National Institute for Health and Care Excellence

Final

Epilepsies in children, young people and adults

[C] Effectiveness of genetic testing in determining the aetiology of epilepsy

NICE guideline NG217

Evidence reviews underpinning recommendations 1.4.1-1.4.5

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Final

These evidence reviews were developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists

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Evidence review for effectiveness of genetic testing in determining the aetiology of epilepsy

Review question

What is the effectiveness of genetic testing in determining the aetiology of epilepsy?

Introduction

The epilepsies are, where possible, classified as syndromes defined by clinical and neurophysiological features. Increasingly we are able to identify a cause for the epilepsy syndrome, particularly in those with complex drug resistant epilepsies. Recent years have seen the identification of a growing number of gene mutations that cause epilepsy providing important information for patients and families. Most, but not all, of the gene mutations that cause epilepsy are not inherited and occur spontaneously in affected individuals. Improved understanding of the underlying mechanisms by which gene changes cause epilepsy may lead to new developments in treatment. The main aim of this review is to determine the diagnostic yield of genetic testing in people with epilepsy.

Summary of the protocol

Please see Table 1for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	People with confirmed epilepsy
Intervention	The following types of genetic tests will be considered: • Chromosomal microarray analysis (CMA)/ Microarray-based comparative genomic hybridization (aCGH) • Karyotyping • Single-gene testing • Gene-panel testing • Whole exome sequencing (WES) • Whole genome sequencing (WGS)
Comparison	• No genetic testing
Outcomes	• Diagnostic yield of any genetic abnormality

aCGH: array comparative genomic hybridization; CMA: chromosomal microarray analysis; WES: whole exome sequencing; WGS: whole genone sequencing

For further details see the review protocol in appendix A.

Methods and process

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 (supplementary document 1).

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

Clinical evidence

Included studies

Thirty-nine observational studies (prospective/ retrospective single-arm cohort and cross-sectional studies) were identified for inclusion in this review (Allen 2015, Allen 2016, Angione 2019, Borlot 2017, Borlot 2019, Boutry-Kryza 2015, Coppola 2019, Costain 2019, Demos 2019, Dimassi 2016, Ezugha 2010, Galizia 2012, Hamdan 2017, Hildebrand 2016, Howell 2018, Jang 2019, Ko 2018, Kobayashi 2016, Kodera 2013, Kothur 2018, Lindy 2018, Oates 2018, Ostrander 2018, Palmer 2018, Papuc 2019, Parrini 2017, Peng 2019, Perucca 2017, Peycheva 2018, Ream 2014, Rim 2018, Snoeijen-Schouwenaars 2019, Symonds 2019, Tsang 2019, Tsuchida 2018, Tumiene 2018, Ware 2019, Wirrell 2015, Yuskaitis 2018).

In addition, 1 systematic review (Fernandez 2019) evaluating the diagnostic yield of 3 different tests and including 20 observational studies was identified (Bartnik 2012, Berg 2017, Butler 2017, Della Mina 2015, Dyment 2015, Helbig 2014, Helbig 2016, Hrabik 2015, Lamke 2012, Mefford 2010, Mefford 2011, Mercimek-Mahmutoglu 2015, Michaud 2014, Moller 2016, Olson 2014, Retterer 2016, Segal 2016, Trump 2016, Veeramah 2013, Wang 2014).

Twenty-one studies provided information on the diagnostic yield of chromosomal microarray analysis (CMA) in people with epilepsies (Allen 2015, Angione 2019, Bartnik 2012, Berg 2017, Borlot 2017, Boutry-Kryza 2015, Coppola 2019, Ezugha 2010, Falizia 2012, Helbig 2014, Howell 2018, Hrabik 2015, Mefford 2010, Mefford 2011, Michaud 2014, Olson 2014, Papuc 2019, Peycheva 2018, Ream 2014, Tsang 2019, Wirrell 2015).

Two studies provided information on the diagnostic yield of karyotyping (Ream 2014, Wirrell 2015).

Four studies provided information for single-gene testing (Angione 2019, Howell 2018, Ream 2014, Wirrell 2015).

Twenty-six studies provided information for gene-panel testing (Angione 2019, Berg 2017, Borlot 2019, Butler 2017, Della Mina 2015, Hildebrand 2016, Howell 2018, Jang 2019, Ko 2018, Kodera 2013, Kothur 2018, Lemke 2012, Lindy 2018, Mercimek-Mahmutoglu 2015, Moller 2016, Oates 2018, Parrini 2017, Peng 2019, Ream 2014, Rim 2018, Segal 2016, Symonds 2019, Trump 2016, Wang 2014, Ware 2019, Wirrell 2015).

Twenty-four studies provided information for whole exome sequencing (WES) (Allen 2016, Angione 2019, Berg 2017, Costain 2019, Demos 2019, Dimassi 2016, Dyment 2015, Helbig 2016, Howell 2018, Kobayashi 2016, Michaud 2014, Palmer 2018, Papuc 2019, Peng 2019, Perucca 2017, Ream 2014, Retterer 2015, Snoeijen-Schouwenaars 2019, Tsang 2019, Tsuchida 2018, Tumiene 2018, Veeramah 2013, Ware 2019, Yuskaitis 2018).

Three studies provided information for whole genome sequencing (WGS) (Hamdan 2017, Howell 2018, Ostrander 2018).

For ease of interpretation, all genetic tests have been referred to in the summary of clinical studies and in the adapted GRADE tables (appendix F) as per the names outlined in the protocol. However, the included studies may have referred to these with alternative names, which would have been reflected in the clinical evidence tables (appendix D). For example, in appendix D, CMA may have been reported as array comparative genomic hybridization (aCGH); gene-panel testing as epilepsy panel, epilepsy gene panel, gene panel, gene panel analysis, next generation sequencing (NGS) panel testing and WGS as whole-genome analysis (WGA).

The included studies are summarised in Table 2 to Table 7.Table 2: Summary of included studies for CMA

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2 for CMA,

Table 3 for karyotyping, Table 4 for single-gene testing, Table 5 for gene-panel testing, Table 6 for WES, and Table 7 for WGS.

Table 2: Summary of included studies for CMA

Study	Population	Genetic test
Allen 2015 Single-arm retrospective cohort Ireland	N=51 children with unexplained severe early onset epilepsy Age at seizure onset: 4.7 months (range 1 to 12 months) 49% male The proportion of people with developmental delay was not reported	CMA
Angione 2019 Single-centre retrospective chart review US	N=77 people with myoclonic-atonic seizures Age was not reported 75% male The proportion of people with developmental delay was not reported	CMA, single-gene testing, WES
Borlot 2017 Cross-sectional Canada	N=143 adults with unexplained childhood onset epilepsy and intellectual disability Age¥: 24.6 years (SD 10.8 years) 48% male All adults presented with intellectual disability	CMA

Study	Population	Genetic test
Boutry-Kryza 2015 Multicentre prospective cohort study France	N= 73 infants with infantile spasms Demographic characteristics were not reported	CMA
Coppola 2019 Multicentre retrospective cohort study UK, Belgium, Italy, US, Poland	N=1225 people with epilepsy plus comorbid conditions Demographic characteristics were not reported	CMA
Ezugha 2010 Retrospective chart review US	N=22 children with epilepsy Age¥: 5.7 years (SD 5 years) 55% males 90% presented with learning disabilities	CMA
Galizia 2012 Retrospective cohort study UK	N=82 adults with drug-resistant epilepsy Age¥: 18 to 81 years old 51.9% males (based on n=54, average age of the remaining was not reported) The proportion of people with developmental delay was not reported	CMA
Howell 2018 Population based study (prospective and retrospective) Australia	N= 114 infants with severe epilepsies of infancy (genetic testing done in n=74) Demographic characteristics were not reported	CMA, single-gene testing, gene-panel testing, WES, WGS
Papuc 2019 Single-arm cohort study Switzerland	N=63 children with epileptic encephalopathies or developmental and epileptic encephalopathies Age¥: 7 months (range 1 to 51 months) Proportion of males was not reported	CMA, WES

Study	Population	Genetic test
	All children presented with at least moderate intellectual disability	
Peycheva 2018 Retrospective cohort Bulgaria	N=92 people with epilepsy and intellectual disability, generalized epilepsy, autistic signs and congenital abnormalities Age[¥]: between 1 and 22 years 54% males All presented with some degree of intellectual disability	CMA
Ream 2014 Single-arm retrospective cohort study US	N= 29 children with drug-resistant epilepsy Age at epilepsy onset: 2.5 years (SD 3.1 years) 48.2% males 89.65% presented with developmental delay	Karyotyping, CMA, single-gene testing, gene-panel testing, WES
Tsang 2019 Single-arm cohort study China	N=50 children with drug-resistant epilepsy Age at seizure onset: 7 months (range 1 day to 9.3 years) 56% males The proportion of children with developmental delay was not reported	CMA, WES
Wirrell 2015 Single-arm prospective cohort study US	N=251 children with infantile spasms Age at seizure onset: 7.1 months (SD 3.6 months) 53.6% males The proportion of infants with infantile spasms was not reported	CMA, karyotyping, single-gene testing, gene-panel testing, WES

CMA: chromosomal microarray analysis; SD: standard deviation; WES: whole exome sequencing; *WGS: whole genome sequencing*

[¥]*Age is at assessment unless otherwise specified*

If the study included people with epilepsy and people with other condition(s), only data for those with epilepsy was reported

Table 3: Summary of the included studies for karyotyping

Study	Population	Genetic test
Ream 2014 Single-arm retrospective cohort study US	N= 29 children with drug-resistant epilepsy Age at seizure onset (SD): 2.5 year (3.1 years) 48.2% males 89.65% presented with developmental delay	Karyotyping, CMA, single-gene testing, gene-panel testing, WES
Wirrell 2015 Single-arm prospective cohort study US	N=251 children with infantile spasms Age at seizure onset: 7.1 months (SD 3.6 months) 53.6% males The proportion of infants with infantile spasms was not reported	CMA, karyotyping, single-gene testing, gene-panel testing, WES

CMA: chromosomal microarray analysis; WES: whole exome sequencing
¥Age is at assessment unless otherwise specified
If the study included people with epilepsy and people with other condition(s), only data for those with epilepsy was reported

Table 4: Summary of the included studies for single-gene testing

Study	Population	Genetic test
Angione 2019 Single-centre retrospective chart review US	N=77 people with myoclonic-atonic seizures Age was not reported 75% male The proportion of people with developmental delay was not reported	CMA, single-gene testing, gene-panel testing (number of genes tested was not specified), WES
Howell 2018 Population based study (prospective and retrospective) Australia	N= 114 infants with severe epilepsies of infancy (genetic testing done in n=74) Demographic characteristics were not reported	CMA, single-gene testing, gene-panel testing, WES, WGS
Ream 2014 Single-arm retrospective cohort study US	N= 29 children with drug-resistant epilepsy Age at seizure onset: 2.5 years (SD 3.1 years) 48.2% males	Karyotyping, CMA, single-gene testing, gene-panel testing, WES

Study	Population	Genetic test
	89.65% presented with developmental delay	
Wirrell 2015 Single-arm prospective cohort study US	N=251 children with infantile spasms Age at seizure onset: 7.1 months (SD 3.6 months) 53.6% males The proportion of infants with developmental delay was not reported	CMA, karyotyping, single-gene testing, gene-panel testing, WES

CMA: chromosomal microarray analysis; SD: standard deviation; WES: whole exome sequencing; WGS: whole genome sequencing
¥Age is at assessment unless otherwise specified
If the study included people with epilepsy and people with other condition(s), only data for those with epilepsy was reported

Table 5: Summary of the included studies for gene-panel testing

Study	Population	Genetic test
Angione 2019 Single-centre retrospective chart review US	N=77 people with myoclonic-atonic seizures Age was not reported 75% male The proportion of people with developmental delay was not reported	CMA, single-gene testing, gene-panel testing, WES
Borlot 2019 Cross-sectional US	N=64 adults with long-standing epilepsy and intellectual disability Age¥: 31 years (SD 9.6 years) All adults presented with intellectual disability	Gene-panel testing (126, 183, 184 or 185 genes)
Fernandez 2019 Systematic review of observational studies US	K=20 studies, including people with epilepsy of unknown aetiology k=4 studies including children and k=16 including adults and children k=1 included people with developmental delay only, the other studies reported people with and without people with developmental delay or did not provide information regarding learning disabilities	CMA, gene-panel testing (from 46 to 265 genes) and WES

Study	Population	Genetic test
Hildebrand 2016 Retrospective cohort study Australia	N=255 people with focal epilepsy without a known acquired cause Demographic characteristics were not reported	Gene-panel testing (11 genes)
Howell 2018 Population based study (prospective and retrospective) Australia	N= 114 infants with severe epilepsies of infancy Demographic characteristics were not reported	CMA, single-gene testing, gene-panel testing (number of genes tested was not specified), WES, WGS
Jang 2019 Single-arm retrospective cohort study South Korea	N=112 children with a seizure onset before the age of 1 Demographic characteristics were not reported	Gene-panel testing (79 to 127 genes)
Ko 2018 Single-arm cohort study South Korea	N=278 children with developmental and epileptic encephalopathy Age and proportion of males was not reported All children had progressive developmental deterioration or a known developmental and epileptic encephalopathy	Gene-panel testing (172 genes)
Kodera 2013 Single-centre cohort study with positive controls Japan	N=68 early onset epileptic encephalopathies Age¥: < 1-year-old 53% males All children had developmental delay	Gene-panel testing (35 genes)
Kothur 2018 Single-arm retrospective cohort Australia	N=105 children with epileptic encephalopathy *Demographic characteristics only reported for* people *with pathogenic and likely pathogenic variants:* Age¥: between 0.3 months and 11 years 57% males	Gene-panel testing (47 or 71 genes)

Study	Population	Genetic test
	86% presented with developmental delay	
Lindy 2018 Single-arm retrospective cohort US	N=8565 people with epilepsy and neurodevelopmental disorders Demographic characteristics were not reported	Gene-panel testing (70 genes)
Oates 2018 Single-arm prospective cohort study UK	N=96 children with early-onset (<2 years) epilepsy, treatment resistant epilepsy, epilepsy of unknown cause, or familial epilepsy where the genetic cause was unknown Age¥: between 2 months and 19.9 years The proportion of males and people with developmental delay was not reported	Gene-panel testing (45, 76, 85, or 102 genes)
Parrini 2017 Single-arm prospective cohort study Italy	N=349 children with drug-resistant paediatric epilepsies Demographic characteristics were not reported	Gene-panel testing (30 or 95 genes)
Peng 2019 Pilot prospective cohort China	N=273 children with paediatric drug resistant epilepsy Age¥: 13.2 months (SD 20.8) 65% males The proportion of people with developmental delay was not reported	Gene-panel testing (initially 308 genes, then updated to include 540 genes), WES
Ream 2014 Single-arm retrospective cohort study US	N= 29 children with drug-resistant epilepsy Age at seizure onset (SD): 2.5 years (SD 3.1 years) 48.2% males 89.65% presented with developmental delay	Karyotyping, CMA, single-gene testing, gene-panel testing, WES

Study	Population	Genetic test
Rim 2018 Single-arm prospective cohort South Korea	N=74 children with intractable early onset epilepsy Age at epilepsy onset: 7.5 months (SD 7.8 months) The proportion of males was not reported 83.8% presented with developmental delay	Gene-panel testing (172 genes)
Symonds 2019 Cohort study UK	N=343 children with epilepsy Age¥: under 36 months old The proportion of males was not reported 30.1% had developmental delay	Gene-panel testing (104 genes)
Ware 2019 Single-group cohort study Australia	N=16 children with infantile onset developmental and epileptic encephalopathies Age at epilepsy onset: 6 months (range 3 days to 20 months) 31% males All children had evidence of developmental delay, plateauing or regression	Gene-panel testing (423 genes), WES
Wirrell 2015 Single-arm prospective cohort study US	N=251 children with infantile spasms Age at epilepsy onset: 7.1 months (SD 3.6 monthd) 53.6% males The proportion of infants with infantile spasms was not reported	CMA, karyotyping, single-gene testing, gene-panel testing, WES

CMA: chromosomal microarray analysis; SD: standard deviation; WES: whole exome sequencing; WGS: whole genome sequencing
¥Age is at assessment unless otherwise specified
If the study included people with epilepsy and people with other condition(s), only data for those with epilepsy was reported

Table 6: Summary of the included studies for WES

Study	Population	Genetic test
Allen 2016 Single-arm retrospective cohort Ireland	N=50 children with early-onset epileptic encephalopathies Age¥: under 2 years old The proportion of males and people with developmental delay was not reported	WES
Angione 2019 Single-centre retrospective chart review US	N=77 people with myoclonic-atonic seizures Age was not reported 75% male The proportion of people with developmental delay was not reported	CMA, single-gene testing, WES
Costain 2019 Retrospective cohort study Canada	N=197 people with childhood epilepsy Age¥: years, median (range): 4.5 (0 to 17) 93% male 92.8% presented with developmental delay	WES
Demos 2019 Two-arm prospective cohort study Canada	N=180 infants with early-onset epilepsy Age at epilepsy onset: 18 months (range 0.03 to 60 months) 43% males 61% presented with global developmental delay	WES
Dimassi 2016 Single-arm cohort France	N=10 infants with infantile spasms Demographic characteristics were not reported	WES
Fernández 2019 Systematic review of observational studies US	K=20 studies, including people with epilepsy of unknown aetiology k=4 studies including children and k=16 including adults and children k=1 included people with developmental delay only, the other	CMA, gene-panel testing, and WES

Study	Population	Genetic test
	studies reported people with and without people with developmental delay or did not provide information regarding learning disabilities	
Howell 2018 Population based study (prospective and retrospective) Australia	N= 114 infants with severe epilepsies of infancy (up to n=74 undergoing genetic testing) Demographic characteristics were not reported	CMA, single-gene testing, gene-panel testing, WES, WGS
Kobayashi 2016 Single-arm retrospective cohort study Japan	N=11 children with early-onset epileptic encephalopathies Age at onset: between 2 and 11 months 36% males All children presented with developmental delay	WES
Palmer 2018 Single-centre cohort study Australia	N=32 children with infantile-onset epileptic encephalopathy Age¥: 46.6 months Proportion of males was not reported All children presented with developmental stagnation or regression	WES
Papuc 2019 Single-arm cohort study Switzerland	N=63 children with epileptic encephalopathies or developmental and epileptic encephalopathies Age¥: 7 months (range 1 to 51 months) Proportion of males was not reported All children presented with at least moderate intellectual disability	CMA, WES

Study	Population	Genetic test
Peng 2019 Pilot prospective cohort China	N=273 children with paediatric drug resistant epilepsy Age¥: 13.2 months (SD 20.8 months) 65% males The proportion of people with developmental delay was not reported	Gene-panel testing (initially 308 genes, then updated to include 540 genes), WES
Perucca 2017 Single-arm cohort study Australia	N= 40 people with focal epilepsies Age¥: 32.5 years (range 2 to 74 years) 60% males 2.5% with intellectual disability	WES
Ream 2014 Single-arm retrospective cohort study US	N= 29 children with drug-resistant epilepsy Age at seizure onset: 2.5 years (SD 3.1 years) 48.2% males 89.65% presented with developmental delay	Karyotyping, CMA, single-gene testing, gene-panel testing, WES
Snoeijen-Schouwenaars 2019 Single-arm retrospective cohort study The Netherlands	N=100 people with unexplained epilepsy Age¥: 24.1 years (SD 16.2 years) 55% males All presented with developmental delay	WES
Tsang 2019 Single-arm cohort study China	N=50 children with drug-resistant epilepsy Age at onset: 7 months (range 1 day to 9.3 years) The proportion of children with developmental delay was not reported	CMA, WES
Tsuchida 2018 Single-centre cohort study Japan	N=294 children with early-onset epileptic encephalopathies Age was not reported 57.7% males All presented with developmental delay	WES

Study	Population	Genetic test
Tumiene 2018 Single-arm retrospective cohort study Slovenia	N=86 people with syndromic epilepsy The proportion of males was not reported Age was not reported 79% presented with developmental delay	WES
Ware 2019 Single-group cohort study Australia	N=16 children with infantile onset developmental and epileptic encephalopathies Age at onset: 6 months (range 3 days to 20 months) All children had evidence of developmental delay, plateauing or regression	Gene-panel testing (423 genes), WES
Wirrell 2015 Single-arm prospective cohort study US	N=251 children with infantile spasms Age at epilepsy onset: 7.1 months (SD 3.6 months) 53.6% males The proportion of infants with infantile spasms was not reported	CMA, karyotyping, single-gene testing, gene-panel testing, WES
Yuskaitis 2018 Single-arm retrospective multicentre cohort study US, Canada	N=126 children with infantile spasms of known cause (WES data was available for n=100) Age[¥]: 5.25 months (range 1.50 to 11 months) 43.6% males 25.5% had developmental delay	WES

CMA: chromosomal microarray analysis; SD: standard deviation; WES: whole exome sequencing; WGS: whole genome sequencing
[¥]Age is at assessment unless otherwise specified
If the study included people with epilepsy and people with other condition(s), only data for those with epilepsy was reported

Table 7: Summary of the included studies for WGS

Study	Population	Genetic test
Hamdan 2017 Multicentre single arm cohort study Canada	N=197 people with developmental and epileptic encephalopathies Age and proportion of males was not reported All people had learning disabilities or global developmental delay	WGS

Study	Population	Genetic test
Howell 2018 Population based study (prospective and retrospective) Australia	N= 114 infants with severe epilepsies of infancy Demographic characteristics were not reported	CMA, single-gene testing, gene-panel testing, WES, WGS
Ostrander 2018 Single-arm cohort study US	N=14 children with infantile epileptic encephalopathy Age¥: between 0 and 7 months 36% males All children presented with developmental delay	WGS

CMA: chromosomal microarray analysis; WES: whole exome sequencing; WGS: whole genome sequencing
¥Age is at assessment unless otherwise specified
If the study included people with epilepsy and people with other condition(s), only data for those with epilepsy was reported

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

- Very low quality evidence showed that the overall proportion of people with pathogenic and likely pathogenic abnormalities identified with CMA were 10%.

  Proportion of people with pathogenic and likely pathogenic abnormalities identified with CMA in subgroups were as follows:
  - Children <3 years old at seizure onset: 4%
  - People with learning disability, including neurodevelopmental disorders: 11%
- Very low quality evidence showed that the overall proportion of people with pathogenic and likely pathogenic variants identified with karyotyping were 30%.

  All participants in the overall pooled estimate were children <3 years old at seizure onset.
- Very low quality evidence showed that the overall proportion of people with pathogenic and likely pathogenic variants identified with single-gene testing were 13%.

  Proportion of people with pathogenic and likely pathogenic variants identified with simple-gene testing in subgroups were as follows:
  - Children <3 years old at seizure onset: 15%
- Very low quality evidence showed that the overall proportion of people with pathogenic and likely pathogenic variants identified with gene-panel testing were 18%.

  Proportion of people with pathogenic and likely pathogenic variants identified with gene-panel testing in subgroups were as follows:
  - Children <3 years old at seizure onset: 38%
  - People with learning disabilities/difficulties, including neurodevelopmental disorders: 11%

- Very low quality evidence showed that the overall proportion of people with pathogenic and likely pathogenic variants identified with WES were 34%.

  Very low quality evidence showed that the proportion of people with pathogenic and likely pathogenic variants identified with WES in subgroups were as follows:
  - Children <3 years old at seizure onset: 26%
  - People with learning disabilities/ difficulties, including neurodevelopmental disorders: 33%
- Very low quality evidence showed that the proportion of people with pathogenic and likely pathogenic variants identified in subgroup analyses for point along the pathway were as follows:
  - People who received early WES and limited metabolic testing: 53%
  - People who only received limited metabolic testing but not WES testing: 45%
- Very low quality evidence showed that the overall proportion of people with pathogenic and likely pathogenic variants identified with WGS were 55%.

  Proportion of people with pathogenic and likely pathogenic variants identified with WGS in subgroups were as follows:
  - People with learning disabilities/ difficulties, including neurodevelopmental disorders: 90%

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

One relevant study was identified in a literature review of published economic evidence on this topic (Plumpton 2015; see appendix H and appendix I for summary and full evidence tables). The study considered the cost-effectiveness of HLA-A*31:01 genotyping prior to prescription of carbamazepine for epilepsy compared to standard care. The study considered a population representative of carbamazepine-naive patients with focal-onset seizures who were newly diagnosed, who had failed treatment with previous monotherapy, or who had entered a period of remission from seizures but had relapsed after withdrawal of treatment.

The analysis was a cost-utility analysis measuring effectiveness in terms of quality adjusted life years (QALYs). The analysis adopted the perspective of the NHS & PSS.

Excluded studies

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

Summary of studies included in the economic evidence review

The base-case results of Plumpton 2015 suggest that HLA-A*31:01 genotyping prior to prescription of carbamazepine for epilepsy is more effective and more costly than standard care (that is carbamazepine prescribed without testing) in patients with focal epilepsy, who had failed treatment with previous monotherapy, or who had entered a period of remission from seizures but had relapsed after withdrawal of treatment. The estimated base-case incremental cost-effectiveness ratio (ICER) of £12,808 per

QALY is below the conventional threshold range specified by NICE to represent cost-effective use of resources of £20,000 per QALY.

Uncertainty was assessed using deterministic and probabilistic sensitivity analysis. Results were found to be sensitive to the remission rates of both lamotrigine and valproate, health state utilities (mostly of lamotrigine), and costs associated with carbamazepine and lamotrigine treatment. It was also found that the cost-effectiveness of the test depended on the choice of alternative anti-epileptic medications (ASMs), and the order in which ASMs are prescribed (for example, equalizing the cost, utility, and efficacy of lamotrigine with valproate resulted in testing being more expensive and less effective). However as stated in the paper, because valproate is not routinely recommended as a first line treatment option in focal epilepsy, comparisons against newer ASMs may be more appropriate. In probabilistic sensitivity analysis HLA-A*31:01 testing was found to have 80% probability of being cost-effective at a threshold of £20,000 per QALY, and 88% probability of being cost-effective at a threshold of £30,000 per QALY.

Despite being a UK study considering the NHS perspective, the study was considered to be only partially applicable. This is because the study doesn't directly address the review question posed in the guideline, as the economic analysis focused on pharmacogenetics rather than on the diagnostic yield of genetic testing. The study was deemed to have minor limitations, as it meets most of the requirements of an adequate economic evaluation (see Developing NICE guidelines: appendix H).

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Resource impact

One relevant study was identified in a literature review of published economic evidence on this topic (Plumpton 2015; see appendix H and appendix I for summary and full evidence tables). The study considered the cost-effectiveness of HLA-A*31:01 genotyping prior to prescription of carbamazepine for epilepsy compared to standard care. However, this review question was not prioritised for bespoke economic modelling. To aid considerations of cost-effectiveness the cost of genetic testing for epilepsy have been reported using the UK Genetic Testing Network (UKGTN - https://ukgtn.nhs.uk/) in November 2019.

Table 6 reports the NHS costs for the genetic tests for epilepsy covered by the evidence review. The UKGTN report costs of performing a genetic test at individual NHS laboratories. Where multiple laboratories offer the same tests the lowest cost has been presented. These costs only include the costs of performing the genetic test and do not cover follow-on costs including discussing results with individuals and changes to treatment as a result. Only the costs associated with post-natal testing were considered as all other testing was beyond the scope of the review question.

Where possible a cost per diagnosis of genetic abnormality has been presented based on results of the accompanying clinical evidence review. This is calculated by dividing the NHS cost by diagnostic yield estimated in the clinical evidence review. Again this analysis does not include follow-on costs.

Table 8: Cost per diagnosis of genetic abnormality

Genetic test	NHS cost	Cost per diagnosis of genetic abnormality	Source
Chromosomal microarray analysis (CMA)	N/A	Not estimable	UKGTN
Karyotyping	N/A	Not estimable	UKGTN
Single-gene testing for Dravet Syndrome	£525b	£4,038	UKGTN
	£140c	£1,077	
Single-gene testing for Epilepsy, Pyridoxine-Dependent	£460a	£3,538	UKGTN
	£185c	£1,423	
Single-gene testing for EEEI, 1	£90c	£692	UKGTN
Single-gene testing for EEEI, 2	£500b	£3,846	UKGTN
	£160c	£1,231	
Single-gene testing for EEEI, 4	£400a	£3,077	UKGTN
Single-gene testing for EEEI, 9	£250a	£2,692	UKGTN
	£350b	£2,692	
Single-gene testing for Myoclonic Epilepsy Of Unverricht And Lundborg	£205c	£1,577	UKGTN
Single-gene testing for Myoclonic Epilepsy Associated With Ragged-Red Fibers	£75c	£577	UKGTN
Single-gene testing for Seizures, Sensorineural Deafness, Ataxia, Mental Retardation, And Electrolyte Imbalance	£185a	£1,423	UKGTN
48 Gene-panel testing for Epilepsy Disorders	£825a	£4,583	UKGTN
36 Gene-panel testing for EEEI	£750a	£4,167	UKGTN
72 Gene-panel testing for EEEI	£750a	£4,167	UKGTN
11 Gene-panel testing for Episodic Movement, Migraine and Epileptic Disorders (Brain Channelopathies)	£900a	£5,000	UKGTN
	£200d	£1,111	
Whole exome sequencing (WES): 110 Gene Exome Panel for Epilepsy Disorders	£1300a	£3,939	UKGTN
Whole genome sequencing (WGS)	N/A	Not estimable	UKGTN

EEEI: Epileptic Encephalopathy, Early Infantile; UKGTN: UK Genetic Testing Network; N/A: not available
a: Sequencing of the entire coding region of gene (s); b: Sequencing of the entire coding region of gene (s) PLUS copy number analysis; c: Targeted mutation analysis; d: Sequencing of selected exons

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee identified a single outcome as relevant for this review question. Diagnostic yield provides the proportion of people with pathogenic and likely pathogenic variants assessed in a specific sample. This outcome was prioritised because it describes how well a given genetic test performs in detecting variants in people with epilepsy.

The quality of the evidence

The quality of the evidence was assessed with a modified GRADE approach, using the same principles of GRADE for assessing the quality of the evidence, but a different form of presentation as GRADE is not yet available for single-arm prevalence studies. The quality of the evidence was considered to be very low for most of the outcomes. All the studies recruited a single cohort of people and performed one or more genetic tests. Although there was evidence for all the genetic tests identified in the protocol, the data was very sparse; studies included participants with epilepsies of different types and severities, and recruited in different clinical settings (for example, some were recruited in a tertiary hospital of a single country, while others were recruited across different tiers of care of different countries). Inclusion criteria varied widely, and while some studies had well defined criterion, others were population-based, which may over or under estimate the reported yield of genetic variants. These limitations mean that the overall estimates for each of the genetic tests were imprecise and heterogeneous.

The domain 'risk of bias' was assessed with the JBI checklist, and most studies were considered to be at very high risk of bias, mainly due to the sampling approaches used and concerns regarding how representative the samples were. As per the adapted GRADE approach, many of the outcomes were also downgraded due to high levels of imprecision in the estimated proportions. Other concerns included very high between-study heterogeneity amongst the included studies, for which random effects model was considered. Possible causes for this substantial heterogeneity are believed to be the variability among the included studies characteristics, such as the variety of designs, point along the pathway when genetic testing was undertaken, or excessive clinical diversity of the individuals included. It was not considered that sensitivity analyses would identify the cause for heterogeneity as excluding a few studies from the analyses on the basis of specific characteristics could add undue emphasis on post-hoc data dependent analysis. Additionally, it was not believed that this will lead to solid results, particularly when it was already established that the underlying cause of heterogeneity was not due to a single factor. Outcomes were downgraded for inconsistency, as appropriate, and the committee interpreted the evidence taking these limitations into consideration. Overall, the committee agreed that the evidence was of insufficient quality and supplemented the information provided by the review with their clinical experience and awareness of the wider literature.

The committee decided not to make a research recommendation on genetic testing as they were aware of large studies assessing the role of genetics in people with epilepsy and, as a result, they prioritised other topics for future research.

Benefits and harms

In recent years, many new genes have been identified as causing epilepsy. Genetic diagnoses can provide information about prognosis and treatment options, which can lead to improved outcomes.

The genetic tests appraised in this evidence review provided variable yields of pathogenic and likely pathogenic variants in people with epilepsy. Therefore, the committee used the evidence alongside their clinical knowledge and experience to make the recommendations.

Given the complexity of genetic testing and the implications it may have, the committee agreed that a neurologist or geneticist should be involved in discussions if

there are uncertainties about whether to offer genetic testing or which genetic test to undertake in a person with epilepsy.

The committee noted that healthcare professionals should refer to the NHS National Genomic Test Directory, which provides information on which tests are commissioned by the NHS in England, when should they be performed and the eligibility criteria. Recommendations are also in line with the NHS National Genomic Test Directory.

Deciding to undertake genetic testing may be complicated, and is important that the person with epilepsy understands the implications. A genetic diagnosis may or may not result in more effective treatment. Furthermore, the specific gene variant that is found may be inherited, which has implications for the parents and potential off-spring of the individual. Waiting for a genetic test and receiving the results can cause a mixture of emotions including fear, anxiety and guilt, therefore families should be supported about this and appropriate consent should be obtained prior to genetic testing.

The committee noted that the type of genetic test to undertake will vary depending on the type of epilepsy, age of onset and associated clinical features. Furthermore, the evidence did not support one type of genetic test over another, so the committee agreed that genetic testing should be considered in situations that are likely to yield positive diagnostic results.

Whole genome sequencing is not limited to selected genes, and looks for variants in all the protein-coding regions in the genome. The committee agreed that this type of testing should be used for people with epilepsy of unknown cause with early onset epilepsy (<2 years old) or with certain clinical features as this group has higher yield of demonstrable genetic variants.

The committee agreed that whole genome sequencing can also be considered in people with epilepsy of unkown cause with onset between 2 and 3 years if agreed with a specialist multidisciplinary team. The diagnostic yield in this group of people is affected by other co-occurring conditions and EEG and MRI findings, therefore the multidisciplinary team should integrate the clinical evaluations and agree on the best approach taking these into account.

Cost effectiveness and resource use

One economic evaluation was identified and considered by the committee in making recommendations for this question. This study was a cost-utility analysis that compared the cost-effectiveness of HLA-A*31:01 genotyping prior to prescription of carbamazepine for epilepsy to standard care in a hypothetical cohort of adult patients with newly diagnosed epilepsy, who had failed treatment with previous monotherapy, or who had entered a period of remission from seizures but had relapsed after withdrawal of treatment. Based on the cost-effectiveness results of the available evidence, the committee noted that genetic testing for HLA-A*31:01 is likely to represent a cost-effective use of health care resource, in order to reduce the incidence of cutaneous adverse drug reactions in patients being prescribed carbamazepine for epilepsy.

The committee highlighted that the evidence appraised in the economic evidence review did not provide any relevant data to make recommendations, as the analysis focused on pharmacogenetic testing rather than on the diagnostic yield of genetic testing. The committee agreed that, whilst the study took a UK NHS and PSS perspective and was deemed to only have minor methodological limitations it was

considered not fully applicable to the decision problem. Therefore, the committee used their clinical knowledge and experience to make the recommendations, and not the economic evidence. As this review question was not prioritised for bespoke economic modelling as clinical evidence to inform downstream outcomes was not available, a costing of genetic tests was therefore undertaken using the reported costs from the UK Genetic Testing Network in November 2019 to aid considerations of cost-effectiveness. The committee highlighted that there were not large cost differences between genetic tests importantly in those between single gene and panel of genes. This difference was even less pronounced when considered as a cost per diagnosis based on the values reported in the clinical evidence review. This suggested that it could be less costly to provide individuals with testing for a panel of genes rather than further sequential single gene testing. The committee believed that this was most likely to be the case where a single gene test for a person had already returned a negative result.

Based on the available evidence and their clinical knowledge and expertise, the committee agreed that the recommendations could potentially increase the number of people who receive a genetic test, and the number of people who are referred for genetic counselling; however, they discussed how the recommendations may help to reduce the number of unnecessary tests. Therefore, the committee noted that all recommendations were not likely to lead to any significant impact upon resource use, by improving the consistency in current practice with regard to who should and should not have a genetic testing.

Recommendations supported by this evidence review

This evidence review supports recommendation section 1.4.1-1.4.5.

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Appendices

Appendix A – Review protocols

Review protocol for review question: What is the effectiveness of genetic testing in determining the aetiology of epilepsy?

Table 9: Review protocol for effectiveness of genetic testing in determining the aetiology of epilepsy

Field	Content
PROSPERO registration number	CRD42019136276
Review title	Genetic testing in epilepsy
Review question	What is the effectiveness of genetic testing in determining the aetiology of epilepsy?
Objective	The objective of this review is to determine the diagnostic yield of genetic testing. This will provide information as to who and when people should be tested (by looking at yield in different sub-categories)
Searches	The following databases will be searched: • CDSR • CENTRAL • DARE • HTA • MEDLINE & MEDLINE In-Process and Other Non-Indexed Citations • Embase • EMCare Searches will be restricted by: • Date: 1995 onwards (as this is when the first epilepsy gene was identified) • English language studies

Field	Content
	• Human studies The full search strategies for MEDLINE database will be published in the final review.
Condition or domain being studied	Epilepsy
Population	Inclusion: • People with confirmed epilepsy Exclusion: • Newborn babies (under 28 days) with acute symptomatic seizures
Interventions	The following types of genetic tests will be considered: • Chromosomal microarray analysis (CMA)/ Microarray-based Comparative Genomic Hybridization (aCGH) • Karyotyping • Single-gene testing • Gene-panel testing • Whole exome sequencing (WES) • Whole genome sequencing (WGS)
Comparator	No genetic testing
Types of study to be included	• Systematic review/meta-analyses of RCT or cohort studies • RCT • Prospective/retrospective cohort studies (comparative and single arm) • Cross-sectional studies Note: For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual.
Other exclusion criteria	Studies with a mixed population (this is, including children, young people and adults with confirmed epilepsy and another condition different to epilepsy) will be excluded, unless subgroup analysis for epilepsy has been reported.

Field	Content
	Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias
Context	Recommendations will apply to those receiving care in any healthcare settings (for example, community, primary, secondary care).
Primary outcomes (critical outcomes)	• Diagnostic yield of any genetic abnormality
Secondary outcomes (important outcomes)	• None
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs • JBI checklist for prevalence studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer

Field	Content	
Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Data synthesis Yield data will be extracted from the studies, and where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as absolute rates of yield. Heterogeneity Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. I^2 values of greater than 50% and 75% will be considered as significant and very significant heterogeneity, respectively. In the presence of heterogeneity, sub-group analysis will be conducted. Exact sub-group analysis may vary depending on differences identified within included studies. If heterogeneity cannot be explained using these methods, random effects model will be used. If heterogeneity remains above 75% and cannot be explained by sub-group analysis; reviewers will consider if meta-analysis is appropriate given characteristics of included studies. Validity The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/	
Analysis of sub-groups	If enough data is identified, the following strata will be analysed separately: • Results from studies conducted at different time point along the pathway of care (as described by investigators) • adults and children • children will be split into those younger than 3 years and those 3 years and above • those with and without learning difficulties/disabilities, including neurodevelopmental disorders	
Type and method of review	☐	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☒	Epidemiologic

Field	Content		
	☐	Service Delivery	
	☐	Other (please specify)	
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Country	England		
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Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	x	x
	Piloting of the study selection process	x	x
	Formal screening of search results against eligibility criteria	x	x
	Data extraction	x	x
	Risk of bias (quality) assessment	x	x
	Data analysis	x	x
Named contact	5a. Named contact National Guideline Alliance 5b. Named contact e-mail epilepsies@nice.org.uk 5c. Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
Review team members	NGA technical team		

Field	Content
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance, which is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists. NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.
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.
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
Other registration details	Not applicable
URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019136276
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.
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Additional information	

Field	Content
Details of final publication	www.nice.org.uk

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimal important difference; NICE: National Institute for Health and Care Excellence; RCT: Randomised Controlled Trial; RoB: Risk of Bias; SD: Standard Deviation.

Appendix B – Literature search strategies

Literature search strategies for review question: What is the effectiveness of genetic testing in determining the aetiology of epilepsy?

Clinical

Database(s): EMCare, MEDLINE and Embase (Multifile) – OVID

EMCare 1995 to 2021 April 07; Embase Classic+Embase 1947 to 2021 April 07; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 2021 April 07, 2021
Date of last search: 07 April 2021

Multifile database codes: emcr=EMCare; emczd=Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	searches
1	exp epilepsy/ or landau kleffner syndrome/ or exp seizure/ or "seizure, epilepsy and convulsion"/
2	1 use emczd, emcr
3	exp epilepsy/ or seizures/ or seizures, febrile/ or exp status epilepticus/
4	3 use ppez
5	(convulsion* or dravet syndrome or epilep* or continous spike wave of slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6	or/2,4-5
7	infantile spasm/ use emczd, emcr or spasms, infantile/ use ppez or (((early or infantile) adj2 myoclonic adj2 encephalopath*) or ((early or infantile) adj2 epileptic adj2 encephalopath*) or epileptic spasm* or ((flexor or infantile or neonatal) adj2 (seizure* or spasm*)) or generali?ed flexion epileps* or hypsarrhythmia* or ((jacknife or jack nife or lightening or nodding or salaam) adj (attack* or convulsion* or seizure* or spasm*)) or massive myoclonia or minor motor epilepsy or propulsive petit mal or spasm in*1 flexion or spasmus nutans or west syndrome*).ti,ab.
8	myoclonic astatic epilepsy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez or ((myoclonic adj2 (astatic or atonic)) or (myoclonic adj3 (seizure* or spasm*)) or doose* syndrome or mae or generali?ed idiopathic epilepsy).ti,ab. or ((absence or astatic or atonic or tonic or tonic clonic) adj2 (seizure* or spasm*)).ti,ab.
9	exp benign childhood epilepsy/ use emczd, emcr or epilepsy, rolandic/ use ppez or (bcects or bects or brec or benign epilepsy or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 epileps*) or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 (convulsion* or epileps* or seizure* or spasm*)) or (benign adj3 (convulsion* or epileps*) adj2 centrotemporal adj2 spike*) or cects or ((centralopathic or centrotemporal or temporal-central focal) adj (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) adj2 (convulsion* or epileps* or seizure* or spasm*))).ti,ab.
10	landau kleffner syndrome/ use emczd, emcr, ppez or (dravet or lennox gastaut or lgs or (landau adj2 kleffner) or smei).ti,ab.
11	severe myoclonic epilepsy in infancy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez or (dravet*1 or (intractable childhood epilepsy adj2 (generalised tonic clonic or gtc)) or icegtc* or (severe adj2 (myoclonic or polymorphic) adj2 epilepsy adj2 infancy) or smeb or smei).ti,ab.
12	or/6-11
13	genetic screening/ use emczd, emcr or exp genetic testing/ use ppez
14	((gene or genes or genetic or next generation) adj2 (analys* or screen* or sequencing or test*)).ti,ab.

#	searches
15	or/13-14
16	karyotyping/ use emczd, emcr or exp karyotyping/ use ppez
17	(karyotyping* or (karyotyp* adj2 (analys* or screen* or sequenc* or test*))).ti,ab.
18	or/16-17
19	whole exome sequencing/ use emczd, emcr,ppez
20	(((complete or entire or full or whole) adj (exome or transcriptome) adj (analys* or screen* or sequencing or test*)) or wes).ti,ab.
21	or/19-20
22	whole genome sequencing/ use emczd, emcr or exp whole genome sequencing/ use ppez
23	(((complete or entire or full or whole) adj genome adj (analy* or screen* or sequencing or test*)) or wgs).ti,ab.
24	or/22-23
25	(((gene* panel or multigen* or multi gen* or multiple gen*) adj2 (analys* or sequencing or test*) adj2 panel*) or ((gene* or multigen* or multi gen* or multiple gen*) adj2 panel* adj2 (analys* or screen* or sequencing or test*))).ti,ab.
26	(single gen* adj2 (analys* or screen* or sequencing or test*)).ti,ab.
27	microarray analysis/ use emczd, emcr or chromosome analysis/ use emczd, emcr or exp microarray analysis/ use ppez
28	(array comparative genomic hybridi* or ((array or matrix) adj cgh) or acgh or (((chromosom* or snp or whole genome) adj microarray) or micro array) or microarray-based comparative genomic hybridi?ation).ti,ab.
29	or/27-28
30	or/15,18,21,24-26,29
31	12 and 30
32	limit 31 to english language
33	limit 32 to yr="1995 -current"
34	((letter.pt. or letter/ or note.pt. or editorial.pt. or case report/ or case study/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or ((animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.)
35	34 use emez
36	((letter/ or editorial/ or news/ or exp historical article/ or anecdotes as topic/ or comment/ or case report/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or ((animals not humans).sh. or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.)
37	36 use mesz
38	35 or 37
39	33 not 38

Database(s): Cochrane Library

Cochrane Database of Systematic Reviews, Issue 4 of 12, April 2021; Cochrane Central Register of Controlled Trials, Issue 4 of 12, April 2021

Date of last search 07 April 2021

#	searches
1	mesh descriptor: [epilepsy] explode all trees
2	mesh descriptor: [seizures] this term only
3	mesh descriptor: [seizures, febrile] this term only
4	mesh descriptor: [status epilepticus] explode all trees
5	(convulsion* or “dravet syndrome” or epilep* or “continous spike wave of slow sleep” or “landau kleffner syndrome” or “lennox gastaut syndrome” or “infant* spasm*” or seizure* or “west syndrome”):ti,ab
6	(((early or infantile) near/2 myoclonic near/2 encephalopath*) or ((early or infantile) near/2 epileptic near/2 encephalopath*) or “epileptic spasm*” or ((flexor or infantile or neonatal) near/2 (seizure* or spasm*)) or “generali?ed flexion epileps*” or hypsarrhythmia* or ((jacknife or “jack nife” or lightening or nodding or salaam) next (attack* or convulsion* or seizure* or spasm*)) or “massive myoclonia” or “minor motor epilepsy” or “propulsive petit mal” or “spasm in* flexion” or “spasmus nutans” or “west syndrome*”):ti,ab
7	((myoclonic near/2 (astatic or atonic)) or (myoclonic near/3 (seizure* or spasm*)) or “doose* syndrome” or mae or “generali?ed idiopathic epilepsy”) or ((absence or astatic or atonic or tonic or tonic clonic) near/2 (seizure* or spasm*)):ti,ab
8	(bcects or bects or brec or “benign epilepsy” or (benign near/2 (childhood or neonatal or pediatric or paediatric) near/2 epileps*) or (benign near/2 (childhood or neonatal or pediatric or paediatric) near/2 (convulsion* or epileps* or seizure* or spasm*)) or (benign near/3 (convulsion* or epileps*) near/2 centrotemporal near/2 spike*) or cects or ((centralopathic or centrotemporal or “temporal-central focal”) next (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near/2 (convulsion* or epileps* or seizure* or spasm*))):ti,ab
9	(dravet or “lennox gastaut” or lgs or (landau near/2 kleffner) or smei) :ti,ab
10	(dravet* or (“intractable childhood epilepsy” near/2 (generalised tonic clonic or gtc)) or icegtc* or (severe near/2 (myoclonic or polymorphic) near/2 epilepsy near/2 infancy) or smeb or smei) :ti,ab
11	{or #1-#10}
12	mesh descriptor: [genetic testing] explode all trees
13	mesh descriptor: [karyotyping] explode all trees
14	mesh descriptor: [whole exome sequencing] this term only
15	mesh descriptor: [microarray analysis] explode all trees
16	mesh descriptor: [whole genome sequencing] explode all trees
17	((gene or genes or genetic or “next generation”) near/2 (analys* or screen* or sequencing or test*)):ti,ab
18	(karyotyping* or (karyotyp* near/2 (analys* or screen* or sequenc* or test*))):ti,ab
19	(((complete or entire or full or whole) next (exome or transcriptome) next (analys* or screen* or sequencing or test*)) or wes) :ti,ab
20	(((complete or entire or full or whole) next genome next (analy* or screen* or sequencing or test*)) or wgs) :ti,ab
21	(((“gene* panel” or multigen* or “multi gen*” or “multiple gen*”) near/2 (analys* or sequencing or test*) near/2 panel*) or ((gene* or multigen* or “multi gen*” or “multiple gen*”) near/2 panel* near/2 (analys* or screen* or sequencing or test*))):ti,ab
22	(“single gen*” near/2 (analys* or screen* or sequencing or test*)):ti,ab
23	(“array comparative genomic hybridi*” or ((array or matrix) next cgh) or acgh or (((chromosom* or snp or whole genome) next microarray) or “micro array”) or “microarray-based comparative genomic hybridi?ation”) :ti,ab

#	searches
24	{or #12-#23}
25	#11 and #24 with Cochrane Library publication date from Jan 1995 to april 2021

Database(s): DARE; HTA database - CRD
Date of last search: 07 April 2021

#	searches
1	mesh descriptor epilepsy explode all trees
2	mesh descriptor seizures this term only
3	mesh descriptor seizures, febrile this term only
4	mesh descriptor status epilepticus explode all trees
5	(convulsion* or “dravet syndrome” or epilep* or “continous spike wave of slow sleep” or “landau kleffner syndrome” or “lennox gastaut syndrome” or “infant* spasm*” or seizure* or “west syndrome”)
6	(((early or infantile) near2 myoclonic near2 encephalopath*) or ((early or infantile) near2 epileptic near2 encephalopath*) or “epileptic spasm*” or ((flexor or infantile or neonatal) near2 (seizure* or spasm*)) or “generali?ed flexion epileps*” or hypsarrhythmia* or ((jacknife or “jack nife” or lightening or nodding or salaam) next (attack* or convulsion* or seizure* or spasm*)) or “massive myoclonia” or “minor motor epilepsy” or “propulsive petit mal” or “spasm in* flexion” or “spasmus nutans” or “west syndrome*”)
7	((myoclonic near2 (astatic or atonic)) or (myoclonic near3 (seizure* or spasm*)) or “doose* syndrome” or mae or “generali?ed idiopathic epilepsy”) or ((absence or astatic or atonic or tonic or tonic clonic) near2 (seizure* or spasm*))
8	(bcects or bects or brec or “benign epilepsy” or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 epileps*) or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 (convulsion* or epileps* or seizure* or spasm*)) or (benign near3 (convulsion* or epileps*) near2 centrotemporal near2 spike*) or cects or ((centralopathic or centrotemporal or “temporal-central focal”) next (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near2 (convulsion* or epileps* or seizure* or spasm*)))
9	(dravet or “lennox gastaut” or lgs or (landau near2 kleffner) or smei)
10	(dravet* or (“intractable childhood epilepsy” near2 (generalised tonic clonic or gtc)) or icegtc* or (severe near2 (myoclonic or polymorphic) near2 epilepsy near2 infancy) or smeb or smei)
11	{or #1-#10}

Economic

Database(s): MEDLINE & Embase (Multifile) - OVID
Embase Classic+Embase 1947 to 2021 March 31; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 31, 2021
Date of last search: 31 March 2021

Multifile database codes: emczd=Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	searches
1	exp epilepsy/ or exp seizure/ or "seizure, epilepsy and convulsion"/
2	1 use emczd
3	exp epilepsy/ or seizures/ or seizures, febrile/ or exp status epilepticus/
4	3 use ppez
5	(epilep* or seizure* or convuls*).ti,ab. or (continous spike wave of slow sleep or infant* spasm*).ti,ab.

#	searches
6	(seizure and absence).sh. use emczd, emcr or seizures/ use ppez or ((absence adj2 (convulsion* or seizure*)) or ((typical or atypical) adj absenc*) or petit mal* or pyknolepsy or typical absence*).ti,ab.
7	(atonic seizure or tonic seizure).sh. use emczd, emcr or exp seizures/ use ppez or ((drop or akinetic or atonic or tonic) adj2 (attack* or epileps* or seizure* or convulsion*)).ti,ab. or brief seizure.ti,ab. or (tonic adj3 atonic adj3 (attack* or epileps* or seizure* or convulsion*)).ti,ab.
8	exp benign childhood epilepsy/ use emczd, emcr or epilepsy, rolandic/ use ppez or (bcects or bects or brec or benign epilepsy or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 epileps*) or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 (convulsion* or epileps* or seizure* or spasm*)) or (benign adj3 (convulsion* or epileps*) adj2 centrotemporal adj2 spike*) or cects or ((centralopathic or centrotemporal or temporal-central focal) adj (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) adj2 (convulsion* or epileps* or seizure* or spasm*))).ti,ab.
9	exp generalized epilepsy/ use emczd, emcr or exp epilepsy, generalized/ use ppez
10	(((akinetic or atonic or central or diffuse or general or generali?ed or idiopathic or tonic) adj3 (epilep* or seizure*)) or ((childhood absence or juvenile absence or myoclonic or myoclonia or myoclonic astatic or myoclonus or gtcs) adj2 epilep*) or (epilepsy adj2 eyelid myoclonia) or (ige adj2 phantom absenc*) or impulsive petit mal or (janz adj3 (epilep* or petit mal)) or jeavons syndrome* or ((janz or lafora or lafora body or lundborg or unverricht) adj2 (disease or syndrome)) or ((jme or jmes) and epilep*) or perioral myoclon*).ti,ab.
11	infantile spasm/ use emczd, emcr or spasms, infantile/ use ppez or (((early or infantile) adj2 myoclonic adj2 encephalopath*) or ((early or infantile) adj2 epileptic adj2 encephalopath*) or epileptic spasm* or ((flexor or infantile or neonatal) adj2 (seizure* or spasm*)) or generali?ed flexion epileps* or hypsarrhythmia* or ((jacknife or jack nife or lightening or nodding or salaam) adj (attack* or convulsion* or seizure* or spasm*)) or massive myoclonia or minor motor epilepsy or propulsive petit mal or spasm in*1 flexion or spasmus nutans or west syndrome*).ti,ab.
12	landau kleffner syndrome/ use emczd, emcr, ppez or (dravet or lennox gastaut or lgs or (landau adj2 kleffner) or smei).ti,ab.
13	lennox gastaut syndrome/ use emczd, emcr or lennox gastaut syndrome/ use ppez or generalized epilepsy/ use emczd, emcr or epileptic syndromes/ use ppez
14	(child* epileptic encephalopath* or gastaut or lennox or lgs).ti,ab.
15	myoclonus seizure/ use emczd, emcr or seizures/ use ppez or ((myoclon* adj2 (absence* or epileps* or seizure* or jerk* or progressive familial epilep* or spasm* or convulsion*)) or ((lafora or unverricht) adj2 disease) or muscle jerk).ti,ab.
16	myoclonic astatic epilepsy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez or ((myoclonic adj2 (astatic or atonic)) or (myoclonic adj3 (seizure* or spasm*)) or doose* syndrome or mae or generali?ed idiopathic epilepsy).ti,ab. or ((absence or astatic or atonic or tonic or tonic clonic) adj2 (seizure* or spasm*)).ti,ab.
17	exp epilepsies, partial/ use ppez or exp focal epilepsy/ use emczd, emcr or ((focal or focal onset or local or partial or simple partial) adj3 (epileps* or seizure*)).ti,ab.
18	severe myoclonic epilepsy in infancy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez
19	(dravet*1 or (intractable childhood epilepsy adj2 (generalised tonic clonic or gtc)) or icegtc* or (severe adj2 (myoclonic or polymorphic) adj2 epilepsy adj2 infancy) or smeb or smei).ti,ab.
20	epilepsy, tonic-clonic/ use ppez or epilepsy, generalized/ use ppez or generalized epilepsy/ use emczd, emcr or grand mal epilepsy/ use emczd, emcr or (((clonic or grand mal or tonic or (tonic adj3 clonic)) adj2 (attack* or contraction* or convuls* or seizure*)) or gtcs or (generali* adj (contraction* or convuls* or insult or seizure*))).ti,ab.
21	or/2,4-20
22	exp budgets/ or exp "costs and cost analysis"/ or exp economics, hospital/ or exp economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or economics/ or exp "fees and charges"/ or value of life/
23	22 use ppez
24	budget/ or exp economic evaluation/ or exp fee/ or funding/ or health economics/ or exp health care cost/
25	24 use emczd
26	budget*.ti,ab.
27	cost*.ti.
28	(economic* or pharmaco economic* or pharmacoeconomic*).ti.
29	(price* or pricing*).ti,ab.
30	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
31	(financ* or fee or fees).ti,ab.
32	(value adj2 (money or monetary)).ti,ab.
33	or/23,25-32
34	21 and 33
25	limit 34 to engish language

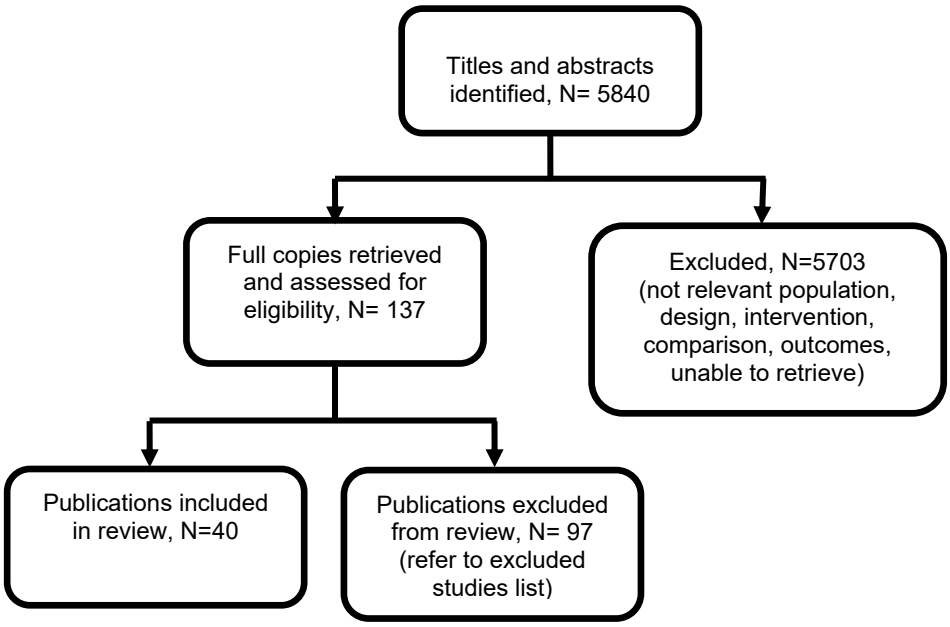
Database(s): NHS Economic Evaluation Database (NHS EED), HTA database – CRD
Date of last search: 31 March 2021

#	Searches
1	mesh descriptor epilepsy explode all trees
2	mesh descriptor seizures this term only
3	mesh descriptor seizures, febrile this term only
4	mesh descriptor status epilepticus explode all trees
5	(epilep* or seizure* or convuls*) or ("continous spike wave of slow sleep" or "infant* spasm*")
6	((absence near2 (convulsion* or seizure*)) or ((typical or atypical) next absenc*) or "petit mal*" or pyknolepsy or "typical absence*")
7	mesh descriptor seizures explode all trees
8	((drop or akinetic or atonic or tonic) near2 (attack* or epileps* or seizure* or convulsion*)) or "brief seizure" or (tonic near3 atonic near3 (attack* or epileps* or seizure* or convulsion*))
9	mesh descriptor epilepsy, rolandic this term only
10	(bcects or bects or brec or "benign epilepsy" or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 epileps*) or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 (convulsion* or epileps* or seizure* or spasm*)) or (benign near3 (convulsion* or epileps*) near2 centrotemporal near2 spike*) or cects or ((centralopathic or centrotemporal or "temporal-central focal") near (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near2 (convulsion* or epileps* or seizure* or spasm*)))
11	mesh descriptor epilepsy, generalized this term only
12	(((akinetic or atonic or central or diffuse or general or generali?ed or idiopathic or tonic) near3 (epilep* or seizure*)) or (("childhood absence" or "juvenile absence" or myoclonic or myoclonia or "myoclonic astatic" or myoclonus or gtcs) near2 epilep*) or (epilepsy near2 "eyelid myoclonia") or (ige near2 phantom absenc*) or "impulsive petit mal" or (janz near3 (epilep* or "petit mal")) or "jeavons syndrome*" or ((janz or lafora or "lafora body" or lundborg or unverricht) near2 (disease or syndrome)) or ((jme or jmes) and epilep*) or "perioral myoclon*")
13	mesh descriptor spasms, infantile this term only
14	(((early or infantile) near2 myoclonic near2 encephalopath*) or ((early or infantile) near2 epileptic near2 encephalopath*) or "epileptic spasm*" or ((flexor or infantile or neonatal) near2 (seizure* or spasm*)) or "generali?ed flexion epileps*" or hypsarrhythmia* or ((jacknife or "jack nife" or lightening or nodding or salaam) next (attack* or convulsion* or seizure* or spasm*)) or "massive myoclonia" or "minor motor epilepsy" or "propulsive petit mal"or "spasm in* flexion" or "spasmus nutans" or "west syndrome*")
15	mesh descriptor landau kleffner syndrome this term only
16	(dravet or "lennox gastaut" or lgs or (landau near2 kleffner) or smei)
17	mesh descriptor lennox gastaut syndrome this term only
18	mesh descriptor epileptic syndromes this term only
19	("child* epileptic encephalopath*" or gastaut or lennox or lgs)
20	((myoclon* near2 (absence* or epileps* or seizure* or jerk* or "progressive familial epilep*" or spasm* or convulsion*)) or ((lafora or unverricht) near2 disease) or "muscle jerk")
21	mesh descriptor epilepsies, myoclonic explode all trees
22	((myoclonic near2 (astatic or atonic)) or (myoclonic near3 (seizure* or spasm*)) or "doose* syndrome" or mae or "generali?ed idiopathic epilepsy") or ((absence or astatic or atonic or tonic or "tonic clonic") near2 (seizure* or spasm*))
23	mesh descriptor epilepsies, partial explode all trees
24	((focal or "focal onset" or local or partial or "simple partial") near3 (epileps* or seizure*))
25	mesh descriptor epilepsies, myoclonic this term only
26	(dravet*1 or ("intractable childhood epilepsy" near2 ("generalised tonic clonic" or gtc)) or icegtc* or (severe near2 (myoclonic or polymorphic) near2 epilepsy near2 infancy) or smeb or smei)
27	mesh descriptor epilepsy, tonic-clonic this term only
28	mesh descriptor epilepsy, generalized this term only
29	(((clonic or "grand mal" or tonic or (tonic near3 clonic)) near2 (attack* or contraction* or convuls* or seizure*)) or gtcs or (generali* next (contraction* or convuls* or insult or seizure*)))
30	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29

Appendix C – Clinical evidence study selection

Clinical study selection for: What is the effectiveness of genetic testing in determining the aetiology of epilepsy?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What is the effectiveness of genetic testing in determining the aetiology of epilepsy?

Table 10: Clinical evidence tables

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Full citation Allen, N. M., Conroy, J., Shahwan, A., Ennis, S., Lynch, B., Lynch, S. A., King, M. D., Chromosomal microarray in unexplained severe early onset epilepsy - A single centre cohort, European Journal of Paediatric Neurology, 19, 390-394, 2015 **Ref Id** 1097104 **Country/ies where the study was carried out** Ireland **Study design** Single-arm retrospective cohort study	**Sample size** N=51 children with unexplained severe early onset epilepsy **Characteristics** Age at seizure onset, months, median (range): 4.7 months (day 1-12 months) Age of follow up, years, mean (range): 5.8 (1-14 years) Males, n (%): 25 (49%) Developmental delay, n (%): NR Good developmental outcome, n (%): 3 (5.9%)	**Genetic test** Chromosomal microarray (array-comparative genomic hybridisation, CGH). Yield of "diagnostic results' were reported. Diagnostic results consisted of likely clinically significant or pathogenic CNVs (diagnostic), uncertain CNVs and unlikely significant CNVs.	**Sample selection** Previously extensively investigated infants with unexplained severe epilepsy. No further information given. Point along the pathway whether these patients were reviewed was not reported.	**Diagnostic yield** CMA: 3/51 (5.9%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies 1. Was the sample frame appropriate to address the target population? Yes 2. Were study participants sampled in an appropriate way? Yes, all children meeting the inclusion criteria during the timeframe were included 3. Was the sample size adequate? no, sample size calculations were not performed, but sample size was small (<150 participants) 4. Were the study subjects and the

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	Electro-clinical phenotype, n (%): Ohtahara syndrome, 5 (9.8), Migrating partial seizures of infancy, 1 (2%), Dravet syndrome spectrum, 4 (7.8%), Infantile spasms, 23 (45.1%), Non-specific (focal), 15 (29.4%), Non-specific (generalised), 3 (5.9%) **Inclusion criteria** • Children referred (between the years 1998-2013) with unexplained early onset (<1 year) epileptic encephalopathy or unexplained refractory epilepsy with abnormal development **Exclusion criteria** • Children with inborn errors of metabolism, brain structural abnormalities (including cortical dysplasia), previous				setting described in detail? Unclear. No description of the hospital/ area the children are recruited from. Children's basic characteristics were included. **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Unclear if there were any children who declined to participate. One family declined testing. **6.** Were valid methods used for the identification of the condition? Unclear. Not reported. **7.** Was the condition measured in a standard, reliable way for all participants? Unclear. Not stated in the methods. **8.** Was there appropriate statistical analysis? no (no 95% CI were reported) **9.** Was the response rate adequate, and if not,

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	causative genetic diagnoses or disease processes explaining their epileptic disorder • Six children who died prior to the use of array CGH • One lost to follow up • One family declined testing				was the low response rate managed appropriately? Yes. The only children who did not have the test were those who had died, lost to follow up and one child's family declined testing (unclear if this was at eligibility stage or testing stage) **10.** Overall quality: Low
Full citation Allen, N. M., Conroy, J., Shahwan, A., Lynch, B., Correa, R. G., Pena, S. D. J., McCreary, D., Magalhaes, T. R., Ennis, S., Lynch, S. A., King, M. D., Unexplained early onset epileptic encephalopathy: Exome screening and phenotype expansion, Epilepsia, 57, e12-e17, 2016 **Ref Id** 1097371 **Country/ies where the study was carried out** Republic of Ireland **Study design**	**Sample size** N= 50 (early onset epileptic encephalopathies (EOEEs)) **Characteristics** Age, months, mean (SD): 95% under 1 year. The others under 2 years. Males, n (%): Not specified Developmental delay, n (%): Not specified	**Genetic test** Whole exome sequencing (WES): targeting 137 epilepsy-associated genes.	**Sample selection** Selected betwee n 1997 and 2012 at a single centre. Unclear if they were consecutive.	**Diagnostic yield** WES: 11/50 (22%) were considered to have disease-causing variants in known epileptic encephalopathy and epilepsy-associated genes. 10 of which were de novo: STXBP1 (n = 3), KCNB1 (n = 2), KCNT1 (n = 1), KCNA2 (n = 1), DNM1 (n = 1), SCN2A (n = 1), and SCN1A (n = 1)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? no, single centre study **2.** Were study participants sampled in an appropriate way? no, unclear how they were recruited **3.** Was the sample size adequate? No, <150 and no calculation undertaken

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Single arm cohort study	**Inclusion criteria** • Children with unexplained early onset epileptic encephalopathies (EOEEs) without specific etiology **Exclusion criteria** • People were investigated previously for inborn errors of metabolism, structural brain malformation (magnetic resonance [MR] imaging), single-gene disorders, and chromosomal microarray, and only patients with negative results were included				**4.** Were the study subjects and the setting described in detail? no, very little background detail of the subjects **5.** Was the data analysis conducted with sufficient coverage of the identified sample? yes **6.** Were valid methods used for the identification of the condition? yes **7.** Was the condition measured in a standard, reliable way for all participants? yes, International League Against Epilepsy (ILAE) classification. **8.** Was there appropriate statistical analysis? no 95% CI reported **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? yes, all responded Overall quality: low

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Full citation Angione, K., Eschbach, K., Smith, G., Joshi, C., Demarest, S., Genetic testing in a cohort of patients with potential epilepsy with myoclonic-atonic seizures, Epilepsy Research, 150, 70-77, 2019 **Ref Id** 1098440 **Country/ies where the study was carried out** US **Study design** Single centre retrospective chart review	**Sample size** N= 77 peole with epilepsy with myoclonic-atonic seizures (EMAS) **Characteristics** Age, months, mean (SD): not detailed Males, n (%): 58 (75%) Developmental delay, n (%): overall number not specified. 66% had a positive family history for neurologic disease. **Inclusion criteria** • Children with potential epilepsy with myoclonic-atonic seizures (EMAS) / Doose syndrome. A definitive diagnosis of EMAS was not required. **Exclusion criteria** • Any clinical or electrographic evidence of drop seizures or a clear structural etiology on imaging	**Genetic test** 59 (77%) had at least one genetic test. 37 had chromosomal microarray analysis (aCGH) 16 had single-gene testing: most commonly for SCN1A, SLC2A1, and POLG1 51 had at epilepsy panel: four different epilepsy panels utilized with number of genes analysed ranging from 38 – 89. 6 had whole exome sequencing (WES) 37 had chromosomal microarray analysis (aCGH)	**Sample selection** Epilepsy onset between May 2004 and April 2017. Relevant charts in this period were reviewed.	**Diagnostic yield** Chromosomal microarray analysis (aCGH): 1/37 (2.7%), abnormal finding that was potentially clinically significant Single gene testing: 0/16 (0%) Epilepsy panel: 2/51 (4%) were found to have pathogenic variants, one in the SCN1A gene and one in the GABRG2 gene, both of which have previously been associated with EMAS WES: 2/6 (33%) Abnormal findings which were felt to at least partially explain symptoms, including a de novo pathogenic variant in CHD2, a de novo likely pathogenic variant in CSNK2A1, and	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies 1. Was the sample frame appropriate to address the target population? no, single centre study 2. Were study participants sampled in an appropriate way? Yes, consecutive people over a time frame 3. Was the sample size adequate? No, not for all tests. 4. Were the study subjects and the setting described in detail? No, limited details outside of gender. 5. Was the data analysis conducted with sufficient coverage of the identified sample? Yes 6. Were valid methods used for the identification of the condition? Yes, it was stated that it was not

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				compound heterozygous variants in PIGN.	necessary to have definitive diagnosis **7.** Was the condition measured in a standard, reliable way for all participants? Yes, again only consideration of a diagnosis of EMAS **8.** Was there appropriate statistical analysis? No, 95% confidence intervals not included **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: moderate
Full citation Borlot, F., Regan, B. M., Bassett, A. S., Stavropoulos, D. J., Andrade, D. M., Prevalence of pathogenic copy number variation in adults with pediatric-onset epilepsy and intellectual disability, JAMA Neurology, 74, 1301-1311, 2017 **Ref Id**	**Sample size** N=143 (adults with unexplained childhood-onset epilepsy and intellectual disability) **Characteristics** Age, years, mean (SD): 24.6 (10.8) Males, n (%): 69 (48)	**Genetic test** DNA screening was performed using genome-wide microarray platforms. Pathogenicity of CNVs was assessed based on the American College of Medical Genetics guidelines. The Residual Variation Intolerance Score was used to evaluate genes	**Sample selection** Recruited from the Toronto Western Hospital epilepsy outpatient clinic from January 1, 2012 through December 31, 2014 meeting the inclusion criteria.	**Diagnostic yield** CMA: 23/143 (16.1%) and 4 affected relatives. 16 of the 23 probands underwent further genetic testing through gene panels and whole exome and whole genome sequencing, and	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? Yes **2.** Were study participants sampled in an appropriate

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1097685 **Country/ies where the study was carried out** Canada **Study design** Cross-sectional study of a cohort of adults with epilepsy	Developmental delay, n (%): All have intellectual disability Seizure type only reported for those with 1 or more pathogenic or likely pathogenic CNV. **Inclusion criteria** • Onset of seizures between birth and adolescence and ongoing seizure activity throughout adulthood • Intellectual disability of any degree, diagnosed through a formal neuropsychological evaluation and classified according to the International Statistical Classification of Diseases and Related Health Problems, Tenth REvision (when IQ test results were available) or DSM-5 (when patients could not be tested) • Neither obvious causal structural	within the identified CNVs that could play a role in each patient's phenotype. DNA of all patients was screened for CNVs using clinical genome-wide microarray platforms; labeling and hybridization were performed following standard protocols using plat- form 4 × 180K Oligonucleotide Array (Agilent Technologies) and CytoSure interpret (Oxford Gene Technologies) analysis software. Some samples were studied with CytoScan HD SNP Array (Affymetrix) genomic platform and ChAS (Affymetrix) analysis software. Those with CNV of interest were offered segregation testing. Available relatives were tested with fluorescence in situ hybridization (FISH) analysis. Whenever known epilepsy genes were	Point along the pathway where these patients were reviewed as not reported.	no additional pathogenic variants were identified.	way? Unclear how many who met the inclusion criteria agreed to participate and how many didn't. **3.** Was the sample size adequate? no, sample size calculation were not performed, sample size small (<150 participants) **4.** Were the study subjects and the setting described in detail? Yes **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Unclear, no information on whether participants declined to participate **6.** Were valid methods used for the identification of the condition? Yes, ISCDRHP 10th edition and DSM-5. **7.** Was the condition measured in a standard, reliable way for all participants? Yes

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	abnormalities in their neuroimaging studies nor evident metabolic conditions that could explain their symptoms **Exclusion criteria** • Patients presenting with a classic phenotype of chromosomal abnormalities (for example, Down syndrome) • Patients previously diagnosed with well-known single gene variants that cause seizure phenotypes (for example, sodium channel, neuronal type I, a subunit [SCN1A][OMIM 182389], and cyclin-dependent kinase-like 5 [CDKL5] [OMIM 300203]	within the deleted or duplicated interval and there was a correlation with the pa- tient's phenotype, the CNV was considered to be pathogenic			**8.** Was there appropriate statistical analysis? no (no 95%CI were reported) **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? Unclear how many agreed to have the genetic test and ended up having it. **10.**Overall quality: Low
Full citation Borlot, F., de Almeida, B. I., Combe, S. L., Andrade, D. M., Filloux, F. M., Myers, K. A., Clinical utility of	**Sample size** N=64 (long-standing epilepsy and intellectual disability)	**Genetic test** Epilepsy gene panel including up to 185 genes associated with syndromic and	**Sample selection** University of Utah. January 2017 to June	**Diagnostic yield** 14/64 = 21.8%; four males, ten females, mean age = 32.1 years, SD =	**Limitations** **The quality of this study was assessed using the JBI checklist for prevalence studies**

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multigene panel testing in adults with epilepsy and intellectual disability, Epilepsia, 60, 1661-1669, 2019 **Ref Id** 1098462 **Country/ies where the study was carried out** US **Study design** Single centre retrospective cross-sectional study	**Characteristics** **Age, years, mean (SD):** 31 (9.6) years **Males, n (%):** 32 (50%) **Developmental delay, n (%):** Not specified but intellectual disability was stated in the population description **Inclusion criteria** Adults with long-standing epilepsy, according to the International League Against Epilepsy 2014 definition, and intellectual disability **Exclusion criteria** People with a classical phenotype consistent with known chromosomal abnormalities (eg, Down syndrome) not requiring a genetic panel for proper diagnosis and (2) acquired brain abnormality identified on	nonsyndromic causes of epilepsy and other neurological conditions curated by Invitae Eighteen people were tested for 126 genes (primary epilepsy genes), 31 people for 183 genes (primary + preliminary evidence epilepsy genes), 14 people for 184 genes (primary + preliminary evidence epilepsy genes + PTEN [10 people] or FLNA [4 people]), and one people for 185 genes (primary + preliminary evidence epilepsy genes + PTEN + FLNA).	2018. Data used in consecutive people who met the inclusion criteria and also were given the gene panel.	±10.2, median = 31.5 years) were found to have pathogenic or likely pathogenic variants. Pathogenic or likely pathogenic variants were identified in the following genes: SCN1A (three people), GABRB3 and UBE3A (two people for both genes combined), KANSL1, SLC2A1, KCNQ2, SLC6A1, HNRNPU, STX1B, SCN2A, PURA, and CHD2 (one single person for each gene).	1. Was the sample frame appropriate to address the target population? No, single centre study 2. Were study participants sampled in an appropriate way? Yes, Consecutive people who met the inclusion criteria. 3. Was the sample size adequate? No, <150 and no calculation undertaken 4. Were the study subjects and the setting described in detail? Yes 5. Was the data analysis conducted with sufficient coverage of the identified sample? Yes 6. Were valid methods used for the identification of

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	neuroimaging that could explain recurrent seizures (eg, hypoxic-ischemic injury, stroke, metastatic brain disease)				the condition? Yes, ILAE 7. Was the condition measured in a standard, reliable way for all participants? yes 8. Was there appropriate statistical analysis? No 95% CIs 9. Was the response rate adequate, and if not, was the low response rate managed appropriately? No Unclear why this group received a gene panel Overall quality: moderate **Other information**
Full citation Boutry-Kryza, N., Labalme, A., Ville, D., de Bellescize, J., Touraine, R., Prieur, F., Dimassi, S., Poulat, A. L., Till, M., Rossi, M., Bourel-Ponchel, E., Delignieres, A., Le Moing, A. G., Rivier, C.,	**Sample size** N=73 (Infantile Spasms syndrome [ISs]) **Characteristics** Age, months, mean (SD): Not detailed	**Genetic test** Chromosomal microarray analysis (aCGH) and molecular analysis of 5 genes: CDKL5, STXBP1, KCNQ2, and GRIN2A, whose variants cause	**Sample selection** Recruited 2010 to 2012 in 3 university hospitals.	**Diagnostic yield** People with a pathogenic or potentially pathogenic mutation/CNV Chromosomal microarray	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
des Portes, V., Edery, P., Calender, A., Sanlaville, D., Lesca, G., Molecular characterization of a cohort of 73 patients with infantile spasms syndrome, European Journal of Medical Genetics, 58, 51-58, 2015 **Ref Id** 1067540 **Country/ies where the study was carried out** France **Study design** Multi-centre prospective cohort study	Males, n (%): Not detailed Developmental delay, n (%): Not detailed **Inclusion criteria** • Children with epileptic spasms, recorded by video-EEG, and pattern of hypsarrhythmia or significant alteration of background activity with multifocal or sometimes bilateral synchronous spikes **Exclusion criteria** • The main causes of infantile spams were excluded: acquired causes, Down syndrome, cerebral malformation, tuberous sclerosis, metabolic diseases. All male people with ARX mutation. People with epileptic manifestations occurring before the	different types of epileptic encephalopathies, including ISs, as well as MAGI2, which was suggested to be related to a subset of ISs.		analysis (aCGH) and molecular analysis: 11/73 (15%) These included 6 point variants found in CDKL5 (n ¼ 3) and STXBP1 (n ¼ 3), 3 microdeletions (10 Mb in 2q24.3, 3.2 Mb in 5q14.3 including the region upstream to MEF2C, and 256 kb in 9q34 disrupting EHMT1), and 2 microduplications (671 kb in 2q24.3 encompassing SCN2A, and 11.93 Mb in Xq28).	the target population? Yes **2.** Were study participants sampled in an appropriate way? No, unclear if consecutive or representative **3.** Was the sample size adequate? No, <150 and no calculation undertaken **4.** Were the study subjects and the setting described in detail? No, there was little detail on the study subjects **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Yes **6.** Were valid methods used for the identification of the condition? Unclear what criteria was used **7.** Was the condition measured in a standard, reliable way for all participants? Yes, standardised testing

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	onset of spasms were not excluded.				**8.** Was there appropriate statistical analysis? No 95% confidence intervals reported **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? Yes Overall quality: low
Full citation Coppola, A., Cellini, E., Stamberger, H., Saarentaus, E., Cetica, V., Lal, D., Djemie, T., Bartnik-Glaska, M., Ceulemans, B., Helen Cross, J., Deconinck, T., Masi, S. D., Dorn, T., Guerrini, R., Hoffman-Zacharska, D., Kooy, F., Lagae, L., Lench, N., Lemke, J. R., Lucenteforte, E., Madia, F., Mefford, H. C., Morrogh, D., Nuernberg, P., Palotie, A., Schoonjans, A. S., Striano, P., Szczepanik, E., Tostevin, A., Vermeesch, J. R., Van Esch, H., Van Paesschen, W., Waters, J. J., Weckhuysen, S., Zara, F., Jonghe, P. D., Sisodiya, S. M., Marini, C., Lehesjioki, A. E., Craiu, D., Talvik, T., Caglayan, H., Serratosa, J.,	**Sample size** N=1255 (epilepsy plus comorbid conditions) included and 1097 remained after genetic data quality control **Characteristics** Age, months, mean (SD): not detailed Males, n (%): not detailed Developmental delay, n (%): All people had comorbid features that might be intellectual disability, psychiatric symptoms, and other neurological and non-neurological features. **Inclusion criteria**	**Genetic test** Genomic hybridization or single nucleotide polymorphism array: chromosomal microarray analysis (aCGH)	**Sample selection** Preexisting CNV data, derived from array CGH or SNP array conducted for clinical or research purposes, were collected from eight specialist epilepsy and/or genetic centres	**Diagnostic yield** Pathogenic autosomal CNV: 122/1097 (11%) Possibly pathogenic CNVs. 142/1097 (12.7%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? Yes, multi-country, multicentre **2.** Were study participants sampled in an appropriate way? No, unclear if consecutive people used **3.** Was the sample size adequate? Yes **4.** Were the study subjects and the setting described in detail? No, very little

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Sterbova, K., Moller, R. S., Hjalgrim, H., Lerche, H., Weber, Y., Helbig, I., von Spiczak, S., Barba, C., Bogaerts, A., Boni, A., Galizia, E. C., Chiari, S., Di Gacomo, G., Ferrari, A., Guarducci, S., Giglio, S., Holmgren, P., Leu, C., Melani, F., Novara, F., Pantaleo, M., Peeters, E., Pisano, T., Rosati, A., Sander, J., Schoeler, N., Stankiewicz, P., Striano, S., Suls, A., Traverso, M., Vandeweyer, G., Van Dijck, A., Zuffardi, O., Diagnostic implications of genetic copy number variation in epilepsy plus, Epilepsia, 60, 689-706, 2019 **Ref Id** 1098484 **Country/ies where the study was carried out** UK, Belgium, Italy, US, Poland **Study design** Multicentre retrospective cohort study	• Adults and children with epilepsy plus comorbid features, including intellectual disability, psychiatric symptoms, and other neurological and nonneurological features. **Exclusion criteria** • None detailed though some results were not utilised due to genetic data quality control				specific detail of the population provided **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Yes **6.** Were valid methods used for the identification of the condition? Yes **7.** Was the condition measured in a standard, reliable way for all participants? ILAE criteria **8.** Was there appropriate statistical analysis? No 95% CIs provided **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? Yes, a number of people's data removed but the great majority analysed Overall quality: moderate

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Full citation Costain, G., Cordeiro, D., Matviychuk, D., Mercimek-Andrews, S., Clinical Application of Targeted Next-Generation Sequencing Panels and Whole Exome Sequencing in Childhood Epilepsy, Neuroscience, 418, 291-310, 2019 **Ref Id** 1297722 **Country/ies where the study was carried out** Canada **Study design** Retrospective cohort study	**Sample size** N=197 people with childhood epilepsy **Characteristics** Age at first consultation, years, median (range): 4.5 (0 to 17) Males, n (%): 93 (42.7) Developmental delay, n (%): 183 (92.8%) **Inclusion criteria** • Those with epilsepsy and referred to the relevant study clinic for investigations • Those who underwent genetic testing because of the following: dysmorphic features, movement disorder, neurodegenerative clinical course, severe global developmental delay, past medical history of seizures or well-controlled seizures after initiation of ASMs	**Genetic test** Whole excome sequencing (WES)	**Sample selection** Patients were referred for molecular diagnostic laboratory testing using WES. No further details were provided.	**Diagnostic yield** WES: 25/75	**Limitations** **The quality of this study was assessed using the JBI checklist for prevalence studies** 1. Was the sample frame appropriate to address the target population? yes 2. Were study participants sampled in an appropriate way? Yes, consecutive people over a time frame 3. Was the sample size adequate? Yes 4. Were the study subjects and the setting described in detail? No, no details were provided 5. Was the data analysis conducted with sufficient coverage of the identified sample? Yes 6. Were valid methods used for

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	Exclusion criteria • Those with pathogenic CNV, abnormal diagnostic metabolic investigations or targeted direct Sanger sequencing				the identification of the condition? Unclear; by the title it seems that all participants had epilepsy and neurodevelopmental disorders, but in the methods section it is stated: "the cohort included 8565 consecutive individuals with epilepsy and/or NDD" 7. Was the condition measured in a standard, reliable way for all participants? Unclear, no details were provided 8. Was there appropriate statistical analysis? No, 95% confidence intervals not included 9. Was the response rate adequate, and if not, was the low response rate

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					managed appropriately? yes Overall quality: moderate
Full citation Demos, M., Guella, I., DeGuzman, C., McKenzie, M. B., Buerki, S. E., Evans, D. M., Toyota, E. B., Boelman, C., Huh, L. L., Datta, A., Michoulas, A., Selby, K., Bjornson, B. H., Horvath, G., Lopez-Rangel, E., Van Karnebeek, C. D. M., Salvarinova, R., Slade, E., Eydoux, P., Adam, S., Van Allen, M. I., Nelson, T. N., Bolbocean, C., Connolly, M. B., Farrer, M. J., Diagnostic yield and treatment impact of targeted exome sequencing in early-onset epilepsy, Frontiers in Neurology, 10 (MAY) (no pagination), 2019 **Ref Id** 1090195 **Country/ies where the study was carried out** Canada **Study design**	**Sample size** N= 180 (undefined cause of epilepsy) of which: N=127 retrospective, epilepsy diagnosis > 6 months before the study, standard clinical approach to genetic testing (variable genetic tests which include gene by gene approach using Sanger sequencing, small epilepsy gene panels using high throughput sequencing, and/or mitochondrial DNA sequencing) N=53 prospective, epilepsy diagnosis <6 months before study enrollment date, limited to no genetic testing **Characteristics** Age at epilepsy onset, months, median (range): 18 (0.03-60)	**Genetic test** Targeted Whole Exome Sequencing with limited Sanger sequencing validation (case specific basis). Analysis was restricted to 620 genes previously implicated in epilepsy. Yield of "diagnostic results" were reported. Diagnostic results consisted of pathogenic/likely variants.	**Sample selection** Patients were enrolled between December 2014 and September 2018 from the BC Children's Hospital in British Columbia. Point along the pathway were split to <6 months (limited to no genetic testing) and > 6 months from enrollment (standard clinical approach to genetic testing (variable genetic tests which include gene by gene approach using Sanger sequencing, small epilepsy gene panels using high	**Diagnostic yield** WES: 59/180 (33%) of which 21/53 (40%) were from the prospective diagnosis arm and 38/127 (30%) were from the retrospective diagnosis arm.	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies 1. Was the sample frame appropriate to address the target population? Yes 2. Were study participants sampled in an appropriate way? Unclear presume consecutive. Describes enrollment between December 2014 and September 2018. 3. Was the sample size adequate? Yes (although no sample size calculation was provided, n>150) 4. Were the study subjects and the setting described in detail? Unclear. The study subjects were described in detail.

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Two-arm prospective cohort study	Males, n (%): 77 (43%) Global developmental delay, n (%): 110 (61) Calculated from supplementary data table 2. **Inclusion criteria** • Enrolled between December 2014 and September 2018 • Seizure onset at ≤5 years of undefined cause after clinical evaluation, EEG, brain MRI and chromosome microarray investigations **Exclusion criteria** • Self limiting benign electroclinical syndromes such as Childhood Absence Epilepsy (onset >4 years)- excluded as likely to have multifactorial inheritance		throughput sequencing, and/or mitochondrial DNA sequencing) and had an undefined cause of their epilepsy.		The setting wasnt. Unclear if it was based at the BC Children's Hospital (they gave approval). **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Unclear. No information given if any patients declined participation **6.** Were valid methods used for the identification of the condition? Yes. ILAE **7.** Was the condition measured in a standard, reliable way for all participants? Yes. **8.** Was there appropriate statistical analysis? no (no 95% CI were reported) **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? Unclear. No description of whether

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					patients declined to have genetic testing. Overall quality: Low
Full citation Dimassi, S., Labalme, A., Ville, D., Calender, A., Mignot, C., Boutry-Kryza, N., de Bellescize, J., Rivier-Ringenbach, C., Bourel-Ponchel, E., Cheillan, D., Simonet, T., Maincent, K., Rossi, M., Till, M., Mougou-Zerelli, S., Edery, P., Saad, A., Heron, D., des Portes, V., Sanlaville, D., Lesca, G., Whole-exome sequencing improves the diagnosis yield in sporadic infantile spasm syndrome, Clinical Genetics, 89, 198-204, 2016 **Ref Id** 1097422 **Country/ies where the study was carried out** France **Study design** Single arm cohort study	**Sample size** N=10 people with the condition (Infantile spasms syndrome (ISs)). Their unaffected parents were analysed too. **Characteristics** Age, months, mean (SD): Not detailed Males, n (%): Not detailed Developmental delay, n (%): Not detailed for the population **Inclusion criteria** • People with electro-clinical spasms, recorded by video-EEG, and pattern of hypsarrhythmia or significant alteration of background activity with multifocal or bilateral synchronous spikes. **Exclusion criteria**	**Genetic test** Whole-exome sequencing (WES).	**Sample selection** Unclear how they were sampled.	**Diagnostic yield** Probable pathogenic mutation: 4/10 (40%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? yes **2.** Were study participants sampled in an appropriate way? no, unclear how they were sampled **3.** Was the sample size adequate? No, small sample size of 10 **4.** Were the study subjects and the setting described in detail? No, very little description of subjects and setting **5.** Was the data analysis conducted with sufficient coverage of the identified sample? yes **6.** Were valid methods used for the

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	• People with main causes of ISs: acquired causes, cerebral malformation, tuberous sclerosis, and metabolic diseases). Family history of seizures and consanguinity.				identification of the condition? yes **7.** Was the condition measured in a standard, reliable way for all participants? yes **8.** Was there appropriate statistical analysis? no confidence intervals included **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? yes, all responded Overall quality: low quality
Full citation Ezugha, H., Anderson, C. E., Marks, H. G., Khurana, D., Legido, A., Valencia, I., Microarray analysis in children with developmental disorder or epilepsy, Pediatric Neurology, 43, 391-394, 2010 **Ref Id** 1099533 **Country/ies where the study was carried out**	**Sample size** N=82 (neurodevelopmental disorders) N=22 of these had epilepsy **Characteristics** Age, years, mean (SD): 5.7 (5) Males, n (%): 45 (55%) Developmental delay, n (%): 20 of 22 children	**Genetic test** Chromosomal microarray analysis (aCGH). Comprised of two tests: targeted bacteria artificial chromosome comparative genomic hybridization microarray and the single nucleotide polymorphism microarray.	**Sample selection** January 2006 to June 2009. Unclear whether all relevant charts were reviewed.	**Diagnostic yield** Of the 22 children with epilepsy. Abnormal results of chromosomal microarray 8/22 (36.3%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? Single centre study that touches on epilepsy but focuses on a boarder population **2.** Were study participants sampled

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
US **Study design** Retrospective chart review	with epilepsy had mental retardation/delay All people manifested a normal karyotype. **Inclusion criteria** • Children with neurodevelopmental disorders who were referred for epilepsy, speech delay, motor impairment, or autism. **Exclusion criteria** • None detailed				in an appropriate way? Unclear how the charts were selected **3.** Was the sample size adequate? Small sample size of people with epilepsy **4.** Were the study subjects and the setting described in detail? Yes **5.** Was the data analysis conducted with sufficient coverage of the identified sample? It was a varied group but there were 20 people with epilepsy **6.** Were valid methods used for the identification of the condition? Unclear how epilepsy was diagnosed **7.** Was the condition measured in a standard, reliable way for all participants? Yes, test was standardised **8.** Was there appropriate statistical analysis? No

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					confidence intervals presented **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? All selected had responses Overall quality: low **Other information** Several clinical variables were collected: the presence of mental retardation or developmental delay, autism, learningdisability, motor impairment, hypotonia, dysmorphic features, and epilepsy.
Full citation Fernandez, I. S., Loddenkemper, T., Gainza-Lein, M., Sheidley, B. R., Poduri, A., Diagnostic yield of genetic tests in epilepsy: A meta-analysis and cost-effectiveness study, Neurology, 92, E418-E428, 2019 **Ref Id**	**Sample size** K=20 studies, including people with epilepsy of unknown aetiology k=4 studies including children and k=16 including adults and children	**Genetic test** Chromosomal microarray analysis (CMA), gene-panel testing (variable number of genes tested, see diagnostic yield section), Whole exome sequencing (WES). A genetic test was considered diagnostic when a genetic variant	**Sample selection** Studies meeting the inclusion criteria were included and meta-analysed according to genetic testing	**Diagnostic yield** Chromosomal microarray analysis (CMA) Mefford 2010: 46/517 (8.89%) Mefford 2011: 13/315 (4.1%)	**Limitations** The quality of this systematic review and meta-analysis was assessed using ROBIS Tool to assess risk of bias in systematic reviews Domain 1: Study eligibility criteria 1.1 Did the review adhere to pre-defined objectives

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
1090209 **Country/ies where the study was carried out** US **Study design** Systematic review and meta-analysis of single-arm cohort studies	k=1 included people with developmental delay only, the other studies reported people with and without people with developmental delay or did not provide information regarding learning disabilities The individual characteristics of the included studies were as follows: Bartnik 2012 N=102 people with isolated epilepsy (n=50) or epilepsy plus intellectual disability, dysmorphism, ASD or other neurologic abnormalities (N=52) Berg 2017 N=775 children and adolescents with newly diagnosed epilepsy with an onset at less than 3 years of age Butler 2017 N=339 people with epilepsy Dyment 2015	was definitely pathogenic or likely pathogenic.		Bartnik 2012: 10/102 (9.8%); 3/50 (6%) in patients with isolated epilepsy; 7/52 (13.4%) in patients with epilepsy and other neurologic conditions Michaud 2014: 6/44 (13.6%) Helbig 2014: 16/223 (7.1%) Olson 2014: 40/805 (4.9%) Hrabik 2015: 11/147 (7.4%) Berg 2017: 32/188 (17%, 95% CI 11% to 23%) Gene-panel testing Lemke 2012 (265 genes): 16/33 (48.4%) Wang 2014 (53 genes or 38	and eligibility criteria: no information 1.2 Were the eligibility criteria appropriate for the review question? no information, eligibility criteria was not reported 1.3 Were eligibility criteria unambiguous? no information, eligibility criteria was not reported 1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate? no information, eligibility criteria was not reported 1.5 Were any restrictions in eligibility criteria based on sources of information appropriate? no information, eligibility criteria was not reported Concerns regarding specification of study eligibility criteria: unclear Domain 2: Identification and selection of studies 2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? probably not, only PubMed was searched

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	N=11 people with epilepsy Helbig 2014 N=223 children with childhood epilepsies and complex phenotypes including structural brain lesions Helbig 2016 N=293 people with epilepsy Hrabik 2015 N=147 people with epilepsy Lemke 2012 N=33 people with epilepsy Mefford 2010 N=517 people with idiopathic epilepsy, mostly without an intellectual disability Mefford 2011 N=315 people wit epileptic encephalopathies Mercimek-Mahmutoglu 2015 N=93 with intractable epilepsy, global			genes): 6/28 (21.4%) Della Mina 2015 (67 genes): 9/19 (47.3%) in patients with a clinical presentation suggestive of a specific syndrome; 3/12 (25%) in patients with a phenotype not suggestive of any specific syndrome Mercimek-Mahmutoglu 2015 (38 to 327 genes): 12/93 (12.9%) Trump 2016 (46 genes): 60/323 (18.5%) Segal 2016 (87 or 855 genes): 7/49 (14.2%) Moller 2016 (46 genes): 49/216 (22.6%) Berg 2017 (number of genes not specified):	2.2 Were methods additional to database searching used to identify relevant reports? No 2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? Probably yes 2.4 Were restrictions based on date, publication format, or language appropriate? Probably yes 2.5 Were efforts made to minimise error in selection of studies? Probably yes Concerns regarding methods used to identify/ select studies: low Domain 3: Data collection and study appraisal 3.1 Were efforts made to minimise error in data collection? no information was provided 3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? yes 3.3 Were all relevant study results collected for use in the synthesis? yes 3.4 Was risk of bias (or methodology quality)

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	developmental delay, not recognisable syndromic features, and cognitive dysfunction Michaud 2014 N=18 children with infantile spasms Della Mina 2015 N=19 people with isolated or syndromic epilepsy Moller 2016 N=216 people with different types of epilepsy Olson 2014 N=805 people with epilepsy Retterer 2016 N=830 people with epilepsy Segal 2016 N=49 people with refractory epilepsy Trump 2016 N=323 with early-onset seizure disorders but without major structural brain malformations			31/114 (27.1%, 95% CI 17% to 38%) Butler 2017 (110 genes): 62/339 (18.2%) Whole exome sequencing (WES) Veeramah 2013: 7/10 (7%) Michaud 2014: 13/18 (72.2%) Dyment 2015: 7/9 (77.7%) in families with a diagnosis and 8/11 (72.7%) in affected individuals Retterer 2015:232/830 (27.9%) Helbig 2016: 112/293 (38.2%) Berg 2017: 11/33 (33.3%, 95% CI 16% to 51%)	formally assessed using appropriate criteria? no 3.5 Were efforts made to minimise error in risk of bias assessment? no information Concerns regarding methods used to collect data and appraise studies: unclear Domain 4: synthesis and findings 4.1 Did the synthesis include all studies that it should? probably yes, but since inclusion criteria was not reported, it is not possible to assess whether synthesis included all studies that it should 4.2 Were all pre-defined analyses reported or departures explained? yes 4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? yes 4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis? yes

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	Veeramah 2013 N=10 children with refractory epilepsy, normal or unspecific neuroimaging, and a variable combination of neurodevelopmental disorders, such as ASD, cognitive impairment, and motor deficits Wang 2014 N=28 people with epilepsy **Characteristics** Bartnik 2012 Demographic characteristics were not reported Berg 2017 Age, months, median (IQR): 7.5 (4.2 to 16.5) Males, n (%): 408 (52.6%) Developmental delay, n (%): no information was provided Butler 2017 Demographic characteristics were not reported				(random effects model was used) 4.5 Were the findings robust, for example, as demonstrated through funnel plot or sensitivity analyses? yes 4.6 Were biases in primary studies minimal or addressed in the synthesis? yes Concerns regarding synthesis and findings: low Risk of bias in the review: low The quality of each of the studies included in the systematic review and meta-analysis was assessed using the JBI checklist for prevalence studies Bartnik 2012 Was the sample frame appropriate to address the target population? unclear (sample frame not described) Were study participants sampled in an appropriate way? unclear

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	Dyment 2015 Age: Between 1 to 3 weeks and 36 years old Males, n (%): not reported Developmental delay, n (%): not reported Helbig 2014 Demographic characteristics were not reported Helbig 2016 Age: mixed (adults and children) Males, n (%): 167 (53.2%) Developmental delay, n (%): 282 (89.8%) Hrabik 2015 Age:patients were between birth to 23 years Males, n (%): 83 (56.5%) Developmental delay, n (%): 117 (79.9%) Lemke 2012 Age: patients were between 2 and 40 years old				Was the sample size adequate? no, <150 Were the study subjects and the setting described in detail? no, participant's characteristics were not described in detail and subjects either Was the data analysis conducted with sufficient coverage of the identified sample? yes Were valid methods used for the identification of the condition? unclear (no details were reported) Was the condition measured in a standard, reliable way for all participants? unclear Was there appropriate statistical analysis? no, 95% CIs were not reported Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: very low Berg 2017 1. Were study participants sampled in an appropriate way? yes

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	Males, n (%): 17 (51.5%) Developmental delay, n (%): 24 (72.7%) Mefford 2010 Demographic characteristics were not reported Mefford 2011 Demographic characteristics were not reported Mercimek-Mahmutoglu 2015 Age, years, mean (SD): 3.6 (3.35) Males, n (%): not reported Developmental delay, n (%): 110/110 (100%) Michaud 2014 Age, months, mean: 5.5 Males, n (%): 22 (50%) Developmental delay, n (%): 40 (91%) Della Mina 2015 Age: between 8 months and 17 years old Males, n (%): 14 (73.6%)				2. Was the sample size adequate? yes (> 150 participants) 3. Were the study subjects and the setting described in detail? yes 4. Was the data analysis conducted with sufficient coverage of the identified sample? yes 5. Were valid methods used for the identification of the condition? unclear, no information was provided 6. Was the condition measured in a standard, reliable way for all participants? unclear, no information was provided 7. Was there appropriate statistical analysis? yes 8. Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: moderate

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	Developmental delay, n (%): not reported Moller 2016 Age: not reported; n= 49 (23%) of the patients were above 18 years old Males, n (%): not reported Developmental delay, n (%): not reported Olson 2014 Age (at onset), months, mean (SD): between 5 weeks and 2 years Males, n (%): not reported Developmental delay, n (%): not reported Retterer 2016 Age, months, mean (SD): 11.4 (13.2) Males, n (%): not reported Developmental delay, n (%): 1574 (51.8%) Segal 2016 Age (onset of seizures), months, mean (SD): 2.6 (0 to 17 years old) Males, n (%): 28 (57.14%)				Butler 2017 1. Was the sample frame appropriate to address the target population? yes 2. Were study participants sampled in an appropriate way? unclear 3. Was the sample size adequate? yes (>150 participants) 4. Were the study subjects and the setting described in detail? no, not enough detail was provided 5. Was the data analysis conducted with sufficient coverage of the identified sample? yes 6. Were valid methods used for the identification of the condition? unclear 7. Was the condition measured in a standard, reliable way for all participants? unclear 8. Was there appropriate statistical analysis?

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	Developmental delay, n (%): 30 (61.2%) Trump 2016 Age, median age of onset (range): 1 day (1 day to 2 years and 11 months) Males, n (%): not reported Developmental delay, n (%): not reported Veeramah 2013 Demographic characteristics were not reported Wang 2014 Demographic characteristics were not reported **Inclusion criteria** • Epilepsy of unknown aetiology, in patients without clinical features suggestive of a specific genetic syndrome, and with a genetic diagnosis being considered **Exclusion criteria**				no, 95% CIs were not reported 9. Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: low Dyment 2015 1. Was the sample frame appropriate to address the target population? unclear 2. Were study participants sampled in an appropriate way? unclear 3. Was the sample size adequate? yes (> 150 participants) 4. Were the study subjects and the setting described in detail? no, some characteristics were not reported 5. Was the data analysis conducted with sufficient coverage of the identified sample? unclear 6. Were valid methods used for the

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	• Not reported				identification of the condition? unclear 7. Was the condition measured in a standard, reliable way for all participants? unclear 8. Was there appropriate statistical analysis? no, 95% CIs have not been reported 9. Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: very low <u>Helbig 2014</u> 1. Was the sample frame appropriate to address the target population? ye 2. Were study participants sampled in an appropriate way? yes 3. Was the sample size adequate? yes (> 150 participants) 4. Were the study subjects and the setting described in detail? no

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					5. Was the data analysis conducted with sufficient coverage of the identified sample? yes 6. Were valid methods used for the identification of the condition? yes (ILAE classification) 7. Was the condition measured in a standard, reliable way for all participants? yes 8. Was there appropriate statistical analysis? no, 95% CIs were not reported 9. Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: moderate <u>Helbig 2016</u> 1. Were study participants sampled in an appropriate way? yes 2. Was the sample size adequate? yes (> 150 participants)

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					3. Were the study subjects and the setting described in detail? yes 4. Was the data analysis conducted with sufficient coverage of the identified sample? yes 5. Were valid methods used for the identification of the condition? unclear, no information was provided 6. Was the condition measured in a standard, reliable way for all participants? unclear, no information was provided 7. Was there appropriate statistical analysis? yes 8. Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: moderate Hrabik 2015

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					1. Was the sample frame appropriate to address the target population? yes 2. Were study participants sampled in an appropriate way? yes 3. Was the sample size adequate? no, <150 4. Were the study subjects and the setting described in detail? yes 5. Was the data analysis conducted with sufficient coverage of the identified sample? yes 6. Were valid methods used for the identification of the condition? yes 7. Was the condition measured in a standard, reliable way for all participants? unclear 8. Was there appropriate statistical analysis? unclear 9. Was the response rate adequate, and if not,

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					was the low response rate managed appropriately? yes Overall quality: moderate <u>Lemke 2012</u> 1. Was the sample frame appropriate to address the target population? yes 2. Were study participants sampled in an appropriate way? unclear 3. Was the sample size adequate? no, <150 4. Were the study subjects and the setting described in detail? yes 5. Was the data analysis conducted with sufficient coverage of the identified sample? yes 6. Were valid methods used for the identification of the condition? yes 7. Was the condition measured in a standard, reliable way for all participants? yes

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					8. Was there appropriate statistical analysis? no, 95% CIs were not reported 9. Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: moderate <u>Mefford 2010</u> 1. Was the sample frame appropriate to address the target population? yes 2. Were study participants sampled in an appropriate way? yes 3. Was the sample size adequate? yes (> 150 participants) 4. Were the study subjects and the setting described in detail? no 5. Was the data analysis conducted with sufficient coverage of the identified sample? yes 6. Were valid methods used for the

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					identification of the condition? no 7. Was the condition measured in a standard, reliable way for all participants? yes 8. Was there appropriate statistical analysis? no 9. Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: moderate <u>Mefford 2011</u> 1. Was the sample frame appropriate to address the target population? yes 2. Were study participants sampled in an appropriate way? yes 3. Was the sample size adequate? yes (> 150 participants) 4. Were the study subjects and the setting described in detail? no

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					5. Was the data analysis conducted with sufficient coverage of the identified sample? yes 6. Were valid methods used for the identification of the condition? yes 7. Was the condition measured in a standard, reliable way for all participants? yes 8. Was there appropriate statistical analysis? yes 9. Was the response rate adequate, and if not, was the low response rate managed appropriately? Yes Overall quality: high <u>Mercimek-Mahmutoglu 2015</u> 1. Was the sample frame appropriate to address the target population? yes 2. Were study participants sampled

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					in an appropriate way? yes 3. Was the sample size adequate? no (< 150 participants) 4. Were the study subjects and the setting described in detail? yes 5. Was the data analysis conducted with sufficient coverage of the identified sample? yes 6. Were valid methods used for the identification of the condition? yes 7. Was the condition measured in a standard, reliable way for all participants? yes 8. Was there appropriate statistical analysis? no 9. Was the response rate adequate, and if not, was the low response rate managed appropriately?yes Overall quality: high Michaud 2014

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					1. Was the sample frame appropriate to address the target population? yes 2. Were study participants sampled in an appropriate way? yes 3. Was the sample size adequate? no, <150 4. Were the study subjects and the setting described in detail? yes 5. Was the data analysis conducted with sufficient coverage of the identified sample? yes 6. Were valid methods used for the identification of the condition? no 7. Was the condition measured in a standard, reliable way for all participants? no 8. Was there appropriate statistical analysis? yes 9. Was the response rate adequate, and if not, was the low response

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					rate managed appropriately? yes Overall quality: moderate <u>Della Mina 2015</u> 1. Was the sample frame appropriate to address the target population? yes 2. Were study participants sampled in an appropriate way? yes 3. Was the sample size adequate? no, <150 4. Were the study subjects and the setting described in detail? yes 5. Was the data analysis conducted with sufficient coverage of the identified sample? yes 6. Were valid methods used for the identification of the condition? yes 7. Was the condition measured in a standard, reliable way for all participants? yes

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					8. Was there appropriate statistical analysis? no 9. Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: high <u>Moller 2016</u> 1. Was the sample frame appropriate to address the target population? yes 2. Were study participants sampled in an appropriate way? yes 3. Was the sample size adequate? yes (> 150 participants) 4. Were the study subjects and the setting described in detail? no 5. Was the data analysis conducted with sufficient coverage of the identified sample? yes 6. Were valid methods used for the

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					identification of the condition? yes 7. Was the condition measured in a standard, reliable way for all participants? yes 8. Was there appropriate statistical analysis? yes 9. Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: high <u>Olson 2014</u> 1. Was the sample frame appropriate to address the target population? yes 2. Were study participants sampled in an appropriate way? yes 3. Was the sample size adequate? yes (> 150 participants) 4. Were the study subjects and the setting described in detail? no

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					5. Was the data analysis conducted with sufficient coverage of the identified sample? yes 6. Were valid methods used for the identification of the condition? yes 7. Was the condition measured in a standard, reliable way for all participants? yes 8. Was there appropriate statistical analysis? yes 9. Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: high <u>Retterer 2016</u> 1. Was the sample frame appropriate to address the target population? yes 2. Were study participants sampled in an appropriate way? yes

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					3. Was the sample size adequate? yes (> 150 participants) 4. Were the study subjects and the setting described in detail? no 5. Was the data analysis conducted with sufficient coverage of the identified sample? yes 6. Were valid methods used for the identification of the condition? yes 7. Was the condition measured in a standard, reliable way for all participants? yes 8. Was there appropriate statistical analysis? yes 9. Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: high Segal 2016

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					1. Was the sample frame appropriate to address the target population? yes 2. Were study participants sampled in an appropriate way? yes 3. Was the sample size adequate? no (< 150 participants) 4. Were the study subjects and the setting described in detail? yes 5. Was the data analysis conducted with sufficient coverage of the identified sample? yes 6. Were valid methods used for the identification of the condition? yes 7. Was the condition measured in a standard, reliable way for all participants? yes 8. Was there appropriate statistical analysis? no 9. Was the response rate adequate, and if not, was the low response

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					rate managed appropriately?yes Overall quality: high <u>Trump 2016</u> 1. Were study participants sampled in an appropriate way? yes 2. Was the sample size adequate? yes (> 150 participants) 3. Were the study subjects and the setting described in detail? yes 4. Was the data analysis conducted with sufficient coverage of the identified sample? yes 5. Were valid methods used for the identification of the condition? unclear, no information was provided 6. Was the condition measured in a standard, reliable way for all participants? unclear, no

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					information was provided 7. Was there appropriate statistical analysis? yes 8. Was the response rate adequate, and if not, was the low response rate managed appropriately? yes 9. Overall quality: moderate <u>Veeramah 2013</u> 1. Was the sample frame appropriate to address the target population? yes 2. Were study participants sampled in an appropriate way? yes 3. Was the sample size adequate? no (< 150 participants) 4. Were the study subjects and the setting described in detail? yes 5. Was the data analysis conducted with sufficient coverage of

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					the identified sample? yes 6. Were valid methods used for the identification of the condition? yes 7. Was the condition measured in a standard, reliable way for all participants? yes 8. Was there appropriate statistical analysis? no 9. Was the response rate adequate, and if not, was the low response rate managed appropriately? es Overall quality: high <u>Wang 2014</u> 1. Was the sample frame appropriate to address the target population? yes 2. Were study participants sampled in an appropriate way? yes 3. Was the sample size adequate? no (< 150 participants)

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					4. Were the study subjects and the setting described in detail? yes 5. Was the data analysis conducted with sufficient coverage of the identified sample? yes 6. Were valid methods used for the identification of the condition? yes 7. Was the condition measured in a standard, reliable way for all participants? yes 8. Was there appropriate statistical analysis? no 9. Was the response rate adequate, and if not, was the low response rate managed appropriately?yes Overall quality: high
Full citation Galizia, E. C., Srikantha, M., Palmer, R., Waters, J. J., Lench, N., Ogilvie, C. M., Kasperaviciu-te, D., Nashef,	**Sample size** N=82 (adults with drug-resistant epilepsy). 54 from The National Hospital of Neurology	**Genetic test** Array CGH was performed at both centres.	**Sample selection** Two centres; NHNN and KCH	**Diagnostic yield** NHNN array CGH: 7/52 (13.5) KCH	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
L., Sisodiya, S. M., Array comparative genomic hybridization: Results from an adult population with drug-resistant epilepsy and co-morbidities, European Journal of Medical Genetics, 55, 342-348, 2012 **Ref Id** 410470 **Country/ies where the study was carried out** UK **Study design** Retrospective cohort study. Two separate cohorts at different locations with slightly different inclusion criterion (see below).	and Neurosurgery (NHNN) and 28 from King's College Hospital NHS Foundation Trust (KCH). **Characteristics** Baseline characteristics were only given for the NHNN cohort. Age, years, range: 18-81. No other age data was provided. Males, n (%): NHNN 27 (51.9) Developmental delay, n (%): NHNN 33 (63.4) Epilepsy classification, n (%): NHNN; Focal 39 (75), primary Generalised 2 (3.8), Unclassified 10 (19.2), Mixed 1 (1.9) Co-morbidities, yes, n (%): NHNN 37 (71.1) **Inclusion criteria** • NHNN inclusion criteria: ○ Presence of epilepsy in combination with ≥1 of the following characteristics	NHNN: North East Thames Regional Genetics Service, using the NimbleGen 12 135 K, whole genome v3.0 array chip, according to the manufacturer's instructions. KCH:Guy's and St Thomas' NHS Foundation Trust South East Thames Regional Cytogenetics Laboratory as part of their clinical diagnostic service, using an Agilent custom platform comprising approximately 44,000 probes across the genome Yield of "diagnostic results" were reported for both centres. Diagnostic results were classed as: NHNN: "Likely pathogenic, benign and unknown significance" KCH: "normal (only with variants recognised in control populations), showing CNVs of likely pathogenic significance, and showing CNVs of uncertain significance".	NHNN: Those meeting the inclusion criteria and had an array CGH (array comparative genomic hybridization) performed during the 18 month period (2009-2010) KCH: All those who had array CGH and had the investigation recommended (as per the inclusion criteria) between September 10 2009 and August 17 2010. Point along the pathway where these patients were reviewed was not reported.	array CGH: 5/25 (20) In the KCH group, there were 3 individuals with a 15q13.3 microdeletion, tested during the audit period, who were related to another known case and have therefore been excluded from analysis	**1.** Was the sample frame appropriate to address the target population? Yes **2.** Were study participants sampled in an appropriate way? Yes **3.** Was the sample size adequate? No, sample size calculations were not performed, and sample size was small (<150 participants) **4.** Were the study subjects and the setting described in detail? No, no baseline characteristics given for the KCH cohort. **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Unclear. No information on who was eligible but did not receive the test **6.** Were valid methods used for the identification of the condition? Yes,

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	determined from medical records: ○ developmental delay/intellectual disability, as determined by formal neuropsychometric testing or clinical assessment/ contemporary documentation of developmental delay ○ dysmorphism ○ family history of epilepsy, neuropsychiatric disorder or learning disability, as defined by the presence of ≥ first or second degree relative ○ personal history of a psychiatric disorder ○ other co-morbidities (including developmental anomalies, abnormal neuroimaging, migraine) • KCH inclusion criteria: ○ Array CGH performed at KCH				Epilepsy was classified according to the International League Against Epilepsy (ILAE) Commission on Classification and Terminology, 2005-2009. **7.** Was the condition measured in a standard, reliable way for all participants? Yes **8.** Was there appropriate statistical analysis? No (no 95% CIs were reported) **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? Unclear, no information provided on patients who declined the test. Overall quality: Low

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	who had this investigation recommended between September 10 2009 and August 17 2010 ○ Test offered based on a similar criteria to NHNN cohort but excluding abnormal neuroimaging or migraine • The criteria were: ○ a history of epilepsy of unknown aetiology associated with any of the following: ○ developmental delay ○ learning disability ○ dysmorphism ○ mental health problems including autistic spectrum disorders and/or family history of the same **Exclusion criteria** • None described.				
Full citation	**Sample size**	**Genetic test**	**Sample selection**	**Diagnostic yield**	**Limitations**

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Hamdan, F. F., Myers, C. T., Cossette, P., Lemay, P., Spiegelman, D., Laporte, A. D., Nassif, C., Diallo, O., Monlong, J., Cadieux-Dion, M., Dobrzeniecka, S., Meloche, C., Retterer, K., Cho, M. T., Rosenfeld, J. A., Bi, W., Massicotte, C., Miguet, M., Brunga, L., Regan, B. M., Mo, K., Tam, C., Schneider, A., Hollingsworth, G., FitzPatrick, D. R., Donaldson, A., Canham, N., Blair, E., Kerr, B., Fry, A. E., Thomas, R. H., Shelagh, J., Hurst, J. A., Brittain, H., Blyth, M., Lebel, R. R., Gerkes, E. H., Davis-Keppen, L., Stein, Q., Chung, W. K., Dorison, S. J., Benke, P. J., Fassi, E., Corsten-Janssen, N., Kamsteeg, E. J., Mau-Them, F. T., Bruel, A. L., Verloes, A., Ounap, K., Wojcik, M. H., Albert, D. V. F., Venkateswaran, S., Ware, T., Jones, D., Liu, Y. C., Mohammad, S. S., Bizargity, P., Bacino, C. A., Leuzzi, V., Martinelli, S., Dallapiccola, B., Tartaglia, M., Blumkin, L., Wierenga, K. J., Purcarin, G., O'Byrne, J. J., Stockler, S.,	N=197 (Epilepsy and intellectual disability [ID]) and their unaffected parents were tested **Characteristics** Age, months, mean (SD): Not detailed Males, n (%): Not detailed Developmental delay, n (%): All people had ID or global developmental delay, **Inclusion criteria** • People, likely to be children, with intractable epilepsy, ID or global developmental delay, absence of malformations or focal and multifocal structural abnormalities on brain MRI; and absence of parental consanguinity and family history of epilepsy, ID, or autism in first-degree relatives.	Whole genome sequencing (WGS)	Recruited at 3 centres. Unclear if consecutive.	Pathogenic or likely pathogenic variants: in 50/197 (25%) subjects in genes that, when mutated, have been shown to cause DEE and/or ID.	The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? Multicentre study **2.** Were study participants sampled in an appropriate way? Unclear how sampling was undertaken **3.** Was the sample size adequate? Yes **4.** Were the study subjects and the setting described in detail? Little detail outside of inclusion criteria **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Yes **6.** Were valid methods used for the identification of the condition? Yes, part of a larger recruitment process

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Lehman, A., Keren, B., Nougues, M. C., Mignot, C., Auvin, S., Nava, C., Hiatt, S. M., Bebin, M., Shao, Y., Scaglia, F., Lalani, S. R., Frye, R. E., Jarjour, I. T., Jacques, S., Boucher, R. M., Riou, E., Srour, M., Carmant, L., Lortie, A., Major, P., Diadori, P., Dubeau, F., D'Anjou, G., Bourque, G., Berkovic, S. F., Sadleir, L. G., Campeau, P. M., Kibar, Z., Lafreniere, R. G., Girard, S. L., Mercimek-Mahmutoglu, S., Boelman, C., Rouleau, G. A., Scheffer, I. E., Mefford, H. C., Andrade, D. M., Rossignol, E., Minassian, B. A., Michaud, J. L., High Rate of Recurrent De Novo Mutations in Developmental and Epileptic Encephalopathies, American Journal of Human Genetics, 101, 664-685, 2017 **Ref Id** 1097755 **Country/ies where the study was carried out** Canada **Study design**	**Exclusion criteria** • None detailed				**7.** Was the condition measured in a standard, reliable way for all participants? Yes, standardised testing. **8.** Was there appropriate statistical analysis? No confidence intervals reported **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? All people responded. Overall quality: moderate

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Multicentre single arm cohort study					
Full citation Hildebrand, M. S., Myers, C. T., Carvill, G. L., Regan, B. M., Damiano, J. A., Mullen, S. A., Newton, M. R., Nair, U., Gazina, E. V., Milligan, C. J., Reid, C. A., Petrou, S., Scheffer, I. E., Berkovic, S. F., Mefford, H. C., A targeted resequencing gene panel for focal epilepsy, Neurology, 86, 1605-1612, 2016 **Ref Id** 1089196 **Country/ies where the study was carried out** Australia **Study design** Retrospective cohort study	**Sample size** N= 255 (focal epilepsy without a known acquired cause) **Characteristics** Age, months, mean (SD): NR Males, n (%): NR Developmental delay, n (%): NR Type of epilepsy, n (%): temporal lobe epilepsy (TLE) 151 (59), frontal lobe epilepsy 50 (19.6), mesial temporal lobe epilepsy with hippocampal sclerosis 14 (5.5), occipital epilepsy 5 (2), parietal lobe epilepsy 2 (0.8), temporal and occipital lobe epilepsy 2(0.8), Focal unspecified 31 (12). Sporadic case, n (%): 200 (78) **Inclusion criteria**	**Genetic test** For most samples, whole venous blood was obtained and genomic DNA extracted using a Qiagen QIAamp DNA Maxi Kit (Valencia, CA) according to the manufacturer's instructions. In some cases, only saliva samples were available, and DNA was extracted from these specimens using a prepITL2P kit (DNA Genotek Inc, Ontario, Canada) according to the manufacturer's instructions. Targeted re-sequencing gene panel (11 genes) Variants meeting the following criteria were excluded from further analysis: clustered variants (window size of 10) and those variants with an allele balance .0.75, quality ,30, quality by depth ,5, or unique capture events ,5.	**Sample selection** Recruited from the first-seizure and epilepsy clinics at Austin Health, from the private practices of the investigators and by referral for genetics research over a period of 25 years, regardless of reported family history of epilepsy. Use of a validated seizure questionnaire and personal evaluation and review of medical records, including EEG and neuroimaging investigations. MRI of no lesion (Hippocampal sclerosis was allowed) or normal CT scan	**Diagnostic yield** Gene-panel testing (11 genes): 2/251 (0.8)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies 1. Was the sample frame appropriate to address the target population? Unclear, very limited information given. 2. Were study participants sampled in an appropriate way? Unclear sampling strategy 3. Was the sample size adequate? Yes, although no sample size calculation, >150 patients were included. 4. Were the study subjects and the setting described in detail? No, hardly any information given. 5. Was the data analysis conducted with sufficient coverage of the identified sample? Unclear, no information given on

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	• Patients with focal epilepsy without a known acquired cause (regardless of reported family history) **Exclusion criteria** • None described	Diagnostic results consisted of pathogenic, likely pathogenic, uncertain significance or benign. "Pathogenic or likely pathogenic variants had to (1) be very rare (for example, present in #5 alleles in ;63,000 exomes of ExAC database and no homozygotes re-ported), (2) arise de novo or segregate with the disorder, (3) be predicted to damage an important protein domain, and (4) be associated with an established epilepsy phenotype for the given gene".	and no history of an acquired insult. Point along the pathway where these patients were reviewed was not reported.		the number of patients eligible and those that agreed to participate **6.** Were valid methods used for the identification of the condition? No definitions described just 'focal epilepsy without a known acquired cause'. **7.** Was the condition measured in a standard, reliable way for all participants? Yes **8.** Was there appropriate statistical analysis? No (no 95% CIs were reported) **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? Unclear, no description of those who agreed to participate and who actually had the gene panel testing done Overall quality: Very low
Full citation	**Sample size**	**Genetic test**	**Sample selection**	**Diagnostic yield** CMA: 4/74 (5.4%)	**Limitations**

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Howell, K. B., Eggers, S., Dalziel, K., Riseley, J., Mandelstam, S., Myers, C. T., McMahon, J. M., Schneider, A., Carvill, G. L., Mefford, H. C., Scheffer, I. E., Harvey, A. S., A population-based cost-effectiveness study of early genetic testing in severe epilepsies of infancy, Epilepsia, 59, 1177-1187, 2018 **Ref Id** 1089933 **Country/ies where the study was carried out** Australia **Study design** Population based study (prospective and retrospective)	N= 114 (up to n=74 undergoing genetic testing) **Characteristics** Demographic characteristics were not reported **Inclusion criteria** • Infants with severe epilepsies of infancy under 18 months old **Exclusion criteria** • Not reported	CMA, single-gene testing, gene panel (4 genes), WES, WGS	Ascertainment was retrospective for those presenting during 2011 and 2012 and prospective for those presenting between 2013 and 2015.	Single-gene testing: 5/49 (10.2%) Gene-panel testing (4 genes): 1/49 (2%) WES: 6/49 (12.2%) WGS: 4/74 (5.4%)	The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? yes **2.** Were study participants sampled in an appropriate way? yes **3.** Was the sample size adequate? no **4.** Were the study subjects and the setting described in detail? no **5.** Was the data analysis conducted with sufficient coverage of the identified sample? yes **6.** Were valid methods used for the identification of the condition? yes **7.** Was the condition measured in a standard, reliable way for all participants? yes **8.** Was there appropriate statistical analysis? no

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					9. Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: high
Full citation Jang, S. S., Kim, S. Y., Kim, H., Hwang, H., Chae, J. H., Kim, K. J., Kim, J. I., Lim, B. C., Diagnostic Yield of Epilepsy Panel Testing in Patients With Seizure Onset Within the First Year of Life, Front NeurolFrontiers in neurology, 10, 988, 2019 **Ref Id** 1119524 **Country/ies where the study was carried out** South Korea **Study design** Single-arm retrospective cohort study	**Sample size** N=112 children with seizure onset before the age of 1 **Characteristics** Not reported **Inclusion criteria** • Seizure onset before the age of 1 • No structural abnormality on MRI • No suspected single genetic cause from medical examinations **Exclusion criteria** • Those with febrile seizures without subsequent afebrile seizures • Those with West Syndrome	**Genetic test** Epilepsy gene-panel. n=31 patients were screened with the first kit (79 genes); n=61 were screened with the second kit (119 genes), and n=20 were screened with the third kit (127 genes). Genetic abnormalities were defined as pathogenic and likely pathogenic CNV variants (ACMG classification), and therefore causative of the phenotype. To validate CNVs, chromosomal microarray analysis was conducted.	**Sample selection** Patients meeting the inclusion criteria were retrospectively selected to participate in the study. No further details regarding sample selection have been reported.	**Diagnostic yield** Epilepsy gene-panel (79 to 127 genes), number of patients with identified pathogenic or likely pathogenic variants/ total number of patients assessed: 53/112 (47.3%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1**. Was the sample frame appropriate to address the target population? yes **2.** Were study participants sampled in an appropriate way? unclear (no details were provided) **3.** Was the sample size adequate? no, sample size calculations were not performed, but sample size was small (<150 participants) **4.** Were the study subjects and the setting described in detail? no, setting was not described and participant's characteristics were not reported **5.** Was the data analysis conducted with sufficient

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					coverage of the identified sample? yes, although some patients were screened for more genes than others and reasons for this discrepancy were not reported **6.** Were valid methods used for the identification of the condition? yes, according to ILAE definitions **7**. Was the condition measured in a standard, reliable way for all participants? yes **8.** Was there appropriate statistical analysis? no (no 95% CIs were reported) **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: low
Full citation Ko, A., Youn, S. E., Kim, S. H., Lee, J. S., Kim, S., Choi, J. R., Kim, H. D., Lee, S. T., Kang, H. C., Targeted gene panel and genotype-phenotype correlation in children with developmental	**Sample size** N=278 (developmental and epileptic encephalopathy (DEE)) **Characteristics** Age, months, mean (SD): not detailed	**Genetic test** Customized gene panel that included 172 genes.	**Sample selection** Unrelated people recruited from March 2015 to June 2017 in one hospital. Unclear if consecutive	**Diagnostic yield** Pathogenic monogenic variants: 103/278 (37.1%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
and epileptic encephalopathy, Epilepsy research, 141, 48-55, 2018 **Ref Id** 1068265 **Country/ies where the study was carried out** Republic of Korea **Study design** Single arm cohort study	<u>Males, n (%):</u> not detailed <u>Developmental delay, n (%):</u> all people had progressive developmental deterioration or a known developmental and epileptic encephalopathy syndrome **Inclusion criteria** • Children with seizure onset before the age of 3 years, multiple epileptiform discharges with severely disorganized background, activity on electroencephalography (EEG), progressive developmental deterioration or a known developmental and epileptic encephalopathy syndrome **Exclusion criteria** • Significant structural lesion detected on		people who met the inclusion criteria.		population? Single centre study in mainly Korean people **2.** Were study participants sampled in an appropriate way? Unclear how they were sampled **3.** Was the sample size adequate? Yes **4.** Were the study subjects and the setting described in detail? Little detail outside of inclusion criteria **5.** Was the data analysis conducted with sufficient coverage of the identified sample? yes **6.** Were valid methods used for the identification of the condition? Yes, ILAE 2010 **7.** Was the condition measured in a standard, reliable way for all participants? Yes, standardised testing **8.** Was there appropriate statistical analysis? No

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	brain magnetic resonance imaging, metabolic abnormalities, abnormalities detected on previous genetic tests.				confidence intervals included **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? Yes, all responded Overall quality: moderate
Full citation Kobayashi, Y., Tohyama, J., Kato, M., Akasaka, N., Magara, S., Kawashima, H., Ohashi, T., Shiraishi, H., Nakashima, M., Saitsu, H., Matsumoto, N., High prevalence of genetic alterations in early-onset epileptic encephalopathies associated with infantile movement disorders, Brain and Development, 38, 285-292, 2016 **Ref Id** 1067825 **Country/ies where the study was carried out** Japan **Study design** Single arm prospective cohort study	**Sample size** N= 11 (early onset epileptic encephalopathies [EOEE] with involuntary movements such as hyperkinetic movements and hand stereotypies) **Characteristics** Age, months, mean (SD): NR Age at onset, months, range: 2-11 Males, n (%): 4 (36) Developmental delay, n (%): 11 (100) Type of epilepsy, n (%): West syndrome 9 (82), nonsyndromic epilepsy 2 (18)	**Genetic test** High resolution melting analysis, n=1 Whole-exome sequencing (WES), n=10. Genomic DNA was captured using a SureSelect Human All Exon v4 or v5 Kit (Agilent Technologies, Santa Clara, CA, US) in nine patients or a SeqCap EZ Exome Library v2.0 (Roche NimbleGen, Madison, WI, US) in one patient, then was sequenced on a HiSeq2000 (Illumina, San Diego, CA, US) with 101- bp paired-end reads. 7 patients had trio-based WES, 3 patients proband only WES. All variants were	**Sample selection** Recruited from Nishi-Niigata Chuo National Hospital in Niigata, Japan between 2007 and 2013. Point along the pathway where these patients were reviewed was not reported.	**Diagnostic yield** WES: 8/10 (80%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? Yes **2.** Were study participants sampled in an appropriate way? Yes, all those meeting the inclusion criteria were included **3.** Was the sample size adequate? No, sample size calculations were not performed and the sample size was small (<150 participants) **4.** Were the study subjects and the

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	Inclusion criteria • Onset within 1 year after birth • Frequent epileptic seizures including spasms • Severe developmental delay • Cognitive impairment • Accompanying involuntary movements such as chorea, dyskinesia, ballism, and/or hand stereotypies **Exclusion criteria** • Males analysed by Sanger sequencing and had ARX variants or who were diagnosed with Rett syndrome and carried an MECP2 mutation	validated as de novo events by Sanger sequencing. Diagnostic results consisted of 'pathogenic variants'.			setting described in detail? No, patient current age was not reported. Unclear how long they had the epilepsy for. **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Yes, they "included all patients who met the inclusion criteria within the specified period, and did not exclude any eligible patients." **6.** Were valid methods used for the identification of the condition? Yes, epilepsy types were determined by an epileptologist on the basis of clinical history, imaging and EEG findings in accordance with epilepsy classifications of the ILAE. **7.** Was the condition measured in a standard, reliable way for all participants? Yes

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					8. Was there appropriate statistical analysis? No (no 95% CI were reported) **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? Likely yes. No description that anyone did not have the test out of the eligible patients. Overall quality: Moderate
Full citation Kodera, H., Kato, M., Nord, A. S., Walsh, T., Lee, M., Yamanaka, G., Tohyama, J., Nakamura, K., Nakagawa, E., Ikeda, T., Ben-Zeev, B., Lev, D., Lerman-Sagie, T., Straussberg, R., Tanabe, S., Ueda, K., Amamoto, M., Ohta, S., Nonoda, Y., Nishiyama, K., Tsurusaki, Y., Nakashima, M., Miyake, N., Hayasaka, K., King, M. C., Matsumoto, N., Saitsu, H., Targeted capture and sequencing for detection of mutations causing early onset epileptic encephalopathy, Epilepsia, 54, 1262-1269, 2013	**Sample size** N=68 (Early onset epileptic encephalopathies (EOEEs). 15 were positive controls and 53 were in the diagnostic group. **Characteristics** Age, months, mean (SD): <1 years old Males, n (%): 36 (53%) Developmental delay, n (%): All people had impairment of cognitive, sensory, and motor development	**Genetic test** Gene-panel testing of 35 genes using target capture sequencing and variant detection	**Sample selection** Unclear how sample was selected	**Diagnostic yield** Pathogenic variants: 12/53 (23%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? Single centre study in Japan **2.** Were study participants sampled in an appropriate way? Unclear how the sampling occurred **3.** Was the sample size adequate? No, <150 and no calculation undertaken

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Ref Id 1088173 **Country/ies where the study was carried out** Japan **Study design** Single centre cohort study with positive controls	Pathway: No prior genetic testing in the intervention group **Inclusion criteria** • People with early onset epileptic encephalopathies (EOEEs) **Exclusion criteria** • None detailed				**4.** Were the study subjects and the setting described in detail? Little detail outside of inclusion criteria **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Yes **6.** Were valid methods used for the identification of the condition? Reasoned why the ILEA criteria was not used **7.** Was the condition measured in a standard, reliable way for all participants? Standard ised testing **8.** Was there appropriate statistical analysis? No confidence intervals **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? Yes, all respoded Overall quality: low

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Full citation Kothur, K., Holman, K., Farnsworth, E., Ho, G., Lorentzos, M., Troedson, C., Gupta, S., Webster, R., Procopis, P. G., Menezes, M. P., Antony, J., Ardern-Holmes, S., Dale, R. C., Christodoulou, J., Gill, D., Bennetts, B., Diagnostic yield of targeted massively parallel sequencing in children with epileptic encephalopathy, Seizure, 59, 132-140, 2018 **Ref Id** 1089957 **Country/ies where the study was carried out** Australia **Study design** Single-arm retrospective cohort	**Sample size** N= 105 (epilepsy of unknown cause) **Characteristics** Only the raw data of those with pathological/ likely pathological variants was reported. Age, months, mean (SD): Age range at onset; 1 day - 3.8 years. Current age, range 0.3 - 11 years. Males, n (%): 17 (57) Developmental delay, n (%): 4 (13) patients have normal cognitive outcome after epilepsy. The rest of the patients range from mild to Severe delay. **Inclusion criteria** • Patients with epilepsy who underwent the EE panel using MPS testing between January 2014 and September 2016 at The Children's Hospital at Westmead (CHW)	**Genetic test** Gene panel testing (target epileptic encephalopathy panel of 47 known genes then expanded to include 71 known genes)/ Massively parallel sequencing testing. Illumina TruSight One panel. Variants were classified as pathogenic/likely pathogenic/VOUS/likely benign/benign according to the 2015 American College of Medical Genetics and Genomics (ACMG) guidelines based on a combination of previous reports in the literature, computational analysis, functional, and population data. Diagnostic results consisted of pathogenic and likely pathogenic variants which were validated using Sanger sequencing in the proband.	**Sample selection** Unclear method of recruitment. Patients underwent clinical triage by a group of neurologists prior to the testing. It was not consecutive as some patients who were thought to have a low diagnostic yield/ were participating in other studies were excluded. The etiological investigations were performed either as inpatient admission/ outpatient follow up. Point along the pathway where these patients were reviewed was not reported.	**Diagnostic yield** Gene-panel testing (47 or 71 genes): 30/105 (28.5) 37 patients had the 47 gene panel, 68 patients had the 71 gene panel.	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? Unclear not all the demographics of the included patients were included. **2.** Were study participants sampled in an appropriate way? Not described. Not all those that met the inclusion criteria were included. **3.** Was the sample size adequate? No, sample size calculations were not performed and sample size was small (<150 participants) **4.** Were the study subjects and the setting described in detail? No, only baseline characteristics of those with the pathological/ likely pathological variants.

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	• Prioritization for EE panel testing if they had ongoing seizures, persistently abnormal EEG and no cause was found despite investigations or if a specific monogenic epilepsy was suspected **Exclusion criteria** • Children with cortical malformation of the brain and those with pathogenic copy number variants on CGH microarray				**5.** Was the data analysis conducted with sufficient coverage of the identified sample? No, seems to be a select group that is likely to have a higher diagnostic yield. **6.** We excluded 5 patients in pre MPS group and 7 patients in Post MPS group in whom diagnosis was already suspected by the treating clinician based on electroclinical phenotype and biochemical testing. **7.** Twenty-eight patients were not tested either due to enrolment in other research genetic studies, or because the diagnostic yield was considered low in the clinical triage meeting by the neurologists. **8.** Were valid methods used for the identification of the condition? Yes, ILAE classification and previously used

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					classification in epileptic encephalopathy studies were used. **9.** Was the condition measured in a standard, reliable way for all participants? Yes **10.** Was there appropriate statistical analysis? No (no 95% CIs were reported) **11.** Was the response rate adequate, and if not, was the low response rate managed appropriately? Unclear, no information on whether anyone declined the testing. Overall quality: Very low
Full citation Lindy, A. S., Stosser, M. B., Butler, E., Downtain-Pickersgill, C., Shanmugham, A., Retterer, K., Brandt, T., Richard, G., McKnight, D. A., Diagnostic outcomes for genetic testing of 70 genes in 8565 patients with epilepsy and	**Sample size** N=8565 patients with epilepsy and neurodevelopmental disorders **Characteristics** Not reported **Inclusion criteria**	**Genetic test** Gene-panel testing (70 genes). Positive results were defined as the presence of 1 or 2 pathogenic or likely pathogenic variants in a single gene	**Sample selection** Patients were referred for molecular diagnostic laboratory testing using 1 of 5 gene panel-testing, as the discretion of	**Diagnostic yield** Gene-panel testing (70 genes): 1315/8565 (15.4%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? yes

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
neurodevelopmental disorders, Epilepsia, 59, 1062-1071, 2018 **Ref Id** 1068288 **Country/ies where the study was carried out** US **Study design** Single-arm retrospective cohort study	Not reported **Exclusion criteria** Not reported		the clinician. No further details were provided.		**2.** Were study participants sampled in an appropriate way? Yes, consecutive people over a time frame **3.** Was the sample size adequate? Yes **4.** Were the study subjects and the setting described in detail? No, no details were provided **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Yes **6.** Were valid methods used for the identification of the condition? Unclear; by the title it seems that all participants had epilepsy and neurodevelopmental disorders, but in the methods section it is stated: "the cohort included 8565 consecutive individuals with epilepsy and/or NDD" **7.** Was the condition measured in a

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					standard, reliable way for all participants? Unclear, no details were provided **8.** Was there appropriate statistical analysis? No, 95% confidence intervals not included **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: moderate
Full citation Oates, S., Tang, S., Rosch, R., Lear, R., Hughes, E. F., Williams, R. E., Larsen, L. H. G., Hao, Q., Dahl, H. A., Moller, R. S., Pal, D. K., Incorporating epilepsy genetics into clinical practice: A 360degreeevaluation, npj Genomic Medicine, 3 (1) (no pagination), 2018 **Ref Id** 1090032 **Country/ies where the study was carried out** UK	**Sample size** N=96 (early onset (<2 years) epilepsy, treatment resistant epilepsy of unknown cause or familial epilepsy where the genetic cause was unknown) **Characteristics** Age at seizure onset: age at testing, median (range) Neonatal (0-1month): Neonatal epileptic encephalopathy	**Genetic test** Gene panel analysis for 45 (n=11),76 (n=11), 85 (n=49) and 102 (n=23) genes. 2 patients were referred to the epilepsy genetic service with existing positive gene panel results from another provider. Potentially pathogenic variants were validated through conventional Sanger sequencing, and, if possible, parents were included for segregation analysis when indicated.	**Sample selection** Patients were referred to King's Health Partners epilepsy genetics service for molecular diagnostic testing, between November 2014 and September 2016. Two patients died during the testing process.	**Diagnostic yield** Gene panel analysis (45,76,85 or 102 genes):19/96 (20%) By age at seizure onset: 0-1month: 10/16 (63%) 2-24months: 7/34 (21%) >2 years: 2/46 (4%) Also reports the diagnostic yield by epilepsy syndrome. 23%	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? Yes **2.** Were study participants sampled in an appropriate way? Yes, all referral routes (tertiary referral or a regional specialist epilepsy clinic).Unclear if consecutive once

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Study design Prospective cohort study	n=14; 3.75 (0.2-16.9)years Benign neonatal n=2; age at testing 0.2 (0.2)years Infantile (2-24 months): Infantile EE n=19; 7.5 (0.3-22.9)years FS/TLE spectrum n=4; 6.1 (1.3-18.3)years Infantile spasms n=11; 6.5 (0.5-12.2)years Childhood (>2years): NFLE/SHE n=6; 13.7 (5.6-17.6) years Generalised (LGS-like) n=9; 15.1 (3.4-19.9)years Early-onset absence n=4; 7.45 (1.4-14.7) Epilepsy-Aphasia spectrum n=11; 10.8 (7.3-17.2) Familial focal epilepsy n=8; 10.45 (4.0-14.5) Refractory focal epilepsy n=8; 9 (4.4-17.4) Many patients were tested years after onset or diagnosis including one adult patient and two post mortem. Males, n (%): 55 (57) Developmental delay, n (%): NR	Classification: benign, VUS or pathogenic variants for the purposes of genetic counselling. For predicted possibly damaging variants where segregation analysis could be performed, we required the variant to meet one of the following criteria to constitute a likely pathogenic variant: de novo in early-onset severe epilepsy syndromes, segregation with the disorder, inheritance from an unaffected parent but previously reported in other families with the same phenotype and incomplete penetrance, or adherence to a recessive X-linked or parent-of- origin mode of inheritance.	Three pathways for genetic testing: either being seen (i) in the specialist epilepsy genetic clinic, as above (n = 40); (ii) by a paediatric neurologist (n = 7) or paediatric epileptologist (n = 37) at one of the two tertiary centres; or (iii) seen by a general paediatrician (n = 12) with a special interest in epilepsy at a district general hospital, with referrals made in discussion with their linked paediatric epileptologist. Point along the pathway where these patients were reviewed was not reported.	amongst drug resistant cases.	meeting inclusion criteria. **3.** Was the sample size adequate? No, sample size calculations were not performed and the sample size was small (<150 participants) **4.** Were the study subjects and the setting described in detail? Yes **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Unclear/ no information as to whether eligible patients declined participation. **6.** Were valid methods used for the identification of the condition? Yes "Patients were operationally categorized into broad epilepsy syndromes because many did not fit into the International League Against Epilepsy

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	Drug resistant, n (%): 49/77 (64) **Inclusion criteria** • Either early onset (<2 years) epilepsy, treatment resistant epilepsy of unknown cause or familial epilepsy where the genetic cause was unknown • Epilepsy as their primary diagnosis • Referred to the King's Health Partners epilepsy genetics service for molecular diagnostic testing, between November 2014 and September 2016 **Exclusion criteria** Children with suspected typical Dravet Syndrome (OMIM 607208) or Glut-1 Deficiency syndromes (OMIM 606777) as they undergo single gene testing Patients with brain malformations (as they				classification of epilepsy syndromes". **7.** Was the condition measured in a standard, reliable way for all participants? Yes **8.** Was there appropriate statistical analysis? no (no 95% CIs were reported) **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately?Yes, assume there was an adequate response as there is no missing data described. Unclear if there were participants who had agreed and consequently declined testing. Overall quality: Moderate

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	are tested on a separate gene panel)				
Full citation Ostrander, B. E. P., Butterfield, R. J., Pedersen, B. S., Farrell, A. J., Layer, R. M., Ward, A., Miller, C., DiSera, T., Filloux, F. M., Candee, M. S., Newcomb, T., Bonkowsky, J. L., Marth, G. T., Quinlan, A. R., Whole-genome analysis for effective clinical diagnosis and gene discovery in early infantile epileptic encephalopathy, npj Genomic Medicine, 3 (1) (no pagination), 2018 **Ref Id** 1098288 **Country/ies where the study was carried out** US **Study design** Single arm cohort study	**Sample size** N=14 (early infantile epileptic encephalopathy [EIEE]). The parents were also tested. **Characteristics** Age, range (SD): 0-7 months old Males, n (%): 5 (36%) Developmental delay, n (%): People with EIEE typically exhibit developmental delay, profound intellectual impairment. **Inclusion criteria** • Children with early infantile epileptic encephalopathy (EIEE) for whom no underlying diagnosis was identified **Exclusion criteria** • People with established genetic,	**Genetic test** Whole-genome analysis (WGA)	**Sample selection** People were recruited from 2015 to 2016.	**Diagnostic yield** **Pathogenic or likely pathogenic mutation:** 14/14 (100%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? Yes **2.** Were study participants sampled in an appropriate way? Unclear if any sampling technique was used **3.** Was the sample size adequate? It was a small sample **4.** Were the study subjects and the setting described in detail? Detailed descriptions of the participants **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Yes **6.** Were valid methods used for the identification of the

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	metabolic, structural, or birth trauma-related causes.				condition? Standardised testing **7.** Was the condition measured in a standard, reliable way for all participants? Yes **8.** Was there appropriate statistical analysis? No confidence intervals reported **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately?Yes Overall quality: moderate
Full citation Palmer, E. E., Schofield, D., Shrestha, R., Kandula, T., Macintosh, R., Lawson, J. A., Andrews, I., Sampaio, H., Johnson, A. M., Farrar, M. A., Cardamone, M., Mowat, D., Elakis, G., Lo, W., Zhu, Y., Ying, K., Morris, P., Tao, J., Dias, K. R., Buckley, M., Dinger, M. E., Cowley, M. J., Roscioli, T., Kirk, E. P., Bye, A., Sachdev, R. K., Integrating exome sequencing into a diagnostic	**Sample size** N=32 (Infantile-onset epileptic encephalopathy [EE]). Unaffected parents tested. **Characteristics** Age, months, mean : 46.6 Males, n (%): not detailed	**Genetic test** Whole exome sequencing (WES)	**Sample selection** All children meeting the inclusion criteria in 1 hospital who were born from 2000 to 2013 were considered. 12 were excluded based on consent or ability obtain sufficient DNA.	**Diagnostic yield** Pathogenic/likely pathogenic variants: WES: 16/32 (50%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? Single centre study **2.** Were study participants sampled in an appropriate way? Yes, all people

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
pathway for epileptic encephalopathy: Evidence of clinical utility and cost effectiveness, Molecular genetics & genomic medicine, 6, 186-199, 2018 **Ref Id** 1090041 **Country/ies where the study was carried out** Australia **Study design** Single centre cohort study	Developmental delay, n (%): The inclusion criteria included developmental stagnation or regression. The severity varied. **Inclusion criteria** • Children with infantile-onset epileptic encephalopathy (EE) who remained undiagnosed after first-tier assessment. These are people with drug-resistant epilepsy for a minimum of 6 months, seizure onset accompanied by adverse impact on development such as developmental stagnation or regression, an infantile-onset of seizures (before 18 months), and at least one electroencephalogram (EEG) that was significantly abnormal with diffusely poorly organized background				meeting the criteria we considered. **3.** Was the sample size adequate? No, <150 and no calculation undertaken **4.** Were the study subjects and the setting described in detail? Few details prior to testing. There are extensive details of people who had a pathogenic mutation. **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Yes **6.** Were valid methods used for the identification of the condition? Yes, ILAE **7.** Was the condition measured in a standard, reliable way for all participants? Standard ised testing **8.** Was there appropriate statistical analysis? No confidence intervals **9.** Was the response rate adequate, and if not,

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	and marked bihemispheric epileptogenic activity. **Exclusion criteria** • Clear genetic/other etiological diagnosis previously established on first-tier ssessment				was the low response rate managed appropriately? A number of people could not be analysed because DNA could not be obtained. Overall quality: low
Full citation Papuc, S. M., Abela, L., Steindl, K., Begemann, A., Simmons, T. L., Schmitt, B., Zweier, M., Oneda, B., Socher, E., Crowther, L. M., Wohlrab, G., Gogoll, L., Poms, M., Seiler, M., Papik, M., Baldinger, R., Baumer, A., Asadollahi, R., Kroell-Seger, J., Schmid, R., Iff, T., Schmitt-Mechelke, T., Otten, K., Hackenberg, A., Addor, M. C., Klein, A., Azzarello-Burri, S., Sticht, H., Joset, P., Plecko, B., Rauch, A., The role of recessive inheritance in early-onset epileptic encephalopathies: a combined whole-exome sequencing and copy number study, European Journal of Human Genetics, 27, 408-421, 2019	**Sample size** N=63 (epileptic encephalopathies or developmental and epileptic encephalopathy) **Characteristics** Age at onset, months, median (range): 7 (1-51) Males, n (%): not detailed Developmental delay, n (%): all people had at least moderate intellectual disability **Inclusion criteria** • People with developmental delay and onset of epilepsy	**Genetic test** Chromosomal microarray analysis (aCGH) Whole-exome sequencing (WES)	**Sample selection** Recruited from 2013 to 2015. Unclear if a consecutive group investigated.	**Diagnostic yield** Pathogenic variants that unequivocally explain diagnosis: chromosomal microarray analysis: 5/63 (8%) disease-associated variants: whole-exome sequencing (WES): 20/60 (33%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies 1. Was the sample frame appropriate to address the target population? Single centre study in Switzerland. 2. Were study participants sampled in an appropriate way? Unclear if any sampling techniques were used. 3. Was the sample size adequate? No, <150 and no calculation undertaken 4. Were the study subjects and the setting described in

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Ref Id 1098628 **Country/ies where the study was carried out** Switzerland **Study design** Single centre, single arm cohort study	below the age of 4.5 years, pharmacoresistance for at least 6 months, no persistent spike wave focus in EEG, absence of specific malformations on cerebral MRI, unknown etiology after standard clinical evaluation including an extended targeted metabolic screening **Exclusion criteria** • None detailed				detail? Yes, many details of the population were provided. **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Yes **6.** Were valid methods used for the identification of the condition? Yes, ILAE criteria **7.** Was the condition measured in a standard, reliable way for all participants? Standard ised testing. **8.** Was there appropriate statistical analysis? No confidence intervals and some variation in reports of the outcomes of the two tests **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? Yes, the large majority responded.

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					Overall quality: Low
Full citation Parrini, E., Marini, C., Mei, D., Galuppi, A., Cellini, E., Pucatti, D., Chiti, L., Rutigliano, D., Bianchini, C., Virdo, S., De Vita, D., Bigoni, S., Barba, C., Mari, F., Montomoli, M., Pisano, T., Rosati, A., Guerrini, R., Diagnostic Targeted Resequencing in 349 Patients with Drug-Resistant Pediatric Epilepsies Identifies Causative Mutations in 30 Different Genes, Hum MutatHuman mutation, 38, 216-225, 2017 **Ref Id** 1119525 **Country/ies where the study was carried out** Italy **Study design** Single-arm prospective cohort study	**Sample size** N=349 **Characteristics** Not reported **Inclusion criteria** • Those with drug-resistant epilepsy (defined as people in whom adequate trials of 2 tolerated and appropriately chosen antiepileptic drugs were tried but did not achieve seizure freedom. Epilepsies were defined according to the ILAE guidelines) **Exclusion criteria** • Not reported	**Genetic test** Gene-panel testing, a panel of 30 or 95 genes associated with epilepsy was used. 'Pathogenic' and 'likely pathogenic' variants were defined according to the ACMG guidelines.	**Sample selection** The cohort consisted of a consecutive group of patients referred from the paediatric unit of a hospital with no obvious developmental or acquired brain injury abnormalities on 1.5 T or 3T MRI.	**Diagnostic yield** Gene-panel testing (30 to 95 genes; authors used more than one gene panel): 71/349 (20.3%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies 1. Was the sample frame appropriate to address the target population? yes, the sample consisted in patients referred from the paediatric unit 2. Were study participants sampled in an appropriate way? yes 3. Was the sample size adequate? yes, although sample size calculations were not performed, the size was large (>350 participants) 4. Were the study subjects and the setting described in detail? no, there were no enough details provided about the setting or participant's characteristics 5. Was the data analysis conducted with

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					sufficient coverage of the identified sample? yes, all participants received diagnostic testing **6.** Were valid methods used for the identification of the condition? yes, ILAE criteria **7.** Was the condition measured in a standard, reliable way for all participants? yes **8.** Was there appropriate statistical analysis? no, 95% CI were not reported **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: moderate
Full citation Peng, J., Pang, N., Wang, Y., Wang, X. L., Chen, J., Xiong, J., Peng, P., Zhu, C. H., Kessi, M. B., He, F., Yin, F., Next-generation sequencing improves treatment efficacy and reduces hospitalization in children with drug-resistant	**Sample size** N=273 (paediatric drug resistant epilepsy [DRE]) **Characteristics** Age, months, mean (SD): 13.2 (20.8) Males, n (%): 177 (65)	**Genetic test** Whole exome sequencing (WES): Clinical WES: n=58 (atypical clinical manifestations) WES: n=74 Gene panel (initially 308 genes, then updated to included 540 genes):	**Sample selection** Unclear. Study design was approved by the institutional review board of Xiangya Hospital of Central South University, China.	**Diagnostic yield** Overall diagnostic yield for disease causing mutations: 86/273 (31.5%) Clinical WES: 26/58 (44.8%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? Unclear if Xiangya Hospital was the only

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
epilepsy, CNS Neuroscience and Therapeutics, 25, 14-20, 2019 **Ref Id** 1090310 **Country/ies where the study was carried out** China **Study design** Pilot prospective cohort	<u>Developmental delay, n (%):</u> NR <u>Seizure type, n (%):</u> spasms 141 (51.6), focal seizures 68 (24.9). 17.2% (47/273) had > 1 seizure type <u>Diagnoses prior to NGS</u>: Dravet syndrome (31/86, 36%), West syndrome (19/86, 22.1%), epilepsy combined with global developmental delay (GDD) (14/86, 16.3%), epilepsy with focal seizures (10/86, 11.6%), MMSPI (3/86, 3.5%), PME(3/86, 3.5%), EOEE((2/86, 2.3%), OS(2/86, 2.3%), EIEE19(1/86,1.2%), and epilepsy with GTCS(1/86,1.2%) **Inclusion criteria** • Children with unexplained DRE • No obvious brain abnormalities • No infection	n=141 tested by this method Diagnostic yield described as 'disease causing mutations'.	From this presume the study was carried out at Xiangya Hospital. Unclear if consecutive, if any patients declined participation or if they agreed, didnt go ahead with the test for some reason. Point along the pathway where these patients were reviewed was not reported.	<u>Epilepsy related gene panel:</u> 46/141 (32.6) WES: 13/74 (17.3)	setting/ its catchment area **2.** Were study participants sampled in an appropriate way? Unclear. No description of sampling method **3.** Was the sample size adequate? Yes **4.** Were the study subjects and the setting described in detail? No the setting was not fully described. No information on developmental delay. **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Unclear. No information as to whether potentially included/eligible patients were not recruited **6.** Were valid methods used for the identification of the condition? Yes, “Drug-resistant epilepsy” was defined as Kwan

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	• No autoimmune etiology **Exclusion criteria** • None described				et al previously reported. **7.** Was the condition measured in a standard, reliable way for all participants? Yes **8.** Was there appropriate statistical analysis? No (no 95% CIs were reported) **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? Unclear. No mention of missing data however, patients may not have been included in the study if they refused the test. Overall quality: Low
Full citation Perucca, P., Scheffer, I. E., Harvey, A. S., James, P. A., Lunke, S., Thorne, N., Gaff, C., Regan, B. M., Damiano, J. A., Hildebrand, M. S., Berkovic, S. F., O'Brien, T. J., Kwan, P., Real-world utility of whole exome sequencing with targeted	**Sample size** N=40 (focal epilepsies) Characteristics Age, median (range): 32.5 (2-74) years Males, n (%): 24 (60%)	**Genetic test** Whole exome sequencing (WES): 64 genes were selected for interpretation	**Sample selection** Recruited consecutive people in 2014 across two centres.	**Diagnostic yield** Pathogenic or likely pathogenic variants: 5/40 (12.5%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? Yes

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
gene analysis for focal epilepsy, Epilepsy Research, 131, 1-8, 2017 **Ref Id** 1097874 **Country/ies where the study was carried out** Australia **Study design** Single arm cohort study	Developmental delay, n (%): 1 person (2.5%) had mild intellectual disability. **Inclusion criteria** • People who are over 4 weeks old, a diagnosis of focal epilepsy, no epileptogenic lesion detected on brain MRI, and a family history of febrile seizures or any type of epilepsy in at least one first- or second-degree relative. **Exclusion criteria** • Previous genetic testing (except for chromosomal microarray), severe intellectual disability, benign epilepsy				**2.** Were study participants sampled in an appropriate way? Yes, Consecutive people meeting the inclusion criteria **3.** Was the sample size adequate? No, <150 and no calculation undertaken **4.** Were the study subjects and the setting described in detail? Yes, all required details **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Yes **6.** Were valid methods used for the identification of the condition? Unclear what criteria were used **7.** Was the condition measured in a standard, reliable way for all participants? Yes, standardised test regime

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					8. Was there appropriate statistical analysis? No confidence intervals provided **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? Yes Overall quality: moderate
Full citation Peycheva, V., Kamenarova, K., Ivanova, N., Stamatov, D., Avdjieva-Tzavella, D., Alexandrova, I., Zhelyazkova, S., Pacheva, I., Dimova, P., Ivanov, I., Litvinenko, I., Bozhinova, V., Tournev, I., Simeonov, E., Mitev, V., Jordanova, A., Kaneva, R., Chromosomal microarray analysis of Bulgarian patients with epilepsy and intellectual disability, Gene, 667, 45-55, 2018 **Ref Id** 1098305 **Country/ies where the study was carried out** Bulgaria	**Sample size** N= 92 people with intellectual disability (ID), generalized epilepsy, autistic signs and congenital abnormalities **Characteristics** Age, range: 1-22 years Males, n (%): 50 (54) Developmental delay, n (%): NR Intellectual disability, %: 99; mild 32, moderate 22, severe 14, underfined 21 Positive family history for any seizures or DD/ID, n (%): 47 (51)	**Genetic test** Chromosomal microarray analysis (CMA) The variants were classified in three subgroups based on their size, gene content, inheritance and presence in the literature and related databases: pathogenic, uncertain clinical significance (UCS) and benign.	**Sample selection** 92 patients were referred by clinicians from major neurologic clinics in Bulgaria. Point along the pathway where these patients were reviewed was not reported.	**Diagnostic yield** CMA: 14/92 (15.2%), pathogenic/ possible pathogenic CMA: 8/92 (8.7%), pathogenic	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? Unclear where the patients came from/ geographical location **2.** Were study participants sampled in an appropriate way? Unclear method of recruitment **3.** Was the sample size adequate? No, sample size calculations were not performed, and

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Study design Prospective cohort	Seizure type, %: refractory generalised tonic-clonic seizures 66, myoclonic 20, absence seizures 18. **Inclusion criteria** • Presence of any epilepsy and manifesting intellectual disability phenotype **Exclusion criteria** • Dravet syndrome (Sanger sequencing was done to rule this out) • GLUT1 deficiency syndrome (direct sequencing of SLC2A1 gene to rule this out)				sample size was small (<150) **4.** Were the study subjects and the setting described in detail? No, the setting was not described. **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Unclear, no description of the eligible population/ who agreed to participate and who didn't. **6.** Were valid methods used for the identification of the condition? Yes for ID. No mention of epilepsy classifications. **7.** Was the condition measured in a standard, reliable way for all participants? Yes **8.** Was there appropriate statistical analysis? No (no 95% CIs were reported) **9.** Was the response rate adequate, and if not,

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					was the low response rate managed appropriately? Unclear if all those eligible agreed to participate and took the test. No missing data described. Overall quality: Very low
Full citation Ream, M. A., Mikati, M. A., Clinical utility of genetic testing in pediatric drug-resistant epilepsy: a pilot study, Epilepsy & behavior : E&B, 37, 241-248, 2014 **Ref Id** 1097025 **Country/ies where the study was carried out** US **Study design** Single-arm retrospective cohort study	**Sample size** N=29 children with drug-resistant epilepsy **Characteristics** **Main population (N= 25)** Age (at epilepsy onset), years, mean (SD): 2.5 (3.1) Age (initial evaluation), years, mean (range): 6.8 (6.8) Males, n (%): 12 (48.2) Developmental delay, n (%): 24 (89.65) **Additional participants (N=4) [established patients who underwent WES**	**Genetic test** Karyotyping, chromosomal microarray analysis (CMA), single-gene testing, gene-panel testing (number of genes not reported), whole exome sequencing (WES). Yield of "diagnostic results" were reported. Diagnostic results consisted of mutations previously reported as being disease-causing and likely disease-causing.	**Sample selection** Patients were retrospectively reviewed and those meeting the inclusion criteria were included in the study. Decisions to perform genetic testing was at the discretion of the clinicians, based on the lack of an alternative definitive nongenetic aetiology and suspicion of a genetic cause. Point along the pathway where	**Diagnostic yield** Karyotyping: 1/7 (14.3%) CMA: 2/12 (16.7%) Single-gene panel: 2/13 (15.4%) Gene-panel testing (number of genes was not reported): 6/13 (46.2%) WES: 1/6 (16.7%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies 1. Was the sample frame appropriate to address the target population? yes 2. Were study participants sampled in an appropriate way? yes, consecutive sample and everyone meeting the inclusion criteria was included 3. Was the sample size adequate? no, sample size

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	during the study period) Age (epilepsy onset), months, mean (range): 6.8 (6.8) Males, n (%): 2 (50) Developmental delay, n (%): 24 (96) **Inclusion criteria** • Presence of paediatric resistance epilepsy or drug resistance epilepsy • One of the following tests done: karyotype, CMA, gene sequencing of specific single genes/ gene panels, WES **Exclusion criteria** • Not reported		these patients were reviewed was not reported.		calculations were not performed, but sample size was small (<150 participants) **4.** Were the study subjects and the setting described in detail? yes, setting described in details and participant's characteristics were reported **5.** Was the data analysis conducted with sufficient coverage of the identified sample? no, genetic tests were not conducted in all participants **6.** Were valid methods used for the identification of the condition? yes, according to ILAE definitions **7.** Was the condition measured in a standard, reliable way for all participants? yes **8.** Was there appropriate

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					statistical analysis? no (no 95% CIs were reported) 9. Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: moderate **Other information**
Full citation Rim, J. H., Kim, S. H., Hwang, I. S., Kwon, S. S., Kim, H. W., Cho, M. J., Ko, A., Youn, S. E., Kim, J., Lee, Y. M., Chung, H. J., Lee, J. S., Kim, H. D., Choi, J. R., Lee, S. T., Kang, H. C., Efficient strategy for the molecular diagnosis of intractable early-onset epilepsy using targeted gene sequencing, BMC Medical Genomics, 11, 6, 2018 **Ref Id** 1098320	**Sample size** N= 74 (intractable early onset epilepsy (EOE)) **Characteristics** Age at seizure onset, months, mean (SD): 7.5 (7.8) Seizures before the age of 1, n (%): 63 (85.1) Males, n (%): NR Global developmental delay, n (%): 62 (83.8)	**Genetic test** Targeted gene sequencing using a next generation sequencing (172 genes were included). For small nucleotide variations, pathogenic and likely pathogenic variants as well as VUSs needing parental study were examined using Sanger sequencing. Diagnostic results consisted of pathogenic or likely pathogenic variants.	**Sample selection** Recruited from the epilepsy clinic in Severance Children's Hospital from March 2015 to May 2016. As a nationwide referral center for EOE, patient population generally includes severe epilepsy patients with unknown causes.	**Diagnostic yield** NGS panel testing (172 genes): 28/74 (37.8%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies 1. Was the sample frame appropriate to address the target population? Yes, nationwide referral centre 2. Were study participants sampled in an appropriate way? Unclear, method of sampling was not described in the paper 3. Was the sample size adequate? No,

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Country/ies where the study was carried out South Korea **Study design** Prospective cohort	Seizure type: Epileptic spasms 70.3%, generalised 33.8%, focal seizure 21.6%. Two patients had all 3 seizure types. History of neonatal seizures, n (%): 11 (15.0) History of status epilepticus, n (%): 6 (8.1) Two unexpected premature deaths (pneumonia and sudden infantile death syndrome) The epilepsy syndrome was diagnosed most commonly as infantile spasm (IS) (n = 51), followed by Dravet syndrome (n = 2), malignant migrating focal seizures in infancy (MMFI) (n = 1), and Doose syndrome (n = 1). **Inclusion criteria** • Unrelated pediatric patients with EOE without a known cause		For the diagnosis of specific epilepsy syndrome, patients were classified according to the 2010 International League Against Epilepsy classification [8] and previous diagnostic criteria. Point along the pathway where these patients were reviewed was not reported.		sample size calculations were not performed and sample size was small (<150 participants) **4.** Were the study subjects and the setting described in detail? Yes **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Unclear, no information in the study as to the number of eligible patients and whether patients declined to participate **6.** Were valid methods used for the identification of the condition? Yes **7.** Was the condition measured in a standard, reliable way for all participants? Yes **8.** Was there appropriate statistical analysis? no (no 95% CIs were reported) **9.** Was the response rate adequate, and if not,

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	• Seizure onset before the age of 3 years • Multiple epileptiform discharges with severely disorganised background activity on EEG • Diagnosed with drug-resistant epilepsy and progressive developmental delay or with a known epileptic encephalopathy syndrome • No structural lesion detected with brain MRI • No metabolic abnormalities • No abnormalities detected with previous genetic tests • Offspring of assymptomatic Korean parents **Exclusion criteria** • None described.				was the low response rate managed appropriately?Unclear . No suggestions of missing data, however the methods did not describe whether there were any drop outs/ patients declining testing. Overall quality: Low
Full citation Snoeijen-Schouwenaars, F. M., van Ool, J. S., Verhoeven, J. S., van Mierlo, P., Braakman, H. M. H.,	**Sample size** N=100 (Unexplained epilepsy) **Characteristics**	**Genetic test** Whole exome sequencing (WES) performed in two steps.	**Sample selection** 100 adults or children retrospectively	**Diagnostic yield** Classified as (likely) pathogenic: 25/100 (25%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Smeets, E. E., Nicolai, J., Schoots, J., Teunissen, M. W. A., Rouhl, R. P. W., Tan, I. Y., Yntema, H. G., Brunner, H. G., Pfundt, R., Stegmann, A. P., Kamsteeg, E. J., Schelhaas, H. J., Willemsen, M. H., Diagnostic exome sequencing in 100 consecutive patients with both epilepsy and intellectual disability, Epilepsia, 60, 155-164, 2019 **Ref Id** 1098668 **Country/ies where the study was carried out** The Netherlands **Study design** Retrospective single centre, single arm cohort study	Age, years, mean (SD) (range): 24.1 (16.2) (2.8 to 67.6) Males, n (%): 55 (55%) Developmental delay, n (%): All people had borderline or worse intellectual disability **Inclusion criteria** • People with unexplained epilepsy and intellectual disability (intelligence quotient ≤ 85). Unexplained etiology of (active) epilepsy, according to the International League Against Epilepsy classification. This could be present as an associated feature; it was not necessary to have epilepsy as a main phenotypic feature. Unexplained intellectual disability according to International Classification of Diseases, 10th revision and	Step 1: restricted to the latest versions of ID and/or epilepsy gene panels. Step 2: exome analysis was extended to all genes. The results were classified according to the American College of Medical Genetics and Genomics guidelines. This was trio analysis for 66 people	included in a single centre		**1.** Was the sample frame appropriate to address the target population? No, single centre study across a broad population **2.** Were study participants sampled in an appropriate way? Yes, consecutive people meeting the inclusion criteria **3.** Was the sample size adequate? Yes **4.** Were the study subjects and the setting described in detail? Yes, details of people included provided **5.** Was the data analysis conducted with sufficient coverage of the identified sample? No, retrospective analysis of responders **6.** Were valid methods used for the identification of the condition? Yes, ILAE and DSM **7.** Was the condition measured in a

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	Diagnostic and Statistical Manual of Mental Disorders, 5th edition, defined as having both reduced intellectual functioning (intelligence quotient < 70) and impaired adaptive abilities to cope with the daily demands of the social environment. In addition, people with borderline intellectual functioning (intelligence quotient = 70-85) were included. **Exclusion criteria** • None detailed				standard, reliable way for all participants? Yes, same testing strategy **8.** Was there appropriate statistical analysis? No confidence intervals provided **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? All responded Overall quality: moderate
Full citation Symonds, J. D., Zuberi, S. M., Stewart, K., McLellan, A., O'Regan, M., MacLeod, S., Jollands, A., Joss, S., Kirkpatrick, M., Brunklaus, A., Pilz, D. T., Shetty, J., Dorris, L., Abu-Arafeh, I., Andrew, J., Brink, P., Callaghan, M., Cruden, J., Diver, L. A., Findlay, C., Gardiner, S., Grattan, R., Lang, B., MacDonnell, J.,	**Sample size** N=343 (presenting with epilepsy) **Characteristics** Age: All under 36 months of age Males, n (%): Not detailed Developmental delay, n (%): 106 (30.1%) had	**Genetic test** Custom-designed 104 gene epilepsy panel	**Sample selection** Recruited at 20 regional paediatric departments and 4 tertiary children's hospitals from 2014 to 2017.	**Diagnostic yield** Subgroup of population who had a diagnosis of epilepsy by the final follow-up: Pathogenic and likely pathogenic: 76/263 (28.9%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? Yes, multicentre study **2.** Were study participants sampled

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
McKnight, J., Morrison, C. A., Nairn, L., Slean, M. M., Stephen, E., Webb, A., Vincent, A., Wilson, M., Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort, Brain : a journal of neurology, 142, 2303-2318, 2019 **Ref Id** 1098678 **Country/ies where the study was carried out** Scotland **Study design** Multicentre cohort study	concerns about development expressed at the time of recruitment, and 115 (33.5%) had developmental concerns raised at their most recent follow-up **Inclusion criteria** • Children under 36 months old presenting with epilepsy (recurrent unprovoked seizures) and an episode of febrile or afebrile status epilepticus (seizures >30 minutes) and at least 2 febrileor afebrile epileptic seizures within a 24 hour period and a second prolonged (>10 minutes) febrile seizure, over any time period. **Exclusion criteria** • An aetiology that would fully explain seizures was identified either prior to or at first presentation with				in an appropriate way? Unclear if it was consecutive **3.** Was the sample size adequate? Yes **4.** Were the study subjects and the setting described in detail? Yes, various aspects of population described **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Yes, subgroup of people with epilepsy diagnosis was utilised. **6.** Were valid methods used for the identification of the condition? Unclear if published diagnostic criteria used **7.** Was the condition measured in a standard, reliable way for all participants? Similar testing regime conducted in all **8.** Was there appropriate statistical analysis? No

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
	seizures. Examples of such aetiologies were meningitis, hypoxic ischaemic encephalopathy in the neonate, or focal seizures in an infant with a perinatal stroke.				confidence intervals reported **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? All but 1 had required test Overall quality: moderate
Full citation Tsang, M. H. Y., Leung, G. K. C., Ho, A. C. C., Yeung, K. S., Mak, C. C. Y., Pei, S. L. C., Yu, M. H. C., Kan, A. S. Y., Chan, K. Y. K., Kwong, K. L., Lee, S. L., Yung, A. W. Y., Fung, C. W., Chung, B. H. Y., Exome sequencing identifies molecular diagnosis in children with drug-resistant epilepsy, Epilepsia Open, 4, 63-72, 2019 **Ref Id** 1098691 **Country/ies where the study was carried out** Hong Kong: China **Study design** Multicentre, single arm cohort study	**Sample size** N=50 children with drug-resistant epilepsy **Characteristics** Age at onset, median (range): 7 months (1 day to 9.3 years) Males, n (%): 28 (56%) Developmental delay, n (%): Study population developmental delay was not detailed **Inclusion criteria** • People with neonatal, infantile, or childhood-onset drug resistant epilepsy. **Exclusion criteria** • None detailed	**Genetic test** Singleton clinical chromosomal microarray (CMA): 546 genes Whole exome sequencing (WES)	**Sample selection** Recruited in 2 hospitals.	**Diagnostic yield** Singleton clinical chromosomal microarray (CMA): pathogenic or likely pathogenic mutations: 0/50 (0%) Whole exome sequencing (WES): pathogenic or likely pathogenic mutations: 6/50 (12%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? yes, multicentre study in China **2.** Were study participants sampled in an appropriate way? Unclear whether any formal sampling method was used or if they were consecutive **3.** Was the sample size adequate? No, n=<150 and no calculations undertaken **4.** Were the study subjects and the

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					setting described in detail? Yes, though no details of population development delay **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Yes **6.** Were valid methods used for the identification of the condition? Yes, by ILAE criteria **7.** Was the condition measured in a standard, reliable way for all participants? Yes, standardised testing regime **8.** Was there appropriate statistical analysis? No confidence intervals reported **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? All responded Overall quality: moderate

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Full citation Tsuchida, N., Nakashima, M., Kato, M., Heyman, E., Inui, T., Haginoya, K., Watanabe, S., Chiyonobu, T., Morimoto, M., Ohta, M., Kumakura, A., Kubota, M., Kumagai, Y., Hamano, S. I., Lourenco, C. M., Yahaya, N. A., Ch'ng, G. S., Ngu, L. H., Fattal-Valevski, A., Weisz Hubshman, M., Orenstein, N., Marom, D., Cohen, L., Goldberg-Stern, H., Uchiyama, Y., Imagawa, E., Mizuguchi, T., Takata, A., Miyake, N., Nakajima, H., Saitsu, H., Miyatake, S., Matsumoto, N., Detection of copy number variations in epilepsy using exome data, Clinical Genetics, 93, 577-587, 2018 **Ref Id** 1098388 **Country/ies where the study was carried out** Japan **Study design** Single centre, single group cohort study	**Sample size** N=294 (106 had early-onset epileptic encephalopathies [EOEEs]) **Characteristics** Age, months, mean (SD): Children at onset of epilepsy Males, n (%): 97 (57.7%) Developmental delay, n (%): Not sprecified People from Japan, Israel, Malaysia, Brazil and Turkey **Inclusion criteria** • People with epilepsy who were children at onset. **Exclusion criteria** • None detailed	**Genetic test** Whole-exome sequencing (WES)	**Sample selection** People referred to a single centre. Unclear if any sampling methods were used.	**Diagnostic yield** Pathogenic CNVs: 144/294 (49%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? Varied studied population **2.** Were study participants sampled in an appropriate way? Unclear how they were sampled **3.** Was the sample size adequate? Yes, over 150 people **4.** Were the study subjects and the setting described in detail? Very little description of the subjects and setting **5.** Was the data analysis conducted with sufficient coverage of the identified sample? All people in the sample were tested **6.** Were valid methods used for the identification of the

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					condition? Unclear what criteria was used **7.** Was the condition measured in a standard, reliable way for all participants? Standard ised testing used **8.** Was there appropriate statistical analysis? No confidence intervals provided **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? All people responded Overall quality: low
Full citation Tumiene, B., Maver, A., Writzl, K., Hodzic, A., Cuturilo, G., Kuzmanic-Samija, R., Culic, V., Peterlin, B., Diagnostic exome sequencing of syndromic epilepsy patients in clinical practice, Clinical Genetics, 93, 1057-1062, 2018 **Ref Id** 1098390	**Sample size** N=86 people with syndromic epilepsy **Characteristics** Age, months, mean (SD): not detailed Males, n (%): not detailed Developmental delay, n (%): 68 (79) people had intellectual	**Genetic test** A bioinformatic panel of 862 epilepsy or seizure-associated genes was applied to Mendeliome (4813 genes) or whole-exome sequencing data as a first stage, while the second stage included untargeted variant interpretation.	**Sample selection** All people undergoing diagnostic exome sequencing in 1 centre.	**Diagnostic yield** Pathogenic and likely pathogenic variants: 42/86 (49%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? Consecuti ve people at a single centre **2.** Were study participants sampled in an appropriate

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Country/ies where the study was carried out Slovenia **Study design** Single centre, single group retrospective study	disability/developmental delay/autism spectrum disorder **Inclusion criteria** • All people with epilepsy or seizures with diagnostic exome sequencing (DES) data. Criteria for DES testing were familial or sporadic epilepsy or seizures associated with a neurodevelopmental disorder and/or congenital malformations **Exclusion criteria** • Not detailed				way? Yes, the criteria for testing was appropriate. **3.** Was the sample size adequate? No, <150 and no calculation undertaken **4.** Were the study subjects and the setting described in detail? Little detail provided **5.** Was the data analysis conducted with sufficient coverage of the identified sample? Unclear details of study population **6.** Were valid methods used for the identification of the condition? No diagnostic criteria stated **7.** Was the condition measured in a standard, reliable way for all participants? Varying tests given to the population **8.** Was there appropriate statistical analysis? No

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					confidence intervals provided **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? Retrospective study utilising only responders Overall quality: very low
Full citation Ware, T. L., Huskins, S. R., Grinton, B. E., Liu, Y. C., Bennett, M. F., Harvey, M., McMahon, J., Andreopoulos-Malikotsinas, D., Bahlo, M., Howell, K. B., Hildebrand, M. S., Damiano, J. A., Rosenfeld, A., Mackay, M. T., Mandelstam, S., Leventer, R. J., Harvey, A. S., Freeman, J. L., Scheffer, I. E., Jones, D. L., Berkovic, S. F., Epidemiology and etiology of infantile developmental and epileptic encephalopathies in Tasmania, Epilepsia Open, 4, 504-510, 2019 **Ref Id** 1098707	**Sample size** N=16 (infantile onset developmental and epileptic encephalopathies [DEEs]). 5 people had established etiology based on history and neuroimaging. **Characteristics** Age at seizure onset, median (range): 6 months (3 days to 20 months) Males, n (%): 5 (31%) Developmental delay, n (%): All people had evidence of developmental delay, plateauing, or regression.	**Genetic test** Initially a gene panel test: 423 genes Then whole exome sequencing (WES) for people who were negative aCMG classification	**Sample selection** Consecutive people identified through contact with all Tasmanian paediatricians and paediatric neurologists and comprehensive review of EEG reports.	**Diagnostic yield** Pathogenic or likely pathogenic: gene panel testing: 3/11 (27%) Pathogenic or likely pathogenic: WES: 3/8 (38%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? Yes, multicentre study **2.** Were study participants sampled in an appropriate way? yes, consecutive people **3.** Was the sample size adequate? Very small sample **4.** Were the study subjects and the setting described in detail? Yes, details provided

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Country/ies where the study was carried out Australia **Study design** Multicentre, single group cohort study	**Inclusion criteria** • People with onset of seizures <2 years of age, epileptiform features on EEG, frequent seizures defined as >daily for a week or >weekly for a month, and evidence of developmental delay, plateauing, or regression. Infants with infantile spasms were included irrespective of seizure frequency. **Exclusion criteria** • People with acute symptomatic seizures such as those associated with hypoxic-ischemic encephalopathy				**5.** Was the data analysis conducted with sufficient coverage of the identified sample? Yes **6.** Were valid methods used for the identification of the condition? Unclear which criteria were used **7.** Was the condition measured in a standard, reliable way for all participants? Standard ised testing regime. **8.** Was there appropriate statistical analysis? No confidence intervals provided **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? All responded Overall quality: Moderate
Full citation	**Sample size** N= 251 infantile spasms	**Genetic test** Chromosomal microarray analysis,	**Sample selection**	**Diagnostic yield** CMA: 12/87 (13.7%)	**Limitations** The quality of this study was assessed using the

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Wirrell, E. C., Shellhaas, R. A., Joshi, C., Keator, C., Kumar, S., Mitchell, W. G., How should children with West syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium, Epilepsia, 56, 617-625, 2015 **Ref Id** 864121 **Country/ies where the study was carried out** US **Study design** Single-arm prospective cohort study	**Characteristics** Age (at spasms onset), months, mean (SD): 7.1 (SD 3.6) Males, n (%): 134 (53.6%) Developmental delay, n (%): not reported **Inclusion criteria** • History of consistent epileptic spasms and EEG showing hypsarrhythmia, modified hypsarrhythmia or background slowing, multifocal spikes, and electroclinical spasms **Exclusion criteria** • Children with early infantile epileptic encepahlopathy	Karyotyping, single-gene testing, Whole Exome Sequencing. Clear abnormalities were genetic mutations that were indicated to be pathogenic based on the laboratory report and/or review of the medical literature.	Data was sampled prospectively and etiology data was missing for one of the included patients. Genetic testing was performed on 141 children.	Karyotyping: 12/32 (37.5%) Single-gene testing: 11/24 (45.83%) Gene-panel testing (number of genes not reported): 11/34 (32.35%) WES: 0/4	JBI checklist for prevalence studies 1. Was the sample frame appropriate to address the target population? yes 2. Were study participants sampled in an appropriate way? yes 3. Was the sample size adequate? yes 4. Were the study subjects and the setting described in detail? yes 5. Was the data analysis conducted with sufficient coverage of the identified sample? yes 6. Were valid methods used for the identification of the condition? yes 7. Was the condition measured in a standard, reliable way for all participants? unclear, no

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					information was provided **8.** Was there appropriate statistical analysis? no, 95% CIs were not reported **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? yes Overall quality: high
Full citation Yuskaitis, C. J., Ruzhnikov, M. R. Z., Howell, K. B., Allen, I. E., Kapur, K., Dlugos, D. J., Scheffer, I. E., Poduri, A., Sherr, E. H., Infantile Spasms of Unknown Cause: Predictors of Outcome and Genotype-Phenotype Correlation, Pediatric Neurology, 87, 48-56, 2018 **Ref Id** 1098418 **Country/ies where the study was carried out** US, Canada	**Sample size** N=126 children with infantile spasms of unknown cause (note that WES data was available for n=100) **Characteristics** *Characteristics for N=126* Age, months, median (range): 5.25 (1.50 to 11) Males, n (%): 58 (43.6)	**Genetic test** Whole exome sequencing (WES). Pathogenic and likely pathogenic variants (ACMG guidelines) were selected to ascertain diagnostic yield.	**Sample selection** Patients were selected through the EPGP Clinical Centers by screening clinical data.	**Diagnostic yield** WES: 15/100 (15%)	**Limitations** The quality of this study was assessed using the JBI checklist for prevalence studies **1.** Was the sample frame appropriate to address the target population? yes **2.** Were study participants sampled in an appropriate way? yes **3.** Was the sample size adequate? no, sample size calculations were not performed, but

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
Study design Retrospective multicentre cohort study	Developmental delay (before the onset of IS), n (%): 26 (25.5) **Inclusion criteria** • A history of infantile spasms before 1 year of age • EEG with hypsarrhythmia or modified hypsarrhythmia • No positive genetic or metabolic tests at the time of enrollment **Exclusion criteria** • Those with severe developmental delay prior to the onset of IS • Lack of adequate medical records after the onset of infantile spasms • Presence of structural abnormalities, including focal cortical dysplasia on MRI				sample size was small (<150 participants) **4.** Were the study subjects and the setting described in detail? yes, setting described in detail and participant's characteristics were reported **5.** Was the data analysis conducted with sufficient coverage of the identified sample? no, genetic tests were not conducted in all participants **6.** Were valid methods used for the identification of the condition? unclear (criteria used was not specified) **7.** Was the condition measured in a standard, reliable way for all participants? yes **8.** Was there appropriate statistical analysis? no (no 95% CIs were reported) **9.** Was the response rate adequate, and if not, was the low response

Study details	Number of participants and participant's characteristics	Test	Methods	Outcomes	Comments
					rate managed appropriately? yes Overall quality: moderate

Appendix E – Forest plots

Forest plots for review question: What is the effectiveness of genetic testing in determining the aetiology of epilepsy?

This section includes plots representing the meta-analysis of the diagnostic yield (this is, the proportion of pathogenic and likely pathogenic genetic variants) of the different genetic genetic tests. Results are provided as overall estimates and by subgroups. Estimates from single studies are not presented here, but the quality assessment for these estimates is provided in the adapted GRADE profiles in appendix F.

Figure 2: Genetic test 1. Chromosomal microarray analysis (CMA): overall pooled estimate

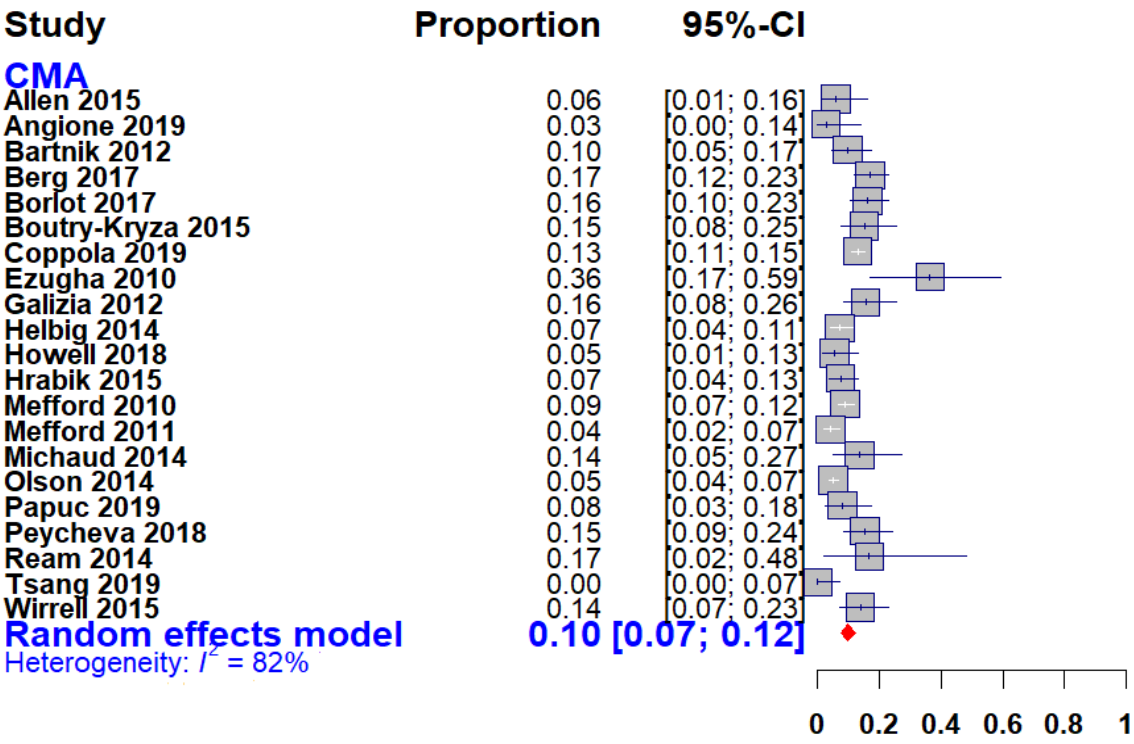


Figure 3: Genetic test 1. Chromosomal microarray analysis (CMA): subgroup analysis for children <3 years old at seizure onset

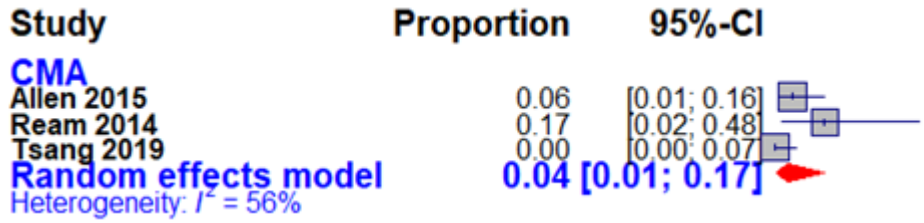


Figure 4: Genetic test 1. Chromosomal microarray analysis (CMA): subgroup analysis for people with learning difficulties/ disabilities, including neurodevelopmental disorders

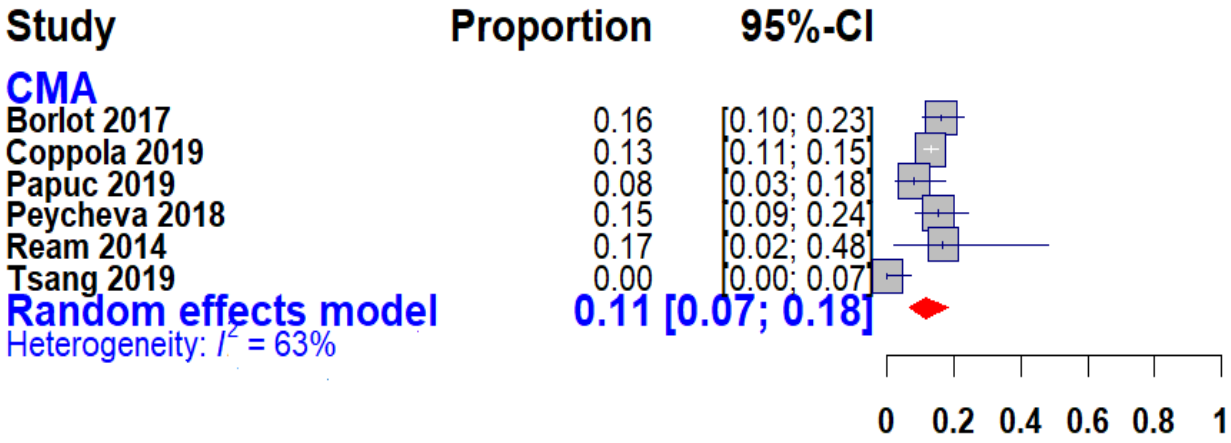


Figure 5: Genetic test 2. Karyotyping: overall pooled estimate; all children <3 years old at seizure onset

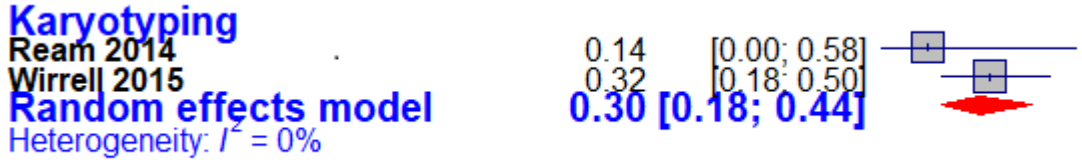


Figure 6: Genetic test 3. Single-gene testing: overall estimate

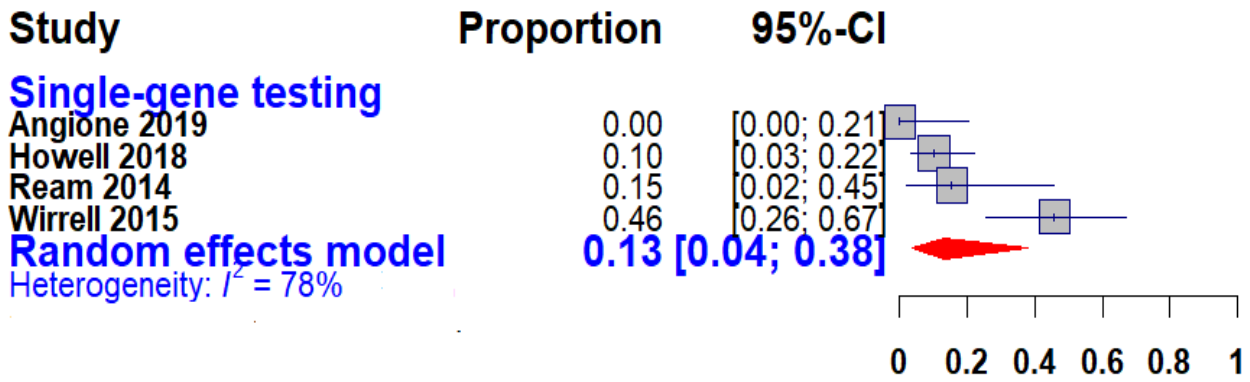


Figure 7: Genetic test 4. Gene-panel testing: overall estimate

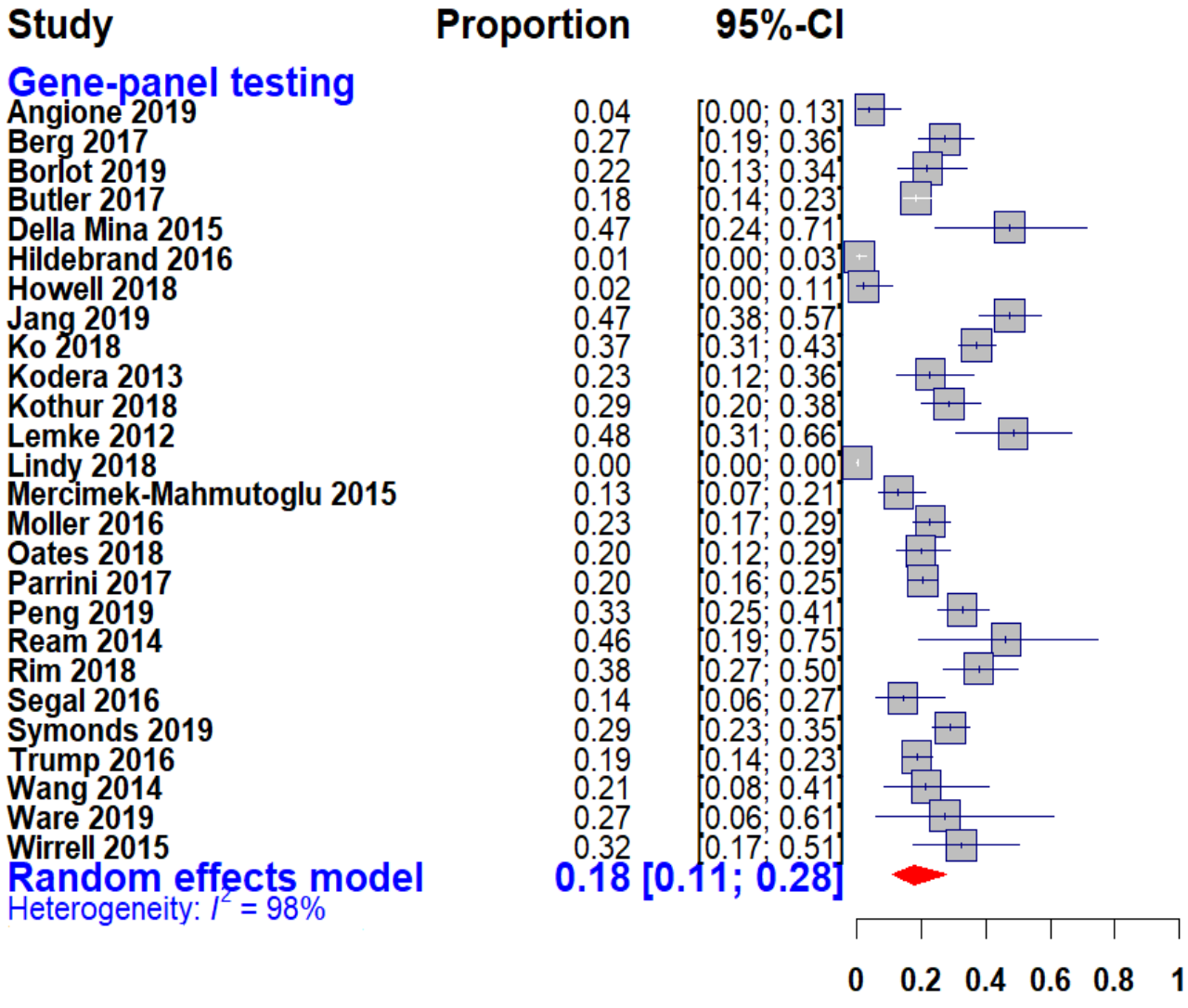


Figure 8: Genetic test 4. Gene-panel testing: subgroup analysis for children <3 years old at seizure onset

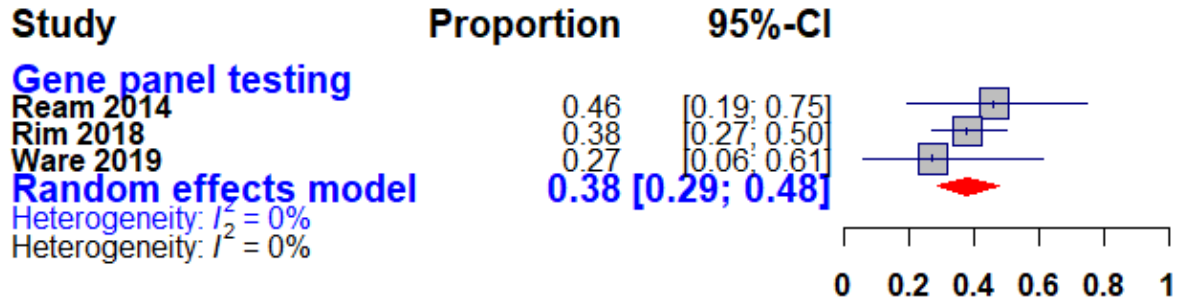


Figure 9: Genetic test 4. Gene-panel testing: subgroup analysis for people with learning difficulties/ disabilities, including neurodevelopmental disorders

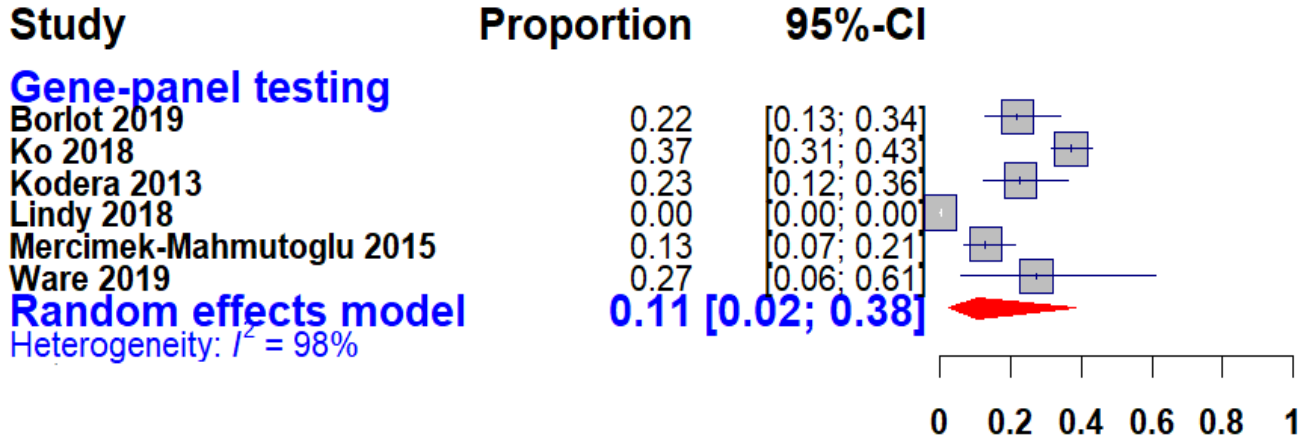


Figure 10: Genetic test 5. Whole exome sequencing (WES): overall estimate

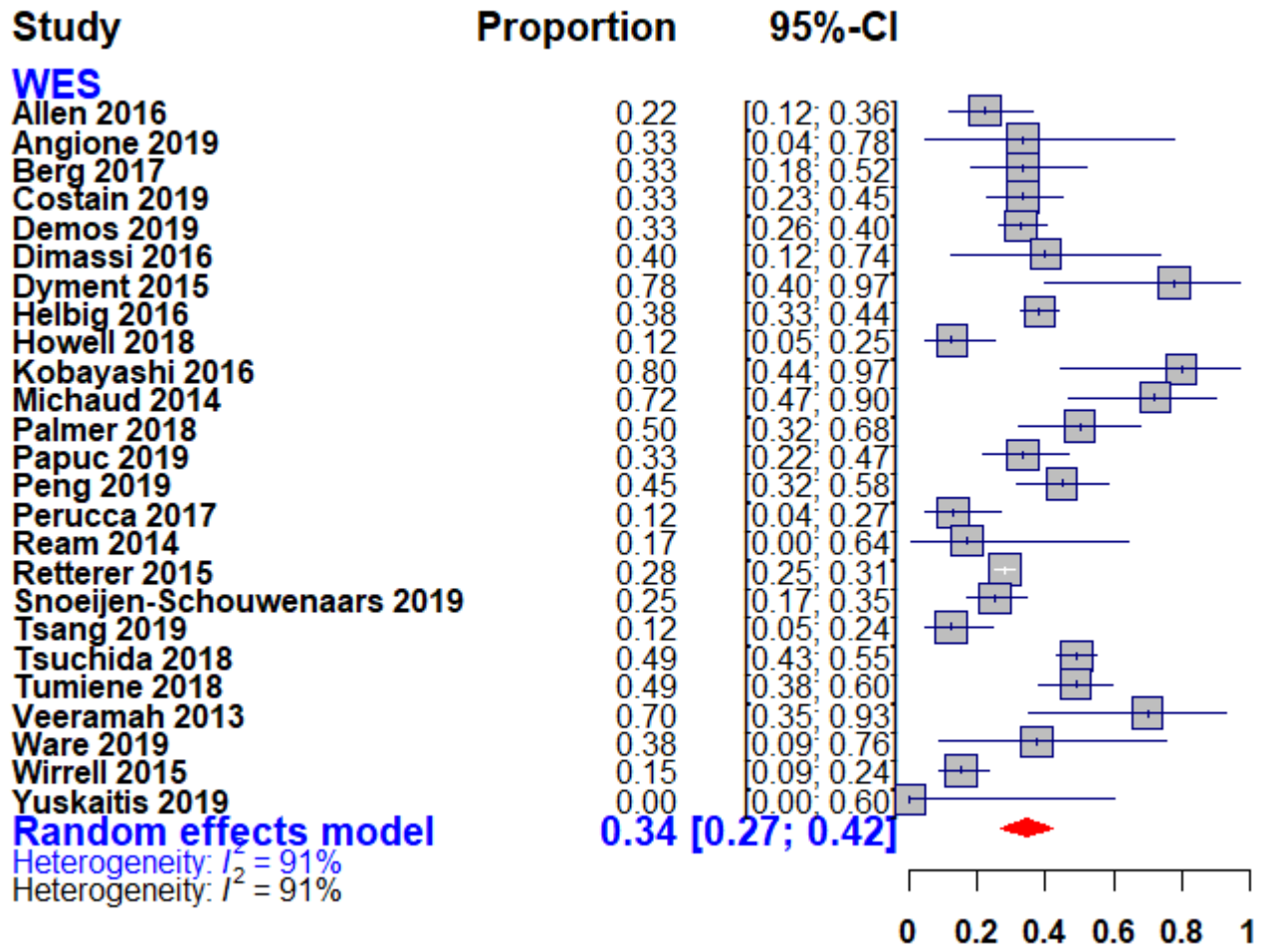


Figure 11: Genetic test 5. Whole exome sequencing (WES): subgroup analysis for children <3 years old at seizure onset

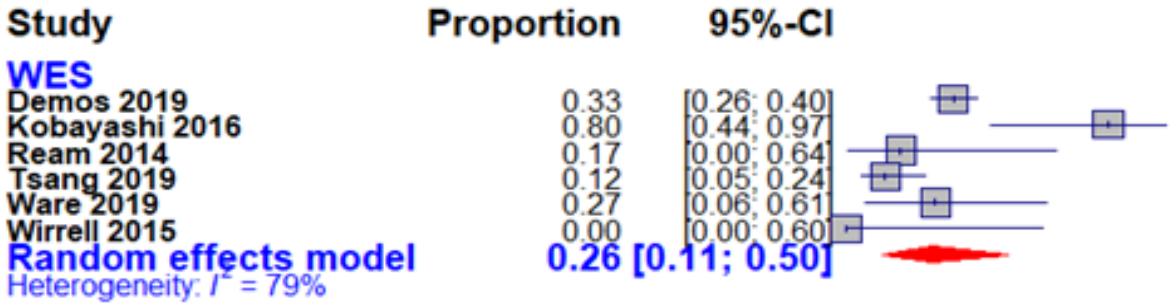


Figure 12: Genetic test 5. Whole exome sequencing (WES): subgroup analysis for people with learning difficulties/ disabilities, including neurodevelopmental disorders

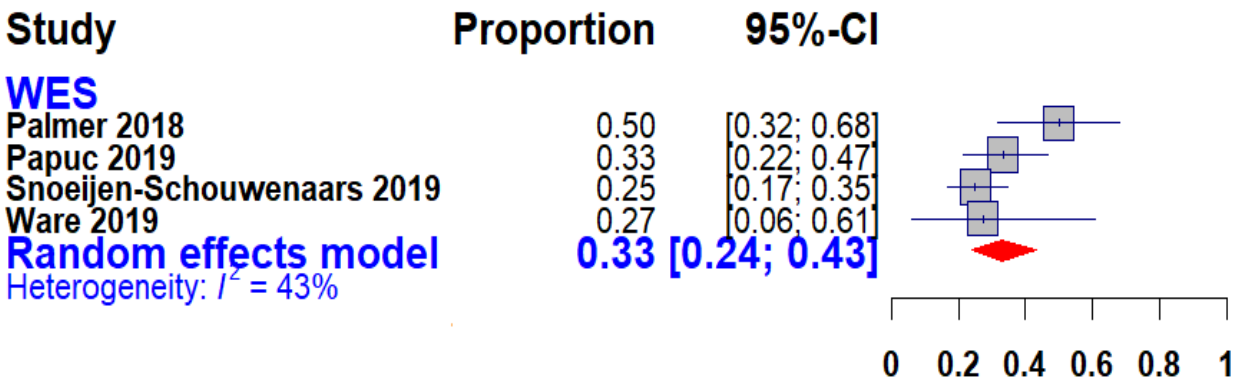


Figure 13: Genetic test 6. Whole genome sequencing (WGS): overall estimate

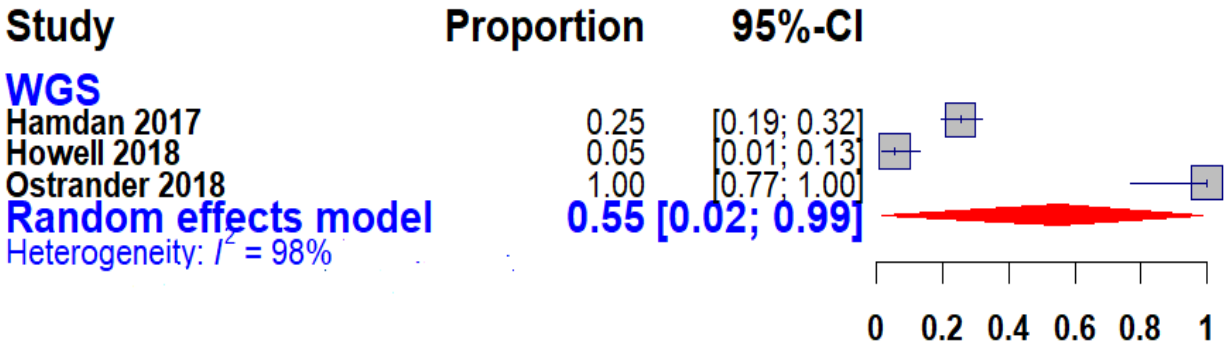
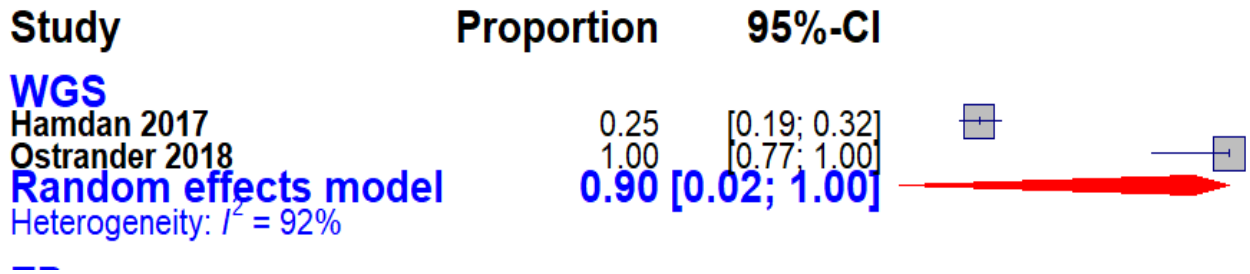


Figure 14: Genetic test 6. Whole genome sequencing (WGS): subgroup analysis for people with learning difficulties/ disabilities, including neurodevelopmental disorders



Appendix F – Adapted GRADE tables

Adapted GRADE tables for review question: What is the effectiveness of genetic testing in determining the aetiology of epilepsy?

Table 11: Clinical evidence profile for genetic test 1. Chromosomal microarray analysis (CMA): overall pooled estimate

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number with a pathogenic or likely pathogenic variant	Number assessed	Proportion (95% CI)	Quality	Importance
21[1]	Observational studies	Very serious[2]	Very serious[3]	No serious indirectness	No serious imprecision	411	4219	0.10 (0.07 to 0.12)	⊕OOO VERY LOW	CRITICAL

1 Allen 2015, Angione 2019, Bartnik 2012, Berg 2017, Borlot 2017, Boutry-Kryza 2015, Coppola 2019, Ezugha 2010, Galizia 2012, Helbig 2014, Howell 2018, Hrabik 2015, Mefford 2010, Mefford 2011, Michaud 2014, Olson 2014, Papuc 2019, Peycheva 2018, Ream 2014, Tsang 2019, Wirrell 2015
2 Very serious risk of bias in the evidence contributing to the outcomes as per JBI checklist for prevalence studies
3 Very serious heterogeneity (I^2=82%)

Table 12: Clinical evidence profile for genetic test 1. CMA: subgroup analysis for children <3 years old at seizure onset

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number with a pathogenic or likely pathogenic variant	Number assessed	Proportion (95% CI)	Quality	Importance
3[1]	Observational studies	Very serious[2]	Serious[3]	No serious indirectness	Very serious[4]	5	113	0.04 (0.01 to 0.17)	⊕OOO VERY LOW	CRITICAL

1 Allen 2015, Ream 2014, Tsang 2019
2 Very serious risk of bias in the evidence contributing to the outcomes as per JBI checklist for prevalence studies
3 Serious heterogeneity (I^2=56%)
4 Number of events <150

Table 13: Clinical evidence profile for genetic test 1. CMA: subgroup analysis for people with learning difficulties/ disabilities, including neurodevelopmental disorders

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number with a pathogenic or likely pathogenic variant	Number assessed	Proportion (95% CI)	Quality	Importance
6[1]	Observational studies	Serious[2]	Serious[3]	Serious[4]	Serious[5]	186	1457	0.11 (0.07 to 0.18)	⊕OOO VERY LOW	CRITICAL

1 Borlot 2017, Coppola 2019, Papuc 2019, Peycheva 2018, Ream 2014, Tsang 2019
2 Serious risk of bias in the evidence contributing to the outcomes as per JBI checklist for prevalence studies
3 Serious heterogeneity (I^2=63%)
4 Population in indirect in 2 of the studies (between 1 and 4% of the population for 2 studies did not have learning difficulties)
5 Number of events >150 but <300

Table 14: Clinical evidence profile for genetic test 2. Karyotyping: overall pooled estimate; all children <3 years old at seizure onset

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number with a pathogenic or likely pathogenic variant	Number assessed	Proportion (95% CI)	Quality	Importance
2[1]	Observational studies	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[3]	13	44	0.30 (0.18 to 0.44)	⊕OOO VERY LOW	CRITICAL

1 Ream 2014, Wirrell 2015
2 Serious risk of bias in the evidence contributing to the outcomes as per JBI checklist for prevalence studies
3 Number of events <150

Table 15: Clinical evidence profile for genetic test 3. Single-gene testing: overall estimate

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number with a pathogenic or likely pathogenic variant	Number assessed	Proportion (95% CI)	Quality	Importance
4[1]	Observational studies	Serious[2]	Serious[3]	No serious indirectness	Very serious[4]	18	102	0.13 (0.04 to 0.38)	⊕OOO VERY LOW	CRITICAL

1 Angione 2019, Howell 2018, Ream 2014, Wirrell 2015
2 Serious risk of bias in the evidence contributing to the outcomes as per JBI checklist for prevalence studies
3 Serious heterogeneity (I^2= 78%)
4 Number of events <150

Table 16: Clinical evidence profile for genetic test 3. Single-gene testing: subgroup analysis for children <3 years old at seizure onset

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number with a pathogenic or likely pathogenic variant	Number assessed	Proportion (95% CI)	Quality	Importance
1[1]	Observational studies	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[3]	2	13	0.15 (0.02 to 0.45)	⊕OOO VERY LOW	CRITICAL

1 Ream 2014
2 Serious risk of bias in the evidence contributing to the outcomes as per JBI checklist for prevalence studies
3 Number of events <150

Table 17: Clinical evidence profile for genetic test 4. Gene-panel testing: overall pooled estimate

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number with a pathogenic or likely pathogenic variant	Number assessed	Proportion (95% CI)	Quality	Importance
26[1]	Observational studies	Very serious[2]	Very serious[3]	No serious indirectness	No serious imprecision	2044	11400	0.18 (0.11 to 0.28)	⊕OOO VERY LOW	CRITICAL

1 Angione 2019, Berg 2017, Borlot 2019, Butler 2017, Della Mina 2015, Hildebrand 2016, Howell 2018, Jang 2019, Ko 2018, Kodera 2013, Kothur 2018, Lemke 2012, Lindy 2018, Mercimek-Mahmutoglu 2015, Moller 2016, Oates 2018, Parrini 2017, Peng 2019, Ream 2014, Rim 2018, Segal 2016, Symonds 2019, Trump 2016, Wang 2014, Ware 2019, Wirrell 2015
2 Serious risk of bias in the evidence contributing to the outcomes as per JBI checklist for prevalence studies
3 Very serious heterogeneity (I^2= 98%)

Table 18: Clinical evidence profile for genetic test 4. Gene-panel testing: subgroup analysis for children <3 years old at seizure onset

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number with a pathogenic or likely pathogenic variant	Number assessed	Proportion (95% CI)	Quality	Importance
3[1]	Observational studies	Very serious[2]	No serious inconsistency	No serious indirectness	Very serious[3]	37	98	0.38 (0.29 to 0.48)	⊕OOO VERY LOW	CRITICAL

1 Ream 2014, Rim 2018, Ware 2019
2 Very serious risk of bias in the evidence contributing to the outcomes as per JBI checklist for prevalence studies
3 Number of events <150

Table 19: Clinical evidence profile for genetic test 4. Gene-panel testing: subgroup analysis for people with learning difficulties/ disabilities, including neurodevelopmental disorders

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number with a pathogenic or likely pathogenic variant	Number assessed	Proportion (95% CI)	Quality	Importance
6[1]	Observational studies	Very serious[2]	Very serious[3]	No serious indirectness	No serious imprecision	1459	9064	0.11 (0.02 to 0.38)	⊕OOO VERY LOW	CRITICAL

1 Borlot 2019, Ko 2018, Kodera 2013, Lindy 2018, Mercimek-Mahmutoglu 2015, Ware 2019
2 Very serious risk of bias in the evidence contributing to the outcomes as per JBI checklist for prevalence studies
3 Very serious heterogeneity (I^2= 98%)

Table 20: Clinical evidence profile for genetic test 5. Whole exome sequencing (WES): overall estimate

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number with a pathogenic or likely pathogenic variant	Number assessed	Proportion (95% CI)	Quality	Importance
23[1]	Observational studies	Very serious[2]	Very serious[3]	No serious indirectness	No serious imprecision	763	2353	0.34 (0.27 to 0.42)	⊕OOO VERY LOW	CRITICAL

1 Allen 2016, Angione 2019, Berg 2017, Costain 2019, Demos 2019, Dimassi 2016, Dyment 2015, Helbig 2016, Howell 2018, Kobayashi 2016, Michaud 2014, Palmer 2018, Papuc 2019, Peng 2019, Perucca 2017, Ream 2014, Retterer 2015, Snoeijen-Schouwenaars 2019, Tsang 2019, Tsuchida 2018, Tumiene 2018, Veeramah 2013, Ware 2019, Wirrell 2015, Yuskaitis 2018
2 Very serious risk of bias in the evidence contributing to the outcomes as per JBI checklist for prevalence studies
3 Very serious heterogeneity (I^2= 91%)

Table 21: Clinical evidence profile for genetic test 5. Whole exome sequencing (WES): subgroup analysis for point along the pathway (early WES and limited metabolic testing versus no WES testing)

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number with a pathogenic or likely pathogenic variant	Number assessed	Proportion	Quality	Importance
1[1]	Observational studies	Low[2]	No serious inconsistency	No serious indirectness	Very serious[3]	Early WES and limited metabolic testing: 46 No WES testing:39	86	Early WES and limited metabolic testing: 0.53 (0.42 to 0.64) No WES testing: 0.45 (0.35 to 0.56)	⊕OOO VERY LOW	CRITICAL

1 Howell 2018
2 Serious risk of bias in the evidence contributing to the outcomes as per JBI checklist for prevalence studies
3 Number of events <150

Table 22: Clinical evidence profile for genetic test 5. Whole exome sequencing (WES): subgroup analysis for children <3 years old at seizure onset

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number with a pathogenic or likely pathogenic variant	Number assessed	Proportion (95% CI)	Quality	Importance
6[1]	Observational studies	Very serious[2]	Very serious[3]	No serious indirectness	Very serious[4]	78	261	0.26 (0.11 to 0.50)	⊕OOO VERY LOW	CRITICAL

1 Demos 2019, Kobayashi 2016, Ream 2014, Tsang 2019, Ware 2019, Wirrell 2015
2 Very serious risk of bias in the evidence contributing to the outcomes as per JBI checklist for prevalence studies
3 Very serious heterogeneity (I^2= 79%)
4 Number of events <150

Table 23: Clinical evidence profile for genetic test 5. Whole exome sequencing (WES): subgroup analysis for people with learning difficulties/ disabilities, including neurodevelopmental disorders

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number with a pathogenic or likely pathogenic variant	Number assessed	Proportion (95% CI)	Quality	Importance
4[1]	Observational studies	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[3]	64	203	0.33 (0.24 to 0.43)	⊕OOO VERY LOW	CRITICAL

1 Palmer 2018, Papuc 2019, Snoeijen-Schouwenaars 2019, Ware 2019
2 Serious risk of bias in the evidence contributing to the outcomes as per JBI checklist for prevalence studies
3 Number of events <150

Table 24: Clinical evidence profile for genetic test 6. Whole genome sequencing (WGS): overall estimate

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number with a pathogenic or likely pathogenic variant	Number assessed	Proportion (95% CI)	Quality	Importance
3[1]	Observational studies	Serious[2]	Very serious[3]	No serious indirectness	Very serious[4]	68	285	0.55 (0.02 to 0.99)	⊕OOO VERY LOW	CRITICAL

1 Hamdan 2017, Howell 2018, Ostrander 2018
2 Serious risk of bias in the evidence contributing to the outcomes as per JBI checklist for prevalence studies
3 Very serious heterogeneity (I^2= 98%)
4 Number of events <150

Table 25: Clinical evidence profile for genetic test 6. Whole genome sequencing (WGS): subgroup analysis for people with learning difficulties/ disabilities, including neurodevelopmental disorders

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Number with a pathogenic or likely pathogenic variant	Number assessed	Proportion (95% CI)	Quality	Importance
2[1]	Observational studies	Serious[2]	Very serious[3]	No serious indirectness	Very serious[4]	64	211	0.90 (0.02 to 1)	⊕OOO VERY LOW	CRITICAL

1 Hamdan 2017, Ostrander 2018
2 Serious risk of bias in the evidence contributing to the outcomes as per JBI checklist for prevalence studies
3 Very serious heterogeneity (I^2= 92%)
4 Number of events <150

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the effectiveness of genetic testing in determining the aetiology of epilepsy?

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information

Appendix H – Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of genetic testing in determining the aetiology of epilepsy?

Table 26: Economic evidence tables for genetic screening for HLA-A*31:01 prior to initiation of carbamazepine in people epilepsy

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
Author & year: Plumpton 2015 **Country:** United Kingdom **Type of economic analysis:** Cost Utility Analysis **Source of funding:** Author was supported by the NIHR Cochrane Programme Grant Scheme 10/4001/18: Clinical and cost effectiveness of interventions for epilepsy in the NHS; and the NIHR Invention for Innovation (i4i)	**Interventions in detail:** HLA-A*31:01 genotyping Genetic testing for HLA-A*31:01 allele in patients for prior identification of patients susceptible to cutaneous ADRs to carbamazepine, with following prescribing conditional on test results of carbamazepine (test negatives) or lamotrigine (test positives). Standard of care Prescribing carbamazepine without genetic testing for HLA-A*31:01 allele	**Population characteristics:** All patients enter the model with newly diagnosed focal epilepsy, who had failed treatment with previous monotherapy, or who had entered a period of remission from seizures but had relapsed after withdrawal of treatment. **Modelling approach:** Decision tree and Markov model **Source of base-line and effectiveness data:** Estimates of base-line clinical data were obtained from various sources from published literature, including a previous NICE guideline on management of epilepsy (CG137), the Standard and New Antiepileptic Drugs (SANAD –Marson 2007 and 2011), a published network meta-analysis (Tudur 2007), and purposive reviews of the literature. **Source of cost data:**	**QALYs** • 15.7744 QALYs for the HLA-A*31:01 genotyping group • 15.7510 QALYs for standard of care group **Incremental costs with HLA-A*31:01 genotyping:** • £300.39 **Incremental QALYs with HLA-A*31:01 genotyping:** • 0.023 QALYs **ICER:** • £12,808 **Deterministic sensitivity analysis:** The results were sensitive to: • estimated remission rates for alternative ASMs (this is, lamotrigine, valproate) • utility and costs of lamotrigine As noted by the Authors, the prescription of lamotrigine as the second-line ASM only in the test scenario is likely to be an important driver of the model (as when remission	**Perspective:** • UK NHS **Currency:** • UK pound sterling (£) **Cost year:** • 2010/11 **Time horizon:** • Lifetime **Discounting:** • 3.5% per year **Applicability:** Despite being a UK study considering the NHS perspective, the study was considered to be only partially applicable. This is because the study doesn't directly address the review question posed in the guideline, as the economic analysis focused on pharmacogenetics rather

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
scheme: A biomarker panel to predict, diagnose, and prevent HLA-mediated serious adverse drug reactions (II-LB-0313-20008).		Cost data were obtained from different sources: • costs associated with carbamazepine, lamotrigine, and valproate treatment were taken from the SANAD trial (Marson 2007 and 2011) • costs associated with managing cutaneous adverse drug reactions were estimated by conducting a systematic review of the literature • costs associated with genotyping were provided by the NHS Blood and Transplant service, and inflated to 2010/2011 values Costs were all inflated to 2010/2011, using NHS or Personal Social Services Research Unit values **Source of QoL data:** Utilities estimates (based on EQ-5D data) for baseline QoL associated with carbamazepine, lamotrigine, or valproate treatment were derived directly from the SANAD trial (Marson 2007 and 2011). QoL values for other health states were based on data from multiple sources[A]: • disutilities in relation to maculopapular exanthema (Poole 2010) • disutilities in relation to hypersensitivity syndrome (Hofhuis 2008; Haber 2005)	rates, utility and costs values for lamotrigine were set equivalent to those of valproate, HLA-A*31:01 genotyping was dominated, being both more costly and less effective than not testing **Probabilistic sensitivity analysis:** HLA-A*31:01 genotyping was found to have • 80% probability of being cost-effective at a conventional threshold of £20,000 per QALY • 88% probability of being cost-effective at a conventional threshold of £30,000 per QALY	than on the diagnostic yield of genetic testing. **Limitations:** The study meets most quality criteria. The only potential limitation was associated the estimates of the effect of interventions under evaluations. These were not derived from a systematic review, but were considered similar in magnitude to the best available estimates. **Other comments:** [A] It was assumed that the immediate disutility associated with: • maculopapular exanthema was equivalent to atopic dermatitis • hypersensitivity syndrome was equivalent to sepsis • Stevens-Johnson syndrome was equivalent to severe burns And that the long-term disutilities for all three types of ADR were taken from patient-level data for

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
		• disutilities in relation to Stevens-Johnson syndrome (Öster 2009; Haber 2005)		survivors of toxic epidermal necrolysis

ADRs: adverse drug reactions; ASM: anti-epileptic medication; CUA: cost utility analysis; EQ-5D: EuroQol- 5 Dimension; ICER: incremental cost effectiveness ratio; NICE: National Institute for Health and Care Excellence; NIHR: National Institutes of Health Research; QALY: quality adjusted life year; QoL: quality of life.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the effectiveness of genetic testing in determining the aetiology of epilepsy?

Study and country	Limitations	Applicability	Other comments	Incremental costs	Incremental effects	ICER	Uncertainty
Author & year: Plumpton 2015 **Country:** United Kingdom **Interventions:** HLA-A*31:01 genotyping *versus* Standard of care	Minor limitations[1]	Partially applicable[2]	**Type of economic analysis:** CUA **Time horizon:** Lifetime **Primary measure of outcome:** QALY	£300.39	0.023 QALYs	£12,808/QALY	**Deterministic sensitivity analyses:** The results[3] were sensitive to: estimated remission rates for alternative ASMs (i.e. lamotrigine, valproate) utility and costs of lamotrigine **PSA:** HLA-A*31:01 genotyping was found to have 80% probability of being cost-effective at a conventional threshold of £20,000 per QALY 88% probability of being cost-effective at a conventional threshold of £30,000 per QALY

ASM: anti-epileptic medication; CUA: cost utility analysis; ICER: incremental cost effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality adjusted life year.
1 The study meets most quality criteria. The only potential limitation was associated the estimates of the effect of interventions under evaluations. These were not derived from a systematic review, but were considered similar in magnitude to the best available estimates
2 Despite being a UK study considering the NHS perspective, the study was considered to be only partially applicable. This is because it doesn't directly address the review question posed in the guideline (but it is partially addressed by the pharmacogenetics intervention evaluated)
*3 As noted by the Authors, the prescription of lamotrigine as the second-line ASM only in the test scenario is likely to be an important driver of the model (as when remission rates, utility and costs values for lamotrigine were set equivalent to those of valproate, HLA-A*31:01 genotyping was dominated, being both more costly and less effective than not testing*

Appendix J – Economic analysis

Economic evidence analysis for review question: What is the effectiveness of genetic testing in determining the aetiology of epilepsy?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded clinical and economic studies for review question: What is the effectiveness of genetic testing in determining the aetiology of epilepsy?

Clinical studies

Table 27: Excluded studies and reasons for their exclusion

Excluded studies - Genetic testing in epilepsy	
Study	**Reason for Exclusion**
Albuz, B., Ozdemir, O., Silan, F., The high frequency of chromosomal copy number variations and candidate genes in epilepsy patients, Clinical Neurology and Neurosurgery, 202, 106487, 2021	Study design does not meet the inclusion criteria: case series
Bagnall, R. D., Crompton, D. E., Cutmore, C., Regan, B. M., Berkovic, S. F., Scheffer, I. E., Semsarian, C., Genetic analysis of PHOX2B in sudden unexpected death in epilepsy cases, Neurology, 83, 1018-1021, 2014	No relevant objective: to assess whether a specific gene contributes to SUDEP
Bardakjian, T. M., Helbig, I., Quinn, C., Elman, L. B., McCluskey, L. F., Scherer, S. S., Gonzalez-Alegre, P., Genetic test utilization and diagnostic yield in adult patients with neurological disorders, Neurogenetics, 19, 105-110, 2018	Study was conducted in an overall sample of people with neurological disorders; results were not stratified for epilepsies
Berkovic, S. F., Goldstein, D. B., Heinzen, E. L., Laughlin, B. L., Lowenstein, D. H., Lubbers, L., Stewart, R., Whittemore, V., Angione, K., Bazil, C. W., Bier, L., Bluvstein, J., Brimble, E., Campbell, C., Cavalleri, G., Chambers, C., Choi, H., Cilio, M. R., Ciliberto, M., Cornes, S., Delanty, N., Demarest, S., Devinsky, O., Dlugos, D., Dubbs, H., Dugan, P., Ernst, M. E., Gibbons, M., Goodkin, H. P., Helbig, I., Jansen, L., Johnson, K., Joshi, C., Lippa, N. C., Marsh, E., Martinez, A., Millichap, J., Mulhern, M. S., Numis, A., Park, K., Pippucci, T., Poduri, A., Porter, B., Regan, B., Sands, T. T., Scheffer, I. E., Schreiber, J. M., Sheidley, B., Singhal, N., Smith, L., Sullivan, J., Taylor, A., Tolete, P., Afgani, T. M., Aggarwal, V., Burgess, R., Dixon-Salazar, T., Hemati, P., Milder, J., Petrovski, S., Revah-Politi, A., Stong, N., The Epilepsy Genetics Initiative: Systematic reanalysis of diagnostic exomes increases yield, Epilepsia, 60, 797-806, 2019	Study reports on new diagnoses made after re-analyzing a group of patients, not on the overall yield of a given genetic test
Berkovic, S. F., Grinton, B., Dixon-Salazar, T., Laughlin, B. L., Lubbers, L., Milder, J., Goldstein, D. B., Heinzen, E. L., Bier, L., Ernst, M. E., Lippa, N. C., Mulhern, M. S., Afgani, T. M., Stong, N., Lowenstein, D. H., Cornes, S., Johnson, K., Stewart, R., Whittemore, V., Angione, K., Demarest, S., Gibbons, M., Joshi, C., Park, K., Bazil, C. W., Choi, H., Bluvstein, J., Devinsky, O., Dugan, P., Tolete, P., Brimble, E., Campbell, C., Chambers, C., Goodkin, H., Jansen, L., Cilio, M. R., Numis, A., Singhal, N., Sullivan, J., Ciliberto, M., Delanty, N., Dlugos,	Study reports on 3 novel disease-causing variants of protein coding and not on the overall yield of a given genetic test

Excluded studies - Genetic testing in epilepsy	
D., Dubbs, H., Helbig, I., Martinez, A., Gallentine, W., Makati, M. A., Marsh, E., Moskovich, Y., Millichap, J., Poduri, A., Sheidley, B., Smith, L., Taylor, A., Porter, B., Sands, T. T., Riviello, J. J., Scheffer, I. E., Aggarwal, V., Allen, A. S., Hamid, R., Helbig, K. L., Tang, S., Meisler, M. H., Petrovski, S., Pfotenhauer, J., De novo variants in the alternative exon 5 of SCN8A cause epileptic encephalopathy, Genetics in Medicine, 20, 275-281, 2018	
Bodian, D. L., Kothiyal, P., Hauser, N. S., Pitfalls of clinical exome and gene panel testing: alternative transcripts, Genetics in Medicine, 21, 1240-1245, 2019	This study assessed alternative transcripts to study if this will provide a diagnosis for more patients, but did not assess the diagnostic yield of a diagnostic test
Brunklaus, A., Dorris, L., Ellis, R., Reavey, E., Lee, E., Forbes, G., Appleton, R., Cross, J. H., Ferrie, C., Hughes, I., Jollands, A., King, M. D., Livingston, J., Lynch, B., Philip, S., Scheffer, I. E., Williams, R., Zuberi, S. M., The clinical utility of an SCN1A genetic diagnosis in infantile-onset epilepsy, Developmental Medicine & Child Neurology, 55, 154-61, 2013	Diagnostic yield of genetic abnormalities was not reported
Byeon, J. H., Shin, E., Kim, G. H., Lee, K., Hong, Y. S., Lee, J. W., Eun, B. L., Application of array-based comparative genomic hybridization to pediatric neurologic diseases, Yonsei Medical Journal, 55, 30-36, 2014	Diagnostic yield of genetic abnormalities was not reported
Cavalleri, G. L., Petrovski, S., Fitzsimons, M., Delanty, N., EHealth as a Facilitator of Precision Medicine in Epilepsy, Biomedicine Hub, 2, 137-145, 2017	Commentary/ narrative review
Chaiyasap, P., Kulawonganunchai, S., Srichomthong, C., Tongsima, S., Suphapeetiporn, K., Shotelersuk, V., Whole genome and exome sequencing of monozygotic twins with trisomy 21, discordant for a congenital heart defect and epilepsy, PLoS ONE [Electronic Resource], 9, e100191, 2014	Diagnostic yield of genetic abnormalities was not reported
Chan, C. K., Low, J. S. Y., Lim, K. S., Low, S. K., Tan, C. T., Ng, C. C., Whole exome sequencing identifies a novel SCN1A mutation in genetic (idiopathic) generalized epilepsy and juvenile myoclonic epilepsy subtypes, Neurological Sciences, 41, 591-598, 2020	Study design does not meet the inclusion criteria: case series
Che, N., Zu, G., Zhou, T., Wang, X., Sun, Y., Tan, Z., Liu, Y., Wang, D., Luo, X., Zhao, Z., Zhang, Y., Wei, M., Yin, J., Aberrant Expression of miR-323a-5p in Patients with Refractory Epilepsy Caused by Focal Cortical Dysplasia, Genetic Testing and Molecular Biomarkers, 21, 3-9, 2017	Diagnostic yield of genetic abnormalities was not reported
Chen, W. J., Xiong, Z. Q., Wei, W., Ni, W., Tan, G. H., Guo, S. L., He, J., Chen, Y. F., Zhang, Q. J., Li, H. F., Lin, Y., Murong, S. X., Xu, J., Wang, N., Wu, Z. Y., Exome sequencing identifies truncating mutations in PRRT2 that cause paroxysmal kinesigenic dyskinesia, Nature Genetics, 43, 1252-1255, 2011	Diagnostic yield of genetic abnormalities was not reported

Excluded studies - Genetic testing in epilepsy	
Chen, X., Jin, J., Wang, Q., Xue, H., Zhang, N., Du, Y., Zhang, T., Zhang, B., Wu, J., Liu, Z., A de novo pathogenic CSNK1E mutation identified by exome sequencing in family trios with epileptic encephalopathy, Human Mutation, 40, 281-287, 2019	Diagnostic yield of genetic abnormalities was not reported
Chen, Y., Wu, L., Fang, Y., He, Z., Peng, B., Shen, Y., Xu, Q., A novel mutation of the nicotinic acetylcholine receptor gene CHRNA4 in sporadic nocturnal frontal lobe epilepsy, Epilepsy Research, 83, 152-156, 2009	Diagnostic yield of genetic abnormalities was not reported
Chen, Z. R., Liu, D. T., Meng, H., Liu, L., Bian, W. J., Liu, X. R., Zhu, W. W., He, Y., Wang, J., Tang, B., Su, T., Yi, Y. H., Homozygous missense TPP1 mutation associated with mild late infantile neuronal ceroid lipofuscinosis and the genotype-phenotype correlation, Seizure, 69, 180-185, 2019	Diagnostic yield of genetic abnormalities was not reported
Cossee, M., Faivre, L., Philippe, C., Hichri, H., De Saint-Martin, A., Laugel, V., Bahi-Buisson, N., Lemaitre, J. F., Leheup, B., Delobel, B., Demeer, B., Poirier, K., Biancalana, V., Pinoit, J. M., Julia, S., Chelly, J., Devys, D., Mandel, J. L., ARX polyalanine expansions are highly implicated in familial cases of mental retardation with infantile epilepsy and/or hand dystonia, American Journal of Medical Genetics, Part A, 155, 98-105, 2011	Diagnostic yield of genetic abnormalities was not reported
Dang, H., Zou, L., Tian, J., Liu, J., Feng, X., Lin, M., Xu, B., Etiologic classification of infantile spasms using positron emission/magnetic resonance imaging and the efficacy of adrenocorticotropic hormone therapy, European Journal of Nuclear Medicine and Molecular Imaging, 47, 1585-1595, 2020	Diagnostic yield of genetic abnormalities was not reported
De Kovel, C. G. F., Trucks, H., Helbig, I., Mefford, H. C., Baker, C., Leu, C., Kluck, C., Muhle, H., Von Spiczak, S., Ostertag, P., Obermeier, T., Kleefuss-Lie, A. A., Hallmann, K., Steffens, M., Gaus, V., Klein, K. M., Hamer, H. M., Rosenow, F., Brilstra, E. H., Kasteleijn-Nolst Trenite, D., Swinkels, M. E. M., Weber, Y. G., Unterberger, I., Zimprich, F., Urak, L., Feucht, M., Fuchs, K., Moller, R. S., Hjalgrim, H., De Jonghe, P., Suls, A., Ruckert, I. M., Wichmann, H. E., Franke, A., Schreiber, S., Nurnberg, P., Elger, C. E., Lerche, H., Stephani, U., Koeleman, B. P. C., Lindhout, D., Eichler, E. E., Sander, T., Recurrent microdeletions at 15q11.2 and 16p13.11 predispose to idiopathic generalized epilepsies, Brain, 133, 23-32, 2010	Diagnostic yield of genetic abnormalities was not reported
Dibbens, L. M., Mullen, S., Helbig, I., Mefford, H. C., Bayly, M. A., Bellows, S., Leu, C., Trucks, H., Obermeier, T., Wittig, M., Franke, A., Caglayan, H., Yapici, Z., Sander, T., Eichler, E. E., Scheffer, I. E., Mulley, J. C., Berkovic, S. F., Familial and sporadic 15q13.3 microdeletions in idiopathic generalized epilepsy: precedent for disorders with complex inheritance, Human Molecular Genetics, 18, 3626-3631, 2009	Diagnostic yield of genetic abnormalities was not reported

Excluded studies - Genetic testing in epilepsy	
Dimassi, S., Labalme, A., Lesca, G., Rudolf, G., Bruneau, N., Hirsch, E., Arzimanoglou, A., Motte, J., De Saint Martin, A., Boutry-Kryza, N., Cloarec, R., Benitto, A., Ameil, A., Edery, P., Ryvlin, P., De Bellescize, J., Szepetowski, P., Sanlaville, D., A subset of genomic alterations detected in rolandic epilepsies contains candidate or known epilepsy genes including GRIN2A and PRRT2, Epilepsia, 55, 370-378, 2014	Diagnostic yield of genetic abnormalities was not reported
Dimassi, S., Simonet, T., Labalme, A., Boutry-Kryza, N., Campan-Fournier, A., Lamy, R., Bardel, C., Elsensohn, M. H., Roucher-Boulez, F., Chatron, N., Putoux, A., de Bellescize, J., Ville, D., Schaeffer, L., Roy, P., Mougou-Zerelli, S., Saad, A., Calender, A., Sanlaville, D., Lesca, G., Comparison of two next-generation sequencing kits for diagnosis of epileptic disorders with a user-friendly tool for displaying gene coverage, DeCovA, Applied and Translational Genomics, 7, 19-25, 2015	Diagnostic yield of genetic abnormalities was not reported
Dunn, P. J., Maher, B. H., Albury, C. L., Stuart, S., Sutherland, H. G., Maksemous, N., Benton, M. C., Smith, R. A., Haupt, L. M., Griffiths, L. R., Tiered analysis of whole-exome sequencing for epilepsy diagnosis, Molecular Genetics and Genomics, 295, 751-763, 2020	Study design does not meet the inclusion criteria: case series
Elliott, A., Bergner, A., Improving the molecular diagnosis and treatment of epilepsy with complex genetic testing, MLO: medical laboratory observer, 48, 36, 39, 2016	Narrative review
Elmali, A. D., Auvin, S., Bast, T., Rubboli, G., Koutroumanidis, M., How to diagnose and classify idiopathic (genetic) generalized epilepsies, Epileptic Disorders, 22, 399-420, 2020	Narrative review
Evers, C., Staufner, C., Granzow, M., Paramasivam, N., Hinderhofer, K., Kaufmann, L., Fischer, C., Thiel, C., Opladen, T., Kotzaeridou, U., Wiemann, S., Schlesner, M., Eils, R., Kolker, S., Bartram, C. R., Hoffmann, G. F., Moog, U., Impact of clinical exomes in neurodevelopmental and neurometabolic disorders, Molecular Genetics and Metabolism, 121, 297-307, 2017	Diagnostic yield of genetic abnormalities was not reported
Feng, Y. C. A., Howrigan, D. P., Abbott, L. E., Tashman, K., Cerrato, F., Singh, T., Heyne, H., Byrnes, A., Churchhouse, C., Watts, N., Solomonson, M., Lal, D., Heinzen, E. L., Dhindsa, R. S., Stanley, K. E., Cavalleri, G. L., Hakonarson, H., Helbig, I., Krause, R., May, P., Weckhuysen, S., Petrovski, S., Kamalakaran, S., Sisodiya, S. M., Cossette, P., Cotsapas, C., De Jonghe, P., Dixon-Salazar, T., Guerrini, R., Kwan, P., Marson, A. G., Stewart, R., Depondt, C., Dlugos, D. J., Scheffer, I. E., Striano, P., Freyer, C., McKenna, K., Regan, B. M., Bellows, S. T., Leu, C., Bennett, C. A., Johns, E. M. C., Macdonald, A., Shilling, H., Burgess, R., Weckhuysen, D., Bahlo, M., O'Brien, T. J.,	Study design does not meet the inclusion criteria: case-control study

Excluded studies - Genetic testing in epilepsy	
Todaro, M., Stamberger, H., Andrade, D. M., Sadoway, T. R., Mo, K., Krestel, H., Gallati, S., Papacostas, S. S., Kousiappa, I., Tanteles, G. A., Sterbova, K., Vlckova, M., Sedlackova, L., Lassuthova, P., Klein, K. M., Rosenow, F., Reif, P. S., Knake, S., Kunz, W. S., Zsurka, G., Elger, C. E., Bauer, J., Rademacher, M., Pendziwiat, M., Muhle, H., Rademacher, A., van Baalen, A., von Spiczak, S., Stephani, U., Afawi, Z., Korczyn, A. D., Kanaan, M., Canavati, C., Kurlemann, G., Muller-Schluter, K., Kluger, G., Hausler, M., Blatt, I., Lemke, J. R., Krey, I., Weber, Y. G., Wolking, S., Becker, F., Hengsbach, C., Rau, S., Maisch, A. F., Steinhoff, B. J., Schulze-Bonhage, A., Schubert-Bast, S., Schreiber, H., Borggrafe, I., Schankin, C. J., Mayer, T., Korinthenberg, R., Brockmann, K., Dennig, D., Madeleyn, R., Kalviainen, R., Auvinen, P., Saarela, A., Linnankivi, T., Lehesjoki, A. E., Rees, M. I., Chung, S. K., Pickrell, W. O., Powell, R., Schneider, N., Balestrini, S., Zagaglia, S., Braatz, V., Johnson, M. R., Auce, P., Sills, G. J., Baum, L. W., Sham, P. C., Cherny, S. S., Lui, C. H. T., Barisic, N., Delanty, N., Doherty, C. P., Shukralla, A., McCormack, M., El-Naggar, H., Canafoglia, L., Franceschetti, S., Castellotti, B., Granata, T., Zara, F., Iacomino, M., Madia, F., Vari, M. S., Mancardi, M. M., Salpietro, V., Bisulli, F., Tinuper, P., Licchetta, L., Pippucci, T., Stipa, C., Minardi, R., Gambardella, A., Labate, A., Annesi, G., Manna, L., Gagliardi, M., Parrini, E., Mei, D., Vetro, A., Bianchini, C., Montomoli, M., Doccini, V., Marini, C., Suzuki, T., Inoue, Y., Yamakawa, K., Tumiene, B., Sadleir, L. G., King, C., Mountier, E., Caglayan, S. H., Arslan, M., Yapici, Z., Yis, U., Topaloglu, P., Kara, B., Turkdogan, D., Gundogdu-Eken, A., Bebek, N., Ugur-Iseri, S., Baykan, B., Salman, B., Haryanyan, G., Yucesan, E., Kesim, Y., Ozkara, C., Poduri, A., Shiedley, B. R., Shain, C., Buono, R. J., Ferraro, T. N., Sperling, M. R., Lo, W., Privitera, M., French, J. A., Schachter, S., Kuzniecky, R. I., Devinsky, O., Hegde, M., Khankhanian, P., Helbig, K. L., Ellis, C. A., Spalletta, G., Piras, F., Gili, T., Ciullo, V., Reif, A., McQuillin, A., Bass, N., McIntosh, A., Blackwood, D., Johnstone, M., Palotie, A., Pato, M. T., Pato, C. N., Bromet, E. J., Carvalho, C. B., Achtyes, E. D., Azevedo, M. H., Kotov, R., Lehrer, D. S., Malaspina, D., Marder, S. R., Medeiros, H., Morley, C. P., Perkins, D. O., Sobell, J. L., Buckley, P. F., Macciardi, F., Rapaport, M. H., Knowles, J. A., Fanous, A. H., McCarroll, S. A., Gupta, N., Gabriel, S. B., Daly, M. J., Lander, E. S., Lowenstein, D. H., Goldstein, D. B., Lerche, H., Berkovic, S. F., Neale, B. M., Ultra-Rare Genetic Variation in the Epilepsies: A Whole-Exome Sequencing Study	

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of 17,606 Individuals, American Journal of Human Genetics, 105, 267-282, 2019	
Gokben, S., Onay, H., Yilmaz, S., Atik, T., Serdaroglu, G., Tekin, H., Ozkinay, F., Targeted next generation sequencing: the diagnostic value in early-onset epileptic encephalopathy, Acta Neurologica Belgica, 117, 131-138, 2017	Study design does not meet the inclusion criteria: case series
Hardies, K., Weckhuysen, S., De Jonghe, P., Suls, A., Lessons learned from gene identification studies in Mendelian epilepsy disorders, European Journal of Human Genetics, 24, 961-967, 2016	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Hartmann, C., Von Spiczak, S., Suls, A., Weckhuysen, S., Buyse, G., Vilain, C., Van Bogaert, P., De Jonghe, P., Cook, J., Muhle, H., Stephani, U., Helbig, I., Mefford, H. C., Investigating the genetic basis of fever-associated syndromic epilepsies using copy number variation analysis, Epilepsia, 56, e26-e32, 2015	Study design does not meet the inclusion criteria: case series
Haug, K., Kremerskothen, J., Hallmann, K., Sander, T., Dullinger, J., Rau, B., Beyenburg, S., Lentze, M. J., Barnekow, A., Elger, C. E., Propping, P., Heils, A., Mutation screening of the chromosome 8q24.3-human activity-regulated cytoskeleton-associated gene (ARC) in idiopathic generalized epilepsy, Molecular and Cellular Probes, 14, 255-260, 2000	Diagnostic yield of genetic abnormalities was not reported
He, N., Lin, Z. J., Wang, J., Wei, F., Meng, H., Liu, X. R., Chen, Q., Su, T., Shi, Y. W., Yi, Y. H., Liao, W. P., Evaluating the pathogenic potential of genes with de novo variants in epileptic encephalopathies, Genetics in Medicine, 21, 17-27, 2019	Diagnostic yield of genetic abnormalities was not reported
Heinzen, E. L., Depondt, C., Cavalleri, G. L., Ruzzo, E. K., Walley, N. M., Need, A. C., Ge, D., He, M., Cirulli, E. T., Zhao, Q., Cronin, K. D., Gumbs, C. E., Campbell, C. R., Hong, L. K., Maia, J. M., Shianna, K. V., McCormack, M., Radtke, R. A., O'Conner, G. D., Mikati, M. A., Gallentine, W. B., Husain, A. M., Sinha, S. R., Chinthapalli, K., Puranam, R. S., McNamara, J. O., Ottman, R., Sisodiya, S. M., Delanty, N., Goldstein, D. B., Exome sequencing followed by large-scale genotyping fails to identify single rare variants of large effect in idiopathic generalized epilepsy, American Journal of Human Genetics, 91, 293-302, 2012	Diagnostic yield of genetic abnormalities was not reported
Helbig, I., Barcia, G., Pendziwiat, M., Ganesan, S., Mueller, S. H., Helbig, K. L., Vaidiswaran, P., Xian, J., Galer, P. D., Afawi, Z., Specchio, N., Kluger, G., Kuhlenbaumer, G., Appenzeller, S., Wittig, M., Kramer, U., van Baalen, A., Nabbout, R., Whole-exome and HLA sequencing in Febrile infection-related epilepsy syndrome, Annals of Clinical and Translational Neurology, 7, 1429-1435, 2020	Diagnostic yield of genetic abnormalities was not reported
Helbig, I., Riggs, E. R., Barry, C. A., Klein, K. M., Dyment, D., Thaxton, C., Sadikovic, B., Sands, T. T., Wagnon, J. L., Liaquat, K., Cilio, M. R.,	Diagnostic yield of genetic abnormalities was not reported

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Mirzaa, G., Park, K., Axeen, E., Butler, E., Bardakjian, T. M., Striano, P., Poduri, A., Siegert, R. K., Grant, A. R., Helbig, K. L., Mefford, H. C., The ClinGen Epilepsy Gene Curation Expert Panel-Bridging the divide between clinical domain knowledge and formal gene curation criteria, Human Mutation, 39, 1476-1484, 2018	
Helbig, K. L., Lauerer, R. J., Bahr, J. C., Souza, I. A., Myers, C. T., Uysal, B., Schwarz, N., Gandini, M. A., Huang, S., Keren, B., Mignot, C., Afenjar, A., Billette de Villemeur, T., Heron, D., Nava, C., Valence, S., Buratti, J., Fagerberg, C. R., Soerensen, K. P., Kibaek, M., Kamsteeg, E. J., Koolen, D. A., Gunning, B., Schelhaas, H. J., Kruer, M. C., Fox, J., Bakhtiari, S., Jarrar, R., Padilla-Lopez, S., Lindstrom, K., Jin, S. C., Zeng, X., Bilguvar, K., Papavasileiou, A., Xin, Q., Zhu, C., Boysen, K., Vairo, F., Lanpher, B. C., Klee, E. W., Tillema, J. M., Payne, E. T., Cousin, M. A., Kruisselbrink, T. M., Wick, M. J., Baker, J., Haan, E., Smith, N., Corbett, M. A., MacLennan, A. H., Gecz, J., Biskup, S., Goldmann, E., Rodan, L. H., Kichula, E., Segal, E., Jackson, K. E., Asamoah, A., Dimmock, D., McCarrier, J., Botto, L. D., Filloux, F., Tvrdik, T., Cascino, G. D., Klingerman, S., Neumann, C., Wang, R., Jacobsen, J. C., Nolan, M. A., Snell, R. G., Lehnert, K., Sadleir, L. G., Anderlid, B. M., Kvarnung, M., Guerrini, R., Friez, M. J., Lyons, M. J., Leonhard, J., Kringlen, G., Casas, K., El Achkar, C. M., Smith, L. A., Rotenberg, A., Poduri, A., Sanchis-Juan, A., Carss, K. J., Rankin, J., Zeman, A., Raymond, F. L., Blyth, M., Kerr, B., Ruiz, K., Urquhart, J., Hughes, I., Banka, S., Hedrich, U. B. S., Scheffer, I. E., Helbig, I., Zamponi, G. W., Lerche, H., Mefford, H. C., De Novo Pathogenic Variants in CACNA1E Cause Developmental and Epileptic Encephalopathy with Contractures, Macrocephaly, and Dyskinesias, American Journal of Human Genetics, 103, 666-678, 2018	Diagnostic yield of genetic abnormalities was not reported
Hernandez, C. C., XiangWei, W., Hu, N., Shen, D., Shen, W., Lagrange, A. H., Zhang, Y., Dai, L., Ding, C., Sun, Z., Hu, J., Zhu, H., Jiang, Y., Macdonald, R. L., Altered inhibitory synapses in de novo GABRA5 and GABRA1 mutations associated with early onset epileptic encephalopathies, Brain : a journal of neurology., 05, 2019	Diagnostic yield of genetic abnormalities was not reported
Heyne, H. O., Artomov, M., Battke, F., Bianchini, C., Smith, D. R., Liebmann, N., Tadigotla, V., Stanley, C. M., Lal, D., Rehm, H., Lerche, H., Daly, M. J., Helbig, I., Biskup, S., Weber, Y. G., Lemke, J. R., Targeted gene sequencing in 6994 individuals with neurodevelopmental disorder with epilepsy, Genetics in Medicine., 2019	Diagnostic yield of genetic abnormalities was not reported

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Hochstenbach, R., Buizer-Voskamp, J. E., Vorstman, J. A. S., Ophoff, R. A., Genome arrays for the detection of copy number variations in idiopathic mental retardation, idiopathic generalized epilepsy and neuropsychiatric disorders: Lessons for diagnostic workflow and research, Cytogenetic and Genome Research, 135, 174-202, 2011	Literature review, no relevant data could be extracted for inclusion. References checked for inclusion
Hoffman-Zacharska, D., Szczepanik, E., Terczynska, I., Goszczanska-Ciuchta, A., Zalewska-Miszkurka, Z., Tataj, R., Bal, J., From focal epilepsy to dravet syndrome -heterogeneity of the phenotype due to SCN1A mutations of the p.Arg1596 amino acid residue in the nav1.1 subunit, Neurologia i Neurochirurgia Polska, 49, 258-266, 2015	Diagnostic yield of genetic abnormalities was not reported
Hwang, S. K., Kwon, S., Early-onset epileptic encephalopathies and the diagnostic approach to underlying causes, Korean Journal of Pediatrics, 58, 407-414, 2015	Literature review, no relevant data could be extracted for inclusion. References checked for inclusion
Iourov, I. Y., Vorsanova, S. G., Kurinnaia, O. S., Zelenova, M. A., Silvanovich, A. P., Yurov, Y. B., Molecular karyotyping by array CGH in a Russian cohort of children with intellectual disability, autism, epilepsy and congenital anomalies, Molecular Cytogenetics, 5 (1) (no pagination), 2012	Study design does not meet the inclusion criteria: case series
Jackson, A., Ward, H., Bromley, R. L., Deshpande, C., Vasudevan, P., Scurr, I., Dean, J., Shannon, N., Berg, J., Holder, S., Baralle, D., Clayton-Smith, J., D. D. D. Study, Exome sequencing in patients with antiepileptic drug exposure and complex phenotypes, Archives of Disease in Childhood, 105, 384-389, 2020	Study design does not meet inclusion criteria: case series
Ji, J., Shen, L., Bootwalla, M., Quindipan, C., Tatarinova, T., Maglinte, D. T., Buckley, J., Raca, G., Saitta, S. C., Biegel, J. A., Gai, X., A semiautomated whole-exome sequencing workflow leads to increased diagnostic yield and identification of novel candidate variants, Cold Spring Harbor Molecular Case Studies, 5, 2019	Study was conducted in an overall sample of people with neurological disorders; results were not stratified for epilepsies
Jiao, Q., Sun, H., Zhang, H., Wang, R., Li, S., Sun, D., Yang, X. A., Jin, Y., The combination of whole-exome sequencing and copy number variation sequencing enables the diagnosis of rare neurological disorders, Clinical Genetics, 96, 140-150, 2019	Unclear definition of what authors considered a "positive" test result and how they categorised epilepsy cases, as the study was conducted in a general population with people with neurological disorders
Jiao, X., Xue, J., Gong, P., Bao, X., Wu, Y., Zhang, Y., Jiang, Y., Yang, Z., Analyzing clinical and genetic characteristics of a cohort with multiple congenital anomalies-hypotonia-seizures syndrome (MCAHS), Orphanet Journal of Rare Diseases, 15 (1) (no pagination), 2020	Study design does not meet inclusion criteria: case series
Kananura, C., Haug, K., Sander, T., Runge, U., Gu, W., Hallmann, K., Rebstock, J., Heils, A., Steinlein, O. K., A splice-site mutation in GABRG2 associated with childhood absence epilepsy and febrile convulsions, Archives of Neurology, 59, 1137-1141, 2002	Study design does not meet the inclusion criteria: case-control study

Excluded studies - Genetic testing in epilepsy	
Kim, S. Y., Jang, S. S., Kim, H., Hwang, H., Choi, J. E., Chae, J. H., Kim, K. J., Lim, B. C., Genetic diagnosis of infantile-onset epilepsy in the clinic: Application of whole-exome sequencing following epilepsy gene panel testing, Clinical Genetics, 99, 418-424, 2021	Study design is not relevant; case series
Lal, D., Reinthaler, E. M., Dejanovic, B., May, P., Thiele, H., Lehesjoki, A. E., Schwarz, G., Riesch, E., Ikram, M. A., Van Duijn, C. M., Uitterlinden, A. G., Hofman, A., Steinbock, H., Gruber-Sedlmayr, U., Neophytou, B., Zara, F., Hahn, A., Gormley, P., Becker, F., Weber, Y. G., Cilio, M. R., Kunz, W., Krause, R., Zimprich, F., Lemke, J. R., Nurnberg, P., Sander, T., Lerche, H., Neubauer, B. A., Palotie, A., Ruppert, A. K., Suls, A., Siren, A., Koeleman, B., Haberlandt, E., Ronen, G. M., Caglayan, H., Hjalgrim, H., Muhle, H., Schulz, H., Helbig, I., Altmuller, J., Geldner, J., Schubert, J., Jabbari, K., Everett, K., Feucht, M., Balestri, M., Nothnagel, M., Striano, P., Moller, R. S., Nabbout, R., Balling, R., Baulac, S., Bianchi, A., La Neve, A., Minetti, C., Giuseppe, C., Evaluation of presumably disease causing SCN1A variants in a cohort of common epilepsy syndromes, PLoS ONE, 11 (3) (no pagination), 2016	Diagnostic yield of genetic abnormalities was not reported
Lee, C., Park, W. Y., Lee, J., Genetic Diagnosis of Dravet Syndrome Using Next Generation Sequencing-Based Epilepsy Gene Panel Testing, Annals of clinical and laboratory science, 50, 625-637, 2020	Study design does not meet the inclusion criteria: case series
Lee, H., Deignan, J. L., Dorrani, N., Strom, S. P., Kantarci, S., Quintero-Rivera, F., Das, K., Toy, T., Harry, B., Yourshaw, M., Fox, M., Fogel, B. L., Martinez-Agosto, J. A., Wong, D. A., Chang, V. Y., Shieh, P. B., Palmer, C. G. S., Dipple, K. M., Grody, W. W., Vilain, E., Nelson, S. F., Clinical exome sequencing for genetic identification of rare mendelian disorders, JAMA - Journal of the American Medical Association, 312, 1880-1887, 2014	Study was conducted in an overall sample of people with mendelian disorders; results were not stratified for epilepsies
Lee, S., Karp, N., Zapata-Aldana, E., Sadikovic, B., Yang, P., Balci, T. B., Prasad, A. N., Genetic Testing in children with Epilepsy: Report of a Single Centre Experience, The Canadian journal of neurological sciences, Le journal canadien des sciences neurologiques., 1-26, 2020	Study design does not meet the inclusion criteria: case series
Lee, S., Kim, S. H., Kim, B., Lee, S. T., Choi, J. R., Kim, H. D., Lee, J. S., Kang, H. C., Genetic diagnosis and clinical characteristics by etiological classification in early-onset epileptic encephalopathy with burst suppression pattern, Epilepsy Research, 163 (no pagination), 2020	Diagnostic yield of genetic abnormalities was not reported
Leu, C., Bautista, J. F., Sudarsanam, M., Niestroj, L. M., Stefanski, A., Ferguson, L., Daly, M. J., Jehi, L., Najm, I. M., Busch, R. M., Lal, D., Neurological disorder-associated genetic variants in individuals with psychogenic nonepileptic seizures, Scientific reports, 10, 15205, 2020	Diagnostic yield of genetic abnormalities was not reported

Excluded studies - Genetic testing in epilepsy	
Li, J., Gao, K., Yan, H., Xiangwei, W., Liu, N., Wang, T., Xu, H., Lin, Z., Xie, H., Wang, J., Wu, Y., Jiang, Y., Reanalysis of whole exome sequencing data in patients with epilepsy and intellectual disability/mental retardation, Gene, 700, 168-175, 2019	Study design does not meet the inclusion criteria: case series
Liu, J., Tong, L., Song, S., Niu, Y., Li, J., Wu, X., Zhang, J., Zai, C. C., Luo, F., Wu, J., Li, H., Wong, A. H. C., Sun, R., Liu, F., Li, B., Novel and de novo mutations in pediatric refractory epilepsy, Molecular Brain, 11, 48, 2018	Study design does not meet inclusion criteria: case series
Lund, C., Brodtkorb, E., Rosby, O., Rodningen, O. K., Selmer, K. K., Copy number variants in adult patients with Lennox-Gastaut syndrome features, Epilepsy Research, 105, 110-117, 2013	Study design does not meet the inclusion criteria: case series
Marques Matos, C., Alonso, I., Leao, M., Diagnostic yield of next-generation sequencing applied to neurological disorders, Journal of Clinical Neuroscience, 67, 14-18, 2019	Study was conducted in an overall sample of people with neurological disorders; results were not stratified for epilepsies
Martin, H. C., Kim, G. E., Pagnamenta, A. T., Murakami, Y., Carvill, G. L., Meyer, E., Copley, R. R., Rimmer, A., Barcia, G., Fleming, M. R., Kronengold, J., Brown, M. R., Hudspith, K. A., Broxholme, J., Kanapin, A., Cazier, J. B., Kinoshita, T., Nabbout, R., W. G. S. Consortium, Bentley, D., McVean, G., Heavin, S., Zaiwalla, Z., McShane, T., Mefford, H. C., Shears, D., Stewart, H., Kurian, M. A., Scheffer, I. E., Blair, E., Donnelly, P., Kaczmarek, L. K., Taylor, J. C., Clinical whole-genome sequencing in severe early-onset epilepsy reveals new genes and improves molecular diagnosis, Human Molecular Genetics, 23, 3200-11, 2014	Study design does not meet the inclusion criteria: case series
McTague, A., Nair, U., Malhotra, S., Meyer, E., Trump, N., Gazina, E. V., Papandreou, A., Ngoh, A., Ackermann, S., Ambegaonkar, G., Appleton, R., Desurkar, A., Eltze, C., Kneen, R., Kumar, A. V., Lascelles, K., Montgomery, T., Ramesh, V., Samanta, R., Scott, R. H., Tan, J., Whitehouse, W., Poduri, A., Scheffer, I. E., Chong, W. K. K., Cross, J. H., Topf, M., Petrou, S., Kurian, M. A., Clinical and molecular characterization of KCNT1-related severe early-onset epilepsy, Neurology, 90, e55-e66, 2018	This study used different types of genetic testing, and it was unclear whether all patients underwent all tests, therefore it is not possible to calculate the diagnostic yield for each of the tests
Mei, D., Parrini, E., Marini, C., Guerrini, R., The Impact of Next-Generation Sequencing on the Diagnosis and Treatment of Epilepsy in Paediatric Patients, Molecular Diagnosis and Therapy, 21, 357-373, 2017	Literature review, no relevant data could be extracted for inclusion. References checked for inclusion
Minardi, R., Licchetta, L., Baroni, M. C., Pippucci, T., Stipa, C., Mostacci, B., Severi, G., Toni, F., Bergonzini, L., Carelli, V., Seri, M., Tinuper, P., Bisulli, F., Whole-exome sequencing in adult patients with developmental and epileptic encephalopathy: It is never too late, Clinical Genetics, 98, 477-485, 2020	Study design does not meet the inclusion criteria: case series
Mitta, N., Menon, R. N., McTague, A., Radhakrishnan, A., Sundaram, S., Cherian, A., Madhavilatha, G. K., Mannan, A. U.,	Study design does not meet the inclusion criteria: case series

Excluded studies - Genetic testing in epilepsy	
Nampoothiri, S., Thomas, S. V., Genotype-phenotype correlates of infantile-onset developmental & epileptic encephalopathy syndromes in South India: A single centre experience, Epilepsy Research, 166 (no pagination), 2020	
Moller, R. S., Hammer, T. B., Rubboli, G., Lemke, J. R., Johannesen, K. M., From next-generation sequencing to targeted treatment of non-acquired epilepsies, Expert Review of Molecular Diagnostics, 19, 217-228, 2019	Narrative review, no relevant data could be extracted for inclusion. References checked for inclusion
Monlong, J., Girard, S. L., Meloche, C., Cadieux-Dion, M., Andrade, D. M., Lafreniere, R. G., Gravel, M., Spiegelman, D., Dionne-Laporte, A., Boelman, C., Hamdan, F. F., Michaud, J. L., Rouleau, G., Minassian, B. A., Bourque, G., Cossette, P., Global characterization of copy number variants in epilepsy patients from whole genome sequencing, PLoS Genetics, 14 (4) (no pagination), 2018	Diagnostic yield of genetic abnormalities was not reported
Na, J. H., Shin, S., Yang, D., Kim, B., Kim, H. D., Kim, S., Lee, J. S., Choi, J. R., Lee, S. T., Kang, H. C., Targeted gene panel sequencing in early infantile onset developmental and epileptic encephalopathy, Brain and Development, 42, 438-448, 2020	Study design does not meet the inclusion criteria: case series
Neuman, R. J., Kwon, J. M., Jilek-Aall, L., Rwiza, H. T., Rice, J. P., Goodfellow, P. J., Genetic analysis of kifafa, a complex familial seizure disorder, American Journal of Human Genetics, 57, 902-910, 1995	Authors did not report which genetic test were used
Nicholl, J., Waters, W., Suwalski, S., Brown, S., Hull, Y., Harbord, M. G., Entwistle, J., Thompson, S., Clark, D., Pridmore, C., Haan, E., Barnett, C., McGregor, L., Liebelt, J., Thompson, E. M., Friend, K., Bain, S. M., Yu, S., Mulley, J. C., Epilepsy with cognitive deficit and autism spectrum disorders: Prospective diagnosis by array CGH, American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics, 162, 24-35, 2013	Study design does not meet the inclusion criteria: case series
Ortega-Moreno, L., Giraldez, B. G., Soto-Insuga, V., Pozo, R. L. D., Rodrigo-Moreno, M., Alarcon-Morcillo, C., Sanchez-Martin, G., Diaz-Gomez, E., Guerrero-Lopez, R., Serratosa, J. M., Lorenzo, G., Garcia-Penas, J. J., Ruiz-Falco, M. L., Perez-Jimenez, M. A., Cantarin, V., Gil-Nagel, A., Toledano, R., Garcia-Perez, A., Verdu, A., Carrascosa, M. C., Vivanco, R., Aznar, G., Armstrong, J., Martorell, L., Fons, C., Garcia-Cazorla, A., Arriola, G., Vazquez, M., Garcia-Romero, M., Perez-Villena, A., Molecular diagnosis of patients with epilepsy and developmental delay using a customized panel of epilepsy genes, PLoS ONE, 12 (11) (no pagination), 2017	Study design does not meet the inclusion criteria: case series
Ottman, R., Poduri, A., Gene tests in adults with epilepsy and intellectual disability, Nature Reviews Neurology, 16, 527-528, 2020	Narrative review

Excluded studies - Genetic testing in epilepsy	
Palmer, E. E., Sachdev, R., Macintosh, R., Genetic Counselling, G. D., Melo, U. S., Mundlos, S., Righetti, S., Kandula, T., Minoche, A. E., Puttick, C., Gayevskiy, V., Hesson, L., Idrisoglu, S., Shoubridge, C., Thai, M. H. N., Davis, R. L., Drew, A. P., Sampaio, H., Andrews, P. I., Lawson, J., Cardamone, M., Mowat, D., Colley, A., Kummerfeld, S., Dinger, M. E., Cowley, M. J., Roscioli, T., Bye, A., Kirk, E., Diagnostic Yield of Whole Genome Sequencing After Non-diagnostic Exome Sequencing or Gene Panel in Developmental and Epileptic Encephalopathies, Neurology, 2021	Diagnostic yield of genetic abnormalities was not reported
Patel, J., Mercimek-Mahmutoglu, S., Epileptic Encephalopathy in Childhood: A Stepwise Approach for Identification of Underlying Genetic Causes, Indian Journal of Pediatrics, 83, 1164-1174, 2016	Narrative review, no relevant data could be extracted for inclusion. References checked for inclusion
Perry, M. S., Poduri, A., Two studies, one message: High yield of genetic testing in infants and young children with severe epilepsies, Epilepsy Currents, 18, 24-26, 2018	Narrative review, no relevant data could be extracted for inclusion. References checked for inclusion
Pfundt, R., Del Rosario, M., Vissers, L. E. L. M., Kwint, M. P., Janssen, I. M., De Leeuw, N., Yntema, H. G., Nelen, M. R., Lugtenberg, D., Kamsteeg, E. J., Wieskamp, N., Stegmann, A. P. A., Stevens, S. J. C., Rodenburg, R. J. T., Simons, A., Mensenkamp, A. R., Rinne, T., Gilissen, C., Scheffer, H., Veltman, J. A., Hehir-Kwa, J. Y., Detection of clinically relevant copy-number variants by exome sequencing in a large cohort of genetic disorders, Genetics in Medicine, 19, 667-675, 2017	Study was conducted in an overall sample of people with genetic disorders; results were not stratified for epilepsies
Poulat, A. L., Lesca, G., Sanlaville, D., Blanchard, G., Lion-Francois, L., Rougeot, C., des Portes, V., Ville, D., A proposed diagnostic approach for infantile spasms based on a spectrum of variable aetiology, European Journal of Paediatric Neurology, 18, 176-82, 2014	Genetic testing was not applied to all patients included in the sample
Rigbye, K. A., van Hasselt, P. M., Burgess, R., Damiano, J. A., Mullen, S. A., Petrovski, S., Puranam, R. S., van Gassen, K. L. I., Gecz, J., Scheffer, I. E., McNamara, J. O., Berkovic, S. F., Hildebrand, M. S., Is FGF13 a major contributor to genetic epilepsy with febrile seizures plus?, Epilepsy Research, 128, 48-51, 2016	Diagnostic yield of genetic abnormalities was not reported
Ritter, D. M., Holland, K., Genetic Testing in Epilepsy, Seminars in Neurology, 40, 730-738, 2020	Narrative review
Riviello, J. J., Jr., Ashwal, S., Hirtz, D., Glauser, T., Ballaban-Gil, K., Kelley, K., Morton, L. D., Phillips, S., Sloan, E., Shinnar, S., American Academy of Neurology, Subcommittee, Practice Committee of the Child Neurology, Society, Practice parameter: diagnostic assessment of the child with status epilepticus (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the	Literature review, no relevant data could be extracted for inclusion. References checked for inclusion

Excluded studies - Genetic testing in epilepsy	
Child Neurology Society, Neurology, 67, 1542-50, 2006	
Routier, L., Verny, F., Barcia, G., Chemaly, N., Desguerre, I., Colleaux, L., Nabbout, R., Exome sequencing findings in 27 patients with myoclonic-atonic epilepsy: Is there a major genetic factor?, Clinical Genetics, 96, 254-260, 2019	Study design does not meet the inclusion criteria: case series
Rudolf, G., de Bellescize, J., de Saint Martin, A., Arzimanoglou, A., Valenti Hirsch, M. P., Labalme, A., Boulay, C., Simonet, T., Boland, A., Deleuze, J. F., Nitschke, P., Ollivier, E., Sanlaville, D., Hirsch, E., Chelly, J., Lesca, G., Exome sequencing in 57 patients with self-limited focal epilepsies of childhood with typical or atypical presentations suggests novel candidate genes, European Journal of Paediatric Neurology, 27, 104-110, 2020	Diagnostic yield of genetic abnormalities was not reported
Sahli, M., Zrhidri, A., Elaloui, S. C., Smaili, W., Lyahyai, J., Oudghiri, F. Z., Sefiani, A., Clinical exome sequencing identifies two novel mutations of the SCN1A and SCN2A genes in Moroccan patients with epilepsy: A case series, Journal of Medical Case Reports, 13 (1) (no pagination), 2019	Study design does not meet inclusion crieria: case series
Sands, T. T., Choi, H., Genetic Testing in Pediatric Epilepsy, Current Neurology and Neuroscience Reports, 17 (5) (no pagination), 2017	Literature review, no relevant data could be extracted for inclusion. References checked for inclusion
Scala, M., Bianchi, A., Bisulli, F., Coppola, A., Elia, M., Trivisano, M., Pruna, D., Pippucci, T., Canafoglia, L., Lattanzi, S., Franceschetti, S., Nobile, C., Gambardella, A., Michelucci, R., Zara, F., Striano, P., Advances in genetic testing and optimization of clinical management in children and adults with epilepsy, Expert Review of Neurotherapeutics, 20, 251-269, 2020	Narrative review
Scott Perry, M., Genetic testing in epileptic encephalopathy: Rosetta stone or just an expensive rock?, Epilepsy Currents, 16, 12-13, 2016	Commentary paper for a fully published article (Mercimek-Mahmutoglu 2015)
Shaw, M., Winczewska-Wiktor, A., Badura-Stronka, M., Koirala, S., Gardner, A., Kuszel,, Kowal, P., Steinborn, B., Starczewska, M., Garry, S., Scheffer, I. E., Berkovic, S. F., Gecz, J., EXOME REPORT: Novel mutation in ATP6V1B2 segregating with autosomal dominant epilepsy, intellectual disability and mild gingival and nail abnormalities, European Journal of Medical Genetics, 63 (4) (no pagination), 2020	Diagnostic yield of genetic abnormalities was not reported
Sithambaram, S. S., Chow, G. C., Prasad, M. P., Whitehouse, W. W., Harrison, R. H., Dixit, A. D., Diagnostic yield of gene panels in patients with severe neurological disorders, Developmental Medicine and Child Neurology, 61, 95, 2019	Conference Abstract
Stefani, S., Kousiappa, I., Nicolaou, N., Papathanasiou, E. S., Oulas, A., Fanis, P., Neocleous, V., Phylactou, L. A., Spyrou, G. M., Papacostas, S. S., Neurophysiological and	Narrative review

Excluded studies - Genetic testing in epilepsy	
Genetic Findings in Patients With Juvenile Myoclonic Epilepsy, Frontiers in Integrative Neuroscience, 14 (no pagination), 2020	
Stodberg, T., Tomson, T., Barbaro, M., Stranneheim, H., Anderlid, B. M., Carlsson, S., Amark, P., Wedell, A., Epilepsy syndromes, etiologies, and the use of next-generation sequencing in epilepsy presenting in the first 2 years of life: A population-based study, Epilepsia, 61, 2486-2499, 2020	Study design does not meet the inclusion criteria: case series
Stosser, M. B., Lindy, A. S., Butler, E., Retterer, K., Piccirillo-Stosser, C. M., Richard, G., McKnight, D. A., High frequency of mosaic pathogenic variants in genes causing epilepsy-related neurodevelopmental disorders, Genetics in Medicine, 20, 403-410, 2018	Patients with pathogenic and likely pathogenic variants were included and it was analysed whether mosaicisms were detected
Thevenon, J., Duffourd, Y., Masurel-Paulet, A., Lefebvre, M., Feillet, F., El Chehadeh-Djebbar, S., St-Onge, J., Steinmetz, A., Huet, F., Chouchane, M., Darmency-Stamboul, V., Callier, P., Thauvin-Robinet, C., Faivre, L., Riviere, J. B., Diagnostic odyssey in severe neurodevelopmental disorders: Toward clinical whole-exome sequencing as a first-line diagnostic test, Clinical Genetics, 89, 700-707, 2016	Not all patients presented with epilepsy
Thomas, R. H., Berkovic, S. F., The hidden genetics of epilepsy-a clinically important new paradigm, Nature Reviews Neurology, 10, 283-92, 2014	Narrative review
Truty, R., Patil, N., Sankar, R., Sullivan, J., Millichap, J., Carvill, G., Entezam, A., Esplin, E. D., Fuller, A., Hogue, M., Johnson, B., Khouzam, A., Kobayashi, Y., Lewis, R., Nykamp, K., Riethmaier, D., Westbrook, J., Zeman, M., Nussbaum, R. L., Aradhya, S., Possible precision medicine implications from genetic testing using combined detection of sequence and intragenic copy number variants in a large cohort with childhood epilepsy, Epilepsia Open, 4, 397-408, 2019	Study design does not meet the inclusion criteria: case series
Zara, F., Specchio, N., Striano, P., Robbiano, A., Gennaro, E., Paravidino, R., Vanni, N., Beccaria, F., Capovilla, G., Bianchi, A., Caffi, L., Cardilli, V., Darra, F., Bernardina, B. D., Fusco, L., Gaggero, R., Giordano, L., Guerrini, R., Incorpora, G., Mastrangelo, M., Spaccini, L., Laverda, A. M., Vecchi, M., Vanadia, F., Veggiotti, P., Viri, M., Occhi, G., Budetta, M., Taglialatela, M., Coviello, D. A., Vigevano, F., Minetti, C., Genetic testing in benign familial epilepsies of the first year of life: Clinical and diagnostic significance, Epilepsia, 54, 425-436, 2013	Diagnostic yield of genetic abnormalities was not reported
Zhang, L., Gao, J., Liu, H., Tian, Y., Lei, W., Li, Y., Guo, Y., Yu, H., Yuan, E., Liang, L., Cui, S., Zhang, X., Pathogenic variants identified by whole-exome sequencing in 43 patients with epilepsy, Human Genomics, 14 (1) (no pagination), 2020	Study design does not meet the inclusion criteria: case series

Excluded studies - Genetic testing in epilepsy	
Zhang, Q., Li, J., Zhao, Y., Bao, X., Wei, L., Wang, J., Gene mutation analysis of 175 Chinese patients with early-onset epileptic encephalopathy, Clinical Genetics, 91, 717-724, 2017	Diagnostic yield of genetic abnormalities was not reported

Economic studies

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information

Appendix L – Research recommendations

Research recommendations for review question: What is the effectiveness of genetic testing in determining the aetiology of epilepsy?

No research recommendations were made for this review question.