

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

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Indication criteria for disease: Friedreich ataxia (FRDA) [FXN]

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for Genetic Testing“
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2. Disease characteristics

2.1 Name of the Disease (Synonyms): *Friedreich ataxia (FRDA)*

2.2 OMIM# of the Disease: *229300*

2.3 Name of the Analysed Genes or DNA/Chromosome Segments:
FXN, frataxin gene, FRDA gene

2.4 OMIM# of the Gene(s): *606829*

2.5 Mutational Spectrum:

In ca. 96%, the patients carry an expanded GAA triplet repeat in intron 1 of the FXN gene. Ca. 4% of the patients are compound heterozygotes for a pathogenic GAA expansion and an inactivating FXN gene mutation.

2.6 Analytical Methods:

PCR, fragment length analysis, direct sequencing

2.7 Analytical Validation

Participation in proficiency tests. Interpretation of the molecular genetic results is unambiguous, as a rule.

2.8 Estimated Frequency of the Disease in Germany

(Incidence at birth ("birth prevalence") or population prevalence):

Prevalence ca. 2/100,000-4/100,000.

2.9 If applicable, prevalence in the ethnic group of investigated person:

not applicable

2.10 Diagnostic Setting:

	Yes.	No.
A. (Differential)diagnostics	<input checked="" type="checkbox"/>	<input type="checkbox"/>
B. Predictive Testing	<input checked="" type="checkbox"/>	<input type="checkbox"/>
C. Risk assessment in Relatives	<input checked="" type="checkbox"/>	<input type="checkbox"/>
D. Prenatal	<input checked="" type="checkbox"/>	<input type="checkbox"/>

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.

The sensitivity in cases with the classical clinical picture of FRDA is high (ca. 99%). However, 25% of the patients with proven FXN mutations manifest an atypical course. These atypical forms have a wide differential diagnostic spectrum with decreased sensitivity, depending on clinical symptoms and family history.

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.

nearly 100%.

3.5 Positive clinical predictive value

(life time risk to develop the disease if the test is positive).

According to the literature, the penetrance is considered complete in proven homozygotes for a typical GAA repeat expansion as well as in compound heterozygotes for a typical GAA repeat expansion and a pathogenic point mutation.

Limitations:

The age at first manifestation varies (sometimes also within a family) considerably, from 5 to more than 50 years. The exact threshold for short repeats is not exactly defined. Therefore, alleles within the border range (about 22 GAA triplets) and pathogenic alleles below 100 GAA repeats may be associated with incomplete penetrance. Such alleles are rare, however.

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:

almost 100%

Index case in that family had not been tested:

The probability with a negative test result of not getting FRDA is almost 100% too.

Limitation: The diagnosis of FRDA by clinical symptoms alone is often unreliable. Therefore, without proven genetic diagnosis of the index patient and depending on symptoms and family history, a variable risk remains to become afflicted with a disorder from the broad differential diagnostic spectrum.

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)

4.1.2 Describe the burden of alternative diagnostic methods to the patient

4.1.3 How ist the cost effectiveness of alternative diagnostic methods to be judged?

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

No.

Yes.

Therapy (please describe)

1) *Avoidance of superfluous therapies under undecided diagnosis*

2) *Regular preventive follow-up for recogniton or prevention of disease-associated complications (mainly cardiomyopathy, cardiac arrhythmias, diabetes mellitus, loss of hearing).*

3) *The genetic diagnosis enables participation in current or future clinical therapeutic studies (e.g. antioxidants, iron chelation, frataxin up-regulation, gene therapy)*

Prognosis (please describe)

A genetically verified diagnosis of FRDA allows prognostic statements and genetic counseling in differentiation to the many diseases with in parts completely different clinical course and/or mode of inheritance (including hereditary neuropathies, many types of ataxias, multisystem atrophies etc.). Sometimes also possible is a genotype/phenotype correlation between individual type of mutation and course/severity of disease and risk of disease-associated complications

Management (please describe)

Preventive medical checkups (see therapy); if necessary, provision of aids, implantation of pacemaker; or appropriate physical therapeutic / orthopedic / surgical therapy and symptomatic drug therapy (diabetes mellitus, bladder dysfunction, spasticity, cardiomyopathy, cardiac arrhythmias).

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.

If the test result is positive (please describe)

Influence on family planning and life plan, choice of occupation, preventive medical checkups (see 4.1.4) and, possibly, early admission to experimental therapeutic studies.

If the test result is negative (please describe)

Influence on family planning and life plan, choice of occupation; psychological relief.

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)?

Specific planning of life and family, choice of occupation, preventive medical checkups.

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.

4.3.2 Can a genetic test in the index patient save genetic or other tests in family members?

Yes, because specific diagnostics in relatives is possible. Else, unspecific differential diagnostics would be tried in symptomatic relatives.

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)

1) *A secure genetic diagnosis is prerequisite for safe genetic counseling of relatives.*

2) *Procurement of the correct diagnosis – irrespective of direct medical consequences – is a value in itself: There is a name now for the disease and its cause is definitely known. Demonstration of a genetic cause eliminates feeling of guilt and “own faults” (exogenous poisons, “incorrect conduct”) which may be relieving.*

3) *The knowledge of the molecular defect and the individual mutation allows (probably more often in the future) the inclusion in clinical therapeutic studies.*