

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

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Indication criteria for disease: **Williams-Beuren syndrome** **[7q11.23; ELN, LIMK1, GTF2I]**

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Ad hoc-Kommission „Indikationskriterien für genetische Diagnostik“

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2. Disease characteristics

2.1 Name of the Disease (Synonyms): *Williams-Beuren syndrome, WBS*

2.2 OMIM# of the Disease: *#194050*

2.3 Name of the Analysed Genes or DNA/Chromosome Segments:
ELN, LIMK1, GTF2I
7q11.23

2.4 OMIM# of the Gene(s):
*ELN *130160*
*LIMK1 *601329*
*GTF2I *601679*

2.5 Mutational Spectrum:
Deletion 7q11.23 of variable size:
1.55 Mb (~ 95% of cases) - 1.84 Mb (~ 5% of cases),
rarely larger deletions of 2-4 Mb.
Clinical phenotype depending on the size of deletion and the genes involved

2.6 Analytical Methods:
FISH, MLPA, qPCR, Microsatellite analysis, Array-CGH

2.7 Analytical Validation
Parallel analysis of positive and negative controls, depending on analytical method

2.8 Estimated Frequency of the Disease in Germany
(Incidence at birth ("birth prevalence") or population prevalence):
1:7 500 - 1:10 000

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

2.10 Diagnostic Setting:

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

Comment:

The vast majority of WBS cases is due to a sporadic genetic event. It is, therefore, not meaningful to analyse relatives without clinical phenotype. In 25-30% of the cases, a parent carries an inversion polymorphism which, however, cannot be detected by the usual WBS analytical methods (FISH, MLPA).

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)

almost 100%, depending on analytical method

3.2 Analytical Specificity

(proportion of negative tests if the genotype is not present)

almost 100%, depending on analytical method

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%, depending on analytical method

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.

almost 100%, depending on analytical method

3.5 Positive clinical predictive value

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

100%, with variable phenotype

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:

practically 100%

Index case in that family had not been tested:

By practically 100%, relatives without clinical symptoms will not develop the disease.

4. Clinical Utility

4.1 (Differential) diagnosis: The tested person is 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 is 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)

depending on clinical symptoms: specific measures of support, surgical correction of existing heart defects, psycho-pharmacological and anti-hypertensive medication, therapy of hypercalcemia by low-calcium diet, ophthalmological treatment of hyperopia and strabism, ear protection for avoiding exposure to high volume noise, physical therapy.

Prognosis (please describe)

Prognosis of clinical sequels depends on clinical symptoms and therapeutic measures.

Management (please describe)

regular cardiologic controls, measurement of blood pressure, neurological and endocrinological surveillance, ultrasound examination of bladder and kidneys, determination of serum and urine calcium and of urine creatinine, tests of thyroid function, vision and hearing, developmental diagnostic testing and corresponding therapeutic actions. Also see the Guidelines of the American Academy of Pediatrics for Patients with Williams-Beuren syndrome; Pediatrics 2001: 107(5), 1192-2004.

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)

Yes, see 4.1.4.

If the test result is negative (please describe)

No, provided the person is really free of clinical symptoms.

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 options

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?

No.

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

No.

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)

Yes. Relatives mainly benefit from knowing the genetic cause of the disease. Patients profit from specific therapies (diet, preventive examinations, supportive measures).