deutsche gesellschaft für humangenetik e.v.

Indication Criteria for Genetic Testing
Evaluation of validity and clinical utility

Indication criteria for disease:
Fragile X mental retardation syndrome [FMR1]
Fragile X tremor/ataxia syndrome (FXTAS) [FMR1]

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2. Disease characteristics

2.1 Name of the Disease (Synonyms):
Fragile X mental retardation syndrome, fra(X) syndrome, Martin-Bell syndrome;
Fragile X tremor/ataxia syndrome, FXTAS

2.2 OMIM# of the Disease: *300624 (fra(X) syndrome), 300623 (FXTAS))*

2.3 Name of the Analysed Genes or DNA/Chromosome Segments: *FMR1*

2.4 OMIM# of the Gene(s): *309550*

2.5 Mutational Spectrum:
Fra(X) syndrome:
Expansion of the CGG trinucleotide repeats in the non-translated region of exon 1 to more than 200 repeats (full mutation) **with aberrant** *methylation of the gene promoter. In < 1% partial FMR1 deletion.*
Very rarely other loss of funtion (LOF) mutations
FXTAS:
Expansion of the CGG trinucleotide repeat in the non-translated region of exon 1 to more than 55 triplets (mostly up to 200) **without aberrant** *methylation of the gene promoter and with over-expression of the FMR1 gene (gain of function, GOF).*

2.6 Analytical Methods:
Southern blot, PCR through the CGG repeat.
Several other PCR based tests and sequencing

2.7 Analytical Validation
Two independent test methods, yearly proficiency tests.

2.8 Estimated Frequency of the Disease in Germany
(Incidence at birth ("birth prevalence") or population prevalence):
Prevalence at birth unknown.
Fra(X) syndrome:
school age: ca. 1:4,000 boys, 1:6,000 girls, world-wide
(source: The National Fragile X Foundation)
FXTAS:
From age 60 on: 1:1,100 males, 1:2,500 females

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:
- *A may include differential diagnostics of premature ovarial insufficiency (POF) of unknown cause.*
- *B: No FMR1 gene test in healthy children!*
- *C includes amongst other tests the search for CGG repeats with 59-200 trinucleotides (premutation) in male and female carriers as well as estimation of the risk for mental retardation in children of female carriers. The premutation, in addition, is a genetic risk factor for premature ovarial insufficiency/menopause in women and for FXTAS in males.*

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3. Test characteristics

	genotype or disease	
	present	absent
test pos.	A	B
test 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)
Examples
Genotype searched for: Full mutation or premutation
   Southern blot: 100%
   PCR through CGG repeat: < 5 % (full mutation), ca. 50% (premutation)
Genotype searched for: Deletion with loss of promoter
   Southern blot: ca. 99% in boys; ca. 75% in girls
Genotype searched for: Point mutation
   Sequencing: ca. 100%

3.2 Analytical Specificity
(proportion of negative tests if the genotype is not present)
Genotype searched for: Full mutation or premutation
   Southern blot: almost 100%
   PCR through CGG repeat: almost 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.
Fra(X) syndrome
   Full mutation: ca. 99% (Southern)
   Deletion with loss of promoter: ca. 1% (Southern)
   Other LOF mutations: < 0.1% (all methods)
FXTAS
   Premutation or full mutation without aberrant promoter methylation: ca. 99% (Southern);
   ca. 50% (PCR through CCG repeat)
Premature ovarial insufficiency
   Premutation ca. 2% (Southern); < 1% (PCR through CGG repeat).

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.
Full mutation: almost 100%
Deletion with loss of promoter: almost 100%
Premutation (= FXTAS risk allele) 99.9% (males); 99.6% (females)
(Source: The National Fragile X Foundation)

3.5 **Positive clinical predictive value**
(life time risk to develop the disease if the test is positive).
Fra(X) syndrome
   Full mutation (more than 200 CGGs): ca. 98%
   Full mutation without aberrant promoter methylation: < 1%
   Full mutation with aberrant promoter methylation: almost 100%
   Methylation mosaic: 0% - 100%
   Genotypic mosaic (premutation plus full mutation): 0% - 100%
FXTAS
   Full mutation with aberrant promoter methylation: 0%
   Premutation or full mutation without aberrant promoter methylation: > 80%
   (males); presumably >10% (females)
Premature ovarial insufficiency/menopause
   Full mutation with aberrant promoter methylation: 0%
   Premutation or full mutation without aberrant promoter methylation: 21-23%

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:
Probability of disease for the test person depends on his prior risk which is determined by the degree of relatedness to the index patient and to the probability of correctness of diagnosis in the index patient.

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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.   ☒

Fra(X) syndrome:

Therapy (please describe)	*Ergotherapy, behaviour therapy, special education, including measures in family, school and occupation for improving cognitive capability of patients with mental and motor handicap and with impaired learning.*
Prognosis (please describe)	*Distinct improvement with early and individually adapted support by specialised professionals, e.g. in fra(X) clinics (for Germany expected soon in the University Hospital of Tübingen).*
Management (please describe)	*The result of genetic diagnostics will guide the evaluation of the child's individual cognitive strengths and weaknesses as well as the optimization of individual support.*

FXTAS:

Therapy (please describe)	*Avoiding/discontinuing ineffective/harmful medications (e.g. Levidopa in cases of FXTAS misdiagnosed as parkinsonism)*

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?
Lifestyle yes; prevention not possible.

If the test result is positive (please describe)
E.g. early family planning if there is the risk of POF, and possibility of prenatal diagnostics.

If the test result is negative (please describe)
No longer feares about further life and family planning.

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)?
No special option; prevention not possible.

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.

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)
Verification of the diagnosis gives the disease a name and often explains their cause. A genetic cause then eliminates the feeling of guilt and "own faults" (exogenous poisons, "incorrect conduct") which may be relieving.