

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

**Indication criteria for disease:**  
**Non-obstructive azoospermia, severe oligozoospermia [AZFa, AZFb, AZFc]**

**1. General information on authorship**

**Name and address of institution:**

Name: *Institute of Human Genetics, University Hospital Münster*  
Address: *Vesaliusweg 12-14*  
Postcode: *D-48149*  
City: *Münster*  
Tel.: *+49-251-83-55401*  
Fax: *+49-251-83-55431*  
E-mail: *wieacker@uni-muenster.de*  
Internet: *http://humangenetik.klinikum.uni-muenster.de*

**Head of the institution:**

Name: *Prof. Dr. med. Peter Wieacker*  
Tel.: *+49-251-83-55401*  
Fax: *+49-251-83-55431*  
E-mail: *wieacker@uni-muenster.de*

**Author of this text, date:**

Name: *Prof. Dr. med. Peter Wieacker*  
Tel.: *+49-251-83-55401*  
Fax: *+49-251-83-55431*  
E-mail: *wieacker@uni-muenster.de*  
Date: *07.10.2007*

**Reviewer, validation date:**

Name: *Prof. Dr. med. Wolfgang Engel*  
Tel.: *+49-551-39-7589*  
Fax: *+49-551-39-9303*  
E-mail: *wengel@gwdg.de*  
Date: *22.11.2007*

**Translator, translation date:**

Name: *Prof. Dr. Ulrich Langenbeck*  
E-mail: *Ulrich.Langenbeck@gmx.net*  
Date: *10.03.2008*

**Re-editor, date:**

Name:  
Tel.:  
Fax:  
E-mail:  
Date:

Authorized by GfH ad hoc commission „Indikationskriterien für genetische Diagnostik“

Date: 20.05.2008

© German Society of Human Genetics (GfH)

german society of human  
genetics  
www.gfhev.de

**Chairman**

Prof. Dr. med. André Reis, Erlangen

**Vice Chairman**

Prof. Dr. med. Olaf Riess, Tübingen  
Prof. Dr. med. Evelin Schröck,  
Dresden

**Treasurer**

PD Dr. rer. nat. Iris Bartels,  
Göttingen

**Secretary**

Prof. Dr. rer. nat. Christine Zühlke,  
Lübeck

**Scientific Advisory Board**

Prof. Dr. rer. nat. Gudrun Rappold,  
Heidelberg  
Prof. Dr. med. Jürgen Kohlhase,  
Freiburg  
Prof. Dr. med. Michael Speicher,  
Graz  
Prof. Dr. med. Jörg Schmidtke,  
Hannover  
(conference president 2008)  
Prof. Dr. med. Klaus Zerres,  
Aachen  
(conference president 2009)  
Prof. Dr. med. Uwe Claussen, Jena  
(conference president 2010)

**Address of chairman**

Institut für Humangenetik  
Universität Erlangen-Nürnberg  
Schwabachanlage 10  
91054 Erlangen  
Tel 0049 (0)9131-852 2318  
Fax 0049 (0)9131-209297  
reis@humgenet.uni-erlangen.de

**GfH-Office**

Dipl.-Soz. Christine Scholz  
Inselkammerstr. 4  
82008 München-Unterhaching  
Telefon+49 (089) 614 56 95 9  
Telefax +49 (089) 55 02 78 56  
organisation@gfhev.de

**Bank Details**

Postbank München  
Konto 231 394 805  
BLZ 700 100 80

**IBAN**

DE19 7001 0080 0231 3948 05

**BIC**

PBNK DEFF

**Vereinsregister München**

VR 12341

Updated by

Date:

## 2. Disease characteristics

2.1 Name of the Disease (Synonyms):

*Non-obstructive Azoospermia / severe oligozoospermia*

2.2 OMIM# of the Disease: *415000*

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

*AZFa, AZFb, and AZFc regions*

2.4 OMIM# of the Gene(s): *415000*

2.5 Mutational Spectrum:

*deletions*

2.6 Analytical Methods:

*PCR*

2.7 Analytical Validation

*depends on region analysed*

2.8 Estimated Frequency of the Disease in Germany

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

*Disordered spermatogenesis is found in 1% of all males. The prevalence of AZF deletions is 15-20% in males with non-obstructive azoospermia and 7-10% in males with severe oligozoospermia. In unselected infertile males the prevalence of AZF deletions is 0.6-1%.*

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 type="checkbox"/>	<input checked="" type="checkbox"/>

Comment: *Before ICSI, an AZF analysis may be important for therapeutic reasons because, as a rule, no sperms are found on TESE in cases with AZFa and AZFb deletions.*

*In contrast, 50% of males with AZFc deletions and an azoospermia in ejaculate have sperms in testis.*

### 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.

*The probability to find an AZF deletion in cases with non-obstructive azoospermia and normal karyotype is 15-20%. In cases with severe oligozoospermia this probability is 7-10%.*

#### 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%, because reduced penetrance is only rarely observed.*

#### 3.5 Positive clinical predictive value

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

*Nearly 100%, because reduced penetrance is only rarely observed.*

#### 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:

*not applicable*

Index case in that family had not been tested:

*not applicable*

## 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

*not applicable*

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

*not applicable*

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

no

yes

Therapy (please describe)

*In about half of the males with AZFc deletions sperms can be found on TESE. Therefore, a prior AZF analysis is useful.*

Prognosis (please describe) *see above*

Management (please describe) *see above*

#### **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?

*No.*

If the test result is positive (please describe)

*not applicable*

If the test result is negative (please describe)

*not applicable*

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?

*Yes.*

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

*In most cases not.*

#### **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?

*not useful*

#### **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)

*In case of a pregnancy after ICSI/TESE therapy, a son will inherit the father's AZF deletion and will be infertile with high probability.*