Annexure 1

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Supp. Table S1 Scoring system to determine germline testing eligibility for CMMRD

	Indication for CMMRD testing	Score
	Mandatory criteria: 1 is mandatory and add if more than one criteria	
1	Carcinoma from the LS spectrum, age < 25 years	3
2	Multiple bowel adenomas at age < 25 years and absence of *APCI*/*MUTYH* mutations or a single high-grade dysplasia/adenoma at age < 25 years	3
3	WHO grade III or IV glioma at age < 25 years	2
4	NHL or T-cell lineage or sPNET at age < 18 years	2
5	Any malignancy at age < 18 years	1
	Additional features: Optional criteria: add if more than one criteria	
6	Clinical signs of NF1 and or > 2 hyper $+$/hypopigmented skin alterations > 1 cm	2
7	Diagnosis of Lynch syndrome in a first- or a second-degree relative	2
8	Carcinoma from LS spectrum in a 1st, 2nd, or 3rd degree relative < 60 years	1
9	A sibling with a malignancy from the LS spectrum, high-grade glioma, sPNET, or NHL	2
10	A sibling with any type of childhood malignancy	1
11	Multiple pilomatricomas in the patient	2
12	One pilomatricoma in the patient	1
13	Agenesis of the corpus callosum or nontherapy-induced cavernoma in the patient	1
14	Consanguineous parents	1
15	Deficiency/reduced levels of IgG 2/4 and /or IgA	1

Abbreviations: CMMRD, constitutional mismatch repair deficiency; Ig, immunoglobulin; LS, Lynch syndrome; NF1, ; NHL, non-Hodgkin lymphoma; sPNET, supratentorial primitive neuroendocrine tumor; WHO, World Health Organization.

Supp. Table S2 CMMRD diagnostic criteria

Criterion		Germline result[a] *PMS2*, *MSH6*, *MSH2*, *MLH1*	Positive ancillary testing	Clinical phenotype
Definitive diagnosis (strong evidence of CMMRD)	1	Biallelic pathogenic variants (P/P)[a], confirmed in trans	Not required unless unaffected > 25 y, then one required	Not required if under age 25 (if no malignancy over age 25, ancillary testing required)
Definitive diagnosis (strong evidence of CMMRD)	2	Biallelic P/LP or LP/LP[a] variants, confirmed in trans	One required unless unaffected by hallmark cancer, then 2 required	Hallmark CMMRD cancer diagnosis > or C4CMMRD criteria of 3 points (then 2 ancillary tests required)
Definitive diagnosis (strong evidence of CMMRD)	3	Heterozygous P or LP variant (±VUS[a] or likely benign variants)	One required	Hallmark CMMRD cancer diagnosis
Definitive diagnosis (strong evidence of CMMRD)	4	No P or LP MMR variants (including VUS/VUS)[b] or no testing available (i.e., deceased proband)	Two required	Hallmark CMMRD cancer diagnosis
Likely diagnosis (moderate evidence of CMMRD)	5	Biallelic P/LP[a] or LP/LP variants confirmed in trans	Not required	C4CMMRD criteria of 3 points
Likely diagnosis (moderate evidence of CMMRD)	6	Heterozygous P or LP variant or no testing available (i.e., deceased proband)	Two required	a. C4CMMRD criteria of 3 points b. Individual < age 18 with NF1 features (i.e., no malignancy or polyposis history) c. Malignancy under age 30

Abbreviations: CMMRD, constitutional mismatch repair deficiency; LP, likely pathogenic; MMR, mismatch repair; P, pathogenic; VUS, variant of unknown significance.
[a]Same gene on both alleles.
[b]Consanguinity supports diagnosis.

