deutsche gesellschaft für humangenetik e.v.

Indication Criteria for Genetic Testing
Evaluation of validity and clinical utility

Indication criteria for disease:
Noonan syndrome
[PTPN11, SOS1, RAF1, KRAS]

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2. Disease characteristics

2.1 Name of the Disease (Synonyms):
Noonan syndrome (NS1, NS3, NS4, NS5), LEOPARD syndrome included

2.2 OMIM# of the Disease:
163950 (NS1), 609942 (NS3), 610733 (NS4), 611553 (NS5), 151100 (LEOPARD syndrome)

2.3 Name of the Analysed Genes or DNA/Chromosome Segments:
PTPN11, SOS1, RAF1, KRAS

2.4 OMIM# of the Gene(s):
176876, 182530, 164760, 190070

2.5 Mutational Spectrum:
The number of mutations differs between the genes (PTPN11: ~60, SOS1: ~25, RAF1: ~15, KRAS: ~15). Beside 2 in-frame deletions of a single PTPN11 codon, only missense mutations have been found, mostly located in certain mutation hotspots which correspond to protein domains. Truncating (nonsense, frameshift, and splice) mutations or larger deletions of one or more exons are hardly to be expected because of the gain-of-function mechanism of the disease.

2.6 Analytical Methods:
Direct coding exon sequencing of the causative genes, perhaps limited to given exons with known mutations.

2.7 Analytical Validation
Internal validation through analysis of known mutations. External validation through exchange of DNA control samples with other diagnostic institutions. Proficiency testing is not yet offered.

2.8 Estimated Frequency of the Disease in Germany
(Incidence at birth ("birth prevalence") or population prevalence):
The population prevalence is estimated as 1:2.000 to 1:3.000.

2.9 If applicable, prevalence in the ethnic group of investigated person:
No significant regional or ethnic differences of prevalence have been described.

2.10 Diagnostic Setting:

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

Comment: *Prenatal diagnosis may be indicated when a parent is affected or, with non-affected parents, if fetal abnormalities are found.*

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)
Almost 100%; will be less if only hot spot exons are analysed.

3.2 **Analytical Specificity**
(proportion of negative tests if the genotype is not present)
Almost 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.
With strict clinical-diagnostic criteria overall ~75-80%.
For the individual known genes:
PTPN11: 50%
SOS1: ~15-20%
RAF1: ~5-10%
KRAS: ~2-3%

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.
Almost 100%

3.5 **Positive clinical predictive value**
(life time risk to develop the disease if the test is positive).
Close to 100%.
The penetrance is almost complete, the expressivity, however, is highly variable. The clinical significance is negligible in mild cases and the facial phenotype can be subtle, particularly in adults. Therefore, the diagnosis may be unknown or never be made in a considerable, yet unestimated, number of mutation carriers.

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:
Approx. 80%, corresponding to the detection rate of mutations.
However, such a strategy is not meaningful as a rule.

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
Clinical examination, supplemented with cardio-sonography if necessary, puts no considerable burden upon the patient.

4.1.3 How ist the cost effectiveness of alternative diagnostic methods to be judged?
Clinical diagnosis is possible without high costs (clinical examination, supplemented with cardio-sonography if necessary).
Status of molecular-genetic diagnostics: Differential diagnosis; securing the diagnosis when clinical diagnosis is uncertain; identification of the causative mutation when a prenatal diagnosis is requested; prognostic statements about special risks associated with specific mutations.

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

No. ☐

Yes. ☒

Therapy (please describe)	*In given cases, the result will influence the indication of growth hormone therapy.*
Prognosis (please describe)	*Increased risk of leukemias and jawbone giant cell tumors (up to possible cherubism) in certain PTPN11 and KRAS mutations. Increased risk of hypertrophic-obstructive cardiomyopathy and arrhythmias with RAF1 mutations. Risk of bad hearing in LEOPARD syndrome typical mutations.*
Management (please describe)	*In given cases specific screening for prevention of cardiologic and hematologic complications. (No standards have been established for preventive management.)*

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?

If the test result is positive (please describe)

If the test result is negative (please describe)

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)?

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?

4.3.2 Can a genetic test in the index patient save genetic or other tests in family members?

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

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)
With only few exceptions, the result of the genetic diagnosis has no immediate medical consequences.
A possible benefit for patients and their relatives may already be the clarification of a diagnosis that could not be obtained definitely by other means. Additional investigations (e.g. for finding an explanation of a sometimes existing retarded development) can be spared. In genetic counseling, a definite recurrence risk can be communicated if the causative mutation is known.