Medical Coverage Policy | Genetic Testing for Epilepsy

EFFECTIVE DATE: 01|01|2024
POLICY LAST REVIEWED: 09|06|2023

OVERVIEW

Epilepsy is a disorder characterized by unprovoked seizures. It is a heterogeneous condition that encompasses many types of seizures and varies in age of onset and severity. Many genetic epilepsies are thought to have a complex, multifactorial genetic basis. There are also numerous rare epileptic syndromes associated with global developmental delay and/or cognitive impairment that occur in infancy or early childhood, and that may be caused by a single-gene pathogenic variant. Genetic testing is commercially available for a large number of genes that may be related to epilepsy.

This policy addresses the following test(s):

- Epilepsy genomic sequence analysis panel, must include analyses for ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19,POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2, and ZEB2 (CPT code 81419
- Genomic Unity® CACNA1A Analysis (Variantyx Inc) (CPT code 0231U)

MEDICAL CRITERIA

Medicare Advantage Plans and Commercial Products

Genomic Unity® CACNA1A Analysis (Variantyx Inc) (CPT code 0231U)
Epilepsy genomic sequence analysis panel (CPT code 81419)
Genetic testing for genes associated with infantile- and early-childhood-onset epilepsy syndromes in which epilepsy is the core clinical symptom is considered medically necessary if a positive test result may:

- Lead to changes in medication managements; AND/OR
- Lead to changes in diagnostic testing such that alternative invasive tests are avoided; AND/OR
- Lead to changes in reproductive decision making.

PRIOR AUTHORIZATION

Medicare Advantage Plans and Commercial Products
Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products and is obtained via the online tool for participating providers. See Related Policies section.

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

Genomic Unity® CACNA1A Analysis (Variantyx Inc) (CPT code 0231U)
Epilepsy genomic sequence analysis panel (CPT code 81419)
Genetic testing for genes associated with infantile- and early-childhood-onset epilepsy syndromes in which epilepsy is the core clinical symptom is considered medically necessary for Medicare Advantage Plans and Commercial Products when the medical criteria above is met.

Genetic testing for epilepsy is considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products when the medical criteria above is not met.

Commercial Products

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. **§27-19-81** described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate section of the Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for applicable laboratory testing and not medically necessary/not covered benefits/coverage.

BACKGROUND

Epilepsy

Epilepsy is defined as the occurrence of 2 or more unprovoked seizures. It is a common neurologic disorder, with approximately 3% of the population developing the disorder over their entire lifespan.

Classification

Epilepsy is heterogeneous in etiology and clinical expression and can be classified in a variety of ways. Most commonly, classification is done by the clinical phenotype, ie, the type of seizures that occur. In 2017, the International League Against Epilepsy (ILAE) updated its classification system that is widely used for clinical care and research purposes. Classification of seizures can also be done on the basis of age of onset: neonatal, infancy, childhood, and adolescent/adult.

Although genetic epilepsies are not discussed in the 2017 ILAE report a 2010 ILAE report identified genetic epilepsies as conditions in which the seizures are a direct result of a known or presumed genetic defect(s). Genetic epilepsies are characterized by recurrent unprovoked seizures in patients who do not have demonstrable brain lesions or metabolic abnormalities. In addition, seizures are the core symptom of the disorder, and other symptomatology is not present, except as a direct result of seizures. This is differentiated from genetically determined conditions in which seizures are part of a larger syndrome, such as tuberous sclerosis, fragile X syndrome, or Rett syndrome.

Genetic epilepsies can be further broken down by type of seizures. For example, genetic generalized epilepsy refers to patients who have convulsive (grand mal) seizures, while genetic absence epilepsy refers to patients with nonconvulsive (absence) seizures. The disorders are also sometimes classified by the age of onset.

The category of genetic epilepsies includes a number of rare epilepsy syndromes that present in infancy or early childhood. These syndromes are characterized by epilepsy as the primary manifestation, without associated metabolic or brain structural abnormalities. They are often severe and sometimes refractory to medication treatment. They may involve other clinical manifestations such as developmental delay and/or intellectual disability, which in many cases are thought to be caused by frequent uncontrolled seizures. In these cases, the epileptic syndrome may be classified as an epileptic encephalopathy, which is described by ILAE as disorders in which the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone and that these can worsen over time.

Genetic Etiology

Most genetic epilepsies are primarily believed to involve multifactorial inheritance patterns. This follows the concept of a threshold effect, in which any particular genetic defect may increase the risk of epilepsy, but is not by itself causative.[6,] A combination of risk-associated genes, together with environmental factors, determines whether the clinical phenotype of epilepsy occurs. In this model, individual genes that increase the susceptibility to epilepsy have a relatively weak impact. Multiple genetic defects, and/or a particular

combination of genes, probably increase the risk by a greater amount. However, it is not well-understood how many abnormal genes are required to exceed the threshold to cause clinical epilepsy, nor is it understood which combination of genes may increase the risk more than others.

Treatment
The condition is generally chronic, requiring treatment with 1 or more medications to adequately control symptoms. Seizures can be controlled by antiepileptic medications in most cases, but some patients are resistant to medications, and further options such as surgery, vagus nerve stimulation, and/or the ketogenic diet can be used.

Pharmacogenomics
Another area of interest for epilepsy is the pharmacogenomics of antiepileptic medications. There are a wide variety of these medications, from numerous different classes. The choice of medications and the combinations of medications for patients who require treatment with more than 1 agent is complex. Approximately one-third of patients are considered refractory to medications, defined as inadequate control of symptoms with a single medication. These patients often require escalating doses and/or combinations of different medications. At present, selection of agents is driven by the clinical phenotype of seizures but has a large trial-and-error component in many refractory cases. The current focus of epilepsy pharmacogenomics is in detecting genetic markers that identify patients likely to be refractory to the most common medications. This may lead to directed treatment that will result in a more efficient process for medication selection, and potentially more effective control of symptoms.

For individuals who have infantile- or early-childhood-onset epileptic encephalopathy who receive testing for genes associated with epileptic encephalopathies, the evidence includes prospective and retrospective cohort studies describing the testing yield. Relevant outcomes are test validity, symptoms, quality of life, functional outcomes, medication use, resource utilization, and treatment-related morbidity. For Dravet syndrome, which appears to have the largest body of associated literature, the sensitivity of testing for *SCN1A* disease-associated variants is high (up to 80%). For other early-onset epileptic encephalopathies, the true clinical sensitivity and specificity of testing are not well-defined. However, studies reporting on the overall testing yield in populations with epileptic encephalopathies and early-onset epilepsy have reported detection rates for clinically significant variants ranging from 7.5% to 57%. The clinical utility of genetic testing occurs primarily when there is a positive test for a known pathogenic variant. The presence of a pathogenic variant may lead to targeted medication management, avoidance of other diagnostic tests, and/or informed reproductive planning. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

CODING

Medicare Advantage Plans and Commercial Products
The following CPT code(s) are considered medically necessary for Medicare Advantage Plans and Commercial Products when the medical criteria above is met:

81419 Epilepsy genomic sequence analysis panel, must include analyses for ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2, and ZEB2

This code can be used for Genomic Unity® CACNA1A Analysis (Variantyx Inc)
0231U CACNA1A (calcium voltage-gated channel subunit alpha 1A) (eg, spinocerebellar ataxia), full gene analysis, including small sequence changes in exonic andintronic regions, deletions, duplications, short tandem repeat (STR) gene expansions, mobile element insertions, and variants in non-uniquely mappable regions

RELATED POLICIES

Biomarker Testing Mandate

PUBLISHED

Provider Update, November 2023

REFERENCES

1. Williams CA, Battaglia A. Molecular biology of epilepsy genes. Exp Neurol. Jun 2013; 244: 51-8. PMID 22178301
2. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. Apr 2017; 58(4): 522-530. PMID 28276060
3. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. Apr 2010; 51(4): 676-85. PMID 20196795
4. Merwick A, O'Brien M, Delanty N. Complex single gene disorders and epilepsy. Epilepsia. Sep 2012; 53 Suppl 4: 81-91. PMID 22946725
5. Miller IO, Sotero de Menezes MA. SCN1A-Related Seizure Disorders. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews. Seattle, WA: University of Washington; 2014.
6. Petrovski S, Kwan P. Unraveling the genetics of common epilepsies: approaches, platforms, and caveats. Epilepsy Behav. Mar 2013; 26(3): 229-33. PMID 23103323
7. Helbig I, Lowenstein DH. Genetics of the epilepsies: where are we and where are we going?. Curr Opin Neurol. Apr 2013; 26(2): 179-85. PMID 23429546
8. Deprez L, Jansen A, De Jonghe P. Genetics of epilepsy syndromes starting in the first year of life. Neurology. Jan 20 2009; 72(3): 273-81. PMID 19153375
9. Chambers C, Jansen LA, Dhamija R. Review of Commercially Available Epilepsy Genetic Panels. J Genet Couns. Apr 2016; 25(2): 213-7. PMID 26536886
10. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. Feb 03 2000; 342(5): 314-9. PMID 10660394
11. Cavalleri GL, McCormack M, Alhusaini S, et al. Pharmacogenomics and epilepsy: the road ahead. Pharmacogenomics. Oct 2011; 12(10): 1429-47. PMID 22008048
12. Food and Drug Administration (FDA). Label: Tegretol. 2018; https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=016608. Accessed December 9, 2022.
13. Food and Drug Administration (FDA). Depakene (valproic acid) Capsules and Oral Solution, Depakote (divalproex sodium) Delayed Release and Depakote ER (Extended Release) Tablets, Depakote Sprinkle Capsules (divalproex sodium coated particles in capsules), Depacon (valproate sodium) Injection. Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) 2015; https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/018081Orig1s064,018082Orig1s047,018723Orig1s056,019680Orig1s043,020593Orig1s034,021168Orig1s033ltr.pdf. Accessed December 8, 2022.
14. Dyment DA, Tétreault M, Beaulieu CL, et al. Whole-exome sequencing broadens the phenotypic spectrum of rare pediatric epilepsy: a retrospective study. Clin Genet. Jul 2015; 88(1): 34-40. PMID 25046240
15. Thevenon J, Milh M, Feillet F, et al. Mutations in SLC13A5 cause autosomal-recessive epileptic encephalopathy with seizure onset in the first days of life. Am J Hum Genet. Jul 03 2014; 95(1): 113-20. PMID 24995870
16. National Center for Biotechnology Information. GTR: Genetic Testing Registry. n.d.; https://www.ncbi.nlm.nih.gov/gtr/. Accessed December 6, 2022.
17. Hirose S, Scheffer IE, Marini C, et al. SCN1A testing for epilepsy: application in clinical practice. Epilepsia. May 2013; 54(5): 946-52. PMID 23586701
18. Mulley JC, Nelson P, Guerrero S, et al. A new molecular mechanism for severe myoclonic epilepsy of infancy: exonic deletions in SCN1A. Neurology. Sep 26 2006; 67(6): 1094-5. PMID 17000989

19. Wu YW, Sullivan J, McDaniel SS, et al. Incidence of Dravet Syndrome in a US Population. Pediatrics. Nov 2015; 136(5): e1310-5. PMID 26438699
20. Esterhuizen AI, Mefford HC, Ramesar RS, et al. Dravet syndrome in South African infants: Tools for an early diagnosis. Seizure. Nov 2018; 62: 99-105. PMID 30321769
21. Peng J, Pang N, Wang Y, et al. Next-generation sequencing improves treatment efficacy and reduces hospitalization in children with drug-resistant epilepsy. CNS Neurosci Ther. Jan 2019; 25(1): 14-20. PMID 29933521
22. Scheffer IE, Bennett CA, Gill D, et al. Exome sequencing for patients with developmental and epileptic encephalopathies in clinical practice. Dev Med Child Neurol. Jan 2023; 65(1): 50-57. PMID 35701389
23. Jiang T, Gao J, Jiang L, et al. Application of Trio-Whole Exome Sequencing in Genetic Diagnosis and Therapy in Chinese Children With Epilepsy. Front Mol Neurosci. 2021; 14: 699574. PMID 34489640
24. Kim SY, Jang SS, Kim H, et al. Genetic diagnosis of infantile-onset epilepsy in the clinic: Application of whole-exome sequencing following epilepsy gene panel testing. Clin Genet. Mar 2021; 99(3): 418-424. PMID 33349918
25. Palmer EE, Sachdev R, Macintosh R, et al. Diagnostic Yield of Whole Genome Sequencing After Nondiagnostic Exome Sequencing or Gene Panel in Developmental and Epileptic Encephalopathies. Neurology. Mar 30 2021; 96(13): e1770-e1782. PMID 33568551
26. Salinas V, Martínez N, Maturo JP, et al. Clinical next generation sequencing in developmental and epileptic encephalopathies: Diagnostic relevance of data re-analysis and variants re-interpretation. Eur J Med Genet. Dec 2021; 64(12): 104363. PMID 34673242
27. Sun D, Liu Y, Cai W, et al. Detection of Disease-Causing SNVs/Indels and CNVs in Single Test Based on Whole Exome Sequencing: A Retrospective Case Study in Epileptic Encephalopathies. Front Pediatr. 2021; 9: 635703. PMID 34055682
28. Lee J, Lee C, Park WY, et al. Genetic Diagnosis of Dravet Syndrome Using Next Generation Sequencing-Based Epilepsy Gene Panel Testing. Ann Clin Lab Sci. Sep 2020; 50(5): 625-637. PMID 33067208
29. Lee S, Karp N, Zapata-Aldana E, et al. Genetic Testing in Children with Epilepsy: Report of a Single-Center Experience. Can J Neurol Sci. Mar 2021; 48(2): 233-244. PMID 32741404
30. Lee J, Lee C, Ki CS, et al. Determining the best candidates for next-generation sequencing-based gene panel for evaluation of early-onset epilepsy. Mol Genet Genomic Med. Sep 2020; 8(9): e1376. PMID 32613771
31. Stödberg T, Tomson T, Barbaro M, et al. 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. Nov 2020; 61(11): 2486-2499. PMID 32964447
32. Berg AT, Coryell J, Saneto RP, et al. Early-Life Epilepsies and the Emerging Role of Genetic Testing. JAMA Pediatr. Sep 01 2017; 171(9): 863-871. PMID 28759667
33. Møller RS, Larsen LH, Johannesen KM, et al. Gene Panel Testing in Epileptic Encephalopathies and Familial Epilepsies. Mol Syndromol. Sep 2016; 7(4): 210-219. PMID 27781031
34. Trump N, McTague A, Brittain H, et al. Improving diagnosis and broadening the phenotypes in early-onset seizure and severe developmental delay disorders through gene panel analysis. J Med Genet. May 2016; 53(5): 310-7. PMID 26993267
35. Wirrell EC, Shellhaas RA, Joshi C, et al. How should children with West syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium. Epilepsia. Apr 2015; 56(4): 617-25. PMID 25779538
36. Mercimek-Mahmutoglu S, Patel J, Cordeiro D, et al. Diagnostic yield of genetic testing in epileptic encephalopathy in childhood. Epilepsia. May 2015; 56(5): 707-16. PMID 25818041
37. Hrabik SA, Standridge SM, Greiner HM, et al. The Clinical Utility of a Single-Nucleotide Polymorphism Microarray in Patients With Epilepsy at a Tertiary Medical Center. J Child Neurol. Nov 2015; 30(13): 1770-7. PMID 25862739
38. Ottman R, Hirose S, Jain S, et al. Genetic testing in the epilepsies--report of the ILAE Genetics Commission. Epilepsia. Apr 2010; 51(4): 655-70. PMID 20100225
39. Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology

and the Practice Committee of the Child Neurology Society. Neurology. Jun 12 2012; 78(24): 1974-80. PMID 22689735
40. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. Epilepsia. Oct 2010; 51(10): 2175-89. PMID 20608959
41. Wilmshurst JM, Gaillard WD, Vinayan KP, et al. Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics. Epilepsia. Aug 2015; 56(8): 1185-97. PMID 26122601
42. National Institute for Health and Care Excellence. Epilepsies: diagnosis and management [CG137]. 2021; https://www.nice.org.uk/guidance/cg137. Accessed December 8, 2022.
43. Ream MA, Mikati MA. Clinical utility of genetic testing in pediatric drug-resistant epilepsy: a pilot study. Epilepsy Behav. Aug 2014; 37: 241-8. PMID 25108116
44. Hoelz H, Herdl C, Gerstl L, et al. Impact on Clinical Decision Making of Next-Generation Sequencing in Pediatric Epilepsy in a Tertiary Epilepsy Referral Center. Clin EEG Neurosci. Jan 2020; 51(1): 61-69. PMID 31554424
45. National Institute of Neurological Disorders and Stroke (NINDS). NINDS Common Data Elements: Epilepsy. 2020, January; https://www.commondataelements.ninds.nih.gov/epilepsy. Accessed December 8, 2022.
46. McKnight D, Bristow SL, Truty RM, et al. Multigene Panel Testing in a Large Cohort of Adults With Epilepsy: Diagnostic Yield and Clinically Actionable Genetic Findings. Neurol Genet. Feb 2022; 8(1): e650. PMID 34926809
47. Alsubaie L, Aloraini T, Amoudi M, et al. Genomic testing and counseling: The contribution of next-generation sequencing to epilepsy genetics. Ann Hum Genet. Nov 2020; 84(6): 431-436. PMID 32533790
48. Johannesen KM, Nikanorova N, Marjanovic D, et al. Utility of genetic testing for therapeutic decision-making in adults with epilepsy. Epilepsia. Jun 2020; 61(6): 1234-1239. PMID 32427350
49. Minardi R, Licchetta L, Baroni MC, et al. Whole-exome sequencing in adult patients with developmental and epileptic encephalopathy: It is never too late. Clin Genet. Nov 2020; 98(5): 477-485. PMID 32725632
50. Hesse AN, Bevilacqua J, Shankar K, et al. Retrospective genotype-phenotype analysis in a 305 patient cohort referred for testing of a targeted epilepsy panel. Epilepsy Res. Aug 2018; 144: 53-61. PMID 29778030
51. Lindy AS, Stosser MB, Butler E, et al. Diagnostic outcomes for genetic testing of 70 genes in 8565 patients with epilepsy and neurodevelopmental disorders. Epilepsia. May 2018; 59(5): 1062-1071. PMID 29655203
52. Miao P, Feng J, Guo Y, et al. Genotype and phenotype analysis using an epilepsy-associated gene panel in Chinese pediatric epilepsy patients. Clin Genet. Dec 2018; 94(6): 512-520. PMID 30182498
53. Butler KM, da Silva C, Alexander JJ, et al. Diagnostic Yield From 339 Epilepsy Patients Screened on a Clinical Gene Panel. Pediatr Neurol. Dec 2017; 77: 61-66. PMID 29056246
54. Tan NC, Berkovic SF. The Epilepsy Genetic Association Database (epiGAD): analysis of 165 genetic association studies, 1996-2008. Epilepsia. Apr 2010; 51(4): 686-9. PMID 20074235
55. Anney RJ, Avbersek A, Balding D, et al. Genetic determinants of common epilepsies: a meta-analysis of genome-wide association studies. Lancet Neurol. Sep 2014; 13(9): 893-903. PMID 25087078
56. Steffens M, Leu C, Ruppert AK, et al. Genome-wide association analysis of genetic generalized epilepsies implicates susceptibility loci at 1q43, 2p16.1, 2q22.3 and 17q21.32. Hum Mol Genet. Dec 15 2012; 21(24): 5359-72. PMID 22949513
57. Guo Y, Baum LW, Sham PC, et al. Two-stage genome-wide association study identifies variants in CAMSAP1L1 as susceptibility loci for epilepsy in Chinese. Hum Mol Genet. Mar 01 2012; 21(5): 1184-9. PMID 22116939
58. Córdoba M, Consalvo D, Moron DG, et al. SLC6A4 gene variants and temporal lobe epilepsy susceptibility: a meta-analysis. Mol Biol Rep. Dec 2012; 39(12): 10615-9. PMID 23065262
59. Nurmohamed L, Garcia-Bournissen F, Buono RJ, et al. Predisposition to epilepsy--does the ABCB1 gene play a role?. Epilepsia. Sep 2010; 51(9): 1882-5. PMID 20491876

60. Kauffman MA, Moron DG, Consalvo D, et al. Association study between interleukin 1 beta gene and epileptic disorders: a HuGe review and meta-analysis. Genet Med. Feb 2008; 10(2): 83-8. PMID 18281914
61. Tang L, Lu X, Tao Y, et al. SCN1A rs3812718 polymorphism and susceptibility to epilepsy with febrile seizures: a meta-analysis. Gene. Jan 01 2014; 533(1): 26-31. PMID 24076350
62. von Podewils F, Kowoll V, Schroeder W, et al. Predictive value of EFHC1 variants for the long-term seizure outcome in juvenile myoclonic epilepsy. Epilepsy Behav. Mar 2015; 44: 61-6. PMID 25625532
63. Kwan P, Poon WS, Ng HK, et al. Multidrug resistance in epilepsy and polymorphisms in the voltage-gated sodium channel genes SCN1A, SCN2A, and SCN3A: correlation among phenotype, genotype, and mRNA expression. Pharmacogenet Genomics. Nov 2008; 18(11): 989-98. PMID 18784617
64. Jang SY, Kim MK, Lee KR, et al. Gene-to-gene interaction between sodium channel-related genes in determining the risk of antiepileptic drug resistance. J Korean Med Sci. Feb 2009; 24(1): 62-8. PMID 19270815
65. Lin CH, Chou IC, Hong SY. Genetic factors and the risk of drug-resistant epilepsy in young children with epilepsy and neurodevelopment disability: A prospective study and updated meta-analysis. Medicine (Baltimore). Mar 26 2021; 100(12): e25277. PMID 33761731
66. Li SX, Liu YY, Wang QB. ABCB1 gene C3435T polymorphism and drug resistance in epilepsy: evidence based on 8,604 subjects. Med Sci Monit. Mar 23 2015; 21: 861-8. PMID 25799371
67. Song C, Li X, Mao P, et al. Impact of CYP2C19 and CYP2C9 gene polymorphisms on sodium valproate plasma concentration in patients with epilepsy. Eur J Hosp Pharm. Jul 2022; 29(4): 198-201. PMID 32868386
68. Zhao T, Yu J, Wang TT, et al. Impact of ABCB1 Polymorphism on Levetiracetam Serum Concentrations in Epileptic Uygur Children in China. Ther Drug Monit. Dec 2020; 42(6): 886-892. PMID 32890316
69. Lu Y, Fang Y, Wu X, et al. Effects of UGT1A9 genetic polymorphisms on monohydroxylated derivative of oxcarbazepine concentrations and oxcarbazepine monotherapeutic efficacy in Chinese patients with epilepsy. Eur J Clin Pharmacol. Mar 2017; 73(3): 307-315. PMID 27900402
70. Hashi S, Yano I, Shibata M, et al. Effect of CYP2C19 polymorphisms on the clinical outcome of low-dose clobazam therapy in Japanese patients with epilepsy. Eur J Clin Pharmacol. Jan 2015; 71(1): 51-8. PMID 25323806
71. Ma CL, Wu XY, Jiao Z, et al. SCN1A, ABCC2 and UGT2B7 gene polymorphisms in association with individualized oxcarbazepine therapy. Pharmacogenomics. 2015; 16(4): 347-60. PMID 25823783
72. Guo Y, Yan KP, Qu Q, et al. Common variants of KCNJ10 are associated with susceptibility and anti-epileptic drug resistance in Chinese genetic generalized epilepsies. PLoS One. 2015; 10(4): e0124896. PMID 25874548
73. Ma CL, Wu XY, Zheng J, et al. Association of SCN1A, SCN2A and ABCC2 gene polymorphisms with the response to antiepileptic drugs in Chinese Han patients with epilepsy. Pharmacogenomics. Jul 2014; 15(10): 1323-36. PMID 25155934
74. Rädisch S, Dickens D, Lang T, et al. A comprehensive functional and clinical analysis of ABCC2 and its impact on treatment response to carbamazepine. Pharmacogenomics J. Oct 2014; 14(5): 481-7. PMID 24567120
75. Yun W, Zhang F, Hu C, et al. Effects of EPHX1, SCN1A and CYP3A4 genetic polymorphisms on plasma carbamazepine concentrations and pharmacoresistance in Chinese patients with epilepsy. Epilepsy Res. Dec 2013; 107(3): 231-7. PMID 24125961
76. Taur SR, Kulkarni NB, Gandhe PP, et al. Association of polymorphisms of CYP2C9, CYP2C19, and ABCB1, and activity of P-glycoprotein with response to anti-epileptic drugs. J Postgrad Med. 2014; 60(3): 265-9. PMID 25121365
77. Haerian BS, Roslan H, Raymond AA, et al. ABCB1 C3435T polymorphism and the risk of resistance to antiepileptic drugs in epilepsy: a systematic review and meta-analysis. Seizure. Jul 2010; 19(6): 339-46. PMID 20605481
78. Sun G, Sun X, Guan L. Association of MDR1 gene C3435T polymorphism with childhood intractable epilepsy: a meta-analysis. J Neural Transm (Vienna). Jul 2014; 121(7): 717-24. PMID 24553780
79. Shazadi K, Petrovski S, Roten A, et al. Validation of a multigenic model to predict seizure control in newly treated epilepsy. Epilepsy Res. Dec 2014; 108(10): 1797-805. PMID 25282706

80. Chung WH, Chang WC, Lee YS, et al. Genetic variants associated with phenytoin-related severe cutaneous adverse reactions. JAMA. Aug 06 2014; 312(5): 525-34. PMID 25096692
81. He XJ, Jian LY, He XL, et al. Association of ABCB1, CYP3A4, EPHX1, FAS, SCN1A, MICA, and BAG6 polymorphisms with the risk of carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in Chinese Han patients with epilepsy. Epilepsia. Aug 2014; 55(8): 1301-6. PMID 24861996
82. Wang W, Hu FY, Wu XT, et al. Genetic susceptibility to the cross-reactivity of aromatic antiepileptic drugs-induced cutaneous adverse reactions. Epilepsy Res. Aug 2014; 108(6): 1041-5. PMID 24856347
83. Bagnall RD, Crompton DE, Cutmore C, et al. Genetic analysis of PHOX2B in sudden unexpected death in epilepsy cases. Neurology. Sep 09 2014; 83(11): 1018-21. PMID 25085640
84. Coll M, Allegue C, Partemi S, et al. Genetic investigation of sudden unexpected death in epilepsy cohort by panel target resequencing. Int J Legal Med. Mar 2016; 130(2): 331-9. PMID 26423924
85. Bagnall RD, Crompton DE, Petrovski S, et al. Exome-based analysis of cardiac arrhythmia, respiratory control, and epilepsy genes in sudden unexpected death in epilepsy. Ann Neurol. Apr 2016; 79(4): 522-34. PMID 26704558
86. Riviello JJ, Ashwal S, Hirtz D, et al. 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 Child Neurology Society. Neurology. Nov 14 2006; 67(9): 1542-50. PMID 17101884
87. Hirtz D, Ashwal S, Berg A, et al. Practice parameter: evaluating a first nonfebrile seizure in children: report of the quality standards subcommittee of the American Academy of Neurology, The Child Neurology Society, and The American Epilepsy Society. Neurology. Sep 12 2000; 55(5): 616-23. PMID 10980722
88. Burgunder JM, Finsterer J, Szolnoki Z, et al. EFNS guidelines on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementias. Eur J Neurol. May 2010; 17(5): 641-8. PMID 20298421
89. Wirrell EC, Laux L, Donner E, et al. Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations From a North American Consensus Panel. Pediatr Neurol. Mar 2017; 68: 18-34.e3. PMID 28284397