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Gene	Disease (MONDO ID)	Transcript
MLH1	Lynch syndrome 1 (MONDO: 0007356)	NM_000249.3
MSH2	Lynch syndrome 1 (MONDO: 0007356)	NM_000251.2
MSH6	Lynch syndrome 1 (MONDO: 0007356)	NM_000179.2
PMS2	Lynch syndrome 1 (MONDO: 0007356)	NM_000535.5

PATHOGENIC CRITERIA		
Criteria	**Criteria Description**	**Specification**
VERY STRONG CRITERIA		
PVS1	Nonsense/frameshift variant introducing Premature Termination Codon (PTC)[a]: 1) ≤ codon 753 in *MLH1* 2) ≤ codon 891 in *MSH2* 3) ≤ codon 1341 in *MSH6* 4) ≤ codon 798 in *PMS2* Refer to Appendix for details.	Gene-Specific
PVS1	Large genomic alterations[a] of single or multi-exon size, specifically: Large genomic deletions OR	General recommendation

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	Large genomic duplications shown by laboratory studies (which define the breakpoints of the duplication) to result in a frameshift before the last splice junction. OR Large genomic duplications shown by laboratory studies (which define the breakpoints of the duplication) to result in an in-frame insertion disrupting a functional domain[b] or protein conformation.	
PVS1	Variants at IVS±1 or IVS±2[a,c] where exon skipping or use of a cryptic splice site disrupts reading frame and is predicted to undergo NMD. Not to be combined with PP3 and not to be used for a confirmed splice defect (see PVS1 for variants where patient mRNA assays indicate splicing aberration). If exon skipping or use of a cryptic splice site preserves reading frame and the altered region is critical to protein function[b] then use PVS1_Strong. If exon skipping or use of a cryptic splice site disrupts reading frame and is NOT predicted to undergo NMD then use PVS1_Moderate.	General recommendation

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PVS1	Variants where mRNA assays using RNA derived from patient constitutional biological samples indicate that the variant allele results in a splicing aberration (with evidence that the variant allele produces no full-length/reference transcript) leading to premature stop codon or in-frame deletion disrupting a functional domain[b] or protein conformation. Splicing aberration must be confirmed in a minigene assay or an additional RNA assay from an independent laboratory if it is not a predicted splice site mutation.	General recommendation
PVS1	Variants in the initiation codon of *MLH1*. For *MSH2* further ATGs exist inframe in exon 1, so this criterion is not applicable at any evidence weight.	Gene-Specific
PS1_VeryStrong	A predicted missense substitution that encodes the same amino acid change with a different underlying nucleotide change as a previously established Class 5 pathogenic missense variant with normal RNA result*, and is absent from appropriate population control reference groups[d] *Otherwise, if the previously established Class 5 pathogenic missense variant truly is a splice defect, the new missense variant also has to be investigated on a functional level for RNA splicing. If the previously classified variant is Class 4, then use PS1_Moderate but the variant being classified cannot exceed Class 4.	General recommendation, Strength
STRONG CRITERIA		
PVS1_Strong	Variants in the initiation codon of *MSH6* or *PMS2*. For *MSH2* further ATGs exist inframe in exon 1, so this criterion is not applicable at any evidence weight.	Gene-Specific, Strength
PVS1_Strong	Presumed by default in tandem duplication of ≥1 exon resulting in a frameshift before the last splice junction. This rule does not apply for variants that involve the UTR (i.e. exon 1 or last exon) and whole gene duplications.	Strength

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PVS1_Strong	G>non-G at last base of exon if first 6 bases of the intron are not GTRRGT. If confirmed to cause a splice defect, then PVS1 should be used instead.	Strength
PVS1_Strong	Variants at IVS±1 or IVS±2[a,c] where exon skipping or use of a cryptic splice site preserves reading frame and the altered region is critical to protein function[b]. Not to be combined with PP3 and not to be used for a confirmed splice defect (see PVS1 for variants where patient mRNA assays indicate splicing aberration).	Strength
PS1	A predicted missense substitution that encodes the same amino acid change with a different underlying nucleotide change as a previously established Class 5 pathogenic missense variant (RNA not tested and not a predicted splice defect).	General recommendation
PS2	*De novo* variants with both maternity and paternity confirmed in a case with MMR deficient LS spectrum tumour[f] (i.e. MSI/immunoloss consistent with affected gene, with no *MLH1* methylation in tumor tissue, with the exception of *MLH1* constitutional promoter methylation. If there is no tumour data, see PS2_Moderate). Refer to Appendix for protein expression consistent with variant location. **2 points per proband** – can be combined with PS2/PM6 points to increase evidence strength as per Table 1	Disease-Specific
PS3	CIMRA[1] Functional Odds for Pathogenicity > 18.7[2] OR MMR function defect following Figure 1 flowchart OR	Disease-Specific

	Variants with monoallelic expression: complete loss of expression (<10% of wild-type in cDNA without puromycin) of the variant allele. Full-length transcript should be analysed with and without NMD block[3]	
PS4	*The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls.*	*N/A*
PP1_Strong	Co-segregation with disease in pedigree(s) with a combined* Bayes Likelihood Ratio[h] >18.7[2] in ≥2 families. *For multiple pedigrees, results are combined. Recommended segregation analysis tool: COOL[4] (COsegregation OnLine) v2 http://fengbj-laboratory.org/cool2/manual.html	Strength
PP4_Strong	≥3 independent CRC/Endometrial MSI-H tumours in ≥2 families using a standard panel of 5-10 markers[g] **and/or** loss of MMR protein expression consistent with the variant location. MSI-H tumour with inconsistent protein expression does not meet PP4_Strong. For *MLH1* variants, *MLH1* promoter methylation is to be excluded in the tumours. Refer to Appendix for protein expression consistent with variant location.	Strength
MODERATE CRITERIA		
PVS1_Moderate	Nonsense/frameshift variant introducing premature termination codon in codons 754,755 or 756 in *MLH1*; between codons 892 & 934 in *MSH2*; between codons 1342 & 1360 in MSH6; between codons 799 & 862 in *PMS2*. Refer to Appendix for details.	Gene-Specific, Strength
PS1_Moderate	A predicted missense substitution that encodes the same amino acid change with a different underlying nucleotide change as a previously established Class 4 likely pathogenic missense variant with normal RNA	Strength

	result*, and is absent from appropriate population control reference groups[d] *Otherwise, if the previously established Class 4 likely pathogenic missense variant truly is a splice defect, the new missense variant also has to be investigated on a functional level for RNA splicing. If the previously classified variant is Class 5, then use PS1_VeryStrong but the variant being classified cannot exceed Class 4.	
PS2_Moderate	*De novo* variants with both maternity and paternity confirmed in a case with LS spectrum tumour[f] (with no tumor data for MSI/immunoloss/methylation, otherwise see PS2) **1 point per proband** – can be combined with PS2/PM6 points to increase evidence strength as per Table 1**.**	Strength
PM1	*Located in a mutational hot spot and/or critical and well-established functional domain.*	*N/A*
PM3	Co-occurrence (in trans/phase unknown) with a known pathogenic/likely pathogenic sequence variant in the same gene in a patient with clinical features consistent with CMMRD and/or documented MMR deficiency in normal cells[e] (Table 3 and Table 4) Use CMMRD "Indication criteria" from Table 3. If ≥3 points then it is consistent with CMMRD. Ancillary testing used to support a diagnosis of CMMRD are listed in Table 4. To use PM3 criteria, the variant has to meet PM2_Supporting criteria. Classification/zygosity of other variant	Disease-Specific

	Pathogenic/Likely Pathogenic *in trans*: 1.0 point; Pathogenic/Likely Pathogenic - phase unknown: 0.5 points Homozygous occurrence (max points from homozygotes = 1.0): 0.5 points Sum all cases with the above evidence to determine the PM3 strength as per Table 2.	
PM4	*Protein length changes due to in-frame deletions/insertions in a non-repeat region or stop-loss variants.*	*N/A*
PM5	Missense change at an amino acid residue where a different missense change was classified as Class 5 pathogenic on the protein level and not due to aberrant splicing. Only use PM5 if PP3 is supporting for the missense change. Use PM5_Supporting if other variant is Class 4 due to a missense alteration. OR Variants affecting the same splice site as a confirmed splice variant with similar or worse splicing *in silico* predictions (recommended splicing algorithms: MaxEntScan, NNSplice, SpiceAI or refer to MMR splicing predictions from http://priors.hci.utah.edu/PRIORS)	General recommendation
PM6	Assumed *de novo* with maternity and/or paternity unconfirmed in a case with LS spectrum tumour[f] (No tumor data for MSI/immunoloss/methylation)	Disease-Specific

	0.5 points per proband – can be combined with PS2/PM6 points to increase evidence strength as per Table 1	
PP1_Moderate	Co-segregation with disease in pedigree(s) with a combined* Bayes Likelihood Ratio[h] >4.3 & ≤18.7[2] *For multiple pedigrees, results are combined. Recommended segregation analysis tool: COOL[4] (COsegregation OnLine) v2 http://fengbj-laboratory.org/cool2/manual.html.	Strength
PP3_Moderate	Missense variant with MAPP+PolyPhen-2 prior probability for pathogenicity >0.81 See http://priors.hci.utah.edu/PRIORS	Strength
PP4_Moderate	2 independent CRC/Endometrial MSI-H tumours using a standard panel of 5-10 markers[g] **and/or** loss of MMR protein expression consistent with the variant location. MSI-H tumour with inconsistent protein expression does not meet PP4_Moderate. For *MLH1* variants, *MLH1* promoter methylation is to be excluded in the tumours. Refer to Appendix for protein expression consistent with variant location.	Strength
PS3_Moderate	CIMRA[1] Functional Odds for Pathogenicity >4.3 and <= 18.7[2]	Strength
SUPPORTING CRITERIA		
PM2_Supporting	Absent/extremely rare (<1 in 50,000 alleles) in gnomAD using the non-cancer dataset.	Disease-Specific, Strength
PP1	Co-segregation with disease in pedigree(s) with a combined* Bayes Likelihood Ratio[h] >2.08 & ≤4.3[2] *with multiple pedigrees, results are combined.	Disease-Specific

	Recommended segregation analysis tool: COOL[4] (COsegregation OnLine) v2 http://fengbj-laboratory.org/cool2/manual.html.	
PP2	*Missense variant in a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease.*	*N/A*
PP3	Missense with MAPP+PolyPhen-2 prior probability for pathogenicity >0.68 & ≤0.81 See http://priors.hci.utah.edu/PRIORS OR Predicted splice defect using http://priors.hci.utah.edu/PRIORS OR Predicted splice defect using recommended splicing algorithms: MaxEntScan, NNSplice, SpiceAI.	Disease-Specific
PP4	1 CRC/Endometrial MSI-H tumour using a standard panel of 5-10 markers[g] **and/or** loss of MMR protein expression consistent with the variant location. MSI-H tumour with inconsistent protein expression does not meet PP4. For *MLH1* variants, *MLH1* promoter methylation is to be excluded in the tumour. Refer to Appendix for protein expression consistent with variant.	Disease-Specific
PS3_Supporting	CIMRA[1] Functional Odds for Pathogenicity >2.08 and <= 4.3[2]	Strength

PM5_Supporting	Missense change at an amino acid residue where a different missense change was classified as Class 4 likely pathogenic on the protein level and not due to aberrant splicing. Only use PM5_Supporting if PP3 is supporting for the missense change. Use PM5 if other variant is Class 5 due to a missense alteration.	General recommendation
PP5	*Reputable source recently reports variant as pathogenic but the evidence is not available to the laboratory to perform an independent evaluation*	*N/A*

BENIGN CRITERIA		
Criteria	**Criteria Description**	**Specification**
STAND ALONE CRITERIA		
BA1	Variant reported to occur in control reference groups[d] above Maximum Credible Allele Frequency (MCAF) cutoffs and excluded as founder pathogenic sequence variants (use continental-scale population frequency on gnomAD to exclude founder effect). For gnomAD, compare MCAF to the Filtering Allele Frequency from the non-cancer dataset. MCAF Cutoffs: *MLH1*: 0.001 (0.1%) *MSH2*: 0.001 (0.1%) *MSH6*: 0.0022 (0.22%) *PMS2*: 0.0028 (0.28%)	Gene-Specific
STRONG CRITERIA		

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BS1	Variants present in control reference groups[d] within the Maximum Credible Allele Frequency (MCAF) cutoffs. For gnomAD, compare MCAF to the Filtering Allele Frequency from the non-cancer dataset. MCAF Cutoffs: *MLH1*: 0.0001-0.001 (0.01-0.1%) *MSH2*: 0.0001-0.001 (0.01-0.1%) *MSH6*: 0.00022-0.0022 (0.022-0.22%) *PMS2*: 0.00028-0.0028 (0.028-0.28%) OR Variants reported to occur in control reference groups[d] above Maximum Credible Allele Frequency (MCAF) cutoffs and not yet excluded as founder pathogenic sequence variants (use continental-scale population frequency on gnomAD to exclude founder effect). For gnomAD, compare MCAF to the Filtering Allele Frequency from the non-cancer dataset. MCAF Cutoffs: *MLH1*: 0.001 (0.1%) *MSH2*: 0.001 (0.1%) *MSH6*: 0.0022 (0.22%) *PMS2*: 0.0028 (0.28%)	Gene-Specific
BS2	Co-occurrence *in trans* with a known pathogenic sequence variant in the same gene in a patient with colorectal cancer after age 45 (or other LS cancer above the median age of onset for that cancer in LS[f]), and who has no previous or current evidence of clinical manifestations of CMMRD – Refer to Table 3 for clinical features of CMMRD.	Disease-Specific

BS3	Variant-specific proficient function in protein and mRNA-based lab assays as per MMR functional assay flowchart in Figure 1. OR Synonymous substitutions and intronic variants with no associated mRNA aberration (either splicing or allelic imbalance) as determined by laboratory assays conducted with nonsense-mediated decay inhibition. Whenever abnormal transcripts are identified at similar levels in controls they will be considered naturally occurring isoforms and not mRNA aberrations. OR CIMRA[1] Functional Odds for Pathogenicity ≤ 0.05[2]	Disease-Specific
BS4	Lack of co-segregation with disease in pedigree(s) with a combined* Bayes Likelihood Ratio[h] <0.05[2] *For multiple pedigrees, results are combined. Recommended segregation analysis tool: COOL[4] (COsegregation OnLine) v2 http://fengbj-laboratory.org/cool2/manual.html	Disease-Specific
BP5_Strong	≥ 4 tumours: CRC/Endometrial tumours with MSS and/or no loss of MMR protein expression and/or LS spectrum tumours[f] with loss of MMR protein(s) that is inconsistent with the gene demonstrating genetic variation. OR	Strength

	≥2 BRAF V600E (CRC only)/*MLH1* methylation (in tumour only) with MSI-H/*MLH1* loss.	
SUPPORTING CRITERIA		
BP1	*Missense variant in gene where only LOF causes disease*	*N/A*
BP2	*Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder; or observed in cis with a pathogenic variant in any inheritance pattern.*	*N/A*
BP3	*In-frame deletions/insertions in a repetitive region without a known function*	*N/A*
BP4	Missense variant with MAPP+PolyPhen-2 prior probability for pathogenicity <0.11 See http://priors.hci.utah.edu/PRIORS OR For intronic and synonymous variants: Predictions from http://priors.hci.utah.edu/PRIORS meet the following qualitative categories (if applicable, depending on the variant type): Reference Splice site information values of “improved” or “minimal” *De Novo* Donor site information is “Weak/Null & Low” or “Innocuous IFD” OR	Disease-Specific

	Recommended splicing algorithms (MaxEntScan, NNSplice, SpliceAI) suggest no impact on gene or gene product.	
BP5	2 or 3 tumours: CRC/Endometrial tumours with MSS and/or no loss of MMR protein expression and/or LS spectrum tumours[f] with loss of MMR protein(s) that is inconsistent with the gene demonstrating genetic variation. OR 1 BRAF V600E (Colon only)/*MLH1* methylation (in tumour only) with MSI-H/*MLH1* loss.	Disease-Specific
BP6	*Reputable source recently reports variant as benign but the evidence is not available to the laboratory to perform an independent evaluation*	*N/A*
BP7	A synonymous (silent) or intronic variant at or beyond +7/–21 (5′/3′ exonic) Variants may satisfy both BP7 and BP4.	General Recommendation
BS3_Supporting	CIMRA[1] Functional Odds for Pathogenicity >0.05 & ≤0.48[2]	Strength
BS4_Supporting	Lack of co-segregation with disease in pedigree(s) with a combined* Bayes Likelihood Ratio[h] >0.05 & ≤0.48[2] *with multiple pedigrees, results are combined. Recommended segregation analysis tool: COOL[4] (COsegregation OnLine) v2 http://fengbj-laboratory.org/cool2/manual.html	Strength

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Key: **Disease-Specific:** Disease-specific modifications based on what is known about Lynch Syndrome; **Gene-Specific:** Gene-specific modifications are based on data for specific genes; **General recommendation:** Criterion is applicable per the original ACMG/AMP guidelines with general notes from the VCEP and/or updated advice from ClinGen; **Strength:** Increasing or decreasing strength of criteria based on the amount of evidence; **N/A:** not applicable for Lynch Syndrome; **None:** no changes made to existing criteria definitions.

RULES FOR COMBINING PATHOGENIC CRITERIA

Pathogenic

1. 1 Very Strong AND
   a. ≥1 Strong OR
   b. ≥2 Moderate OR
   c. 1 Moderate and 1 Supporting OR
   d. ≥2 Supporting
2. ≥2 Strong
3. 1 Strong AND
   a. ≥3 Moderate OR
   b. 2 Moderate AND ≥2 Supporting OR
   c. 1 Moderate AND ≥4 Supporting

Likely Pathogenic

1. 1 Very Strong AND 1 Moderate
2. 1 Strong AND 1--2 Moderate
3. 1 Strong AND ≥2 Supporting
4. ≥3 Moderate
5. 2 Moderate AND ≥2 Supporting
6. 1 Moderate AND ≥4 Supporting

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RULES FOR COMBINING BENIGN CRITERIA

Benign

1. 1 Stand--Alone (BA1)
2. ≥2 Strong (BS1--BS4)

Likely Benign

1. 1 Strong and 1 Supporting
2. ≥2 Supporting

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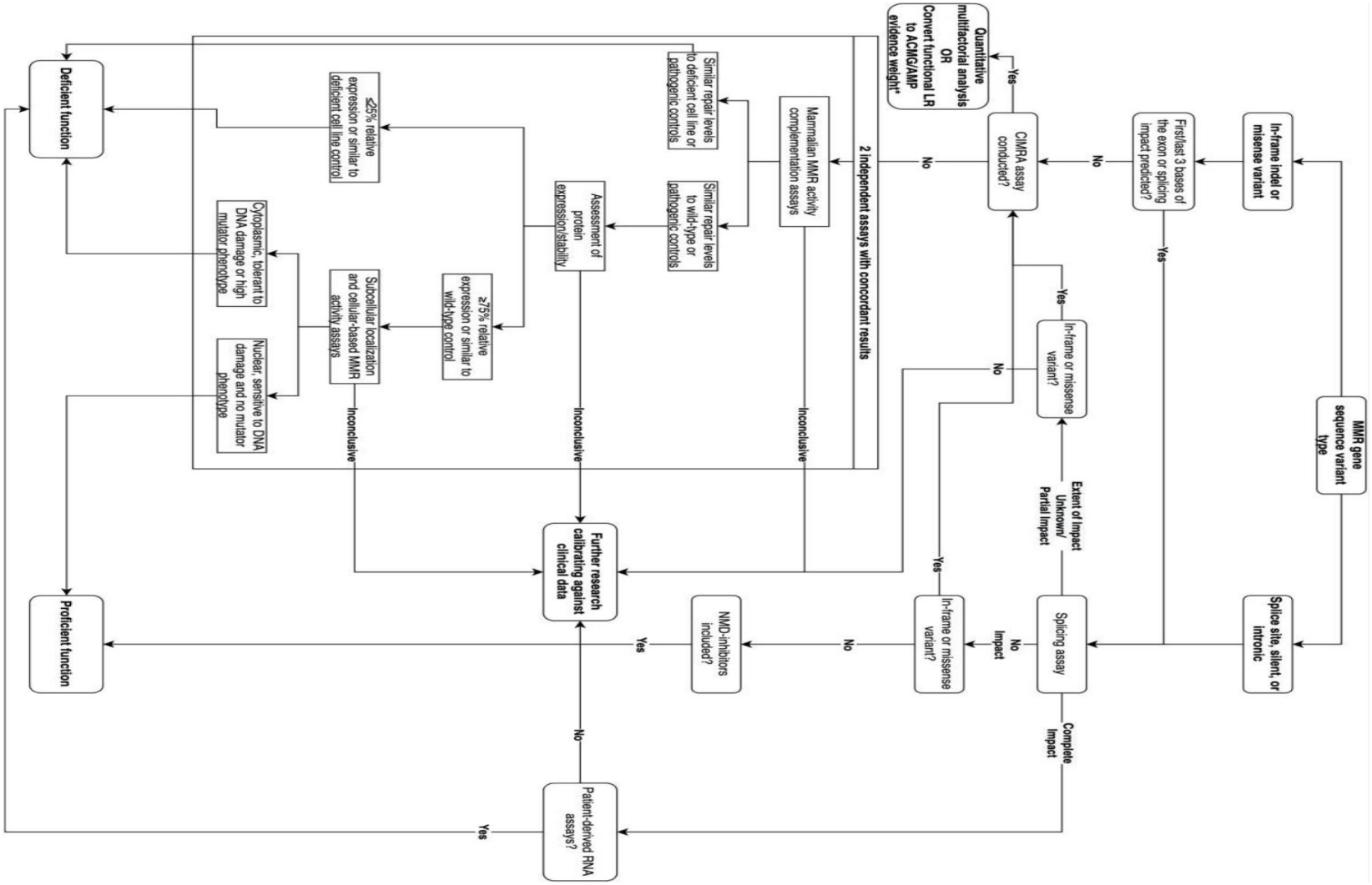

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Figure 1. Flowchart used to assist in interpretation of functional assay data. Adapted from Thompson *et al.* 2020[17].

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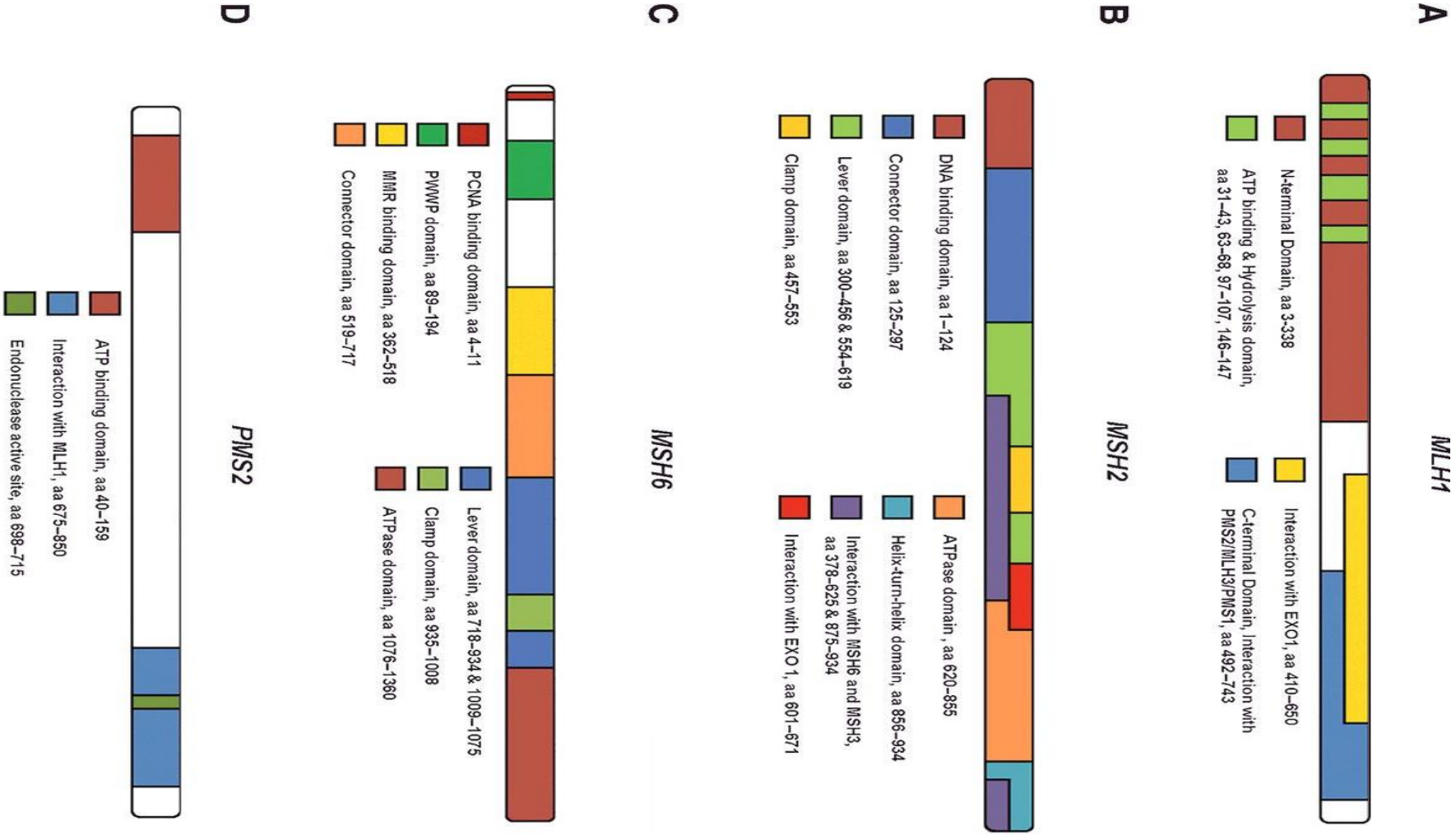

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Figure 2. Linear schematic of mismatch repair gene functional domains according to amino acid positions, adapted from Borras *et al*. 2017[18]

SVI Recommendation for De Novo Criteria (PS2 & PM6) - Version 1.0

https://clinicalgenome.org/site/assets/files/3461/svi_proposal_for_de_novo_criteria_v1_0.pdf

Supporting (PS2_Supporting or PM6_Supporting)	**Moderate** (PS2_Moderate or PM6)	**Strong** (PS2 or PM6_Strong)	**Very Strong** (PS2_VeryStrong or PM6_VeryStrong)
0.5	**1**	**2**	**4**

Table 1: The combined point value of all de novo occurrences is used to determine the applicable evidence strength level.

ClinGen Sequence Variant Interpretation Recommendation for in trans Criterion (PM3) - Version 1.0

https://www.clinicalgenome.org/site/assets/files/3717/svi_proposal_for_pm3_criterion_-_version_1.pdf

Supporting (PM3_Supporting)	**Moderate** (PM3)	**Strong** (PM3_Strong)	**Very Strong** (PM3_VeryStrong)

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0.5	**1**	**2**	**4**

Table 2: Recommendation for determining the appropriate ACMG/AMP evidence strength level for in trans occurrence(s)

Indication criteria for CMMRD testing in cancer patients	Scoring
Indication for CMMRD testing in a cancer patient	**≥3 points**
Malignancies/premalignancies: one is mandatory; if more than one is present in the patient, add the points	
Carcinoma from the LS spectrum* at age <25 years	3 points
Multiple bowel adenomas at age <25 years and absence of *APC*/*MUTYH* mutation(s) or a single high-grade dysplasia adenoma at age <25 years	3 points
WHO grade III or IV glioma at age <25 years	2 points
NHL of T-cell lineage or sPNET at age <18 years	2 points
Any malignancy at age <18 years	1 point
Additional features: optional; if more than one of the following is present, add the points	
Clinical sign of NF1 and/or ≥2 hyperpigmented and/or hypopigmented skin alterations Ø>1 cm in the patient	2 points
Diagnosis of LS in a first-degree or second-degree relative	2 points
Carcinoma from LS spectrum* before the age of 60 in first-degree, second-degree, and third-degree relative	1 point
A sibling with carcinoma from the LS spectrum*, high-grade glioma, sPNET or NHL	2 points
A sibling with any type of childhood malignancy	1 point
Multiple pilomatricomas in the patient	2 points
One pilomatricoma in the patient	1 point
Agenesis of the corpus callosum or non-therapy-induced cavernoma in the patient	1 point
Consanguineous parents	1 point

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Deficiency/reduced levels of IgG2/4 and/or IgA	1 point
***Colorectal, endometrial, small bowel, ureter, renal pelvis, biliary tract, stomach, bladder carcinoma.**	
CMMRD, constitutional mismatch repair deficiency; LS, Lynch syndrome; NHL, non-Hodgkin's lymphomas; sPNET, supratentorial primitive neuroectodermal tumours.	

Table 3: *Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'Care for CMMRD' (C4CMMRD)*[5]

Test	Pros	Cons
Immunohistochemistry (IHC) of the 4 MMR genes on non-neoplastic tissue (ie, skin, normal colon tissue, normal tissue adjacent to malignancy)	► Easily accessible. ► Inexpensive. ► High specificity and sensitivity.	► False positives and negatives can occur. ► Interpretation must be made with care and is operator-dependent. ► Access to non-neoplastic tissue may be invasive
Germline Microsatellite instability (MSI)	► Rapid result. ► Specific for CMMRD.	► May be insensitive to MSH6 deficiency. ► Not widely available commercially outside Europe. ► Uninterpretable results in ~16% of patients.
Ex vivo MSI + methylation tolerance	► High sensitivity and specificity. ► Concordant results with the two tests strengthen interpretation.	► Discordant results between tests may require additional ancillary testing. ► Time to develop lymphoblastic cell line. ► Not widely available commercially outside Europe.

In vitro repair assay	► High sensitivity and specificity	► High sensitivity and specificity
NGS detection, low-level MSI in tissue	► High sensitivity and specificity. ► Cost-effective and scalable.	► Not widely commercially available

Table 4: Examples of ancillary tests available to assist in CMMRD diagnosis, adapted from Aronson *et al.* 2009[6]

Footnotes

a PVS1 criteria is adapted from Tayoun *et al.* 2018[19].
b A known functional protein domain is reported to harbor sequence variants that introduce deleterious changes to protein function (via missense alteration, protein sequence deletion, or protein truncation in the last exon) AND are associated with high risk of cancer. Physical boundaries for functional domains are shown in Figure 2.
c IVS±1 and IVS±2 are the least invariant nucleotides in a splice site[16]
d Outbred control reference groups currently used for this purpose: Genome Aggregation Database non-cancer dataset (gnomad.broadinstitute.org).
e As per CMMRD consortium guidelines[5,6].
f Lynch Syndrome (LS) tumours include: colorectal/colon/rectal, endometrial, ovarian, small bowel/small intestine, renal pelvis, ureter, and stomach/gastric carcinomas, sebaceous skin tumours (adenomas and carcinomas), gliomas.
g Standard MSI markers panel: BAT25, BAT26, BAT40, BAT34, D5S346, D17S250, ACTC, D18S55, D10S197, MYCL[13]; D2S123, D18S69[14]; NR21, NR24, NR27[15]
h Likelihood ratios for segregation can be derived by Bayes factor analysis adapted from the method of Thompson *et al.* 2003[7], as described previously[8]. Penetrance estimates for *MLH1* and *MSH2* are from Jenkins *et al.* 2015[9] and Dowty *et al* 2013[10]; *MSH6* from Baglietto *et al.* 2010[11]; *PMS2* from ten Broeke *et al.* 2015[12]

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APPENDIX

Important Notes

PMS2 NGS results need confirmation by other orthogonal assays as well as functional assessment (e.g. Long-Range or cDNA), if variants are located in the *PMS2CL* pseudogene homologous regions (exons 11-15)

Gene-specific penetrance estimates are available at http://lscarisk.org/

Do not combine PP3 criteria with any PVS1 criteria.

Justification for last exon PVS1 boundaries:
Nonsense/frameshift variant introducing Premature Termination Codon (PTC):

1) ≤ codon 753 in MLH1 using location of known pathogenic variant MLH1:c.2252_2253del

2) ≤ codon 891 in MSH2 using location of known pathogenic variant MSH2:c.2662del

3) ≤ codon 1341 in MSH6 using location of known pathogenic variant MSH6:c.3984_3987dup

4) ≤ codon 798 in PMS2 using 50 bp 3' of the penultimate exon[19].

Protein Expression and consistency with variant location

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ClinGen_InSiGHTColorectalCancer/Polyposis_ACMG_Specifications_v1

This version specified for the following genes: *MLH1, MSH2, MSH6, PMS2* DRAFT VERSION – These guidelines are under review and not yet approved

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In general, for pathogenic variants: an *MLH1* variant is consistent with *MLH1* and *PMS2* loss, an *MSH2* variant is consistent with *MSH2* and *MSH6* loss, an *MSH6* variant is consistent *MSH6* loss and a *PMS2* variant is consistent with *PMS2* loss.

Derivation of probability values from Odds

0.11 probability corresponds to the odds of 0.48 for Benign Supporting level of benign evidence using 0.2 prior – consistent with ACMG Bayesian model[2].
0.68 probability corresponds to the odds of 2.08 for Pathogenic Supporting level of evidence using 0.5 prior – consistent with ACMG Bayesian model[2].
0.81 probability corresponds to the odds of 4.3 for Pathogenic Supporting level of evidence using 0.5 prior – consistent with ACMG Bayesian model[2].

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