deutsche gesellschaft für humangenetik e.v.

Indication Criteria for Genetic Testing
Evaluation of validity and clinical utility

Indication criteria for disease:
Tuberous sclerosis (TSC) [TSC1, TSC2]

1. General information on authorship

Name and address of institution:
Name: *Zentrum für Humangenetik und Laboratoriumsmedizin Dr. Klein & Dr. Rost*
Address: *Lochhamer Str. 29*
Postcode: *D-82152*
City: *Martinsried*
Tel.: *089/8955780*
Fax: *089/89557878*
E-mail: *info@medizinische-genetik.de*
Internet: *www.medizinische-genetik.de*

Head of the institution:
Name: *Dr. med. Hanns-Georg Klein, Dr. med. Imma Rost*
Tel.: *089/8955780*
Fax: *089/89557878*
E-mail: *Hanns-Georg.Klein@medizinische-genetik.de*
Imma.Rost@medizinische-genetik.de

Author of this text, date:
Name: *Dr. rer. nat. Karin Mayer*
Tel.: *089/8955780*
Fax: *089/89557878*
E-mail: *Karin.Mayer@medizinische-genetik.de*
Date: *13.09.2007*

Reviewer, validation date:
Name: *Univ. Prof. Dr. Christa Fonatsch*
und ao. Univ. Prof. Dr. Katharina Wimmer
Tel.: *0043-1-4277-60601*
Fax: *0043-1-4277-9606*
E-mail: *christa.fonatsch@meduniwien.ac.at*
Date: *29.11.2007*

Translator, translation date:
Name: *Prof. Dr. Ulrich Langenbeck*
E-mail.: *Ulrich.Langenbeck@gmx.net*
Date: *25.8.2008*

Re-editor, date:
Name:
Tel.:
Fax:
E-mail:
Date:

Authorized by gfh Ad hoc Committee „Indication Criteria for Genetic Testing“
Date: 21.05.2008

Updated by
Date:

german society of human genetics
www.gfhev.de

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
Prof. Dr. med. Klaus Zerres
Prof. Dr. med. Johannes Zschocke

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

2. Disease characteristics

2.1 Name of the Disease (Synonyms): *Tuberous sclerosis (Tuberous sclerosis complex (TSC)), Bourneville-Pringle disease*

2.2 OMIM# of the Disease: *191100*

2.3 Name of the Analysed Genes or DNA/Chromosome Segments:
TSC1, TSC2

2.4 OMIM# of the Gene(s): *605284, 191092*

2.5 Mutational Spectrum:
Missense, nonsense, and splice mutations; insertions, deletions, genomic rearrangements, microdeletions, intragenic differences of gene dose / changes of copy number (duplications or deletions of one or more exons).
Presently, more than 250 different mutations are known for TSC1 and more than 750 for TSC2.

2.6 Analytical Methods:
For detection of point mutations and small insertions/deletions: Complete analysis of all coding regions and neighbouring intron sequences (splice sites) in genomic DNA, e.g. by direct sequencing or sequencing after DHPLC.
For detection of intragenic deletions and duplications with differences of gene dose: Analysis of both genes e.g. by MLPA (multiplex ligation dependent probe amplification) or quantitative PCR.
For detection of chromosomal rearrangements and microdeletions, particularly TSC2/PKD1 contiguous gene syndromes: e.g. FISH (fluorescence in situ hybridisation).

2.7 Analytical Validation
Direct sequencing of both DNA strands; sequence analysis after DHPLC or another method had yielded a conspicuous result; confirmation of results by a second DNA extraction or a second method; confirmation of intragenic or larger chromosomal deletions by a second method, e.g. quantitative PCR, long range PCR, FISH.

2.8 Estimated Frequency of the Disease in Germany
(Incidence at birth ("birth prevalence") or population prevalence):
birth prevalence 1:7.000.

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:

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)
Assuming a prevalence of 94% point mutations and of 6% intragenic deletions/duplications, microdeletions and rearrangements, germline mutations will be detected in more than 95% if both genes are analysed by multiple methods, including a deletion/duplication screen. Rare splice mutations of both genes in introns with non-conserved splice sites and with unknown prevalence are not detected by DNA based diagnostics, they can only be identified with RNA based methods.

3.2 **Analytical Specificity**
(proportion of negative tests if the genotype is not present)
close to 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.
70-85% if the diagnostic criteria of Roach et al (1998) are fulfilled (corresponding to "TSC established"), depending on the application of one or more analytical methods. Because of variable clinical expressivity lower sensitivities are possible, corresponding to "TSC likely" and "TSC possible".

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.
Possibly 100%

3.5 **Positive clinical predictive value**
(life time risk to develop the disease if the test is positive).
100% penetrance, but extremely variable clinical expressivity.

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:
almost 100%

Index case in that family had not been tested:
85%. This question arises in children who have no clinical symptoms yet, or in adults with minimal clinical symptoms such that the diagnosis cannot be made by clinical criteria alone.

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)

Through clinical and imaging investigations, the diagnosis of TSC can only be made if the diagnostic criteria make this diagnosis at least "likely". In genetic mosaics and in cases with manifestations in single organs only, a diagnosis may be arrived at if the tissue in question is available through surgery or biopsy. Also with weak clinical manifestations (e.g., only an angiomyolipoma (AML) of kidney) the diagnosis of TSC requires the positive detection of a causative mutation in lymphocytes. If the diagnostic criteria for TSC are not fulfilled in a symptomatic parent or another 1st degree relative of an affected person with identified mutation, a mutation analysis can secure the diagnosis.

4.1.2 Describe the burden of alternative diagnostic methods to the patient
During first diagnosis as well as after molecular confirmation of the clinical diagnosis, clinical and imaging investigations are required for follow-up in regular intervals. The lenghth of intervals depends on the clinical findings.

4.1.3 How ist the cost effectiveness of alternative diagnostic methods to be judged?
Not known.

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

No. ☐

Yes. ☒

Therapy (please describe)	*Therapy with mTOR inhibitors (rapamycin, certican) is useful only if signal transduction is disturbed by a TSC1 or TSC2 mutation. Women with a TSC2 mutation have an increased risk to develop lymphangioleiomyomatosis (LAM). Therefore, caution is advisable on implementation of hormonal contraception.*
Prognosis (please describe)	*Different organ manifestations depending on the TSC gene involved. Thus, a pulmonary LAM occurs only in women with a TSC2 mutation.*
Management (please describe)	*Regular interdisciplinary follow-up, adapted to the particular clinical manifestations. Integration into a multidisciplinary TSC clinic.*

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)
In regular intervals, specific follow-up investigations of the organ systems which are potentially involved in TSC. The length of the intervals depends on the clinical findings.

If the test result is negative (please describe)
No need of control investigations if a familial mutation has been excluded.

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)?
Regular interdisciplinary follow-up of the organ systems potentially involved in TSC if the index patient had not been investigated genetically.

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?
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. The genetic diagnosis significantly contributes to classification of the disease if the diagnostic criteria alone are not sufficient for securing the clinical diagnosis. A definite diagnosis is prerequisite for clinical prognosis, specific therapy and legal acceptance as severely disabled person. For many patients the definite genetic diagnosis of TSC ends an diagnostic odyssey. And, the correct diagnosis of TSC enables finding the "right" patient group.