MMR: CanVIG-UK Gene-Specific Guidance

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CanVIG-UK review of *MMR* genes (MLH1/MSH2/MSH6/PMS2): Consensus to use relevant recommendations from the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for **MLH1, MSH2, MSH6, and PMS2 Version 1.0.0** (available at: https://clinicalgenome.org/affiliation/50099).
Additional points of specification are given below where applicable.

Summary: Evidence towards Pathogenicity

Evidence element	Evidence strengths allowed				Use as per VCEP	Additional clarifications/thresholds/data-sources
PVS1	_VSTR	_STR	_MOD		✓	**Communication from VCEP:** The below specifications regarding PVS1 will be incorporated into the VCEP guidelines. In the meantime, please continue to use the VCEP specifications for PVS1 with the below additions: • MLH1: PVS1_VeryStrong for nonsense/frameshift variants within the first 100 coding bp • MSH2: Do not apply PVS1 for nonsense/frameshift variants within the first 100 coding bp • MSH6: PVS1_Strong for nonsense/frameshift variants within the first 100 coding bp • PMS2: PVS1_Strong for nonsense/frameshift variants within exon 1
PS1		_STR	_MOD		✓	
PS2	_VSTR	_STR	_MOD	_SUP	✓	**Clarification/Note:** Cases already used in PP4 or PP1 cannot additionally be used for PS2
PS3		_STR	_MOD	_SUP	✓	
PS4	_VSTR	_STR	_MOD	_SUP	✓	**Clarification/Note:** Do not use for case counting, as per VCEP. In addition, NDRS case-control data can be used for case-control analysis per CanVIG-UK Consensus Specification: • Controls should represent appropriate ethnicity and sex. (i.e. both male and female UKBiobank controls can be used) • As this is an enriched series, OR≥10 is required • If there are ≤6 case observations, recommend to cap application of PS4 at Strong ○ *If there are low numbers (e.g. ≤3) and application of PS4 is critical to classification of Likely Pathogenic instead*

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td>of VUS, consider confirming case phenotype.
• Current data/denominator counts for base substitutions are available at CanVar-UK
• For non-base-substitutions i.e. deletions/duplications/insertions, NDRS counts can be accessed from CanVIG-UK
• A variant observation cannot be included within the case count used for PS4 case-control analyses if the same family has been used for family history scoring within PP4.</td></tr>
<tr><td>PM1</td><td></td><td></td><td></td><td></td><td>✓</td><td></td></tr>
<tr><td>PM2</td><td></td><td></td><td></td><td>_SUP</td><td>✓</td><td></td></tr>
<tr><td>PM3</td><td>_VSTR</td><td>_STR</td><td>_MOD</td><td>_SUP</td><td>✓</td><td></td></tr>
<tr><td>PM4</td><td></td><td></td><td></td><td></td><td>✓</td><td>Clarification/Note:
This code is disallowed as per VCEP. MDT discussion may be considered for specific variants where PM4 would affect overall variant classification.</td></tr>
<tr><td>PM5</td><td></td><td></td><td>_MOD</td><td>_SUP</td><td>✓</td><td></td></tr>
<tr><td>PM6</td><td></td><td></td><td></td><td></td><td>✓</td><td></td></tr>
<tr><td>PP1</td><td></td><td>_STR</td><td>_MOD</td><td>_SUP</td><td>✓</td><td>Clarification/Note:
Cases already used in PP4 or PS2 cannot additionally be used for PP1.</td></tr>
<tr><td>PP2</td><td></td><td></td><td></td><td></td><td>✓</td><td></td></tr>
<tr><td>PP3</td><td></td><td></td><td>_MOD</td><td>_SUP</td><td>✓</td><td></td></tr>
<tr><td>PP4</td><td></td><td>_STR</td><td>_MOD</td><td>_SUP</td><td>✓</td><td>Communication from VCEP:
The below specifications regarding family history scoring will be incorporated into the VCEP guidelines.
In the meantime, please continue to use the VCEP guidance for tumour scoring, and the below guidance for family history scoring:

Family History Scoring:
<table>
<tr><td></td><td>Isolated single primary or first cancer in proband/family (≥50, 40-49, <40)</td><td>Additional family members* orcancers in proband; for each cancer (≥50, 40-49,<40):</td><td>Evidence Points</td></tr>
<tr><td>Colon (CRC), Endometrium (EC), TCC (renal pelvis/ureter only), small bowel</td><td>(2, 4, 6)</td><td>(4, 6, 8)</td><td rowspan="2">Divide the sum offamily history scores across available families by 7 to get the evidence points
• 7= 1EP= sup
• 14= 2EP= mod</td></tr>
<tr><td>Rectum, ovary, gastric, hepatobiliary, pancreas, TCC (bladder)</td><td>(1, 2, 3)</td><td>(2, 3, 4)</td></tr>
</table>
These scores have been derived from odds ratios of detection of MMR variants in Manchester data series (courtesy of Evans, Woodward)
• *For a multiplex family cluster of ≤3 cases, relatives should be FDRs of each other. In a family cluster of ≥4 cases, one unaffected intervening relative is allowed withinthe cluster
• The proband is the youngest case in the family with CRC/EC
• A family can only be included for family history scoring when there is concordanttumour data available supporting mismatch repair deficiency (i.e. MSI/IHC) in an individual carrying the variant in question
• Not all individuals contributing family history points within</td></tr>
</table>

						a family cluster need to have been shown to carry the variant in question • Those tested for the variant and proven not to have it should not contribute family history points • A family cannot be used for family history scoring for PP4 if the same family has already been included within the case counts for case-control analyses within PS4(but can be used for tumour scoring) • The variant must be present at a frequency of ≤0.002% in individuals from the Non-Finnish European population from gnomAD v4.1 and ≤1 individuals from each of the other ethnic groups within gnomAD v4.1. • Where family history score influences final classification (e.g. at VUS/likely pathogenic boundary), cancer family history should be confirmed through cancerregistry • The tumour scoring and family history scoring should be used in combination • A single family can contribute no more than 2 evidence points • The same individual can contribute to both tumour and family history scoring • A maximum of 2 evidence points can be awarded for a single publication • Cases used for PM3 (biallelic)/PP1(segregation) cannot be used additionally for tumour/family history scoring within PP4

Summary: Evidence towards Benignity

BA1/BS1	_SA	_STR			✓	
BS2		_STR			✓	
BS3		_STR		_SUP	✓	
BS4		_STR		_SUP	✓	
BP1					✓	
BP2					✓	
BP3					✓	
BP4				_SUP	✓	
BP5		_STR		_SUP	✓	
BP7				_SUP	✓	

Version History/Amendments

Revised version	Date	Section	Update	Amended by	Approved by
1.4	***03/11/2021***	PP4/PS4	Tumour and family history scoring information combined together in PP4, tumour scoring system updated. Ordering of evidence criteria amended.	Turnbull	CStAG
1.4	***02/12/2021***	PS4	Addition of guidance on using NHSD datafor case-control analyses	Garrett	CStAG
1.4	***17/12/2021***	PVS1	Addition of recommendations for truncating variants within first 100bp	Callaway	CStAG
1.4	***17/12/2021***	PS4/PM2	Addition of recommendation for non-cancer female controls to be used for PMS6 and PMS2	Turnbull	CStAG
1.4	***05/01/2022***	PM3/PP1/ PP4	Clarification that a case cannot be used for PP4 if has already been used for PM3/PP1and vice versa	Garrett	Turnbull
1.5	***25/05/2022***	PM2	Removal of requirement for gnomAD controls to be NFE	Garrett	CStAG

1.6	***30/06/2023***	PS4	Update on case-counting approach where variant seen in multiple cases but also observed in control datasets.	Allen/Garrett	CStAG
1.6	***04/07/2023***	PVS1	Clarification that guidance applies to initiation codon variants	Allen	CStAG
1.6	***04/07/2023***	PS4/PM2	Update of wording to match consensus specification, and removal of sex-matching as requirement for MSH6 and PMS2	Allen/Garrett	CStAG
1.6	***23/10/2023***	BA1/BS1	Clarification of MTAF usage and filtering allele frequency. Addition and clarification of data used in calculation of MTAF for each gene.	Callaway	CStAG
1.7	***25/04/2024***	PP4	Wording change to accommodate somatic variants; 'Only individuals/tumours proven to carry the variant in question can contribute tumour data'; updated notes to refer to gnomAD v4.1 instead of v2 and clarification that only one individual needs to have tumour data for PP4 family history scoring	CStAG	CStAG
1.7	***30/04/2024***	BA1/BS1	Removed statement regarding cancer-free controls as this is now redundant with gnomAD v4.1; replaced PopMAX with Grpmax to align with gnomAD wording.	Allen	CStAG
1.7	***20/05/2024***	PM3	Added statement to note caution in inferring pathogenicity for the monoallelic CMMRD phenotype as variants may be hypomorphic	Allen	CStAG
1.8	***12/08/2025***	PP5/BP6	Codes removed (no longer in use)	Allen	Turnbull
1.8	***12/08/2025***	PS4	Added caution when applying PS4 using the NDRS dataset when there are ≤6 case observations	CStAG	CStAG
2.0	***07/10/2025***	Guidance, all	Switch from using CanVIG consensus specification to the InSiGHT VCEP specifications	Allen	CStAG
2.0	***07/10/2025***	PM4	Added statement on MDT discussion when PM4 application may impact overall classification	Allen	CStAG