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CLINICAL UTILITY GENE CARD UPDATE

Clinical utility gene card for: Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*) - update 2012

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Lynch syndrome/HNPCC.

1.2 OMIM# of the disease

276300, 613244.

1.3 Name of the analysed genes or DNA/chromosome segments

MLH1, MSH2, MSH6, PMS2, and *EPCAM.*

1.4 OMIM# of the gene(s)

MLH1 (120436), *MSH2* (609309), *MSH6* (600678), *PMS2* (600259), *EPCAM* (185535).

1.5 Mutational spectrum

Point mutations, large deletions and duplications, large genomic insertions and promoter methylation.

1.6 Analytical methods

Stepwise analyses:

1. Clinical selection according to the Amsterdam II criteria and revised Bethesda guidelines.[1,2]
2. Study of MMR function in tumour cells[3,4]: Immunohistochemical (IHC) study of the four mismatch repair proteins MLH1, MSH2, MSH6, and PMS2. In case of absence of the MLH1 protein, *BRAF* codon 600 characterisation by pyrosequencing, sequencing, TaqMan, SNaPshot, and so on and somatic methylation analysis of the *MLH1* promotor could help to distinguish sporadic from Lynch-associated cancers. In case of an ambiguous result in immunohistochemistry, microsatellite DNA analysis – genotyping of the consensus panel of five mononucleotidic repeats defined in 1998 should be performed additionally[5] (pathogenic missense mutation might be missed without microsatellite analysis[6]). May vary with national settings.
3. Germline analysis[7,8]: The pattern of staining in IHC is suggestive for the underlying gene defect (loss of MLH1/PMS2 – analysis of *MLH1*; loss of MSH2/MSH6 – analysis of *MSH2*; isolated loss of MSH6 – analysis of *MSH6*; isolated loss of PMS2 – analysis of *PMS2*). Germline analysis should include search for point mutations and large genomic deletions/duplications/insertions (e.g., by pre-screening (DHPLC), direct sequencing on gDNA or cDNA level, MLPA including promoter regions and *EPCAM* gene, Southern blot analysis). Mutation analysis of PMS2 should include the analysis on RNA.[9] Germline *MLH1* promoter methylation characterisation by MSP, bisulphite pyrosequencing, or MLPA (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 (Incidence at birth ('birth prevalence') or population prevalence)

Prevalence in colorectal cancer patients about 1–3%.[10]

Estimated prevalence in population about 1:660–1:2000.[11]

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	☒	☐

Comment: Prenatal diagnostic may vary with national settings.

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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)

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

(in case of mutation analysis in the coding area, common splice sites, large genomic deletions/duplications).

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

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 a quantification can only be made case by case.

Not high. Dependent on the indication criteria and the molecular strategy used (primary screening with MSI and IHC or not). Computed by predictive models.[12]

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.

Unknown.

The test has no clinical specificity that goes beyond the analytical specificity (see 2.2) since it is not a test for cancer but for cancer risk.

2.5 Positive clinical predictive value
(life-time risk to develop the disease if the test is positive)
Up to ~80%. Dependent, for example, on the affected *MMR* gene and gender.[13]

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:

The index case in a family has usually already developed cancer before the genetic test.

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?

No ☐	
Yes ☒	
Therapy (please describe)	Likely, but no consensus reached yet.[14]
Prognosis (please describe)	CRCs with MSI have a significantly better prognosis compared with those with intact mismatch repair.[15]
Management (please describe)	Offer for prophylactic hysterectomy and bilateral salpingo-oophorectomy in women who have a pathogenic germline mutation for Lynch syndrome as an option for cancer prevention after a woman's family is completed.[16,17] Method of operation (e.g., segmental resection versus total colorectal resection with ileorectal anastomosis in case of colorectal cancer).[13] May vary with national settings.

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?
If the test result is positive (please describe):

Yes.[18,19] Yearly/two-yearly colorectal cancer screening with complete colonoscopy (and chromocolonoscopy with indigo-carmine) from age 20 to 25. May vary with national settings.

Yearly gynaecological examination; transvaginal sonography in women starting at age 30. May vary with national settings.

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 options 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. May vary with national settings.

Yearly gynaecological examination; transvaginal sonography in women starting at age 30. May vary with national settings.

Cancer prevention with Aspirin under investigation.[14]

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 diagnosis?
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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