deutsche gesellschaft für humangenetik e.v.

# Indication Criteria for Genetic Testing
*Evaluation of validity and clinical utility*

# Indication criteria for disease:
# Adrenoleukodystrophy (ALD) / Adrenomyeloneuropathy (AMN) [ABCD1]

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## 2. Disease characteristics

2.1 Name of the Disease (Synonyms):
*Adrenoleukodystrophy (ALD), Adrenomyeloneuropathy (AMN), Addison disease and cerebral sclerosis, Melanodermic leukodystrophy*

2.2 OMIM# of the Disease: *300100 (ALD)*

2.3 Name of the Analysed Genes or DNA/Chromosome Segments:
*ABCD1, ALD (old name)*

2.4 OMIM# of the Gene(s): *300371 (ABCD1)*

2.5 Mutational Spectrum:
*Mainly (about 71%) point mutations, spread over all 10 exons.*
*Approx. 26% insertions and deletions, 3% deletions of 1 or more exons.*
*Rate of new mutations about 5%.*

2.6 Analytical Methods:
*bi-directional sequencing*

2.7 Analytical Validation
*Bi-directional sequencing. After index case, analysis of additional family members (control samples). Comparison to data base entries and journal data. Verification with an independent molecular genetic method (e.g. restriction analysis, ASO-PCR etc.). Quality control through sample exchange.*

2.8 Estimated Frequency of the Disease in Germany
(Incidence at birth ("birth prevalence") or population prevalence):
*Birth prevalence of hemizygotes about 1:42.000 and of hemizygotes plus heterozygotes about 1:16.800.*

2.9 If applicable, prevalence in the ethnic group of investigated person:
*not applicable*

2.10 Diagnostic Setting:

| | Yes. | No. |
|---|---|---|
| A. (Differential)diagnostics | ☒ | ☐ |
| B. Predictive Testing | ☒ | ☐ |
| C. Risk assessment in Relatives | ☒ | ☐ |
| D. Prenatal | ☒ | ☐ |

Comment:

## 3. Test characteristics

| | | genotype or disease | |
|---|---|---|---|
| | | present | absent |
| test | pos. | A | B |
| | neg. | C | D |

A: true positives C: false negatives
B: false positives D: true negatives

| | |
|---|---|
| sensitivity: | A/(A+C) |
| specificity: | D/(D+B) |
| pos. predict. value: | A/(A+B) |
| neg. predict. value: | D/(C+D) |

3.1 **Analytical Sensitivity**
(proportion of positive tests if the genotype is present)
*nearly 100%*

3.2 **Analytical Specificity**
(proportion of negative tests if the genotype is not present)
*nearly 100%*

3.3 **Clinical Sensitivity**
(proportion of positive tests if the disease is present)
The clinical sensitivity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case.
*almost 100%*

3.4 **Clinical Specificity**
(proportion of negative tests if the disease is not present)
The clinical specificity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case.
*close to 95%*

3.5 **Positive clinical predictive value**
(life time risk to develop the disease if the test is positive).
*about 95% for hemizygotes and about 50% for heterozygotes.*

3.6 **Negative clinical predictive value**
(Probability not to develop the disease if the test is negative).
Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

Index case in that family had been tested:
*Nearly 100%*

Index case in that family had not been tested:
*Depending on age and degree of relatedness <2.5%.*

## 4. Clinical Utility

**4.1 (Differential)diagnosis: The tested person ist clinically affected**
(To be answered if in 2.10 "A" was marked)

4.1.1 Can a diagnosis be made other than through a genetic test?

No. ☐ (continue with 4.1.4)
Yes, ☒
clinically. ☐
imaging. ☐
endoscopy. ☐
biochemistry. ☒
electrophysiology. ☐
other (please describe) *in males only*

4.1.2 Describe the burden of alternative diagnostic methods to the patient
*low (blood drawing)*

4.1.3 How ist the cost effectiveness of alternative diagnostic methods to be judged?
*small (analysis of very long chain fatty acids)*

4.1.4 Will disease management be influenced by the result of a genetic test?

No. ☐

Yes. ☒
Therapy (please describe) *Early intervention by bone marrow transplantation and dedicated symptomatic therapy*
Prognosis (please describe) *see above*
Management (please describe)

**4.2 Predictive Setting: The tested person is clinically unaffected but carries an increased risk based on family history**

(To be answered if in 2.10 "B" was marked)

4.2.1 Will the result of a genetic test influence lifestyle and prevention?
*Yes, definitely*

If the test result is positive (please describe)
*Adequate therapeutic options (see 4.1.4), conscious family planning and planning of life.*

If the test result is negative (please describe)
*'Relief' with regard to the familial risk, conscious family planning and planning of life.*

4.2.2 Which options in view of lifestyle and prevention does a person at-risk have if no genetic test has been done (please describe)?
*see 4.2.1 for 'test result is positive'*

**4.3 Genetic risk assessment in family members of a diseased person**

(To be answered if in 2.10 "C" was marked)

4.3.1 Does the result of a genetic test resolve the genetic situation in that family?
*Yes, X-linked inheritance.*

4.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
*No, except for obligate heterozygotes.*

4.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
*Yes.*

**4.4 Prenatal diagnosis**

(To be answered if in 2.10 "D" was marked)

4.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnostic?
*Yes.*

**5. If applicable, further consequences of testing**

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for the patient or his/her relatives? (Please describe)
*The molecular genetic diagnostics may influence family planning. Often it helps clarifying the situation and gives patients and relatives alternative options for deciding about future life.*