

**Indication criteria for genetic testing**  
Evaluation of validity and clinical utility

**Indication criteria for disease:**  
**Congenital bilateral aplasia of vas deferens**  
**(CBAVD) [CFTR]**

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## 2. Disease characteristics

2.1 Name of the Disease (Synonyms):

*Congenital aplasia of vas deferens (CBAVD)*

2.2 OMIM# of the Disease: *277180*

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

2.4 OMIM# of the Gene(s): *602421*

2.5 Mutational Spectrum:

*Point mutations, deletions, duplications and insertions of a few nucleotides, larger deletions. The spectrum of CFTR mutations in CBAVD partly differs from the one in cystic fibrosis.*

2.6 Analytical Methods:

*PCR, sequencing, MLPA*

2.7 Analytical Validation

*Accuracy nearly 100%*

2.8 Estimated Frequency of the Disease in Germany

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

*1-2% of all infertile males, about 6% of all males with azospermia.*

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

Comment: *The prenatal diagnostics aims at recognition of cystic fibrosis which also is due to CFTR mutations. A CFTR diagnostics should be offered to mate and relatives if the mutation has been found in the index patient.*

### 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)

*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.

*In ca. 70% of the patients 2 mutations (the 5T allele included) are found on sequencing the CFTR gene. Only 1 mutation or a single 5T allele is found in ca. 13%.*

*About 8% of the cases have CBAVD associated with renal agenesis. This disease is inherited in autosomal-dominant manner and is not caused by mutations in the CFTR gene.*

#### 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.

*Northern European populations have a heterozygote frequency of 1:25.*

*Therefore, the specificity for a diagnosis of heterozygosity by detection of a single mutation is 24/25. The specificity of diagnosing disease by detection of 2 mutations is almost 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:

*Not useful because private mutations are frequently found in families with CBAVD.*

## 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) *Clinical and imaging investigations may suggest*

*the diagnosis of CBAVD. The diagnosis is established by demonstrating normal spermiogenesis on testicular biopsy.*

4.1.2 Describe the burden of alternative diagnostic methods to the patient

*Distress through the surgical procedure of testicular biopsy.*

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

*The cost effectiveness of alternative methods in comparison to gene tests depends on the extent of the molecular genetic analysis (Detection or exclusion of common mutations vs. gene sequencing).*

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

no

yes

Therapy (please describe)

Prognosis (please describe)

Management (please describe) *Increased risk of cystic fibrosis for a child after ICSI therapy. The CBAVD patient's mate should therefore be offered CFTR diagnostics.*

#### 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)

*It is recommended to test the mate before ICSI therapy.*

If the test result is negative (please describe)

*Search for renal anomalies.*

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)?

*not applicable*

#### 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?

No.

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

*not applicable*

#### 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, *with regard to cystic fibrosis.*

#### 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. *Knowing the cause of the infertility is useful for the patient as well as for his family.*