deutsche gesellschaft für humangenetik e.v.

Indication Criteria for Genetic Testing
Evaluation of validity and clinical utility

Indication criteria for disease:
DiGeorge syndrome, Velocardio-facial syndrome 2, Shprintzen syndrome [22q11.2, TBX1; 10p13-p14]

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Date: 20.05.2008

Updated by
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2. Disease characteristics

2.1 Name of the Disease (Synonyms):
DiGeorge syndrome (DGS), velo-cardio-facial syndrome (VCFS), Shprintzen syndrome, DGS/VCFS spectrum 2 (DGS/VCFS2; similar phenotype), 22q11.2 micro-duplication syndrome (overlapping phenotype)

2.2 OMIM# of the Disease: *188400 (DGS), 192430 (VCFS), 601362 (DGS/VCFS2), 608363 (micro-duplication 22q11.2)*

2.3 Name of the Analysed Genes or DNA/Chromosome Segments:
22q11.2, TBX1; 10p13-p14

2.4 OMIM# of the Gene(s): *602054 (TBX1)*

2.5 Mutational Spectrum:
deletions in 22q11.2 and 10p13-p14 of variable location and size, duplications in 22q11.2, point mutations in TBX1

2.6 Analytical Methods:
normal cytogenetics, FISH, MLPA, quantitative PCR, array CGH, sequencing

2.7 Analytical Validation
parallel analysis of positive and negative controls, depending on method

2.8 Estimated Frequency of the Disease in Germany
(Incidence at birth ("birth prevalence") or population prevalence):
Prevalence at birth 1:5,000

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: -

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)
95%, depending on analytical method

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.
95%

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%, but expressivity of the disease is highly variable.
With conspicuous family history in the order of 95% (mosaics).
With uninformative family history nearly 100%.

Remark: In familial cases, mosaics may be found in 'healthy' persons, and complete deletions may be associated with a 'normal' phenotype. However, as a rule, also 'healthy'deletion carriers manifest minimal symptoms.

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

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:
can only be clarified through analysis of the non-affected person

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)	*Calcium supplementation, treatment of gastro-esophageal reflux*
Prognosis (please describe)	*moderate*
Management (please describe)	*Prevention of complications (e.g. from immunodeficiency), specific checkups of relevant organ systems, support of development, very complex care by experienced pediatricians, social support through patient organisations.*

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)
Yes, see 4.1.4

If the test result is negative (please describe)
Depends on clinical manifestation

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)?
No special options.

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, but only when the relatives are tested too.

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?
Unaffected or only minimally affected relatives can be diagnosed by the test and then profit from preventive measures (e.g. calcium). If a deletion ist detected in a parent, a prenatal diagnosis is possible in a subsequent pregnancy.

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, parents are certain about the cause of the disease and patients profit from specific therapies and checkups.