deutsche gesellschaft für humangenetik e.v.

Indication Criteria for Genetic Testing
Evaluation of validity and clinical utility

german society of human genetics
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Ad hoc Committee „Indication Criteria for Genetic Testing“
Ad hoc-Kommission „Indikationskriterien für genetische Diagnostik“

Chairman of the Committee

Prof. Dr. med. Jörg Schmidtke,
Institute of Human Genetics
Hannover Medical School
Carl-Neuberg-Str. 1
30625 Hannover
Tel. 0049 (0)511-532 6538
Fax 0049 (0)511 532 5865
schmidtke.joerg@mh-hannover.de

Members of the Committee

Prof. Dr. med. Gabriele Gillessen-Kaesbach
Prof. Dr. med. Tiemo Grimm
Prof. Dr. med. André Reis
Prof. Dr. med. Eberhard Schwinger
Prof. Dr. med. Peter Wieacker
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gfh Council (§26 BGB)

Prof. Dr. med. André Reis, Erlangen
Prof. Dr. med. Olaf Riess, Tübingen
Prof. Dr. med. Evelin Schröck, Dresden

gfh Office

Dipl.-Soz. Christine Scholz
Inselkammerstr. 5
82008 München-Unterhaching
Tel. 0049 (0)89-61 45 69 59
Fax 0049 (0)89-55 02 78 56
organisation@gfhev.de

Banking account
Postbank München
Konto 231 394 805
BLZ 700 100 80
IBAN DE19 7001 0080 0231 3948 05
BIC PBNK DEFF

register of associations Munich
VR 12341

Indication criteria for disease:
XY type gonadal dysgenesis

1. General information on authorship

Name and address of institution:
Name: *Institute of Human Genetics, University of Münster*
Address: *Vesaliusweg 12-14*
Postcode: *D-48149*
City: *Münster*
Tel.: *+49-251-83-55401*
Fax: *+49-251-83-55431*
E-mail: *humangenetik@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. rer.nat. Gerd Scherer*
Tel.: *+49-761-270-7030*
Fax: *+49-761-270-7041*
E-mail: *gerd.scherer@humangenetik-freiburg.de*
Date: *29.11.2007*

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 Committee „Indication Criteria for Genetic Testing“
Date: 20.05.2008

Updated by
Date:

2. Disease characteristics

2.1 Name of the Disease (Synonyms):
XY type gonadal dysgenesis, Swyer syndrome

2.2 OMIM# of the Disease: *306100*
Beware: This OMIM assignment is misleading, because XY type gonadal dysgenesis due to SRY mutations is not an X-linked but a Y-chromosomally inherited disease.

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

2.4 OMIM# of the Gene(s): *480000*

2.5 Mutational Spectrum:
Deletions, point mutations, small rearrangements

2.6 Analytical Methods:
PCR, DNA sequencing

2.7 Analytical Validation
nearly 100%

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

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:
C: SRY mutations almost always are new mutations. However, siblings may be affected if there is gonadal mosaicism in the father.
D: Prenatal diagnosis may help to clarify a discrepancy between chromosomal sex (XY karyotype) and ultrasound imaging (female external genitalia), although such a discrepancy has also many other causes (e.g. androgen insensitivity, disorders of steroid hormone synthesis, other causes of XY gonadal dysgenesis, and syndromal disorders).

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)
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.
Female patients with XY gonadal dysgenesis have SRY mutations in 15-25%: About half are larger deletions, the rest point mutations or smaller rearrangements. Mutations also in some other genes cause XY gonadal dysgenesis. The symptoms of syndromal forms may lead to diagnosis.

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:
see 3.3

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

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)	*Patients with definite XY gonadal dysgenesis have a 20-30% risk of developing a gonadal tumor. Therefore, a prophylactic gonadectomy is indicated.*
Prognosis (please describe)	*see above*
Management (please describe)	*See above. Substitution with estrogen/gestagen combination.*

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?
Not applicable

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?
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.

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.