deutsche gesellschaft für humangenetik e.v.

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Indication Criteria for Genetic Testing
Evaluation of validity and clinical utility

Indication criteria for disease:
Cranio-fronto-nasal syndrome (CFNS) [EFNB1]

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-muenter.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: *01.06.2007*

Reviewer, validation date:
Name: *Dr. Wolfram Kress*
Tel.: *+49-931-888-4064*
Fax: *+49-931-888-4069*
E-mail: *WKress@biozentrum.uni-wuerzburg.de*
Date: *18.06.2007*

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:

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
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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

Authorized by gfh Ad hoc Committee „Indication Criteria for Genetic Testing"

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2. Disease characteristics

2.1 Name of the Disease (Synonyms): *Cranio-fronto-nasal syndrome (CFNS)*

2.2 OMIM# of the Disease: *304110*

2.3 Name of the Analysed Genes or DNA/Chromosome Segments: *EFNB1*

2.4 OMIM# of the Gene(s): *300035*

2.5 Mutational Spectrum:
point mutations, deletions or insertions of a few nucleotides, larger deletions until gross deletions and 'contiguous gene syndromes'

2.6 Analytical Methods:
DNA sequencing, various methods for detection of deletions (e.g. PCR, Southern blot analysis)

2.7 Analytical Validation
nearly 100%, except for the possibility of undetected mosaics

2.8 Estimated Frequency of the Disease in Germany
(Incidence at birth ("birth prevalence") or population prevalence):
Unknown in Germany, more than 100 molecularly proven cases are published worldwide

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

2.10 Diagnostic Setting:

	Yes.	No.
A. (Differential)diagnostics	☒	☐
B. Predictive Testing	☐	☒
C. Risk assessment in Relatives	☒	☐
D. Prenatal	☒	☐

Comment: *Predictive diagnosis is not relevant because the anomalies are congenital. Molecular genetic diagnosis may be indispensible for risk assessment in relatives because e.g. male carriers may have mild or no physical signs.*

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3. Test characteristics

	genotype or disease	
	present	absent
test pos.	A	B
test 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%, if the diagnostics take into account the possible spectrum of mutations and if there is no mosaicism.

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.
Ca. 90%. Locus heterogeneity cannot be excluded yet.

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% in females. Males typically express only mild symptoms that are easily overlooked, e.g. hypertelorism.

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:
nearly 100%

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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)	*Therapy is symptomatic, surgery of craniosynostosis and cosmetic surgery can be considered*
Prognosis (please describe)	*Prognosis of CFNS can be estimated more reliably with genetic analysis. E.g., agenesis of corpus callosum is not, as a rule, associated with mental retardation in this disease.*
Management (please describe)	*Targeted search for treatable symptoms, e.g. diaphragmatic hernia.*

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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)
No.

If the test result is negative (please describe)
No.

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)?
none

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?
This question is not relevant because the anomalies are congenital.

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)
The diagnostics has consequences for patients and relatives (see 4.1.4 and 4.3). And, generally, a certain diagnosis is a value in itself.