.e. epileptiform waveforms) *[Most studies detecting epilepsy overall, but van diessen[200] detecting partial epilepsy specifically, and Kimiskidis[109] detecting genetic generalised epilepsy]*	9 [43, 94, 109, 111, 179, 184, 194, 200, 213] Stroink[184] has 2 cohorts (single and multiple seizures) and Watson, 2012[213] has 3 cohorts (ages 16-39, 40-64 and 65 or over). Thus, there are 12 datapoints from 9 studies	2348	Neurophysiologist, epileptologists, clinical physiologists and pediatric neurologists	Detailed clinical findings over prolonged follow up period Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses [however, for Kimiskidis (2017) non-epilepsy group were healthy controls]	0.40 [0.26, 0.56] 0.80 [0.52, 0.96] 0.24 [0.09, 0.45] 0.33 [0.24, 0.44] 0.40 [0.31, 0.50] 0.40 [0.30, 0.50] 0.60 [0.47, 0.72] 0.40 [0.28, 0.52] 0.55 [0.43, 0.66] 0.70 [0.66, 0.75] 0.56 [0.48, 0.63] 0.77 [0.60, 0.90] **Pooled (95% CrI): 0.508(0.393-0.625)**	0.95 [0.87, 0.98] 0.80 [0.59, 0.93] 1.00 [0.72, 1.00] 0.87 [0.82, 0.91] 0.95 [0.90, 0.99] 0.99 [0.96, 1.00] 0.88 [0.74, 0.96] 0.99 [0.96, 1.00] 0.77 [0.70, 0.83] 0.77 [0.69, 0.84] 0.78 [0.64, 0.88] 0.91 [0.77, 0.98] **Pooled (95% CrI): 0.920(0.846-0.966)**	**Sensitivity**				
							serious[a]	serious[b]	serious[d]	serious[c]	VERY LOW
							Specificity				
							serious[a]	serious[b]	serious[d]	serious[c]	VERY LOW
Sleep-deprived interictal EEG – abnormal (i.e. epileptiform waveforms)	3[81, 84, 159]	499	Resident/consultant in neurology	Collegial discussion of detailed clinical findings over prolonged follow up period	0.25 [0.15, 0.36] 0.45 [0.27, 0.64] 0.41 [0.33, 0.50] **Pooled (95% CrI): 0.362(0123-0.699)**	0.99 [0.97, 1.00] 0.90 [0.70, 0.99] 0.91 [0.83, 0.96] **Pooled (95% CrI): 0.962(0.697-0.997)**	**Sensitivity**				
							serious[a]	none	none	none	MOD
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
				Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses [for Kimiskidis (2017): healthy controls]			serious[a]	none	none	serious[c]	LOW
24 hour sleep deprivation interictal EEG– abnormal (i.e. epileptiform waveforms) *DETECTING FOCAL EPILEPSY* *Not included in meta-analysis above as same participants already included in Renzel (2015) 'overall epilepsy' cohort*	1[159]	226	Interpreted by resident and consultant in neurology and clinical neurophysiology	Collegial discussion following ILAE guidelines, and EEG evidence Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses	0.17 [0.09, 0.29]	0.99 [0.97, 1.00]	**Sensitivity**				
							serious[a]	none	NA	none[c]	MOD
							Specificity				
							serious[a]	none	NA	none[c]	MOD
24 hour sleep deprivation interictal EEG– abnormal (i.e. epileptiform waveforms)	1[159]	179	Interpreted by resident and consultant in neurology and clinical neurophysiology	Collegial discussion following ILAE guidelines, and EEG evidence	0.64 [0.31, 0.89]	0.99 [0.97, 1.00]	**Sensitivity**				
							serious[a]	none	NA	serious[c]	LOW
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
DETECTING GENERALISED EPILEPSY *Not included in meta-analysis above as same participants already included in Renzel (2015) 'overall epilepsy' cohort*				Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses			serious[a]	none	NA	none[c]	MOD
Ambulatory interictal EEG (16-24 hrs, including sleep) – abnormal (i.e. epileptiform waveforms)	1 [81]	52	Resident/consultant in neurology	Clinical record surveyed for clinical, imaging and diagnosis at 1 year data (ILAE) Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses [for Kimiskidis (2017): healthy controls]	0.63 [0.44, 0.79]	0.95 [0.75, 1.00]	**Sensitivity**				
							serious[a]	none	NA	serious[c]	LOW
							Specificity				
							serious[a]	none	NA	serious[c]	LOW
Prolonged ambulatory interictal EEG using epileptiform	1 [102]	72	Electroencephalographers	Summation of retrospective medical records and expert opinion	0.58 [0.43, 0.72]	0.95 [0.77, 1.00]	**Sensitivity**				
							none	none	NA	serious[c]	MOD

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
discharges only as definition of a positive test				Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses			**Specificity**				
							none	none	NA	serious[c]	MOD
Prolonged ambulatory interictal EEG using either epileptiform discharges or non-epileptiform abnormalities as definitions of a positive test	1 [102]	72	Electroencephalographers	Summation of retrospective medical records and expert opinion Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses	0.78 [0.64, 0.88]	0.59 [0.36, 0.79]	**Sensitivity**				
							none	none	NA	none	HIGH
							Specificity				
							none	none	NA	serious[c]	MOD
Routine interictal EEG with provocation with hyperventilation, intermittent phototic stimulation and	1 [102]	72	Electroencephalographers	Summation of retrospective medical records and expert opinion	0.26 [0.15, 0.40]	1.00 [0.85, 1.00]	**Sensitivity**				
							none	none	NA	none	HIGH
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
eye opening/closing, using epileptiform discharges as definition of positive test				Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses			none	none	NA	serious[c]	MOD
Routine interictal EEG with provocation with hyperventilation, intermittent phototic stimulation and eye opening/closing, using either epileptiform or non-epileptiform abnormalities as definitions of a positive test	1 [102]	72	Electroencephalographers	Summation of retrospective medical records and expert opinion Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses	0.62 [0.47, 0.75]	0.55 [0.32, 0.76]	**Sensitivity**				
							none	none	NA	serious[c]	MOD
							Specificity				
							none	none	NA	serious[c]	MOD
Early sporadic epileptiform discharges (first 30 minutes of the EEG recordings) *DETECTING NCSE*	1[114]	NC	neurophysiology experts	Critical care continuous EEG Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses	0.214[e]	0.908[e]	**Sensitivity**				
							serious[a]	none	NA	NA[c]	MOD
							Specificity				
							serious[a]	none	NA	NA[c]	MOD

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Computational biomarker looking at the synchrony between EEG channels and the normalised power spectrum from a short resting state interictal EEG (does not require epileptiform discharges). Details of the threshold of synchrony not given.	1 [171]	68	Trained clinical EEG technician	EEG monitoring Non-epilepsy group: Healthy controls	0.57 [0.37, 0.75] The above data is based on the fact that at 100% specificity we have 56.7% sensitivity The paper also reports (based on the ROC curves) that at 100% sensitivity, 65.8% specificity is attainable	1.00 [0.91, 1.00]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	none	VERY LOW
Synchronisation likelihood (SL) based on standard EEG after a first seizure. The Theta band SL values were tested for accuracy, but details or specific threshold not given	1 [62]	161	NR	Medical chart review with a 1 year follow up (ILAE) Non-epilepsy group: unclear	0.61 [0.48, 0.74]	0.76 [0.67, 0.84]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	none	VERY LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Interictal fast ripple (250-500Hz) events, based on scalp EEG. Single 10-minute epoch per patient. Existence of fast ripples = positive test. *(INFANTS WITH TUBEROUS SCLEROSIS COMPLEX-ASSOCIATED EPILEPSY)*	1 [28]	11	Trained clinicians	Video EEG Non-epilepsy group: healthy controls	1.00 [0.59, 1.00]	1.00 [0.40, 1.00]	**Sensitivity**				
							serious[a]	Serious[b]	NA	Very serious[c]	VERY LOW
							Specificity				
							serious[a]	Very serious[b]	NA	Very serious[c]	VERY LOW
Functional network approach. Periods of resting-state EEG, free of abnormal slowing or epileptiform activity, were selected to construct functional networks of correlated activity. The statistical interdependencies for each pair of	1[200]	70	Clinical epileptologist	EEG/clinical and 1 year follow up Non-epilepsy group: healthy controls]	0.96 [0.78–1.00]	0.95 [0.76–1.00]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
EEG electrode time series are considered as functional connectivity and used to construct a functional network per subject for each of the four epochs and were averaged per subject. Details of thresholds not provided *DETECTING PARTIAL EPILEPSY*											
Early rhythmic and periodic EEG patterns of ictal-interictal uncertainty (RPPIIU) *DETECTING NCSE*	1[114]	NC	neurophysiology experts	Critical care continuous EEG Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses	0.643[e]	0.846[e]	**Sensitivity**				
							serious[a]	none	NA	NA[c]	MOD
							Specificity				
							serious[a]	none	NA	NA[c]	MOD

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Early sporadic epileptiform discharges OR Early rhythmic and periodic EEG patterns of 'ictal-interictal uncertainty' *DETECTING NCSE*	1[114]	NC	neurophysiology experts	Critical care continuous EEG Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses	0.857[e]	0.754[e]	**Sensitivity**				
							serious[a]	none	NA	NA[c]	MOD
							Specificity				
							serious[a]	none	NA	NA[c]	MOD
Resting state 10-15 min high density EEG. The cortical source activity was obtained and whole-brain directed functional connectivity was estimated in the theta, alpha and beta frequency bands. No threshold information available *DETECTING TEMPORAL LOBE EPILEPSY*	1[205]	75	NR	EEG/clinical Non-epilepsy group: healthy controls]	0.95 [0.83, 0.99]	0.86 [0.70, 0.95]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Routine EEG using Salzburg criteria. ICTAL for Jaraba[100] but unclear for other two studies *DETECTING NCSE*	3[87, 100, 124] Note there are 2 cohorts from Goselink, 2019[87] – patients suspected of NCSE and patients not suspected of NCSE	366	Nuclear medicine or neurophysiology experts	All data including clinical, EEG, imaging, lab tests etc Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses	0.98 [0.88, 1.00] 0.61 [0.43, 0.77] 0.67 [0.35, 0.90] 1.00 [0.03, 1.00] **Pooled (95%CrIs): 0.838(0.430-0.986)**	0.90 [0.81, 0.95] 0.89 [0.67, 0.99] 0.89 [0.81, 0.95] 0.89 [0.81, 0.95] **Pooled (95%CrIs): 0.899(0.782-0.959)**	**Sensitivity**				
							serious[a]	none	none	serious[c]	LOW
							Specificity				
							serious[a]	none	none	serious[c]	LOW
Ictal EEG (without access to video or observation) – abnormal (i.e. epileptiform waveforms)	1 [39]	43	fellowship trained epileptologist	Surgical or by long term follow up Non-epilepsy group: PNES	0.89 [0.71, 0.98]	0.94 [0.70, 1.00]	**Sensitivity**				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							serious[a]	serious[b]	NA	serious[c]	VERY LOW
Quantitative ICTAL EEG interpreted by PICU clinicians in real time – abnormal	1 [166]	101	PICU clinicians	Clinical neurophysiologist retrospective review qEEG	1.00 [0.74, 1.00]	0.88 [0.79, 0.94]	**Sensitivity**				
							serious[a]	none	NA	serious[c]	LOW
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
waveforms (INFANTS)				Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses			serious[a]	none	NA	serious[c]	LOW
Headset-type continuous video EEG monitoring – detection of abnormal patterns, such as periodic discharges, rhythmic delta activity, spikes and wave and continuous slow discharges *DETECTING NCSE*	1[68]	50	1 neurointensivist and one board certified neurophysiologist	Video EEG Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses	0.71 [0.44, 0.90]	0.97 [0.84, 1.00]	**Sensitivity**				
							serious[a]	none	NA	Very serious[c]	VERY LOW
							Specificity				
							serious[a]	none	NA	serious[c]	LOW
No event video EEG (at least 16 hours)	1 [111]	340	NR	Full definitive diagnosis based on full medical records and a minimum of 1 clinic visit in 1 year of follow up	0.54 [0.44, 0.64]	0.88 [0.83, 0.92]	**Sensitivity**				
							Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
				Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses			Very serious[a]	serious[b]	NA	serious[c]	VERY LOW

(a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

(b) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect

(c) Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed one of the clinical thresholds (0.90 or 0.60), and downgraded by 2 increments when the confidence interval around the point estimate crossed both of the clinical thresholds. The upper clinical threshold marked the point above which recommendations would be possible, and the lower clinical threshold marked the point below which the tool would be regarded as of little clinical use.

(d) Inconsistency was assessed by visual inspection of the sensitivity/specificity plots, or data (if 2 studies). The evidence was downgraded by 1 increment if there was no overlap of 95% confidence intervals. If a meta-analysis had been carried out, sub-grouping was carried out when I^2 was >50%, according to the strategies listed in the protocol. However, in no circumstance did sub-grouping explain the heterogeneity observed, and so sub-grouping was not carried out. For single studies no evaluation was made and 'not applicable' was recorded.

(e) No confidence intervals were presented because there was insufficient information available or there was a mismatch between the raw data and the accuracy results.

Table 8: Clinical evidence summary: diagnostic test accuracy of different Magnetoencephalography / Transcranial Magnetic Stimulation tests for detection of epilepsy. Where detection is of a specific type of epilepsy, rather than epilepsy overall, this is stated clearly in the first column.

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Magnetoencephalography with simultaneous EEG (MEG-EEG). Interictal. No details of threshold available.	1 [65]	52	Trained physicians	1 year follow up, including all data Non-epilepsy group: those initially suspected of epilepsy but with no differential diagnoses	0.41 [0.21, 0.64]	0.93 [0.78, 0.99]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Serious[a]	Serious[b]	NA	serious[c]	VERY LOW
Paired pulse Transcranial Magnetic Stimulation with EEG (TMS-EEG) immediately after hyperventilation. Interictal. No details of threshold available.	1 [109]	36	NR	consensus by 2 experienced epileptologists who reached consensus based on clinical and lab data Non-epilepsy group: healthy controls	1.00 [0.86, 1.00]	0.73 [0.39, 0.94]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Very serious[c]	VERY LOW
Paired pulse TMS-EEG during	1 [109]	36	NR	consensus by 2 experienced	0.78[e]	0.89[e]	**Sensitivity**				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
hyperventilation. Interictal. No details of threshold available.				epileptologists who reached consensus based on clinical and lab data Non-epilepsy group: healthy controls			Serious[a]	Serious[b]	NA	NA	LOW
							Specificity				
							Serious[a]	Serious[b]	NA	NA	LOW
Paired pulse TMS-EEG at rest. Interictal. No details of threshold available.	1 [109]	36	NR	consensus by 2 experienced epileptologists who reached consensus based on clinical and lab data Non-epilepsy group: healthy controls	0.85[e]	0.89[e]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	NA	LOW
							Specificity				
							Serious[a]	Serious[b]	NA	NA	LOW
Single pulse TMS-EEG at rest. Interictal. No details of threshold available.	1 [109]	36	NR	consensus by 2 experienced epileptologists who reached consensus based on clinical and lab data	0.6[e]	0.82[e]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	NA	LOW
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
				7Non-epilepsy group: healthy controls			Serious[a]	Serious[b]	NA	NA	LOW

(a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

(b) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect

(c) Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed one of the clinical thresholds (0.90 or 0.60), and downgraded by 2 increments when the confidence interval around the point estimate crossed both of the clinical thresholds. The upper clinical threshold marked the point above which recommendations would be possible, and the lower clinical threshold marked the point below which the tool would be regarded as of little clinical use.

(d) Inconsistency was assessed by visual inspection of the sensitivity/specificity plots, or data (if 2 studies). The evidence was downgraded by 1 increment if there was no overlap of 95% confidence intervals. For single studies no evaluation was made and 'not applicable' was recorded.

(e) No confidence intervals were presented because there was insufficient information available or there was a mismatch between the raw data and the accuracy results.

Table 9: Clinical evidence summary: diagnostic test accuracy of different psychological measurements for detection of epilepsy. Where detection is of a specific type of epilepsy, rather than epilepsy overall, this is stated clearly in the first column.

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Personality Assessment scale: Psychogenic nonepileptic seizures (PNES) scale; threshold <1	1 [196]	184	NR	Video EEG Non-epilepsy group: PNES	0.85 [0.77, 0.91]	0.59 [0.47, 0.70]	**Sensitivity**				
							Very serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
							Specificity				
							Very serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
Personality Assessment scale: SOM-C (conversion) scale; threshold <70	1 [196]	184	NR	Video EEG Non-epilepsy group: PNES	0.83 [0.75, 0.90]	0.59 [0.47, 0.70]	**Sensitivity**				
							Very serious[a]	Serious[b]	NA	None[c]	VERY LOW
							Specificity				
							Very serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
Personality Assessment scale: SOM (somatic complaints); threshold <70	1 [196]	184	NR	Video EEG Non-epilepsy group: PNES	0.73 [0.64, 0.81]	0.56 [0.44, 0.67]	**Sensitivity**				
							Very serious[a]	Serious[b]	NA	None[c]	VERY LOW
							Specificity				
							Very serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
	1 [196]	184	NR	Video EEG	0.82 [0.73, 0.88]	0.45 [0.34, 0.57]	**Sensitivity**				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Personality Assessment scale: SOM-S (somatisation); threshold <70				Non-epilepsy group: PNES			Very serious[a]	Serious[b]	NA	none[c]	VERY LOW
							Specificity				
							Very serious[a]	Serious[b]	NA	none	VERY LOW
Personality Assessment scale: DEP-P (Depression-physiological); threshold <70	1 [196]	184	NR	Video EEG Non-epilepsy group: PNES	0.86 [0.78, 0.92]	0.49 [0.38, 0.61]	**Sensitivity**				
							Very serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
							Specificity				
							Very serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
Personality Assessment scale: DEP-P (Depression); threshold <60	1 [196]	184	NR	Video EEG Non-epilepsy group: PNES	0.61 [0.52, 0.71]	0.63 [0.51, 0.74]	**Sensitivity**				
							Very serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
							Specificity				
							Very serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
Personality Assessment scale: ANX-P (Anxiety-Physiological); threshold <60	1 [196]	184	NR	Video EEG Non-epilepsy group: PNES	0.68 [0.58, 0.77]	0.57 [0.45, 0.69]	**Sensitivity**				
							Very serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
							Specificity				
							Very serious[a]	Serious[b]	NA	serious[c]	VERY LOW
Wilkus measure of hysteria and hypochondriasis: A patients has pseudoseizures if any of the following are true: a) hysteria or	2[181, 215]	69	Trained psychometrists	Video EEG Non-epilepsy group: PNES	0.74 [0.54, 0.89] 0.80 [0.44, 0.97]	0.59 [0.36, 0.79] 0.90 [0.55, 1.00]	**Sensitivity**				
							Very serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
							Specificity				
							Very serious[a]	Serious[b]	NA	Very serious[c]	VERY LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
hypochondriasis score >=70 and one of the two highest points in the profile (disregarding the masculinity-femininity and social introversion scales, b) hysteria or hypochondriasis score >=80 and not necessarily among the two highest points, c) hysteria and hypochondriasis both >59 and both 10 points higher than the depression scale. In a sample where ONLY epilepsy and PNES patients are known to exist then this test could be used to show that epilepsy exists if NONE of these conditions exists.											
Structured Interview of malingered	1 [26]	120	NR	Video EEG	0.55 [0.36, 0.74]	0.76 [0.66, 0.84]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Symptomatology questionnaire; threshold <14				Non-epilepsy group: PNES			**Specificity**				
							Serious[a]	Serious[b]	NA	none[c]	VERY LOW
Structured Interview of malingered Symptomatology questionnaire; threshold <16	1 [26]	120	NR	Video EEG Non-epilepsy group: PNES	0.69 [0.49, 0.85]	0.71 [0.61, 0.80]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
							Specificity				
							Serious[a]	Serious[b]	NA	none[c]	VERY LOW
multivariate model of psychometric testing using 4 measures of cognitive ability – vocabulary, information, Boston naming test and letter fluency (unclear description in article)	1 [199]	105	Masters level psychometrist, predoc intern or postdoc fellow	Video EEG Non-epilepsy group: PNES	0.92 [0.83, 0.97]	0.45 [0.28, 0.64]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
							Specificity				
							Serious[a]	Serious[b]	NA	serious[c]	VERY LOW
Number of panic attack symptoms <5	1 [92]	354	NR	Video EEG Non-epilepsy group: PNES	0.65 [0.57, 0.74]	0.70 [0.64, 0.76]	**Sensitivity**				
							Very serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
	1 [10]	41		Video EEG	0.52 [0.32, 0.71]	0.29 [0.08, 0.58]	**Sensitivity**				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
lifetime axis 1 (no details or score threshold available)			Trained psychiatrist	Non-epilepsy group: PNES			Serious[a]	Serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Serious[a]	Serious[b]	NA	none	LOW
Current axis 1 (no details or score threshold available)	1 [10]	41	Trained psychiatrist	Video EEG Non-epilepsy group: PNES	0.30 [0.14, 0.50]	0.57 [0.29, 0.82]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	none[c]	LOW
							Specificity				
							Serious[a]	Serious[b]	NA	serious[c]	VERY LOW
Current axis II (no details or score threshold available)	1 [10]	41	Trained psychiatrist	Video EEG Non-epilepsy group: PNES	0.19 [0.06, 0.38]	0.64 [0.35, 0.87]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	None[c]	LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
Any psychological trauma (yes/No). Criteria not given.	1 [10]	41	Trained psychiatrist	Video EEG Non-epilepsy group: PNES	0.33 [0.17, 0.54]	0.14 [0.02, 0.43]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	None[c]	LOW
							Specificity				
							Serious[a]	Serious[b]	NA	none[c]	VERY LOW

(a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

(b) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect

(c) Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed one of the clinical thresholds (0.90 or 0.60), and downgraded by 2 increments when the confidence interval around the point estimate crossed both of the clinical thresholds. The upper clinical threshold marked the point above which recommendations would be possible, and the lower clinical threshold marked the point below which the tool would be regarded as of little clinical use.

(d) Inconsistency was assessed by visual inspection of the sensitivity/specificity plots, or data (if 2 studies). The evidence was downgraded by 1 increment if there was no overlap of 95% confidence intervals. For single studies no evaluation was made and 'not applicable' was recorded.

(e) No confidence intervals were presented because there was insufficient information available or there was a mismatch between the raw data and the accuracy results.

Table 10: Clinical evidence summary: diagnostic test accuracy of different linguistic tests for detection of epilepsy. Where detection is of a specific type of epilepsy, rather than epilepsy overall, this is stated clearly in the first column.

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Linguistic analysis following guidelines from the German EpiLing project (rater 1) – threshold of >4.5 **Unclear if the accuracy data refer to detection of epilepsy or PNES**	1 [161]	20	Neurologist 1	Video EEG. Non-epilepsy group: PNES	0.86 [0.42, 1.00]	0.85 [0.55, 0.98]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	Very serious[c]	VERY LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Very serious[c]	VERY LOW
Linguistic analysis following guidelines from the German EpiLing project (rater 2) with threshold of >7.5 **Unclear if the accuracy data refer to detection of epilepsy or PNES**	1 [161]	20	Neurologist 2	Video EEG. Non-epilepsy group: PNES	0.71 [0.29, 0.96]	0.92 [0.64, 1.00]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	Very serious[c]	VERY LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW

(a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.
(b) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect

(c) Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed one of the clinical thresholds (0.90 or 0.60), and downgraded by 2 increments when the confidence interval around the point estimate crossed both of the clinical thresholds. The upper clinical threshold marked the point above which recommendations would be possible, and the lower clinical threshold marked the point below which the tool would be regarded as of little clinical use.

(d) Inconsistency was assessed by visual inspection of the sensitivity/specificity plots, or data (if 2 studies). The evidence was downgraded by 1 increment if there was no overlap of 95% confidence intervals. For single studies no evaluation was made and 'not applicable' was recorded.

(e) No confidence intervals were presented because there was insufficient information available or there was a mismatch between the raw data and the accuracy results.

Table 11: Clinical evidence summary: diagnostic test accuracy of EMG tests for detection of epilepsy. Where detection is of a specific type of epilepsy, rather than epilepsy overall, this is stated clearly in the first column.

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Single channel surface EMG (on biceps muscle belly). ICTAL. Decision based on expert review, but criteria unclear.	1 [97]	34	Board certified neurologists	Video EEG. Non-epilepsy group: PNES	0.77(0.64-0.86)[e]	0.96(0.89-0.99)[e]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	none[c]	LOW
							Specificity				
							Serious[a]	Serious[b]	NA	serious[c]	VERY LOW
Single channel surface EMG (on biecps muscle belly). ICTAL. Decision based on automated criteria (score between 0-25 with a score of 8 or above = epilepsy).	1 [97]	20	Automated	Video EEG. Non-epilepsy group: PNES	0.87 [0.60, 0.98]	0.79 [0.54, 0.94]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Very serious[c]	VERY LOW

(a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

(b) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect

(c) Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed one of the clinical thresholds (0.90 or 0.60), and downgraded by 2 increments when the confidence interval around the point estimate crossed both of the clinical thresholds. The upper clinical threshold marked the point above which recommendations would be possible, and the lower clinical threshold marked the point below which the tool would be regarded as of little clinical use.

(d) Inconsistency was assessed by visual inspection of the sensitivity/specificity plots, or data (if 2 studies). The evidence was downgraded by 1 increment if there was no overlap of 95% confidence intervals. For single studies no evaluation was made and 'not applicable' was recorded.

(e) No confidence intervals were presented because there was insufficient information available or there was a mismatch between the raw data and the accuracy results.

Table 12: Clinical evidence summary: diagnostic test accuracy of accelerometer tests for detection of epilepsy. Where detection is of a specific type of epilepsy, rather than epilepsy overall, this is stated clearly in the first column.

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Wrist accelerometer. ICTAL. (Bayly, 2013 used visual review of time-frequency maps by epileptologist, but criteria unclear. Kusmakar, 2018 used review of the Poincare-derived temporal variations by epileptologists but again criteria unclear)	2 [20, 116]	124	epileptologists	Clinical consensus /Video EEG. Non-epilepsy group: PNES	0.75 [0.35, 0.97] 0.87 [0.72, 0.96]	0.93 [0.80, 0.98] 0.70 [0.53, 0.84]	**Sensitivity**				
							none[a]	Serious[b]	NA	Very serious[c]	LOW
							Specificity				
							none[a]	Serious[b]	NA	serious[c]	LOW
Wrist accelerometer. ICTAL. (automated). Bayly, 2013 used the co-efficient of variation of the frequency of movements, using a threshold of 32% [<32% = PNES and >=32% = epilepsy]). Kusmakar, 2018 used an automated classifier built	3 [20,137,116]	163	Automated	Clinical consensus/ Video EEG. Non-epilepsy group: PNES	0.91 [0.59, 1.00] 0.73 [0.39, 0.94] 0.95 [0.83, 0.99] **Pooled (95% CrIs): 0.895(0.558-0.986)**	0.93 [0.82, 0.99] 1.00 [0.75, 1.00] 0.95 [0.85, 0.99] **Pooled (95% CrIs): 0.955(0.805-0.994)**	**Sensitivity**				
							Serious[a]	Serious[b]	none	serious[c]	VERY LOW
							Specificity				
							Serious[a]	Serious[b]	none	serious[c]	VERY LOW

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
using TI and DDI of Poincare-derived temporal variations, but thresholds not provided. Naganur, 2018 used K-means clustering and support vector machines, but details not available.											

(a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

(b) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect

(c) Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed one of the clinical thresholds (0.90 or 0.60), and downgraded by 2 increments when the confidence interval around the point estimate crossed both of the clinical thresholds. The upper clinical threshold marked the point above which recommendations would be possible, and the lower clinical threshold marked the point below which the tool would be regarded as of little clinical use.

(d) Inconsistency was assessed by visual inspection of the sensitivity/specificity plots, or data (if 2 studies). The evidence was downgraded by 1 increment if there was no overlap of 95% confidence intervals. For single studies no evaluation was made and 'not applicable' was recorded.

(e) No confidence intervals were presented because there was insufficient information available or there was a mismatch between the raw data and the accuracy results

Table 13: Clinical evidence summary: diagnostic test accuracy of initial diagnosis at admission for detection of epilepsy. Where detection is of a specific type of epilepsy, rather than epilepsy overall, this is stated clearly in the first column.

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
ED assessment. Included full blood examination and tests for blood glucose levels, liver function, urea and electrolytes, as well as calcium and magnesium. Drug and ethanol levels were performed on a case-by-case basis. Computed tomography (CT) neuroimaging was usually performed for all patients presenting with first seizures, unless there is a contraindication. Cerebrospinal fluid (CSF) examination is performed when meningitis or encephalitis is suspected.	1 [99]	219	ED doctors	Final diagnosis using index test data plus imaging, EEG, longer follow up and consensus Non-epilepsy group: range of people without epilepsy initially suspected of epilepsy (not restricted to one differential diagnosis)	0.73 [0.66, 0.80]	0.32 [0.18, 0.49]	**Sensitivity**				
							serious[a]	none[b]	NA	none	MOD
							Specificity				
							serious[a]	none[b]	NA	none[c]	MOD

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Impression of admitting epileptologist, based on review of history, physical and available diagnostic testing as documented in the medical record prior to vEEG.	1 [143]	439	Admitting epileptologist	Clinical consensus/ Video EEG. Non-epilepsy group: range of people without epilepsy initially suspected of epilepsy (not restricted to one differential diagnosis)	0.91 [0.82, 0.96]	0.86 [0.82, 0.90]	**Sensitivity**				
							Serious[a]	none[b]	NA	serious[c]	LOW
							Specificity				
							Serious[a]	none[b]	NA	none[c]	MOD
Initial Clinical diagnosis. Attending pediatric neurologist completed an extensive questionnaire on description of events, including postictal signs, possible provoking factors, medical history and family history. (CHILDREN)	1 [184]	536	Paediatric neurologist	Diagnosis based on 5 year follow up Non-epilepsy group: range of people without epilepsy initially suspected of epilepsy (not restricted to one differential diagnosis)	0.98 [0.96, 0.99]	0.86 [0.79, 0.91]	**Sensitivity**				
							Serious[a]	serious[b]	NA	none[c]	LOW
							Specificity				
							Serious[a]	serious[b]	NA	serious[c]	VERY LOW

(a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.
(b) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect
(c) Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around

the point estimate crossed one of the clinical thresholds (0.90 or 0.60), and downgraded by 2 increments when the confidence interval around the point estimate crossed both of the clinical thresholds. The upper clinical threshold marked the point above which recommendations would be possible, and the lower clinical threshold marked the point below which the tool would be regarded as of little clinical use.

(d) Inconsistency was assessed by visual inspection of the sensitivity/specificity plots, or data (if 2 studies). The evidence was downgraded by 1 increment if there was no overlap of 95% confidence intervals. For single studies no evaluation was made and 'not applicable' was recorded.

(e) No confidence intervals were presented because there was insufficient information available or there was a mismatch between the raw data and the accuracy results.

Table 14: Clinical evidence summary: diagnostic test accuracy of other miscellaneous physiological scales for detection of epilepsy. Where detection is of a specific type of epilepsy, rather than epilepsy overall, this is stated clearly in the first column.

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Hyperventilation and blood gas recovery. Interictal. If patient <65years, had an additional hyperventilation test (40 breaths per minute for 3 minutes. End tidal CO2 level had to be <2.5% after hyperventilation. Blood gases measured. Hyperventilation test considered negative if end tidal CO2 did not restore to >90% baseline value after 3 minutes recovery.	1 [94]	83	Neuro physio logist	Specific semiology Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses	0.16 [0.06, 0.32]	0.43 [0.29, 0.59]	**Sensitivity**				
							serious[a]	serious[b]	NA	none	LOW
							Specificity				
							serious[a]	serious[b]	NA	none	LOW
Head up tilt test. Interictal. (No details available in paper)	1 [43]	49	NR	EEG plus clinical findings, over prolonged follow up Non-epilepsy group:	0.20 [0.01, 0.72]	0.09 [0.03, 0.22]	**Sensitivity**				
							serious[a]	none	NA	serious[c]	LOW
							Specificity				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
				Population suspected of epilepsy but with no known differential diagnoses			serious[a]	none	NA	none	MOD
Epifinder application (a clinical decision support tool). Epifinder's algorithm is a form of artificial intelligence that is based on pattern recognition. It utilises standardised terminology and heuristic algorithms that produce a list of differential diagnoses based on pattern recognition of a cluster of semiology against ILAE-defined epilepsy criteria	1 [144]	53	epilepsy trained neurologist	Video EEG Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses	0.88 [0.70, 0.98]	0.85 [0.66, 0.96]	**Sensitivity**				
							serious[a]	none	NA	serious[c]	LOW
							Specificity				
							serious[a]	none	NA	serious[c]	LOW
Hypnosis Induction Profile	1 [107]	40	physician	Video EEG	0.69 [0.41, 0.89]	0.42 [0.22, 0.63]	**Sensitivity**				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
(HIP) score (threshold of <=9). Interictal.				Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses			serious[a]	none	NA	serious[c]	LOW
							Specificity				
							serious[a]	none	NA	serious[c]	LOW
Not having an event during hypnosis	1 [107]	40	physician	Video EEG Non-epilepsy group: Population suspected of epilepsy but with no known differential diagnoses	0.88 [0.62, 0.98]	0.46 [0.26, 0.67]	**Sensitivity**				
							serious[a]	none	NA	serious[c]	LOW
							Specificity				
							serious[a]	none	NA	serious[c]	LOW
Review of systems	1 [11]	60	physician	Video EEG	0.90 [0.73, 0.98]	0.40 [0.23, 0.59]	**Sensitivity**				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
questionnaire (threshold of <2.5)				Non-epilepsy group: PNES			Very serious[a]	serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Very serious[a]	serious[b]	NA	none	VERY LOW
Frontal Lobe Epilepsy and Parasomnias (FLEP) scale. Filled in on basis of reports from partners or relatives. Threshold not provided. *DETECTING NOCTURNAL FRONTAL LOBE EPILEPSY*	1 [58]	62	Research Assistant	Video EEG Non-PC epilepsy group: arousal parasomnia and sleep disorder	1.00 [0.89, 1.00]	0.90 [0.74, 0.98]	**Sensitivity**				
							Serious[a]	Serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
Frontal Lobe Epilepsy and Parasomnias (FLEP) scale. Filled in on basis of reports from partners or relatives.Threshold not provided. *DETECTING NOCTURNAL FRONTAL LOBE EPILEPSY*	1 [58]	62	Experienced physician	Video EEG Non-PC epilepsy group: arousal parasomnia and sleep disorder	1.0(0.86-1.00)	0.93 (0.79-0.98)	**Sensitivity**				
							Serious[a]	Serious[b]	NA	serious[c]	VERY LOW
							Specificity				
							Serious[a]	Serious[b]	NA	Serious[c]	VERY LOW
	1 [131]	49		Video EEG	0.50 [0.16, 0.84]	1.00 [0.91, 1.00]	**Sensitivity**				

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
FLEP scale (excluding those with scores in uncertain range of 1-3). Filled in on basis of reports from partners or relatives. Threshold >3			Medical doctor	Non-epilepsy group: Parasomnias and idiopathic RBD			None[a]	serious[b]	NA	serious[c]	LOW
							Specificity				
							None[a]	serious[b]	NA	none	MOD
FLEP scale (including those with scores in uncertain range of 1-3 = NFLE). Filled in on basis of reports from partners or relatives. Threshold >0	1 [131]	71	Medical doctor	Video EEG Non-epilepsy group: Parasomnias and idiopathic RBD	0.71 [0.42, 0.92]	0.72 [0.58, 0.83]	**Sensitivity**				
							None[a]	serious[b]	NA	serious[c]	LOW
							Specificity				
							None[a]	serious[b]	NA	serious[c]	LOW
Nocturnal frontal lobe epilepsy (including those with scores in uncertain range of 1-3 = NO NFLE). Filled in on basis of reports from partners or relatives.Threshold>3	1 [131]	71	Medical doctor	Video EEG Non-epilepsy group: Parasomnias and idiopathic RBD	0.29 [0.08, 0.58]	1.00 [0.94, 1.00]	**Sensitivity**				
							None[a]	serious[b]	NA	none	MOD
							Specificity				
							None[a]	serious[b]	NA	none	MOD

(a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

(b) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect

(c) Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed one of the clinical thresholds (0.90 or 0.60), and downgraded by 2 increments when the confidence interval around the point estimate

crossed both of the clinical thresholds. The upper clinical threshold marked the point above which recommendations would be possible, and the lower clinical threshold marked the point below which the tool would be regarded as of little clinical use.

(d) Inconsistency was assessed by visual inspection of the sensitivity/specificity plots, or data (if 2 studies). The evidence was downgraded by 1 increment if there was no overlap of 95% confidence intervals. For single studies no evaluation was made and 'not applicable' was recorded.

(e) No confidence intervals were presented because there was insufficient information available or there was a mismatch between the raw data and the accuracy results.

STRATUM 2: Differentiation between specific types of epilepsy

Table 15: Clinical evidence summary: diagnostic test accuracy of different serum measurements for differentiation of people with autoimmune epilepsy from people with other epilepsy sub-types.

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Antibody prevalence in Epilepsy (APE) score; threshold >=4. Interictal. DETECTING AUTOIMMUNE EPILEPSY	1 [64]	387	NR	CNS-specific antibodies Non-autoimmune epilepsy group: other epilepsy groups	0.98 [0.88, 1.00]	0.78 [0.73, 0.82]	**Sensitivity**				
							Serious[a]	none[b]	NA	Serious[c]	LOW
							Specificity				
							Serious[a]	none[b]	NA	None	MOD
Antibody prevalence in Epilepsy2 (APE2) score; threshold not reported. Interictal. DETECTING AUTOIMMUNE EPILEPSY	1 [132]	219	NR	Detection of NSAb Non-autoimmune epilepsy group: new onset focal epilepsy	0.435[e]	0.791[e]	**Sensitivity**				
							Serious[a]	none[b]	NA	NA	MOD
							Specificity				
							Serious[a]	none[b]	NA	NA	MOD

(a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

(b) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect

(c) Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed one of the clinical thresholds (0.90 or 0.60), and downgraded by 2 increments when the confidence interval around the point estimate crossed both of the clinical thresholds. The upper clinical threshold marked the point above which recommendations would be possible, and the lower clinical threshold marked the point below which the tool would be regarded as of little clinical use.

(d) Inconsistency was assessed by visual inspection of the sensitivity/specificity plots, or data (if 2 studies). The evidence was downgraded by 1 increment if there was no overlap of 95% confidence intervals. For single studies no evaluation was made and 'not applicable' was recorded.

(e) No confidence intervals were presented because there was insufficient information available or there was a mismatch between the raw data and the accuracy results.

Table 16: Clinical evidence summary: diagnostic test accuracy of different psychological measurements for differentiation of people with autoimmune epilepsy from people with other epilepsy sub-types.

Index Test	Number of studies	n	Interpreter of index test	Gold standard used in study	Sensitivity (95% CI)	Specificity (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	GRADE
Addenbrooke's cognitive examination (ACE) attention domain (threshold >=0) Interictal. DETECTING AUTOIMMUNE EPILEPSY	1 [132]	219	NR	Detection of NSAb Non-autoimmune epilepsy group: new onset focal epilepsy	0.667[e]	0.849[e]	**Sensitivity**				
							Serious[a]	none[b]	NA	NA	MOD
							Specificity				
							Serious[a]	none[b]	NA	NA	MOD

(f) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

(g) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect

(h) Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed one of the clinical thresholds (0.90 or 0.60), and downgraded by 2 increments when the confidence interval around the point estimate crossed both of the clinical thresholds. The upper clinical threshold marked the point above which recommendations would be possible, and the lower clinical threshold marked the point below which the tool would be regarded as of little clinical use.

(i) Inconsistency was assessed by visual inspection of the sensitivity/specificity plots, or data (if 2 studies). The evidence was downgraded by 1 increment if there was no overlap of 95% confidence intervals. For single studies no evaluation was made and 'not applicable' was recorded.

(j) No confidence intervals were presented because there was insufficient information available or there was a mismatch between the raw data and the accuracy results.

See Appendix D for full evidence tables.

1.2.6 Economic evidence

1.2.6.1 Included studies

No health economic studies were included.

1.2.6.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.2.7 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.2.8 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness. All unit costs sourced from NHS reference costs 2018-2019 [140REF]. The unit costs included are EEG, ECG, MRI, CT, PET, SPECT and neurology appointments.

Other unit costs of relevance include blood tests (full blood count, liver function, glucose, and electrolytes) and venous blood gas (for accident and emergency admissions only). NHS reference costs list directly accessed pathology services unit costs as between £1 and £8.

Table 17: Electroencephalogram (EEG) unit costs

Conventional EEG, EMG or Nerve conduction Studies			
Adults (19 years and over)			
Currency code: AA33C	**Activity**	**Unit Cost**	**Total Cost**
Total	190,268	£199	£37,938,282
Elective	125	£1,952	£243,961
Non-elective long stay	157	£2,993	£469,837
Non-elective short stay	1,007	£827	£832,773
Day case	808	£807	£651,783
Regular day or night admissions	86	£993	£85,361
Outpatient procedures	141,294	£205	£28,914,172
Directly accessed diagnostic services	46,791	£144	£11,264,379
Children (18 years and under)			
Currency code: AA33D	**Activity**	**Unit Cost**	**Total Cost**
Total	22,390	£340	£7,607,597
Elective	210	£1,186	£248,995
Non-elective long stay	77	£2,885	£222,125
Non-elective short stay	609	£1,422	£866,025
Day case	2,614	£651	£1,702,333
Regular day or night admissions	2	£1,092	£2,183
Outpatient procedures	18,591	£241	£4,471,167
Directly accessed diagnostic services	287	£330	£94,768

Complex Long-term EEG monitoring			
Currency code: AA80Z	**Activity**	**Unit Cost**	**Total Cost**
Total	4,902	£2,067	£10,133,610
Elective	3,808	£2,126	£8,096,765
Non-elective long stay	476	£2,960	£1,409,167
Non-elective short stay	257	£1,182	£303,834
Day case	358	£901	£322,713
Regular day or night admissions	1	£674	£674
Outpatient procedures	-	-	-
Directly accessed diagnostic services	2	£228	£457
Standard Long-term EEG monitoring			
Currency code: AA81Z	**Activity**	**Unit Cost**	**Total Cost**
Total	2,020	£491	£991,134
Elective	395	£994	£392,797
Non-elective long stay	118	£2,106	£248,475
Non-elective short stay	74	£860	£63,634
Day case	10	£1,217	£12,166
Regular day or night admissions	2	£1,809	£3,619
Outpatient procedures	1,308	£193	£252,104
Directly accessed diagnostic services	113	£162	£18,339

Table 18: Electrocardiogram (ECG) unit costs

ECG monitoring or stress testing			
Currency code: EY51Z	**Activity**	**Unit Cost**	**Total Cost**
Total	565,058	£102	£57,831,246
Elective	46	£643	£29,599
Non-elective long stay	4	£3,575	£14,300
Non-elective short stay	53	£783	£41,524
Day case	2,700	£464	£1,252,196
Regular day or night admissions	397	£457	£181,594
Outpatient procedures	330,956	£136	£45,047,653
Directly accessed diagnostic services	230,902	£49	£11,264,379

Table 19: Magnetic Resonance Imaging (MRI) unit costs

Currency code	Currency description	Activity	Unit Cost	Total Cost
RD01A	MRI Scan of One Area, without Contrast, 19 years and over	1,440,377	£136	£196,146,270
RD01B	MRI Scan of One Area, without Contrast, between 6 and 18 years	62,170	£138	£8,592,099
RD01C	MRI Scan of One Area, without Contrast, 5 years and under	16,609	£135	£2,246,755
RD02A	MRI Scan of One Area, with Post-Contrast Only, 19 years and over	239,007	£151	£36,014,012
RD02B	MRI Scan of One Area, with Post-Contrast Only, between 6 and 18 years	7,569	£172	£1,301,693
RD02C	MRI Scan of One Area, with Post-Contrast Only, 5 years and under	1,374	£141	£193,099

Currency code	Currency description	Activity	Unit Cost	Total Cost
RD03Z	MRI Scan of One Area, with Pre- and Post-Contrast	45,069	£215	£9,703,024
RD04Z	MRI Scan of Two or Three Areas, without Contrast	117,642	£142	£16,648,325
RD05Z	MRI Scan of Two or Three Areas, with Contrast	24,148	£204	£4,934,540
RD06Z	MRI Scan of more than Three Areas	45,209	£194	£8,771,400
RD07Z	MRI Scan Requiring Extensive Patient Repositioning	5,477	£263	£1,442,365

Table 20: Computerised Tomography (CT) unit costs

Currency code	Currency description	Activity	Unit Cost	Total Cost
RD20A	CT Scan of One Area, without Contrast, 19 years and over	827,230	£83	£68,854,114
RD20B	CT Scan of One Area, without Contrast, between 6 and 18 years	13,504	£97	£1,308,085
RD20C	CT Scan of One Area, without Contrast, 5 years and under	13,579	£66	£894,029
RD21A	CT Scan of One Area, with Post-Contrast Only, 19 years and over	235,143	£107	£25,196,786
RD21B	CT Scan of One Area, with Post-Contrast Only, between 6 and 18 years	1,172	£133	£155,768
RD21C	CT Scan of One Area, with Post-Contrast Only, 5 years and under	695	£172	£119,719
RD22Z	CT Scan of One Area, with Pre- and Post-Contrast	24,731	£105	£2,586,066
RD23Z	CT Scan of Two Areas, without Contrast	55,248	£93	£5,123,143
RD24Z	CT Scan of Two Areas, with Contrast	230,506	£104	£23,883,214
RD25Z	CT Scan of Three Areas, without Contrast	24,080	£103	£2,475,934
RD26Z	CT Scan of Three Areas, with Contrast	358,745	£115	£41,322,696
RD27Z	CT Scan of more than Three Areas	83,205	£111	£9,201,145

Table 21: Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) unit costs

Currency code	Currency description	Activity	Unit Cost	Total Cost
RN07A	PET, 19 years and over	18,314	£830	£15,193,497
RN07B	PET, between 6 and 18 years	51	£215	£10,964
RN07C	PET, 5 years and under	5	£119	£595
RN08A	SPECT, 19 years and over	16,068	£319	£5,125,070
RN08B	SPECT, between 6 and 18 years	199	£332	£66,144
RN08C	SPECT, 5 years and under	26	£236	£6,145

Table 22: Neurology appointment costs

Neurology appointments	
Consultant led – adults	
Non-Admitted Face-to-Face Attendance, Follow-up	£169

Neurology appointments	
Consultant led – adults	
Non-Admitted Face-to-Face Attendance, First	£220
Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	£237
Multiprofessional Non-Admitted Face-to-Face Attendance, First	£245
Non-consultant led – adults	
Non-Admitted Face-to-Face Attendance, Follow-up	£115
Non-Admitted Face-to-Face Attendance, First	£113
Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	£1,019
Multiprofessional Non-Admitted Face-to-Face Attendance, First	£127
Consultant led – children	
Non-Admitted Face-to-Face Attendance, Follow-up	£305
Non-Admitted Face-to-Face Attendance, First	£435
Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	£284
Multiprofessional Non-Admitted Face-to-Face Attendance, First	£412
Non-consultant led – children	
Non-Admitted Face-to-Face Attendance, Follow-up	£240
Non-Admitted Face-to-Face Attendance, First	£851
Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	£311
Multiprofessional Non-Admitted Face-to-Face Attendance, First	£445

1.3 Review question: What is the most clinically and cost-effective approach for diagnosis of epilepsies?

1.3.1 Summary of the protocol

For full details see the review protocol in 0.

Table 23: PICO characteristics of review question

Population	Inclusion: Strata: • Children and adults with suspected epilepsy. • Children and adults with epilepsy, where uncertainty remains as to the type of epilepsy Exclusion: New-born babies with acute symptomatic seizures
Intervention	Any comparison of diagnostic strategies used in studies (these do not have to contain EEG or ECG but are likely to do so).
Comparison	Each other
Outcomes	• mortality • seizures (we will collect both binary data and time to event data) • seizure frequency • time to withdrawal of treatment • quality of life (any validated scores) • any adverse events Follow up: any available but stratify to <1 yr, 1-5 yrs, >5 yrs
Study design	RCTs only

1.3.2 Methods and process

This review is a review of trials that have compared health-related outcomes in people randomised to different diagnostic tests. Tests may differ in their influence on later health outcomes through stimulating a more or less appropriate treatment approach by virtue of their differing diagnostic accuracies. In addition, tests may influence outcomes such as quality of life through other effects unrelated to accuracy, such as patient comfort, duration of testing or length of time for results. Whilst accuracy is not measured directly in such randomised trials, the advantage of such studies is that they demonstrate clinical efficacy. In contrast a diagnostic accuracy study can only demonstrate the intrinsic diagnostic accuracy of the test and is unable to show how that accuracy affects health outcomes. However, such randomised trials are not commonly undertaken, and may provide equivocal results, and so a diagnostic accuracy review was also undertaken.

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.3.3 Effectiveness evidence

1.3.3.1 Included studies

Two studies were included in the review.[165, 218] These are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary in Table 3.

Both included studies comprised patients undergoing emergency care due to reduced consciousness. They may therefore lack some applicability to the target population of this review, who require a diagnostic work-up because they have a clinical history suggestive of epilepsy.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.3.3.2 Excluded studies

See the excluded studies list in Appendix K.

1.3.4 Summary of studies included in the effectiveness evidence

Table 24: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes
Rossetti, 2020 [165]	Continuous EEG (30-48 hours) versus routine EEG (2 x 30 mins over 48 hours)	364 inpatients from Switzerland in intensive care units with impaired consciousness; mean age 63.75 years. Inclusion: Inpatients >18 years in intensive or intermediate care units having impaired consciousness of any aetiology, defined as GCS of 11 or less or a FOUR score of 12 or less; referred from the treating team for EEG Exclusion: Weekend patients; patients in palliative care; those risking invasive procedures within 48 hours; those with recent (<36 hours) seizures or SE (96 hours)	Mortality at 6 months Seizures at 6 months Adverse events at 6 months

Study	Intervention and comparison	Population	Outcomes
Zehtabchi, 2014[218]	Micro EEG + routine care versus routine care	149 patients from USA; mean age 65. Inclusion All adult (18 year and older) ED patients with AMS, defined as any alteration in level of responsiveness or alertness or arousability, presenting as lethargy, delirium, confusion, agitation, coma, disinhibition, labile/blunted affects, or unexpected psychosis. Exclusion criteria included patients with immediately correctable causes of AMS (including finger stick or serum glucose less than 60 mg/dL); hypothermia (body temperature below 35.0°C); hyperthermia, heat exhaustion, or heat stroke; opioid overdose responding to naloxone; patients who were unable to undergo EEG recordings (e.g., severe scalp injury); hemodynamically unstable patients (systolic blood pressure < 90 mm Hg); uncooperative or combative patients; and patients who were discharged, admitted, or transferred before enrolment. Patients who had overt seizures in the ED were only included if they experienced prolonged postictal periods (at the discretion of the ED attending physician).	Mortality during inpatient period

1 See Appendix D for full evidence tables.

1.3.5 Summary of the effectiveness evidence

Table 25: Clinical evidence summary: continuous EEG vs Routine EEG

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with intervention (95% CI)
Mortality	364 (1 study) 6 months	⨁⨁⨁⊖ MODERATE[a] due to risk of bias	RR 1.01 (0.82 to 1.25)	Moderate	
				484 per 1000	5 more per 1000 (from 87 fewer to 121 more)
Health Related Quality of life	No evidence found				
seizures	368 (1 study) 6 months	⨁⨁⨁⊖ MODERATE[a] due to risk of bias	RR 3.59 (1.68 to 7.63)	Moderate	
				44 per 1000	113 more per 1000 (from 30 more to 290 more)
Adverse events	368 (1 study) 6 months	⨁⨁⊖⊖ LOW[a,b] due to risk of bias, imprecision	RR 0.83 (0.60 to 1.15)	Moderate	
				306 per 1000	52 fewer per 1000 (from 122 fewer to 46 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with intervention (95% CI)
Seizure frequency	No evidence found				
Time to withdrawal of treatment	No evidence found				
a The study had serious risk of bias due to possible selection bias b The confidence intervals crossed the lower MID of 0.8					

Table 26: Clinical evidence summary: micro EEG + routine care versus routine care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with intervention (95% CI)
Mortality	149 (1 study) unclear follow up	⊖⊖⊖⊖ VERY LOW[a, b] due to risk of bias, imprecision	RR 1.04 (0.27 to 4.01)	Moderate	
				53 per 1000	2 more per 1000 (from 38 fewer to 158 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with intervention (95% CI)
Health Related Quality of life	No evidence found				
seizures	No evidence found				
Adverse events	No evidence found				
Seizure frequency	No evidence found				
Time to withdrawal of treatment	No evidence found				
a The study had serious risk of bias due to possible selection bias b The confidence intervals crossed the upper and lower MIDS of 0.8 and 1.25					

See Appendix F for full GRADE tables

1.3.6 Economic evidence

1.3.6.1 Included studies

No health economic studies were included.

1.3.6.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.3.7 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.3.8 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness. All unit costs sourced from NHS reference costs 2018-2019 [140]. The unit costs included are EEG, ECG, MRI, CT, PET, SPECT and neurology appointments.

Other unit costs of relevance include blood tests (full blood count, liver function, glucose, and electrolytes) and venous blood gas (for accident and emergency admissions only). NHS reference costs list directly accessed pathology services unit costs as between £1 and £8.

Table 27: Electroencephalogram (EEG) unit costs

Conventional EEG, EMG or Nerve conduction Studies			
Adults (19 years and over)			
Currency code: AA33C	**Activity**	**Unit Cost**	**Total Cost**
Total	190,268	£199	£37,938,282
Elective	125	£1,952	£243,961
Non-elective long stay	157	£2,993	£469,837
Non-elective short stay	1,007	£827	£832,773
Day case	808	£807	£651,783
Regular day or night admissions	86	£993	£85,361
Outpatient procedures	141,294	£205	£28,914,172
Directly accessed diagnostic services	46,791	£144	£11,264,379
Children (18 years and under)			
Currency code: AA33D	**Activity**	**Unit Cost**	**Total Cost**
Total	22,390	£340	£7,607,597
Elective	210	£1,186	£248,995
Non-elective long stay	77	£2,885	£222,125
Non-elective short stay	609	£1,422	£866,025
Day case	2,614	£651	£1,702,333
Regular day or night admissions	2	£1,092	£2,183
Outpatient procedures	18,591	£241	£4,471,167
Directly accessed diagnostic services	287	£330	£94,768

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Complex Long-term EEG monitoring			
Currency code: AA80Z	**Activity**	**Unit Cost**	**Total Cost**
Total	4,902	£2,067	£10,133,610
Elective	3,808	£2,126	£8,096,765
Non-elective long stay	476	£2,960	£1,409,167
Non-elective short stay	257	£1,182	£303,834
Day case	358	£901	£322,713
Regular day or night admissions	1	£674	£674
Outpatient procedures	-	-	-
Directly accessed diagnostic services	2	£228	£457
Standard Long-term EEG monitoring			
Currency code: AA81Z	**Activity**	**Unit Cost**	**Total Cost**
Total	2,020	£491	£991,134
Elective	395	£994	£392,797
Non-elective long stay	118	£2,106	£248,475
Non-elective short stay	74	£860	£63,634
Day case	10	£1,217	£12,166
Regular day or night admissions	2	£1,809	£3,619
Outpatient procedures	1,308	£193	£252,104
Directly accessed diagnostic services	113	£162	£18,339

2 **Table 28: Electrocardiogram (ECG) unit costs**

ECG monitoring or stress testing			
Currency code: EY51Z	**Activity**	**Unit Cost**	**Total Cost**
Total	565,058	£102	£57,831,246
Elective	46	£643	£29,599
Non-elective long stay	4	£3,575	£14,300
Non-elective short stay	53	£783	£41,524
Day case	2,700	£464	£1,252,196
Regular day or night admissions	397	£457	£181,594
Outpatient procedures	330,956	£136	£45,047,653
Directly accessed diagnostic services	230,902	£49	£11,264,379

3 **Table 29: Magnetic Resonance Imaging (MRI) unit costs**

Currency code	Currency description	Activity	Unit Cost	Total Cost
RD01A	MRI Scan of One Area, without Contrast, 19 years and over	1,440,377	£136	£196,146,270
RD01B	MRI Scan of One Area, without Contrast, between 6 and 18 years	62,170	£138	£8,592,099
RD01C	MRI Scan of One Area, without Contrast, 5 years and under	16,609	£135	£2,246,755
RD02A	MRI Scan of One Area, with Post-Contrast Only, 19 years and over	239,007	£151	£36,014,012
RD02B	MRI Scan of One Area, with Post-Contrast Only, between 6 and 18 years	7,569	£172	£1,301,693

Currency code	Currency description	Activity	Unit Cost	Total Cost
RD02C	MRI Scan of One Area, with Post-Contrast Only, 5 years and under	1,374	£141	£193,099
RD03Z	MRI Scan of One Area, with Pre- and Post-Contrast	45,069	£215	£9,703,024
RD04Z	MRI Scan of Two or Three Areas, without Contrast	117,642	£142	£16,648,325
RD05Z	MRI Scan of Two or Three Areas, with Contrast	24,148	£204	£4,934,540
RD06Z	MRI Scan of more than Three Areas	45,209	£194	£8,771,400
RD07Z	MRI Scan Requiring Extensive Patient Repositioning	5,477	£263	£1,442,365

Table 30: Computerised Tomography (CT) unit costs

Currency code	Currency description	Activity	Unit Cost	Total Cost
RD20A	CT Scan of One Area, without Contrast, 19 years and over	827,230	£83	£68,854,114
RD20B	CT Scan of One Area, without Contrast, between 6 and 18 years	13,504	£97	£1,308,085
RD20C	CT Scan of One Area, without Contrast, 5 years and under	13,579	£66	£894,029
RD21A	CT Scan of One Area, with Post-Contrast Only, 19 years and over	235,143	£107	£25,196,786
RD21B	CT Scan of One Area, with Post-Contrast Only, between 6 and 18 years	1,172	£133	£155,768
RD21C	CT Scan of One Area, with Post-Contrast Only, 5 years and under	695	£172	£119,719
RD22Z	CT Scan of One Area, with Pre- and Post-Contrast	24,731	£105	£2,586,066
RD23Z	CT Scan of Two Areas, without Contrast	55,248	£93	£5,123,143
RD24Z	CT Scan of Two Areas, with Contrast	230,506	£104	£23,883,214
RD25Z	CT Scan of Three Areas, without Contrast	24,080	£103	£2,475,934
RD26Z	CT Scan of Three Areas, with Contrast	358,745	£115	£41,322,696
RD27Z	CT Scan of more than Three Areas	83,205	£111	£9,201,145

Table 31: Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) unit costs

Currency code	Currency description	Activity	Unit Cost	Total Cost
RN07A	PET, 19 years and over	18,314	£830	£15,193,497
RN07B	PET, between 6 and 18 years	51	£215	£10,964
RN07C	PET, 5 years and under	5	£119	£595
RN08A	SPECT, 19 years and over	16,068	£319	£5,125,070
RN08B	SPECT, between 6 and 18 years	199	£332	£66,144
RN08C	SPECT, 5 years and under	26	£236	£6,145

Table 32: Neurology appointment costs

Neurology appointments	
Consultant led – adults	
Non-Admitted Face-to-Face Attendance, Follow-up	£169
Non-Admitted Face-to-Face Attendance, First	£220
Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	£237
Multiprofessional Non-Admitted Face-to-Face Attendance, First	£245
Non-consultant led – adults	
Non-Admitted Face-to-Face Attendance, Follow-up	£115
Non-Admitted Face-to-Face Attendance, First	£113
Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	£1,019
Multiprofessional Non-Admitted Face-to-Face Attendance, First	£127
Consultant led – children	
Non-Admitted Face-to-Face Attendance, Follow-up	£305
Non-Admitted Face-to-Face Attendance, First	£435
Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	£284
Multiprofessional Non-Admitted Face-to-Face Attendance, First	£412
Non-consultant led – children	
Non-Admitted Face-to-Face Attendance, Follow-up	£240
Non-Admitted Face-to-Face Attendance, First	£851
Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	£311
Multiprofessional Non-Admitted Face-to-Face Attendance, First	£445

1.4 Evidence statements

1.4.1 Effectiveness/Qualitative

None.

1.4.2 Economic

No relevant economic evaluations were identified.

1.5 The committee's discussion of the evidence

1.5.1 The outcomes that matter most

1.5.1.1 Diagnostic accuracy review

For the diagnostic accuracy review the outcomes were sensitivity and specificity. The committee considered that both outcomes are important because the harms of reduced sensitivity and the harms of reduced specificity are similar in the context of epilepsy diagnosis. Reduced sensitivity means that some people who truly have epilepsy will not be successfully detected by the index test. These people will therefore remain undiagnosed and untreated, which can have serious consequences. Reduced specificity means that some people who truly do not have epilepsy will be misdiagnosed as having epilepsy. These people may receive unnecessary treatments, where possible harms are not ameliorated by benefits.

The committee agreed that ideally the thresholds for recommendation of index tests should be a sensitivity of 0.9 and a specificity of 0.9. Use of any test achieving this threshold would mean that no more than 10% of people with epilepsy would suffer a missed diagnosis (false negatives), and that no more than 10% of people without epilepsy would be misdiagnosed with epilepsy (false positives). Because it was thought that the harms of reduced specificity may be slightly less dangerous than the harms of reduced sensitivity, it was agreed some leeway might be made in cases where a test had specificity slightly below 0.9. However, it was agreed that sensitivity had to exceed 0.9 to allow recommendation.

1.5.1.2 RCT review

All outcomes (mortality, seizures, seizure frequency, time to withdrawal of treatment, quality of life and any adverse events) were considered critical and of equal priority for decision-making.

1.5.2 The quality of the evidence

1.5.2.1 Diagnostic accuracy review

Most of the evidence was graded as low or very low. The main reasons for this were a lack of blinding of index tests and gold standard tests, which may have caused detection bias. Imprecision of estimates also occurred frequently, partly due to the small sample sizes of some studies. Other studies also did not report 95% confidence intervals, or did not report raw data sufficiently clearly to allow calculation of 95% confidence intervals, which prevented assessment of precision for these studies. In addition, some studies used a ‘case-control’ approach. In such studies the overall sample were purposefully derived from one group of people who had epilepsy, and from another group who did not have epilepsy but instead had a specific differential diagnosis (such as psychogenic non epileptic seizures). This results in the non-epilepsy group in such studies being more homogeneous than would be expected in the protocol population, where participants were meant to be drawn consecutively from a more heterogeneous sample of people who were suspected of epilepsy. This reduced the representativeness of the population in such ‘case-control’ studies, and a downgrade for indirectness was therefore made.

1.5.2.2 RCT review

Evidence was graded as moderate to very low in both comparisons (*continuous EEG versus routine EEG*, and *micro-EEG plus routine care versus routine care only*). Risk of bias was related to a lack of reporting of allocation concealment in all outcomes across both comparisons. Imprecision varied between no serious imprecision and very serious imprecision across all outcomes in both comparisons, which fully explained the variability in overall grade observed.

1.5.3 Benefits and harms

The committee considered the evidence relating to the different types of index test used, in order to decide if any tests or strategies should be recommended. The index tests were divided into categories and discussed in turn, and the sections below relate to each discrete discussion. Discussion of the diagnostic accuracy and RCT evidence has been integrated where appropriate.

Discussion of benefits and harms in relation to the diagnostic accuracy evidence was simplified by the fact that the higher the sensitivity and specificity of an index test, the

greater the benefits resulting from the index test achieving many true positive and true negative results, and the lower their harms resulting from index tests leading to fewer false positive and false negative results. As the committee were focussed on selecting tests where the sensitivity and specificity were very high, benefits were automatically optimised, and harms were automatically reduced. Discussion of benefits and harms in relation to RCT evidence is only discussed in the EEG section, as the two included RCTs were restricted to evaluating different methods of EEG.

Stratum 1: Differentiating between epilepsy and non-epilepsy

Semiology, signs and symptoms

Few semiological findings had adequate sensitivity and specificity to be considered for recommendation, but epileptologist observation of 'eye opening or widening at onset of seizure' and 'eyes open during seizure' during an in-hospital seizure video had excellent sensitivity and good specificity for differentiation between epilepsy and psychogenic non-epileptic seizures (PNES). However, these findings were not felt to be wholly relevant to the customary diagnostic situation, where in-hospital video-recordings of seizures would not normally be available. In a situation where hospital video recordings of seizures would be available, the gold standard method of video-EEG would normally be possible anyway, making such index tests unnecessary. Therefore, a recommendation specifically relating to using these semiological findings as individual diagnostic tests was not made.

The only sign or symptom-related finding with high accuracy was epileptologist history-taking and examination. Evidence from a high-powered study suggested that clinical diagnosis by an epileptologist, without ancillary assistance from any technological adjuncts such as EEG or imaging, was able to provide very good sensitivity and specificity for differentiating between epilepsy and any type of non-epilepsy in adults. In other words, these data suggested very small risks of a missed diagnosis and low risks of a misdiagnosis. The validity of this finding was enhanced by the fact that the gold standard for this study was video-EEG, which is regarded as the most valid method. These findings underlined the committee's existing clinical view that patients should be referred to a specialist for diagnosis as soon as possible. Although the evidence was in adults, the recommendation was extended to children and young people on the basis that the committee did not think that the diagnostic accuracy of an expert clinical diagnosis would be affected by the patient's age. Therefore, a recommendation was made that children, young people and adults should be referred to an expert clinician for assessment and diagnosis.

The committee also agreed that eye-witness reports of the seizure should be collected as a central part of the history taking by the expert. It was agreed that without witness-reports the history will lack information on essential features of a seizure than can increase the accuracy of a diagnosis. In addition, it was agreed that if video information is available, such as from mobile phones belonging to friends or family, this should also be used. It should be noted that the direct evidence relating to eye-witness reports and mobile phone video did *not* suggest either could be usefully used alone as an accurate diagnostic test, but the committee agreed that as part of the array of information collected in the history, they would enhance the accuracy of diagnosis by the expert clinician.

Serum measures

The committee considered the evidence for the use of serum measures, such as prolactin, lactate, anion gap, glial fibrillary astrocytic protein levels and ammonia, as post-ictal methods to diagnose epilepsy (differentiating between epilepsy and PNES). One study demonstrated that a paired prolactin test taken at 15 minutes and 2 hours

after a seizure had high sensitivity for detection of generalised clonic tonic seizures, but the specificity indicated that 25% of people with no epilepsy might be mis-diagnosed by this test. Furthermore, the confidence intervals were wide, suggesting that the true result in the population might be much lower than that observed in the sample. Overall, the committee did not think that the sensitivity and specificity for any serum test were adequate, with unacceptable levels of harm likely to result from missed diagnoses or misdiagnoses. Therefore, no recommendations to use such tests were made..

ECG

In the one study examining this area, the ECG data were poorly reported, and it was unclear how the sensitivity and specificity had been evaluated. The committee were aware of existing guidance and practice relating to the use of ECG in investigation of people who have had episode of loss of consciousness. A 12-lead ECG is an accepted part of any initial evaluation of a patient with loss of consciousness to assess for underlying conduction abnormalities or abnormalities of QT interval or S and T waves. These might be important findings for diagnosis of a cardiac cause of loss of consciousness. A positive ECG increases the likelihood that there is a cardiac cause of a loss of consciousness and the NICE guideline provides guidance on red flag abnormalities that merit urgent assessment (Transient loss of consciousness ('blackouts') in over 16s, Clinical guideline [CG109]). An ECG will not rule in or rule out epilepsy, but the committee agreed with existing guidance and practice that ECG should be available alongside other tests and investigations to contribute to the overall information informing an accurate diagnosis made by an expert.

The committee also considered that non-epileptic seizure type events may be caused by metabolic disorders such as hypoglycaemia. Therefore, the committee also agreed, by consensus, that evaluation for metabolic disorders including hypoglycaemia should be included in the initial assessment.

Imaging tests

The diagnostic accuracy of MRI, CT, and single photon emission computed tomography (SPECT) were considered by the committee. 4T MRI and SPECT both demonstrated reasonable accuracy, but this did not reach the pre-hoc threshold set at 0.9 for sensitivity and close to 0.9 for specificity, and the uncertainty of estimates was high. Overall, none of the imaging devices were able to demonstrate sufficient sensitivity and specificity to assure the committee that the harms of false negatives and false positives would not be excessive. The committee therefore did not recommend any imaging modality for diagnostic purposes. However, the committee were aware of the importance of imaging in determining the presence of underlying structural causes of known epilepsy, and agreed that it was important to recommend that they continue to be used for that purpose.

EEG tests

The committee discussed the potential utility of EEG tests as an interictal test, allowing testing schedules that were not fully constrained by the timing of seizures. Routine interictal EEG, as well as ambulatory and provoked interictal EEG, demonstrated very good specificity alongside very poor sensitivity for detection of epilepsy. This indicated that routine EEG results could be useful for ‘ruling a patient in’ if epileptiform or other abnormalities were observed on the EEG trace, because the low specificity indicates that very few people *without* epilepsy will demonstrate such abnormalities. However, routine EEG cannot be used to ‘rule’ out epilepsy in a patient with a negative EEG, because a very large proportion of people with a true diagnosis of epilepsy do not show epileptiform abnormalities on a routine EEG.

Therefore, the committee agreed that routine EEG could be used to *support* a pre-existing clinical diagnosis of epilepsy, but should never be used to *exclude* a diagnosis. EEG could therefore not be usefully used as a solitary test, and the committee agreed it should never be requested unless reasonable certainty already existed that epilepsy was present.

The evidence suggested that some provoking manoeuvres such as hyperventilation might improve sensitivity. The committee therefore recommended that provoking manoeuvres could be applied during routine EEG when possible, but that the small risks of such manoeuvres (such as an induced seizure, with its associated risks) should be considered and relayed to the patients before testing. In addition, some evidence suggested that ambulatory EEG had better sensitivity than routine EEG, with specificity that was equal to routine EEG. This was supported by RCT evidence showing that ambulatory EEG picked up more seizures than routine EEG. The committee therefore recommended that ambulatory EEG could be used when possible or available. These recommendations concerning the addition of provoking manoeuvres and ambulatory methods were not made because it was thought that increased sensitivity would allow EEG to be used as an independent definitive test; in neither case did the evidence suggest that the elevated sensitivity would be high enough. However, in both cases the slight improvement in sensitivity permitted increased confidence that EEG findings could be even more appropriately used as one piece of supporting information in the overall diagnostic picture.

The timing of EEG was also discussed. No data were found relating to the association between time after seizure and diagnostic accuracy, but the consensus was that the earlier that EEG could be carried out, the higher the diagnostic accuracy. For this reason, a recommendation was made that EEG should be carried out as quickly as possible after the seizure, and the committee agreed this is ideally within 72 hours.

Evidence concerning the use of EEG synchrony measures was also discussed. It is believed that increased synchrony of cortical firing is a common feature of brain physiology in people with epilepsy. Therefore, although abnormalities of the interictal EEG trace may not be a sensitive indicator of epilepsy, measures of synchrony may be more useful. Some of the results in the literature appeared to support this idea, with two studies demonstrating excellent sensitivity and specificity for detection of partial epilepsy and temporal lobe epilepsy using this method. However, the confidence intervals around these estimates were wide, and the studies did not provide enough technical information to allow a full understanding of the exact nature of the test as it would be used clinically. The committee discussed how these testing methods are currently in the experimental stages and that they are not in general clinical use. Therefore, no recommendations in this area were made.

Finally, the committee discussed the particular limitations of EEG in detecting frontal lobe seizures due to anatomical barriers to electrode detection in the frontal lobe region. The committee also discussed how EEG may have some ability to differentiate between focal and generalised seizures. However due to the lack of direct evidence from the review and the greater importance of other topics, the committee agreed that these areas did not warrant recommendations.

<u>Magnetoencephalography / Transcranial magnetic stimulation tests</u>

Most of the evidence suggested that magnetoencephalography / transcranial magnetic stimulation tests had an inadequate combination of sensitivity and specificity. One study showed excellent sensitivity for paired pulse TMS with EEG immediately after hyperventilation, but specificity was low enough to yield an

unacceptable number of misdiagnoses. Therefore, no recommendations were made in this area.

Psychological tests

Several psychological tests were considered, such as domains of the Personality Assessment Scale, or the Structured Interview of Malingered Symptomology. In all cases these were used to differentiate epilepsy from psychogenic non-epileptic seizures. However, the committee agreed that none of the measures had a sufficiently good combination of high sensitivity and high specificity to permit recommendations.

Linguistic tests

One study evaluated the diagnostic accuracy of linguistic analysis of a patient's later description of seizure events. The sensitivity and specificity were reasonably high when measured by one experimental rater, but the confidence intervals were very wide, making it possible that the values were significantly below this. The other rater had far inferior sensitivity, with even wider confidence intervals. In addition, the reporting in the paper was unclear and it was not obvious whether the paper was reporting detection of epilepsy or detection of psychogenic non-epileptic seizures. Therefore, no recommendations were made in relation to this evidence.

Electromyography (EMG) and accelerometers

The committee discussed how EMG and accelerometers may be used to differentiate between epilepsy and PNES by detecting different patterns of motor unit activity or kinesiology during a seizure. Wrist accelerometers analysed with an automated algorithm proved to have good sensitivity and excellent specificity. Unfortunately, the data were based on sparse data, which resulted in wide confidence intervals. Therefore, the committee were unable to have sufficient confidence in the estimates to make a recommendation.

Initial diagnosis at admission

Three papers that utilised a variety of tests in order to make an initial diagnosis were considered by the committee. Two of the studies involved expert neurologists, and the tests included a history and available diagnostic testing without EEG. Both of these studies demonstrated very good sensitivity and good specificity, and the committee agreed that these findings confirmed those found in the semiology section suggesting that expert clinical diagnosis is highly accurate. This reinforced the decision to recommend initial referral to an expert for assessment.

Miscellaneous tests

Although most of the miscellaneous tests failed to have sufficient accuracy, the Epifinder, an artificial intelligence application which utilises pattern recognition to assist diagnosis, had good sensitivity and specificity. Unfortunately, the confidence intervals were too wide to permit sufficient certainty of results and so no recommendations were made..

Stratum 2: Differentiating between epilepsy sub-types

The committee discussed the evidence concerning differentiation between autoimmune epilepsy and other epilepsy, but none of the index tests evaluated were sufficiently accurate to warrant recommendation.

1.5.4 Cost effectiveness and resource use

No health economic studies were identified for this review question. Unit costs were presented to aid committee consideration of cost effectiveness.

The committee discussed the clinical evidence presented and noted that, adults, children and young people with new onset of seizures should be referred urgently for assessment of epilepsy. Initial assessment for epilepsy in current practice encompasses taking a detailed history of the persons seizures – including eyewitness accounts and video footage of these seizures if available – and conducting an ECG. Additional tests include neuroimaging and EEG. However, the committee noted an EEG should not be used to exclude a diagnosis of epilepsy.

The recommendations made by the committee ensure adults, children and young people with new onset of seizures are referred urgently for assessment of epilepsy by a specialist in epilepsy diagnosis and ensure the appropriate diagnostic tests to diagnose epilepsy are undertaken. A missed diagnosis of epilepsy can result in poor clinical outcomes for patients. Patients with missed diagnosis of epilepsy will unlikely be aware of the high risks associated with seizures for example, the risk of SUDEP and other related epilepsy accidents (e.g., drowning in the bath or being involved in a road traffic accident as a result of experiencing an unexpected seizure). For a non-drug refractory epilepsy population, SMRs for patients with epilepsy are highest in the first two years of an epilepsy diagnosis. Therefore, ensuring epilepsy patients are diagnosed and given appropriate advice as early as possible is imperative in reducing the risk of epilepsy mortality which is achieved by rendering patients' seizure free on the appropriate ASMs. With a missed diagnosis of epilepsy patients who should be receiving ASMs will not be receiving these.

The committee noted that if an EEG is requested in current practice, this is not typically received by the patient within 72 hours (which is the ideal time frame recommended by the committee). In current practice an EEG would be carried out within 2-3 weeks. However, receiving an EEG within 72 hours once an EEG has been requested by a healthcare professional allows for more timely diagnosis of epilepsy.

The committee acknowledged that many epilepsy service centres are often limited by staff and equipment availability but noted the same number of people would be referred for an EEG – the EEG would just be undertaken at an earlier date. The committee did, however note that many epilepsy service centres will already be working at full capacity to maintain the current levels of service provision. The recommendation made by the committee states that, an EEG should be performed as soon as possible, stipulating that the ideal time frame is within 72 hours. Overall, the committee concluded that gradually decreasing the time frame for which people receive an EEG across epilepsy services would not result in a substantial resource impact. For epilepsy services already working at full capacity, in the short-term, additional resources may be required whilst neurophysiologists accommodate a change in practice. However, overall, once epilepsy services have adapted to offering EEGs for the diagnosis of epilepsy at a reduced time frame, epilepsy service centres will reach a new equilibrium for service provision, and no additional costs will be associated with this recommendation.

All other recommendations made are largely reflective of UK current practice. In current practice a small proportion of people will procced to sleep EEG if routine EEG is normal due to a strong clinical suspicion of generalised epilepsy. Ambulatory EEG may be performed for people who present with an initial seizure but there is strong clinical suspicion that there have been previous undeclared of unrecognised events.

In general, the majority of people who receive a routine EEG will not receive additional diagnostic EEG's. However, these tests can provide useful information leading to better tailored health care.

Overall, the QALY gains associated with a correct diagnosis of epilepsy are highly likely to be cost effective. The recommendations made ensure people will receive a timely and appropriate diagnosis of epilepsy. Therefore, tailored health care plans will be implemented in the most feasible time frame possible, resulting in greater health outcomes for patients. As the committee made recommendations that were largely reflective of UK current practice, this recommendation is not expected to result in a significant resource impact.

1.5.5 Recommendations supported by this evidence review

This evidence review supports recommendations 1.2.1 – 1.2.10.

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Appendices

Appendix A Review protocols

A.1 Review protocol: Diagnostic accuracy of point of care devices

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	Diagnostic accuracy of diagnostic strategies for epilepsies
2.	Review question	What is the most accurate approach for 1) diagnosis of epilepsy, and 2) differentiation between types of epilepsy
3.	Objective	To determine the diagnostic strategy that is the most sensitive and specific for each stratum. The lower the number of missed diagnoses and the lower the number of misdiagnoses the greater the value of the strategy.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language Other searches: • None The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.

5.	Condition or domain being studied	Epilepsies (all sub-types)
6.	Population	Inclusion: Strata: • Children and adults with suspected epilepsy. • Children and adults with epilepsy, where uncertainty remains as to the type of epilepsy Exclusion: Newborn babies with acute symptomatic seizures
7.	Index tests	Any diagnostic strategies used in papers to detect 1) epilepsy, 2) type of epilepsy. Note that these do not necessarily need to include EEG or ECG, but are likely to do so.
8.	Gold standard	Any gold standard used in the studies.
9.	Types of study to be included	Cross-sectional/prospective/retrospective diagnostic studies, or any study containing a diagnostic accuracy analysis
10.	Other exclusion criteria	Non English-language studies • Studies that do not report sensitivity and specificity, or insufficient data to derive these values. • Non-English language studies.
11.	Context	Accurate diagnosis of epilepsy and epilepsy type is essential to allow early and appropriate management.
12.	Primary outcomes (critical outcomes)	• • Sensitivity • • Specificity • • Raw data to calculate 2x2 tables to calculate sensitivity and specificity (number of true positives, true negatives, false positives and false negatives).
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of these potentially eligible studies will be retrieved and assessed in line with the criteria outlined above. A standardised form will be used to extract data from the included studies (see Developing NICE guidelines: the manual section 6.4).

15.	Risk of bias (quality) assessment	Risk of bias quality assessment will be assessed using QUADAS-2. 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible data will be meta-analysed where appropriate (if at least 3 studies reporting data at the same diagnostic threshold) in WinBUGS. Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Heterogeneity will be assessed by visual inspection of the sensitivity and specificity plots and summary area under the curve (AUC) plots. Particular attention will be placed on sensitivity, determined by the committee to be the primary outcome for decision making. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software.
17.	Analysis of sub-groups	Unconditional stratification Diagnosis of epilepsy v diagnosis of specific type of epilepsy (see notes on right) Conditional stratification (sub-grouping) If heterogeneity is identified, where data is available, subgroup analysis will be carried out for the following subgroups: • Age: <2, 2-11, 11-18, 18-55, >55 • Learning disability vs no learning disability • Head injury vs no head injury • Type of epilepsy • Gender Who carried out the index tests
18.	Type and method of review	☐ Intervention ☒ Diagnostic ☐ Prognostic

		☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date			
22.	Anticipated completion date			
23.	Stage of review at time of this submission	Review stage	Started	
		Preliminary searches	☐	
		Piloting of the study selection process	☐	
		Formal screening of search results against eligibility criteria	☐	
		Data extraction	☐	
		Risk of bias (quality) assessment	☐	
		Data analysis	☐	
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail		

		5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre:
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10112.
29.	Other registration details	N/A
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Diagnosis, Epilepsy
33.	Details of existing review of same topic by same authors	N/A
34.	Current review status	☒ Ongoing ☐ Completed but not published

		☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35.	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

A.2 Review protocol for diagnostic strategies

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Clinical efficacy and cost effectiveness of diagnostic strategies for epilepsies
2.	Review question	What is the most clinically and cost-effective approach for diagnosis of epilepsies?
3.	Objective	To determine the diagnostic strategy that 1) leads to the best overall clinical outcome, and 2) that is the most cost-effective.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language Other searches: • None The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant.

		The full search strategies database will be published in the final review.
5.	Condition or domain being studied	Epilepsies (all sub-types)
6.	Population	Inclusion: Strata: • Children and adults with suspected epilepsy. • Children and adults with epilepsy, where uncertainty remains as to the type of epilepsy Exclusion: New-born babies with acute symptomatic seizures
7.	Interventions	Any comparison of diagnostic strategies used in studies (these do not have to contain EEG or ECG but are likely to do so).
8.	Comparator	Each other
9.	Types of study to be included	RCTs.
10.	Other exclusion criteria	Non-English language studies; conference abstracts.
11.	Context	Seeking knowledge of the health outcomes from different diagnostic strategies is probably the most appropriate approach.
12.	Primary outcomes (critical outcomes)	• mortality • seizures (we will collect both binary data and time to event data) • seizure frequency • time to withdrawal of treatment • quality of life (any validated scores) • any adverse events Follow up: any available but stratify to <1 yr., 1-5 yrs., >5 yrs.
13.	Secondary outcomes	social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale)

	(important outcomes)	cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) in children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) educational outcomes placement breakup (change in care location) Follow up: any available but stratify to <1 yr., 1-5 yrs., >5 yrs.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of these potentially eligible studies will be retrieved and assessed in line with the criteria outlined above. A standardised form will be used to extract data from the included studies (see Developing NICE guidelines: the manual section 6.4).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: papers were included /excluded appropriately a sample of the data extractions correct methods are used to synthesise data a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome.

		Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.
17.	Analysis of sub-groups	<u>Unconditional stratification</u> Follow up categories (<1 yr, 1-5yrs, >5yrs) People prior to diagnosis vs people with diagnosis of epilepsy but no confirmation of type <u>Conditional stratification</u> If heterogeneity is identified, where data is available, subgroup analysis will be carried out for the following subgroups: • age: <2, 2-11, 11-18, 18-55, >55 • Learning disability vs no learning disability • Head injury vs no head injury • Type of epilepsy • Gender • Who carries out the tests
(18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative

		☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date			
22.	Anticipated completion date			
23.	Stage of review at time of this submission	**Review stage**	**Started**	
		Preliminary searches	☐	
		Piloting of the study selection process	☐	
		Formal screening of search results against eligibility criteria	☐	
		Data extraction	☐	
		Risk of bias (quality) assessment	☐	
		Data analysis	☐	
24.	Named contact	**5a. Named contact** National Guideline Centre **5b Named contact e-mail**		

		5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre:
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10112.
29.	Other registration details	N/A
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Diagnosis, Atrial Fibrillation
33.	Details of existing review of same topic by same authors	N/A

34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35.	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

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A.3 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2004 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[138] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with "Minor limitations" then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with "Very serious limitations" then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:*

	• UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 (including any such studies included in the previous guideline(s)) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B Literature search strategies

This literature search strategy was used for the following reviews:

- What is the most accurate approach for 1) diagnosis of epilepsy, and 2) differentiation between types of epilepsy?
- What is the most clinically and cost-effective approach for diagnosis of epilepsies?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[138]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 33: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 23 August 2019	Randomised controlled trials Systematic review studies Diagnostic tests studies Exclusions
Embase (OVID)	1974 – 23 August 2019	Randomised controlled trials Systematic review studies Diagnostic tests studies Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 8 of 12 CENTRAL to 2020 Issue 8 of 12	None
Epistemonikos (The Epistemonikos Foundation)	Inception to 23 August 2019	Systematic review studies

Medline (Ovid) search terms

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/
5.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/

9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Magnetic Resonance Imaging/
28.	((magnetic or nuclear) adj2 resonance adj3 imag*).ti,ab.
29.	(MRI or NMR or NMRI or fMRI or MR or DWI).ti,ab.
30.	Electroencephalography/
31.	(Electroencephalography or electroencephalogram or EEG or video telemetry).ti,ab.
32.	Electrocardiography/
33.	(Electrocardiograph* or Electrocardiogram* or ECG or EKG).ti,ab.
34.	Tomography, X-Ray Computed/
35.	((Computerised or computed or computer) adj2 Tomograph*).ti,ab.
36.	((CT or CAT) adj2 (scan* or xray or x-ray)).ti,ab.
37.	(brain adj2 scan*).ti,ab.
38.	Magnetoencephalography/
39.	(Magnetoencephalography or Magneto-encephalography).ti,ab.
40.	(MEG adj2 scan*).ti,ab.
41.	exp Tomography, Emission-Computed/
42.	(positron-Emission Tomography or Single-Photon Emission).ti,ab.
43.	((PET or SPECT) adj2 scan*).ti,ab.
44.	Magnetic Resonance Spectroscopy/
45.	magnetic Resonance Spectroscopy.ti,ab.
46.	(stereoelectroencephalograph* or stereoencephalograph* or stereoelectroencephalogram* or stereoencephalogram* or SEEG).ti,ab.
47.	or/27-46
48.	26 and 47
49.	randomized controlled trial.pt.
50.	controlled clinical trial.pt.
51.	randomi#ed.ti,ab.
52.	placebo.ab.
53.	randomly.ti,ab.
54.	Clinical Trials as topic.sh.

55.	trial.ti.
56.	or/49-55
57.	Meta-Analysis/
58.	exp Meta-Analysis as Topic/
59.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
60.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
61.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
62.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
63.	(search* adj4 literature).ab.
64.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
65.	cochrane.jw.
66.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
67.	or/57-66
68.	exp "sensitivity and specificity"/
69.	(sensitivity or specificity).ti,ab.
70.	((pre test or pretest or post test) adj probability).ti,ab.
71.	(predictive value* or PPV or NPV).ti,ab.
72.	likelihood ratio*.ti,ab.
73.	likelihood function/
74.	((area under adj4 curve) or AUC).ti,ab.
75.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
76.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
77.	gold standard.ab.
78.	or/68-77
79.	48 and (56 or 67 or 78)

1 **Embase (Ovid) search terms**

1.	exp epilepsy/
2.	seizure/
3.	epileptic state/
4.	febrile convulsion/
5.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/

17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	*nuclear magnetic resonance imaging/
26.	((magnetic or nuclear) adj2 resonance adj3 imag*).ti,ab.
27.	(MRI or NMR or NMRI or fMRI or MR or DWI).ti,ab.
28.	*electroencephalography/
29.	(Electroencephalography or electroencephalogram or EEG or video telemetry).ti,ab.
30.	*electrocardiography/
31.	(Electrocardiograph* or Electrocardiogram* or ECG or EKG).ti,ab.
32.	*x-ray computed tomography/
33.	((Computerised or computed or computer) adj2 Tomograph*).ti,ab.
34.	((CT or CAT) adj2 (scan* or xray or x-ray)).ti,ab.
35.	(brain adj2 scan*).ti,ab.
36.	*magnetoencephalography/
37.	(Magnetoencephalography or Magneto-encephalography).ti,ab.
38.	(MEG adj2 scan*).ti,ab.
39.	exp *computer assisted emission tomography/
40.	(positron-Emission Tomography or Single-Photon Emission).ti,ab.
41.	((PET or SPECT) adj2 scan*).ti,ab.
42.	*nuclear magnetic resonance spectroscopy/
43.	magnetic Resonance Spectroscopy.ti,ab.
44.	(stereoelectroencephalograph* or stereoencephalograph* or stereoelectroencephalogram* or stereoencephalogram* or SEEG).ti,ab.
45.	or/25-44
46.	24 and 45
47.	random*.ti,ab.
48.	factorial*.ti,ab.
49.	(crossover* or cross over*).ti,ab.
50.	((doubl* or singl*) adj blind*).ti,ab.
51.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
52.	crossover procedure/
53.	single blind procedure/
54.	randomized controlled trial/
55.	double blind procedure/
56.	or/47-55
57.	systematic review/
58.	meta-analysis/
59.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
60.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
61.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.

62.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
63.	(search* adj4 literature).ab.
64.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
65.	cochrane.jw.
66.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
67.	or/57-66
68.	exp "sensitivity and specificity"/
69.	(sensitivity or specificity).ti,ab.
70.	((pre test or pretest or post test) adj probability).ti,ab.
71.	(predictive value* or PPV or NPV).ti,ab.
72.	likelihood ratio*.ti,ab.
73.	((area under adj4 curve) or AUC).ti,ab.
74.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
75.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
76.	diagnostic accuracy/
77.	diagnostic test accuracy study/
78.	gold standard.ab.
79.	or/68-78
80.	46 and (56 or 67 or 79)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Epilepsy] explode all trees
#2.	MeSH descriptor: [Seizures] this term only
#3.	MeSH descriptor: [Status Epilepticus] explode all trees
#4.	MeSH descriptor: [Seizures, Febrile] this term only
#5.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome):ti,ab
#6.	(OR #1-#5)
#7.	MeSH descriptor: [Magnetic Resonance Imaging] this term only
#8.	((magnetic or nuclear) NEAR/2 resonance NEAR/3 imag*):ti,ab
#9.	(MRI or NMR or NMRI or fMRI or MR or DWI):ti,ab
#10.	MeSH descriptor: [Electroencephalography] this term only
#11.	(Electroencephalography or electroencephalogram or EEG or "video telemetry"):ti,ab
#12.	MeSH descriptor: [Electrocardiography] this term only
#13.	(Electrocardiograph* or Electrocardiogram* or ECG or EKG):ti,ab
#14.	MeSH descriptor: [Tomography, X-Ray Computed] this term only
#15.	((Computerised or computed or computer) NEAR/2 Tomograph*):ti,ab
#16.	((CT or CAT) NEAR/2 (scan* or xray or x ray)):ti,ab
#17.	(brain NEAR/2 scan*):ti,ab
#18.	MeSH descriptor: [Magnetoencephalography] this term only
#19.	(Magnetoencephalography or "Magneto encephalography"):ti,ab
#20.	(MEG NEAR/2 scan*):ti,ab
#21.	MeSH descriptor: [Tomography, Emission-Computed] explode all trees

#22.	("positron Emission Tomography" or "Single Photon Emission"):ti,ab
#23.	((PET or SPECT) NEAR/2 scan*):ti,ab
#24.	MeSH descriptor: [Magnetic Resonance Spectroscopy] this term only
#25.	("Magnetic Resonance Spectroscopy"):ti,ab
#26.	(stereoelectroencephalograph* or stereoencephalograph* or stereoelectroencephalogram* or stereoencephalogram* or SEEG):ti,ab
#27.	(OR #7-#26)
#28.	#6 AND #27

Epistemonikos search terms

1.	(advanced_title_en:("status epilepticus" OR "dravet syndrome" OR epilep* OR convuls* OR "continuous spike wave" OR "slow sleep" OR "landau kleffner syndrome" OR "lennox gastaut syndrome" OR "infant* spasm*" OR seizure* OR "west syndrome") OR advanced_abstract_en:("status epilepticus" OR "dravet syndrome" OR epilep* OR convuls* OR "continuous spike wave" or "slow sleep" OR "landau kleffner syndrome" OR "lennox gastaut syndrome" OR "infant* spasm*" OR seizure* OR "west syndrome")) AND (advanced_title_en:("Magnetic Resonance Imaging" OR MRI OR NMR OR NMRI OR fMRI OR MR OR DWI OR Electroencephalography OR electroencephalogram OR EEG OR "video telemetry" OR Electrocardiograph* OR Electrocardiogram* OR ECG OR EKG OR "Computerised Tomograph*" OR "computed Tomograph*" OR "computer Tomograph*" OR "CAT scan*" OR "CT scan*" OR "brain scan" OR Magnetoencephalography OR "Magneto-encephalography" OR MEG OR "positron-Emission Tomography" OR "Single-Photon Emission" OR "PET scan*" OR "SPECT scan*" OR "magnetic Resonance Spectroscopy" OR stereoelectroencephalograph* OR stereoencephalograph* OR stereoelectroencephalogram* OR stereoencephalogram* OR SEEG) OR advanced_abstract_en:("Magnetic Resonance Imaging" OR MRI OR NMR OR NMRI OR fMRI OR MR OR DWI OR Electroencephalography OR electroencephalogram OR EEG OR "video telemetry" OR Electrocardiograph* OR Electrocardiogram* OR ECG OR EKG OR "Computerised Tomograph*" OR "computed Tomograph*" OR "computer Tomograph*" OR "CAT scan*" OR "CT scan*" OR "brain scan" OR Magnetoencephalography OR "Magneto-encephalography" OR MEG OR "positron-Emission Tomography" OR "Single-Photon Emission" OR "PET scan*" OR "SPECT scan*" OR "magnetic Resonance Spectroscopy" OR stereoelectroencephalograph* OR stereoencephalograph* OR stereoelectroencephalogram* OR stereoencephalogram* OR SEEG))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to an Epilepsies population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics and quality of life studies.

Table 34: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	Health Economics 1 January 2014 – 13 May 2021 Quality of Life 1946 – 13 May 2021	Health economics studies Quality of life studies Exclusions
Embase	Health Economics 1 January 2014 – 13 May 2021	Health economics studies Quality of life studies

Database	Dates searched	Search filter used
	Quality of Life 1974 – 13 May 2021	Exclusions
Centre for Research and Dissemination (CRD)	HTA - Inception – 13 May 2021 NHSEED - Inception to 31 March 2015	None

1 **Medline (Ovid) search terms**

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.

38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	quality-adjusted life years/
45.	sickness impact profile/
46.	(quality adj2 (wellbeing or well being)).ti,ab.
47.	sickness impact profile.ti,ab.
48.	disability adjusted life.ti,ab.
49.	(qal* or qtime* or qwb* or daly*).ti,ab.
50.	(euroqol* or eq5d* or eq 5*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/44-61
63.	26 and (43 or 62)

1 **Embase (Ovid) search terms**

1.	exp *epilepsy/
2.	*landau kleffner syndrome/
3.	exp *seizure/
4.	"seizure, epilepsy and convulsion"/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/

17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	quality adjusted life year/
40.	sickness impact profile/
41.	(quality adj2 (wellbeing or well being)).ti,ab.
42.	sickness impact profile.ti,ab.
43.	disability adjusted life.ti,ab.
44.	(qal* or qtime* or qwb* or daly*).ti,ab.
45.	(euroqol* or eq5d* or eq 5*).ti,ab.
46.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
47.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
48.	(hui or hui1 or hui2 or hui3).ti,ab.
49.	(health* year* equivalent* or hye or hyes).ti,ab.
50.	discrete choice*.ti,ab.
51.	rosser.ti,ab.
52.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
53.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
54.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
55.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
56.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
57.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
58.	or/39-57
59.	24 and (38 or 58)

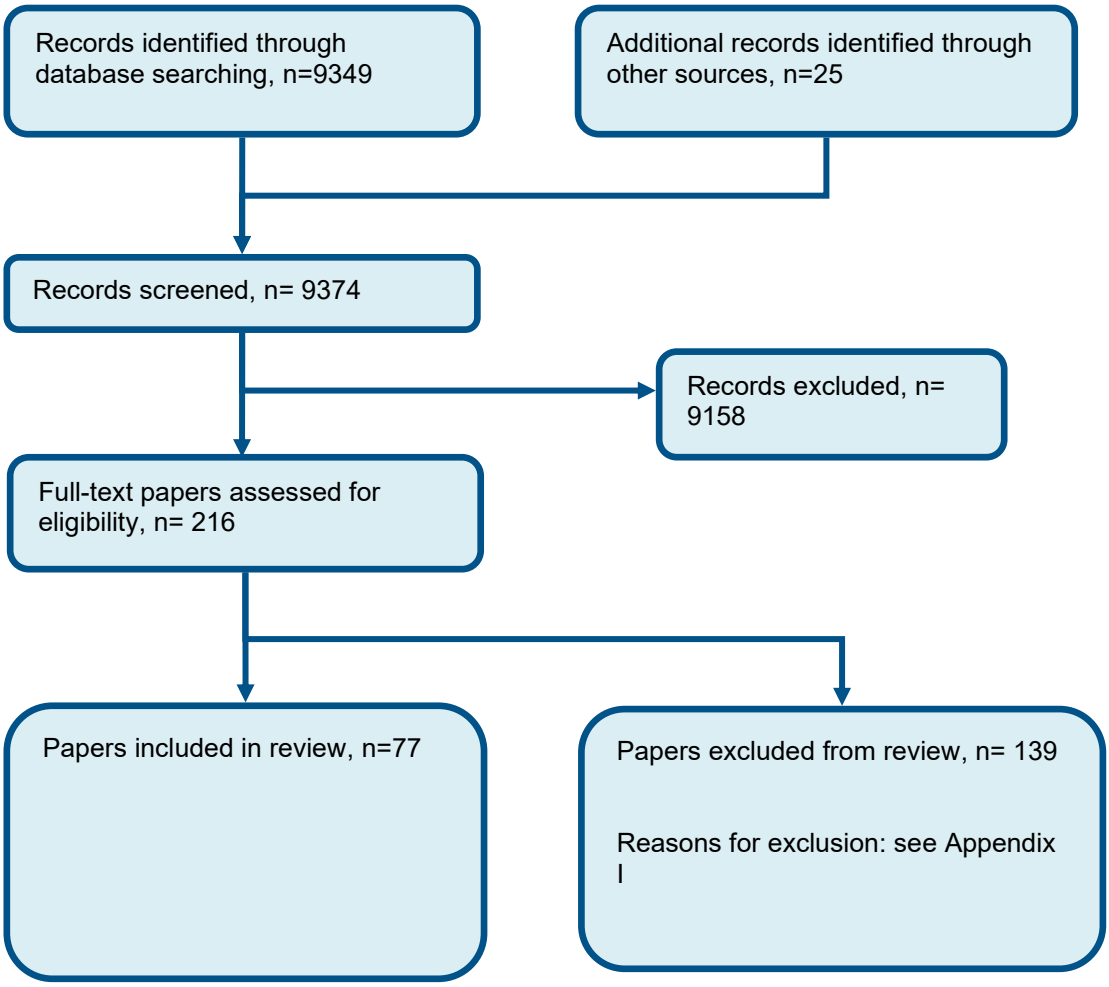
1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Epilepsy EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Seizures EXPLODE ALL TREES

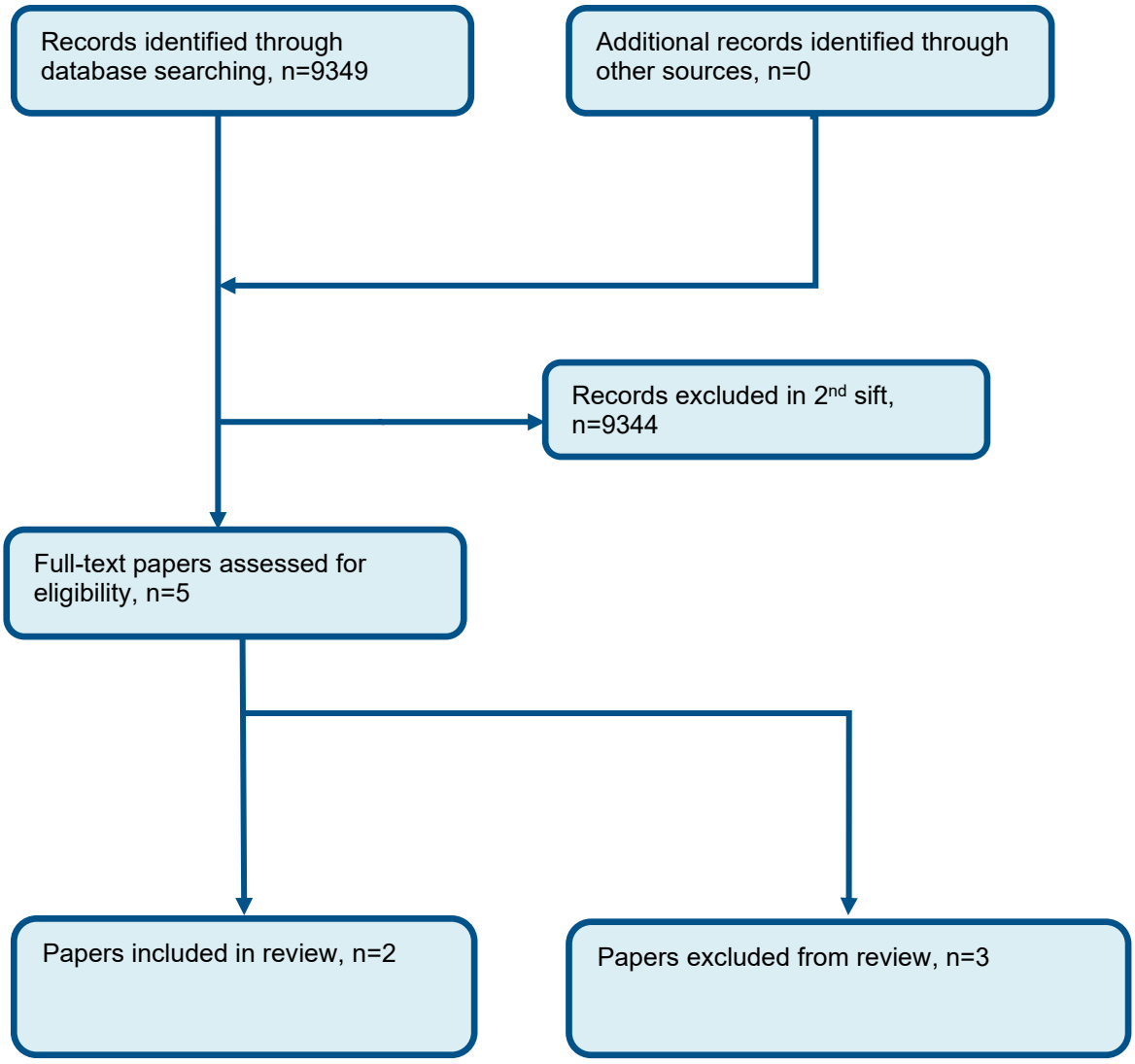
#3.	MeSH DESCRIPTOR Status Epilepticus EXPLODE ALL TREES
#4.	MeSH DESCRIPTOR Seizures, Febrile EXPLODE ALL TREES
#5.	((dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome))
#6.	#1 OR #2 OR #3 OR #4 OR #5

Appendix C Clinical evidence selection

C.1 Flow chart of clinical study selection for the review of diagnostic accuracy



C.2 Flow chart of clinical study selection for the review of clinical efficacy of diagnostic strategies



Appendix D Clinical evidence tables

D.1 Clinical evidence Diagnostic accuracy

Table 35: Tatum, 2020[193]

Reference	**Tatum, 2020[193]**
Study type	Observational
Recruitment	Convenience sample of 44 non-consecutive patients who volunteered a smartphone video
Setting	8 academic epilepsy centres (level IV, as certified by National Association of Epilepsy Centres)
Country	USA
Sample size	44
Mean/median age	Mean 45.1 years (range 20-82)
Gender	70% female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Smartphone videos were taken by witness (carers/family/friends)
Other general sample characteristics	None reported
Inclusion criteria	18 years or older; voluntary consent; had completed a history assessment and physical examination; outpatients referred with events that could be epilepsy; submitted an outpatient smartphone video of their primary ictal event; underwent gold standard test of video-EEG; >95% of each survey completed by reviewers; had a final diagnosis

Reference	**Tatum, 2020[193]**
Exclusion criteria	<18 years; pregnant; incomplete or absent history/physical examination; no smartphone video; did not undergo gold standard; confirmed history of mixed epileptic and non-epileptic events; declined study participation; no informed consent
Index test(s), including number of repetitions and duration	• Patients provided a witness-generated outpatient smartphone video. Videos were of an observable event and represented the disabling/most common episode resulting in epilepsy clinic evaluation and prompting vide-EEG. Instructions for acquiring and uploading smartphone video were provided to optimise recovery of information, requesting a recording of a single typical event, encompassing the whole body, lasting about 2 minutes and demonstrating interactivity with the patient. Most patients submitted a single video as instructed; when several were submitted the most informative and representative video was chosen based on the duration and historical depiction of ictal phenomenology. Average duration 2.23 minutes. Video interpretation was carried out by 10 epilepsy experts and 9 senior neurology residents without plans for epilepsy or sleep medicine fellowship. They were blinded to gold standard diagnosis. • History and physical examination done by 3 experts, lasting an average of 60 minutes
Gold standard	Single diagnostic video-EEG (VEM) session in a hospital-based, academic, tertiary care epilepsy monitoring unit and received a final definitive diagnosis. Mean duration of 3.1(sd=1.9) days. VEM was obtained at a NAEC level IV Epilepsy Centre. Final diagnosis following VEM was rendered by prominent epilepsy experts. Unclear if blinding to index test occurred.
Accuracy results	**Diagnosis of Epilepsy** <u>Smartphone</u> All reviewers: Sensitivity 0.596(0.498-0.689); Specificity 0.910(0.872-0.940) Experts only: Sensitivity 0.768(0.636-0.870); Specificity 0.933(0.883-0.966) Residents only: Sensitivity 0.415(0.281-0.559); Specificity 0.883(0.817-0.932) <u>History and physical examination</u> 3 experts: Sensitivity 1.0(0.692-1.0); Specificity 0.889(0.708-0.976)
Source of funding	Mayo clinic;
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious

Reference	Tatum, 2020[193]
	Indirectness (QUADAS 2 - applicability): None

Table 36: **Hoefnagels, 1991[94]**

Reference	Hoefnagels, 1991[94]
Study type	Observational prospective
Recruitment	consecutive
Setting	Patients referred to the neurological department because of transient loss of consciousness by GPs (46%) and other physicians
Country	Holland
Sample size	119
Mean/median age	Not reported
Gender	56 women and 63 men
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Neurophysiologist coded EEG (blinded to clinical details); cardiologist assessed ECG; hyperventilation test and blood tests unclear
Other general sample characteristics	Not reported
Inclusion criteria	All consecutive patients (> 15 years of age) referred to the neurological department because of one or more episodes of transient loss of consciousness. Transient loss of consciousness was defined as an episode of less than one hour with inability to maintain posture and to recall events during the episode.

Reference	**Hoefnagels, 1991[94]**
Exclusion criteria	Patients with loss of consciousness due to trauma or subarachnoid haemorrhage and patients with pre-diagnosis of epilepsy.
Index test(s), including number of repetitions and duration	• Routine interictal EEG (21 channels, 30 minutes) – coded as normal, localised epileptiform, generalised epileptiform, localised slowing without epileptiform. • If patient <65years, had an additional hyperventilation test (40 breaths per minute for 3 minutes. End tidal CO2 level had to be <2.5% after hyperventilation. Blood gases measured. Hyperventilation test considered negative if end tidal CO2 did not restore to >90% baseline value after 3 minutes recovery. • Standard ECG given and assessed as normal or abnormal according to the QT-interval. • Laboratory examination of serum sodium, potassium, calcium, phosphate, glucose, urea, ESR, liver function and FBC.
Gold standard	A definitive diagnosis of seizure was given by: movements during loss of consciousness and identified clonic movements from a range of movements imitated by the interviewer; if an eyewitness observed automatisms, such as chewing or lip smacking, during loss of consciousness; if the patient reported an unequivocal aura, such as a strange smell, preceding the event; if the patient felt confused immediately after the event (inability to recognise familiar persons or environment);if the patient had tongue biting. Unclear if needed just one of these or all of these to trigger a diagnosis.
Accuracy results	45/119 with seizure according to gold standard: 23 recurrent seizures (7 generalised and 16 partial) and 22 single seizure (4 related to alcohol). Thus 23/119 with epilepsy. Interictal EEG **Results only given for seizure, not recurrent seizures (epilepsy):** TP 18, FN: 27; FP 4; TN 69; sensitivity 0.40, specificity 0.95. Hyperventilation **Results only given for seizure, not recurrent seizures (epilepsy):** TP 6, FN: 31; FP 26; TN 20; sensitivity 0.162, specificity 0.435 ECG. Results unclearly reported

Reference	**Hoefnagels, 1991[94]**
	Lab tests Results unclearly reported
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): Serious (included single seizures as GS+ event)

Table 37: Keezer, 2016[102]

Reference	**Keezer, 2016[102]**
Study type	Observational
Recruitment	consecutive
Setting	Montreal Neurological Institute and Hospital
Country	Canada
Sample size	72
Mean/median age	Median 35 (IQR: 24-47.5)
Gender	Female 61%
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Electroencephalographer, a member of the Canadian Society of Clinical Neurophysiologist with >20 years of experience in clinical epilepsy and electroencephalogy.

Reference	**Keezer, 2016[102]**
Other general sample characteristics	Epilepsy aetiology: remote symptomatic/structural 65%, idiopathic/cryptogenic 26%; those with diagnosed epilepsy receiving antiepileptic drugs 98%
Inclusion criteria	All patients undergoing a prolonged ambulatory EEG (paEEG); medical record at the MNI to allow expert to ascertain clinical diagnosis of epilepsy or not
Exclusion criteria	None
Index test(s), including number of repetitions and duration	• Routine EEG. The standard procedure at the onset of every prolonged ambulatory EEG (paEEG) done at the MNI involved a brief period of in-hospital monitoring and activation procedures, including hyperventilation (lasting 3 minutes), intermittent photic stimulation (flash frequency ranging from 1 to 20 Hz, with eyes closed), and eye opening/closure. This first portion of the recording, including the activation procedures and the first 30 minutes of the EEG recording, was defined as the rEEG. All rEEG were done without sleep deprivation. • Prolonged ambulatory EEG (paEEG). The remainder of the recording, done as an ambulatory at-home study, was defined as the paEEG. Given that every paEEG was done immediately following the rEEG in the same individual, this created 2 perfectly matched EEG samples. This matching ensured that all potential predictors of diagnostic accuracy were controlled for (e.g., antiepileptic drugs, epilepsy type, and seizure frequency). Median paEEG duration 22.5 hours (IQR 22-23) All recordings were done with the Harmonie 32-channel EEG system (Stellate, Montreal, Canada), with scalp electrodes placed according to the international 10-20 system, equipped with a patient-activated event button and an event diary. The data were reviewed and analysed using Stellate Systems Harmonie software (Montreal, Canada). Data samples for review were generated by the standard “processors” included in the Harmonie software package. Tester blinded to GS result
Gold standard	One neurologist, a fellow of the Royal College of Physicians of Canada, reviewed medical records to identify those individuals with epilepsy. To minimize verification bias (i.e., constructing the reference standard with prior knowledge of the index test results), the assessor relied on the documented medical history and event semiology. Additional data collected were subject age, sex, epilepsy aetiology, the use of antiepileptic drug(s), and reason for referral by the treating physician. Epilepsy was operationally defined as 2 or more unprovoked epileptic seizures occurring at least 24 hours apart.
Accuracy results	**Diagnosis of Epilepsy** Note that the sample were previously diagnosed with epilepsy/no epilepsy - this study was therefore performed with a retrospective but blinded gold standard.

Reference	**Keezer, 2016[102]**
	50/72 with GS+ (epilepsy) Routine EEG using epileptiform discharges only Sensitivity: 0.26(0.159-0.396); specificity: 1.0 (0.851-1.00) paEEG using epileptiform discharges only Sensitivity: 0.58(0.442-0.706); specificity: 0.955 (0.782-0.992) Routine EEG using epileptiform or non-epileptiform discharges Sensitivity: 0.62(0.481-0.741); specificity: 0.545 (0.347-0.731) paEEG using epileptiform or non-epileptiform discharges Sensitivity: 0.78(0.648-0.872); specificity: 0.591 (0.387-0.767)
Source of funding	No conflicts declared
Limitations	Risk of bias (QUADAS 2 – risk of bias): No serious risk of bias Indirectness (QUADAS 2 - applicability): None

Table 38: Schmidt, 2016[171]

Reference	**Schmidt, 2016[171]**
Study type	Observational
Recruitment	Case-control strategy
Setting	Epilepsy clinics at St Thomas's Hospital, London
Country	UK
Sample size	68
Mean/median age	Range of 16-59 years

Reference	**Schmidt, 2016[171]**
Gender	Not reported
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Trained clinical EEG technician
Other general sample characteristics	Not reported
Inclusion criteria	IGE individuals were drug naïve
Exclusion criteria	Not reported
Index test(s), including number of repetitions and duration	Computational biomarker based on extent of synchrony between EEG channels and the normalised power spectrum from a short resting state interictal EEG. Critically this does not require epileptiform discharges. A trained clinical EEG technician identified a 20-s-long GSW and artefact-free segment of eyes-closed “resting state” EEG activity from the initial stage of the recordings from each participant. These data were band-pass filtered using a Butterworth filter between 0.5 and 70 Hz, and band-stop filtered between 48 and 52 Hz to remove power-line artefacts. Because signal amplitude may vary between individuals due to different anatomic features (such as the size and shape of the cranium) the data were normalized by dividing the power spectrum in each channel by the total power in the spectrum averaged across all channels. This normalized power preserves relative differences in power between channels. The EEG segments were then band-pass filtered into either the alpha (8–13 Hz) or low alpha bands (6–9 Hz). For segments band-pass filtered in the low alpha band, functional networks were inferred using the Phase-Locking Factor (PLF) and phase-lags.
Gold standard	This was a ‘case-control’ design where 38 healthy controls and 30 people with a diagnosis of Idiopathic Generalised Epilepsy (IGE) were recruited. A diagnosis of epilepsy was confirmed in each IGE case by an experienced epilepsy specialist through observation of typical generalized spike-wave (GSW) activity on EEG either spontaneously or following hyperventilation or photic stimulation. For 10 of these people, the diagnosis was confirmed following an initial routine EEG. For the remaining 20, diagnosis was confirmed following sleep-deprived or longer-term EEG monitoring (including sleep). Similar healthy control EEG was collected at King’s College Hospital EEG department.

Reference	Schmidt, 2016[171]
Accuracy results	**Diagnosis of Idiopathic Generalised Epilepsy** Successively optimizing the channel location and value of the local coupling constant to give the highest levels of sensitivity and specificity in each training set, the local coupling biomarker resulted in 56.7% sensitivity (given 100% specificity) and 65.8% specificity (given 100% sensitivity).
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious Indirectness (QUADAS 2 - applicability): Serious, as samples taken from 2 clearly defined populations (epilepsy/no epilepsy) rather than the general population suspected of epilepsy

Table 39:Vukmir, 2004[209]

Reference	Vukmir, 2004[209]
Study type	Observational retrospective
Recruitment	consecutive
Setting	Emergency department
Country	USA
Sample size	200
Mean/median age	Not reported
Gender	Not reported
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Not reported

Reference	**Vukmir, 2004[209]**
Other general sample characteristics	Seizure: 66%; syncope 18%; TIA 2%; pneumonia 2%; metabolic problems 2%; drug/alcohol toxicity 2%; other 8%
Inclusion criteria	Patients who presented to the emergency department with a clinical symptom complex consistent with seizure, manifested as near or total loss of consciousness, accompanied by abnormal motor activity and/or a post-ictal phase.
Exclusion criteria	<18 years
Index test(s), including number of repetitions and duration	Serum prolactin level was determined as part of the routine seizure protocol in the acute setting, which also included glucose and sodium levels using a commercial sandwich immunoassay method with a normal level of 2.8–29.9mg/ml
Gold standard	A hospital discharge diagnosis of seizure either initially or at the end of the stay. The diagnosis was recorded from ED records if discharged or inpatient discharge record if admitted. The presence of an abnormal electroencephalogram indicated by abrupt onset and termination of repetitive rhythmic activity usually consisting of a sharp or spike wave pattern, during the hospital stay if performed was included as well. Nonspecific EEG activity consisting of diffuse slowing or other nonspecific patterns were not considered diagnostic for seizure.
Accuracy results	**Diagnosis of Epilepsy** Threshold of prolactin was 29.9mg/dl; any value above this was taken as an abnormal value and indicative of seizure. TP 46, FN 63, FP 16, TN 75; sensitivity 0.422(95% CI: 0.329 to 0.515), specificity 0.824 (95% CI: 0.746 to 0.902)
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious Indirectness (QUADAS 2 - applicability): None

Table 40: Choi, 2020[43]

Reference	**Choi, 2020[43]**
Study type	Retrospective
Recruitment	Consecutive
Setting	Department of Paediatrics
Country	South Korea
Sample size	160
Mean/median age	Mean 14.6 years
Gender	Female 59.4%
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Not reported
Other general sample characteristics	Epileptic seizures 10.6%, vasovagal syncope 63.8%, others 25.6%
Inclusion criteria	Under 18 years of age who had been admitted to the Department of Paediatrics or had visited the outpatient clinic or emergency department at Kyung Hee University Hospital (Seoul, South Korea) for TLOC between June 2013 and May 2018. Patients were initially identified who were assigned International Classification of Disease, 10th Revision (ICD-10) billing codes for “syncope and collapse” at the time of the first visit. The medical charts of patients with TLOC as the chief complaint were retrospectively analysed.
Exclusion criteria	Patients who had visited the hospital previously due to TLOC and were diagnosed with any disease; patients who had previously undergone any diagnostic tests; patients who had been diagnosed with acute systemic illness on visiting the hospital due to TLOC; patients who were taking medications that can lead to arrhythmia or orthostasis.
Index test(s), including number of repetitions and duration	ECG Brain CT

Reference	Choi, 2020[43]
	Brain MRI EEG Echocardiogram Head up tilt test
Gold standard	The diagnosis of epileptic seizure was based on clinical features with EEG findings suggesting abnormal neuronal excitability in the brain. Epilepsy was subsequently diagnosed in patients who experienced further unprovoked seizures during the follow-up period according to the ILAE definition.
Accuracy results	**Diagnosis of Epilepsy** ECG: TP 2, FN 12, FP 34, TN 94; Sensitivity 0.143, specificity 0.734 Brain CT: TP 1, FN 4, FP 6, TN 22; Sensitivity 0.200, specificity 0.786 Brain MRI: TP 1, FN 4, FP 1, TN 7; Sensitivity 0.200, specificity 0.875 EEG: TP 12, FN 3, FP 5, TN 20; Sensitivity 0.800, specificity 0.800 Echocardiogram: TP 0, FN 6, FP 2, TN 55; Sensitivity 0.000, specificity 0.965 Head up tilt test: TP 1, FN 4, FP 40, TN 4; Sensitivity 0.200, specificity 0.091
Source of funding	This study was supported by the Basic Science Research Program of the National Research Foundation of Korea funded by the Ministry of Science, ICT and Future Planning (NRF- 2017R1C1B5076772). Declaration of no conflicts of interest
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious Indirectness (QUADAS 2 - applicability): None

Table 41: Derry, 2006[58]

Reference	Derry, 2006[58]
Study type	Observational

Reference	**Derry, 2006[58]**
Recruitment	Case-control strategy
Setting	Tertiary sleep and epilepsy referral centres
Country	Australia
Sample size	62
Mean/median age	27.9 years in NFLE group; 13.2 years in NREM arousal parasomnia group; 69.1 years in REM sleep disorder group
Gender	17 women, 45 men
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Nocturnal Frontal Lobe Epilepsy (NFLE)
Who carried out the index tests	Research assistant without medical training, and physician experienced in the diagnosis of sleep disorders and epilepsy.
Other general sample characteristics	NFLE 50%; atypical parasomnias 17.7%; typical parasomnias 32.3%
Inclusion criteria	Patients who had been referred to a sleep physician or neurologist with a history of nocturnal events of uncertain cause. Individuals with NFLE were eligible for the study if they had a history consistent with NFLE and at least 1 of the following: video-EEG monitoring with clinical or electrographic evidence of nocturnal frontal lobe seizures or a genetic mutation consistent with ADNFLE. Patients with parasomnias were recruited in 2 sub-groups. The first group consisted of subjects who were referred to a sleep clinic for diagnosis of their nocturnal events but in whom a definite diagnosis of “typical” parasomnia was made by the specialist without recourse to video-EEG monitoring. In this group, the diagnosis was made on the basis of the history independently by 3 clinicians (a consultant adult epileptologist, a consultant paediatric epileptologist, and a consultant sleep paediatrician), none of whom were involved in the validation of the FLEP scale. The second group comprised cases in which there was diagnostic uncertainty on the basis of the history alone and in which the diagnosis was established by video-EEG or PSG monitoring. These cases were designated “atypical” parasomnias.
Exclusion criteria	None

Reference	Derry, 2006[58]
Index test(s), including number of repetitions and duration	Frontal Lobe Epilepsy and Parasomnias (FLEP) scale. The FLEP scale was developed by an expert panel following review of the literature. The scale consists of a series of specific questions based on the clinical features of NFLE and parasomnias. Particular consideration was given to the non-rapid eye movement (NREM)arousal parasomnias, such as sleep walking and night terrors, because these conditions are most commonly confused with NFLE, but the scale was designed to be broadly applicable. Questions were designed to address those features that, according to the medical literature and in the experience of the health care professionals involved, are useful in discriminating between the conditions. A choice of possible responses was assigned to each question, each with a score. Responses favouring epilepsy (such as events of brief duration, occurring multiple times per night) scored positively, and those favouring parasomnias (such as coherent speech without recall) scored negatively.

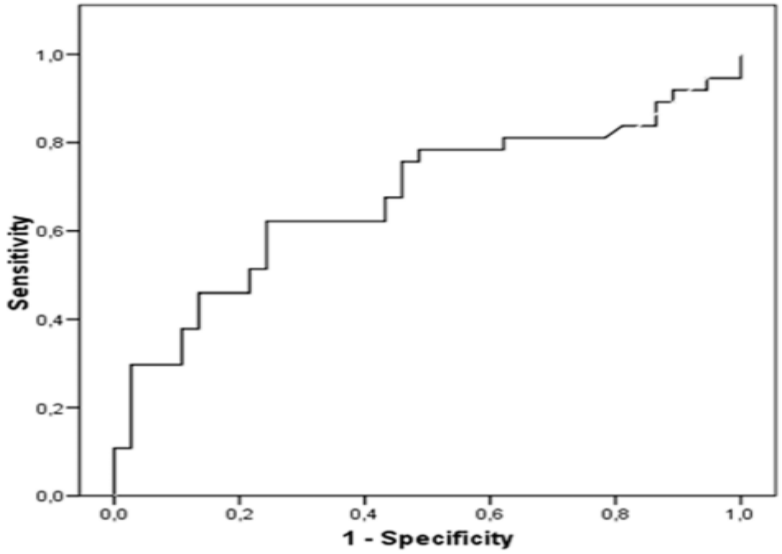
Table. The Frontal Lobe Epilepsy and Parasomnias (FLEP) Scale

Clinical Feature		Score
Age at onset		
At what age did the patient have their first clinical event?	<55 y	0
	≥55 y	−1
Duration		
What is the duration of a typical event?	<2 min	+1
	2-10 min	0
	>10 min	−2
Clustering		
What is the typical number of events to occur in a single night?	1 or 2	0
	3-5	+1
	>5	+2
Timing		
At what time of night do the events most commonly occur?	Within 30 min of sleep onset	+1
	Other times (including if no clear pattern identified)	0
Symptoms		
Are the events associated with a definite aura?	Yes	+2
	No	0
Does the patient ever wander outside the bedroom during the events?	Yes	−2
	No (or certaian)	0
Does the patient perform complex, directed behaviors (eg, picking up objects, dressing) during events?	Yes	−2
	No (or uncertain)	0
Is there a clear history of prominent dystonic posturing, tonic limb extension, or cramping during events?	Yes	+1
	No (or uncertain)	0
Stereotypy		
Are the events highly stereotyped or variable in nature?	Highly stereotyped	+1
	Some variability/uncertain	0
	Highly variable	−1
Recall		
Does the patient recall the events?	Yes, lucid recall	+1
	No or vague recollection only	0
Vocalization		
Does the patient speak during the events and, if so, is there subsequent recollection of this speech?	No	0
	Yes, sounds only or single words	0
	Yes, coherent speech with incomplete or no recall	−2
	Yes, coherent speech with recall	+2
Total score		

Reference	**Derry, 2006[58]**
Gold standard	Expert interview and, when necessary, recording of events using video-EEG monitoring
Accuracy results	**Diagnosis of Nocturnal Frontal Lobe Epilepsy** Interviewer 1 (Research Assistant, not medically trained): sensitivity 1.00 (0.86-1.00), specificity 0.90 (0.73-0.97) Interviewer 2 (Physician): sensitivity 1.00 (0.86-1.00), specificity 0.93 (0.79-0.98)
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious Indirectness (QUADAS 2 - applicability): Serious, as samples taken from 3 clearly defined populations rather than the general population suspected of epilepsy

Table 42: Douw, 2010[62]

Reference	**Douw, 2010[62]**
Study type	Observational
Recruitment	Case-control strategy
Setting	University Medical centre
Country	Holland
Sample size	161
Mean/median age	Mean 52
Gender	51% female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	37% partial, 63% generalised (out of 57 with epilepsy); AEDs 1/57;
Who carried out the index tests	Not reported
Other general sample characteristics	IEDs on EEG 20/57;
Inclusion criteria	<18 years old; evaluated with a standard EEG because of suspected epilepsy after a first possible seizure.
Exclusion criteria	None
Index test(s), including number of repetitions and duration	Synchronisation likelihood, based on standard EEG EEGs were recorded with a digital EEG apparatus from Fp2, Fp1, F8, F7, F4, F3, A2, A1,T4, T3, C4, C3, T6, T5, P4, P3, O2, O1, Fz, Cz and Pz with tin electrodes. Functional connectivity (degree of synchronisation of EEG in the time domain), expressed as the synchronisation likelihood (SL). The SL is based on the concept of generalized synchronization and takes linear as well as nonlinear synchronization between two time series into account. SLs between all pairs of EEG electrodes were determined in the following seven frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), lower alpha (8–10 Hz), upper alpha (10–13 Hz), beta (13–30 Hz), lower gamma (30–45 Hz), and upper gamma (55–80 Hz]). Subsequently, the SL matrix (17617) was

Reference	Douw, 2010[62]
	averaged to obtain a mean connectivity value for each patient and each epoch, after which the four epochs per patient were again averaged. This yielded seven SL values (one for each frequency band) for each patient.
Gold standard	Medical chart review was conducted for all patients to determine whether a clinical diagnosis of epilepsy was reached within a follow-up of one year. Epilepsy defined as two or more epileptic seizures according to the International League Against Epilepsy, with or without IEDs on their EEG
Accuracy results	**Diagnosis of Epilepsy** 57 had a definite diagnosis of epilepsy (20 with interictal epileptiform discharges) Theta band SL: sensitivity 0.62, specificity 0.76 [**threshold value of theta band SL not given**]  **Figure 4. ROC curve of theta band SL as predictor of diagnosis in epilepsy patients without IEDs and their matched non-epilepsy patients (n = 74).** doi:10.1371/journal.pone.0010839.g004

Reference	Douw, 2010[62]
Source of funding	Two authors have projects sponsored by the Dutch Epilepsy Foundation, while another is sponsored by UCB Pharma. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious Indirectness (QUADAS 2 - applicability): Serious, as samples taken from 2 clearly defined populations (epilepsy and non-epilepsy) rather than the general population suspected of epilepsy

Table 43: Geut, 2017[81]

Reference	Geut, 2017[81]
Study type	Observational retrospective
Recruitment	consecutive
Setting	Unclear
Country	Holland
Sample size	104
Mean/median age	Mean 47 years
Gender	Female 35.6%
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Not reported
Other general sample characteristics	Abnormal MRI 11%; 63/104 with epilepsy diagnosis after 1 year

Reference	**Geut, 2017[81]**
Inclusion criteria	Patients with unprovoked focal or generalized seizures who were admitted to the Clinical Neurophysiology department. Unprovoked seizures were defined as convulsive episodes occurring in the absence of precipitating factors. This included seizures of unknown aetiology as well as seizures in relation to a demonstrated pre-existing brain lesion (remote symptomatic seizure). Patients were subsequently selected in whom the routine EEG (including hyperventilation and photic simulation) was normal or did not show convincing IEDs, and either a sdEEG or an aEEG was requested. Finally, both groups were matched for age and gender.
Exclusion criteria	Patients younger than 6 years, patients with known epilepsy and patients with provoked seizures.
Index test(s), including number of repetitions and duration	The index tests were given in mutually exclusive groups (ie one patient experienced only one index test). N=52 in each group. • Ambulatory EEG (aEEG) had a duration of 16–24 h, including sleep. • Sleep-deprived EEG (sdEEG) had a duration of 1.5–3 h, including sleep, and was recorded after complete sleep deprivation during the previous night. EEGs were recorded with 21 electrodes positioned according to the international 10–20 system using a Brainlab EEG system
Gold standard	The patients' clinical record was evaluated for age, sex, first seizure, start of anti-epileptic drugs, MRI or CT results and whether or not diagnosis of epilepsy was made with a follow up of one year. The diagnosis of epilepsy was based on the new ILAE criteria published in 2014
Accuracy results	**Diagnosis of Epilepsy** <u>aEEG</u> TP 20, FN 12, FP 1, TN 19; sensitivity 0.625 (0.44-0.79, specificity 0.95 (0.75-1.0) <u>sdEEG</u> TP 14, FN 17, FP 2, TN 19; sensitivity 0.452 (0.27-0.64), specificity 0.91 (0.70-0.99).
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious Indirectness (QUADAS 2 - applicability): None

Table 44: Albadareen, 2016[6]

Reference	**Albadareen, 2016[6]**
Study type	Observational prospective
Recruitment	consecutive
Setting	Secondary care: University of Kansas Medical centre
Country	USA
Sample size	78 enrolled but after exclusions, 30.
Mean/median age	Mean 34.8 GCS (generalised convulsive seizure), 35.2 PNES-C (psychogenic nonepileptic seizures with convulsion, 40.1 FS (focal seizures)
Gender	57% female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Generalised 62%, Focal 38%
Who carried out the index tests	Not reported
Other general sample characteristics	9 with GCS, 8 with FS and 9 with convulsive non-epileptic psychogenic seizures
Inclusion criteria	Adult patients (≥18 years of age) admitted to the epilepsy monitoring unit for event characterization, seizure focus localization, or treatment optimization
Exclusion criteria	Factors known to be associated with hyperammonaemia: pre-existing liver disease/cirrhosis, current use of valproic acid or 5- fluorouracil, history of gastrointestinal bleeding, hematologic malignancies, and end-stage renal disease; no event during study.
Index test(s), including number of repetitions and duration	Baseline serum ammonia (using Beckman Coulter ammonia reagent) was drawn on admission prior to having a typical event (provided that the patient is at least 24 h event-free). Postictal ammonia was drawn within a window of 15–60 min after the event of concern was recorded as recognized by the patient, a family member, or a house staff. A third ammonia level was drawn 24 h after the spell recorded or prior to discharge, whichever came first. If there were recurrent events within that time frame, the subsequent blood

Reference	Albadareen, 2016[6]
	draws were delayed until 24 h after the last event. The source of all blood draws was venous. Blood samples were immediately placed on ice. Personnel drawing ammonia were blinded to the electrographic characterization of the event.
Gold standard	Epilepsy diagnosed objectively by epileptologist with video-electroencephalography (vEEG) monitoring
Accuracy results	**Diagnosis of Generalised Convulsive Seizure** At a cut-off point of >=80 micromol/L for ammonia levels, there was a sensitivity of 53.9% and a specificity of 100% for detecting GCS.
Source of funding	This study was supported by a Zeigler Investigator Grant at the University of Kansas Medical Centre and Clinical and Translational Science Award grant from National Centre for Advancing Translational Sciences awarded to the University of Kansas Medical Centre for Frontiers: The Heartland Institute for Clinical and Translational Research #UL1TR000001 (formerly #UL1RR033179). The contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health (NIH) or NCATS.
Limitations	Risk of bias (QUADAS 2 – risk of bias): very serious Indirectness (QUADAS 2 - applicability): none

Table 45: Ottman, 2010[146]

Reference	Ottman, 2010[146]
Study type	Observational
Recruitment	consecutive
Setting	Population based study comprising people of Rochester, USA; Case-control strategy
Country	USA
Sample size	342
Mean/median age	54 (0.9)
Gender	61% women

Reference	**Ottman, 2010[146]**
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Idiopathic generalised n=31, cryptogenic focal n=71, symptomatic n=38, unclassifiable n=28
Who carried out the index tests	Not reported
Other general sample characteristics	Only given for n=168 with diagnosis of epilepsy: age at diagnosis <10 years n=56, 10-19 years n=32, >=20 years n=80; history of convulsive seizures 115/168; high school graduate or less n=42, some college n=54, college graduate n=71.
Inclusion criteria	All residents of the city of Rochester, MN, U.S.A., who were born in 1920 or later and had incidence of either epilepsy (two or more unprovoked seizures) or an isolated unprovoked seizure between 1935 and 1994. For each case, a control was selected as a patient who had not had an unprovoked seizure before the case's diagnosis date and who matched the case by sex, birth year (+/-5 years), and length of contact with the medical records linkage system (first contact with an REP provider within one year of that of the case, and medical visit to an REP provider within one year of the case's diagnosis date). Potential controls were not excluded if they had new-onset unprovoked seizures after the case's diagnosis date or if they had febrile or other acute symptomatic seizures. No other exclusions were made in the selection of either cases or controls
Exclusion criteria	See above

Reference	Ottman, 2010[146]
Index test(s), including number of repetitions and duration	General screening interview for epilepsy. Independently of the medical record abstraction, the researchers attempted to interview each case and control. Interviews were administered through a computer-assisted telephone interview. The interview included a screening instrument to screen for lifetime history of seizures, followed by a diagnostic interview to obtain further clinical details in subjects who screened positive.

Table 1. Questions from Screening Instrument[a]

1. Did anyone ever tell you that you had a seizure or convulsion caused by a high fever when you were a child?
2. [Other than the seizure[s] you had because of a high fever] Have you ever had, or has anyone ever told you that you had, a seizure disorder or epilepsy?[b]

Ask the following questions only if subject said "no" to epilepsy or a seizure disorder in q2. Otherwise go to next part of interview

3. [Other than the seizure[s] you had because of a high fever] Have you ever had, or has anyone ever told you that you had, any of the following…[b]
   - A. A seizure, convulsion, fit or spell under any circumstances?
   - B. Uncontrolled movements of part or all of your body such as twitching, jerking, shaking or going limp?
   - C. An unexplained change in your mental state or level of awareness; or an episode of "spacing out" that you could not control?
   - D. Did anyone ever tell you that when you were a small child, you would daydream or stare into space more than other children?
   - E. Have you ever noticed any unusual body movements or feelings when exposed to strobe lights, video games, flickering lights, or sun glare?
   - F. Shortly after waking up, either in the morning or after a nap, have you ever noticed uncontrollable jerking or clumsiness, such as dropping things or things suddenly "flying" from your hands?
   - G. Have you ever had any other type of repeated unusual spells?

[a]Each question could be answered no, yes, possible, or don't know.

[b]Phrase "Other than the seizure[s] you had because of a high fever" added only if subject responded "yes" or "possible" to question 1.

Reference	Ottman, 2010[146]
Gold standard	A comprehensive review of the medical records of each case or control was carried out. Abstraction involved initial review by trained nurse abstractors followed by expert review by the study epileptologists and provided detailed information for the duration of each subject's residence in the Rochester area, including all outpatient examinations, home and emergency room visits, hospitalization records, laboratory tests, and neurologic and other special examinations.
Accuracy results	**Diagnosis of Epilepsy** Sensitivity 0.96, specificity 0.93
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious Indirectness (QUADAS 2 - applicability): Serious, as samples taken from 2 clearly defined populations (epilepsy and non-epilepsy) rather than the general population suspected of epilepsy

Table 46: Benbadis, 1995[25]

Reference	Benbadis, 1995[25]
Study type	Observational
Recruitment	Case-control strategy
Setting	Epilepsy Monitoring Unit
Country	USA
Sample size	108
Mean/median age	Mean: 43.05 years
Gender	56% female
Learning disability?	Not reported
Head injury?	Not reported

Reference	**Benbadis, 1995[25]**
Type of epilepsy	Generalised epilepsy (n=11), localisation-related epilepsy (n=23)
Who carried out the index tests	Unclear who asked about tongue biting, but possibly the efficacy is unrelated to expertise in this case.
Other general sample characteristics	Epilepsy 34/108, pseudo seizures 29/108, syncope 45/108
Inclusion criteria	All patients admitted to a Epilepsy Monitoring Unit for the diagnosis of spells or presurgical evaluation of epilepsy over a 6-month period. Patients selected whose episodes are characterised by bilateral motor phenomena, LOC, or both.
Exclusion criteria	Typical complex partial seizures, with altered awareness but no LOC
Index test(s), including number of repetitions and duration	Tongue biting: patients monitored for 1-17 days(mean 4.6 days) for evidence of tongue biting
Gold standard	Diagnosis based on prolonged electroencephalography video monitoring, using both interictal and ictal data
Accuracy results	**Diagnosis of Epilepsy** TP 8, FN 28, FP 1, TN 73; sensitivity 0.24, specificity 0.99
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious Indirectness (QUADAS 2 - applicability): Serious, as samples taken from 2 clearly defined populations (possible epilepsy and syncope) rather than the general population suspected of epilepsy

Table 47: Bernardo, 2018[28]

Reference	**Bernardo, 2018[28]**
Study type	Observational
Recruitment	Case-control strategy
Setting	University of California Los Angeles Hospital

Reference	**Bernardo, 2018[28]**
Country	USA
Sample size	11
Mean/median age	21.31 months
Gender	36% female
Learning disability?	4 with developmental delay (all in the epilepsy group)
Head injury?	Unclear
Type of epilepsy	Tuberous sclerosis associated epilepsy; focal only n=1, focal and generalised n=3, generalised and epileptic spasms n=1, focal and epileptic spasms n=1, epileptic spasms only n=1; Duration of epilepsy 1-33 months (mean=10.6 months)
Who carried out the index tests	Authors, who were all clinicians. They were trained in IFR detection before the study began.
Other general sample characteristics	Tuberous sclerosis related epilepsy n=7, no epilepsy n=4
Inclusion criteria	Infants with active medically refractive epilepsy; all video EEGs recorded on Nihon Kohden systems; vEEG sampled at 3000Hz; vEEG recorded at 2 h or more from the most recent seizure; human visual identification of interictal scalp FR; at least 1 brain MRI previously obtained. Controls were children with no brain-related diagnoses including epilepsy, autism and developmental delay; underwent a normal overnight scalp vEEG for clinical reasons with normal results.
Exclusion criteria	None reported
Index test(s), including number of repetitions and duration	Existence or not of Interictal Fast Ripple (IFR) events, based on scalp EEG. A single 10-minute epoch per patient with minimal movement artefact was selected by the reviewers who were blinded to gold standard diagnosis. Data analysed via human action and also automatically.
Gold standard	‘Active medically refractive epilepsy’ implies that the diagnosis was well-established, alongside the video-EEG evidence. Those without epilepsy also appear to be definitively non-epilepsy based on inclusion criteria
Accuracy results	**Diagnosis of Epilepsy**

Reference	**Bernardo, 2018[28]**
	IFR ascertained by human action for detecting epilepsy: TP 7, FN 0, FP 0, TN 4; sensitivity 1.0, specificity 1.0 Automated action results cover repeated EEG data from the same patients: sensitivity 0.98, specificity 0.95
Source of funding	Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD); National Institute of Neurological Disorders and Stroke (NINDS)
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious Indirectness (QUADAS 2 - applicability): Serious - only children with Tuberous Sclerosis complex

Table 48: Dogan, 2017[61]

Reference	**Dogan, 2017[61]**
Study type	Observational
Recruitment	Case-control strategy
Setting	Emergency department
Country	Turkey
Sample size	270
Mean/median age	Age range 19-92; median GTCS 44; median PNES 40; median syncope 67.5.
Gender	Female 42%
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	generalised tonic-clonic seizures
Who carried out the index tests	Not reported

Reference	**Dogan, 2017[61]**
Other general sample characteristics	GTCS n=157, PNES n=25, syncope n=88
Inclusion criteria	>=18 years; normal serum pH levels; final definitive diagnosis of generalised tonic-clonic seizures, psychogenic nonepileptic seizures or syncope. Needed to have CT/MRI, EEG and ECG data with observable clinical signs and symptoms.
Exclusion criteria	None reported
Index test(s), including number of repetitions and duration	Serum lactate levels measured in the first 2 hours of the index event, in first 15 mins of admission to ER. Threshold level of serum lactate was 2.2 mmol/l
Gold standard	Final definitive diagnosis of generalised tonic-clonic seizures, psychogenic nonepileptic seizures or syncope. Needed to have CT/MRI, EEG and ECG data with observable clinical signs and symptoms. Lactate levels did not influence final diagnosis
Accuracy results	**Diagnosis of Generalised Tonic Clonic Seizures** >=2.2mmol/l lactate (all patients): TP 133, FN 24, FP 20, TN 93; sensitivity: 0.847, specificity: 0.823 >=2.2mmol/l lactate (male patients): TP 84, FN 7, FP 8, TN 53; sensitivity: 0.923, specificity: 0.869 >=2.2mmol/l lactate (female patients): TP 49, FN 17, FP 12, TN 40; sensitivity: 0.742, specificity: 0.769 On ROC analysis, optimum lactate threshold of 2.43 for males gave sensitivity of 0.85 and specificity of 0.88 On ROC analysis, optimum lactate threshold of 2.26 for females gave sensitivity of 0.70 and specificity of 0.79
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): very serious Indirectness (QUADAS 2 - applicability): Serious, as samples taken from 3 clearly defined populations (epilepsy, psychogenic nonepileptic seizures, syncope) rather than the general population suspected of epilepsy

Table 49: Giorgi, 2013[84]

Reference	**Giorgi, 2013[84]**
Study type	Observational
Recruitment	consecutive
Setting	Neurology unit and Epilepsy centre
Country	Italy
Sample size	210
Mean/median age	41 (12) years
Gender	Female 45%
Learning disability?	Not reported
Head injury?	N=6 with 'traumatic' aetiology
Type of epilepsy	Focal epilepsy 87%, Generalised epilepsy 13%
Who carried out the index tests	Not reported, but SD EEG evaluated by a blinded member of the epilepsy centre.
Other general sample characteristics	Of the 114 with focal epilepsy, 58 had focal symptomatic epilepsy and 56 had focal probably symptomatic epilepsy. Aetiology in focal symptomatic epilepsy patients was vascular (n=29), hippocampal sclerosis (n=11), malformative (n=10), post-traumatic (n=6) or undefined (n=2).
Inclusion criteria	Sleep deprived EEG (SD EEG) requested as a prospective evaluation for suspected epileptic seizures; previous standard waking EEG not showing any interictal abnormalities (IIAs); not under antiepileptic drugs until at least date of SD EEG; previous 1.5T MRI; minimum 1 year follow up; final diagnosis performed in the centre and defined as 'non-epilepsy', 'focal epilepsy' or 'generalised epilepsy'.
Exclusion criteria	Juvenile myoclonic epilepsy;
Index test(s), including number of repetitions and duration	Sleep deprived EEG (SD EEG). Patient told to wake up at 2am and remain awake without taking stimulants until the EEG recording (which needed to be within 15-35 days of the suspected seizure). The SD EEG occurred from 8am to 10.30 am, and all recordings were performed by digital EEG polygraphy with 19 collodium-applied scalp electrodes applied according to the 10-20 system.

Reference	Giorgi, 2013[84]
Gold standard	Final diagnosis obtained after collegial discussion by epileptologists in the centre with at least 5 years' experience in clinical epilepsy. Diagnosis confirmed based on recurrence of clear epileptic unprovoked seizures. Single seizures not included. Most patients also given video EEG or 24 hour dynamic EEGs. Clinical records also evaluated
Accuracy results	**Diagnosis of Epilepsy** 131/210 confirmed with epilepsy. TP 54, FN 77, FP 7, TP 72; sensitivity 0.412, specificity 0.911
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): Serious – all had a normal basal EEG so not representative of general population of people suspected of epilepsy

Table 50: Kimiskidis, 2017[109]

Reference	Kimiskidis, 2017[109]
Study type	Observational
Recruitment	Case-control strategy
Setting	Tertiary outpatient epilepsy clinic
Country	Greece
Sample size	31 (patients n=25, controls n=11)
Mean/median age	Epilepsy patients median 28years, controls median 26 years
Gender	54.8% female
Learning disability?	Not reported

Reference	**Kimiskidis, 2017[109]**
Head injury?	Not reported
Type of epilepsy	Juvenile myoclonic epilepsy (68%), Juvenile myoclonic epilepsy (24%), genetic generalised epilepsy (GGE) with generalised tonic-clonic seizures alone (8%)
Who carried out the index tests	Not reported
Other general sample characteristics	Out of 25 with epilepsy diagnosis, 16 had monotherapy [valproate (n=10), levetiracetam (n=5), lamotrigine (n=1)] and 9 had multiple therapy [levetiracetam + valproate (n=3), levetiracetam + lamotrigine (n=3), levetiracetam + valproate + lamotrigine (n=3)]
Inclusion criteria	Patient group: Patients with GGE; passed TASS questionnaire except epilepsy-related questions; both clinical and EEG features consistent with GGE; at least 2 seizures and on AEDs
Exclusion criteria	Other CNS disorders; comorbid conditions; EEG evidence of focal abnormalities; slow spike and wave discharges or triphasic patterns; centrally acting drugs other than AEDs; past or present substance/ETOH abuse
Index test(s), including number of repetitions and duration	Transcranial Magnetic Stimulation: Paired pulse TMS-EEG. The brain stimulation was carried out by a Magstim Rapid2 magnetic stimulator with a figure of 8 coil over the motor hand area. Various parameters were tried – single/paired stimuli and rest/hyperventilation (during/immediately after). Inter-stimulus interval of TMS was 250ms; n=25 pairs of stimuli or n=15 single stimuli.
Gold standard	Diagnosis by 2 experienced epileptologists who reached consensus based on clinical and laboratory data. Blinded to index test results.
Accuracy results	**Diagnosis of Epilepsy** Routine EEG: For differentiating epilepsy from no epilepsy: TP 6, FN 19, FP 0, TN 11; sensitivity 0.24, specificity 1.0 Using paired pulse immediately after hyperventilation: sensitivity: 1.0, specificity 0.71 Paired pulse during hyperventilation: sensitivity 0.78, specificity 0.89 Paired pulse at rest: sensitivity 0.85, specificity 0.89 Single pulse at rest sensitivity 0.60, specificity 0.82

Reference	**Kimiskidis, 2017[109]**
Source of funding	None reported, but declaration that there were no conflicts of interest
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious Indirectness (QUADAS 2 - applicability): Serious, as samples taken from 2 clearly defined populations (epilepsy and non-epilepsy) rather than the general population suspected of epilepsy

Table 51: Knox, 2018 [111]

Reference	**Knox, 2018 [111]**
Study type	Observational retrospective from patient medical records
Recruitment	consecutive
Setting	Children's Hospital medical centre
Country	USA
Sample size	340
Mean/median age	3.9 years
Gender	Not reported
Learning disability?	36% described as 'abnormal' development
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Not reported
Other general sample characteristics	Follow up time: 3.3 years; 14% on AEDs
Inclusion criteria	First time vEEG without capturing a habitual event; at least 1 year of FU; on hospital database

Reference	**Knox, 2018** [111]
Exclusion criteria	Neonates; diagnosis of epilepsy that predated the initial vEEG study by >1 month; no history of paroxysmal events
Index test(s), including number of repetitions and duration	**'No event' video EEG**; lasted at least 16 hours Routine EEG; lasted 20-40 minutes For both, abnormal EEG defined as presence of epileptiform discharges or sub-clinical seizures
Gold standard	Final definitive diagnosis based on full medical records and a minimum of 1 clinic visit in 1 year of follow up. Often unblinded to EEG results
Accuracy results	**Diagnosis of Epilepsy** <u>No Event vEEG (n=340)</u> TP 52, FN 44, FP 29, TN 215; sensitivity 0.54 (95% CI: 0.44-0.64), specificity: 0.88 (0.84-0.92) <u>Routine EEG (n=202)</u> sensitivity 0.33 (95% CI: 0.20-0.45), specificity: 0.87 (0.82-0.92)
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious Indirectness (QUADAS 2 - applicability): Serious – only in people that had had no event in video EEG. The sensitivity is likely to be reduced as a result.

Table 52: Renzel, 2015[159]

Reference	**Renzel, 2015**[159]
Study type	Observational retrospective

Reference	Renzel, 2015[159]
Recruitment	consecutive
Setting	Unclear
Country	Switzerland
Sample size	237 (69 with diagnosis of epilepsy and 168 without)
Mean/median age	38 (16) years
Gender	93/237 female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Generalised epilepsy 11/69, Focal epilepsy 58/69
Who carried out the index tests	Not reported, but interpreted by a resident and a consultant in neurology and clinical neurophysiology
Other general sample characteristics	On AEDs: 33/237
Inclusion criteria	Age >16; at least one routine EEG because of suspected epilepsy and been subsequently examined with an EEG SD (24 hours); full documentation of history, EEG and diagnosis available; no diagnosis made before SD EEG; no specific epileptiform changes in the EEG before SD-EEG; documented cerebral imaging via MRI within 2 years of EEG recordings
Exclusion criteria	Patients declined use of their data; no final diagnosis available; no adequate documentation of the medication taken; use of highly potent neuroleptic drugs
Index test(s), including number of repetitions and duration	Sleep deprived EEG. 24 hour sleep deprivation prior to EEG. Patients had to stay awake for a complete night on the ward starting from 9pm on the day before the measurement. SD EEG was recorded between 8 and 10am. Patients were encouraged to sleep during the EEG in a semi-dark room. 10-20 system used. T1 and T2 also used in 50.8% of the patients. Duration of SD EEG was 60 minutes. Patients also performed routine trigger movements if not contraindicated: hyperventilation (3 minutes) and intermittent photic stimulation.
Gold standard	Established after collegial discussion for each case by the study investigators according to the ILAE guidelines. At least one of the following had to be present for an epilepsy diagnosis: 1) at least 2 unprovoked

Reference	Renzel, 2015[159]
	seizures 24 hours apart; 2) at least 1 definite epileptic seizure and a high recurrence risk as indicated by the presence of IEAs in standard EEG or SD EEG, or by a typically epileptogenic lesion in the brain MRI fitting to seizure semiology. Generalised epilepsies were diagnosed if typical patterns (i.e., 3/s spike-wave) were seen on EEG or if the following were present in the history: no focal abnormalities in EEG, no epileptogenic lesions in MRI, typical seizure semiology reported. Focal epilepsies were diagnosed if there were focal EEG discharges or if the following were present in the history: cerebral lesions or tumours on MRI with focal abnormalities in EEG at the same place, or typical semiology of focal seizures and focal abnormalities in EEG.
Accuracy results	**Diagnosis of Epilepsy overall** TP 17, FN 52, FP 1, TN 167; sensitivity 0.25, specificity 0.99 **Diagnosis of Focal Epilepsy only** TP 10, FN 48, FP 1, TN 167; sensitivity 0.17, specificity 0.99 **Diagnosis of Generalised Epilepsy only** TP 7, FN 4 FP 1, TN 167; sensitivity 0.64, specificity 0.99
Source of funding	None reported but statement that there was no conflict of interest
Limitations	Risk of bias (QUADAS 2 – risk of bias): serious Indirectness (QUADAS 2 - applicability): none

Table 53: Rosenow, 1998[163]

Reference	Rosenow, 1998[163]
Study type	Observational
Recruitment	consecutive
Setting	Department of Neurology

Reference	**Rosenow, 1998[163]**
Country	Germany
Sample size	40
Mean/median age	103.4 months (absence seizures), 80.8 months (non-epileptic seizures)
Gender	Not reported
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Absence seizures (n=17)
Who carried out the index tests	Principal investigator (physician)
Other general sample characteristics	Duration since onset: 16 months (absence seizures), 24 months (non-epileptic seizures) Average frequency/month: 150 (absence seizures), 30 months (non-epileptic seizures) Average duration (seconds): 10 (absence seizures), 15 (non-epileptic seizures)
Inclusion criteria	Children presenting with a chief complaint of staring spells
Exclusion criteria	None reported
Index test(s), including number of repetitions and duration	Symptom questionnaire. Questionnaire given to parents, with 25 questions covering arrest of activity, unresponsiveness, eye blinking, upward eye rolling, myoclonic twitches, body stiffening, dropping of the head or jaw, complex movements or automatism, and body rocking. Questions also covered age of onset, duration and frequency of the staring spells, presence of learning difficulties. No copy of actual questionnaire available.
Gold standard	Absence seizures defined by generalised seizure patterns recorded during routine EEG or prolonged video EEG. Non epileptic seizures diagnosed after a full clinical evaluation a paediatric epileptologist (blinded to index test results)
Accuracy results	**Diagnosis of Absence seizures**

Reference	Rosenow, 1998[163]
	Twitching of arms or legs: sensitivity 0.23(0.07-0.50); specificity 1.0(0.85-1.00) Urine loss: sensitivity 0.13(0.02-0.38); specificity 1.0(0.85-1.00) Upward eye movements: sensitivity 0.35(0.14-0.62); specificity 0.91(0.72-0.99) Occurrence when tired: sensitivity 0.58(0.33-0.82); specificity 0.74(0.52-0.90) Twitching of arms or legs OR urine loss: sensitivity 0.35(0.15-0.65); specificity 1.0(0.85-1.00) Upward eye movements AND occurrence when tired: sensitivity 0.29(0.07-0.50); specificity 0.96(0.78-1.00)
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious Indirectness (QUADAS 2 - applicability): None

Table 54: Sierra-Marcos, 2011[179]

Reference	Sierra-Marcos, 2011[179]
Study type	Observational
Recruitment	consecutive
Setting	ER
Country	Spain
Sample size	131
Mean/median age	Median 52.42 years
Gender	45% female
Learning disability?	Not reported
Head injury?	Not reported

Reference	**Sierra-Marcos, 2011[179]**
Type of epilepsy	Unclear in terms of final diagnostic definitions.
Who carried out the index tests	Two independent electroencephalographists
Other general sample characteristics	Aetiological factors: 20% toxic-metabolic, 10% cerebral chronic lesions, 10% systemic disorders or fever, 8% acute lesions, 2% sleep deprivation
Inclusion criteria	Adult patients who consulted consecutively for a new onset seizure to the ER; stereotyped paroxysmal spell highly suggested an epileptic seizure
Exclusion criteria	Patients with previous seizures
Index test(s), including number of repetitions and duration	Early EEG Follow up routine EEG Sleep deprived EEG CT
Gold standard	Full clinical, EEG, CT, video EEG AND 12 months follow up
Accuracy results	**Diagnosis of Epilepsy** Direct data not provided in the paper and so sensitivity and specificity only calculable for early EEG* Early EEG: TP 38, FN 25, FP 5, TN 37; sensitivity 0.60, specificity 0.88 *Reported that there were 43 with a positive EEG test for epilepsy and 62 with non-epilepsy result. The PPV and NPV for these were given, allowing the data in the 2x2 table to be calculated. For the other index tests, the samples were different sizes and the PPVs/NPVs were not given, making it impossible to calculate the 2x2 data
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious Indirectness (QUADAS 2 - applicability): None

Table 55: Watson, 2012[213]

Reference	**Watson, 2012[213]**
Study type	Observational
Recruitment	consecutive
Setting	Neurophysiology Department at General Hospital
Country	UK
Sample size	630
Mean/median age	49.5 years; 3 age groups evaluated: 16-39 (mean age 26.6 years), 40-64 (mean age 50) and 65 or over (mean age 74)
Gender	Not reported
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Nationally accredited clinical physiologists and 2 physicians
Other general sample characteristics	None reported
Inclusion criteria	People with EEGs done in the department between July 2006 to December 2009
Exclusion criteria	None reported
Index test(s), including number of repetitions and duration	Routine EEGs performed on XLTEK equipment
Gold standard	Final diagnosis of epilepsy/ no epilepsy, based on all information, including laboratory results, MRI/CT/X ray imaging.
Accuracy results	**Diagnosis of Epilepsy**

Reference	Watson, 2012[213]
	Routine EEG to detect epilepsy in different ages 16-39: TP 42, FN 63, FP 5, TN 106; sensitivity 0.4, specificity 0.95 40-64: TP 37, FN 56, FP 1, TN 122; sensitivity 0.39, specificity 0.99 65 and over: TP 28, FN 42, FP 1, TN 127; sensitivity 0.4, specificity 0.99
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious Indirectness (QUADAS 2 - applicability): None

Table 56: Leitinger, 2016[124]

Reference	Leitinger, 2016[124]
Study type	Observational
Recruitment	consecutive
Setting	3 settings: tertiary referral centre for patients with epilepsy; 2 departments providing general neurology care with emergency rooms.
Country	Denmark and Austria
Sample size	120 (a further 100 patients in the 'control' group were not included in this extraction as not relevant to the accuracy analysis)
Mean/median age	Median 65 (0.8 to 93)
Gender	Female 47%
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Focal 23%; generalised 1%; cryptogenic 11%

Reference	**Leitinger, 2016[124]**
Who carried out the index tests	9 experienced board-certified experts reviewed EEGs on admission (blinded to final diagnoses)
Other general sample characteristics	Somnolence 31%; stupor 9%; coma 27%; pre-existing epilepsy 38%
Inclusion criteria	Aged 4 months or older (if from tertiary centre); 18 years or older (if from the 2 secondary care centres); clinical suspicion of non-convulsive status epilepticus, having a history of decreased cognition/consciousness for at least 10 minutes.
Exclusion criteria	Participants with technically insufficient EEG recordings; EEG recordings lasting <20 minutes.
Index test(s), including number of repetitions and duration	Routine EEG, applying the Salzburg criteria. Recordings were scored as possible NCSE, or not NCSE; The definition of status epilepticus used in this study implied that patients without prominent myoclonic jerks had NCSE but myoclonic status epilepticus (prominent epileptic myoclonic jerks) was not considered as NCSE.
Gold standard	The reference standard was inferred from all clinical and para-clinical data, including EEG readings (but not the results of Salzburg criteria), laboratory data, neuroimaging data, therapeutic response, follow-up, and final outcome. For all patients and recordings, two authors evaluated these data independently, while blinded to the Salzburg criteria scorings
Accuracy results	**Diagnosis of Non Convulsive Status Epilepticus (NCSE)** 43/120 had NCSE according to GS. Using 10s epoch duration, Salzburg EEG criteria for NCSE: sensitivity 0.977(0.879-0.996), specificity 0.896(0.808-0.946
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): no serious risk of bias Indirectness (QUADAS 2 - applicability): none

Table 57: Verhoeven, 2018[205]

Reference	**Verhoeven, 2018[205]**
Study type	Observational

Reference	**Verhoeven, 2018[205]**
Recruitment	Case-control strategy
Setting	University Hospital databases
Country	Switzerland, Belgium and Austria
Sample size	75 (20 left temporal lobe epilepsy, 20 right temporal lobe epilepsy and 35 healthy controls)
Mean/median age	LTLE: 28.25 years, RTLE: 35.15 years; controls: unclear
Gender	LTLE: 50% female, RTLE: 55% female; controls unclear
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Right (50%) and left (50%) temporal lobe epilepsy
Who carried out the index tests	Not reported
Other general sample characteristics	Not reported
Inclusion criteria	Drug resistant TLE, or 'healthy'.
Exclusion criteria	Not reported
Index test(s), including number of repetitions and duration	Resting-state high-density EEG recording data was used. Epochs without interictal spikes were selected. The cortical source activity was obtained for 82 regions of interest and whole-brain directed functional connectivity was estimated in the theta, alpha and beta frequency bands. These connectivity values were then used to build a classification system based on two two-class Random Forests classifiers: TLE vs healthy controls and left vs right TLE.
Gold standard	Drug resistant TLE was definitively diagnosed as follows: unilateral anteromedial localization of the epileptogenic zone confirmed by good surgical outcome (Engel's class I or II, after at least 12 months post-operative follow-up), intracranial EEG or concordant presurgical evaluation methods and the existence of at least a 10–15 min resting state eyes-closed high-density EEG recording (96–256 channels). All patients had interictal activity on long-term EEG concordant with the diagnosis of unilateral TLE. Most of them had extensive presurgical evaluation including ictal video-EEG, PET, SPECT and electric source imaging.

Reference	**Verhoeven, 2018[205]**
	Healthy subjects underwent a resting-state eyes-closed recording using an EEG system (*Electrical Geodesics* system) with 256 electrodes.
Accuracy results	**Diagnosis of Temporal Lobe Epilepsy** Feature selection and classifier training were done in a leave-one-out procedure to compute the mean classification accuracy. The diagnosis classifier (unfortunately details not given) achieved the following: TP: 38, FN 2, FP 5, TN 30; Sensitivity 0.95, specificity 0.857
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious Indirectness (QUADAS 2 - applicability): Serious: non epilepsy group were not suspected of epilepsy

Table 58: van Diessen, 2013[200]

Reference	**van Diessen, 2013[200]**
Study type	Observational
Recruitment	Case-control strategy
Setting	Paediatric neurology department
Country	Holland
Sample size	70 (35 with partial epilepsies and 35 matched controls without epilepsy)
Mean/median age	Partial epilepsy group: 10.1(3.4) years; control group: 9.9 (3.1) years (control group matched on age and gender)
Gender	Partial epilepsy group: 11/35 female; control group: 11/35 female (control group matched on age and gender)
Learning disability?	Not reported
Head injury?	Not reported

Reference	**van Diessen, 2013[200]**
Type of epilepsy	Partial epilepsy
Who carried out the index tests	Clinical epileptologist, but unclear if involved throughout the tests
Other general sample characteristics	Not reported
Inclusion criteria	One or more suspected epileptic event(s) were eligible for our study. Children included who were eventually diagnosed with new onset partial epilepsy.
Exclusion criteria	Children with neurological or psychiatric comorbidities, including developmental delay
Index test(s), including number of repetitions and duration	• Routine interictal EEG recording, using international 10-20 system. • Functional network approach: Periods of resting-state EEG, free of abnormal slowing or epileptiform activity, were selected to construct functional networks of correlated activity. The statistical interdependencies for each pair of EEG electrode time series are considered as functional connectivity and used to construct a functional network per subject for each of the four epochs and were averaged per subject. Multiple network characteristics previously used in functional network epilepsy studies were calculated and these were used to build a robust, decision tree based, prediction model.
Gold standard	The clinical diagnosis of epilepsy was defined by at least two unprovoked seizures within one year, judged by two neurologists to be of epileptic origin. The clinical diagnosis was supported in a subset of patients by epileptiform abnormalities (interictal epileptiform discharges (IEDs) such as sharp waves, (poly) spikes or (poly) spike-wave complexes or abnormal slowing), on routinely performed EEG. In patients clinically diagnosed with epilepsy but with a normal routine EEG recording, the diagnosis was confirmed by subsequent sleep deprivation EEG recordings, neuroimaging or clinical follow-up with history of more highly suspected events. An MRI was performed in all children diagnosed with epilepsy, not classified as idiopathic focal epilepsy. Epilepsy was excluded in the control group, based on clinical history, EEG results, and at least one year of uneventful follow up. This control group was individually matched with the patient group on gender and age.
Accuracy results	**Diagnosis of Partial Epilepsy** Routine epileptiform EEG activity only: sensitivity and specificity of 0.77 and 0.91 respectively. In contrast, the prediction model had a sensitivity of 0.96 [95% CI 0.78–1.00] and specificity of 0.95 [95% CI 0.76–1.00]

Reference	van Diessen, 2013[200]
Source of funding	Epilepsy Fund of the Netherlands (NEF 09-93). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious Indirectness (QUADAS 2 - applicability): Serious as non-epilepsy group not suspected of epilepsy

Table 59: Bayly, 2013[20]

Reference	Bayly, 2013[20]
Study type	Observational
Recruitment	consecutive
Setting	Large urban general hospital
Country	Australia
Sample size	35 (but 56 'events' from these 35 were used as the unit of analysis)
Mean/median age	Epilepsy patients; 33 years, PNES patients 38 years
Gender	23/34 female (in 1 patient gender was not reported as this patient fitted into both PNES and epilepsy groups, and gender was only given for each group separately).
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Epileptologist (blinded)
Other general sample characteristics	None reported

Reference	**Bayly, 2013[20]**
Inclusion criteria	Patients being offered video EEG for the diagnosis of seizure-like events; patients having a convulsive seizure (>10s, with rhythmic movements affecting at least 1 limb) detected by accelerometery during video EEG
Exclusion criteria	None reported
Index test(s), including number of repetitions and duration	Wrist accelerometer data: Movement was measured at the wrist with a lightweight accelerometer held firmly on the wrist with an elastic sweat band to prevent nonbiologic movements. The accelerometer used was an ADXL330 low power, three-axis accelerometer (Analog Devices, Norwood, MA, U.S.A.). The accelerometer had a full scale of +/- 3 g and was sampled at 100 Hz via an embedded electronic data logging board, Logomatic V1.0. The movement frequency could be assessed from 0 to 20 Hz. The data logger was assembled into a mobile, battery-operated unit worn at the waist and connected to the wrist worn accelerometer by ultraflexible shielded minicable. Acceleration in the 3 planes of space was calculated. Two indices tested: • Visual review of time-frequency maps by epileptologist • The co-efficient of variation of the frequency of movements, using a threshold of 32% (<32% = PNES and >=32% = epilepsy).
Gold standard	Convulsive PNES were defined as paroxysmal episodes of jerky limb movement in the absence of ictal electrical discharges in the brain. All patients included in the study experienced rhythmic limb movements or “convulsions.” The gold standard diagnosis of whether these events were epileptic or PNES was determined at a consensus meeting of epileptologists after review of the clinical history, EEG recording, seizure semiology as observed on video recording, and neuropsychiatry and neurology evaluation. This evaluation was done blinded to the results of the accelerometer recording.
Accuracy results	**Diagnosis of Epilepsy** Detection of epilepsy using visual review of time frequency maps (note that raw data are of the events rather than people): TP 6, FN 2, FP 3, TN 38; sensitivity: 0.75, specificity 0.927 (this was the reported result, that excluded 7 events deemed ‘non-diagnostic by the epileptologist. Not possible to calculate accuracy if these 7 events are deemed as non-epilepsy as not reported from which gold standard groups these 7 events are from). Detection of epilepsy using CoV threshold of 32% (note that raw data are of the events rather than people): TP 10, FN 1, FP 3, TN 42; sensitivity: 0.91, specificity 0.93

Reference	Bayly, 2013[20]
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious Indirectness (QUADAS 2 - applicability): Serious – non epilepsy group were psychogenic non-epileptic seizures only, so population not representative of protocol population

Table 60: Azar, 2008[16]

Reference	Azar, 2008[16]
Study type	Observational
Recruitment	Unclear, but probably case-control strategy
Setting	Neurology department
Country	USA
Sample size	40 (24 with epilepsy [15 with generalised seizures and 9 with frontal lobe epilepsy], 16 with pure psychogenic seizures)
Mean/median age	34.4 years
Gender	47.5% female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	15 with generalised seizures and 9 with frontal lobe epilepsy
Who carried out the index tests	Neurologist (main author), and experienced staff in the unit.
Other general sample characteristics	Not reported
Inclusion criteria	Adult patients with epilepsy and generalised tonic-clonic seizures; patients with non-epileptic psychogenic seizures; people with hyper motor seizures from frontal lobe epilepsy

Reference	Azar, 2008[16]
Exclusion criteria	Not reported
Index test(s), including number of repetitions and duration	Ictal and post-ictal physical characteristics, recorded by video. For each seizure, both ictal and postictal features were recorded. The ictal features recorded were seizure duration (defined by beginning and end of clinical movements), eye condition (closed or open), ictal vocalization pattern (present or absent), asynchronous limb movements (present or absent), side-to-side head or body movement (present or absent), pelvic thrusting (present or absent), discontinuous motor activity with pauses (present or absent). The main postictal feature assessed was the postictal breathing. Breathing rate, depth (deep or shallow), loudness and snoring (loud or quiet) and regularity (regular or irregular) were recorded. Other postictal features recorded were postictal responsiveness (present or absent) and postictal confusion (present or absent).
Gold standard	In all groups, the diagnosis was confirmed by prolonged EEG-video monitoring with recording of typical events. Psychogenic seizures had to be spontaneous (not triggered by hyperventilation or other manoeuvre), and had to include prominent motor activity with jerking, thrashing, shaking, or trembling. The diagnosis of frontal lobe epilepsy in patients with hyper motor seizures was definitively confirmed based on one or more of the following criteria: recording of multiple stereotyped events, secondary generalization of typical hyper motor seizures, frontal interictal and ictal discharge on scalp EEG, invasive recordings, or epilepsy surgery with a favourable outcome.
Accuracy results	**Diagnosis of Epilepsy** In paper the frontal lobe and generalised chronic-tonic data were presented separately, but they have been presented pooled for this analysis. The non-epilepsy group were psychogenic non-epileptic seizures. Note that raw data denote events NOT people with events. **Ictal** Eyes open/closed: TP 44, FN 0, FP 3, TN 21; sensitivity: 1.0, specificity 0.875 Vocalisation (Y/N): TP 28, FN 16, FP 3, TN 21; sensitivity: 0.63, specificity 0.875 Side to side head and body turning (Y/N): TP 17, FN 27, FP 15, TN 9; sensitivity: 0.39, specificity 0.375 Asynchronous extremity motion (Y/N): TP 21, FN 23, FP 23, TN 1; sensitivity: 0.48, specificity: 0.04 Pelvic thrusting (Y/N): TP 1, FN 43, FP 2, TN 22; sensitivity: 0.02, specificity: 0.916

Reference	Azar, 2008[16]
	Post ictal Breathing depth deep/shallow: TP 27, FN 17, FP 3, TN 21; sensitivity: 0.61, specificity 0.875 Breathing loudness (loud/quiet): TP 23, FN 21, FP 5, TN 19; sensitivity: 0.52, specificity 0.79 snoring (Y/N): TP 15, FN 29, FP 0, TN 24; sensitivity: 0.34, specificity 1.0 Breathing regularity (Y/N): TP 22, FN 22, FP 5, TN 19; sensitivity: 0.50, specificity: 0.79 agitation (Y/N): TP 15, FN 29, FP 3, TN 21; sensitivity: 0.34, specificity: 0.875 confusion(Y/N): TP 22, FN 7, FP 3, TN 21; sensitivity: 0.76, specificity: 0.875
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious Indirectness (QUADAS 2 - applicability): Serious – non epilepsy group were psychogenic non-epileptic seizures only, so population not representative of protocol population

Table 61: Alving, 1998[7]

Reference	Alving, 1998[7]
Study type	Observational
Recruitment	Case-control strategy
Setting	Department of clinical neurophysiology
Country	Denmark
Sample size	58 (38 epilepsy, 20 pseudo-epileptic seizures)
Mean/median age	Median 28 (range 13-68)
Gender	46/58 female

Reference	**Alving, 1998[7]**
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Simple partial 4/38; complex partial (temporal) 14/38; complex partial (frontal) 6/38; generalised (primary) 5/38; generalised (secondary) 11/32
Who carried out the index tests	Not reported
Other general sample characteristics	None reported
Inclusion criteria	People with diagnosed epilepsy or pseudo-epileptic seizures
Exclusion criteria	Uncertain diagnoses; insufficient seizure description; uncertainty about time elapsed from previous seizure to index seizure; neuroleptic drugs; pregnancy
Index test(s), including number of repetitions and duration	Paired serum prolactin measurements, done 15 minutes post-seizure and 2 hours after the first sample (baseline measure). Magnetic immune-assay technique used. Pre-hoc thresholds denoting epilepsy were 1) a twofold or greater increase in serum prolactin [RI >2], or 2) post-ictal level of 700microU/ml. Post-hoc thresholds were 3) >5.5 x increase in serum prolactin [RI >5.5] and 4) post-ictal levels of 1025 microU/ml.
Gold standard	All patients were evaluated during admission by clinical observation, combined with recording of seizure frequency and severity in relation to alterations in antiepileptic drug (AED) treatment. In addition, seizures were studied by intensive monitoring (video and/or ambulatory cassette EEG) in 30 (79%) of ES and in 17 (85%) of PES patients. In all included cases, diagnostic evaluation was done independently of serum prolactin data.
Accuracy results	**The paper was a little ambiguous at how it presented results in terms of whether the target condition for detection was Epilepsy or PNES. However, it has been assumed that the results refer to diagnosis of epilepsy on the following basis: for the results where >1025 microU/ml were taken as a positive test, the maximum value in the epilepsy group was above this but the maximum value in the PNES was well below this. This would mean that the specificity of this test would indeed have a value of 1.0 (all with the non-epilepsy condition would be correctly denoted as negative as below the threshold)** **Diagnosis of Epilepsy overall** >1025 microU/ml: sensitivity 0.34, specificity 1.0

Reference	Alving, 1998[7]
	RI>5.5: sensitivity 0.20, specificity 1.0 RI>2: sensitivity 0.69, specificity 0.74 **Diagnosis of Complex partial seizures (GS negative was pseudo seizures only and did not include other epilepsy types)** >1025 microU/ml: sensitivity 0.35, specificity 1.0 RI>5.5: sensitivity 0.28, specificity 1.0 RI>2: sensitivity 0.61, specificity 0.74 **Diagnosis of Generalised clonic tonic seizures (GS negative was pseudo seizures only and did not include other epilepsy types)** >1025 microU/ml: sensitivity 0.38, specificity 1.0 RI>5.5: sensitivity 0.20, specificity 1.0 RI>2: sensitivity 0.93, specificity 0.74
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): serious Indirectness (QUADAS 2 - applicability): Serious: non-epilepsy cohort were all PNES and so not representative of protocol population

Table 62: Manni, 2008[131]

Reference	Manni, 2008[131]
Study type	Observational
Recruitment	consecutive
Setting	Outpatient sleep and epilepsy unit (tertiary centre)

Reference	**Manni, 2008[131]**
Country	Italy
Sample size	71 (nocturnal frontal lobe epilepsy, n=14, arousal parasomnias, n=11, idiopathic REM sleep behaviour disorder [RBD], n=46)
Mean/median age	Mean 54(21)
Gender	11/71 female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Nocturnal frontal lobe epilepsy (NFLE)
Who carried out the index tests	Medical doctor
Other general sample characteristics	Not reported
Inclusion criteria	Patients with undefined (epileptic or parasomnic) nocturnal paroxysmal motor-behavioural episodes attending the Sleep Medicine and Epilepsy Unit (an outpatient facility) at the IRCCS "C. Mondino Institute of Neurology" Foundation in Pavia, Italy; final diagnosis of arousal parasomnias, NFLE or idiopathic RBD,
Exclusion criteria	Not reported
Index test(s), including number of repetitions and duration	Frontal Lobe Epilepsy and Parasomnias (FLEP) scale* – Italian version. Scale filled in by medical doctor based on reports given by patients and relatives (blinded to GS). Scores of 0 or less = likely to be parasomnias Scores of 0 to +3 = potentially epilepsy Scores of >+3 = highly likely to be epilepsy *Derry CP, Dvey M, Johns M, Kron K, Glencross D, Marini C, Scheffer IE, Berkovic S. (2006b) Distinguishing sleep disorders from seizures: diagnosing bumps in the night. Arch Neurol 63:705–709.

Reference	Manni, 2008[131]
Gold standard	Final diagnosis based on one or more nocturnal paroxysmal episodes documented on an in-lab, full-night video-EEG polysomnography (VIDEO EEG PSG) recording with extended EEG montages (full-scalp EEG, positioning of leads according to the International 10–20 System: Fp1, Fp2, F3, F4, F7, F8, C3, C4, P3, P4, T3, T4, T5, T6, O1, O2, common reference, with display system used to allow the rearrangement of EEG traces into various montages). In all cases a detailed clinical history, interictal routine EEG, and neuroradiological brain NMR findings were also available. Carried out by 2 physicians blinded to index test results.
Accuracy results	**Diagnosis of Nocturnal Frontal Lobe Epilepsy** Detection of NFLE (excluding those with FLEP scores in the uncertain range of 1-3): TP 4, FN 4, FP 0, TN 41; Sensitivity 0.5, specificity 1.0 The above strategy is reported by the paper, but they incorrectly calculated the sensitivity to be 0.714 (they failed to account for the fact that 6 in the NLFE group had scores of 1-3). However, if we include those with FLEP scores 1-3 as being indicative of NFLE, then: TP 10, FN 4, FP 16, TN 41; sensitivity 0.714, specificity 0.719 And if we include those with FLEP scores 1-3 as being indicative of *no NFLE*, then: TP 4, FN 10, FP 0, TN 57; sensitivity 0.29, specificity 1.0
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): No serious risk of bias Indirectness (QUADAS 2 - applicability): Serious: non-epilepsy cohort were all parasomnias or idiopathic RBD and so not representative of protocol population

Table 63: Jackson, 2016[99]

Reference	Jackson, 2016[99]
Study type	Observational

Reference	**Jackson, 2016[99]**
Recruitment	Consecutive, from database
Setting	Emergency department at a tertiary care facility
Country	Australia
Sample size	219 (final diagnosis of seizure n=181, final diagnosis of non-seizure n=38)
Mean/median age	Median age 45 years (IQR: 28-62)
Gender	40% female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported, but of 181 seizures 110 were first seizures and 71 were recurrent. Of the 110 first seizures, 91 were unprovoked and 19 were provoked.
Who carried out the index tests	ED doctors
Other general sample characteristics	Not reported
Inclusion criteria	Patients referred by the ED to the adult first seizure clinic at Monash medical centre
Exclusion criteria	Not reported
Index test(s), including number of repetitions and duration	Emergency Department assessment: The baseline investigations for first seizure presentations at the Monash Health ED include full blood examination and tests for blood glucose levels, liver function, urea and electrolytes, as well as calcium and magnesium. Drug and ethanol levels are performed on a case-by-case basis. Computed tomography (CT) neuroimaging is usually performed for all patients presenting with first seizures, unless there is a contraindication, such as pregnancy. Cerebrospinal fluid (CSF) examination is performed when meningitis or encephalitis is suspected. In the discharge summary, the ED doctors documented the most likely diagnosis based on their assessment. The ED evaluation was based on the history, examination, CT brain scans, and blood tests.

Reference	**Jackson, 2016[99]**
Gold standard	Final diagnosis: Index test data, PLUS MRI brain scans and EEG data that had been collected after ED discharge, with decision made by study authors (epilepsy specialists).
Accuracy results	**Diagnosis of Epilepsy** TP 133, FN 48, FP 26, TN 12; sensitivity 0.73, specificity 0.32
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): none

Table 64: Stroink, 2003[184]

Reference	**Stroink, 2003[184]**
Study type	Observational prospective
Recruitment	consecutive
Setting	Multicentre hospital-based Dutch-Study of Epilepsy in Childhood
Country	Holland
Sample size	N=760 (536 with multiple seizures, 224 with a single seizure)
Mean/median age	Not reported but inclusion ages were 1 month to 16 years
Gender	Not reported
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	A panel of 4 paediatric neurologists with at least 10 years of experience in paediatric epilepsy

Reference	**Stroink, 2003[184]**
Other general sample characteristics	Not reported
Inclusion criteria	All children aged 1 month to 16 years referred by GP or paediatrician at participating hospital for a single seizure or suspected epilepsy
Exclusion criteria	Children with only neonatal, febrile or other acute symptomatic seizures; children referred from other hospitals for a second opinion
Index test(s), including number of repetitions and duration	• Clinical diagnosis: Attending paediatric neurologist completed an extensive questionnaire on description of events, including postictal signs, possible provoking factors, medical history and family history. In addition, descriptions of the episodes according to the letters to the GPs were made available to the diagnosing panel of 4 paediatric neurologists. The 4 paediatric neurologists then used all the information to form the initial diagnosis. Each paediatric neurologist was only able to make diagnoses on patients they did not see clinically. Unanimous diagnoses were made in all cases. • Standard EEG performed in each child. If no epileptiform discharges a recording after partial sleep deprivation was made, or in small children during a daytime nap. Brain CT scan performed in all children unless anaesthesia was required, or the child had idiopathic generalised epilepsy with absences. For single events the clinical diagnosis was not based on the EEG results or other ancillary studies. For multiple seizures, the EEG results were considered if the panel agreed that the events were suspect for seizures. Standard EEGs were looked at as index tests separately.
Gold standard	Use of original data plus information gained over 5 years of follow up (if epilepsy originally diagnosed), 2 years of follow up (if single seizure) or 1 year of follow up (if no epilepsy diagnosis or single event at baseline).
Accuracy results	**Diagnosis of Epilepsy** Clinical diagnosis: Multiple seizures TP 393 FN 7 FP 19 TN 117; sensitivity 0.983, specificity 0.86 Clinical diagnosis: Single seizures TP 170 FN 4 FP 0 TN 50; sensitivity 0.977, specificity 1.0

Reference	Stroink, 2003[184]
	EEG only: Multiple seizures TP 281 FN 119 FP 31 TN 105; sensitivity 0.703, specificity 0.772 EEG only: Single seizures TP 97 FN 77 FP 11 TN 39; sensitivity 0.557, specificity 0.780
Source of funding	Dutch National Epilepsy Fund (Grants A72 and A85)
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious Indirectness (QUADAS 2 - applicability): Serious – people who had 'definite other diagnoses' (after index test) were excluded, but in reality, these might be part of the population who would be tested.

Table 65: Duez, 2016[65]

Reference	Duez, 2016[65]
Study type	Observational prospective
Recruitment	consecutive
Setting	Department of Clinical Neurophysiology at a University Hospital
Country	Denmark
Sample size	52
Mean/median age	Median 29 years (range 16-76)
Gender	36/52 female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported

Reference	**Duez, 2016[65]**
Who carried out the index tests	Not reported, but index data interpreted by 'trained physicians'.
Other general sample characteristics	Based on gold standard, 22 with 'confirmed epilepsy' after 1 year follow up; 30 with 'not confirmed epilepsy', 20 of which had PNES.
Inclusion criteria	Paroxysmal clinical episodes, suggesting epileptic seizures; at least 3 normal EEG recordings, 2 of which included provocation methods of hyperventilation and photo stimulation and 1 of which was sleep-EEG
Exclusion criteria	Not reported
Index test(s), including number of repetitions and duration	Magnetoencephalography (MEG), using a MEG whole-head 306 channel Elektra Neuromag system with 204 planar gradiometers and 102 magnetometers. Simultaneous EEG data were recorded using a non-magnetic cap and additional electrodes covering the inferior part of the head. Due to large head circumference, 7 were not given EEG. Spontaneous magnetic brain activity (eyes-closed, rest, supine) was recorded for 1 hour at a sampling frequency of 1 khz (for both MEG and EEG).
Gold standard	Diagnostic reference standard was inferred from the diagnosis obtained from the medical chart, after at least one year follow-up after MEG. This was based on all available clinical and para-clinical data for each patient, including description of witnessed seizures, home video recordings of seizures, neuroimaging, laboratory and neurophysiological data. For 34 patients long term video-EEG recordings were available.
Accuracy results	**Diagnosis of Epilepsy** MEG-EEG: TP 9, FN 13, FP 2, TN 28; sensitivity 0.41, specificity 0.93
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious Indirectness (QUADAS 2 - applicability): Serious - Sample were only those with no interictal findings on provoked EEG, so do not truly represent the protocol-defined population.

Table 66: Tews, 2015[194]

Reference	**Tews, 2015[194]**
Study type	Observational retrospective

Reference	**Tews, 2015[194]**
Recruitment	consecutive
Setting	secondary care – teaching hospital
Country	Germany
Sample size	248 for EEG, 176 for MRI
Mean/median age	Mean 6.2(5.3)
Gender	112/248 female
Learning disability?	unclear, although reported that in 91.8% of the children had age-appropriate neurological results at first presentation
Head injury?	unclear
Type of epilepsy	focal seizures 4%, focal seizures with impairment of consciousness (previously known as complex focal) 14.5%, focal seizures with secondary generalization 17.7%, generalised tonic clonic 34.5%, absences 14.1%, other generalised seizures 14.1%, unclassified seizures 1.2%
Who carried out the index tests	Unknown, as based on patient records, but ambiguous and imprecise neuro-imaging results were re-evaluated by a paediatric neurologist and paediatric radiologist
Other general sample characteristics	Not reported
Inclusion criteria	Inclusion criteria: first afebrile seizure; aged 1 mo. to 18 yrs not suffering from pre-existing neurological disorders
Exclusion criteria	Exclusion criteria: situation-related or acute symptomatic seizures resulting from toxic, metabolic, infectious or traumatic reasons were excluded.
Index test(s), including number of repetitions and duration	EEG (n=248): defined as normal (115/248), or non-definitive pathological (47/248), or pathological (86/248). Of the pathological lesions, 77 deemed epileptogenic MRI (n=176): defined as normal (123/176), 53/176 abnormal. Of the abnormal scans, 41 were regarded as potentially epileptogenic

Reference	**Tews, 2015[194]**
Gold standard	Seizure recurrence at 48 months, with use of the International League Against Epilepsy definitions to clinically classify patients as having epilepsy.
Accuracy results	**Diagnosis of Epilepsy** EEG In 73 with epilepsy diagnosis, 33 had normal EEG, 40 had pathological EEG. In 176 with no recurrence (note paper reports 148 but this seems to be an error), 136 had normal EEG and 40 had abnormal EEG (note numbers add to 249!) TP 40 FN 33 FP 40 TN 136 Sen: 0.548 (0.6 reported in paper but raw data described in study text suggests my calculated figure of 0.548) Spec: 0.772 (0.78 in paper but raw data described in study text suggests my calculated figure of 0.772) MRI No raw data given, and inconsistencies in numbers from other parts of paper prohibit calculation of raw data Sen: 0.36 (as reported) Spec: 0.74 (as reported)
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious Indirectness (QUADAS 2 - applicability): None

Table 67: Chen, 2008[39]

Reference	**Chen, 2008[39]**
Study type	Observational
Recruitment	consecutive
Setting	Epilepsy Monitoring Unit
Country	USA
Sample size	43 [27 with epilepsy and 16 with psychogenic non-epileptic seizures (PNES)]
Mean/median age	Mean 33.6
Gender	29/43 female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Localisation; temporal 17, frontal/paracentral region 4, occipital 0, non-localizing onsets 6.
Who carried out the index tests	Interpreted by a fellowship-trained epileptologist (blinded to clinical history and thus GS)
Other general sample characteristics	Not reported
Inclusion criteria	Patients had seizures with behavioural semiology suggestive of partial seizures, with or without secondary generalisation; EEGs from patients with epilepsy all showed recognisable changes though this was not known to blinded readers;
Exclusion criteria	Patients with known mixed epilepsy and PNES
Index test(s), including number of repetitions and duration	• Video alone • EEG alone One event per patient was selected as the first technically adequate event during monitoring. The video or EEG clips were cued to a time 1-3 minutes before the onset of the characteristic behavioural or electroencephalographic background changes. Either the EEG or video was masked – nobody saw both together.

Reference	Chen, 2008[39]
	In addition, semiological features were recorded. DURING SEIZURE
Gold standard	Diagnosis of epilepsy or PNES was considered established by response to surgery, confirmation by invasive recording, response to psychiatric therapy, or surface video-EEG confirmation followed by serial observations for at least a year with no change in diagnosis
Accuracy results	**Diagnosis of Epilepsy** **Video only** TP 25, FN 2, FP 1, TN 15; sensitivity 0.93, specificity 0.94 **EEG only** TP 24, FN 3, FP 1, TN 15; sensitivity 0.89, specificity 0.94 **Semiological features:** **Gradual behavioural build-up to peak intensity, but within 70 seconds (detection of epilepsy)** TP 22, FN 5, FP 1, TN 15; sensitivity 0.82, specificity 0.94 **Automatisms (detection of epilepsy)** TP 14, FN 13, FP 1, TN 15; sensitivity 0.52, specificity 0.94 **Eyes closed at peak of symptoms (detection of epilepsy)** TP 0, FN 25, FP 12, TN 3; sensitivity 0.0, specificity 0.20 **Waxing-waning event tempo (detection of epilepsy)** TP 1, FN 26, FP 11, TN 5; sensitivity 0.04, specificity 0.31 **Non-synchronous movements (detection of epilepsy)** TP 2, FN 25, FP 7, TN 9; sensitivity 0.07, specificity 0.56

Reference	Chen, 2008[39]
	Side to side head movements (detection of epilepsy) TP 0, FN 27, FP 4, TN 12; sensitivity 0.0, specificity 0.75 **Pelvic thrusting (detection of epilepsy)** TP 1, FN 26, FP 5, TN 11; sensitivity 0.04, specificity 0.69 **Expression of pain (detection of epilepsy)** TP 0, FN 27, FP 4, TN 12; sensitivity 0.0, specificity 0.75 **Discernible onset (detection of epilepsy)** TP 27, FN 0, FP 14, TN 2; sensitivity 1.0, specificity 0.125 **Motor behavioural onset (detection of epilepsy)** TP 6, FN 21, FP 3, TN 13; sensitivity 0.22, specificity 0.81 **Head version (detection of epilepsy)** TP 6, FN 21, FP 1, TN 15; sensitivity 0.22, specificity 0.94 **Eye deviation (detection of epilepsy)** TP 5, FN 20, FP 0, TN 15; sensitivity 0.20, specificity 1.0 **Repetitive eye blinks (detection of epilepsy)** TP 1, FN 24, FP 3, TN 12; sensitivity 0.04, specificity 0.80 **Facial grimacing (detection of epilepsy)** TP 3, FN 24, FP 2, TN 14; sensitivity 0.11, specificity 0.88 **Abnormal posturing (detection of epilepsy)** TP 10, FN 17, FP 6, TN 10; sensitivity 0.37, specificity 0.63

Reference	Chen, 2008[39]
	Clonic activities (detection of epilepsy) TP 8, FN 19, FP 3, TN 13; sensitivity 0.30, specificity 0.81 **Vocalisation/speech (detection of epilepsy)** TP 10, FN 17, FP 5, TN 11; sensitivity 0.37, specificity 0.69 **Post-event stertorous breathing (detection of epilepsy)** TP 6, FN 21, FP 0, TN 16; sensitivity 0.22, specificity 1.0 **Discernable offset (detection of epilepsy)** TP 20, FN 7, FP 11, TN 5; sensitivity 0.74, specificity 0.31 **Thrashing/writhing (detection of epilepsy)** TP 4, FN 23, FP 5, TN 11; sensitivity 0.15, specificity 0.69
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious Indirectness (QUADAS 2 - applicability): serious – only people with epilepsy and PNES included which will be different to the normal clinical population

Table 68: Ehsan, 1996[69]

Reference	Ehsan, 1996[69]
Study type	Observational
Recruitment	consecutive
Setting	Epilepsy monitoring unit

Reference	**Ehsan, 1996[69]**
Country	USA
Sample size	50 (36 with epilepsy and 14 with non-epileptic seizures)
Mean/median age	Mean 33 years
Gender	30 female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Tonic-clonic (secondarily generalised) 13; CPS 17; simple partial seizures 6
Who carried out the index tests	Nurses obtained the capillary blood
Other general sample characteristics	Patients had experienced seizures for a mean of 17 years
Inclusion criteria	Patients admitted to epilepsy monitoring unit for video-EEG monitoring for a history of refractory seizures or non-epileptic events; first clinical event only analysed
Exclusion criteria	Not reported
Index test(s), including number of repetitions and duration	Paired capillary prolactin measurement at 15 and 75 minutes after a clinical event in the epilepsy monitoring unit. Abnormal reading defined as a single reading >6.7 ng/ml for the 15-minute reading, or a twofold decrease between the 15 minute sample and the sample obtained 1 hour later
Gold standard	Documentation of seizure type with simultaneous video/audio EEG monitoring
Accuracy results	**Diagnosis of Epilepsy** **15-minute capillary prolactin level above 6.7 ng/ml** TP 25, FN 11, FP 1, TN 13; sensitivity 0.69, specificity 0.93 **2-fold decrease between the 15 minute sample and the sample obtained 1 hour later** TP 25, FN 11, FP 2, TN 12; sensitivity 0.69, specificity 0.86

Reference	Ehsan, 1996[69]
	15-minute capillary prolactin level above 6.7 ng/ml AND 2 fold decrease between the 15 minute sample and the sample obtained 1 hour later TP 20, FN 16, FP 0, TN 14; sensitivity 0.56, specificity 1.0 DURING SEIZURE
Source of funding	Men's and Women's board of the Barrow Neurological Foundation; Sandra Solheim Aiken fellowship Fund
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): None

Table 69: Hanrahan, 2018[90]

Reference	Hanrahan, 2018[90]
Study type	Observational retrospective
Recruitment	Consecutive, though unclear
Setting	Epilepsy Monitoring Unit at University Hospital
Country	USA
Sample size	12 (5 with epilepsy, 4 with Non-Epileptic Behavioural Spells [NEBS] and 3 with syncope)
Mean/median age	Mean 40.6
Gender	33% female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Focal temporal lobe seizure (2), focal extratemporal lobe seizure (2), generalised seizure (1)
Who carried out the index tests	Data collected by a single-blinded researcher. Neurologists at various stages of training – from postgraduate year 1 to board-certified epileptologists

Reference	**Hanrahan, 2018[90]**
Other general sample characteristics	None reported
Inclusion criteria	Patients admitted to the Epilepsy Monitoring Unit for 'spell classification' who had videos taken of their events during the evaluation
Exclusion criteria	Not reported
Index test(s), including number of repetitions and duration	1. Clinical history. Each patient met with a neuropsychologist during their stay who completed a personality evaluation, neurocognitive testing, and documented the patients' descriptions of their typical event. This depiction was then reviewed and summarised into a clinical vignette. These were then used as an index test, where neurologists from a single centre had to classify the vignettes according to epilepsy, NEBS, or another physiologic event. 2. Videos of the event captured during EMU evaluation. These were then used as an index test, where the same neurologists from a single centre had to classify the vignettes according to epilepsy, NEBS, or another physiologic event. The order was randomised. DURING SEIZURE
Gold standard	The paper describes EMU diagnosis as entailing video-EEG, clinical history and witnessed semiology. The reported EMU-confirmed diagnosis was considered final. The diagnosis was also described as 'established'.
Accuracy results	**Diagnosis of epilepsy** <u>Clinical History</u> TP 4, FN 1, FP 1, TN 6; Sensitivity 0.80, specificity 0.86 <u>Video observation</u> TP 5, FN 0, FP 2, TN 5; Sensitivity 1.0, specificity 0.71
Source of funding	National Institutes of Health grant UL1-TR-001857 (non-Industry)
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): None

Table 70: Husain, 2020[97]

Reference	**Husain, 2020[97]**
Study type	Observational prospective
Recruitment	consecutive
Setting	Epilepsy Monitoring Units at VA Epilepsy centres of Excellence.
Country	USA
Sample size	71, but only the 17 having 34 seizure or seizure-like events (15 epilepsy and 19 PNES) were included
Mean/median age	Mean 49.1
Gender	21.1% female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Tonic clonic (8/15 events), Focal with clonic activity (2/15 events), Focal expressing automatisms (5/15 events)
Who carried out the index tests	Four American Board of Psychiatry and Neurology-certified neurologists with epilepsy subspecialty certification, who had been briefly (60 minutes) trained on SEMG features relevant to determining epilepsy. Blinded to other data.
Other general sample characteristics	Hispanic/Latino 7%, White 70.4%, Black/African American 26.8%, American Indian/Alaskan native 2.8%
Inclusion criteria	Patients with a history of ES or PNES admitted to one of 3 EMUs for routine seizure characterisation
Exclusion criteria	Any patients on whom intracranial EEG monitoring was used
Index test(s), including number of repetitions and duration	• sEMG classification of seizure events by expert review. Single channel surface EMG (sEMG) attached unilaterally on the belly of the biceps. Graphical user interface allowed expert review • Automated sEMG classification. As above, but using an automated decision tool. This generated a 'seizure score from 0-25 with a threshold of 8 or above (= epilepsy) DURING SEIZURE
Gold standard	Complete video EEG records independently reviewed by 6 epileptologists with American Board of Psychiatry and neurology subspecialty certifications in epilepsy. Full 24 hour recordings were reviewed by 3

Reference	Husain, 2020[97]
	epileptologists. Events were classified using Fisher et al. (2017) categories. Final decisions were made on a majority rule approach.
Accuracy results	**Diagnosis of epilepsy** **Expert review of sEMG** Raw data unclear; Sensitivity 0.77(0.64-0.86), specificity 0.96(0.89-0.99) **Automated sEMG** TP 13, FN 2, 4, TN 15; sensitivity 0.87(0.60-0.98); specificity 0.79(0.54-0.94)
Source of funding	Self-funded by Brain Sentinel
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): Serious – non epilepsy group were PNES and so not representative of 'non-epilepsy' population in practice

Table 71: Jaraba, 2019[100]

Reference	Jaraba, 2019[100]
Study type	Observational prospective
Recruitment	consecutive
Setting	Epilepsy Unit in University Hospital setting
Country	Spain
Sample size	55 (36 with Non-Convulsive Status Epilepticus [NCSE])
Mean/median age	Median age 62.1 years (range 25-84)
Gender	21/55 female
Learning disability?	Not reported

Reference	**Jaraba, 2019[100]**
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Visual diagnosis performed independently by 2 experts in nuclear medicine blinded to all other clinical information. Third expert used to resolve conflicts.
Other general sample characteristics	Aetiology was vascular 14/36, tumour 5/36, immune 3/36, toxic 2/36, neurodegenerative 1/36, cryptogenic 8/36, another 3/36
Inclusion criteria	All patients undergoing 99mTc-hexamethyl propyleneamine oxime [HMPAO] single photo emission computed tomography [SPECT] [HMPAO-SPECT] as part of their diagnostic workup in the centre; clinical suspicion of NCSE
Exclusion criteria	Patients with sub-optimal EEG recordings; patients with NCSE because of hypoxic-anoxic aetiology; no consensus on diagnosis, where EEG and HMPAO-SPECT were not done simultaneously
Index test(s), including number of repetitions and duration	SPECT scans all performed within 120 minutes from the administration of 740 Mbq of 99mTc-HMPAO. The injection was done during the suspected status epilepticus while patients monitored with vEEG. • Visual analysis: SPECTS considered positive for status Epilepticus when there was at least one area of Focal Uptake compared to the adjacent or contralateral areas of the brain. • Quantitative analysis: Results were compared to a normal database and the difference in terms of the Z score was quantified. EEG using Salzburg criteria also done at the same time DURING SEIZURE
Gold standard	Patients were classified as NCSE or non-NCSE following a consensus decision based on all clinical and paraclinical data, including EEG readings, laboratory data, therapeutic response, follow up and final outcome. Two clinicians evaluated these data independently blinded to HMPAPO-SPECT results. A third clinician was used to resolve conflicts.
Accuracy results	**Diagnosis of NCSE** EEG using Salzburg criteria Sensitivity 0.611, sensitivity 0.89

Reference	Jaraba, 2019[100]
	SSPECTCOM (visual analysis) Sensitivity 0.805, sensitivity 0.895 QtSPECTCOM (quantitative analysis) Sensitivity 0.82, sensitivity 0.81
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): No serious risk of bias Indirectness (QUADAS 2 - applicability): None

Table 72: Okazaki, 2019[144]

Reference	Okazaki, 2019[144]
Study type	Observational prospective
Recruitment	consecutive
Setting	Epilepsy Monitoring unit at a Tertiary epilepsy referral centre
Country	USA
Sample size	57, with 53 having events recorded during EMU stay
Mean/median age	Mean 42 (range 18-78)
Gender	30 females
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Data entered into the Epifinder app by an epilepsy-trained neurologist

Reference	**Okazaki, 2019[144]**
Other general sample characteristics	26 with epilepsy on gold standard and 27 without epilepsy. Of the 27 without epilepsy, 25 had PNS, 1 parasomnia/neurovegetative disorder and 1 with parasomnia.
Inclusion criteria	People aged >18 admitted to having scalp continuous vEEG monitoring for episode classification
Exclusion criteria	People whose monitoring session was inconclusive because of the lack of recorded events
Index test(s), including number of repetitions and duration	Epifinder application – a clinical decision support tool. Downloaded as an application and administered using an iPad. Epifinder's algorithm is a form of artificial intelligence that is based on pattern recognition. It utilises standardised terminology and heuristic algorithms that produce a list of differential diagnoses based on pattern recognition of a cluster of semiology against ILAE-defined epilepsy criteria.
Gold standard	Video-EEG of habitual events, with detailed history taken by a trained epilepsy neurologist
Accuracy results	**Diagnosis of epilepsy** TP 23, FN 3, FP 4, TN 23 Sensitivity 0.884; specificity 0.851. Note that paper gives incorrect sensitivity (0.864), given that the raw data they describe are correct.
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious Indirectness (QUADAS 2 - applicability): None

Table 73: Rowberry, 2020[166]

Reference	**Rowberry, 2020[166]**
Study type	Observational prospective
Recruitment	consecutive
Setting	Paediatric ICU (PICU)
Country	UK

Reference	**Rowberry, 2020[166]**
Sample size	101
Mean/median age	Median (IQR): 4 (2-9.8)
Gender	47.5% female
Learning disability?	Not reported
Head injury?	Traumatic brain injury 14/101
Type of epilepsy	Not reported
Who carried out the index tests	PICU clinicians (doctors and advanced nurse practitioners). They were provided training in qEEG set-up.
Other general sample characteristics	Suspected cerebral ischaemia/infarct 10/101; suspected CNS infection or other encephalopathy 10/101; admission for seizures of status epilepticus 35/101; median time form PICU admission to initiation of qEEG 11hrs
Inclusion criteria	Patients under 18 years identified by PICU clinicians to be at risk of epileptic seizures and commenced on Quantitative EEG (qEEG)
Exclusion criteria	Patients with decompressive craniectomy and allergy to collodion glue
Index test(s), including number of repetitions and duration	Quantitative EEG (qEEG) interpreted by PICU clinicians in real-time as part of routine care. Standard qEEG montage used, comprising eight electrode montage using scalp surface electrodes and NicVue 2.9 system for display of 2 channel aEEG, CDSA and raw EEG. Bedside nurses reviewed the qEEG every hour and flagged up any changes to PICU clinicians. PICU clinicians had to review qEEG recordings at least once every 4 hours or more frequently during an intervention. DURING SEIZURE
Gold standard	A clinical neurophysiologist retrospectively reviewed each qEEG recording to identify epilepsy seizures. The neurophysiologist had access to the same electrophysiology information available to the PICU clinicians. This included the raw EEG.
Accuracy results	**Diagnosis of epileptic seizures** TP 12, FN 0, FP 11, TN 78; sensitivity 1.0 (0.74-1.0), specificity 0.88 (0.79-0.94)

Reference	**Rowberry, 2020[166]**
Source of funding	Birmingham Women's and Children's Research Foundation
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): None

Table 74: Goselink, 2019[87]

Reference	**Goselink, 2019[87]**
Study type	Observational retrospective
Recruitment	consecutive
Setting	University Hospital with large neurocritical care unit, and a national tertiary referral centre for epilepsy and sleep disorders
Country	Holland
Sample size	187 patients yielding 191 EEG studies
Mean/median age	Not reported
Gender	Not reported
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	All EEG reviewers were board-certified clinical neurophysiologists with varying levels of experience that reflects clinical practice. None were familiar with the Salzburg criteria prior to the study.
Other general sample characteristics	Not reported

Reference	Goselink, 2019[87]
Inclusion criteria	All consecutive EEG recordings from both adult and paediatric patients with a clinical suspicion of non-convulsive status epilepticus (NCSE); all consecutive EEG recordings without a clinical suspicion but with an abnormal EEG were included in the clinically 'not suspected for NCSE' group.
Exclusion criteria	Patients with technically insufficient EEG recordings and EEG recordings lasting <30 minutes
Index test(s), including number of repetitions and duration	EEG review using Salzburg criteria by 4 expert neurophysiologists
Gold standard	Expert opinion of another four neurophysiologists who had access to all clinical information, including laboratory tests, imaging studies, response to treatment, follow-up and outcome, as well as all EEG recordings. The consensus view held as the final diagnosis.
Accuracy results	**Diagnosis of NCSE** **Patients with clinically suspected NCSE** Detection of NCSE TP 8, FN 4, FP 9, TN 76; sensitivity 0.667, specificity 0.894 **Patients without clinically suspected NCSE** Detection of NCSE TP 1, FN 0, FP 10, TN 83; sensitivity 1.0, specificity 0.892
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): None

Table 75: Huang, 2019[96]

Reference	Huang, 2019[96]
Study type	Observational prospective

Reference	**Huang, 2019[96]**
Recruitment	consecutive
Setting	Paediatrics, probably secondary care
Country	China
Sample size	12
Mean/median age	Mean (sd) 16(37.1) months
Gender	unclear
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	351 clinicians, 50.5% had been working >=10 years; 72.4% were paediatricians and 27.6% were paediatric neurologists. Each clinician looked at the data from all 12 infants
Other general sample characteristics	Not reported
Inclusion criteria	Infants with paroxysmal events that had been videoed; resolution was high enough to ensure facial features were visible; all possible body movements were recorded; sound in videos is clear, and excessive ventilation sounds can be distinguished.
Exclusion criteria	No consent from caregivers; video >1 minute long (may impair public playback)
Index test(s), including number of repetitions and duration	All participating clinicians did the following: • Medical record: clinicians read a description of the episodes of the 12 infants, which was meant to simulate the process of collecting the medical record at the beginning of the patient visit. The clinicians were meant to make a diagnosis on the basis of this, as epileptic/non epileptic • Medical record, plus watching a <1 minute video of the event
Gold standard	All corresponding descriptions, home videos, and VEEG reports were presented to two senior epileptologists blind to the study purpose, and they made diagnoses accordingly. Events were categorized as epileptic or nonepileptic: if epileptic, the specific seizure type was listed; if nonepileptic, a diagnosis to explain the

Reference	Huang, 2019[96]
	paroxysmal events was given. When the diagnoses from the two epileptologists were not the same, a third epileptologist would review the data and provide the diagnoses. We did not encounter a situation in which all three reviewers could not achieve an agreement.
Accuracy results	**Diagnosis of Epilepsy** **Medical record only:** Sensitivity 0.849, specificity: 0.399 **Medical record AND prior video:** Sensitivity 0.888, specificity: 0.514
Source of funding	The National Key Research and Development Program of China (2016YFC1000707).
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious – accuracy data was a composite figure across 351 clinicians Indirectness (QUADAS 2 - applicability): none

Table 76: Simani, 2018[180]

Reference	Simani, 2018[180]
Study type	Observational prospective
Recruitment	Case-control strategy
Setting	Epilepsy monitoring Unit of an urban hospital
Country	Iran
Sample size	82 (43 with epilepsy, 20 with PNES, 19 healthy controls)
Mean/median age	Mean 30.9 years
Gender	44/82 female
Learning disability?	Not reported

Reference	**Simani, 2018[180]**
Head injury?	Not reported
Type of epilepsy	Focal 48.8%, Generalised 52.1%
Who carried out the index tests	Not reported
Other general sample characteristics	Epilepsy cohort only: Seizure frequency 2-40 per month (mean 14.28 per month); disease duration 1-47 years (mean 14.13 years); AED monotherapy 20.9%, AED polytherapy 79.1%, Serum GFAP 3.69 ng/ml
Inclusion criteria	Patients with a history of recurrent seizures, admitted to EMU for further evaluation; control group comprised healthy volunteers with no history of seizure.
Exclusion criteria	Patients with other medical, neurologic or psychiatric diseases, or history of recent head trauma; medications other than AEDs or psychoactive drugs
Index test(s), including number of repetitions and duration	Post-seizure serum glial fibrillary astrocytic protein (GFAP) serum levels: venous blood samples were obtained from all the patients within 6 h following habitual seizures and randomly from healthy control subjects. The serum GFAP levels were measured using the commercially available sandwich enzyme linked immunosorbent assay kit according to the manufacturer's instructions.
Gold standard	All the patients underwent VIDEO EEG to capture enough habitual events. The epilepsy type was determined by an epileptologist based on ictal and interictal EEG findings and the seizures semiology.
Accuracy results	**Diagnosis of Epilepsy** The analysis was only reported for differentiation of epilepsy and PNES. At a cut-off point of 2.71 ng/ml, sensitivity of detection of epilepsy was 0.72 and specificity was 0.59.
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious Indirectness (QUADAS 2 - applicability): serious – those without epilepsy were all PNES, which may not be representative of the normal clinical population attending for diagnostic assessments

Table 77: Thompson, 2010[196]

Reference	**Thompson, 2010[196]**
Study type	Observational prospective
Recruitment	consecutive
Setting	Regional Epilepsy Centre
Country	USA
Sample size	184 (epilepsy 109, PNES 75)
Mean/median age	Mean 37.0 years
Gender	124/184 female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Not reported
Other general sample characteristics	Epilepsy/PNES: white 87.2%/86.7%; anxiety 55.8/61.1; Depression 59.1/65.7; somatization 57.6/67.8
Inclusion criteria	Patients completing the Personality Assessment Inventory (PAI) and video EEG at the regional epilepsy centre.
Exclusion criteria	Not diagnosed by video EEG as either epilepsy or PNES
Index test(s), including number of repetitions and duration	Personality Assessment Inventory (PAI) scales: 344 item inventory provides results along 22 non-overlapping clinical scales, such as depression, anxiety and somatization) based on the Diagnostic and Statistical Manual of mental Disorders (threshold <1 for epilepsy). There were several sub-scales measured, as follows: • PNES (Psychogenic nonepileptic seizures); threshold for PNES >=1 • SOM-C (conversion); threshold for PNES >=70 • SOM (somatic complaints); threshold for PNES >=70 • SOM-S (somatisation); threshold for PNES >=70 • DEP (Depression); threshold for PNES >=60

Reference	**Thompson, 2010[196]**
	• DEP-P (Depression-physiological); threshold for PNES >=70 • ANX-P (Anxiety-Physiological); threshold for PNES >=60 The thresholds represent the index test +ve scores for detecting *PNES*. As all of the non-PNES group were those with epilepsy, it's possible to use the reverse of these thresholds to define the +ve index threshold for epilepsy (for example, PNES epilepsy threshold would be <1). These thresholds for detecting epilepsy (ES) are in the accuracy results section below.
Gold standard	Video EEG

Accuracy results	**Diagnosis of Epilepsy**
	
	The following sensitivities and specificities are for detection of *epilepsy*. The paper reports the results for detection of PNES, but because the non-PNES group all had epilepsy, it is possible to simply reverse the results for sensitivity and specificity to derive the results for detection of epilepsy. This is why the results below are different to those reported in the paper.
	• PNES (Psychogenic nonepileptic seizures); threshold for ES <1
	  ○ Sensitivity 0.853, specificity 0.587
	• SOM-C (conversion); threshold for ES <70
	  ○ Sensitivity 0.835, specificity 0.587
	• SOM (somatic complaints); threshold for ES <70
	  ○ Sensitivity 0.734, specificity 0.560
	• SOM-S (somatisation); threshold for ES <70
	  ○ Sensitivity 0.817, specificity 0.453
	• DEP (Depression); threshold for ES <60
	  ○ Sensitivity 0.615, specificity 0.627
	• DEP-P (Depression-physiological); threshold for ES <70
	  ○ Sensitivity 0.862, specificity 0.493
	• ANX-P (Anxiety-Physiological); threshold for ES <60
	  ○ Sensitivity 0.679, specificity 0.573

Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious Indirectness (QUADAS 2 - applicability): serious – those without epilepsy were all PNES, which may not be representative of the normal clinical population attending for diagnostic assessments

Table 78: Egawa, 2020[68]

Reference	**Egawa, 2020[68]**
Study type	Observational prospective
Recruitment	consecutive
Setting	Neurological ICU in a General Hospital
Country	Japan
Sample size	50
Mean/median age	Median (range): 72 (52.5-80)
Gender	34% female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Interpretation by one neurointensivist and one board-certified neurophysiologist
Other general sample characteristics	Median SOFA score: 4; median APACHE II score: 16; median GCS: 6; median FOUR score: 10
Inclusion criteria	Altered Mental Status (AMS) with unknown aetiology
Exclusion criteria	Patients with consciousness recovered completely between HS-cv EEG and C-cEEG monitoring; if C-cEEG monitoring was not performed due to unavailability, or if the HS-cv EEG data were not clear enough due to artefact interruption. Those with do not attempt resuscitation (DNAR) declarations were also excluded, considering that earlier initiation of HS-cv EEG was not performed.
Index test(s), including number of repetitions and duration	Headset-type continuous video EEG monitoring (HS-cv EEG monitoring). It has eight electrodes: left frontal, left central, left temporal, O1, right frontal, right central, right temporal, and O2. It can simultaneously transmit EEG data via Bluetooth to a conventional computer and is equipped with a video camera. After setting up the conventional computer, the headset part is assembled by applying gel-type electrodes. Finally, the headset is placed on the patient's head.

Reference	Egawa, 2020[68]
Gold standard	Researchers performed definitive diagnosis of abnormal EEG patterns and NCSE by employing conventional continuous EEG [C-cEEG] monitoring with 21 collodion-type electrodes from the international 10–20 with video camera monitoring. All cEEG records were reviewed by at least two trained neurophysiologists or epileptologists. If any of the EEG findings were equivocal, consensus was used.
Accuracy results	**Diagnosis of Non-Convulsive Status Epilepticus** Sensitivity 0.706 (0.440-0.897), specificity 0.970 (0.842-0.999)
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): None

Table 79: Erba, 2016[73]

Reference	Erba, 2016[73]
Study type	Observational prospective
Recruitment	consecutive
Setting	Epilepsy centres in two countries
Country	Italy and USA
Sample size	21 patients, providing 23 videos. 8 were found by GS to have epilepsy
Mean/median age	>18 but ages not provided
Gender	Not reported
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	6 partial with sec. gen., 1 simple partial, 1 complex partial

Reference	**Erba, 2016[73]**
Who carried out the index tests	All 5-index test raters were board-certified neurologists practicing full time in tertiary epilepsy centres; they had between 2.5- and 30-years' experience of caring for patients with epilepsy, currently spending 30-150 hours per month caring for patients with epilepsy.
Other general sample characteristics	For those not diagnosed with epilepsy by GS, 9/15 had PNES, 4 other non-epileptic seizure and 2 non-definite diagnosis
Inclusion criteria	Aged >18 years; admitted to epilepsy centre
Exclusion criteria	Lacked intellectual capacity to answer questionnaires
Index test(s), including number of repetitions and duration	A representative audio-visual segment (or segments) of video, showing a typical event, but deprived of EEG and other clinical history/data. Of the 5 rater, 4 were completely blinded to EEG and history. One knew EEG and history.
Gold standard	The GS diagnosis was that established by the clinical team after a comprehensive evaluation of the patient's risk factors, comorbidities, psychosocial status, results of neurologic examination and neuroimaging, video semiology, EEG findings including purely electrical seizures, and the results of monitoring other physiologic parameters (ECG [electrocardiography], blood pressure, orthostatic testing, blood sugar, and so on) as appropriate.
Accuracy results	**Diagnosis of epilepsy** (not directly provided in paper, but was calculated from raw data in table 2): Rater 1: TP 7, FN 1, FP 1, TN14; sensitivity 0.875, specificity 0.930 Rater 2: TP 6, FN 2, FP 2, TN13; sensitivity 0. 750, specificity 0.860 Rater 3: TP 3, FN 5, FP 0, TN15; sensitivity 0.375, specificity 1.00 Rater 4: TP 7, FN 1, FP 1, TN14; sensitivity 0.875, specificity 0.930 Rater 5: TP 7, FN 1, FP 0, TN15; sensitivity 0.875, specificity 1.0 All blinded to EEG and history except rater 5. Summation of raters: TP 30, FN 10, FP 4, TN 71; sensitivity 0.750, specificity 0.946
Source of funding	None reported.

Reference	**Erba, 2016[73]**
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): none

Table 80: Koren, 2018[114]

Reference	**Koren, 2018[114]**
Study type	Observational prospective
Recruitment	consecutive
Setting	Neurological department and neurosurgical ICU
Country	Austria
Sample size	85 (but 92 CCEEGs done, meaning 7 had 2 recordings over one or more ICU stays)
Mean/median age	Mean 58.9 years
Gender	44/85 female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Clinical neurophysiologists
Other general sample characteristics	GCS at admission 3-15; duration of ICU stay 4-121 days; convulsive seizures during stay 39/85; NCSE on subsequent CCEE G20/85; acute or progressive brain injury 57/85
Inclusion criteria	Neurological critical care patients with clinically suspected NCSE [unexplained deterioration or fluctuation of consciousness, subtle motor activity (persistent or fluctuating muscle twitching of the face or extremities, manual and oral automatisms) as well as pupillary and ocular movement abnormalities (nystagmus, hippus, mydriasis, or sustained eye deviation).

Reference	Koren, 2018[114]
Exclusion criteria	Not reported
Index test(s), including number of repetitions and duration	Several early findings (first 30 minutes of EEG recordings) were tested: ○ Early sporadic epileptiform discharges (SED) ○ Early rhythmic and periodic EEG patterns of 'ictal-interictal uncertainty' (RPPIIIU) ○ Early SED or RPPIIU ○ Clinical signs of non-convulsive seizures (NCS) ○ Early SED or RPPIIU and clinical signs of NCS ○ Early SED, RPPIIU, or clinical signs of NCS
Gold standard	Critical care continuous EEG (for detection of NCSE). Used 21 electrodes according to the 10-20 system. Recordings performed as soon as possible following clinical suspicion of NCSE (all within 12 hours). EEG data classified according to the ACNS SCCET. Mean recording time was 72 (67) hours [range 5-388 hours]
Accuracy results	**Diagnosis of NCSE** on later CCEEG: ○ Early sporadic epileptiform discharges (SED): sensitivity 0.214, specificity 0.908 ○ Early rhythmic and periodic EEG patterns of 'ictal-interictal uncertainty' (RPPIIIU): sensitivity 0.643, specificity 0.846 ○ Early SED or RPPIIU: sensitivity 0.857, specificity 0.754 ○ Clinical signs of non-convulsive seizures (NCS): sensitivity 0.929, specificity 0.631 ○ Early SED or RPPIIU **and** clinical signs of NCS: sensitivity 0.786, specificity 0.892 ○ Early SED or RPPIIU, **or** clinical signs of NCS: sensitivity 1.0, specificity 0.492
Source of funding	FFG—Austrian Research Promotion Agency grant 826816 (EpiMon).
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious Indirectness (QUADAS 2 - applicability): none

Table 81: Mueller, 2013[136]

Reference	Mueller, 2013[136]
Study type	Observational prospective
Recruitment	Case-control strategy

Reference	**Mueller, 2013[136]**
Setting	Imaging of Neurodegenerative Diseases Centre
Country	USA
Sample size	80 (25 controls, 19 with temporal lobe epilepsy with mesial temporal sclerosis (TLE-MTS), 22 with temporal lobe epilepsy without MTS (TLS-no), 14 with non-lesional frontal lobe epilepsy (FLE)
Mean/median age	Mean 35.9 years
Gender	52/80 female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	19 with temporal lobe epilepsy with mesial temporal sclerosis (TLE-MTS), 22 with temporal lobe epilepsy without MTS (TLS-no), 14 with non-lesional frontal lobe epilepsy (FLE)
Who carried out the index tests	Not reported
Other general sample characteristics	Age of onset: TLE-MTS 10.8 years, TLE-no 24.6 years, FLE: 27.3 years
Inclusion criteria	Not reported, though all patients were reported to be seizure free for at least 24 hours before the MRI study.
Exclusion criteria	Not reported
Index test(s), including number of repetitions and duration	Participants were studied on a 4T MRI and T1 weighted structural and DTI images acquired. Spatially normalized gray matter (GM) and fractional anisotropy (FA) abnormality maps (binary maps with voxels 1 SD below control mean) were calculated for each subject. At the first level, each group's abnormality maps were compared with those from all the other groups using Graphical-Model-based Morphometric Analysis (GAMMA). GAMMA uses a Bayesian network and a Markov random field based contextual clustering method to produce maps of voxels that provide the maximal distinction between two groups and calculates a probability distribution and a group assignment based on this information. The information was then combined in a second level Bayesian network and the probability of each subject to belong to one of the three epilepsy types calculated.
Gold standard	The identification of the epileptogenic focus was based on seizure semiology and prolonged ictal and interictal Video/EEG/Telemetry (VET) in all patients; the presence/absence of MTS in TLE was based on hippocampal subfield volumetry.

Reference	**Mueller, 2013[136]**
Accuracy results	**Diagnosis of TLE-MTS (differentiating from other groups)** Sensitivity 0.84, specificity 0.87 **Diagnosis of TLE-no (differentiating from other groups)** Sensitivity 0.72, specificity 0.87 **Diagnosis of FLE (differentiating from other groups)** Sensitivity 0.64, specificity 0.86 The two-level multi-modality Bayesian network approach was able to distinguish between the three epilepsy types with a reasonably high accuracy even though the majority of the images were completely normal on visual inspection
Source of funding	NIH grant RO1-NS31966
Limitations	Risk of bias (QUADAS 2 – risk of bias): very serious risk of bias Indirectness (QUADAS 2 - applicability): serious – non epilepsy group were healthy controls

Table 82: Naganur, 2018[137]

Reference	**Naganur, 2018[137]**
Study type	Observational prospective
Recruitment	consecutive
Setting	Clinic for video EEG
Country	Australia
Sample size	11 patients (24 seizures: 13 in PNES group and 11 in Epilepsy group)
Mean/median age	Median age PNES: 20 years, ES: 24 years
Gender	14/24 seizures were in women

Reference	**Naganur, 2018[137]**
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Bilateral tonic-clonic 8/11, focal onset evolving to bilateral tonic-clonic 3/11
Who carried out the index tests	Unclear
Other general sample characteristics	None reported
Inclusion criteria	Patients admitted for VEM for the investigation of possible epilepsy were eligible for inclusion. Patients were eligible for inclusion if they experienced one of their typical clinical events of at least 20 seconds (s) in duration in which there was sustained, rhythmic or arrhythmic movements affecting at least one limb. This included patients with purely tonic or hyper motor movements.
Exclusion criteria	Patients experiencing solely non-convulsive seizures were excluded.
Index test(s), including number of repetitions and duration	A wrist-worn device was used to collect accelerometer data from patients during VEM admission, for diagnostic evaluation of convulsive seizures. An automated process, that involved the use of K-means clustering and support vector machines, was used to detect and classify each seizure as ES or PNES. The device utilized was an Apple iPod Touch (4th generation), with an in-built micro-electromechanical system (MEMS) accelerometer. The MEMS accelerometer utilized had a full scale of ± 2.5 g, sampling at a frequency of 50 Hz, and recording the motion data on three axes (x, y, and z) along with a timestamp. The accelerometer was affixed to the patient's wrist for the duration of VEM.
Gold standard	Video EEG diagnoses
Accuracy results	**Diagnosis of Epilepsy** TP 8, FN 3, FP 0, TN 13; sensitivity 0.727, specificity 1.0
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious

Reference	Naganur, 2018[137]
	Indirectness (QUADAS 2 - applicability): Serious: the non-epilepsy group were only PNES and thus not representative of the non-epilepsy population that would be tested

Table 83: Benge, 2012[26]

Reference	Benge, 2012[26]
Study type	Observational prospective
Recruitment	Case control strategy
Setting	Epilepsy monitoring
Country	USA
Sample size	120 (29 with focal epilepsy and 91 with Psychogenic Non-Epilepsy Events)
Mean/median age	Not reported
Gender	Not reported
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Not reported
Other general sample characteristics	SIMS scores by diagnostic group: seizure/PNEE. Neurological 3.03/6.02; affective 4.79/6.86; psychotic 1.31/1.95; low intelligence 2.38/2.16; memory 2.9/5.43; total 14.41/22.42
Inclusion criteria	Case files from patients at a large Veteran's Affairs hospital's continuous video-EEG long term monitoring (LTM) programme
Exclusion criteria	No SIMS data; missing LTM data; unclear LTM results

Reference	**Benge, 2012[26]**
Index test(s), including number of repetitions and duration	The Structured Interview of Malingered Symptomatology (SIMS) is a self-report instruments asking patients about atypical or implausible symptoms.
Gold standard	Video EEG, typically lasting 4-5 days, along with a detailed history
Accuracy results	**Diagnosis of epilepsy** (note that the paper reports detection of PNEE so because this review reports detection of epilepsy, sensitivity and specificity below are the opposite way round to that reported in the paper) At the 'user-manual' cut-point of 14 as threshold: TP 16, FN 13, FP 22, TN 69; sensitivity 0.55, specificity 0.76 At ROC curve, optimal cut-point of 16 as threshold: sensitivity 0.69, specificity 0.71
Source of funding	Department of Veteran Affairs, Epilepsy Centres of Excellence.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious Indirectness (QUADAS 2 - applicability): Serious (non-ES group were PNES so not typical of the population without ES in the wider community. This may influence specificity values.

Table 84: Dubey, 2017[64]

Reference	**Dubey, 2017[64]**
Study type	Observational prospective
Recruitment	consecutive
Setting	Three mayo Clinic centres
Country	USA
Sample size	387 (44 diagnosed with autoimmune epilepsy, 343 with other epilepsy)
Mean/median age	Antibody positive cases median 53 years ; antibody negative cases 44 years
Gender	Antibody positive cases 47.7% female; antibody negative cases 57.4% female
Learning disability?	Not reported

Reference	Dubey, 2017[64]
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Not reported
Other general sample characteristics	Antibody positive/antibody negative: Median APE score 6/2; new onset seizures 72%/33.1%; neuropsychiatric changes 72.7%/25.7%; viral prodrome 20.5%/2.6%; autonomic dysfunction 18.2%/1.5%; faciobrachial dystonic seizures or facial dyskinesias 29.5%/0.6%
Inclusion criteria	Patients in whom autoimmune encephalopathy, autoimmune epilepsy or autoimmune dementia evaluations of serum, CSF, or both were requested; patients with ICD classification of epilepsy or recurrent seizures
Exclusion criteria	Not reported
Index test(s), including number of repetitions and duration	Antibody prevalence in Epilepsy (APE) score, based on a variety of clinical characteristics; threshold of >=4;
Gold standard	CNS-specific antibodies (neural antibody positive) in presence of confirmed diagnosis based on 2 unprovoked seizures at least 24hrs apart or one unprovoked seizure with additional clinical features suggesting a high probability of recurrence
Accuracy results	**Diagnosis of autoimmune epilepsy** APE score (threshold of >=4): sensitivity 0.977, specificity 0.779
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious Indirectness (QUADAS 2 - applicability): none

Table 85: Gonzalez-Cuevas, 2018[86]

Reference	Gonzalez-Cuevas, 2018[86]
Study type	Observational prospective

Reference	**Gonzalez-Cuevas, 2018[86]**
Recruitment	Consecutive. The paper refers to a 'control' group, but these appeared to have been recruited consecutively with the SE patients – their label as 'controls' did not actually mean that the study used a case-control method.
Setting	Single centre with emergency EEG and PCT availability
Country	Spain
Sample size	29
Mean/median age	SE/control: 69.47/55.8
Gender	14/29 female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Status Epilepticus type: remote symptomatic 5/19, acute symptomatic 5/19, cryptogenic 9/19
Who carried out the index tests	Experienced neuroradiologist (blinded)
Other general sample characteristics	Clinical state during PCT (SE/control): normal 0%/20%, impaired consciousness 36.8%/20%, focal deficit or focal symptoms 42%/60%, ongoing focal motor seizures 21%/0%
Inclusion criteria	>=18 years old; PCT acquired immediately following diagnosis; clinical or EEG diagnosis of status epilepticus (SE) established in ER or hospitalisation
Exclusion criteria	Patients with delayed PCT acquisition; allergy to iodinated contrast material; other contraindications for PCT
Index test(s), including number of repetitions and duration	Perfusion computed tomography (PCT) – using hyperperfusion detection
Gold standard	Diagnosis by ictal EEG and clinical semiology
Accuracy results	**Diagnosis of Status Epilepticus** PCT: sensitivity 0.7895 (95% CI: 0.539 – 0.9303), specificity 0.90 (95% CI: 0.5411 – 0.9948)

Reference	Gonzalez-Cuevas, 2018[86]
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): None.

Table 86: Willert, 2004[216]

Reference	Willert, 2004[216]
Study type	Observational prospective
Recruitment	consecutive
Setting	Unclear, but provided continuous VIDEO EEG
Country	Germany
Sample size	52 (32 with focal epilepsy, 12 with psychogenic non-epileptic seizures, 12 healthy controls)
Mean/median age	Epilepsy/PNES: 33.6/37.8
Gender	25/60 female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	27/32 complex partial seizures, 5/32 generalised tonic-clonic seizures
Who carried out the index tests	Not reported
Other general sample characteristics	Baseline predictor levels: PRL (microg/L): ES male 11.0; ES female 9.4 PRL (microg/L): PNES male 8.8; PNES female 10.5 NSE (microg/L): ES male 6.0; ES female 6.8

Reference	**Willert, 2004[216]**
	NSE (microg/L): PNES male 6.1; ES female 5.1 CK (micromol/.L): ES male 1.29; ES female 0.99 CK (micromol/.L): PNES male 1.12; ES female 0.89
Inclusion criteria	Single seizures with an interval of at least 24 hours before and after the seizure; normal levels of NSE, PRL and CK at baseline
Exclusion criteria	Acute disorders of the CNS or endocrinological diseases; pregnancy; medication other than anticonvulsants
Index test(s), including number of repetitions and duration	Serum neuron-specific enolase (NSE) Serum prolactin (PRL) Serum creatine kinase (CK)
Gold standard	Video-EEG and seizures classified according to ILAE
Accuracy results	**Diagnosis of Epilepsy** The paper did not use the healthy controls in the diagnostic accuracy analysis. It reports sensitivity was for epilepsy, and this was calculated as the proportion of all epilepsy patients with elevated serum levels. It reports specificity as the proportion of all PNES patients with normal serum levels. *The only issue with the results are the definitions of 'abnormal levels' for PRL. PRL normal levels are given between 1.75 and 16.5 microg/L: this implies abnormal levels must be BOTH <1.75 and >16.5. However, it has been assumed that for the purposes of this study the abnormal range was >16.5. This is based on the biologically plausible assumption that increases in the true risk of the outcome should be mapped by changes in the value of a biomarker in one direction only. PRL (threshold = >23microg/L [women], >16.5* microg/L [men]) 10 mins post-ictal: sens 0.88, spec 0.58 20 mins post-ictal: sens 0.88, spec 0.67 30 mins post-ictal: sens 0.84, spec 0.75

Reference	Willert, 2004[216]
	60 mins post-ictal: sens 0.62, spec 0.92 6 hrs post-ictal: sens 0.22, spec 0.83 12 hrs post-ictal: sens 0.19, spec 0.83 24 hrs post-ictal: sens 0.12, spec 0.92 NSE (threshold = >=12microg/L) 10 mins post-ictal: sens 0.06, spec 1.00 20 mins post-ictal: sens 0.06, spec 1.00 30 mins post-ictal: sens 0.06, spec 1.00 60 mins post-ictal: sens 0.03, spec 1.00 6 hrs post-ictal: sens 0.12, spec 1.00 12 hrs post-ictal: sens 0.09, spec 1.00 24 hrs post-ictal: sens 0.00, spec 1.00 CK (threshold = >2.8micromol/s.L [women], >3.25micromol/s.L [men]) 10 mins post-ictal: sens 0.00, spec 1.00 20 mins post-ictal: sens 0.00, spec 1.00 30 mins post-ictal: sens 0.00, spec 1.00 60 mins post-ictal: sens 0.00, spec 1.00 6 hrs post-ictal: sens 0.09, spec 1.00 12 hrs post-ictal: sens 0.16, spec 1.00 24 hrs post-ictal: sens 0.19, spec 1.00

Reference	Willert, 2004[216]
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): Serious: non epilepsy all PNES so not typical of non-epilepsy population

Table 87: Tyson, 2018[199]

Reference	Tyson, 2018[199]
Study type	Observational prospective
Recruitment	consecutive
Setting	Academic medical centre
Country	USA
Sample size	105 (72 with epilepsy and 33 with psychogenic non epileptic seizures)
Mean/median age	Epilepsy/PNES: 35.7/39.5
Gender	Epilepsy/PNES: 54.2% female/54.5% female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Trained master's level psychometrist, predoctoral intern or postdoctoral fellow under the supervision of a licensed psychologist board-certified in clinical neuropsychology
Other general sample characteristics	BDI-II (Epilepsy/PNES): 13.2/16.9
Inclusion criteria	Patients with neuropsychological assessments, and data on psychometric testing

Reference	Tyson, 2018[199]
Exclusion criteria	None reported
Index test(s), including number of repetitions and duration	Multivariate model of psychometric testing, using 4 measures of cognitive ability – vocabulary, information, Boston naming test and letter fluency)
Gold standard	EEG evidence of ES, with neurological exam, seizure semiology and neuroradiological findings. Video EEG used to exclude PNES so likely that video EEG was used for all, although not directly stated.
Accuracy results	**Diagnosis of Epilepsy** [>0.5 cut-off]: sens 0.911, spec 0.450
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): Serious: non epilepsy all PNES so not typical of non-epilepsy population

Table 88: Seneviratne, 2017[177]

Reference	Seneviratne, 2017[177]
Study type	Observational prospective
Recruitment	consecutive
Setting	Epilepsy Monitoring Unit
Country	Australia
Sample size	138 (76 with epilepsy, 62 PNES)
Mean/median age	Mean 43 (16.6) years
Gender	52.2% female
Learning disability?	Not reported

Reference	**Seneviratne, 2017[177]**
Head injury?	Not reported
Type of epilepsy	Focal epilepsy 84.9%, Generalised epilepsy 15.1%
Who carried out the index tests	Two investigators, an epileptologist and an EEG technologist
Other general sample characteristics	Not reported
Inclusion criteria	All patients undergoing monitoring at the EMU of Monash Medical Centre; adults aged >=18; diagnosed with PNES or ES
Exclusion criteria	Events with subjective symptoms or without obvious semiological features; electrographic epileptic seizures without clinical semiology
Index test(s), including number of repetitions and duration	Ictal duration – the epileptologist and the technologist studied each video carefully, in synchrony with the EEG, to measure ictal duration. It was measured from the first observable change to the offset of clinical semiology, based on the consensus of the two raters (no evidence of index test blinding).
Gold standard	Video EEG monitoring, and semiology, clinical information and investigation results – final diagnosis based on the consensus opinion of at least 2 epileptologists. Decision made prior to current study (thus blinded from index test result)
Accuracy results	**Diagnosis of epilepsy (note that >1 seizure recorded per participant)** Ictal duration of >60 seconds TP 154, FN 287, FP 243, TN 98; sens 0.349, spec 0.287 Ictal duration of >120 seconds TP 30, FN 411, FP 177, TN 164; sens 0.068, spec 0.481 Ictal duration of >180 seconds TP 11, FN 430, FP 125, TN 216; sens 0.025, spec 0.633 Ictal duration of >240 seconds TP 6, FN 435, FP 100, TN 241; sens 0.014, spec 0.707

Reference	**Seneviratne, 2017[177]**
	Ictal duration of >300 seconds TP 5, FN 436, FP 73, TN 268; sens 0.011, spec 0.786
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): Serious: non epilepsy all PNES so not typical of non-epilepsy population

Table 89: Reuber, 2009[161]

Reference	**Reuber, 2009[161]**
Study type	Observational prospective
Recruitment	consecutive
Setting	Royal Hallamshire Hospital
Country	UK
Sample size	20 (7 with epilepsy and 13 with PNES)
Mean/median age	Epilepsy/PNES: 46/32
Gender	Epilepsy/PNES: 28.6% female/84.6% female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Interview carried out by neurologist (blinded to video EEG). Interviews analysed independently by two linguists (also blinded to other information, including gold standard information).

Reference	**Reuber, 2009[161]**
Other general sample characteristics	**Epilepsy/PNES** Duration of seizures (years): 17/8 Emergency admissions with seizures 71.4%/84.6% Current AED use: 71.4%/61.5% HADS anxiety score: 6/10 HADS depression score: 3/9 Trauma History Questionnaire total events 3/6
Inclusion criteria	Refractory seizure disorders; referred for Video EEG; uncertainty between epilepsy and PNES; szizure captured by video; ictal EEG allowed unequivocal diagnosis of epilepsy or PNES
Exclusion criteria	Combined epilepsy and PNES; admitted for epilepsy surgery evaluation; non-fluent English; unable to complete self-report measures
Index test(s), including number of repetitions and duration	Linguistic analysis of patient's description of events, with interview conducted by the neurologist. Interviews lasted 25-35 minutes and recorded. Interview followed guidelines from the German EpiLing project. The interviews had a very open beginning which made no mention of seizures, allowing patients to determine the initial focus of the conversation. Open questions were used. Direct questions about features such as ictal injuries, tongue biting, incontinence, seizures from sleep, past medical history or previous treatments were avoided to ensure that the linguist's diagnostic decisions would not be biased by medical information. A diagnostic scoring aid (DSA) was then used to convert qualitative linguistic impressions in 17 areas (each regarded as differential to epilepsy or PNES) to 17 different numeric statements for each patient [1=more in keeping with epilepsy, 0=unable to rate or don't know, -1=more in keeping with PNES].
Gold standard	Video EEG, and other clinical information, made by patients' neurologists
Accuracy results	Unclear if the accuracy data refer to detection of epilepsy or PNES. Rater 1 (threshold 4.5): sensitivity: 0.857, specificity 0.846 Rater 2 (threshold 7.5): sensitivity 0.714, specificity 0.923

Reference	Reuber, 2009[161]
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): Serious: non epilepsy all PNES so not typical of non-epilepsy population

Table 90: Noe, 2012[143]

Reference	Noe, 2012[143]
Study type	Observational prospective
Recruitment	consecutive
Setting	Epilepsy Monitoring Unit in a tertiary epilepsy referral centre
Country	USA
Sample size	439 (75 with epilepsy, 364 with non -epilepsy, including PNES, no epileptic physiological spells, mixed or indeterminate)
Mean/median age	Male: 52.6 years; female 45.3 years
Gender	281/439 women
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Admitting epileptologist (board certified in neurology and clinical neurophysiology with an average of 10 years clinical experience post-epilepsy fellowship training.
Other general sample characteristics	Confirmed diagnosis was: Epilepsy 75/439

Reference	Noe, 2012[143]
	PNES 184/439 Physiologic events other than epilepsy 56/439 Mixed PNES and epilepsy 11 Indeterminate 113 (as no events recorded) Of the 56 physiologic events, 13 were cardiovascular events, 11 migraine, 9 movement disorder, 8 sleep disorder, 5 neurodegenerative disorder and 10 other.
Inclusion criteria	Patients admitted to EMU for spell classification
Exclusion criteria	Subjects with a known diagnosis of epilepsy admitted to EMU for pre-surgical evaluation, medication adjustment, status epilepticus, or seizure quantification.
Index test(s), including number of repetitions and duration	Impression of the admitting epidemiologist, based on review of history, physical and available diagnostic testing as documented in the medical record prior to vEEG.
Gold standard	Final diagnosis determined from the discharge summary after vEEG with >=1 typical spell recorded. In detail: the ictal and interictal EEG record and review of ictal semiology, with further support from the history, examination and other available diagnostic test results including head imaging and neurophysiological testing.
Accuracy results	**Diagnosis of epilepsy** TP 68, FN 7, FP 50, TN 314; sensitivity: 0.906 specificity: 0.863
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): None

Table 91: Li, 2017[125]

Reference	Li, 2017[125]
Study type	Observational retrospective chart review

Reference	**Li, 2017[125]**
Recruitment	consecutive
Setting	Tertiary care medical centre ED
Country	USA
Sample size	54 (27 epilepsy and 27 PNES)
Mean/median age	Not reported
Gender	Not reported
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Not reported
Other general sample characteristics	None
Inclusion criteria	ED discharge diagnosis of 'generalised seizures' or 'generalised shaking episodes'; aged >=18 years; well documented spell onset within 24 hours of a basic metabolic panel drawn in the ED
Exclusion criteria	Other documented active medical problems that could cause acidosis and confound the analysis, such as sepsis, alcohol or medicine toxicity
Index test(s), including number of repetitions and duration	Anion Gap (AG) Denver Seizure Score (DSS)
Gold standard	Abnormal interictal EEG showing epileptiform discharges, plus with a documented semiology of their event consistent with a generalised convulsive seizure. Subjects diagnosed as PNES if video EEG confirmed this.
Accuracy results	**Diagnosis of epilepsy** AG in first 2 hours after event (threshold set at >10): sensitivity 0.818, specificity 1.0

Reference	Li, 2017[125]
	No sensitivity and specificity values given for DSS, but reported as similar to AG.
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): serious risk of bias Indirectness (QUADAS 2 - applicability): Serious: non epilepsy all PNES so not typical of non-epilepsy population

Table 92: Kusmakar, 2018[116]

Reference	Kusmakar, 2018[116]
Study type	Observational prospective
Recruitment	consecutive
Setting	Comprehensive epilepsy unit
Country	Australia
Sample size	79
Mean/median age	31.6 years
Gender	60% female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Poincare descriptors evaluated by 2 certified clinical neurologists (blinded to gold standard)
Other general sample characteristics	Diagnoses: Of the 79 patients, 35 had seizures. Of these 20 had convulsive seizures. Of these 11 had generalised tonic clonic seizures, 6 had PNES, 1 had complex partial seizures, 1 had multiple types of seizures and 1 had comorbid epilepsy.

Reference	**Kusmakar, 2018[116]**
	Events: Overall, in the course of evaluation, 12 patients had GTCS events (39 events) and 7 patients had PNES events (44 events). The diagnostic accuracy data are based on the total number of events and so there may be unit of analysis errors
Inclusion criteria	Patients undergoing VIDEO EEG; history of events that mimicked generalised seizures or events characterised by the presence of bilateral convulsions
Exclusion criteria	Patients having intracranial monitoring or with a psychiatric disorder
Index test(s), including number of repetitions and duration	Temporal variations in limb movement patterns, using wrist-worn accelerometer (ACM) devices. Temporal variations in the ACM traces were extracted using Poincare maps. Two indices – tonic index (TI) and dispersion decay index (DDI) were used to quantify the Poincare-derived temporal variations.
Gold standard	Decided by consensus between 2-6 epileptologists, where a decision was made based on clinical history, neuropsychiatric evaluation, neuroimaging, Video EEG for 3 days and observed seizure semiology (blinded to index test).
Accuracy results	**Diagnosis of epilepsy** (note that paper, in contrast, gives data in terms of detection of PNES) An automated classifier built using TI and DDI of Poincare-derived temporal variations: TP 37, FN 2, FP 2, TN 42; sensitivity 0.9487, specificity 0.9545 Blinded review of the Poincare-derived temporal variations by epileptologists: TP 33, FN 5, FP 11, TN 26; sensitivity 0.8684, specificity 0.7027
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): No serious risk of bias Indirectness (QUADAS 2 - applicability): Serious: non epilepsy all PNES so not typical of non-epilepsy population

Table 93: Khan, 2009[107]

Reference	**Khan, 2009[107]**
Study type	Observational prospective

Reference	**Khan, 2009[107]**
Recruitment	consecutive
Setting	Epilepsy centre VEEG unit
Country	USA
Sample size	50 (3 withdrew, 7 no event, 16 with epilepsy and 24 with non-epileptic events)
Mean/median age	Not reported
Gender	57% female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Hypnosis carried out by a physician trained to do so
Other general sample characteristics	Caucasian 87%; completed some college 68%; unemployed 55%; seizures < 3 x per month 25%; 3-8 seizures per month 32%; multiple daily seizures 28%; No AEDs 17%; 1 AED per day 38%; 2 AEDs per day 30%; >2 AEDs per day 15%
Inclusion criteria	Patients being evaluated for a medically refractory seizure disorder; aged 18 or older; able to undergo hypnosis (able to hear and see)
Exclusion criteria	Pregnancy; learning disability; psychosis; under the influence of illicit substances
Index test(s), including number of repetitions and duration	Patients underwent the Hypnotic Induction Profile to assess susceptibility to hypnosis (and HIP score used as index tests as well). Then patients given hypnosis, with suggestion to have a seizure
Gold standard	Continuous VIDEO EEG. Diagnosis made by attending epileptologist
Accuracy results	**Diagnosis of epilepsy (data below calculated from raw data in figures; the results in the text of paper are unclear and appear to be inaccurate)**

Reference	**Khan, 2009[107]**
	HIP score (threshold of <=9): TP 11, FN 5, FP 14, TN 10; sens: 0.6875, spec 0.416 Not having an event during hypnosis: TP 14, FN 2, FP 13, TN 11; sens: 0.875, spec 0.458
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): None

Table 94: Swartz, 2002[186]

Reference	**Swartz, 2002[186]**
Study type	Observational prospective
Recruitment	consecutive
Setting	PET facility
Country	USA
Sample size	462
Mean/median age	Not reported
Gender	Not reported
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	All MRI and CT scans were read by board-certified neuroradiologists (not blinded)
Other general sample characteristics	Not reported
Inclusion criteria	Patients referred to PET facility

Reference	Swartz, 2002[186]
Exclusion criteria	No seizures within 72 hours
Index test(s), including number of repetitions and duration	Positron Emission Tomography with 2-deoxy-2[^{18}F] fluro-D-glucose (FDG-PET)
Gold standard	Ictal video EEG and all other available clinical information, including imaging; adjudicated by 3 epileptologists on consensus
Accuracy results	**Diagnosis of epilepsy sub-types by FDG-PET** Temporal lobe epilepsy: sensitivity 0.70, specificity 0.56 (n=183) Frontal lobe epilepsy: sensitivity 0.57, specificity 0.45 (n=70) Parietal-Occipital lobe epilepsy: sensitivity 0.59, specificity 0.60 (n=24)
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious Indirectness (QUADAS 2 - applicability): None

Table 95: Oliva, 2008[145]

Reference	Oliva, 2008[145]
Study type	Observational prospective
Recruitment	consecutive
Setting	Secondary care with video EEG facilities
Country	Australia
Sample size	84 (66 with epilepsy and 18 with PNES)
Mean/median age	Epilepsy/PNES: 37.4/40.4 years
Gender	42/84 female

Reference	**Oliva, 2008[145]**
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Primary generalised, focal temporal lobe, focal extratemporal lobe
Who carried out the index tests	Medical scientists
Other general sample characteristics	Seizure frequency score: epilepsy 7, PNES 8; Idiopathic 20/66, Symptomatic 24/66, Cryptogenic 56/66, MRI abnormal 29/63
Inclusion criteria	Patients admitted to Royal Melbourne Hospital for inpatient video monitoring, in whom at least 1 convulsive event was captured
Exclusion criteria	None reported
Index test(s), including number of repetitions and duration	Existence of oral lacerations and incontinence. Information collected by medical scientists via direct questioning and examination of the patient after a convulsive event.
Gold standard	Based on consensus of epileptologists based on VEM, all available clinical and investigational data. Blinded to the index test data
Accuracy results	**Diagnosis of epilepsy** Existence of oral lacerations: TP 17, FN 49, FP 0, TN 18; sensitivity 0.26(0.16-0.38), specificity 1.0(0.78-1.0) Existence of incontinence: TP 15, 51, FP 1, TN 17; sensitivity 0.227, specificity 0.940 Existence of oral lacerations AND incontinence: sensitivity 0.08(0.03-0.18), specificity 1.0(0.78-1.0)
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): none

Table 96: Ettinger, 1999[74]

Reference	**Ettinger, 1999[74]**
Study type	Observational retrospective
Recruitment	Case control strategy
Setting	Epilepsy Management Program site
Country	USA
Sample size	39 (16 epilepsy, 23 non-epileptic psychogenic seizures [NES])
Mean/median age	Epilepsy mean age 39, NES mean age 43 (range 18-59 overall)
Gender	30/39 female
Learning disability?	None
Head injury?	Not reported
Type of epilepsy	Focal with secondary generalisation, generalised tonic clonic
Who carried out the index tests	Not reported
Other general sample characteristics	Not reported
Inclusion criteria	Adult patients evaluated at the Epilepsy Management site between 1996-98; epilepsy patients were 1) focal with secondary generalisation, or 2) generalised tonic clonic; documented epilepsy on video-EEG for epilepsy group, and patients with episodes characterised by bilateral motor activity and altered responsiveness, but without video-EEG evidence of seizures or without significant post-ictal prolactin elevation
Exclusion criteria	Learning disability; mixed epileptic/NES; patients with interictal headaches
Index test(s), including number of repetitions and duration	Symptom questionnaire. The responses to the question, ‘what symptoms do you have after a seizure?’ were reviewed.
Gold standard	Documented epilepsy on video-EEG for epilepsy group, and patients with episodes characterised by bilateral motor activity and altered responsiveness, but without video-EEG evidence of seizures or without significant post-ictal prolactin elevation

Reference	Ettinger, 1999[74]
Accuracy results	**Diagnosis of epilepsy** No diagnostic accuracy analysis was performed by the article, but presented data were sufficient to allow the following accuracy data to be produced from 'extra-articular' analysis. For each of the following post-ictal symptoms, the accuracy of the symptom to predict epilepsy is given: Headache: TP 6, FN 10, FP 1, TN 22; sensitivity 0.375, specificity 0.957 Fatigue or lethargy: TP 9, FN 7, FP 3, TN 20; sensitivity 0.563, specificity 0.869 Confusion alone: TP 2, FN 14, FP 3, TN 22; sensitivity 0.125, specificity 0.957 No symptoms: TP 0, FN 16, FP 12, TN 13; sensitivity 0.0, specificity 0.520
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious risk of bias Indirectness (QUADAS 2 - applicability): serious – non epilepsy group were PNES and so not necessarily representative of the non-epilepsy population

Table 97: Reuber, 2016[160]

Reference	Reuber, 2016[160]
Study type	Observational retrospective
Recruitment	Case control strategy
Setting	Department of clinical neurophysiology at Hospital in Sheffield, and Neurology and Neurosurgery hospital
Country	UK
Sample size	300 (100 epilepsy, 100 PNES, 100 syncope)
Mean/median age	Epilepsy/PNES/syncope: 35.4/41.6/53.5 years
Gender	219/300

Reference	**Reuber, 2016[160]**
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Not described
Other general sample characteristics	Epilepsy/PNES/syncope: age at onset 12.2/26.4/39.4 years; hospitalisation at least once 68%/77%/18%; intensive care 16%/16%/1%; family history 28%/29%/24%
Inclusion criteria	Patients with epilepsy or PNES supported by video EEG recordings of typical seizures involving TLOC identified from patient databases; patients with a diagnosis of recurrent syncope supported by pathophysiological evidence
Exclusion criteria	None reported
Index test(s), including number of repetitions and duration	Paroxysmal Event Profile Questionnaire – 86 items focussing on TLOC manifestations, plus 7 further questions related to demographic and clinical features.
Gold standard	Video EEG evidence of diagnosis
Accuracy results	**Diagnosis of epilepsy** The article carried out a binary logistic regression to calculate accuracy for differentiating PNES and epilepsy and for differentiating syncope and epilepsy. Because the focus of this review is on diagnosing epilepsy, the sensitivities and specificities for the two comparisons have been transposed, to effectively yield the accuracy for distinguishing epilepsy from non-epilepsy in each case. <u>Epilepsy (with PNES as the non-epilepsy group)</u> Factor scores: sensitivity 0.72, specificity 0.78 Patient information: sensitivity 0.46, specificity 0.74 Combined: sensitivity 0.74, specificity 0.80 <u>Epilepsy (with syncope as the non-epilepsy group)</u>

Reference	Reuber, 2016[160]
	Factor scores: sensitivity 0.83, specificity 0.87 Patient information: sensitivity 0.68, specificity 0.88 Combined: sensitivity 0.91, specificity 0.92
Source of funding	Sheffield Hospitals Charitable Trust
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious risk of bias Indirectness (QUADAS 2 - applicability): serious – non epilepsy group were PNES or syncope and so not necessarily representative of the non-epilepsy population

Table 98: Rawlings, 2017 [158]

Reference	Rawlings, 2017 [158]
Study type	Observational retrospective
Recruitment	Case control strategy
Setting	Clinical Neurophysiology Department, National Hospital for Neurology and Neurosurgery
Country	UK
Sample size	293 (epilepsy 95, PNES 98, syncope 100)
Mean/median age	Epilepsy/PNES/syncope: 31/43/57.5
Gender	214/293 female
Learning disability?	None - excluded
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Unclear

Reference	**Rawlings, 2017** [158]
Other general sample characteristics	Epilepsy/PNES/syncope: age at TLOC onset 9/25/36.5; number of hospitalisations 1/2/0
Inclusion criteria	Patients with epilepsy or PNES supported by video EEG recordings of typical seizures involving TLOC identified from patient databases; patients with a diagnosis of recurrent syncope supported by pathophysiological evidence
Exclusion criteria	Patients unable to complete the questionnaire without help (learning disability)
Index test(s), including number of repetitions and duration	Panic measures. This was captured by the Paroxysmal Event Profile – this consists of 86 Likert style questions about symptoms, 7 of which were focussed on panic symptoms. This article focusses on the results of these 7 questions relating to panic. The following questions about panic during TLOC were included: (1) During my attacks I feel very frightened; (2) During my attacks I feel that something terrible might happen; (3) During my attacks I am frightened that I am going to die; (4) During my attacks I am frightened that I will lose control; (5) During my attacks I am frightened that I will go crazy; (6) During my attacks my heart pounds and I feel shaky and sweaty; and (7) During my attacks I feel that I have to get out of the situation.
Gold standard	Video EEG evidence of diagnosis
Accuracy results	**Diagnosis of epilepsy** Sensitivity and specificity data were provided for detection of PNES from non-PNES (epilepsy and syncope). However, it was not possible to use this to estimate the accuracy of detection of epilepsy from non-epilepsy (by transposing sensitivity and specificity) as the non-epilepsy group comprised both PNES and syncope. For detection of epilepsy, the article only states the area under the curve of 0.44, but unfortunately does not give the sensitivity and specificity data.
Source of funding	Sheffield Hospitals Charitable Trust
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious risk of bias Indirectness (QUADAS 2 - applicability): serious – non epilepsy group were PNES or syncope and so not necessarily representative of the non-epilepsy population

Table 99: Slater, 1995[181]

Reference	**Slater, 1995[181]**
Study type	Observational prospective
Recruitment	consecutive
Setting	EEG video telemetry unit
Country	USA
Sample size	101 recruited – 49 included in analysis as had events allowing firm diagnosis with GS (27 epilepsy, 22 pseudoseizures) and had the index test
Mean/median age	Unclear for those analysed
Gender	Unclear
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Not reported
Other general sample characteristics	Not specified for those in the analysis
Inclusion criteria	Age >=18; patients admitted to EEG video telemetry unit;
Exclusion criteria	Not reported
Index test(s), including number of repetitions and duration	Wilkus classification guideline: A patients has pseudo seizures if **any of the following** are true: a) hysteria or hypochondriasis score >=70 and one of the two highest points in the profile (disregarding the masculinity-femininity and social introversion scales, b) hysteria or hypochondriasis score >=80 and not necessarily among the two highest points, c) hysteria and hypochondriasis both >59 and both 10 points higher than the depression scale. In a sample where ONLY epilepsy and PNES patients are known to exist then this test could be used to show that epilepsy exists is NONE of these conditions exists.
Gold standard	Video EEG

Reference	**Slater, 1995[181]**
Accuracy results	**Diagnosis of epilepsy** None of the Wilkus conditions satisfied: TP 20, FN 7, FP 9, TN 13; Sensitivity 0.74, specificity 0.59
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious risk of bias Indirectness (QUADAS 2 - applicability): Serious: the non-epilepsy group is only PNES in this study and thus not representative of the non-epilepsy group in the population. This may have large effects on the specificity values derived.

Table 100: Arnold, 1996[10]

Reference	**Arnold, 1996[10]**
Study type	Observational prospective
Recruitment	consecutive
Setting	Video EEG unit
Country	USA
Sample size	45 (27 with epilepsy, 14 with PNES); 4 excluded as no seizure during stay in unit
Mean/median age	PNES 33 years, epilepsy 35 years
Gender	PNES 64% female, epilepsy 48% female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Tonic clonic; intractable
Who carried out the index tests	Trained psychiatrist blinded to GS

Reference	**Arnold, 1996[10]**
Other general sample characteristics	Mean number of epileptic seizures during monitoring: 7.5 (epilepsy), 5.7 (PNES); White ethnicity: 89% (epilepsy), 100% (PNES)
Inclusion criteria	Patients admitted to the inpatient 24-hour video/EEG monitoring unit for people with intractable seizures; aged >18
Exclusion criteria	Not reported
Index test(s), including number of repetitions and duration	Interviews to ascertain the following test data: Lifetime Axis I Current Axis I Current Axis II Trauma history
Gold standard	Video EEG monitoring
Accuracy results	**Diagnosis of epilepsy** Lifetime axis I diagnoses: TP 14, FN 13, FP 10, TN 4; sensitivity 0.51, specificity 0.29 current axis I diagnoses: TP 8, FN 19, FP 6, TN 8; sensitivity 0.30, specificity 0.57 current axis II diagnoses: TP 5, FN 22, FP 5, TN 9; sensitivity 0.18, specificity 0.64 Any trauma: TP 9, FN 18, FP 12, TN 2; sensitivity 0.33, specificity 0.14 (note that this makes trauma a fairly sensitive test for PNES).
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): Serious – no epilepsy group were PNES so not necessarily representative of the general population who would be seeking diagnosis

Table 101: Geyer, 2000[82]

Reference	**Geyer, 2000[82]**
Study type	Observational prospective
Recruitment	Unclear but likely case-control
Setting	Unclear
Country	USA
Sample size	261 (50 with right TLE, 50 with left TLE, 50 with FLE, 11 with generalised epilepsy, 100 with PNES)
Mean/median age	33.75
Gender	104/261 female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	50 with right TLE, 50 with left TLE, 50 with FLE, 11 with generalised epilepsy
Who carried out the index tests	Two study investigators (Neurologists), blinded to GS
Other general sample characteristics	129/161 refractory epilepsy
Inclusion criteria	Patients with TLE, FLE, generalised epilepsy or PNES undergoing video EEG
Exclusion criteria	
Index test(s), including number of repetitions and duration	Existence of pelvic thrusting during seizures. Observed from the videos taken during routine monitoring.
Gold standard	Video EEG
Accuracy results	**Diagnosis of ANY epilepsy (vs non epilepsy [PNES])** TP 18, FN 143, FP 17, TN 83; sensitivity 0.112, specificity 0.83

Reference	**Geyer, 2000[82]**
	Diagnosis of Right TLE (vs all non-right TLE, including PNES) TP 4, FN 46, FP 31, TN 180; sensitivity 0.08, specificity 0.853 **Diagnosis of left TLE (vs all non-left TLE, including PNES)** TP 2, FN 48, FP 33, TN 178; sensitivity 0.04, specificity 0.844 **Diagnosis of FLE (vs all non-FLE, including PNES)** TP 12, FN 38, FP 23, TN 188; sensitivity 0.24, specificity 0.891 **Diagnosis of Generalised Epilepsy (vs all non-generalised epilepsy, including PNES)** TP 0, FN 11, FP 35, TN 176; sensitivity 0.24, specificity 0.834
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious risk of bias Indirectness (QUADAS 2 - applicability): Serious – no epilepsy group were PNES so not necessarily representative of the general population who would be seeking diagnosis

Table 102: Wilkus, 1984[215]

Reference	**Wilkus, 1984[215]**
Study type	Observational prospective
Recruitment	consecutive
Setting	Regional Epilepsy Centre
Country	USA
Sample size	20 in validation group: 10 with epilepsy and 10 with no epilepsy (which were all pseudo epilepsy)

Reference	**Wilkus, 1984[215]**
Mean/median age	Epilepsy mean age 28.2 years;
Gender	female
Learning disability?	No
Head injury?	20% of epilepsy patients; 28% of non-epilepsy patients
Type of epilepsy	Not reported
Who carried out the index tests	Highly trained psychometrists, blinded to the gold standard data
Other general sample characteristics	Epilepsy/non-epilepsy: WAIS verbal IQ 102.48/99.12; WAIS performance IQ 98.04/95.32; WAIS full-scale IQ 100.6/97.32; neuropsychological battery - % of score outside normal limits: 45.96/51.16
Inclusion criteria	Patients referred for inpatient EEG/CCTV monitoring
Exclusion criteria	Not reported
Index test(s), including number of repetitions and duration	MMPI classification: Pseudo-epileptic attacks if 1) hysteria or hypochondriasis is >=70 and one of the two highest points disregarding the masculinity-femininity and social introversion scales, 2) hysteria or hypochondriasis is 80 or higher, even if not among the two highest points, 3)hysteria or hypochondriasis are both higher than 59 and both are at least 10 points higher than depression. Thus, NOT having the criteria for these was taken as a handy way to classify as epilepsy.
Gold standard	Long term Video EEG
Accuracy results	**Diagnosis of epilepsy** TP 8, FN 2, FP 1, TN 9; sensitivity 0.8, specificity 0.9
Source of funding	NIH grants (non-commercial)
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): Serious – no epilepsy group were PNES so not necessarily representative of the general population who would be seeking diagnosis

Table 103: Dixit, 2013[60]

Reference	**Dixit, 2013[60]**
Study type	Prospective
Recruitment	Case control strategy
Setting	Epilepsy Monitoring Unit
Country	USA
Sample size	280
Mean/median age	Not stated
Gender	46.7% female in epilepsy; 74.7% female in PNES
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Not stated
Other general sample characteristics	Trauma/abuse: 15.6% in epilepsy/63.9% in PNES
Inclusion criteria	People evaluated in EMU with video EEG
Exclusion criteria	Unclear diagnosis on vEEG; dual diagnosis of epilepsy/PNES; learning disability; first language not English
Index test(s), including number of repetitions and duration	Existence of >1 co-morbidities from medical records
Gold standard	Video-EEG
Accuracy results	**Diagnosis of epilepsy** >1 comorbidity: TP 33, FN 89, FP 104, TN 54; sensitivity 0.270, specificity 0.342

Reference	Dixit, 2013[60]
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious risk of bias Indirectness (QUADAS 2 - applicability): Serious – no epilepsy group were PNES so not necessarily representative of the general population who would be seeking diagnosis

Table 104: Ettinger, 1998[75]

Reference	Ettinger, 1998[75]
Study type	Observational prospective
Recruitment	consecutive
Setting	Epilepsy Monitoring Unit
Country	USA
Sample size	22 (11 epilepsy, 11 with PNES)
Mean/median age	Range 10-46
Gender	17/22 female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Partial Complex (n=10), Partial with secondary generalisation (n=1)
Who carried out the index tests	Images read by 2 nuclear medicine specialists (blinded)
Other general sample characteristics	None
Inclusion criteria	Patients undergoing continuous video EEG monitoring on EMU; diagnostic testing carried out; episodes associated with impaired consciousness

Reference	**Ettinger, 1998[75]**
Exclusion criteria	No altered awareness; pregnancy; use of neuroleptic agents; unobtainable PRL results; SPECT scans compromised by movement artefact; unacquired SPECT because of failure to inject radioisotope at correct time
Index test(s), including number of repetitions and duration	Postictal and interictal single photon emission computed tomography (SPECT).
Gold standard	Video EEG, blinded to index test
Accuracy results	**Diagnosis of epilepsy** Post-ictal abnormal SPECT: TP 7, FN 4, FP 3, TP 8; sensitivity 0.63, specificity 0.72 Interictal abnormal SPECT: TP 4, FN 7, FP 3, TP 8; sensitivity 0.364, specificity 0.72
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): No serious risk of bias Indirectness (QUADAS 2 - applicability): Serious – no epilepsy group were PNES so not necessarily representative of the general population who would be seeking diagnosis

Table 105: Hendrickson, 2014[92]

Reference	**Hendrickson, 2014[92]**
Study type	Case control strategy
Recruitment	consecutive
Setting	Epilepsy Monitoring Unit
Country	USA
Sample size	354 (epilepsy 130, PNES 224)
Mean/median age	Unclear
Gender	46.9% female in epilepsy group, 74.6% female

Reference	Hendrickson, 2014[92]
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Unclear
Who carried out the index tests	Not reported
Other general sample characteristics	Epilepsy/PNES: average education 12.9 years/12.4 years; age at spell onset 25.7 years/30.6 years
Inclusion criteria	Patients undergoing vEEG monitoring; participated in either neuropsychological or psychological testing; interviewed for panic attack criteria
Exclusion criteria	Unclear diagnosis; episodes secondary to another primary disorder; diagnosis of both PNES and epilepsy
Index test(s), including number of repetitions and duration	Number of panic attack symptoms
Gold standard	vEEG
Accuracy results	**Diagnosis of epilepsy (Note study looked at cut of score of 5 or more but this was geared to detection of PNES; hence the mutually exclusive values have been taken as the threshold for epilepsy)** Cut-off score of <5: TP 85, FN 45, FP 67 TN 157; sensitivity 0.654, specificity 0.701
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious risk of bias Indirectness (QUADAS 2 - applicability): Serious – no epilepsy group were PNES so not necessarily representative of the general population who would be seeking diagnosis

Table 106: Varma, 1996[203]

Reference	Varma, 1996[203]
Study type	Observational prospective

Reference	**Varma, 1996[203]**
Recruitment	Case control strategy
Setting	Neuropsychiatry unit, National Hospital for Neurology and Neurosurgery
Country	UK
Sample size	20 (10 with epilepsy and 10 with PNES).
Mean/median age	Epilepsy: 35.1 years, PNES: 35.5 years
Gender	50% female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Generalised (3), left centro-temporal (1), left temporal (3), right temporal (1), bilateral temporal (1), right fronto-temporal (1)
Who carried out the index tests	SPECT scans analysed visually by an experienced nuclear medicine physician, blinded to GS
Other general sample characteristics	10 with epilepsy were age and sex-matched to 10 with PNES
Inclusion criteria	Patients referred to neurosurgery unit and diagnoses with NES or epilepsy; diagnosis based on video EEG findings
Exclusion criteria	People with dual epilepsy/PNES; brain lesions on CT/MRI
Index test(s), including number of repetitions and duration	Hexamethyl propylene amine oxime single photon emission tomography (HMPAO SPECT) brain imaging. Interictal.
Gold standard	Video EEG
Accuracy results	**Diagnosis of epilepsy** Abnormal SPECT (marked or significant hypoperfusion, not including equivocal hypoperfusion): TP 8, FN 2, FP 2, TN 8; sens: 0.8, spec 0.8

Reference	Varma, 1996[203]
	Abnormal SPECT (any hypoperfusion, including equivocal hypoperfusion): TP 10, FN 0, FP 3, TN 7; sens 1.0, spec 0.7
Source of funding	Sir Jules Thorn Trust (non-commercial)
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious risk of bias Indirectness (QUADAS 2 - applicability): Serious – no epilepsy group were PNES so not necessarily representative of the general population who would be seeking diagnosis

Table 107: Syed, 2011[191]

Reference	Syed, 2011[191]
Study type	Observational prospective
Recruitment	consecutive
Setting	Epilepsy Monitoring Unit
Country	USA
Sample size	35 (23 with ES and 12 with PNES)
Mean/median age	Epilepsy 36 years, PNES 39 years
Gender	Epilepsy 48%, PNES 83%
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Epileptologist or lay-person

Reference	**Syed, 2011[191]**
Other general sample characteristics	Not reported
Inclusion criteria	Seizure patients scheduled for vEEG; VEEG recorded epilepsy or PNES during stay
Exclusion criteria	Not reported
Index test(s), including number of repetitions and duration	• Epileptologist blinded and independent review of seizure videos in terms of the following semiological signs: 1) eye-opening or widening at onset of seizure, 2) abrupt onset, 3) post-ictal confusion/sleep • Eye-witness accounts of seizure in terms of the following semiological signs: 1) eye-opening or widening at onset of seizure, 2) abrupt onset, 3) post-ictal confusion/sleep
Gold standard	Video EEG
Accuracy results	**Diagnosis of epilepsy (subject-level analyses)** *Note that validation cohort used (16 ES and 20 PNES) for video evidence for the following 3 'best' predictors:* Epileptologist video - eye-opening or widening at onset of seizure: sens 1.0, spec 0.84 Epileptologist video - abrupt onset: sens 0.94, spec 0.55 Epileptologist video - post-ictal confusion/sleep: sens 0.81, spec 0.70 *For the following, the original cohort (23 ES and 12 PNES) were used:* Epileptologist video – eyes fixed sens 0.57, spec 0.92 Epileptologist video – unilateral head turning: sens 0.32, spec 1.0 Epileptologist video – nonsensical speech: sens 0.0, spec 0.91 Epileptologist video – clenched mouth: sens 0.09, spec 0.26 Epileptologist video – hand automatisms: sens 0.26, spec 1.0 Epileptologist video – ictal scream: sens 0.22, spec 1.0 Epileptologist video - grasping: sens 0.09, spec 1.0 Epileptologist video – postictal nosewiping: sens 0.23, spec 1.0

Reference	Syed, 2011[191]
	Epileptologist video – postictal aphasia: sens 0.09, spec 1.0 Epileptologist video – postictal snoring: sens 0.35, spec 1.0 Epileptologist video - abrupt offset: sens 0.75, spec 0.70 Epileptologist video – continuous movement: sens 0.57, spec 0.67 Epileptologist video – eyes rolled to back of head: sens 0.52, spec 0.67 Epileptologist video – postictal exhaustion: sens 0.52, spec 0.42 Epileptologist video – postictal heavy breathing: sens 0.44, spec 0.50 Epileptologist video – looking around: sens 0.48, spec 0.25 Epileptologist video – epileptic aura: sens 0.50, spec 0.17 *Note that original cohort used (23 ES and 12 PNES) for eye-witness evidence.* Eye-witness - eye-opening or widening at onset of seizure: sens 0.83, spec 0.25 Eye-witness - abrupt onset: sens 0.48, spec 0.25 Eye-witness - post-ictal confusion/sleep: sens 0.78, spec 0.00
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): Serious – no epilepsy group were PNES so not necessarily representative of the general population who would be seeking diagnosis

Table 108: Asadi-Pooya, 2016[11]

Reference	Asadi-Pooya, 2016[11]
Study type	Observational retrospective

Reference	**Asadi-Pooya, 2016[11]**
Recruitment	Case-control strategy
Setting	Epilepsy Centre
Country	USA
Sample size	60 (30 with epilepsy and 30 with PNES)
Mean/median age	28.6 years
Gender	70% female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Physician or healthcare provider
Other general sample characteristics	Mean scores of ROS questionnaire (see index tests section) in PNES/epilepsy groups for each system: Skin 0.07/0.10; HENT 0.63/0.50; MSK 0.2/0.03; pulmonary 0.17/0.10; cardiovascular 0.07/0.13; GI 0.33/0.20; genitourinary 0.07/0.00; hematologic 0.03/0.03; psychiatry 0.7/0.27; cognition and memory 0.13/0.28. mean of overall ROS scores: PNES 2.43, epilepsy 1.50.
Inclusion criteria	Patients admitted to the Epilepsy Centre with a video-EEG confirmed diagnosis of epilepsy or PNES
Exclusion criteria	Patients with concomitant PNES and epilepsy
Index test(s), including number of repetitions and duration	Review of systems (ROS) questionnaire, which was in the medical records. This covered the following 10 systems, where each was graded as normal or abnormal: skin; head & ear, nose and throat (HENT); musculoskeletal; pulmonary; cardiovascular; gastrointestinal; genitourinary; hematologic; psychiatry; cognition and memory. The questionnaire was completed by the HCP according to the patient's history. Scores were generated by any abnormality yielding a score of 1. Thus, abnormalities in all 10 systems would yield the worst possible score of 10, and abnormalities in none of the systems would yield the best possible score of 0.
Gold standard	Video EEG

Reference	Asadi-Pooya, 2016[11]
Accuracy results	**Diagnosis of epilepsy** At a cut-off of <2.5 (for detection of PNES the cut-off was >=2.5). Sensitivity 0.90, specificity 0.40 (in paper the results for diagnosis of PNES are sensitivity=0.4 and specificity=0.9.)
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious risk of bias Indirectness (QUADAS 2 - applicability): Serious – no epilepsy group were PNES so not necessarily representative of the general population who would be seeking diagnosis

Table 109: Sen, 2007[176]

Reference	Sen, 2007[176]
Study type	Observational retrospective
Recruitment	Unclear but likely to be a case-control strategy
Setting	In-patient assessment centre, tertiary referral centre
Country	UK
Sample size	36 (19 with epilepsy and 17 with PNES); a further 8 had mixed epilepsy and PNES and results are not included here.
Mean/median age	Not reported but likely to be adults
Gender	Not reported
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported

Reference	Sen, 2007[176]
Who carried out the index tests	Consultant epileptologist
Other general sample characteristics	75 convulsions reported by the 45 patients over the 18-month period.
Inclusion criteria	Patients with epilepsy or PNES attending the tertiary centre
Exclusion criteria	Not reported
Index test(s), including number of repetitions and duration	Existence of stertorous post-ictal breathing (noted on video by epileptologist)
Gold standard	Final diagnoses were based on integration of all available data collected over an 18-month period
Accuracy results	**Diagnosis of epilepsy (these data are based on convulsions rather than participants)** TP 25, FN 1, FP 0, TN 34; sensitivity 0.96, specificity 1.0
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Very serious risk of bias Indirectness (QUADAS 2 - applicability): Serious – no epilepsy group were PNES so not necessarily representative of the general population who would be seeking diagnosis

Table 110: Deli, 2021[56]

Reference	Deli, 2021[56]
Study type	Observational retrospective
Recruitment	Consecutive
Setting	Emergency department
Country	UK
Sample size	69 (30 epilepsy, 39 PNES); 8 with mixed epilepsy/PNES who have not been included in these results

Reference	**Deli, 2021[56]**
Mean/median age	Epilepsy: not given; PNES: 36.2
Gender	Epilepsy: not given; PNES:P 59% female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Not clear
Other general sample characteristics	PNES: 59% known to psychiatric services Duration of vEEG: Epilepsy 2.3 minutes; PNES 4.28 minutes Episodes > 2 minutes: 14.8% epilepsy, 61.5% PNES
Inclusion criteria	People with epilepsy or PNES admitted for V-EEG.
Exclusion criteria	None reported
Index test(s), including number of repetitions and duration	Reports of physical symptoms: • Light headedness/dizziness • Sensory disturbances/dysesthesias • Hot flushes • Palpitations
Gold standard	Video EEG
Accuracy results	**Diagnosis of epilepsy** Light headedness: TP 3, FN 27, FP, 31, TN 8; sensitivity 0.10, specificity 0.21 Sensory disturbances/dysesthesias: TP 5, FN 25, FP, 24, TN 15; sensitivity 0.16, specificity 0.38 Hot flushes: TP 0, FN 30, FP, 10, TN 29; sensitivity 0.00, specificity 0.74

Reference	Deli, 2021[56]
	Palpitations: TP 1, FN 29, FP, 8, TN 31; sensitivity 0.03, specificity 0.79
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): Serious – no epilepsy group were PNES so not necessarily representative of the general population who would be seeking diagnosis

Table 111: McGinty, 2021[132]

Reference	McGinty, 2021[132]
Study type	Observational prospective
Recruitment	consecutive
Setting	Two epileptologist practices in an NHS Foundation Trust
Country	UK
Sample size	219 (23 with new onset focal epilepsy that was autoimmune, 196 with new onset focal epilepsy that was not autoimmune)
Mean/median age	49 years
Gender	49.8% female
Learning disability?	Not reported
Head injury?	Not reported
Type of epilepsy	Not reported
Who carried out the index tests	Not reported
Other general sample characteristics	Not reported

Reference	McGinty, 2021[132]
Inclusion criteria	Consecutive adult patients with a diagnosis of new-onset focal epilepsy and their first seizure within the previous 12 months
Exclusion criteria	Not reported
Index test(s), including number of repetitions and duration	ACE attention domain APE2 score
Gold standard	Detection of Neuronal surface-directed antibodies (NSAb)
Accuracy results	**Diagnosis of autoimmune epilepsy** Addenbrooke's cognitive examination (ACE) attention domain (threshold >=0): sensitivity 0.667, specificity 0.849 APE2 score (threshold unclear): sensitivity 0.435, specificity 0.791
Source of funding	None reported.
Limitations	Risk of bias (QUADAS 2 – risk of bias): Serious risk of bias Indirectness (QUADAS 2 - applicability): None

D.1.1 Effectiveness evidence Diagnostic Strategies

Study	ROSSETTI, 2020 trial: Rossetti 2020[165]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=364)
Countries and setting	Conducted in Switzerland; Setting: Multicentre: 4 university teaching hospitals; inpatient
Line of therapy	1st line

Study	ROSSETTI, 2020 trial: Rossetti 2020[165]
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Inpatients >18 years in intensive or intermediate care units having impaired consciousness of any aetiology, defined as GCS of 11 or less or a FOUR score of 12 or less; referred from the treating team for EEG
Exclusion criteria	Weekend patients; patients in palliative care; those risking invasive procedures within 48 hours; those with recent (<36 hours) seizures or SE (96 hours)
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 63.75 years. Gender (M:F): 65.6:33.4. Ethnicity: Not reported
Further population details	
Extra comments	Reason for admission: brain injury 218/368, medical 104/368, surgical 40/368, other 9/368; previous seizures 34/368; GCS before EEG 3 (3-11); patient location during EEG intervention: ICU 346/368, intermediate care unit 17/368, general ward 5/368; final diagnosis: hypoxic-ischaemic encephalopathy 113/368, brain trauma 49/368, intracranial haemorrhage 87/368, toxic-metabolic, not primarily involving brain 23/368, other 68/368
Indirectness of population	No indirectness

Study	ROSSETTI, 2020 trial: Rossetti 2020[165]
Interventions	(n=201) Intervention 1: Diagnostic strategy - Strategy A. Continuous EEG, using 21-23 electrodes following the international 10 to 20 system. Duration 30-48 hours. Concurrent medication/care: video EEG. All EEG interpreters were certified for the American Clinical Neurophysiology Society Standardized Critical Care EEG. Indirectness: No indirectness. (n=201) Intervention 2: Diagnostic strategy - Strategy B. Routine EEG, using 21-23 electrodes following the international 10 to 20 system. Duration 2 x 20–30-minute recordings over 48 hours. Concurrent medication/care: Recorded with video EEG. All EEG interpreters were certified for the American Clinical Neurophysiology Society Standardized Critical Care EEG. Indirectness: No indirectness
Funding	Academic or government funding (Swiss National Science Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STRATEGY A versus STRATEGY B
Protocol outcome 1: Mortality at Define
- Actual outcome: Mortality at 6 months; Group 1: 89/182, Group 2: 88/182
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age, gender, location before hospitalisation. Small differences in terms of reason for admission (more medical reasons for rEEG, more brain injury and surgery reasons for cEEG); Group 1 Number missing: 19, Reason: 3 lost to FU, 10 excluded due to proxy or post-hoc consent refusals, 6 excluded due to double inclusions; Group 2 Number missing: 19, Reason: 1 lost to FU, 17 excluded due to proxy or post-hoc consent refusals, 1 excluded due to death before EEG start

Protocol outcome 2: seizures at Define
- Actual outcome: Seizures detected at 6 months; Group 1: 29/185, Group 2: 8/183
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age, gender, location before hospitalisation. Small differences in terms of reason for admission (more medical reasons for rEEG, more brain injury and surgery reasons for cEEG); Group 1 Number missing: 16, Reason: 10 excluded due to proxy or post-hoc consent refusals, 6 excluded due to double inclusions; Group 2 Number missing: 18, Reason: 17 excluded due to proxy or post-hoc consent refusals, 1 excluded due to death before EEG start

Study	ROSSETTI, 2020 trial: Rossetti 2020[165]
Protocol outcome 3: Adverse events at Define - Actual outcome: In-hospital infection requiring antibiotics at 6 months; Group 1: 47/185, Group 2: 56/183 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age, gender, location before hospitalisation. Small differences in terms of reason for admission (more medical reasons for rEEG, more brain injury and surgery reasons for cEEG); Group 1 Number missing: 16, Reason: 10 excluded due to proxy or post-hoc consent refusals, 6 excluded due to double inclusions; Group 2 Number missing: 18, Reason: 17 excluded due to proxy or post-hoc consent refusals, 1 excluded due to death before EEG start	
Protocol outcomes not reported by the study	Quality of life at Define; Length of stay at Define; seizure frequency at Define; seizures at Define; time to withdrawal of treatment at Define; withdrawal of treatment at Define; Hospitalisation at Define

Study	ZEHTABCHI, 2014 trial: Zehtabchi 2014[218]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=149)
Countries and setting	Conducted in USA; Setting: Urban academic centres
Line of therapy	1st line
Duration of study	Follow up (post intervention): In-hospital
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall

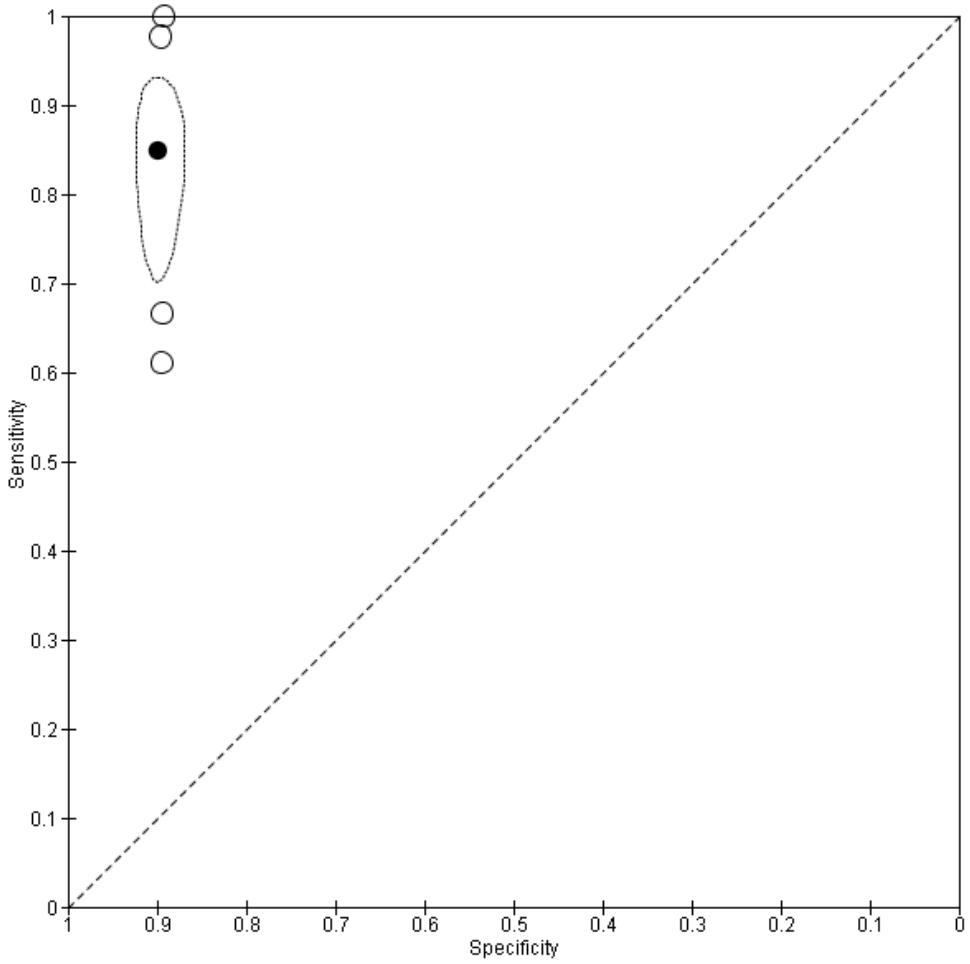
Study	ZEHTABCHI, 2014 trial: Zehtabchi 2014[218]
Subgroup analysis within study	Not applicable
Inclusion criteria	All adult (18 year and older) ED patients with AMS, defined as any alteration in level of responsiveness or alertness or arousability, presenting as lethargy, delirium, confusion, agitation, coma, disinhibition, labile/blunted affects, or unexpected psychosis.
Exclusion criteria	Exclusion criteria included patients with immediately correctable causes of AMS (including finger stick or serum glucose less than 60 mg/dL); hypothermia (body temperature below 35.0°C); hyperthermia, heat exhaustion, or heat stroke; opioid overdose responding to naloxone; patients who were unable to undergo EEG recordings (e.g., severe scalp injury); hemodynamically unstable patients (systolic blood pressure < 90 mm Hg); uncooperative or combative patients; and patients who were discharged, admitted, or transferred before enrolment. Patients who had overt seizures in the ED were only included if they experienced prolonged postictal periods (at the discretion of the ED attending physician).
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): 65.1. Gender (M:F): Define. Ethnicity: Both included institutions operate in an under-served community in central Brooklyn, New York. The population consists mostly of African American and Caribbean American individuals.
Further population details	
Extra comments	History of seizure 50/149; abnormal neurological exam 35/149; acute head injury 11/149;
Indirectness of population	No indirectness
Interventions	(n=73) Intervention 1: Diagnostic strategy - Strategy A. Routine care plus microEEG. Duration 30 minutes. Concurrent medication/care: 30-minute EEG obtained using microEEG, using international 10-20 system via a FDA-approved cap. The micro-EEG is a portable, wireless, batter-operated EEG

Study	ZEHTABCHI, 2014 trial: Zehtabchi 2014[218]
	device. When the recording as complete the recording was saved for review by an on-call epileptologist who reported the EEG findings to the ED attending over the phone within 30 minutes from completion of recording. EEG was collected by medical student research assistants who had received 20 hours of training. Each RA had to have completed at least 10 EEGs approved by the study epileptologists. Indirectness: No indirectness (n=76) Intervention 2: Diagnostic strategy - Strategy B. Routine care. Duration Not reported. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Study funded by industry (NIH grant to Bio-Signal Group Inc)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STRATEGY A versus STRATEGY B Protocol outcome 1: Mortality during in-patient period (undefined) - Actual outcome: In-patient mortality; Group 1: 4/73, Group 2: 4/76 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Age 62 intervention and 68 control; acute head injury 5% intervention and 9% control; Group 1 Number missing: 8, Reason: AMS resolved before enrolment (n=1), became hemodynamically unstable (n=1), became hypoglycaemic (n=2), combative/uncooperative (n=2), disposition/transfer before enrolment (n=2); Group 2 Number missing: 11, Reason: AMS resolved before enrolment (n=4), became hemodynamically unstable (n=2), disposition/transfer before enrolment (n=1)	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Length of stay at Define; seizure frequency at Define; seizures at Define; seizures at Define; time to withdrawal of treatment at Define; withdrawal of treatment at Define; Adverse events at Define

Appendix E Coupled sensitivity and specificity forest plots and sROC curves

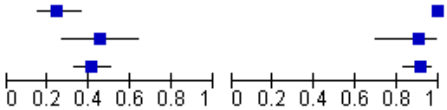
E.1 Diagnostic accuracy

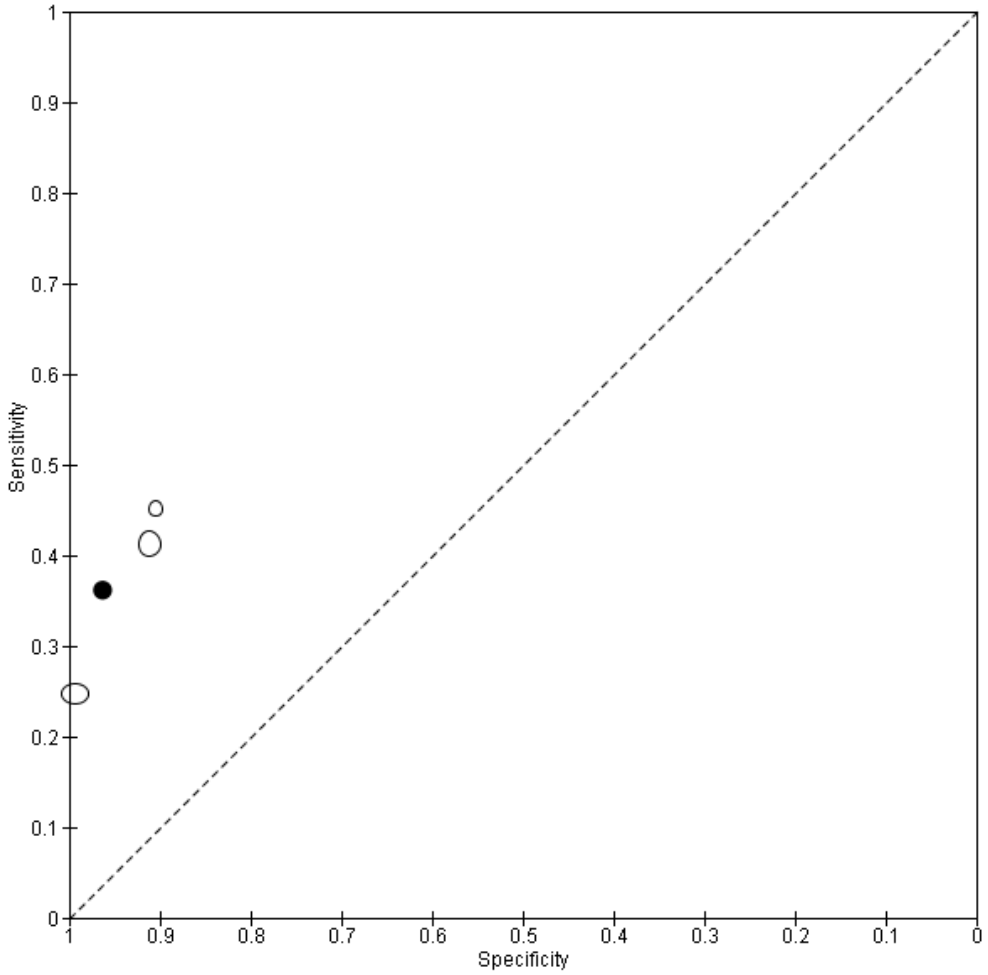
Note that Forest plots are only shown if the study provided raw data, or there was sufficient information to calculate the raw data.



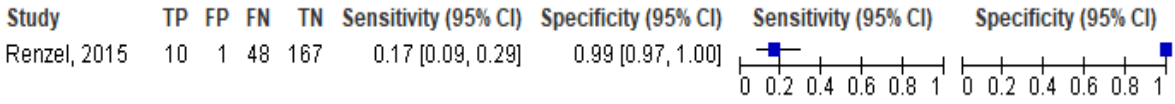
Sleep-deprived interictal EEG – abnormal (i.e. epileptiform waveforms)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Geut, 2017	17	1	52	167	0.25 [0.15, 0.36]	0.99 [0.97, 1.00]
Giorgi, 2013	14	2	17	19	0.45 [0.27, 0.64]	0.90 [0.70, 0.99]
Renzel, 2015	54	7	77	72	0.41 [0.33, 0.50]	0.91 [0.83, 0.96]

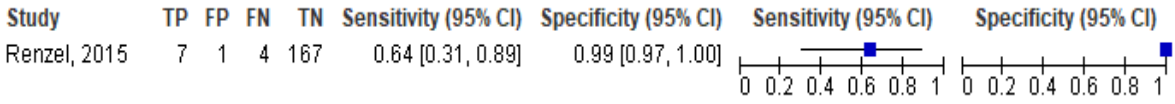




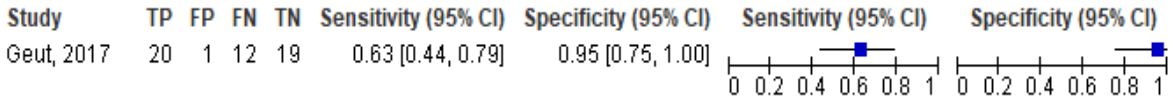
24 hour sleep deprivation interictal EEG– abnormal (i.e. epileptiform waveforms) DETECTING FOCAL EPILEPSY



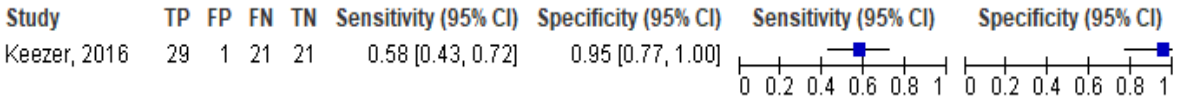
24 hour sleep deprivation interictal EEG– abnormal (i.e. epileptiform waveforms) DETECTING GENERALISED EPILEPSY



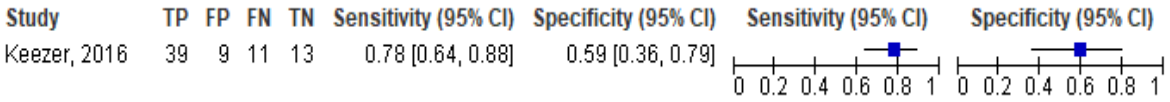
Ambulatory interictal EEG (16-24 hrs, including sleep) – abnormal (i.e. epileptiform waveforms)



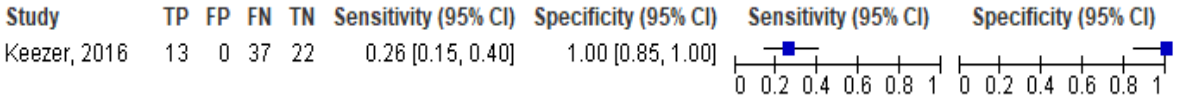
Prolonged ambulatory interictal EEG using epileptiform discharges only as definition of a positive test



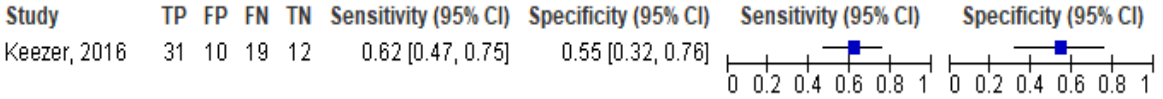
Prolonged ambulatory interictal EEG using either epileptiform discharges or non-epileptiform abnormalities as definitions of a positive test



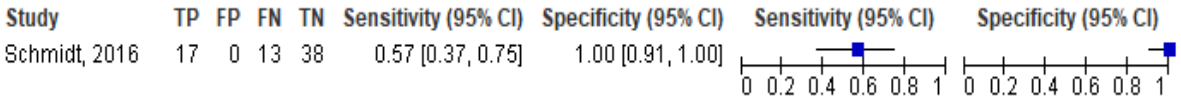
Routine interictal EEG with provocation with hyperventilation, intermittent photic stimulation and eye opening/closing, using epileptiform discharges as definition of positive test



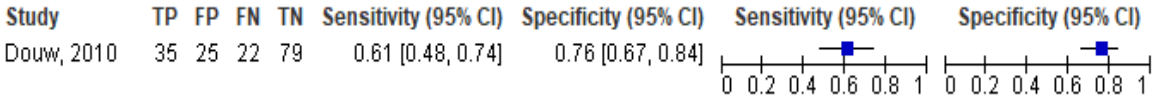
Routine interictal EEG with provocation with hyperventilation, intermittent photic stimulation and eye opening/closing, using either epileptiform or non-epileptiform abnormalities as definitions of a positive test



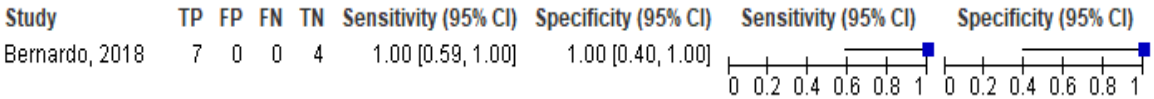
Computational biomarker looking at the synchrony between EEG channels and the normalised power spectrum from a short resting state interictal EEG (does not require epileptiform discharges). Details of the threshold of synchrony not given.



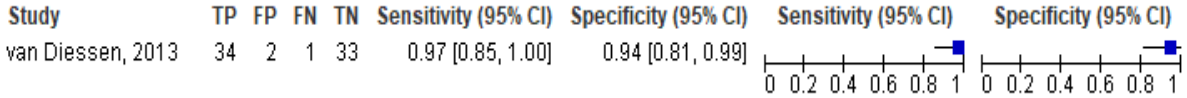
Synchronisation likelihood (SL) based on standard EEG after a first seizure. The Theta band SL values were tested for accuracy, but details or specific threshold not given



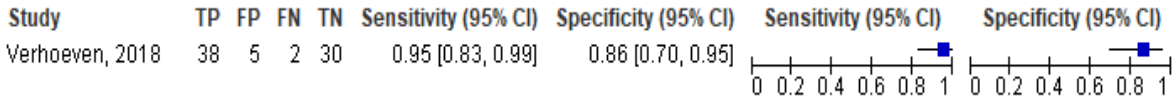
Interictal fast ripple (250-500Hz) events, based on scalp EEG. Single 10-minute epoch per patient. Existence of fast ripples = positive test (INFANTS WITH TUBEROUS SCLEROSIS COMPLEX-ASSOCIATED EPILEPSY)



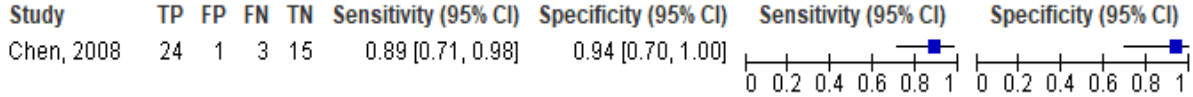
Functional network approach. Periods of resting-state EEG, free of abnormal slowing or epileptiform activity, were selected to construct functional networks of correlated activity. The statistical interdependencies for each pair of EEG electrode time series are considered as functional connectivity and used to construct a functional network per subject for each of the four epochs and were averaged per subject. Details of thresholds not provided. DETECTING PARTIAL EPILEPSY



Resting state high density EEG. The cortical source activity was obtained and whole-brain directed functional connectivity was estimated in the theta, alpha and beta frequency bands. No threshold information available. DETECTING TEMPORAL LOBE EPILEPSY

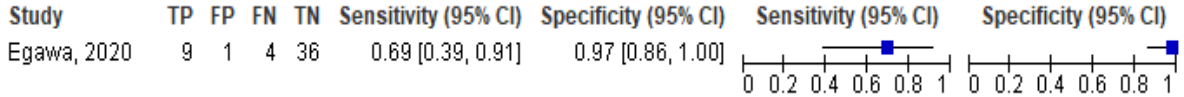


Ictal EEG (without access to video or observation) – abnormal (i.e. epileptiform waveforms)

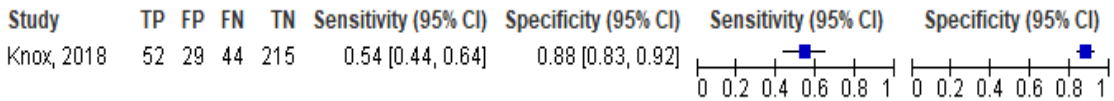


Quantitative ICTAL EEG interpreted by PICU clinicians in real time – abnormal waveforms (INFANTS)

Headset-type continuous video EEG monitoring – detection of abnormal patterns, such as periodic discharges, rhythmic delta activity, spikes and wave and continuous slow discharges. DETECTING NCSE

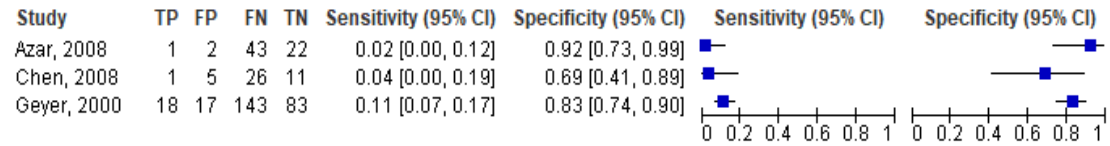


No event video EEG (at least 16 hours)

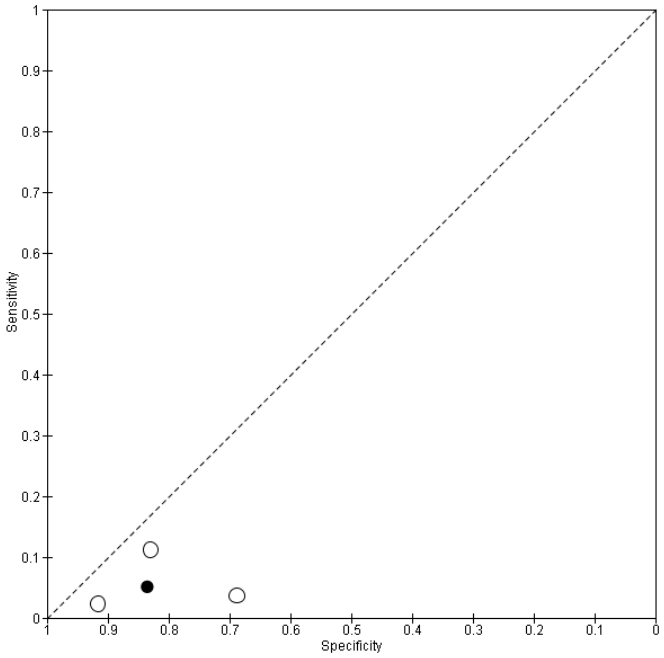


E.1.1.1 Signs/symptoms/semiology

Sign observed by epileptologist on video during seizure – pelvic thrusting

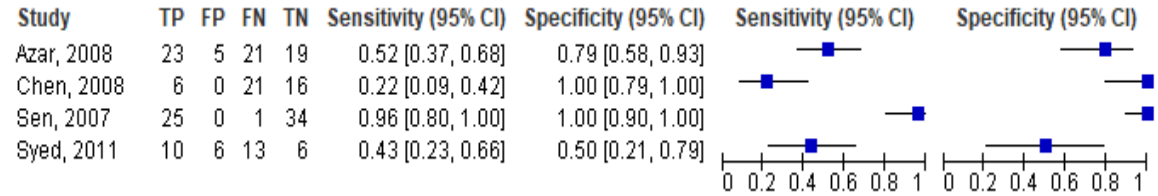


1

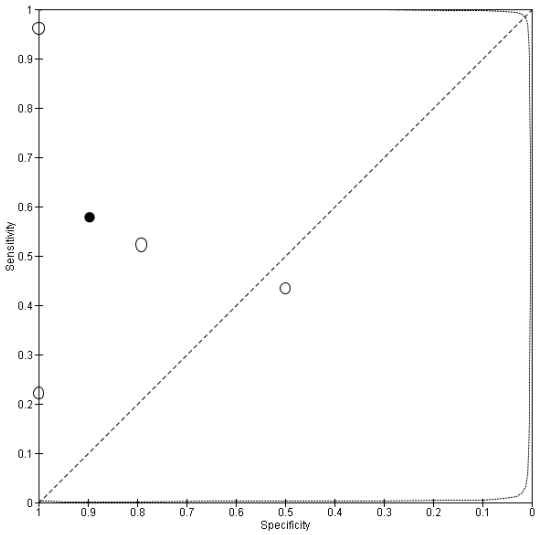


2

3 Stertorious/loud/deep breathing post ictally

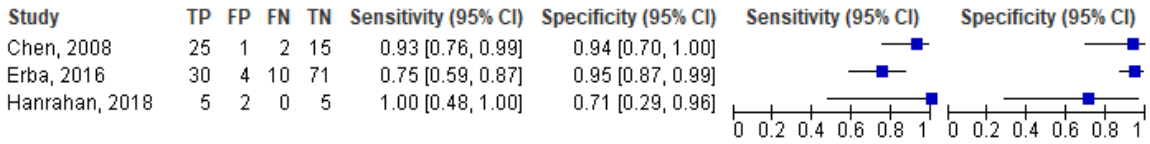


4

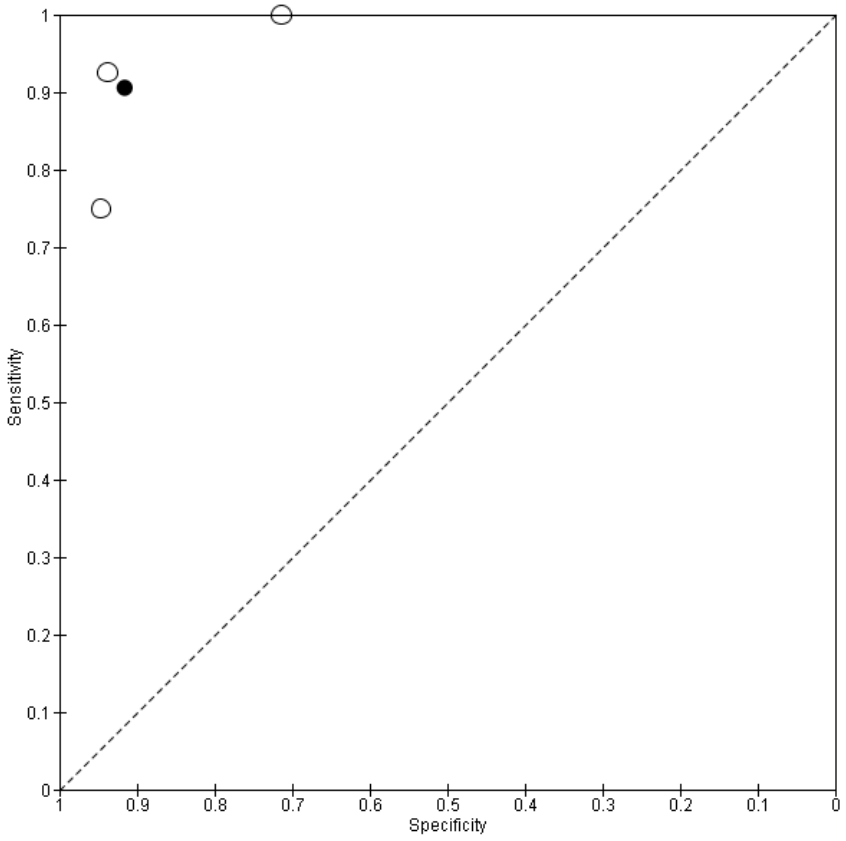


5

6 Use of video information alone during seizure (from Video EEG) without other data to form
7 'diagnosis'.

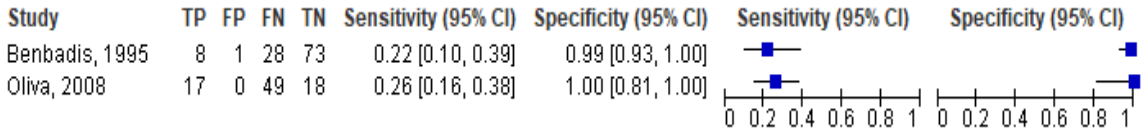


1



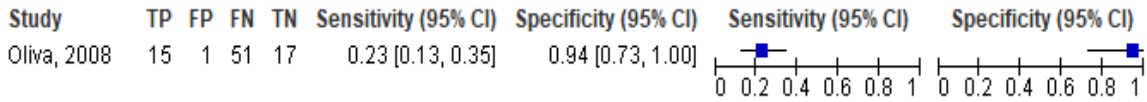
2

3 Tongue biting / oral lacerations during seizure



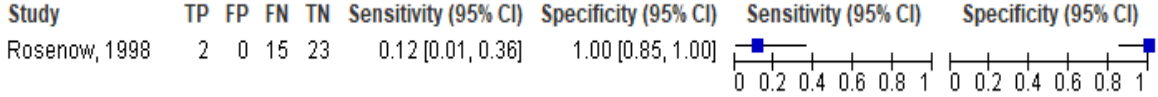
4

5 Incontinence during seizure



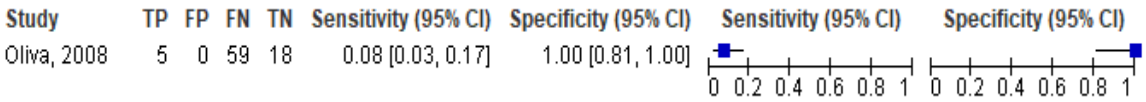
6

7 Urine loss. DETECTING ABSENCE SEIZURES IN INFANTS

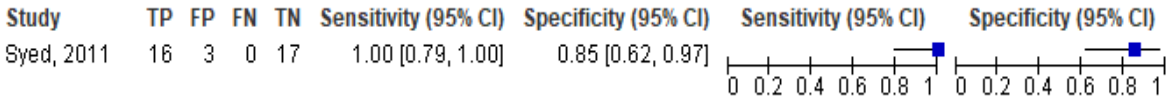


8

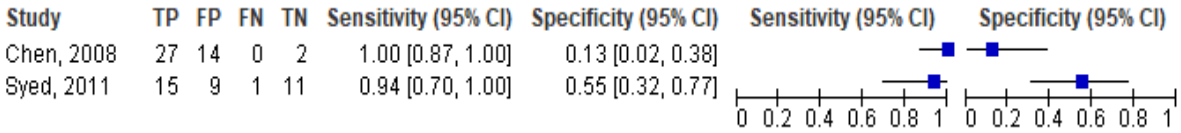
9 Oral lacerations AND incontinence during seizure



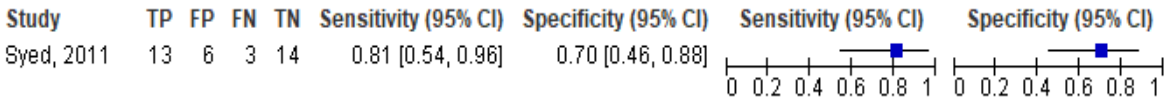
Sign observed by epileptologist on video during seizure - eye opening or widening at onset



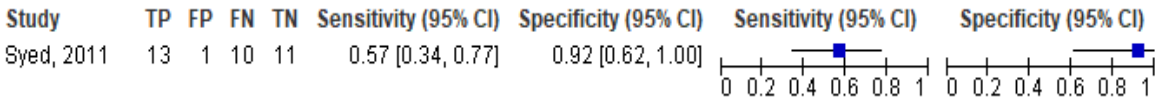
Sign observed by epileptologist on video during seizure - abrupt onset



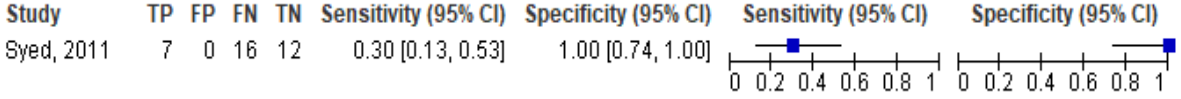
Sign observed by epileptologist on video during seizure – postictal confusion/sleep



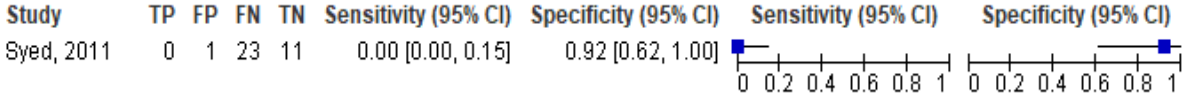
Sign observed by epileptologist on video during seizure – eyes fixed



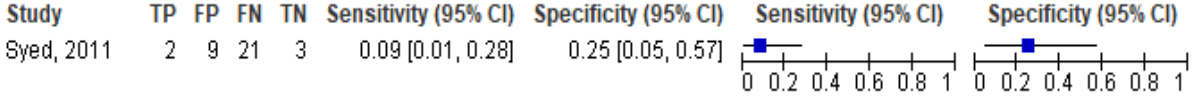
Sign observed by epileptologist on video during seizure – unilateral head turning



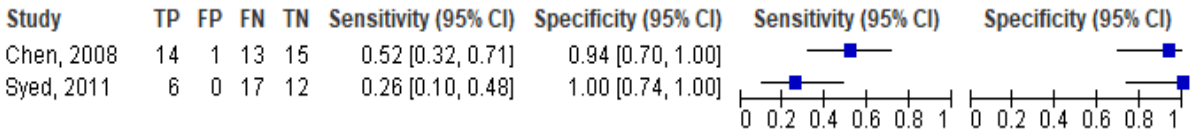
Sign observed by epileptologist on video during seizure – non-sensical speech



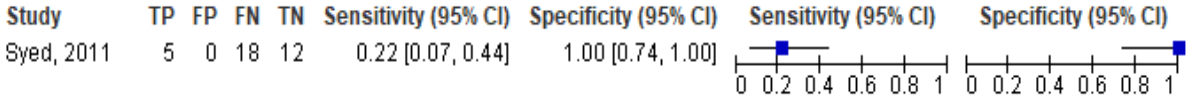
Sign observed by epileptologist on video during seizure – clenched mouth



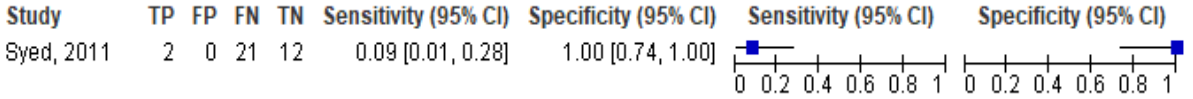
Sign observed by epileptologist on video during seizure – hand automatisms



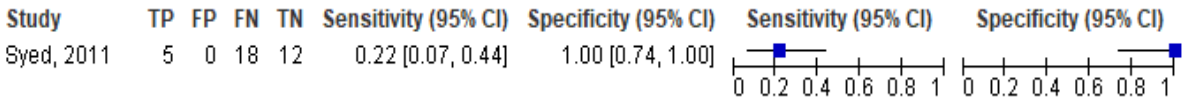
Sign observed by epileptologist on video during seizure – ictal scream



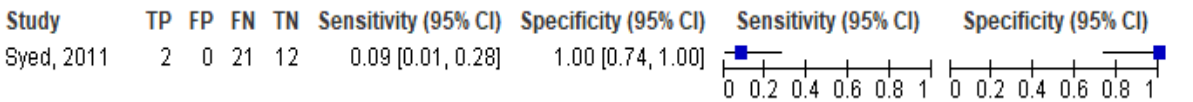
Sign observed by epileptologist on video during seizure - grasping



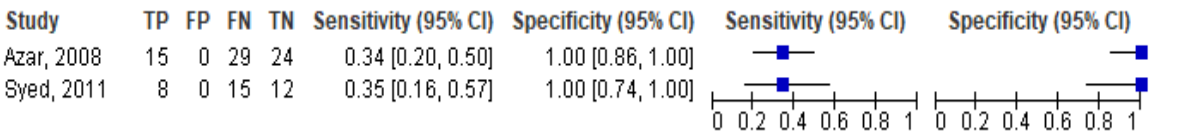
Sign observed by epileptologist on video during seizure – post-ictal nose wiping



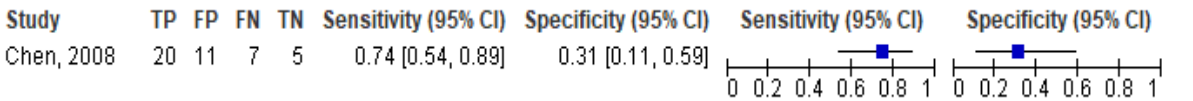
Sign observed by epileptologist on video during seizure - postictal aphasia



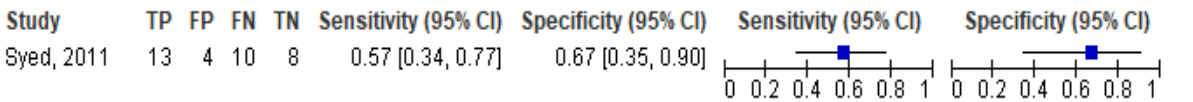
Sign observed by epileptologist on video during seizure - postictal snoring



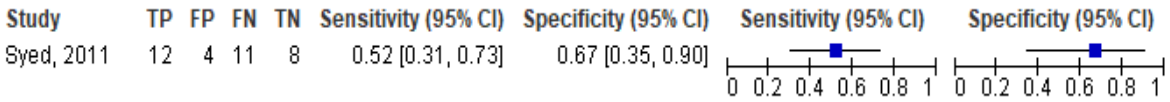
Sign observed by epileptologist on video during seizure – abrupt offset



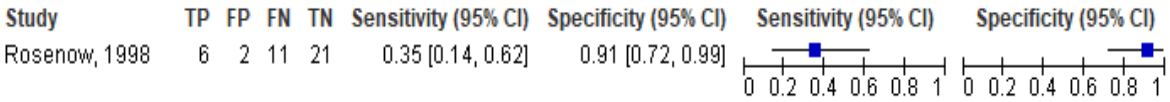
Sign observed by epileptologist on video during seizure – continuous movements



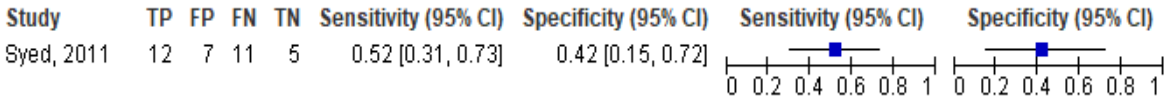
Sign observed by epileptologist on video during seizure – eyes rolled back into head



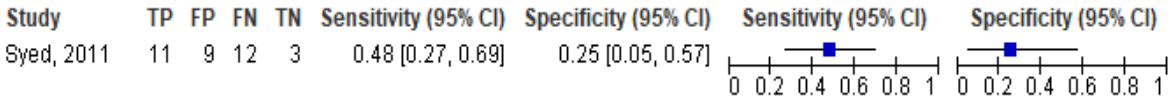
Upward eye movements DETECTING ABSENCE SEIZURES IN INFANTS



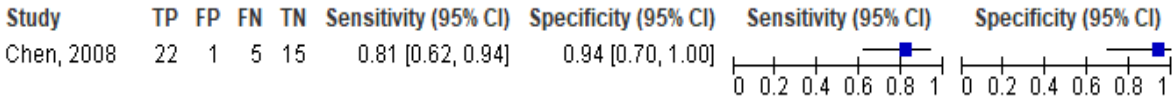
Sign observed by epileptologist on video during seizure – postictal exhaustion



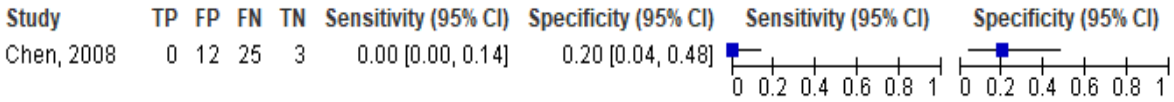
Sign observed by epileptologist on video during seizure – looking around



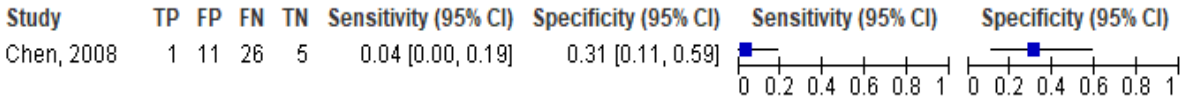
Sign observed by epileptologist on video during seizure - gradual behavioural build-up to peak intensity, but within 70 seconds



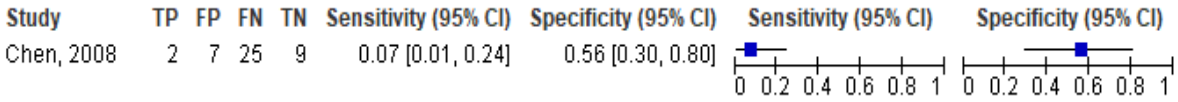
Sign observed by epileptologist on video during seizure – eyes closed at peak



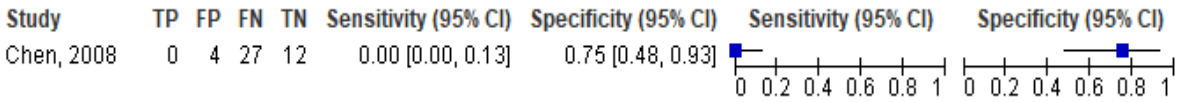
Sign observed by epileptologist on video during seizure – waxing / waning event tempo



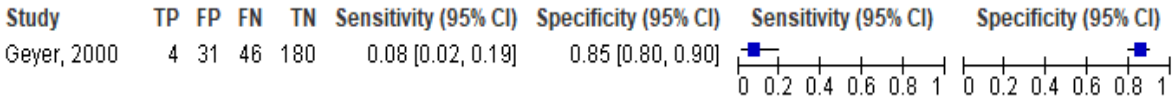
Sign observed by epileptologist on video during seizure – non-synchronous movements



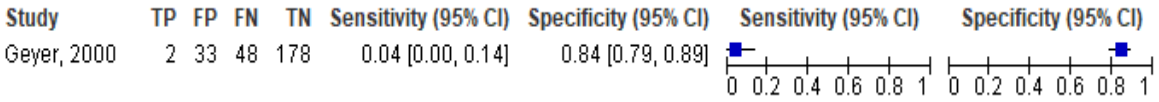
Sign observed by epileptologist on video during seizure – side to side head movements



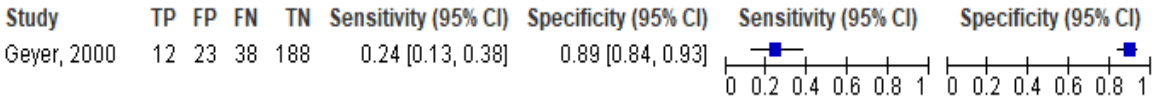
Pelvic thrusting. DETECTING RIGHT TLE



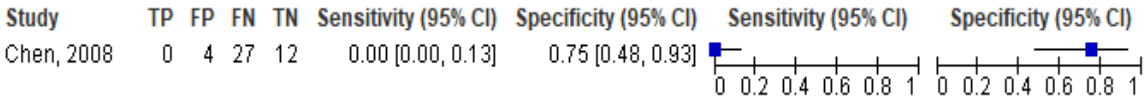
Pelvic thrusting. DETECTING LEFT TLE



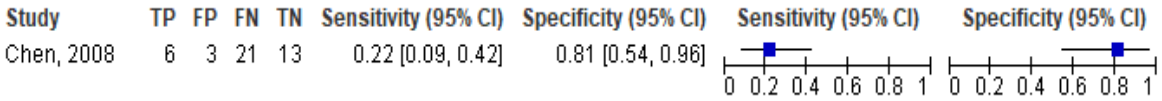
Pelvic thrusting. DETECTING FLE



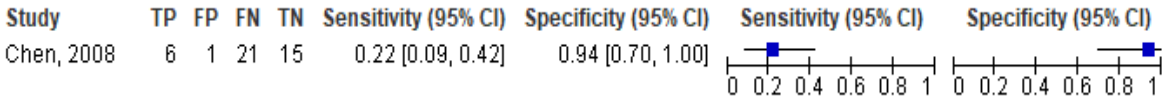
Sign observed by epileptologist on video during seizure – expression of pain



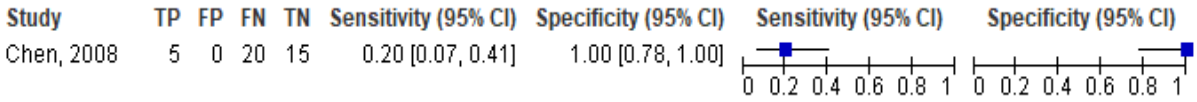
Sign observed by epileptologist on video during seizure – motor behavioural onset



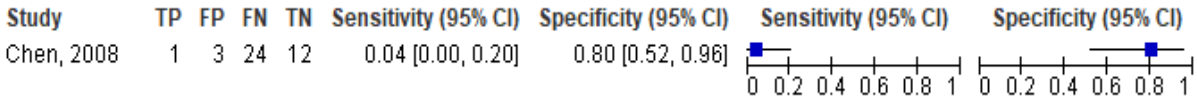
Sign observed by epileptologist on video during seizure – head version



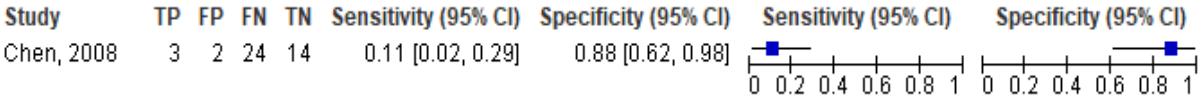
Sign observed by epileptologist on video during seizure – eye deviation



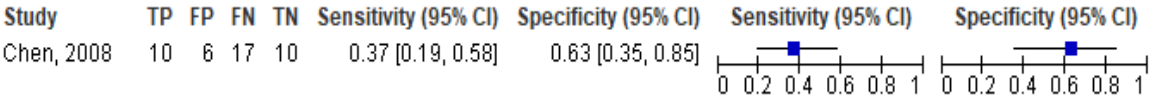
Sign observed by epileptologist on video during seizure – repetitive eye blinks



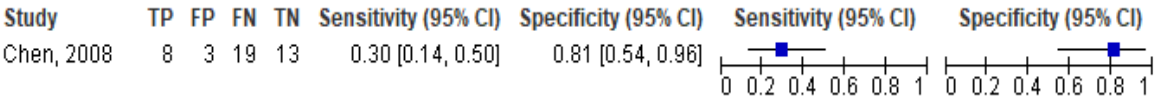
Sign observed by epileptologist on video during seizure – facial grimacing



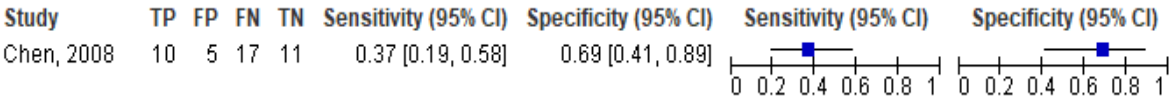
Sign observed by epileptologist on video during seizure – abnormal posturing



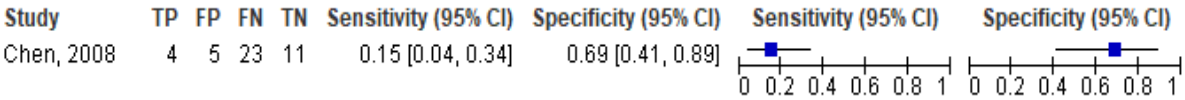
Sign observed by epileptologist on video during seizure – clonic activities



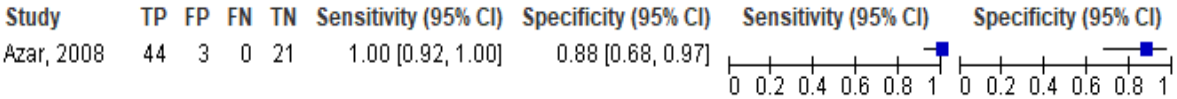
Sign observed by epileptologist on video during seizure – vocalisation/speech



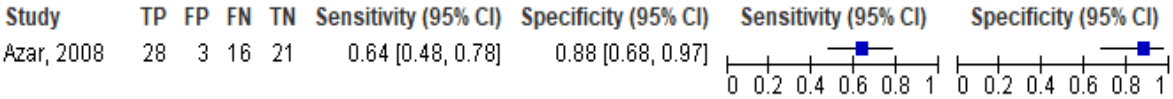
Sign observed by epileptologist on video during seizure – thrashing/writhing



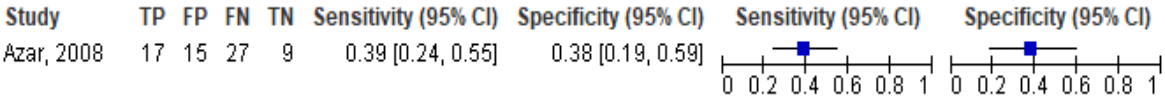
Neurologist observation of video: Ictal eyes open during seizure



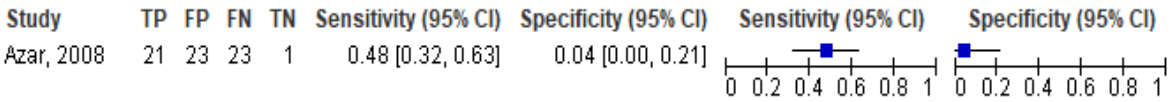
Neurologist observation of video: Ictal vocalisation



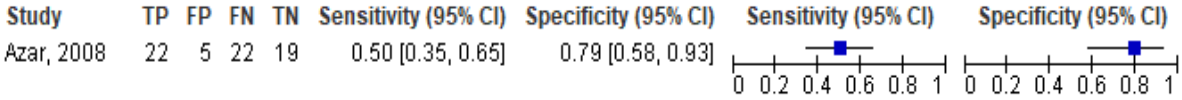
Neurologist observation of video: Ictal side to side head and body turning



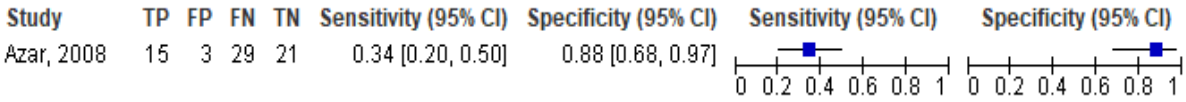
Neurologist observation of video: Ictal asynchronous extremity motion



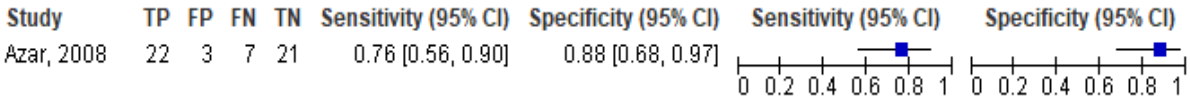
Neurologist observation of video: Post ictal breathing regularity



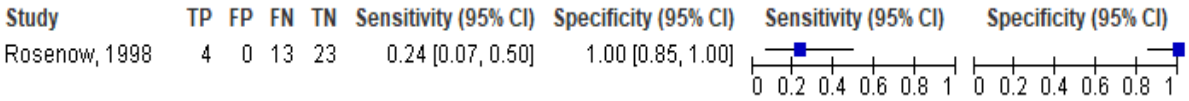
Neurologist observation of video: Post ictal agitation



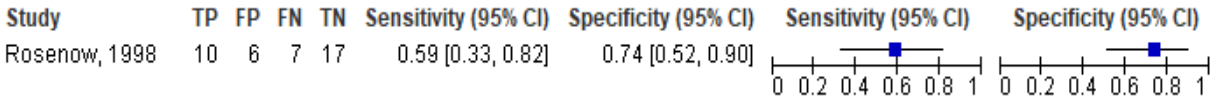
Neurologist observation of video: Post ictal confusion



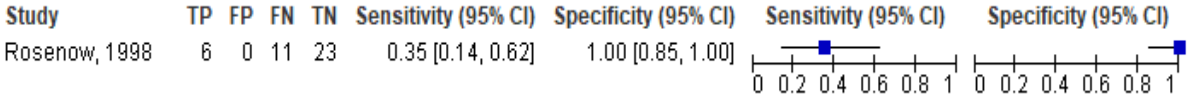
Twitching arms or legs during seizure. DETECTING ABSENCE SEIZURES IN INFANTS



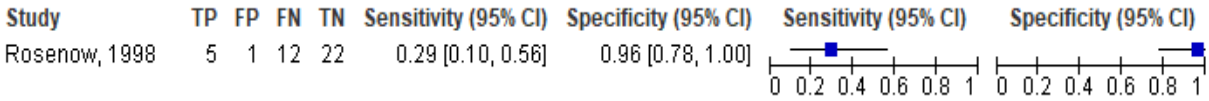
Occurrence of seizure when tired. DETECTING ABSENCE SEIZURES IN INFANTS



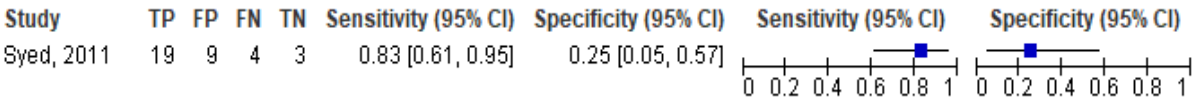
Twitching arms or legs OR urine loss during seizure. DETECTING ABSENCE SEIZURES IN INFANTS



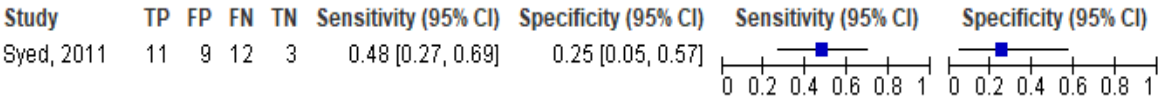
Upward eye movement during seizures and occurrence of seizures when tired. DETECTING ABSENCE SEIZURES IN INFANTS



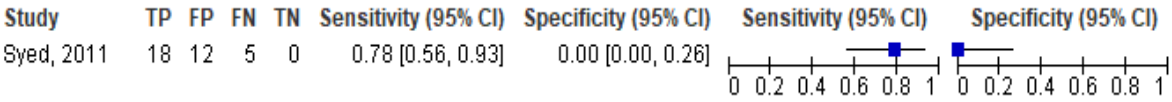
Eyewitness (family/relative) account of eye opening or widening at onset during seizure



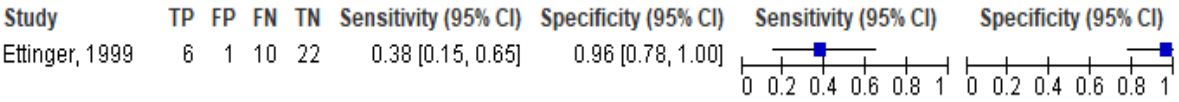
Eyewitness (family/relative) account of abrupt onset during seizure



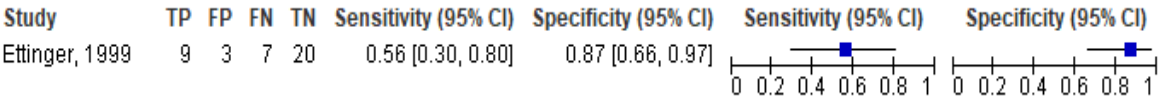
Eyewitness (family/relative) account of post-ictal confusion/sleep



Symptom questionnaire for patients – existence of headache after seizure?

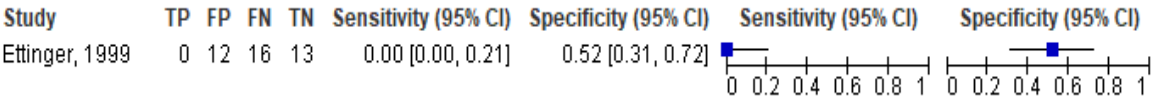


Symptom questionnaire for patients – existence of fatigue or lethargy?

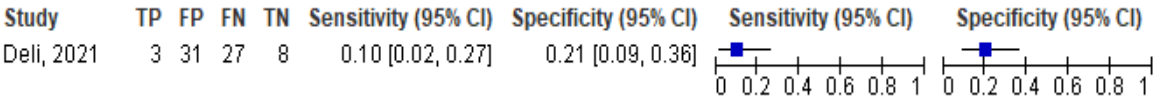


Symptom questionnaire for patients – existence of confusion alone?

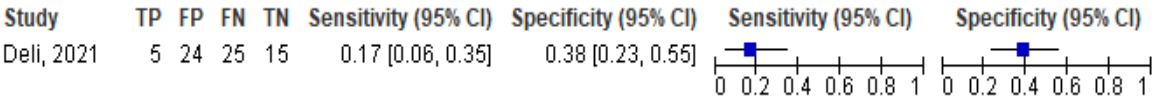
Symptom questionnaire for patients – existence of no symptoms?



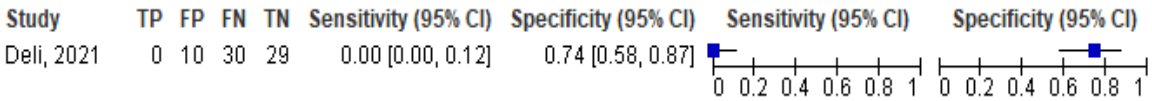
Reports of symptoms - Light headedness



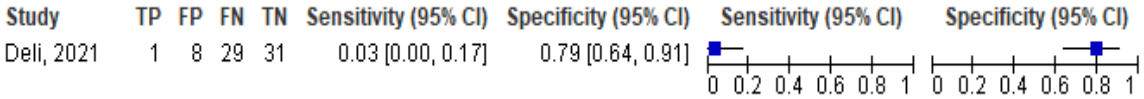
Reports of symptoms – sensory disturbances/dysesthesias



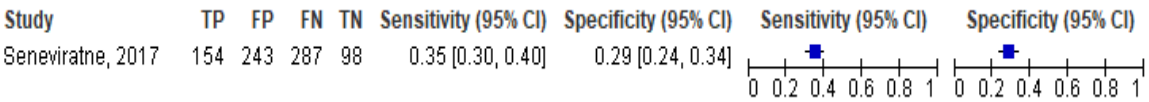
Reports of symptoms – hot flushes



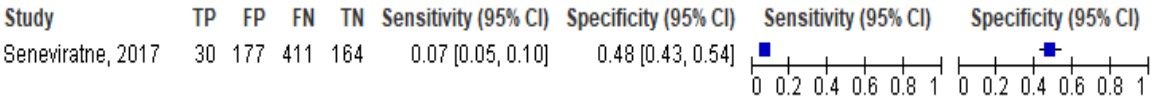
Reports of symptoms - palpitations



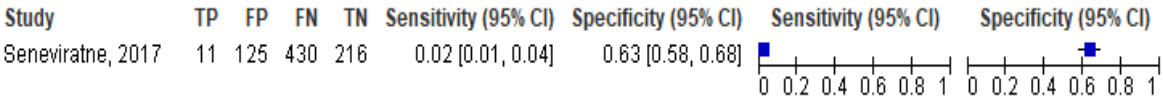
Ictal duration >60s (measured by epileptologist using video)



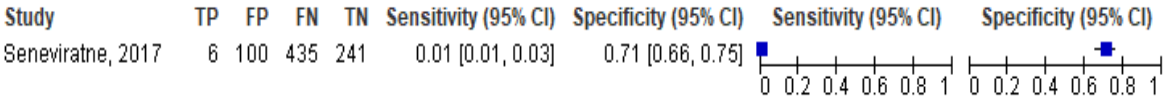
Ictal duration >120s (measured by epileptologist using video)



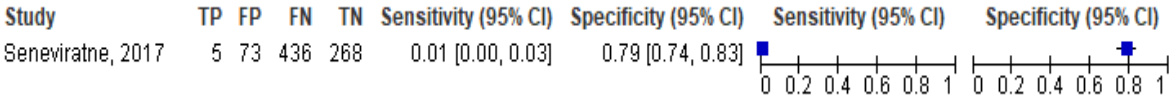
Ictal duration >180s (measured by epileptologist using video)



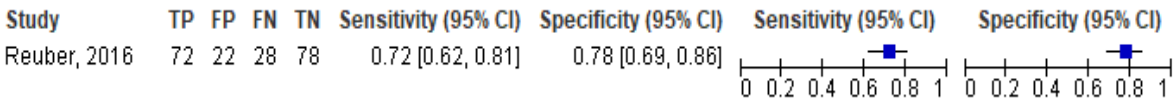
Ictal duration >240s (measured by epileptologist using video)



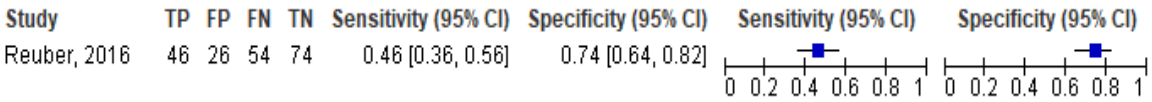
Ictal duration >300s (measured by epileptologist using video)



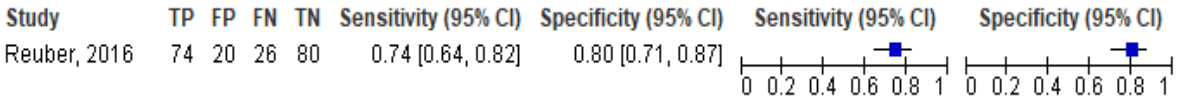
Paroxysmal Event Profile Questionnaire – 'factor scores' (PNES as non-epilepsy group). No details of scoring or thresholds used.



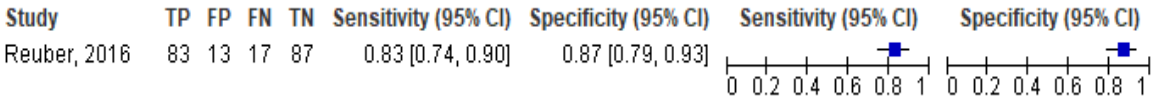
Paroxysmal Event Profile questionnaire – 'patient information' (PNES as non-epilepsy group). No details of scoring or thresholds used.



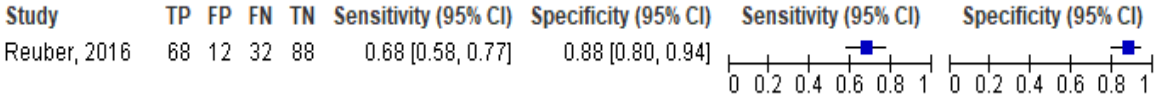
Paroxysmal Event Profile questionnaire – 'combined'(PNES as non-epilepsy group). No details of scoring or thresholds used.



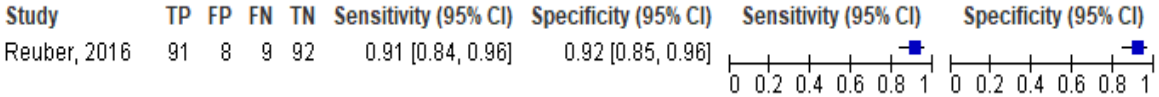
Paroxysmal Event Profile questionnaire – 'factor scores' (syncope as non-epilepsy group). No details of scoring or thresholds used.



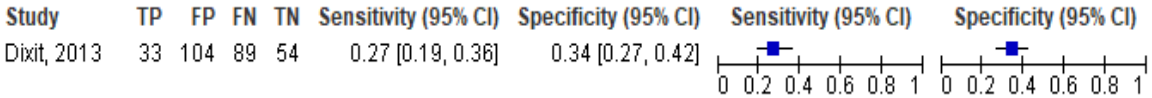
Paroxysmal Event Profile questionnaire- 'patient info' (syncope as non-epilepsy group). No details of scoring or thresholds used.



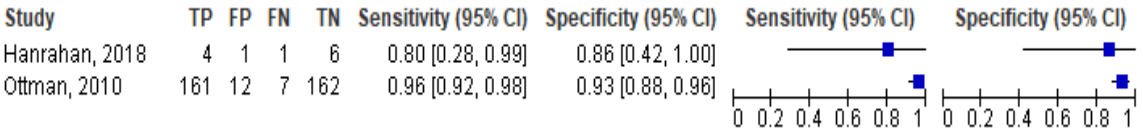
Paroxysmal Event Profile – 'combined' (syncope as non-epilepsy group). No details of scoring or thresholds used.



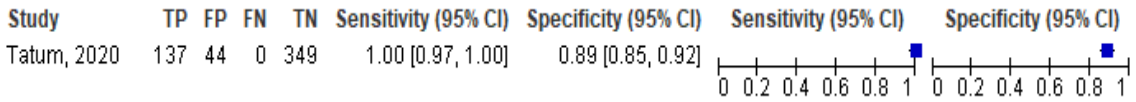
>1 comorbidity on medical records



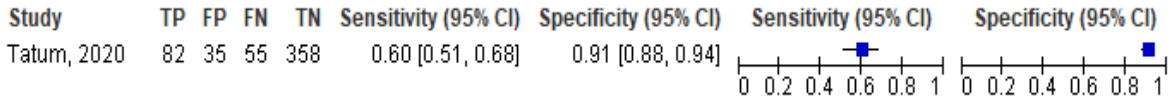
Use of Clinical history / interview to form 'diagnosis'



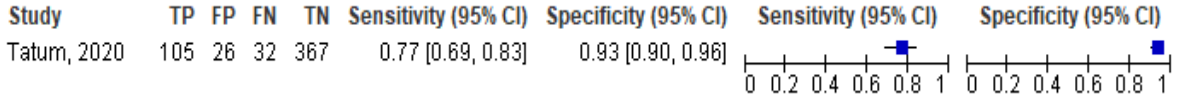
Use of history and physical examination only to form 'diagnosis'



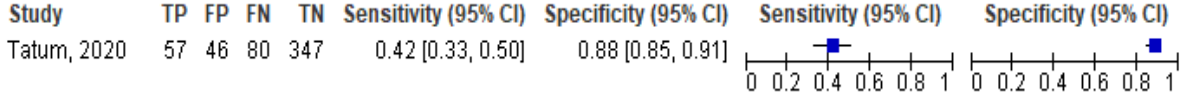
Use of smartphone video taken by witness to form 'diagnosis' (by experts and residents)



Use of smartphone video taken by witness to form 'diagnosis' (by experts only)

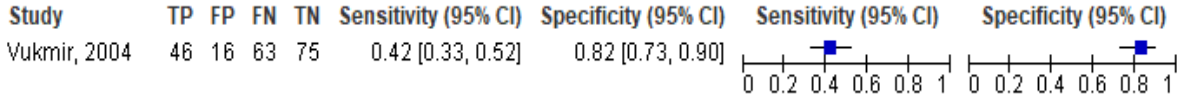


Use of smartphone video taken by witness to form 'diagnosis' (by residents only)

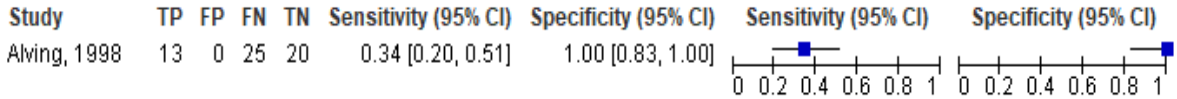


E.1.1.2 Serum measures

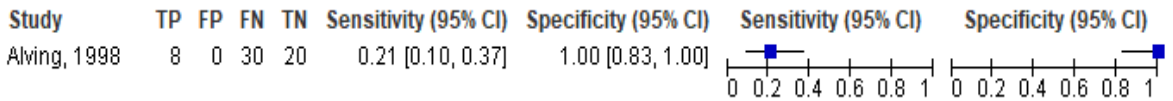
Serum prolactin level at threshold >29.9 mg/dl (indicating epilepsy). This was measured in the ED for patients presenting with recent seizure



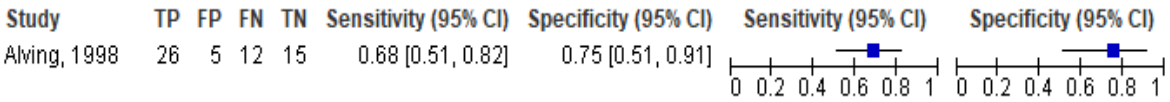
Paired serum prolactin >1025 microU/ml (indicating epilepsy) in immediate post-seizure period



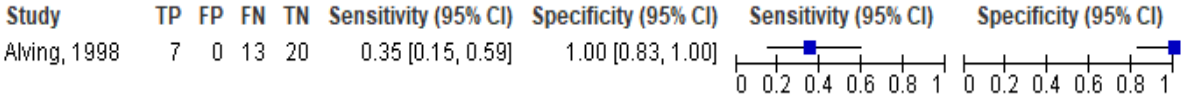
Paired serum prolactin RI > 5.5 in post seizure period (5.5 x increase in serum prolactin between 15 mins post-seizure and 2 hours after baseline sample)



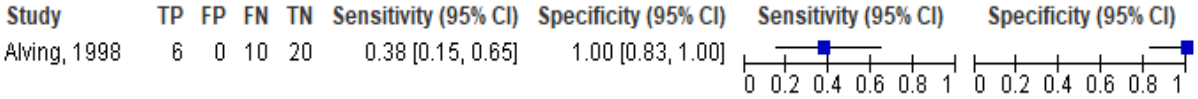
Paired serum prolactin RI > 2 in post seizure period (2 x increase in serum prolactin between 15 mins post-seizure and 2 hours after baseline sample)



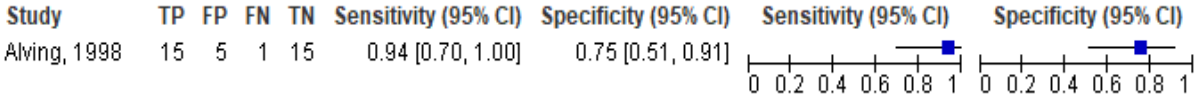
Paired serum prolactin >1025 microU/ml (indicating epilepsy) in immediate post-seizure period. DETECTING COMPLEX PARTIAL SEIZURES



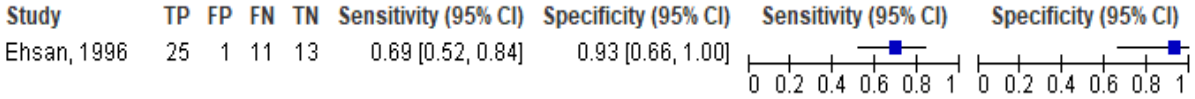
Paired serum prolactin >1025 microU/ml (indicating epilepsy) in immediate post-seizure period. DETECTING GENERALISED CLOINIC TONIC SEIZURES



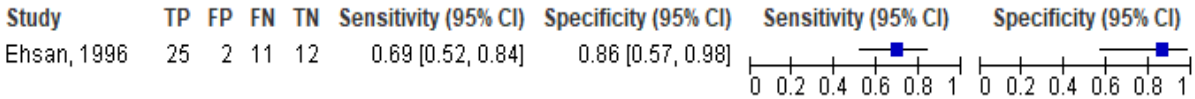
Paired serum prolactin RI > 2 in post seizure period (2 x increase in serum prolactin between 15 mins post-seizure and 2 hours after baseline sample). DETECTING GENERALISED CLONIC TONIC SEIZURES



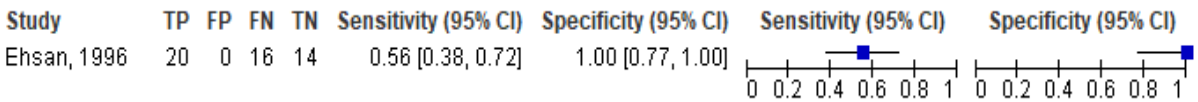
Capillary prolactin level above 6.7 ng/ml at 15 minutes post-seizure



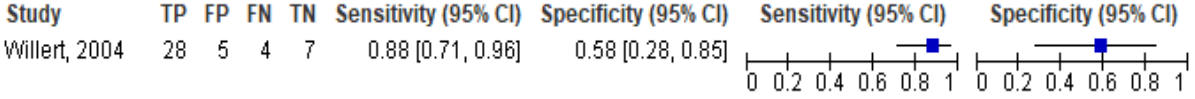
2 fold decrease in capillary prolactin level, between 15 min sample and sample obtained 1 hr later



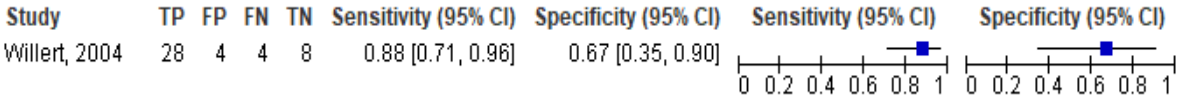
15 min cap prolactin level above 6.7 ng/ml AND a 2 fold decrease between 15 mins and 1 hour post-seizure



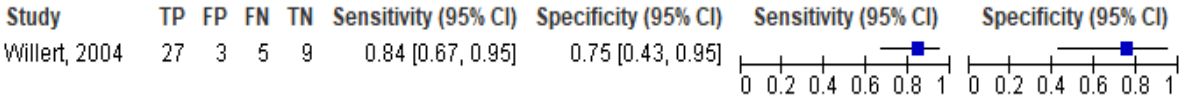
Serum prolactin >23 microg [women]/>16.5 [men] at 10mins post seizure



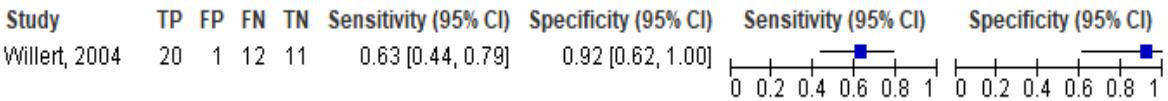
Serum prolactin >23 microg [women]/>16.5 [men] at 20mins post seizure



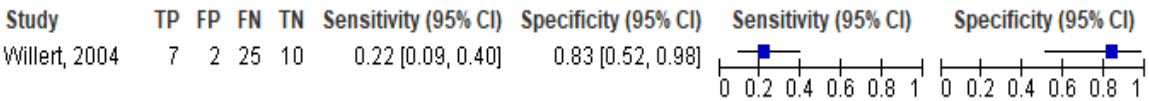
Serum prolactin >23 microg [women]/>16.5 [men] at 30mins post seizure



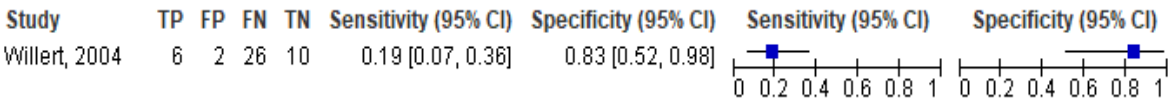
Serum prolactin >23 microg [women]/>16.5 [men] at 60mins post seizure



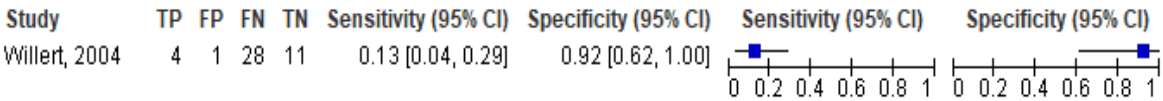
Serum prolactin >23 microg [women]/>16.5 [men] at 6 hours post seizure



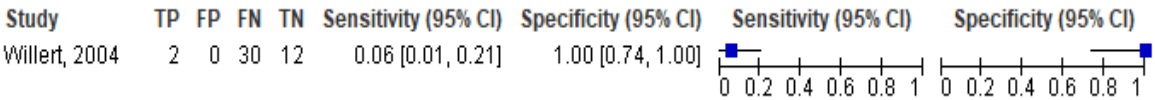
Serum prolactin >23 microg [women]/>16.5 [men] at 12 hours post seizure



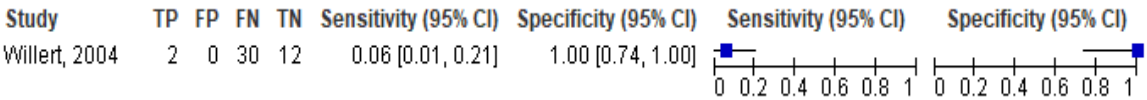
Serum prolactin >23 microg [women]/>16.5 [men] at 24 hours post seizure



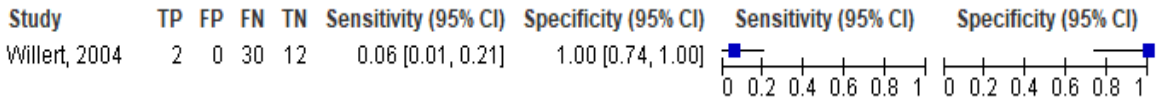
Serum neuron-specific enolase >12 microg/L at 10 minutes post seizure



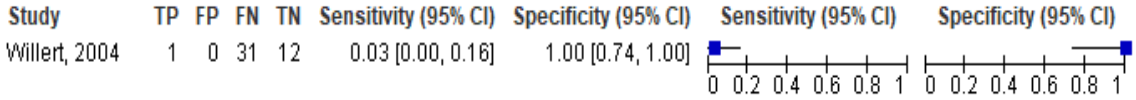
Serum neuron-specific enolase >12 microg/L at 20 minutes post seizure



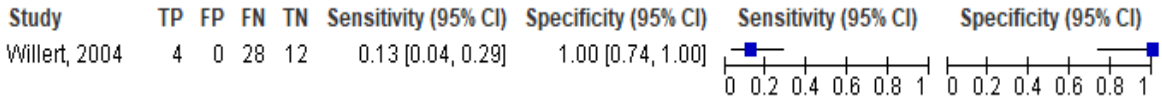
Serum neuron-specific enolase >12 microg/L at 30 minutes post seizure



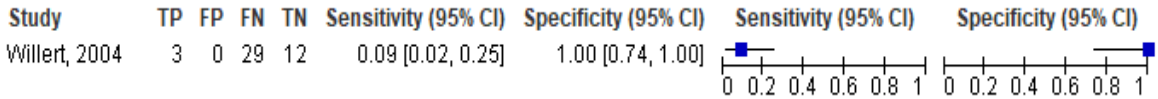
Serum neuron-specific enolase >12 microg/L at 60 minutes post seizure



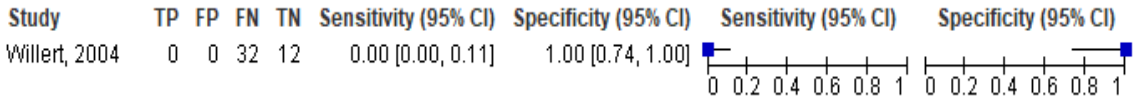
Serum neuron-specific enolase >12 microg/L at 6 hours post seizure



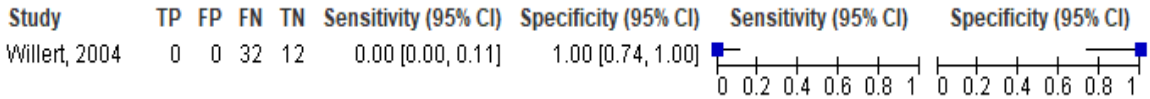
Serum neuron-specific enolase >12 microg/L at 12 hours post seizure



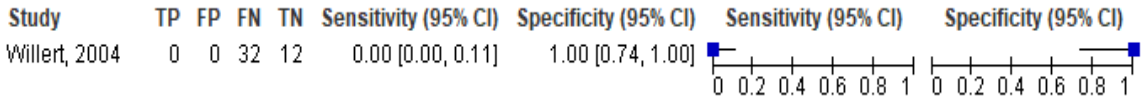
Serum neuron-specific enolase >12 microg/L at 24 hours post seizure



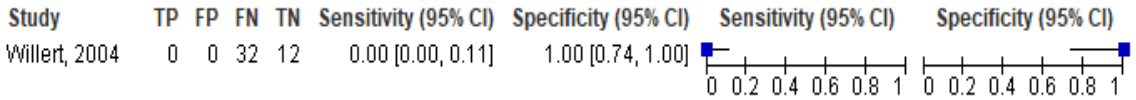
Serum creatine kinase >2.8 [women]/>3.25 [men] at 10 minutes post seizure



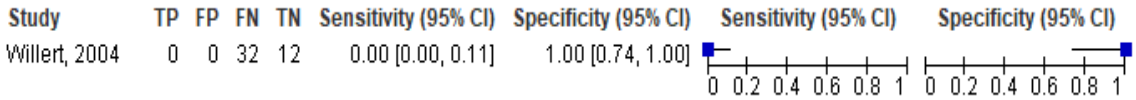
Serum creatine kinase >2.8 [women]/>3.25 [men] at 20 minutes post seizure



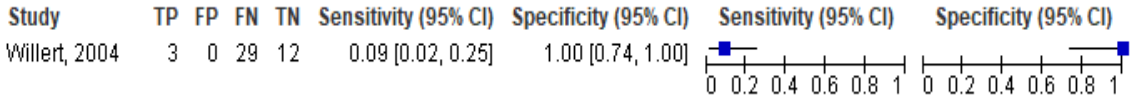
Serum creatine kinase >2.8 [women]/>3.25 [men] at 30 minutes post seizure



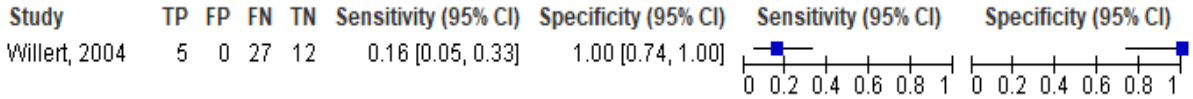
Serum creatine kinase >2.8 [women]/>3.25 [men] at 60 minutes post seizure



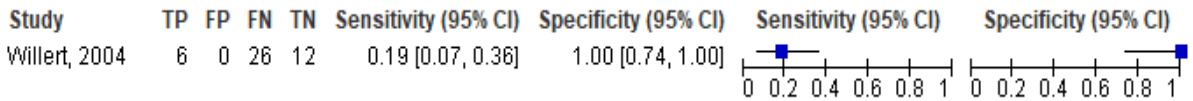
Serum creatine kinase >2.8 [women]/>3.25 [men] at 6 hours post seizure



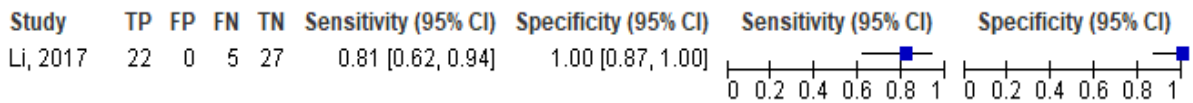
Serum creatine kinase >2.8 [women]/>3.25 [men] at 12 hours post seizure



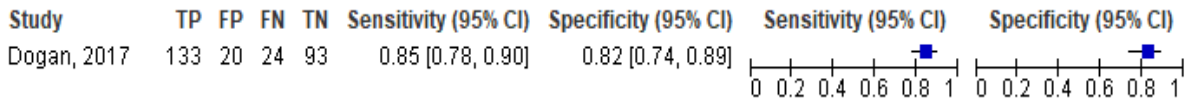
Serum creatine kinase >2.8 [women]/>3.25 [men] at 24 hours post seizure



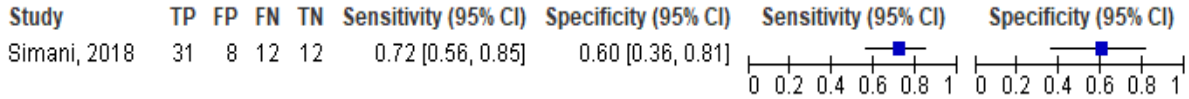
Anion gap in first 2 hrs after seizure event (threshold at >10 mEq/L)



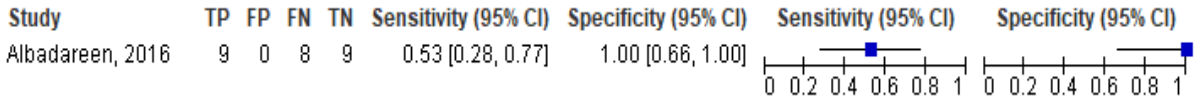
serum lactate 2 hrs post ictal (threshold >=2.2 mmol/L)



Post-seizure (within 6 hours) serum glial fibrillary astrocytic protein levels at threshold of >=2.71 ng/ml

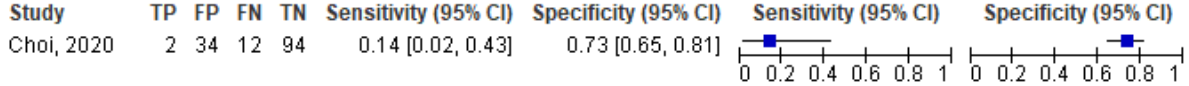


baseline serum ammonia at cut-off of >=80 micromol/L. DETECTING GENERALISED CLONIC TONIC SEIZURES



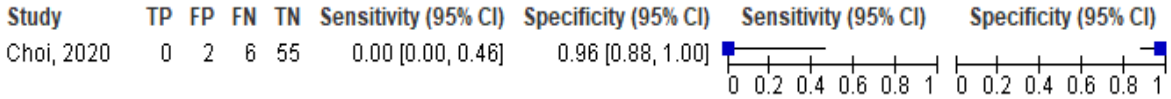
E.1.1.3 ECG

ECG. No details of measures or thresholds used.

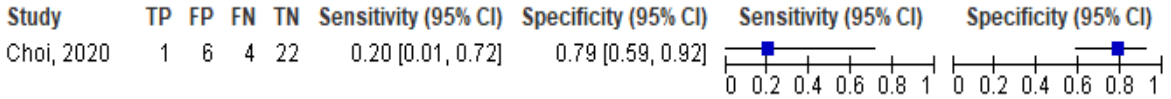


E.1.1.4 Imaging tests

Echocardiogram. No details of measures or threshold available.

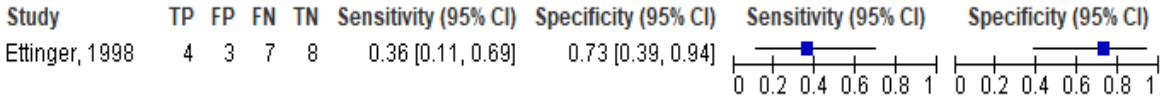


Brain CT. No details of measures or threshold available.

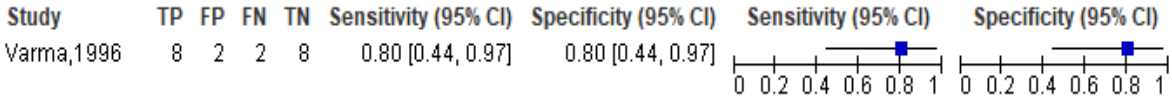


Single photon emission computed tomography (SPECT) - post-ictal abnormal measure

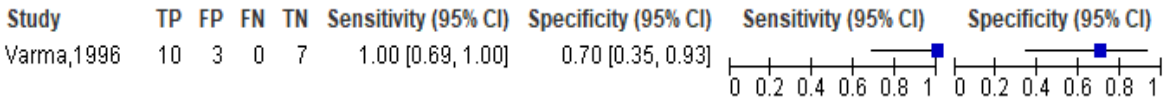
Single photon emission computed tomography (SPECT) - inter-ictal abnormal measure



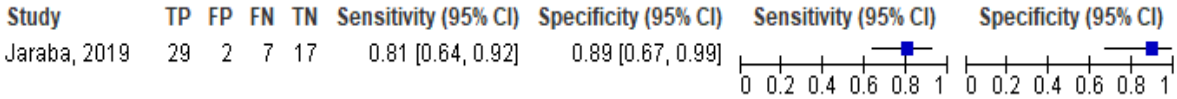
Hexamethyl propylene amine oxime single photon emission tomography (HMPAO SPECT) brain imaging (positive=hypoperfusion not including equivocal hypoperfusion)



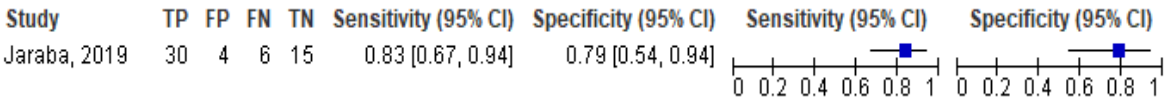
Hexamethyl propylene amine oxime single photon emission tomography (HMPAO SPECT) brain imaging (positive=hypoperfusion including equivocal hypoperfusion)



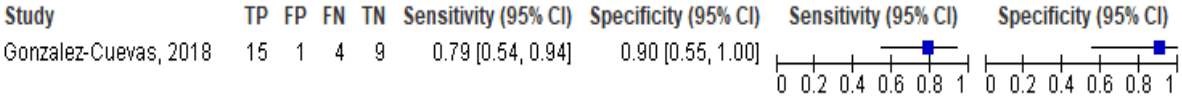
HMPAO-SPECT using visual analysis: SPECTS considered positive for status Epilepticus when there was at least one area of Focal Uptake compared to the adjacent or contralateral areas of the brain. ICTAL. DETECTING NCSE



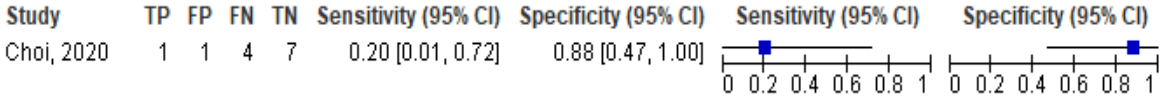
HMPAO-SPECT - QtSPECTCOM using quantitative analysis: Results were compared to a normal database and the difference in terms of the Z score was quantified. ICTAL. DETECTING NCSE



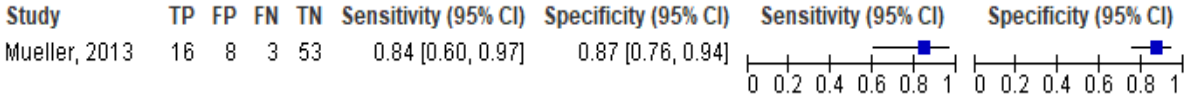
Perfusion computed tomography using hyperperfusion detection. DETECTING STATUS EPILEPTICUS



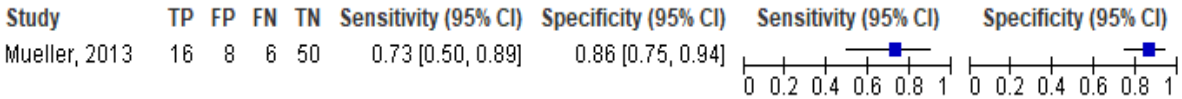
Brain MRI. No details of measures or threshold available.



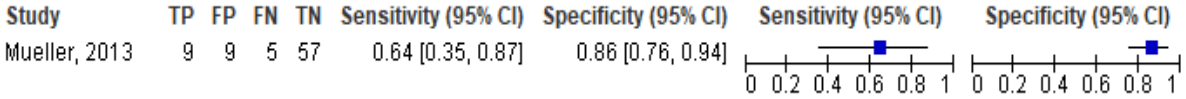
4T MRI: the presence/absence of MTS in TLE was based on hippocampal subfield volumetry. DETECTING TLE with MTS



4T MRI: the presence/absence of MTS in TLE was based on hippocampal subfield volumetry. DETECTING TLE without MTS

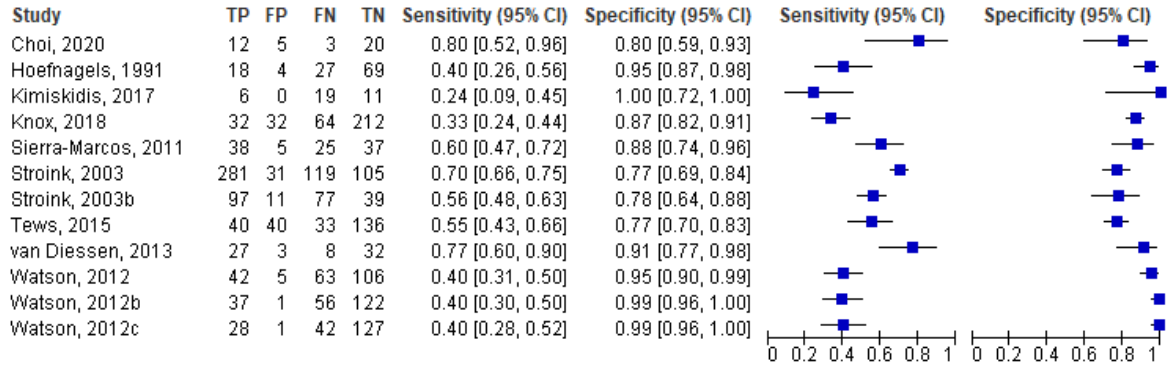


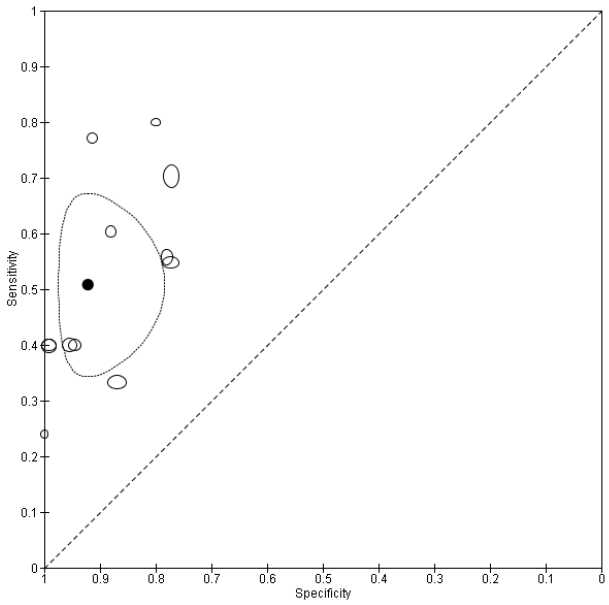
4T MRI. DETECTING FLE



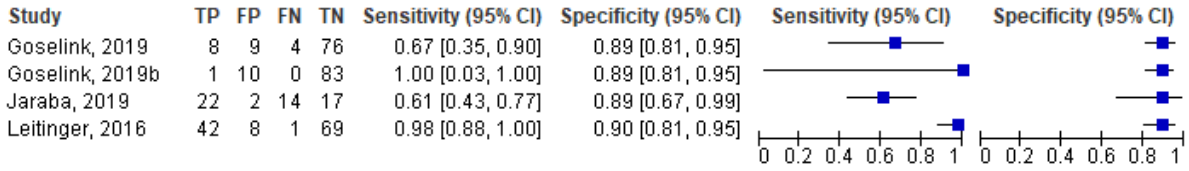
E.1.1.5 EEG tests

Routine interictal EEG



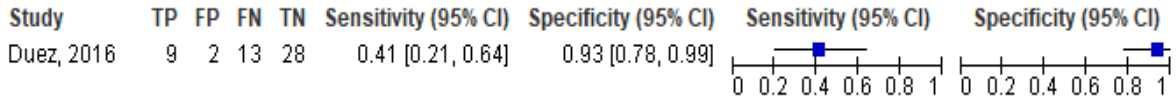


Routine EEG using Salzburg criteria

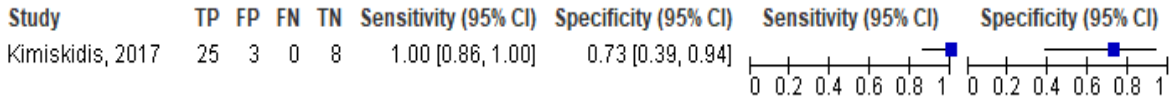


E.1.1.6 Magnetoencephalography / Transcranial Magnetic Stimulation tests

Magnetoencephalography with simultaneous EEG (MEG-EEG). No details of threshold available.

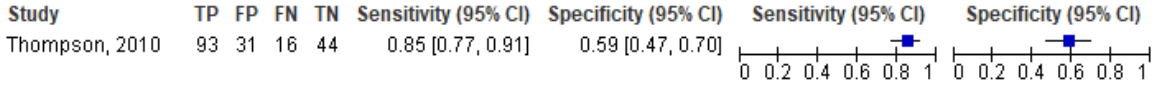


Paired pulse Transcranial Magnetic Stimulation with EEG (TMS-EEG) immediately after hyperventilation. No details of threshold available.

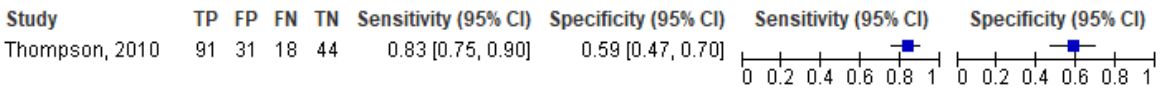


E.1.1.7 Psychological tests

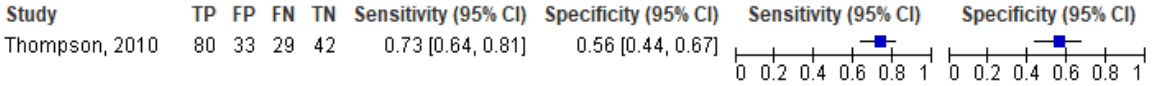
Personality Assessment scale: Psychogenic nonepileptic seizures (PNES) scale; threshold <1



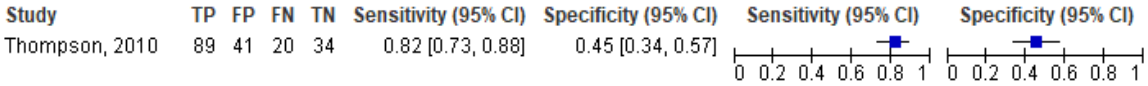
Personality Assessment scale: SOM-C (conversion) scale; threshold <70



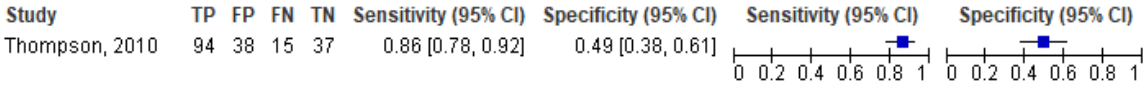
Personality Assessment scale: SOM (somatic complaints); threshold <70



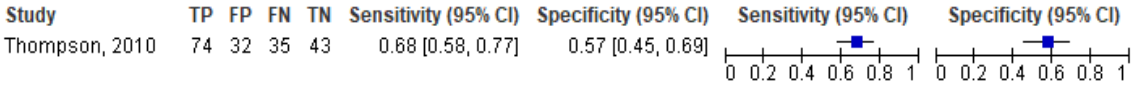
Personality Assessment scale: SOM-S (somatisation); threshold <70



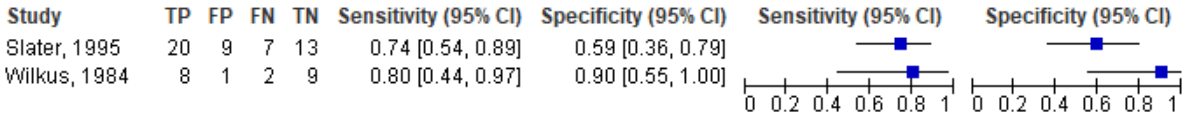
Personality Assessment scale: DEP-P (Depression-physiological); threshold <70



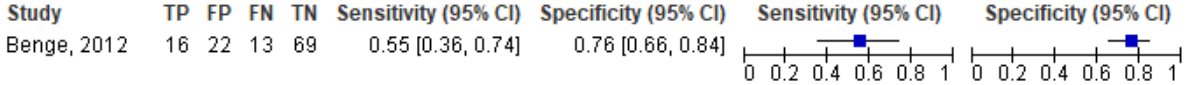
Personality Assessment scale: ANX-P (Anxiety-Physiological); threshold <60



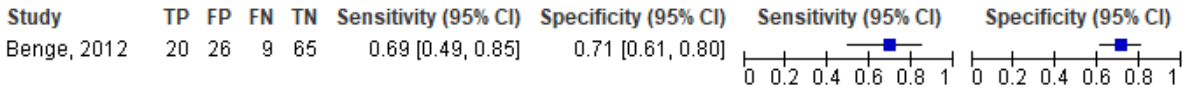
Wilkus measure of hysteria and hypochondriasis: A patients has pseudo seizures if any of the following are true: a) hysteria or hypochondriasis score >=70 and one of the two highest points in the profile (disregarding the masculinity-femininity and social introversion scales, b) hysteria or hypochondriasis score >=80 and not necessarily among the two highest points, c) hysteria and hypochondriasis both >59 and both 10 points higher than the depression scale. In a sample where ONLY epilepsy and PNES patients are known to exist then this test could be used to show that epilepsy exists if NONE of these conditions exists.



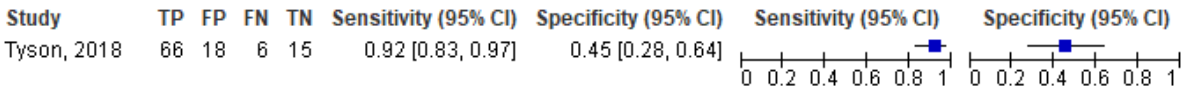
Structured Interview of malingered Symptomatology questionnaire; threshold <14



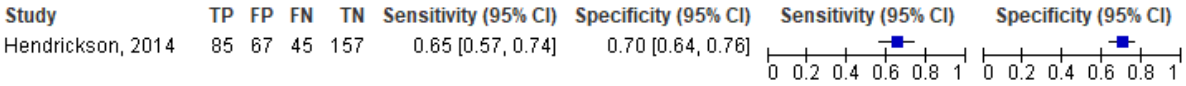
Structured Interview of malingered Symptomatology questionnaire; threshold <16



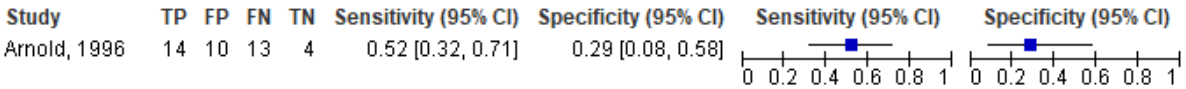
Multivariate model of psychometric testing using 4 measures of cognitive ability – vocabulary, information, Boston naming test and letter fluency (unclear description in article)



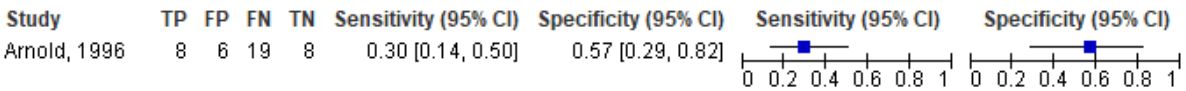
Number of panic attack symptoms <5



lifetime axis 1 (no details or score threshold available)

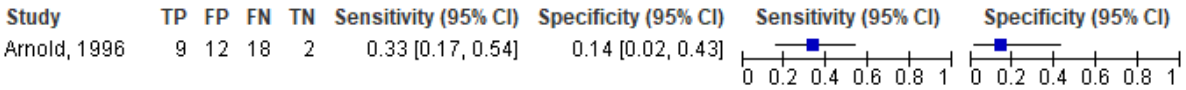


Current axis 1 (no details or score threshold available)



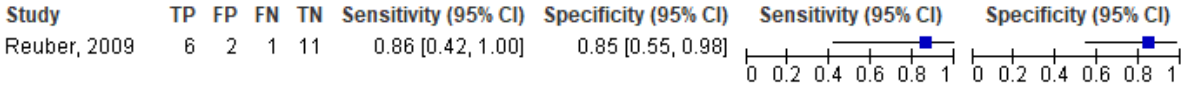
Current axis II (no details or score threshold available)

Any psychological trauma (yes/No). Criteria not given.

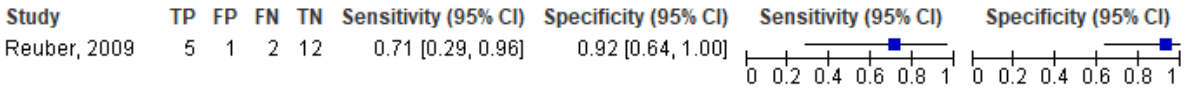


E.1.1.8 Linguistic tests

Linguistic analysis following guidelines from the German EpiLing project (rater 1) – threshold of >4.5

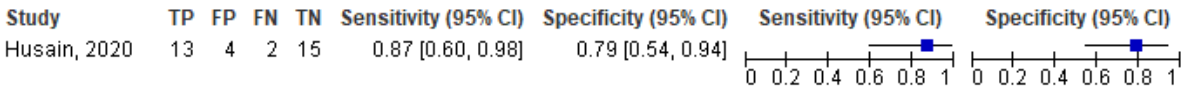


Linguistic analysis following guidelines from the German EpiLing project (rater 2) with threshold of >7.5



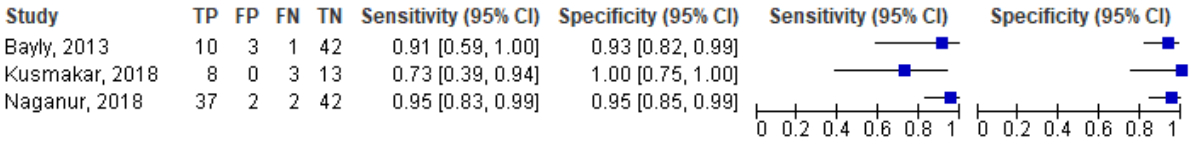
E.1.1.9 EMG tests

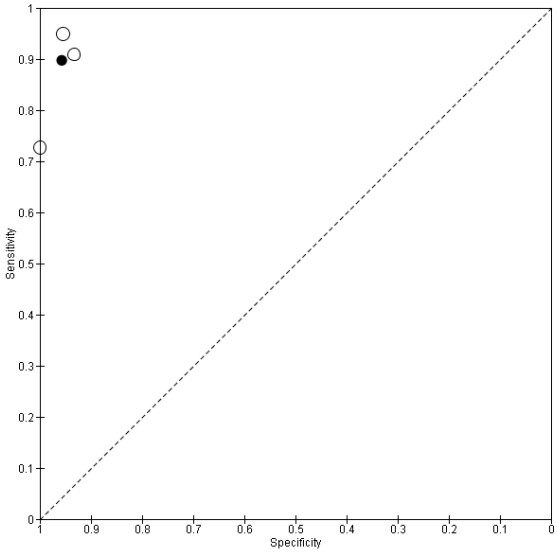
Single channel surface EMG (on biceps muscle belly). ICTAL. Decision based on automated criteria (score between 0-25 with a score of 8 or above = epilepsy).



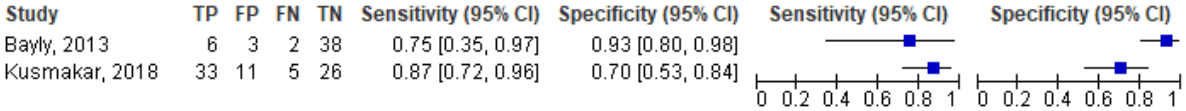
E.1.1.10 accelerometers

Wrist accelerometer. ICTAL. (automated).



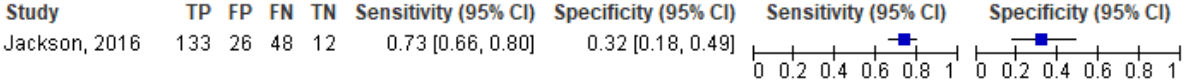


Wrist accelerometer (non-automated). ICTAL. (Bayly, 2013 used visual review of time-frequency maps by epileptologist, but criteria unclear. Kusmakar, 2018 used review of the Poincare-derived temporal variations by epileptologists but again criteria unclear)

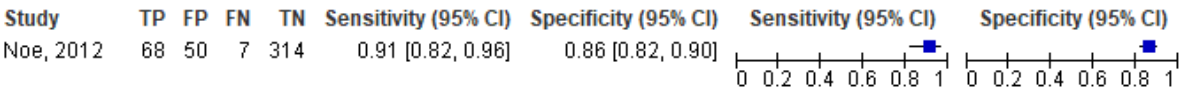


E.1.1.11 Initial diagnosis at admission

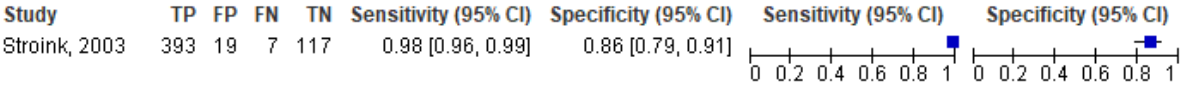
ED assessment. Included full blood examination and tests for blood glucose levels, liver function, urea and electrolytes, as well as calcium and magnesium. Drug and ethanol levels were performed on a case-by-case basis. Computed tomography (CT) neuroimaging was usually performed for all patients presenting with first seizures, unless there is a contraindication. Cerebrospinal fluid (CSF) examination is performed when meningitis or encephalitis is suspected.



Impression of admitting epileptologist, based on review of history, physical and available diagnostic testing as documented in the medical record prior to vEEG.

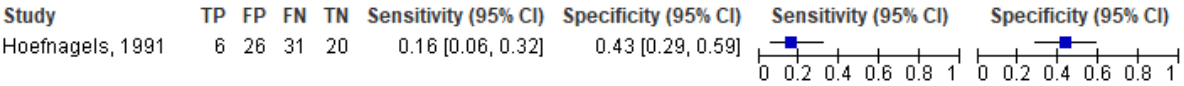


Initial Clinical diagnosis. Attending pediatric neurologist completed an extensive questionnaire on description of events, including postictal signs, possible provoking factors, medical history and family history. (CHILDREN)

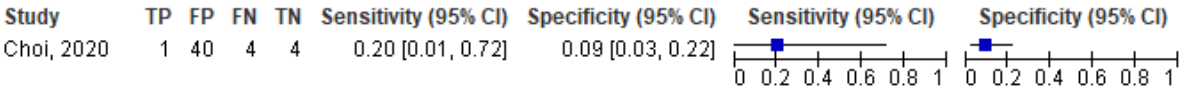


E.1.1.12 Miscellaneous

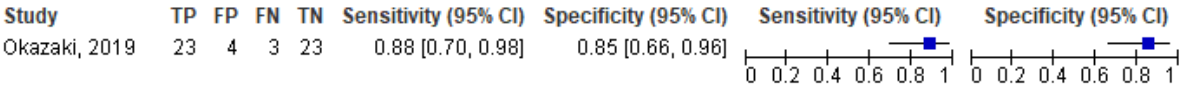
Hyperventilation and blood gas recovery. If patient <65years, had an additional hyperventilation test (40 breaths per minute for 3 minutes. End tidal CO2 level had to be <2.5% after hyperventilation. Blood gases measured. Hyperventilation test considered negative if end tidal CO2 did not restore to >90% baseline value after 3 minutes recovery.



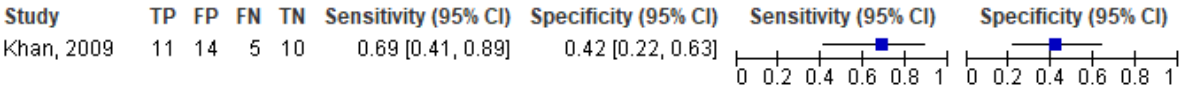
Head up tilt test (no details available in paper)



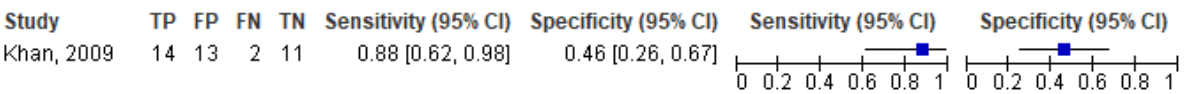
Epifinder application (a clinical decision support tool). Epifinder's algorithm is a form of artificial intelligence that is based on pattern recognition. It utilises standardised terminology and heuristic algorithms that produce a list of differential diagnoses based on pattern recognition of a cluster of semiology against ILAE-defined epilepsy criteria



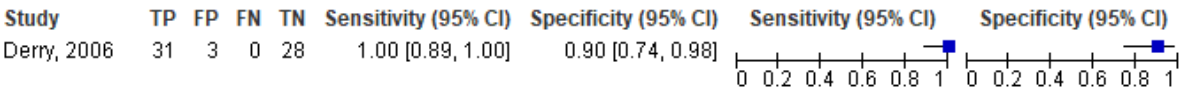
Hypnosis Induction Profile (HIP) score (threshold of <=9)



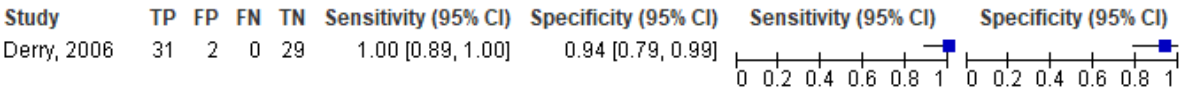
Not having an event during hypnosis



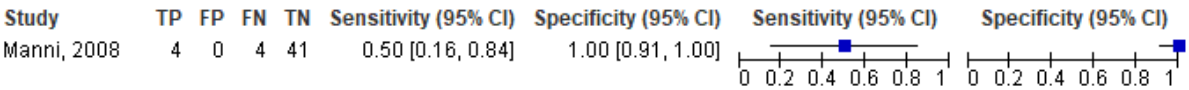
Frontal Lobe Epilepsy and Parasomnias (FLEP) scale. Threshold not provided. DETECTING NOCTURNAL FRONTAL LOBE EPILEPSY



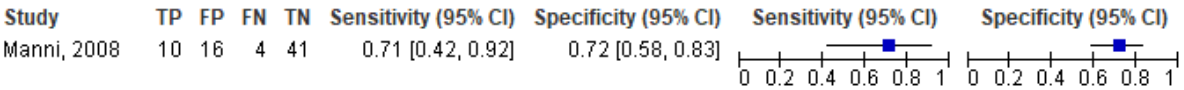
Frontal Lobe Epilepsy and Parasomnias (FLEP) scale. Threshold not provided. DETECTING NOCTURNAL FRONTAL LOBE EPILEPSY



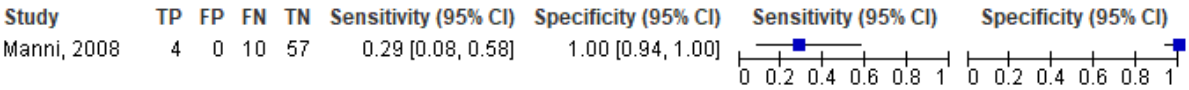
FLEP scale (excluding those with scores in uncertain range of 1-3). Threshold >3



FLEP scale (including those with scores in uncertain range of 1-3 = NFLE). Threshold >0

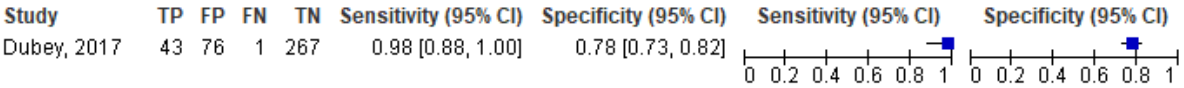


Nocturnal frontal lobe epilepsy (including those with scores in uncertain range of 1-3 = NO NFLE). Threshold>3



E.1.1.13 Stratum 2 – serum measures

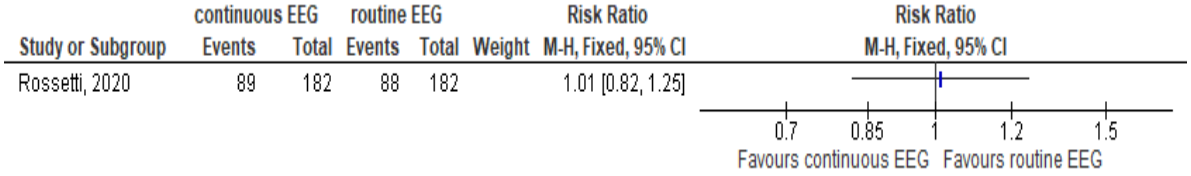
Antibody prevalence in Epilepsy (APE) score; threshold >=4. DETECTING AUTOIMMUNE EPILEPSY



E.2 Diagnostic strategies

E.2.1 Continuous EEG (30-48 hours) versus routine EEG

Figure 1: continuous EEG vs routine EEG for mortality at 6 months



Appendix F GRADE tables

Table 112: Clinical evidence profile: continuous EEG vs Routine EEG

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous EEG	Routine EEG	Relative (95% CI)	Absolute		
Mortality at 6 months												
1	randomised trials	serious[1]	Not applicable	no serious indirectness	No serious imprecision	none	89/182 (48.9%)	31.7% (48.4%)	RR 1.01(0.82 to 1.25)	5 more per 1000 (from 87 fewer to 121 more)	MOD	CRITICAL
Health-related Quality of life (Better indicated by higher values)												
0	No evidence available					none	0	-	-	not pooled		CRITICAL
Seizures at 6 months												
1	randomised trials	serious[1]	Not applicable	no serious indirectness	No serious imprecision	none	29/182 (15.7%)	4.4%	RR 3.59 (1.68 to 7.63)	113 more per 1000 (from 30 more to 290 more)	MOD	CRITICAL
Adverse events at 6 months												
1	randomised trials	serious[1]	Not applicable	no serious indirectness	serious imprecision[2]	none	47/185 (25.4%)	30.6%	RR 0.83 (0.60 to 1.15)	52 fewer per 1000 (from 122 fewer to 46 more)	LOW	CRITICAL
Seizure frequency at 6 months												
0	No evidence available					none	0	-	-	not pooled		CRITICAL
Time to withdrawal of treatment at 6 months												
0	No evidence available					none	0	-	-	not pooled		CRITICAL

a risk of bias was very serious because of possible selection bias
b the confidence intervals crossed the lower MID of 0.8

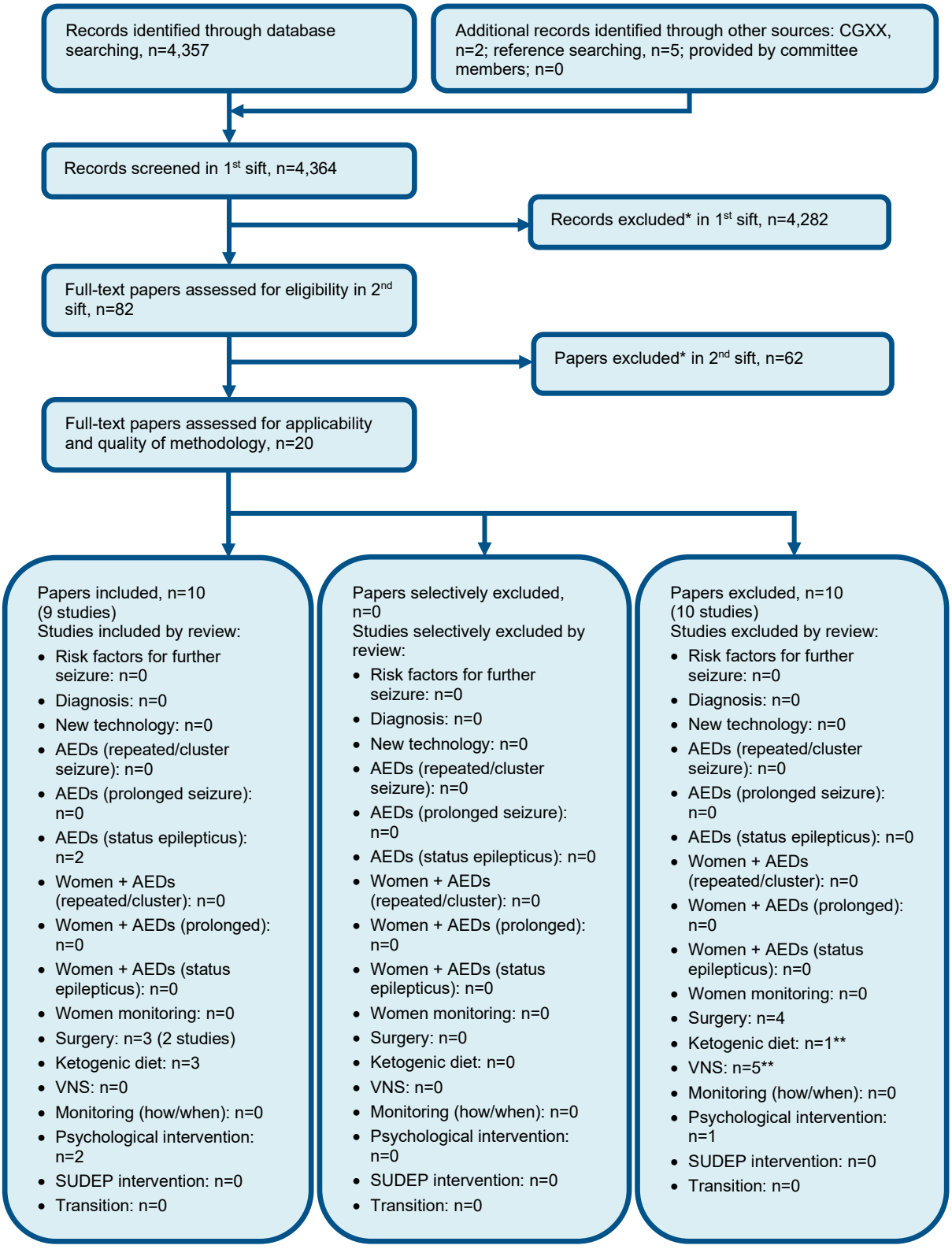
Table 113: Clinical evidence profile: micro EEG + routine care vs Routine care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	micro EEG	Routine care	Relative (95% CI)	Absolute		
Mortality at unclear timepoint												
1	randomised trials	serious[1]	Not applicable	no serious indirectness	Very serious imprecision	none	4/73 (5.5%)	4/76 (5.3%)	RR 1.04(0.27 to 4.01)	2 more per 1000 (from 38 fewer to 158 more)	MOD	CRITICAL
Health-related Quality of life (Better indicated by higher values)												
0	No evidence available					none	0	-	-	not pooled		CRITICAL
Seizures												
0	No evidence available					none	0	-	-	not pooled		CRITICAL
Adverse events												
0	No evidence available					none	0	-	-	not pooled		CRITICAL
Seizure frequency												
0	No evidence available					none	0	-	-	not pooled		CRITICAL
Time to withdrawal of treatment												
0	No evidence available					none	0	-	-	not pooled		CRITICAL

a risk of bias was very serious because of possible selection bias

b the confidence intervals crossed the lower MID of 0.8 and the upper MID of 1.25

Appendix G Health economic evidence selection



* Non-relevant population, intervention, comparison, design or setting; non-English language
**Please note that 1 article related to two questions. For this reason, the numbers listed for each review may not total the number of full text articles assessed for applicability and quality of methodology.

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Appendix H Health economic evidence tables

None.

Appendix I Health economic model

No original economic modelling was undertaken for this review question.

Appendix J QUADAS2 risk of bias assessment

Study	Random selection or case control	Index test with blinding of gold standard test results	Gold standard test with blinding of index test results	Time interval between index and gold standard adequately short (within 1 week)	Loss of data from analysis	Overall risk of bias
Albadareen, 2016[6]	Random	Y	U	U	Y – 78 enrolled but 30 analysed	Very serious
Alving, 1998[7]	Case-control	U	Y	U	N	Serious risk of bias
Arnold, 1996[10]	Random	Y	U	U	N	Serious risk of bias
Asadi-Pooya, 2016[11]	Case-control	U	U	U	N	Very serious risk of bias
Azar, 2008[16]	U	U	U	U	5 lost for post-ictal confusion (all epilepsy group) but none lost from other index tests	Very serious
Bayly, 2013[20]	U	Y	Y	U	None lost from the CoV analysis. 7/56 lost from the analysis for time frequency maps.	Serious
Benbadis, 1995[25]	Case control	U	U	U	N	Very serious
Benge, 2012[26]	Random	U	U	U	N	Serious risk of bias
Bernardo, 2018[28]	Case control	Y	U	U	N	Serious
Chen, 2008[39]	Case-control strategy	Y	U	Okay – 1 year follow up for GS diagnosis so unlikely any people falsely	N	Serious risk of bias

Study	Random selection or case control	Index test with blinding of gold standard test results	Gold standard test with blinding of index test results	Time interval between index and gold standard adequately short (within 1 week)	Loss of data from analysis	Overall risk of bias
				coded as 'no epilepsy'		
Choi, 2020[43]	Random	U	U	U	N	Serious
Deli, 2021[56]	Random	U	U	U	N	Serious risk of bias
Derry, 2006[58]	Case control	Y	Y	U	22/84 not contactable or refused to participate	Serious
Dixit, 2013[60]	Case-control	U	U	U	N	Very serious risk of bias
Dogan, 2017[61]	Case control	U	U	U	N	Very serious
Douw, 2010[62]	Case control	U	U	Okay – 1 year follow up for GS diagnosis so unlikely any people falsely coded as 'no epilepsy'	N	Very serious
Dubey, 2017[64]	Random	U	U	U	N	Serious risk of bias
Duez, 2016[65]	Random	U	U	Okay – 1 year follow up for GS diagnosis so unlikely any people falsely coded as 'no epilepsy'	N	Serious

Study	Random selection or case control	Index test with blinding of gold standard test results	Gold standard test with blinding of index test results	Time interval between index and gold standard adequately short (within 1 week)	Loss of data from analysis	Overall risk of bias
Egawa, 2020[68]	Random	N	N	U	N	Serious risk of bias
Ehsan, 1996[69]	Random	U	U	U	N	Serious risk of bias
Erba, 2016[73]	Random	Y (for 4/5 raters)	U	U	N	Serious risk of bias
Ettinger, 1998[75]	Consecutive	Y	Y	U	N	No serious risk of bias
Ettinger, 1999[74]	Case-control	U	U	U	N	Very serious risk of bias
Geut, 2017[81]	Random	U	U	Okay – 1 year follow up for GS diagnosis so unlikely any people falsely coded as 'no epilepsy'	N	Serious
Geyer, 2000[82]	Case-control	Y	U	U	N	Very serious risk of bias
Giorgi, 2013[84]	Random	Y	U	U	N	Serious risk of bias
Gonzalez-Cuevas, 2018[86]	Random	Y	U	U	N	Serious risk of bias
Goselink, 2019[87]	Random	U	U	U	N	Serious risk of bias
Hanrahan, 2018[90]	Unclear	U	U	U	N	Serious risk of bias
Hendrickson, 2014[92]	Case-control	U	U	U	N	Very serious risk of bias
Hoefnagels, 1991[94]	Random	Y for EEG	U	Okay – 14 month follow up for GS diagnosis so	N	Serious risk of bias

Study	Random selection or case control	Index test with blinding of gold standard test results	Gold standard test with blinding of index test results	Time interval between index and gold standard adequately short (within 1 week)	Loss of data from analysis	Overall risk of bias
				unlikely any people falsely coded as 'no epilepsy'		
Huang, 2019[96]	Random	U	Y	U	N	Serious risk of bias
Husain, 2020[97]	Random	Y	U	U	N – only 17/71 people's data analysed but there is no other way that a study of events could occur	Serious risk of bias
Jackson, 2016[99]	Random	Y	N	U	N	Serious risk of bias
Jaraba, 2019[100]	Random	Y	Y	U	N	No serious risk of bias
Keezer, 2016[102]	Random	Y	Y	U	N	No serious risk of bias
Khan, 2009[107]	Random	U	U	U	3 withdrew consent-<10%	Serious risk of bias
Kimiskidis, 2017[109]	Case control	U	Unclear – but epileptologists determining GS were 'not involved in the index test' measurement	U	N	Serious
Knox, 2018 [111]	Random	U	N	Okay – 1 year follow up for GS diagnosis so unlikely any	Yes – 223 excluded for being followed up for < 1year. These may have had	Very serious

Study	Random selection or case control	Index test with blinding of gold standard test results	Gold standard test with blinding of index test results	Time interval between index and gold standard adequately short (within 1 week)	Loss of data from analysis	Overall risk of bias
				people falsely coded as 'no epilepsy'	systematically different accuracy profiles	
Koren, 2018[114]	Random	N	N	U	N	Serious risk of bias
Kusmakar, 2018[116]	Random	Y	Y	U	N	No serious risk of bias
Leitinger, 2016[124]	Random	Y	Y	U	N	No serious risk of bias
Li, 2017[125]	Random	U	U	U	N	Serious risk of bias
Manni, 2008[131]	Random	Y	Y	U	The presented results excluded 22 people who had unclear index test results. However the data were clearly presented and so it was possible to calculate the accuracy with these included	No serious risk of bias
McGinty, 2021[132]	Random	U	U	U	N	Serious risk of bias
Mueller, 2013[136]	Case control strategy	U	U	U	N	Very serious risk of bias
Naganur, 2018[137]	Case control strategy	U	U	U	N	Very serious risk of bias
Noe, 2012[143]	Random	U	U	U	N	Serious risk of bias
Okazaki, 2019[144]	Random	U	U	U	N - 4 excluded because of no event (but <10%)	Serious risk of bias

Study	Random selection or case control	Index test with blinding of gold standard test results	Gold standard test with blinding of index test results	Time interval between index and gold standard adequately short (within 1 week)	Loss of data from analysis	Overall risk of bias
Oliva, 2008[145]	Random	U	Y	U	N	Serious risk of bias
Ottman, 2010[146]	Case control	Y	U	U	Participation rate among eligible subjects only 34%	Very serious
Rawlings, 2017 [158]	Case-control	U	U	U	N	Very serious risk of bias
Renzel, 2015[159]	Random	Unclear but same investigators assessed	Unclear but same investigators assessed	Probably	No	Serious
Reuber, 2009[161]	Random	U	Y	U	N	Serious risk of bias
Reuber, 2016[160]	Case-control	U	U	U	N	Very serious risk of bias
Rosenow, 1998[163]	Random	Performed by patient's parent who would probably know diagnosis (though unclear)	Unclear for those with absence seizures; however GS diagnosis of those with non epileptic seizures were blinded to index test results	U	No – occasional loss of data for some index tests but <10%	Serious
Rowberry, 2020[166]	Random	U	U	U	N	Serious risk of bias
Schmidt, 2016[171]	Case control	U	U	U	U	Very serious
Sen, 2007[176]	Case-control	U	U	U	N	Very serious risk of bias
Seneviratne, 2017[177]	Random	U	Y	U	N	Serious risk of bias
Sierra-Marcos, 2011[179]	Random	Index tests conducted by 2 'independent' physiologists	U	Okay – 1 year follow up for GS diagnosis so	>10% (26/131) not included in evaluation of early EEG	Serious

Study	Random selection or case control	Index test with blinding of gold standard test results	Gold standard test with blinding of index test results	Time interval between index and gold standard adequately short (within 1 week)	Loss of data from analysis	Overall risk of bias
				unlikely any people falsely coded as 'no epilepsy'		
Simani, 2018[180]	Case control	U	U	U	N	Very serious risk of bias
Slater, 1995[181]	Case-control	U	U	U	N	Very serious risk of bias
Stroink, 2003[184]	Random	Y – index test results finalised prior to gold standard results	N – the gold standard included the index test findings, with information from follow up period in addition	Okay – 1-5 year follow up for GS diagnosis so unlikely any people falsely coded as 'no epilepsy'	Y – 221/881 initially excluded for having a "definite other diagnosis".	Serious risk of bias
Swartz, 2002[186]	Random	N	N	U	>10%	Very serious risk of bias
Syed, 2011[191]	Random	Y	U	U	N	Serious risk of bias
Tatum, 2020[193]	Random	Y	U	U	Only 1% of sample had a smartphone video to volunteer	Serious
Tews, 2015[194]	Random	U	U	Okay – 4 year follow up for GS diagnosis so unlikely any people falsely	N	Serious

Study	Random selection or case control	Index test with blinding of gold standard test results	Gold standard test with blinding of index test results	Time interval between index and gold standard adequately short (within 1 week)	Loss of data from analysis	Overall risk of bias
				coded as 'no epilepsy'		
Thompson, 2010[196]	Case control	U	U	U	Y – 19 excluded for valid PAI profiles	Very serious risk of bias
Tyson, 2018[199]	Random	U	U	U	N	Serious risk of bias
van Diessen, 2013[200]	Case-control	U	U	U	N	Very serious
Varma, 1996[203]	Case-control	Y	U	U	N	Very serious risk of bias
Verhoeven, 2018[205]	Case-control	U	U	U	N	Very serious
Vukmir, 2004[209]	Random	U	U	U	N	Serious
Watson, 2012[213]	Random	U	U	U	N	Serious
Wilkus, 1984[215]	Random	Y	U	U	N	Serious risk of bias
Willert, 2004[216]	Random	U	U	U	N	Serious risk of bias

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Appendix K Excluded studies

K.1 Excluded clinical studies

Table 114: Studies excluded from the clinical review

Reference	Reason for exclusion
Aass, 1956[1]	No diagnostic accuracy analysis; no gold standard
Ahdab, 2014[2]	No diagnostic accuracy analysis; no gold standard
Alam-Eldeen, 2015[4]	No diagnostic accuracy analysis; no gold standard
Alapirtti, 2012[5]	No diagnostic accuracy analysis; no gold standard
Al-Qudah, 1999[3]	No diagnostic accuracy analysis; no gold standard
An, 2016[8]	No sensitivity or specificity data presented, and no data from which to calculate them. AUC data presented but outside scope of review.
Angus-Leppan, 2008[9]	No diagnostic accuracy analysis; no gold standard
Asano, 2005[12]	No diagnostic accuracy analysis; no gold standard
Ashrafi, 2010[13]	RCT but not comparing true diagnostic strategies
Aydin, 2012[14]	All in sample had epilepsy; accuracy of lateralisation, not epilepsy sub-type
Azar, 2010[15]	Cancelled order
Barras, 2019[17]	Detecting generalised tonic clonic (GTC) seizures. However, the non-GTC group contained some with focal seizures as well as some without epilepsy. Therefore, this paper does not fit into either stratum – neither differentiating GTC from no epilepsy, nor GTC from other epilepsy
Barry, 2000[18]	No diagnostic accuracy analysis for detecting epilepsy
Batalha, 2010[19]	Not in English
Beghi, 2020[21]	Predominantly use of Italian conversational analysis as a diagnostic marker (majority of conversations in Italian) - not relevant for non-Italian-speaking patients
Bell, 1998[22]	No diagnostic accuracy analysis carried out
Benbadis, 1996[24]	No clear description of the gold standard
Benbadis, 2005[23]	Unable to determine the accuracy of detecting epilepsy from the data (the study was detecting PNES, and the non-PNES group comprised groups additional to people with epilepsy)
Beniczky, 2013[27]	The gold standard was not a gold standard for an epilepsy diagnosis, but instead a gold standard for detection of epileptiform activity during testing.
Bettini, 2014[29]	No diagnostic accuracy analysis; no gold standard
Bianchi, 2019[30]	No diagnostic accuracy analysis; no gold standard
Biberon, 2020[31]	Use of French conversational analysis as a diagnostic marker - not relevant for non-French-speaking patients
Bouma, 2016[32]	Review - references checked
Bozorg, 2009[34]	CONFERENCE PAPER
Bozorg, 2010[33]	No diagnostic accuracy analysis; no gold standard
Brenner, 2015[35]	The gold standard was not a gold standard for an epilepsy diagnosis, but instead a gold standard for detection of epileptiform activity during testing.
Bronen, 1996[36]	Not concerning diagnostic accuracy of detecting epilepsy or types of epilepsy, but instead the accuracy of detecting brain abnormalities in people already diagnosed with epilepsy
Buttle, 2019[37]	Neonates
Chemmanam, 2009[38]	No diagnostic accuracy analysis; no gold standard
Chen, 1995[40]	No diagnostic accuracy analysis; no gold standard
Chen, 2016[41]	No diagnostic accuracy analysis; no gold standard
Chochoi, 2017[42]	Gold standard not definitive - a third category of 'possible epilepsy' made it an inappropriate gold standard for a diagnostic accuracy review.
Chowdhury, 2013[44]	No specificity data (only those with GS positive status in study)
Cobb, 1954[45]	No diagnostic accuracy analysis; no gold standard
Collins, 1988[46]	Gold standard diagnosis insufficiently described
Colon, 2009[47]	Gold standard not definitive - a third category of 'possible epilepsy' made it an inappropriate gold standard for a diagnostic accuracy review.

Reference	Reason for exclusion
Colon, 2017[48]	Gold standard not definitive - a third category of 'possible epilepsy' made it an inappropriate gold standard for a diagnostic accuracy review.
Cornaggia, 2016[49]	Use of Italian conversational analysis as a diagnostic marker - not relevant for non-Italian-speaking patients
Cragar, 2003[50]	Unable to determine the accuracy of detecting epilepsy from the data (the study was detecting PNES, and although only PNES and ES patients were included, those with PNES and ES concurrently were classified, for diagnostic accuracy purposes, as PNES)
Cuthill, 2005[51]	SR - references checked
Dash, 2016[52]	Study provided diagnostic accuracy for carers' description of semiological signs compared to the gold standard of VEEG. However, it appears likely that the gold standard of VEEG simply confirmed the nature of the semiological signs manifested by the patient rather than the diagnosis itself. Thus, the diagnostic accuracy data in relation to that index test is not relevant to this review. The study also provided some data on the type of seizure inferred from home video and medical history, in relation to the type of seizure inferred from the gold standard of VEEG. Unfortunately, although the marginal data for a 2x2 table were provided, the data required to populate the 2x2 interior cells were not available, nor were they calculable.
De Paola, 2016[53]	Unable to determine the accuracy of detecting epilepsy from the data (the study was detecting PNES, and although only PNES and ES patients were included, those with PNES and ES concurrently were classified, for diagnostic accuracy purposes, as PNES)
Deacon, 2003[54]	The gold standard was not a gold standard for an epilepsy diagnosis, but instead a gold standard for detection of epileptiform activity during testing.
del Barrio, 2016[55]	Diagnostic tool to diagnose psychogenic seizures
DeRoos, 2009[57]	RCT, but no protocol outcomes
Dhanuka, 2001[59]	No diagnostic accuracy analysis; no gold standard
Du Pont-Thibodeau, 2017[63]	The gold standard was not a gold standard for an epilepsy diagnosis, but instead a gold standard for detection of epileptiform activity during testing.
Dyken, 1974[66]	Abstract
Ebersole, 1983[67]	Inadequate gold standard - EEG without video or use of other clinical assessment
El-Kader, 2009[70]	Paper not available in UK or for purchase
Elmer, 2020[71]	Did not address specificity
Elzawahry, 2010[72]	No diagnostic accuracy analysis; no gold standard
Evans, 2010[76]	Neonates
Foley, 1995[77]	No diagnostic accuracy analysis
Fonseca Hernandez, 2018[78]	No diagnostic accuracy analysis
Frenkel, 2011[79]	Neonates
Gates, 1985[80]	Unable to determine the accuracy of detecting epilepsy from the data (the study was detecting PNES, and although only PNES and ES patients were included, those with PNES and ES concurrently were classified, for diagnostic accuracy purposes, as PNES)
Gilbert, 2000[83]	Review - references checked
Goenka, 2018[85]	The gold standard was not a gold standard for an epilepsy diagnosis, but instead a gold standard for detection of epileptiform activity during testing.
Granados Sanchez, 2018[88]	detection of mesial temporal sclerosis, which is associated with TLE but is not in itself a sub-type of epilepsy
Grau-Lopez, 2017[89]	No proper gold standard: 'high clinical suspicion' and 'low clinical suspicion'.
Hauf, 2009[91]	No diagnostic accuracy analysis
Hernandez-Ronquillo, 2020[93]	Predictive study; protocol
Hong, 2014[95]	detection of focal cortical dysplasia, which is associated with ETLE but is not in itself a sub-type of epilepsy
Izadyar, 2018[98]	No clear definition of the gold standard
Kadivar, 2019[101]	Review
Kerr, 2017[103]	Results unclear
Kerr, 2017[105]	Results appear to be for detection of PNES, though this is not entirely clear; because non-PNES were not exclusively people with epilepsy, we cannot infer accuracy for detection of epilepsy from these results
Kerr, 2018[104]	Unable to determine the accuracy of detecting epilepsy from the data (the study was detecting PNES, and the non-PNES were not solely those with epilepsy, but included other groups such as physiologic non-epileptic events

Reference	Reason for exclusion
	as well. This meant that exchanging sensitivity and specificity data was not a viable strategy to derive data relating to accuracy of detection of epilepsy)
Khamis, 2012[106]	No specificity data (only those with GS positive status in study)
Khurana, 2006[108]	Diagnostic accuracy for detecting syncope and breath holding but not epilepsy
King, 1998[110]	No diagnostic accuracy analysis; no gold standard
Kolls, 2007[112]	No clear definition of the gold standard
Koome, 2016[113]	No adequate gold standard method described
Koster, 2020[115]	Gold standard not definitive - a third category of 'possible epilepsy' made it an inappropriate gold standard for a diagnostic accuracy review.
Kuyk, 1999[117]	No clear definition of the gold standard
Lalgudi Ganesan, 2018[118]	The gold standard was not a gold standard for an epilepsy diagnosis, but instead a gold standard for detection of epileptiform activity during testing.
Lancman, 1994[119]	No gold standard for epilepsy
Laroia, 1998[120]	Neonates
Lawley, 2015[121]	SR - references checked
Lawley, 2016[122]	No diagnostic accuracy analysis; no gold standard
Lee, 2008[123]	Not diagnosing epilepsy or type of epilepsy
Limotai, 2019[127]	Gold standard combined epilepsy with 'probable seizures'.
Limotai, 2020[126]	protocol
Liu, 2017[128]	Neonates
Liu, 2018[129]	No sensitivity or specificity data presented in a form that could be used
Manez Miro, 2018[130]	No clear definition of the gold standard: 'final diagnosis at discharge'
McGonigal, 2002[133]	Population suspected of non-epileptic seizures; not a population suspected of epilepsy
McKenzie, 2017[134]	The gold standard was not a gold standard for an epilepsy diagnosis, but instead a gold standard for detection of epileptiform activity during testing. 92% had been previously diagnosed with epilepsy, but only 51/205 had epileptiform activity on the gold standard.
Morales, 1995[135]	Neonates
Nguyen-Michel, 2016[139]	No diagnostic accuracy analysis; no gold standard
Nitzschke, 2011[141]	No clear definition of the gold standard: 'final diagnosis at discharge'
Nitzschke, 2012[142]	No clear definition of the gold standard: 'final diagnosis at discharge'
Ouyang, 2020[147]	Gold standard admitted to being insufficient by authors - the seizures in some of those deemed to have a positive gold standard diagnosis of epilepsy were 'insufficient for an absolute diagnosis of epilepsy'.
Paldino, 2017[148]	accuracy of detection of seizure focus, not diagnosis
Papagno, 2017[149]	Use of Italian conversational analysis as a diagnostic marker - not relevant for non-Italian-speaking patients
Patel, 2016[150]	No specificity evaluation
Pedersen, 2016[151]	No clear definition of the gold standard
Pensirikul, 2013[152]	The gold standard was not a gold standard for an epilepsy diagnosis, but instead a gold standard for detection of epileptiform activity during testing.
Pollard, 2013[153]	Gold standard was only ictal EEG and not any other data. Also, this gold standard was not applied to control groups
Rafiei, 2004[154]	No protocol outcomes covered
Rakshasbhuvankar, 2017[155]	Neonates
Ramanujam, 2018[156]	Sensitivity and specificity data for PNES but no sensitivity and specificity data (or raw data from which it could be calculated) for epilepsy
Rasmussen, 1987[157]	Abstract
Robles, 2015[162]	Gold standard diagnosis insufficiently described
Rossetti, 2018[164]	protocol
Saeed, 2010[167]	Not available
Sargolzaei, 2015[168]	No description of gold standard method
Satpute, 2014[169]	CONFERENCE PAPER
Schindler, 2001[170]	The gold standard was not a gold standard for an epilepsy diagnosis, but instead a gold standard for detection of epileptiform activity during testing.
Schoenenberger, 1994[172]	No diagnostic accuracy analysis for detection of epilepsy
Schorner, 1987[173]	No specificity analysis possible as all participants had temporal lobe epilepsy
Schramke, 2010[174]	No diagnostic accuracy analysis

Reference	Reason for exclusion
Schreiner, 2003[175]	No diagnostic accuracy analysis; no gold standard
Shah, 2020[178]	SR - references checked
Slooter, 2006[182]	The gold standard was not a gold standard for an epilepsy diagnosis, but instead a gold standard for detection of epileptiform activity during testing.
Stewart, 2010[183]	The gold standard was not a gold standard for an epilepsy diagnosis, but instead a gold standard for detection of epileptiform activity during testing.
Sun, 2018[185]	The gold standard was not a gold standard for an epilepsy diagnosis, but instead a gold standard for detection of epileptiform activity during testing.
Swingle, 2020[187]	The gold standard was not a gold standard for an epilepsy diagnosis, but instead a gold standard for detection of epileptiform activity during testing.
Swisher, 2015[188]	No clear definition of the gold standard
Syed, 2008[190]	Unable to determine the accuracy of detecting epilepsy from the data (the study was detecting PNES, and although only PNES and ES patients were included, those with PNES and ES concurrently were classified, for diagnostic accuracy purposes, as PNES)
Syed, 2009[189]	Unable to determine the accuracy of detecting epilepsy from the data (the study was detecting PNES, and although only PNES and ES patients were included, those with PNES and ES concurrently were classified, for diagnostic accuracy purposes, as PNES)
Tafakhori, 2011[192]	No diagnostic accuracy analysis; no gold standard
Thangavelu, 2016[195]	Gold standard diagnosis insufficiently described
Titgemeyer, 2020[197]	The gold standard was not a gold standard for an epilepsy diagnosis, but instead a gold standard for detection of epileptiform activity during testing.
Topjian, 2015[198]	The gold standard was not a gold standard for an epilepsy diagnosis, but instead a gold standard for detection of epileptiform activity during testing.
van Donselaar, 1992[201]	Unclear gold standard - appeared to be simply recurrence of seizures, which would not 'diagnose' epilepsy
Vanderzant, 1986[202]	No gold standard method described for diagnosis of epilepsy
Velasco, 2011[204]	detection of mesial temporal sclerosis, which is associated with TLE but is not in itself a sub-type of epilepsy
Vespa, 2020[206]	No diagnostic accuracy analysis; no gold standard
Vilyte, 2019[207]	Gold standard diagnosis insufficiently described
Von Oertzen, 2002[208]	accuracy of detection of seizure focus, not diagnosis
Wagner, 2005[210]	Gold standard diagnosis insufficiently described
Wang, 2019[211]	The gold standard was not a gold standard for an epilepsy diagnosis, but instead a gold standard for detection of epileptiform activity during testing.
Wardrope, 2018[212]	SR - references checked
Weber, 2017[214]	No clear definition of the gold standard
Yan, 2017[217]	The gold standard was not a gold standard for an epilepsy diagnosis, but instead a gold standard for detection of epileptiform activity during testing.
Zibrandtsen, 2017[219]	The gold standard was not a gold standard for an epilepsy diagnosis, but instead a gold standard for detection of epileptiform activity during testing.
Zou, 2017[220]	Gold standard diagnosis insufficiently described

K.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 115: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	