

Indication criteria for genetic testing
Evaluation of validity and clinical utility

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Indication criteria for disease:
Complete Androgen insensitivity (CAIS) [AR]

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2. Disease characteristics

2.1 Name of the Disease (Synonyms): *Complete androgen insensitivity, complete androgen resistance, testicular feminisation (no longer used)*

2.2 OMIM# of the Disease: *300068*

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

2.4 OMIM# of the Gene(s): *313700*

2.5 Mutational Spectrum:
Point mutations (about 90%), deletions or insertions of small number of oligonucleotides, larger deletions

2.6 Analytical Methods:
DNA sequencing, PCR or Southern blot analysis for detection of deletions

2.7 Analytical Validation
almost 100%.

2.8 Estimated Frequency of the Disease in Germany
(Incidence at birth ("birth prevalence") or population prevalence):
Prevalence at birth about 1:40,000

2.9 If applicable, prevalence in the ethnic group of investigated person:
none

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 checked="" type="checkbox"/>	<input type="checkbox"/>
D. Prenatal	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Comment: *A prenatal diagnosis of CAIS is possible if the mutation is known in the index patient. However, because of the phenotype a prenatal diagnosis is only rarely requested. Very rarely, the same mutation may cause a complete as well as a partial androgen insensitivity in the same family.*

3. Test characteristics

		Genotyp bzw. Krankheit	
		vorhanden	fehlend
Test	pos.	A	B
	neg.	C	D

A: richtig Positive C: falsch Negative
 B: falsch Positive D: richtig Negative

Sensitivität: $A/(A+C)$
Spezifität: $D/(D+B)$
pos. prädikt. Wert: $A/(A+B)$
neg. prädikt. Wert: $D/(C+D)$

3.1 Analytical Sensitivity

(proportion of positive tests if the genotype is present)

practically 100%

3.2 Analytical Specificity

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

practically 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.

Estimated more than 90% if phenotype and endocrine parameters definitely point to androgen insensitivity. Other enzymatic defects of steroid hormone synthesis must be excluded, mainly a 17-hydroxy-steroid dehydrogenase deficiency.

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).

nearly 100%

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:

In such cases the analysis is not useful because mostly private mutations are present in the families.

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)

Gonadectomy after puberty must be discussed because there is a certain risk (estimated 5-10%) of malignant transformation.

Prognosis (please describe)

There is no reliable correlation between mutation and expression of androgen insensitivity. The same mutation may be found in complete and partial androgen insensitivity. Variable expressivity is sometimes seen within the same family.

Management (please describe)

Increased risk of inguinal hernia; 5-10% risk of malignant gonadal tumors, so that gonadectomy after puberty with subsequent hormone substitution must be discussed; psychological support may be needed.

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?

If the test result is positive (please describe)

If the test result is negative (please describe)

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)?

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, but see to 2.10.

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)

Not applicable, there are consequences.