Short human genetics opinion for a health insurer

Trio exome in developmental disorder and epilepsy

Medical necessity of trio exome sequencing in a child with global developmental disorder, epilepsy, microcephaly and a normal chromosomal microarray analysis

Fictitious sample case – case, persons, events and instruction are simulated, not a real expert opinion. Cited sources are real.

Instructed by	Private health insurer (private Krankenversicherung) [fictitious], Benefits Department	Reference	KV-2026-04417 [fictitious]
Insured person	M. R. [fictitious], born 2022	Date	8 November 2026

Result in brief

For the broad clinical picture described here, exome sequencing is, according to current knowledge, the professionally better-founded next investigation. An epilepsy panel is not unsuitable in principle but would cover only part of the causes under consideration. The trio approach is the preferred strategy because it directly detects newly arisen variants and facilitates classification of the mode of inheritance. It is not a mandatory prerequisite for any exome diagnostics.

1. Instruction and question

The insurer requests an opinion on the cost estimate of a human genetics institute [fictitious] for trio exome sequencing (child and both parents). It asks whether the test is medically necessary, whether an epilepsy gene panel is sufficient and whether testing the parents as well is required. The opinion is based on the fictitious file. Classification under the tariff and the law is reserved to the insurer.

2. Records

The following applies to this fictitious sample case: the four-year-old boy shows global developmental delay. He walked independently at 26 months and actively speaks about ten words. Since the age of 22 months he has had focal and bilateral tonic-clonic seizures, which are only partially controlled under two antiepileptic drugs used in succession. Drugs, dosages and tolerability are not documented in the files. Head circumference is below the 3rd percentile. Cranial MRI is unremarkable apart from mildly delayed myelination, and metabolic investigations and chromosomal microarray analysis are normal. The parents are healthy and not consanguineous, and there are no other affected family members. The treating paediatric neurologist justifies the request with the possible therapeutic relevance of a diagnosis.

3. Assessment

Indication. The combination of global developmental disorder, early-onset epilepsy and microcephaly suggests a genetic cause. The stepwise diagnostic work-up already performed has largely excluded structural, metabolic and larger chromosomal causes. Whether drug resistance in the strict sense is present cannot be assessed in the absence of information on drugs and dosage. This is not decisive for the question at hand. A confirmed diagnosis can influence the choice of therapy, end further diagnostic investigations and clarify the recurrence risk.

Role of exome sequencing. A meta-analysis with a multidisciplinary consensus statement found a diagnostic yield of exome sequencing in neurodevelopmental disorders of 36%, and of 53% with additional associated findings, compared with 15 to 20% for microarray analysis in earlier studies. The authors recommend exome sequencing as a first-tier test [1]. The guideline of the American College of Medical Genetics and Genomics recommends exome or genome sequencing as a first- or second-tier test in developmental disorders or intellectual disability [2].

Panel or exome. An epilepsy panel examines only the preselected genes. In a predominantly epileptological picture, a comprehensive panel can be a reasonable choice. In a meta-analysis, the yield was 28% in epilepsy with intellectual disability and 37% with early seizure onset. Exome sequencing performed numerically better than panels, but the difference was not statistically significant [3]. In the present case,

the broader phenotype favours the exome: with microcephaly and global developmental disorder, causes come into consideration that, depending on panel composition, are not covered. A normal panel result would then probably entail a further investigation. The specific coverage of the panel offered is not described in the files.

Trio approach. In a large exome study of families with severe, undiagnosed developmental disorders, an estimated 42% of affected individuals carried a disease-causing newly arisen variant [4]. Simultaneous comparison with the parental data detects such variants directly, classifies the mode of inheritance and supports assessment under the ACMG/AMP standard, in which confirmed de novo occurrence is a criterion in its own right. Alternatively, the child can be tested alone and abnormal variants subsequently checked specifically in the parents. This is possible, but usually slower and more laborious when there are several candidate variants. The trio approach is therefore the preferred, but not the only possible, strategy.

4. Answers to the questions

Question 1: Is trio exome sequencing medically necessary?

> **Answer:** On the basis of the available findings and the current state of science, exome sequencing is the professionally indicated next diagnostic step. The trio approach is the preferred strategy for this.

Question 2: Is an epilepsy gene panel sufficient?

> **Answer:** For the broad phenotype described here, a panel is less suitable because it covers only part of the causes. It is not unsuitable in principle. The assessment depends on the scope of the specific panel.

Question 3: Is testing of the parents required?

> **Answer:** It is professionally sensible and particularly helpful for detecting newly arisen variants. Subsequent targeted testing of the parents would be a possible, usually less efficient alternative.

8 November 2026

Prof. Dr. med. Christian T. Thiel-Hirschmann, MBA
Specialist in Human Genetics, Adjunct Professor at Friedrich-Alexander-Universität Erlangen-Nürnberg

References

1. Srivastava S, Love-Nichols JA, Dies KA, et al. Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders. Genet Med. 2019, 21(11): 2413-2421. doi:10.1038/s41436-019-0554-6
2. Manickam K, McClain MR, Demmer LA, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021, 23(11): 2029-2037. doi:10.1038/s41436-021-01242-6
3. Stefanski A, Calle-López Y, Leu C, et al. Clinical sequencing yield in epilepsy, autism spectrum disorder, and intellectual disability: A systematic review and meta-analysis. Epilepsia. 2021, 62(1): 143-151. doi:10.1111/epi.16755
4. Deciphering Developmental Disorders Study. Prevalence and architecture of de novo mutations in developmental disorders. Nature. 2017, 542(7642): 433-438. doi:10.1038/nature21062