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HUMAN GENETICS EXPERT OPINION

Court Expert Opinion on Order for Evidence | Liability Law

Cystic Fibrosis (CF) | Misclassification of a CFTR variant as VUS (ACMG Class 3) despite existing ClinVar entry as pathogenic | Liability of the contracted laboratory

Case Number	LG [City] - Ref. [XX] O [XXXX]/[YY] (Sample Case)
Client	Regional Court [City], [Civil Division XX], Order for the Taking of Evidence dated [Date]
Plaintiffs	Mr. and Mrs. M., as legal representatives of their daughter Lena M. (fictitious)
Defendant	Laboratory for Human Genetics [Name] LLC (fictitious)
Expert	Prof. Dr. med. Christian T. Thiel, MBA
Qualifications	Board-certified specialist in human genetics; University Hospital Erlangen; 30 years of clinical and scientific experience; expert witness for courts and insurance carriers
Date	March 28, 2026
Subject	Lena M. [fictitious], born [date], female; Diagnosis: Cystic Fibrosis (CF; OMIM #219700)
Key Issue	Was the classification of the CFTR variant c.[XXXX] as a variant of unknown significance (VUS, ACMG Class 3) by the defendant laboratory at the time the findings were issued correct according to the current state of medical science, or does it constitute an error that is causally responsible for the plaintiff's harm?

Statement pursuant to Sections 407, 407a of the German Code of Civil Procedure (ZPO)

Pursuant to the decision of the Regional Court of [City], the undersigned was appointed as a neutral expert. He declares that he has prepared this expert opinion impartially, to the best of his knowledge and belief, and without regard to any interests of the parties. He affirms that he has no personal or financial relationship with any of the parties or with the defendant laboratory. The expert opinion is based on the laboratory documents submitted, relevant scientific literature, and the state of medical science and practice applicable at the time the laboratory issued its findings.

1. Court's Assignment and Questions

By order of [Date], the Regional Court of [City], [Civil Division], commissioned the undersigned to prepare a human genetic expert opinion on the following questions:

1. Did the classification of the second CFTR variant detected in the child Lena M. as a variant of unknown significance (VUS, ACMG Class 3) by the defendant laboratory at the time the findings were issued correspond to the state of the art and the applicable quality standards for human genetic laboratories?

2. At the time the laboratory issued its findings, was information available in publicly accessible, scientifically recognized databases (in particular ClinVar) that would have justified or required a classification as pathogenic (ACMG Class 4 or 5)?
3. What standard of care must a human genetics laboratory apply when classifying variants, and did the defendant laboratory adhere to this standard?
4. What are the clinical and harm-related consequences for the affected patient and their family resulting from an erroneous classification as a VUS compared to a correct classification as pathogenic?
5. Is the reclassification of the variant as pathogenic (ACMG Class 4 or 5) to be performed at the time of the expert opinion correct, and should it have been performed at the time of the laboratory diagnosis?

2. Investigation Materials and Methodology

2.1 Submitted documents

- Complete report of findings from the defendant laboratory (Date: [Date of initial findings]), including raw data, evaluation protocols and internal quality assurance documentation
- ClinVar database entries for the CFTR variant in question at the time of the laboratory diagnosis and as of the present (as of March 2026)
- CFTR2 database entries regarding the variant in question
- Pediatric and pulmonology medical records of Lena M. (history since diagnosis)
- Sweat test result (chloride concentration) and newborn screening findings
- Complete diagnostic report on the first CFTR variant (classified as ACMG Class 5; undisputedly pathogenic)
- Written statements of both parties, as well as the complaint and answer
- Relevant scientific publications, guidelines (ACMG/AMP 2015, ClinGen recommendations, CFTR2 database description), and quality standards (accreditation guidelines for human genetic laboratories, DAKKS, ISO 15189)

2.2 Methodology of the Expert Evaluation

The question of whether the variant classification by the defendant laboratory was erroneous must be assessed based on the state of scientific knowledge at the time the findings were issued. A retrospective assessment based on current knowledge is not possible. The so-called ex-ante standard is of decisive relevance in this regard. It should be noted that if relevant data—which was generally accessible in relevant scientific databases (ClinVar, CFTR2) at the time the findings were issued and which a diligent laboratory should have been able to access and take into account—was not considered, a breach of due diligence must be assumed. This circumstance also applies if the entry into the databases was made only shortly before the date of the report.

The expert standard applied here is based on the quality standards that a specialist in human genetics with a subspecialty in molecular genetic diagnostics at an accredited laboratory was required to adhere to when issuing the report at the relevant time. The focus is therefore not on the ideal, but on what is customary in everyday laboratory practice and required by the guidelines.

3. Facts

3.1 Initial Clinical Findings

During newborn screening, an elevated concentration of immunoreactive trypsinogen (IRT) was detected in the patient Lena M. The subsequent sweat test revealed a chloride concentration of [XX] mmol/l (pathological, threshold > 60 mmol/l). The child's clinical presentation manifested as recurrent respiratory tract infections and failure to thrive. Due to the suspicion of cystic fibrosis, molecular genetic CFTR testing was ordered.

3.2 Report issued by the defendant laboratory

On [Date], the defendant laboratory issued a molecular genetic report with the following content:

Report from the defendant laboratory (Date: [Date])

Variant 1: NM_000492.4(CFTR): c.1521_1523delCTT (p.Phe508del) Classification of Variant 1: Pathogenic (ACMG Class 5) – undisputedly correct

Variant 2: NM_000492.4(CFTR): c.[fictitious variant, e.g., c.3196C>T, p.Arg1066Cys]

Classification of Variant 2 (by the laboratory): Variant of Unknown Significance (VUS, ACMG Class 3) – SUBJECT OF DISPUTE

Interpretation of findings in the laboratory report: 'The finding is not conclusively diagnostic for cystic fibrosis. Based on the molecular genetic results, CF can neither be definitively confirmed nor ruled out. Clinical correlation is required.'

3.3 ClinVar data available at the time of reporting

The signatory has examined the ClinVar database for the entry regarding the CFTR variant c.[fictitious] at issue. The following picture emerges:

Criterion	At the time of the report ([Date])	At the time of the expert opinion (March 2026)
ClinVar entry available	Yes	Yes
ClinVar overall rating	**Pathogenic (4 submitters)**	Pathogenic (8 submitters)
Oldest entry in ClinVar	**[Date, at least 6 months prior to the finding]**	[Date]
CFTR2 entry	**Yes - listed as CF-causing**	Yes - listed as CF-causing
Publications in PubMed	**At least [X] publications with disease association**	[X] publications
Laboratory classification	**VUS (ACMG Class 3) - ABNORMAL**	N/A
Correct classification	Pathogenic (ACMG Class 4 or 5)	Pathogenic (ACMG Class 4 or 5)

It is of crucial importance that, at the time the defendant laboratory issued its report, the CFTR variant in question had already been classified as pathogenic in ClinVar by at least four independent submitters and was listed in the CFTR2 database as causing cystic fibrosis. This information was publicly available and, had a thorough search been conducted, should have been included in the classification.

4. Family history and mode of inheritance

Cystic fibrosis is inherited in an autosomal recessive manner. A confirmed CF diagnosis requires the detection of two pathogenic CFTR variants in trans (i.e., on different alleles, one inherited from each parent). In the present case:

- Father: heterozygous carrier of variant 1 (p.Phe508del, ACMG Class 5) – confirmed by molecular genetic testing
- Mother: heterozygous carrier of variant 2 (c.[fictitious], subject of the dispute) – confirmed by molecular genetics
- Patient: compound heterozygous; inherited one variant from each parent (in trans configuration)

The mode of inheritance and the patient's compound heterozygous configuration are undisputed. The sole issue in dispute is whether variant 2, transmitted by the mother, was correctly classified.

Had both variants been correctly classified as pathogenic, the diagnosis of cystic fibrosis would have been molecularly confirmed. The erroneous VUS classification prevented this confirmation of the diagnosis and led to the damages claimed by the plaintiff.

5. CFTR Gene, Cystic Fibrosis, and Variant Classification

5.1 The CFTR Gene and Cystic Fibrosis

Cystic fibrosis (CF; OMIM #219700; ICD-11 CA27) is the most common life-shortening autosomal recessive inherited disease in the Caucasian population (incidence approx. 1:2,500). The cause of the disease lies in biallelic pathogenic variants in the CFTR gene (Cystic Fibrosis Transmembrane Conductance Regulator; 7q31.2; NM_000492.4). [1, 2] The CFTR gene encodes a cAMP-regulated chloride channel in epithelial cells (see also [3]). Pathogenic variants lead to a loss of function of the CFTR protein, resulting in elevated chloride levels in sweat (diagnostically useful: sweat test) and thick, viscous mucus in the lungs, pancreatic ducts, and other organs. [1, 2] To date, more than 2,000 variants in the CFTR gene have been described in the scientific literature. The majority of these are rare or private. For clinical use, the correct classification of each detected variant is of essential importance, as a genetic CF diagnosis is only confirmed upon detection of two pathogenic variants (compound heterozygous or homozygous). [1,3]

5.2 The CFTR2 Database as a Specialized Resource

For the CFTR gene, the CFTR2 database (cftr2.org) is an internationally recognized, disease-specific expert database developed specifically for the clinical classification of CFTR

variants. [3] **Consulting the CFTR2 database is considered standard practice when evaluating CFTR variants.** It provides information on variants found in well-characterized CF patient cohorts and indicates whether a variant is classified as 'CF-causing,' 'non-CF-causing,' or 'varying clinical consequences.' An entry classified as 'CF-causing' is a very strong argument for a pathogenic classification.

5.3 ACMG/AMP Classification System

The 2015 classification system developed by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) (Richards et al. [4]) defines five classes:

Class	Designation	Clinical Implications
Class 5	Pathogenic	Causal for disease; useful for clinical decisions
Class 4	Likely pathogenic	Strong evidence of causality; clinically useful
Class 3	VUS (variant of unknown significance)	Unclear significance; NOT useful for clinical decision-making
Class 2	Likely benign	Strong evidence against causality
Class 1	Benign	No disease causation

Critical distinction for the present case: **A VUS classification (Class 3) means, by definition, that the variant should NOT be used for clinical decisions and does not justify a CF diagnosis.** A correct classification as pathogenic (Class 4 or 5), on the other hand, would have immediately justified the CF diagnosis. This distinction is at the heart of the plaintiff's claim for damages.

6. Analysis of the classification by the defendant laboratory

6.1 Reconstruction of the diagnostic situation at the time of the laboratory testing

The undersigned has reconstructed the state of knowledge available at the time the defendant laboratory issued its findings using publicly accessible databases and scientific publications. The data sets in ClinVar, CFTR2, and PubMed at the time of the findings are decisive.

The following ACMG/AMP criteria would have been applicable upon careful review at the time of the findings:

ACMG criterion	Findings as of [Date]	Assessment
PS4 (strong)	Variant documented in at least 4 CF patients in ClinVar and CFTR2	Met
PM3 (moderate)	Compound heterozygous with a confirmed pathogenic variant (p.Phe508del) described in CF patients	Met
PP5 (supporting)	Several renowned laboratories have listed the variant as pathogenic in ClinVar	**Met - ignored by the laboratory**
PP4 (supporting)	Child's phenotype (sweat test positive, symptoms) highly specific for CF	Met
PM2 (moderate)	Variant extremely rare in control cohorts (gnomAD)	Met
Overall assessment	Pathogenic or likely pathogenic (Class 4 or 5)	**FALSELY classified as Class 3 by the laboratory**

6.2 The role of the ClinVar database and the obligation to consult it

ClinVar (clinvar.ncbi.nlm.nih.gov) is a publicly accessible, free database maintained by the National Center for Biotechnology Information (NCBI), into which laboratories worldwide submit their variant classifications. It is one of the most important resources for variant assessment and is explicitly named in the ACMG/AMP guidelines [4] as well as the ClinGen recommendations as a database to be consulted.

At the time the defendant laboratory issued its report, the variant in question had been classified as pathogenic in ClinVar by at least four independent, renowned laboratories, at least two of which had expert status ("expert panel" or "reviewed by expert panel"). **The failure to consider these entries in the variant classification constitutes a serious breach of due diligence.**

The obligation to consult ClinVar in routine diagnostics arises from:

- The 2015 ACMG/AMP guidelines [4]: Criterion PP5 requires the consultation of ClinVar entries from recognized laboratories
- The ACMG Laboratory Standards [5]: Accredited human genetic laboratories are required to integrate relevant databases into their workflow
- The general duty of care: A laboratory operating with due diligence must have consulted publicly accessible, relevant knowledge sources at the time of reporting findings
- ISO 15189 (Quality Management for Medical Laboratories): Requirement for up-to-date, validated reference databases in the analytical process

6.3 The CFTR2 database: A specialized resource with binding authority for CF diagnostics

In this case, the CFTR2 database is of particular importance. This database was developed specifically for the clinical classification of CFTR variants and represents the highest level of evidence for CF-specific variant assessment. [3] **At the time of the finding**, **the variant c.[fictitious] was listed in CFTR2 as 'CF-causing.'** A CF-specialized laboratory

that does not consult CFTR2 or ignores its entries, deviates from acceptable laboratory practice.

7. Expert assessment of the classification

7.1 Was the VUS classification incorrect at the time of the finding?

Expert's Key Finding

Yes. The classification of the CFTR variant c.[fictitious] as a VUS (ACMG Class 3) by the defendant laboratory was incorrect at the time the report was issued. It did not correspond to the current state of the art or the quality standards required for accredited human genetic laboratories. Upon careful consultation of the data available in ClinVar and CFTR2 at the time of the report, the variant should have been classified as pathogenic (ACMG Class 4 or 5).

The reasoning in detail:

1. At the time of the report, the variant in question was classified as pathogenic in ClinVar by at least four independent submitters. The ACMG criterion PP5 (recognized source classifies variant as pathogenic) was thus clearly met.
2. The variant was listed as 'CF-causing' in the CFTR2 database. According to the current consensus of the CF expert community, this corresponds to ACMG criterion PS4 (variant documented in affected individuals).
3. The child exhibited a phenotype highly specific for CF (positive sweat test, symptoms), fulfilling ACMG criterion PP4.
4. In combination with the indisputably pathogenic variant 1 (p.Phe508del) in a compound heterozygous configuration in the presence of a CF-typical phenotype, the requirements for classification as pathogenic or at least likely pathogenic were met upon careful application of the ACMG/AMP criteria.
5. No exculpatory criteria (benign or likely benign) are apparent that would have precluded a pathogenic classification.

7.2 Standard: Diligence of a competent human genetics laboratory

The standard of care to be applied here is that of a competent, diligent human genetics laboratory accredited for CF diagnostics. This standard includes:

- Systematic consultation of relevant databases (ClinVar, CFTR2, HGMD) as part of the documented evaluation workflow
- Application of the ACMG/AMP classification criteria [4] to all identified variants
- Consideration of the clinical context (sweat test, symptoms) during interpretation
- Critical review of VUS classifications for plausibility, particularly when the clinical phenotype suggests a disease
- Documentation of the rationale for the classification in the report

The defendant laboratory did not adhere to this standard. The VUS classification was the result of incomplete research and an incorrect application of the classification criteria.

7.3 Distinction: Reasonable disagreement versus clear error

Variant classification is not always unambiguous. There are borderline cases in which different laboratories, with the same level of knowledge, may arrive at reasonably different results —especially for VUS with limited evidence. However, the present case does not constitute such a borderline case.

If, at the time of reporting, at least four independent submitters in ClinVar classify a variant as pathogenic and the CFTR2 database lists it as CF-causing, then the divergent classification as a VUS is not a reasonable exercise of discretion, but **a clear error not supported by expert judgment.**

8. Causality Assessment and Extent of Damage

8.1 Causal link between error and damage

The causal link between the erroneous VUS classification and the damages claimed by the plaintiff must be assessed according to the principles of causality under tort law (adequate causality; protective purpose of the violated norm).

The correct classification as pathogenic would have led directly to a confirmed CF diagnosis for the patient. This diagnosis implies:

- Early initiation of CF-specific therapy (mucolytic therapy, respiratory physical therapy, antibiotic prophylaxis for pulmonary exacerbations; if eligible for CFTR modulators, combination therapy with ivacaftor/tezacaftor/elexacaftor such as Kaftrio)
- Early referral to a CF center with interdisciplinary expertise
- Regular follow-up examinations (lung function, nutritional status, microbiology)
- Accurate information for parents regarding the 25% recurrence risk for each subsequent child
- Option for prenatal diagnosis or preimplantation genetic testing (PGT-M) for future pregnancies

The CF diagnosis was delayed due to the incorrect VUS classification. The duration of the delay, the specific medical course during this period, and the resulting harm to the patient's health are the subject of the clinical-medical assessment by the pulmonology-pediatrics expert and will not be re-evaluated here.

8.2 Damages to the parents: Loss of reproductive autonomy

A separate claim by the plaintiffs concerns the loss of reproductive autonomy. After receiving the report with the VUS classification, the parents had no reliable basis for accurately assessing the risk of recurrence of CF in future children and for making appropriate decisions (prenatal diagnosis, preimplantation genetic diagnosis, or decision against further pregnancy).

Had the classification been correctly identified as pathogenic, the 25% recurrence risk (autosomal recessive inheritance, both parents carriers of one pathogenic variant each) would have been correctly communicated. The failure to disclose this risk constitutes an independent, liability-giving harm. The specific circumstances and the extent of potential harm (for example, the birth of another affected child) can be inferred from the plaintiff's statement of facts. The assessment of these facts is a matter for the court.

9. Conclusion / Expert Assessment

Summary of the expert findings

1. **Incorrect classification:** The classification of the CFTR variant c.[fictitious] as a VUS (ACMG Class 3) by the defendant laboratory was incorrect at the time the report was issued. It did not correspond to the current state of scientific knowledge nor to the quality standards required for accredited human genetic laboratories.
2. **Correct Classification:** Based on the data available in ClinVar (at least 4 submitters: pathogenic) and CFTR2 (CF-causing) at the time of the report, the variant should have been classified as pathogenic (ACMG Class 4 or 5). The current classification as pathogenic is correct and should have been made at the time of the report.
3. **Breach of duty of care:** The defendant laboratory either failed to conduct the research required by applicable quality standards (ACMG/AMP guidelines 2015, ISO 15189, DAKKS requirements) in the relevant databases or incorrectly weighted the results. This constitutes a breach of the laboratory's duty of care.
4. **No reasonable margin of discretion:** In the case of a variant that, at the time of the findings, was classified as pathogenic in ClinVar by at least four independent submitters and listed as CF-causing in CFTR2, this is not a gray-area situation with a reasonable margin of discretion, but rather a clear error.
5. **Causation:** The erroneous classification was a sufficient cause for the delay in the patient's CF diagnosis, for the parents not receiving accurate information regarding the risk of recurrence, and for the resulting consequential damages to occur.

The foregoing expert findings are rendered to the best of my knowledge and belief, impartially and conscientiously, in accordance with Sections 407 and 407a of the German Code of Civil Procedure (ZPO). The undersigned certifies that he is not in a relationship of dependency with the parties and has no financial interest in the outcome of the proceedings.

9a. Recommendations for the Further Proceedings

From an expert's perspective, the undersigned recommends that the court clarify the following aspects further or have them assessed by appropriate experts:

1. Clinical-pediatric assessment: What specific medical harm resulted from the delay in the CF diagnosis? (Responsible: Pediatrics / Pulmonology)

2. Calculation of economic damages: What additional costs were incurred due to the delayed diagnosis and necessary follow-up treatments?
3. Internal laboratory documentation: The court should request the complete internal quality documentation of the defendant laboratory as of the date of the findings, in particular: Which databases were consulted at the time of the findings? Was a search conducted in ClinVar and CFTR2? Is this documented?
4. Possible systemic errors: Did the laboratory have a documented workflow for consulting ClinVar and CFTR2 at the time of the diagnosis? If not: Systemic quality deficiency with potential relevance for further findings.

9b. Clinical and Social-Legal Classification of Cystic Fibrosis

To classify the harm, the clinical significance of a timely CF diagnosis must be presented:

- Modern CFTR modulators (Kaftrio/Trikafta: elexacaftor/tezacaftor/ivacaftor) are approved for patients aged 2 years and older with at least one F508del variant and have revolutionized the prognosis of CF. The prerequisite for their reimbursement eligibility is a confirmed CF diagnosis with two proven pathogenic variants. [7,8]
- A delayed diagnosis means a delayed initiation of this highly effective therapy and a longer progression of lung disease without adequate treatment.
- Life expectancy in CF has improved dramatically thanks to CFTR modulators; early initiation of therapy correlates with better long-term outcomes. [7]
- Law on Severe Disabilities (SGB IX): CF is generally assessed with a GdB of 50–100, depending on the severity. In cases of impaired lung function and organ involvement, GdB 80–100 are common; disability codes H and G may be considered.

Every month of delayed diagnosis and treatment in CF can lead to irreversible lung damage and a measurable deterioration in long-term prognosis. This must be taken into account when calculating the degree of disability.

10. References

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Erlangen, March 28, 2026

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