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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*)

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)
HNPCC/Lynch syndrome.

1.2 OMIM# of the disease
120435.

1.3 Name of the analysed genes or DNA/chromosome segments
MLH1, *MSH2*, *MSH6*, and *PMS2*.

1.4 OMIM# of the gene(s)
MLH1 (NM_000248, U07418), MSH2 (NM_000251, U03911), MSH6 (NM_000179, U54777), PMS2 (NM_000535).

1.5 Mutational spectrum
Point mutations, large deletions and duplications, promoter methylation.

1.6 Analytical methods
Stepwise analyses:

(1) Clinical selection[1]: Lynch-related cancer (colon, rectum, endometrium, urinary tract, small bowel, biliary tract, ovary, stomach). Sporadic before 50 years of age, first-degree relative or prior Lynch-related cancer.
(2) Study of MMR function in tumour cells[2]: microsatellite DNA analysis—genotyping of the consensus panel of five mononucleotidic repeats defined in 1998. Immunohistochemical study of the four mismatch repair proteins MLH1, MSH2, MSH6, and PMS2 (in case of MSI or in the absence of genotyping). *BRAF* codon 600 characterisation by pyrosequencing, sequencing, TaqMan, SNaPshot, and so on (in case of absence of the MLH1 protein).
(3) Germline analysis[3]: *MSH2* and/or *MLH1* screening for point mutations by pre-screening (DHPLC) or direct sequencing, and for large genomic anomalies by MLPA including promoter regions and *EPCAM* gene. *MSH6* or *PMS2* screening for point mutations by pre-screening or direct sequencing, and for large genomic anomalies by MLPA (in case of negative results for *MSH2/MLH1* screening, according to the tumour MMR status). *MLH1* promoter methylation characterisation by MSP, bisulphite pyrosequencing (useful for diagnostic purpose, not for predictive testing).

1.7 Analytical validation
Confirmation of mutation in an independent biological sample of the index case or an affected relative.

In case of deletion/duplication of one exon, confirm with a second technique/kit based on different primers.

1.8 Estimated frequency of the disease in Germany (incidence at birth ('birth prevalence') or population prevalence)
Prevalence in colorectal cancer patients about 1–3%.
Prevalence in population about 1:500–1:1000.

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

1.10 Diagnostic setting

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

2. TEST CHARACTERISTICS

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

2.1 Analytical sensitivity
(proportion of positive tests if the genotype is present)
Nearly 100%.

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2.2 Analytical specificity
(proportion of negative tests if the genotype is not present)
Above 95%.

Assuming a complete screening of all genes.

Variants of unknown significance might be re-classified as deleterious a posteriori.

2.3 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 only a quantification can be made case by case.

Not high and dependent on the indication criteria.

Computed by predictive models.

2.4 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.

Depends on age and family history.

Above 95%.

2.5 Positive clinical predictive value
(lifetime risk to develop the disease if the test is positive)
About 80%.

2.6 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:
About 95% (lifetime risk of colorectal cancer, the most frequent Lynch-related cancer, is 4% in the general population).

Index case in that family had not been tested:
This is an unusual and not recommended approach.

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 to 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?
Likely, but no consensus reached yet.

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

3.2.1 Will the result of a genetic test influence lifestyle and prevention?
Yes.[4,5]

If the test result is positive (please describe):
Yearly/two-yearly colorectal cancer screening with complete colonoscopy and chromocolonoscopy with indigo-carmine from age 20 to 25.
Yearly gynaecological examination; transvaginal sonography in women starting at age 30.

If the test result is negative (please describe):
Intensified screening not required.
Screening as recommended for the general population (according to the country guidelines).

3.2.2 Which option in view of lifestyle and prevention does a person at risk have if no genetic test has been done (please describe)?
Yearly/two-yearly colorectal cancer screening with complete colonoscopy and chromocolonoscopy with indigo-carmine from age 20 to 25.

Yearly gynaecological examination; transvaginal sonography in women starting at age 30.

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, autosomal dominant inheritance.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Yes, recommendation for screening applies only to mutation carriers and persons at risk.

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 diagnostic?
Technically feasible, generally not recommended, may vary with national settings.

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 his/her relatives? (please describe)

Support for family life organisation.
Cause assessment of a severe disease, known to be transmissible to next generations.
Efficiency of subsequent clinical management.
Risk calculation of unaffected relatives.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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