deutsche gesellschaft für humangenetik e.v.

Indication Criteria for Genetic Testing
Evaluation of validity and clinical utility

Indication criteria for disease:
Hemochromatosis [HFE]

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2. Disease characteristics

2.1 Name of the Disease (Synonyms):
Hereditary Hemochromatosis (Hemochromatosis type 1)

2.2 OMIM# of the Disease: *235200*

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

2.4 OMIM# of the Gene(s): *235200*

2.5 Mutational Spectrum:
In the German population, almost 90% of those afflicted with hemochromatosis are homozygous for the mutation C282Y (ref. [1]). Ca. 3.6% of the patients are compound heterozygotes for the mutations C282Y and H63D. In ca. 7% of the patients only a single or none of the above mutations is found. Overall, ca. 20 different mutations in the HFE gene have been described til now. The prevalence of most of these mutations is unknown in the different populations. Also their clinical significance is not always known.

2.6 Analytical Methods:
A greater number of reliable techniques is available for the moleculecular genetic diagnostics of hemochromatosis. The mutations C282Y and H63D can be detected e.g. by PCR, restriction digest and agarose gel electrophoresis (RFLP diagnostics). Several suppliers offer commercial kits.

2.7 Analytical Validation
Internal validation by testing known mutations, external validadion through proficiency tests. During the Hannover pilot study of hemochromatosis screening (ref. [2]) several test characteristics had been validated (see point 3).

2.8 Estimated Frequency of the Disease in Germany
(Incidence at birth ("birth prevalence") or population prevalence):
Prevalence of at risk genotypes: 2-5/1,000. Penetrance of the genotype is incomplete: With increasing age, the majority of the homozygotes manifests conspicuous laboratory parameters of iron metabolism, but only part of the homozygotes develop the clinical manifestations of hemochromatosis. The penetrance is higher in males (percent figures differ widely, however, because of differing study designs).

2.9 If applicable, prevalence in the ethnic group of investigated person:
The prevalence in non-European populations is significantly less.

2.10 Diagnostic Setting:

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

Comment: *Predictive diagnostics only after age 18.*

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)
97% (ref. [2])
98.4% (ref. [3])

3.2 **Analytical Specificity**
(proportion of negative tests if the genotype is not present)
100% (ref. [2])
99.8% (ref. [3])

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.
90%

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.
ca. 99%

3.5 **Positive clinical predictive value**
(life time risk to develop the disease if the test is positive).
Ca. 1% for the full clinical picture.
Ca. 20-50% for manifestation of symptoms that are typical of hemochromatosis.

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:
practically 100%

Index case in that family had not been tested:
98%

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)	*liver biopsy*

4.1.2 Describe the burden of alternative diagnostic methods to the patient
The liver biopsy is a risky intervention which may be omitted if genetic data are available. It should only be performed after the genetic diagnostics and only if the results of the genetic test do not sufficiently explain the clinical state of the patient.

4.1.3 How ist the cost effectiveness of alternative diagnostic methods to be judged?
The costs differ depending on the state of the disease. An early genetically proven diagnosis helps to avoid later alternative and expensive diagnostics.

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

No. ☐

Yes. ☒

Therapy (please describe)	*Venesection therapy.*
Prognosis (please describe)	*Very good prognosis if venesection therapy is started early. The more the disease is progressed at diagnosis, the worse is the prognosis. Liver dysfunction is often reversible. Other symptoms, like for example arthropathies, cannot be cured in most cases. Life expectancy is normal if venesection therapy is started early.*
Management (please describe)	*At the time of diagnosis internistic checkup for possible organ involvement that may require specialist care. The venesection therapy can be performed/organised by the general practitioner, sometimes also by blood banks.*

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)
Healthy persons with a risk genotype may prevent manifestation of the disease by giving blood regularly.

If the test result is negative (please describe)
No prevention needed, reassurance of the test person.

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 biochemical follow-up (ferritin, transferrin saturation), venesection therapy if abnormal test results are obtained.

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?

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 immediate medical benefit is obvious in hemochromatosis, not only for the patients but also for their relatives ("cascade" screening for risk validation). Additional benefits can be seen with regard to planning for the future. In the Hannover pilot study of hemochromatosis screening, 70% of participants mentioned that they had gained personal benefits from the study (ref. [4]).

References:

[1] Graf & Stuhrmann, J. Lab. Med. 24: 229-235, 2000
[2] Stuhrmann et al., Eur. J. Hum. Genet. 13: 69-78, 2005
[3] Palomaki et al., Genet. Med. 5: 440-443, 2003
[4] Stuhrmann et al., Genet. Testing 9: 242-254, 2005