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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Retinoblastoma

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)
Retinoblastoma.

1.2 OMIM# of the disease
180200.

1.3 Name of the analysed genes or DNA/chromosome segments
RB1.

1.4 OMIM# of the gene(s)
180200.

1.5 Mutational spectrum
Germline mutations: point mutations, deletions, insertions. Somatic mutations (tumour only): point mutations, deletions, insertions, epigenetic silencing (somatic), chromosomal rearrangements (somatic loss of heterozygosity).

1.6 Analytical methods
Chromosome analysis, FISH, sequence analysis, MLPA/quantitative multiplex PCR, testing for loss of heterozygosity, methylation analysis.

Addendum:

(1) RB1 testing is proposed for all patients with a retinoblastoma diagnosis irrespective of the nature at the time of presentation (unilateral, bilateral, sporadic, familial).

(2) In patients with retinoblastoma who also present with dysmorphic features and/or developmental delay chromosomal analysis, FISH or array CGH analysis is performed first.

(3) If tumour tissue is available, the aim is to determine the mutations that inactivate the two RB1 alleles (either two somatic mutations or one somatic mutation and a germline mutation). Analytical methods for the study of DNA from tumours include sequence analysis, MLPA/quantitative multiplex PCR, testing for loss of heterozygosity and methylation analysis.

Following identification of the mutations that inactivate the two RB1 alleles, constitutional DNA (for example, extracted from blood) is tested for the presence of these mutations.

(4) If no tumour tissue is available, the aim is to determine a mutation that inactivates one of the two RB1 alleles. Analytical methods for the study of DNA from blood include sequence analysis and MLPA/quantitative multiplex PCR.

(5) Mutational mosaicism is not uncommon in patients with isolated (sporadic) retinoblastoma. Methods for mutation detection in DNA from blood must be sensitive enough to permit the detection of mutant alleles present in only a fraction of the DNA analysed.

1.7 Analytical validation
In some cases (for example, single-exon deletions detected by MLPA), the results of semiquantitative methods should be confirmed by an independent technique (long-range PCR – sequencing, RNA analysis, segregation of genetic variation).

1.8 Estimated frequency of the disease (incidence at birth ('birth prevalence') or population prevalence)
Prevalence of retinoblastoma: 1/15 000 to 1/20 000 (40% bilateral, 60% unilateral).

Hereditary retinoblastoma susceptibility present in 50% of patients (all familial cases, almost all sporadic bilateral cases, and 13% of unilateral cases).

1.9 If applicable, prevalence in the ethnic group of the investigated person
Not applicable.

1.10 Diagnostic setting

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

Comment:
Not applicable.

2. TEST CHARACTERISTICS

	Genotype or disease		A: True positives B: False positives	C: False negative D: True negative
	Present	Absent		
Test				
Positive	A	B	Sensitivity:	A/(A+C)
			Specificity:	D/(D+B)
Negative	C	D	Positive predictive value:	A/(A+B)
			Negative predictive value:	D/(C+D)

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2.1 Analytical sensitivity
(proportion of positive tests if the genotype is present)
95% (identification of the pathogenic mutation in one allele of the RB1 gene in the DNA of blood of a patient with hereditary retinoblastoma).[1]

2.2 Analytical specificity
(proportion of negative tests if the genotype is not present)
100%.

2.3 Clinical sensitivity
(proportion of positive tests if the disease is present)
95% (identification of a pathogenic mutation in one allele of the RB1 gene in the DNA of blood of a patient with hereditary retinoblastoma).[1]

2.4 Clinical specificity
(proportion of negative tests if the disease is not present)
100% (no pathogenic mutation of the RB1 gene in DNA is identified in the DNA of blood of an individual who has no hereditary retinoblastoma).

2.5 Positive clinical predictive value
(lifetime risk to develop the disease if the test is positive)
Average 90% (penetrance of hereditary retinoblastoma).[2,3]

2.6 Negative clinical predictive value
(probability of not developing 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:
100% if a mutation is identified for index case.

Index case in that family had not been tested:
Not determined.

3. CLINICAL UTILITY

3.1 (Differential) diagnosis: The tested person is clinically affected
(To be answered if in 1.10 'A' was marked)

3.1.1 Can a diagnosis be made other than through a genetic test?

No	☒ (continue with 3.1.4)	
Yes	☐	
	Clinically	☐
	Imaging	☐
	Endoscopy	☐
	Biochemistry	☐
	Electrophysiology	☐
	Other (please describe)	

3.1.2 Describe the burden of alternative diagnostic methods for the patient
Not applicable.

3.1.3 How is the cost-effectiveness of alternative diagnostic methods to be judged?
Not applicable.

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

No	☐	
Yes	☒	
	Therapy (please describe)	
	Prognosis (please describe)	
	Management (please describe)	If hereditary retinoblastoma is established in a child with isolated unilateral retinoblastoma, then intensifying the surveillance of the remaining eye should be considered.

3.2 Predictive setting: The tested person is clinically unaffected but carries an increased risk based on family history
(To be answered if 'B' was marked in 1.10)

3.2.1 Will the result of a genetic test influence lifestyle and prevention?
If the test is positive, an eye examination is to be carried out every 3–4 weeks until the age of 1 year, after which every 2–3 months until the age of 5 years; thereafter, an annual examination for lifetime is recommended; young and/or uncooperative children usually require examination under anaesthesia. To detect second non-ocular tumours in individuals with retinoblastoma, physicians and parents should promptly evaluate complaints of bone pain or lumps because of the high risk of sarcomas; however, there are no specific guidelines. Agents/circumstances to avoid limiting exposures to DNA-damaging agents (radiotherapy, tobacco, and UV light) may reduce the excess cancer risks in hereditary retinoblastoma survivors. Testing of relatives at risk: Use of molecular genetic testing for early identification of asymptomatic at-risk children in a family improves diagnostic certainty and reduces the need for costly screening procedures in those at-risk family members who have not inherited the disease-causing mutation.[4]

If the test result is negative (please describe):
If the test is negative, surveillance is not required.

3.2.2 Which options in view of lifestyle and prevention does a person at-risk have if no genetic test has been carried out (please describe)?
Eye examination every 3–4 weeks until the age of 1 year and then less frequently until the age of 5 years is recommended; young and/or uncooperative children usually require examination under anaesthesia. To detect second non-ocular tumours in individuals with retinoblastoma, physicians and parents should promptly evaluate complaints of bone pain or lumps because of the high risk of sarcomas; however, no specific screening protocols exist. Limitation exposures to DNA-damaging agents (radiotherapy, tobacco and UV light) may reduce the excess cancer risks in hereditary retinoblastoma survivors. Testing of relatives at risk: Use of molecular genetic testing for early identification of asymptomatic at-risk children in a family improves diagnostic certainty and reduces the need for costly screening procedures in those at-risk family members who have not inherited the disease-causing mutation.

3.3 Genetic risk assessment in family members of a diseased person
(To be answered if in 1.10 'C' was marked)

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?
Yes:

– if a germline mutation is found, genetic testing clarifies the risk for all family members.[4]

– if two mutations are found in the tumour and the patient is not heterozygous for either of these mutations, then these mutations would have occurred in somatic cells, that is, neither of them are inherited from parents (post-zygotic mutations). No further tests and screening are recommended for siblings. The patient's offspring is still at risk (possible somatic mosaicism).

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Yes: identification of two post-zygotic mutations in a patient (see 3.3.1).

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
Yes.

3.4 Prenatal diagnosis
(To be answered if in 1.10 'D' was marked)

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnosis?
Yes (identification of germline mutations in a patient with hereditary retinoblastoma).

4. 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 for his/her relatives? (Please describe).

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