ScienceDirect

The Lancet Oncology

Volume 25, Issue 5, May 2024, Pages 668-682

Articles

# Clinical and biological landscape of constitutional mismatch-repair deficiency syndrome: an International Replication Repair Deficiency Consortium cohort study

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https://doi.org/10.1016/S1470-2045(24)00026-3

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## Summary

### Background

Constitutional mismatch repair deficiency (CMMRD) syndrome is a rare and aggressive cancer predisposition syndrome. Because a scarcity of data on this condition contributes to management challenges and poor outcomes, we aimed to describe the clinical spectrum, cancer biology, and impact of genetics on patient survival in CMMRD.

### Methods

In this cohort study, we collected cross-sectional and longitudinal data on all patients with CMMRD, with no age limits, registered with the International Replication Repair Deficiency Consortium (IRRDC) across more than 50 countries. Clinical data were extracted from the IRRDC database, medical records, and physician-completed case record forms. The primary objective was to describe the clinical features, cancer spectrum, and biology of the condition. Secondary objectives included estimations of cancer incidence and of the impact of the specific mismatch-repair gene and genotype on cancer onset and survival, including after cancer surveillance and immunotherapy interventions.

### Findings

We analysed data from 201 patients (103 males, 98 females) enrolled between June 5, 2007 and Sept 9, 2022. Median age at diagnosis of CMMRD or a related cancer was 8·9 years (IQR 5·9–12·6), and median follow-up from diagnosis was 7·2 years (3·6–14·8). Endogamy among minorities and closed communities contributed to high homozygosity within countries with low consanguinity. Frequent dermatological manifestations (117 [93%] of 126 patients with complete data) led to a clinical overlap with neurofibromatosis type 1 (35 [28%] of 126). 339 cancers were reported in 194 (97%) of 201 patients. The cumulative cancer incidence by age 18 years was 90% (95% CI 80–99). Median time between cancer diagnoses for patients with more than one cancer was 1·9 years (IQR 0·8–3·9). Neoplasms developed in 15 organs and included early-onset adult cancers. CNS tumours were the most frequent (173 [51%] cancers), followed by gastrointestinal (75 [22%]), haematological (61 [18%]), and other cancer types (30 [9%]). Patients with CNS tumours had the poorest overall survival rates (39% [95% CI 30–52] at 10 years from diagnosis; log-rank p<0·0001 across four cancer types), followed by those with haematological cancers (67% [55–82]), gastrointestinal cancers (89% [81–97]), and other solid tumours (96% [88–100]). All cancers showed high mutation and microsatellite indel burdens, and pathognomonic mutational signatures. *MLH1* or *MSH2* variants caused earlier cancer onset than *PMS2* or *MSH6* variants, and inferior survival (overall survival at age 15 years 63% [95% CI 55–73] for *PMS2*, 49% [35–68] for *MSH6*, 19% [6–66] for *MLH1*, and 0% for *MSH2*; p<0·0001). Frameshift or truncating variants within the same gene caused earlier cancers and inferior outcomes compared with missense variants (p<0·0001). The greater deleterious effects of *MLH1* and *MSH2* variants as compared with *PMS2* and *MSH6* variants persisted despite overall improvements in survival after surveillance or immune checkpoint inhibitor interventions.

## Interpretation

The very high cancer burden and unique genomic landscape of CMMRD highlight the benefit of comprehensive assays in timely diagnosis and precision approaches toward surveillance and immunotherapy. These data will guide the clinical management of children and patients who survive into adulthood with CMMRD.

## Funding

The Canadian Institutes for Health Research, Stand Up to Cancer, Children's Oncology Group National Cancer Institute Community Oncology Research Program, Canadian Cancer Society, Brain Canada, The V Foundation for Cancer Research, BioCanRx, Harry and Agnieszka Hall, Meagan's Walk, BRAINchild Canada, The LivWise Foundation, St Baldrick Foundation, Hold'em for Life, and Garron Family Cancer Center.

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## Introduction

DNA mismatch repair (MMR) is essential for genome stability. Mismatch errors during DNA replication are recognised and repaired by the MMR system and DNA polymerases.[1] Hence, aberrations in the MMR genes—*MLH1* (mutL homolog 1), *MSH2* (mutS homolog 2), *MSH6* (mutS homolog 6), and *PMS2* (PMS1 homolog 2)—result in uncontrolled mutagenesis, leading to cancers harbouring hypermutation, microsatellite instability, and unique genomic signatures.[2]

Germline heterozygous pathogenic variants affecting any MMR gene results in Lynch syndrome, in which adults commonly develop gastrointestinal and genitourinary cancers.[3] Biallelic (homozygous or compound heterozygous) germline pathogenic variants of MMR genes result in the autosomal recessive constitutional mismatch-repair deficiency (CMMRD) syndrome.[1, 4, 5] Although gastrointestinal cancers occur in both Lynch syndrome and CMMRD, there are key differences in cancer phenotype and disease severity between these syndromes. First, in contrast to Lynch syndrome, young patients with CMMRD develop a broader spectrum of neoplasms, including CNS, haematological, and other cancer types, which can be synchronous or metachronous, resulting in death within the first two to three decades of life.[1, 6, 7, 8] Second, patients with CMMRD harbour diverse, multisystemic, non-neoplastic manifestations that resemble genetic disorders such as neurofibromatosis type 1,[9] tuberous sclerosis, and other polyposis syndromes. CMMRD is presumed to have a higher prevalence in consanguineous communities in low-income and middle-income countries.[10] Unlike in Lynch syndrome,[3] the impacts of the affected gene or genotype on cancer prevalence, presentation, and patient outcomes in CMMRD remain relatively unknown.[8] The lack of knowledge regarding gene–phenotype or genotype–phenotype associations, tumour biology, and behaviour of CMMRD cancers, combined with the highly diverse clinical and cancer manifestations, leads to delayed diagnosis and contributes to poor outcomes for patients with CMMRD.

## Research in context

### Evidence before the study

We searched PubMed for studies on constitutional mismatch-repair deficiency (CMMRD) published between Jan 1, 2000, and June 30, 2023, in English, using a combination of the following search terms: “constitutional mismatch repair deficiency”, “CMMRD”, “biallelic mismatch repair deficiency”, “BMMRD”, “CMMRD AND genotype-phenotype.” Beyond case reports and small series, we identified only one study that mentioned exploring gene, genotype, and phenotype correlations in CMMRD. This study reported that microsatellite instability scores in a functional assay had higher values for truncating variants, but no other clinical or biological associations were identified. It was hypothesised that a correlation of mismatch-repair (MMR) genotype with disease phenotype was probable, which was not observable in that study due to the small sample size (n=56). In addition, some clinical observations mentioned in previous case studies could be random or chance associations, or co-associations due to a high prevalence of homozygosity and consanguinity in many of these families. Overall, a comprehensive analysis of the gene, genotype, and phenotype links in this relatively rare yet frequently reported syndrome is lacking.

### Added value of this study

We leveraged the collaborative network of an international, multicentre consortium to report novel clinical associations, providing several insights into the biology of CMMRD. In addition to the highest reported cumulative incidence for cancers (90% by age 18 years and 100% by age 40 years) among almost all predisposition syndromes, perhaps our most important observation is the impact of the specific gene type on disease phenotype and outcome. Patients with germline *MLH1* and *MSH2* variants were less frequent than those with *PMS2* and *MSH6* variants, in stark contrast to their relative prevalence in the heterozygous Lynch syndrome. Patients with *MLH1* or *MSH2* showed higher homozygosity, lower prevalence of variants likely to be causing

premature protein truncation or loss, earlier onset of cancers, a distinct spectrum of neoplasia, and inferior survival that persisted even after cancer surveillance and immune-checkpoint inhibitor treatment of patients. These findings suggested that *MLH1* and *MSH2* genes tolerate a limited spectrum of significant variants, yet have a more aggressive phenotype, thereby reflecting the relative gene dependencies in the MMR machinery. Additional novel clinical observations included an earlier onset of adult-type cancers with MMR deficiency signatures and biology in emerging young adult patients, a predominance of homozygous patients with CMMRD in relatively segregated immigrant, indigenous, or minority communities in countries with a low population prevalence of consanguinity, features of overlap and distinction from other genetic syndromes like neurofibromatosis type 1, and the differential biological impact of mutation versus microsatellite indel accumulation in distinct types of CMMRD cancers.

**Implications of all the available evidence**

Taken together, the current evidence suggests that refinement of diagnostic criteria should include functional genomic assays for improved diagnosis of the syndrome, that guidelines should incorporate continued cancer surveillance for adult cancer types in patients surviving beyond childhood, and that management and prognosis needs to be tailored to both cancer genomics as well as a patient's germline gene and genotype.

Over the past decade, work by collaborative groups has been key in establishing robust diagnostic criteria for CMMRD, combining both clinical and functional genomic analyses.[4, 5, 11, 12, 13, 14] Timely diagnosis leads to early cancer detection through surveillance,[15, 16] avoidance of ineffective chemotherapeutic agents, and introduction of immune-checkpoint inhibitors (ICIs) for the treatment of CMMRD cancers.[17, 18, 19]

Nevertheless, the current knowledge on CMMRD is largely based on small case series and literature reviews.[4, 6, 7, 8, 10, 19, 20] To clarify the patient phenotype, spectrum, and genomic profile of CMMRD cancers, and to determine gene–phenotype or genotype–phenotype associations, we established the International Replication Repair Deficiency Consortium (IRRDC). We register patients with replication repair-deficient cancers globally through active collaboration with physicians across more than 50 countries. In the current study, we aimed to summarise the largest dataset of patients with CMMRD and their cancers to identify novel clinical and biological insights affecting surveillance and immunotherapy outcomes for these patients.

## Methods

### Study design and participants

The study is a comprehensive analysis of patients with CMMRD enrolled by the IRRDC between June 5, 2007 and Sept 9, 2022, with no age limits, using all the data collected in the database on these patients over this period. Following enrolment into the IRRDC, CMMRD diagnoses were confirmed by the consortium genetic counsellor (MA) using updated criteria.[5] Clinical data were extracted from the IRRDC database, medical records, and physician-completed case record forms (appendix 1 pp 7–8). Biological sex and country of origin were collected as a component of this case record form. Gender and ethnicity were not collected. Updated criteria for neurofibromatosis type 1 were used to clinically identify patients with CMMRD with a phenotypic overlap.[21]

Patients were enrolled after ethics approval (SickKids research ethics board, reference number 1000048813) and written informed parental or patient consent or assent had been obtained.

## Procedures

After enrolment into the IRRDC, each patient had blood and tumour material collected and sequenced centrally at The Centre for Applied Genomics at The Hospital for Sick Children (SickKids; Toronto, ON, Canada). These sequencing data are securely stored in the IRRDC database and were used in this study. All subsequent analyses using the stored sequencing data (ie, sequence alignment, variant calling and filtering, variant annotation, COSMIC signature, tumour mutation burden [TMB], and microsatellite instability analyses) were done specifically for the current study. The detailed methods for sequencing and downstream analysis can be found in the appendix 1 (pp 1–6).[11, 22]

The presence or absence of parental consanguinity for each patient was ascertained from the family or from respective clinicians through the case record form, clinical summaries, or direct communications. The population prevalence of consanguinity for each country was defined as low (<5%) or high (≥5%).[23]

The affected MMR gene was ascertained with use of standard clinical criteria. Variants in *MSH6, PMS2, MLH1*, and *MSH2* were identified by clinical genetic testing as part of registration to the IRRDC. Individual gene variants were grouped as either frameshift or truncating variants or missense variants on the basis of predicted effects on the protein. For patients without formal genetic testing, the MMR gene affected, variant, and zygosity were identified from sequencing data with matched pedigree and immunohistochemistry. Histology was centrally reviewed by CH.

To better elucidate the mutagenic processes in CMMRD cancers, we did whole-exome sequencing and low-pass genome sequencing on all available tumours. Whole-exome sequencing was done on MMR-deficient tumours, each with matched blood. TMB and secondary somatic tumour mutations in *POLE* or *POLD1, TP53, RAS–MAPK* pathway (including *NF1*), and *ATRX* genes were identified using the bioinformatic pipeline outlined in appendix 1 (pp 3–5). TMB was defined as the total number of somatic single-nucleotide variants (SNVs) divided by the observed coverage in megabases, to express the result as mutations per megabase.

Low-pass genome sequencing was done on blood and tumour tissues for the functional low-coverage whole genome instability characterisation (LOGIC) assay, which generates an MMRDness score that accurately reflects the total genomic microsatellite indel burden (appendix 1 p 5).[11] The previously established threshold of 0 was used to distinguish between MMR proficiency and MMR deficiency; otherwise, absolute values of MMRDness were used for intergroup comparisons.

Identification of germline variants was done as described in appendix 1 (p 2). For patients in whom germline testing was done, each variant identified was first annotated as missense, nonsense, silent, frameshift (insertion, deletion, or duplication), frameshift (stop codon), splice site, or in-frame, based on the annotation in clinical databases.[24] We subsequently annotated all frameshift variants and stop codon variants (including SNV nonsense variants) as “frameshift or truncating” and all missense variants as “missense.” All compound heterozygous patients in whom at least one allele was identified as a missense variant were grouped as missense. Splice site, in-frame, and silent SNVs were grouped as either frameshift or truncating variants or missense variants on the basis of the predicted protein effect described in clinical databases[24] (absent or altered protein, respectively).

## Statistical analyses

The primary objective was to describe the clinical features, cancer spectrum, and biology of CMMRD by collecting cross-sectional and longitudinal data on all registered patients. Secondary objectives included the estimation of cancer incidence and the impact of affected gene and genotype on cancer type, onset, and survival, including after cancer surveillance and immunotherapy. Descriptive statistics were used for all analyses. Normality of distribution was tested using the Kolmogorov–Smirnov test. Continuous variables were reported as median and IQR. Comparisons between groups were done with Fisher's exact or $\chi^2$ tests for categorical variables, or with Mann–Whitney *U* tests for continuous variables. Patients with missing data for specific subanalyses were excluded from that analysis.

An empirical cumulative distribution function was used to depict age distribution for cancers. A cumulative incidence function was used to depict time to occurrence of subsequent cancers. Competing risk of death was incorporated in the cumulative incidence function calculation, from first to second cancer, and from second to third cancer. Cancer incidence at specific age cutoffs was reported with 95% CIs. The Kaplan–Meier method was used to estimate survival, with a log-rank test used to compare survival between groups. For the analysis of the effect of MMR gene and surveillance on survival, survival was calculated from date of birth until date of death or last follow-up.

For the analysis of cancer type or the effects of MMR gene or ICI treatment on survival in patients with advanced cancers, survival was calculated from the date of cancer diagnosis until the date of death or last follow-up. Censoring was administrative at the end of the study period, except for some patients (<5%) who were censored at their last follow-up date. To assess the impact of affected gene on tumour-specific outcomes, CNS tumours were analysed, as they are the predominant cancer type associated with the worst survival. To assess the impact of affected gene on cancer diagnosis, CNS and gastrointestinal cancers were used as the two most common cancer types with sufficient numbers for statistical analyses. To assess the impact of variant type on cancer onset and outcome, comparisons were made between variant types for all MMR genes together and for *PMS2* separately (this being the gene most commonly affected). The timepoints of interest for estimated or projected survival were chosen on the basis of the clinical question and the median survival time among study participants as follows: 15 years for all analyses of patient survival from birth (median 16 years); 10 years for survival after cancer diagnosis (median 6 years); and 5 years for survival after ICI treatment (median 3·6 years), a relatively novel therapy used for metastatic or advanced cancers, which had a modest follow-up time at study closure. Multivariable Cox proportional hazards models were used to assess the association between clinically relevant variables (including age at diagnosis of CMMRD [for surveillance analysis] or cancer [for ICI analysis], sex, country, affected MMR gene, and first cancer diagnosis [CNS *vs* others]) and survival following cancer surveillance or ICI treatment. For each variable tested, Cox regression with time-dependent covariates was done to verify the proportional hazards assumption.

Analyses were done with SPSS (version 20) and R (version 4.2.1). All p values were two-sided and the significance level was set at 0·05.

## Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

# Results

201 individuals from 160 families were diagnosed with CMMRD and enrolled in the IRRDC between June 5, 2007 and Sept 9, 2022, including 103 males and 98 females. Median age at diagnosis was 8·9 years (IQR 5·9–12·6; range 0·8–39·5; table). The end date of follow-up was Sept 9, 2022. The median follow-up time from diagnosis of CMMRD was 7·2 years (IQR 3·6–14·8), and varied across different regions of residence (appendix 1 p 9). Distribution of countries, clinical features, and regional differences are shown in appendix 1 (p 19) and appendix 2 (pp 1–3).

Table. Characteristics of study cohort

| | **Patients (n=201)** |
|---|---|
| Sex | |
| Male | 103 (51%) |
| Female | 98 (49%) |
| Age at diagnosis, years* | 8·9 (5·9–12·6) |
| Germline mismatch-repair gene affected | |
| *PMS2* | 131 (65%) |
| *MSH6* | 52 (26%) |
| *MLH1* | 12 (6%) |
| *MSH2* | 5 (2%) |
| Unknown | 1 (<1%) |
| History of parental consanguinity | 104/193 (54%) |
| Family history of any cancer | 103/117 (88%) |
| Lynch syndrome-spectrum cancers in parents | 9/127 (7%) |
| Region of residence | |
| North America | 93 (46%) |
| Europe | 34 (17%) |
| Middle East | 42 (21%) |
| Asia–Pacific† | 30 (15%) |
| South America | 2 (1%) |

Data are n (%), n/N (%), or median (IQR). CMMRD=constitutional mismatch-repair deficiency.

* Age at diagnosis of CMMRD or first presentation with cancer leading to subsequent CMMRD diagnosis.

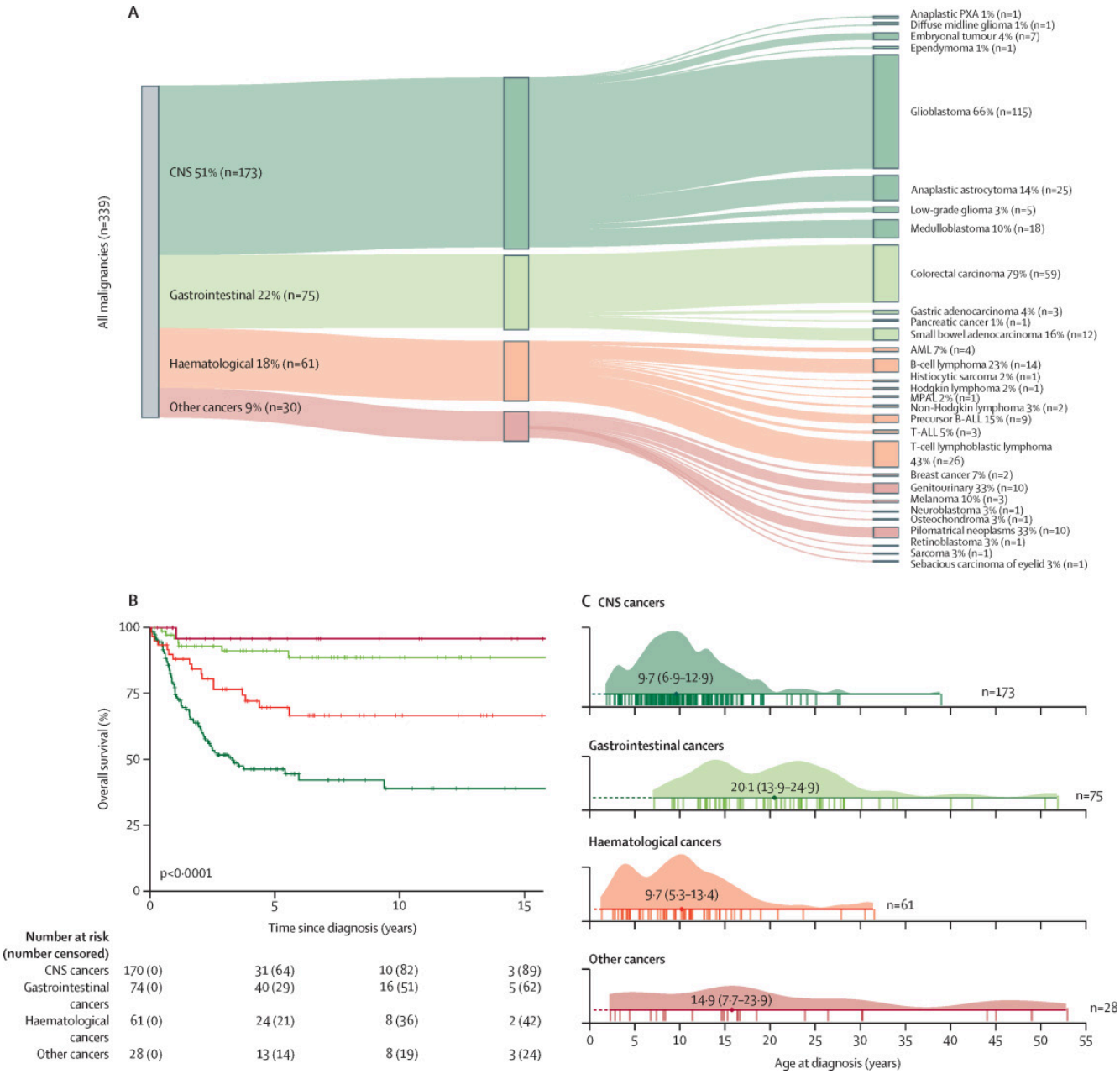
† Includes South Asia and Oceania.

A history of cancer was common in the extended family (103 [88%] of 117 patients with available data). The prevalence of Lynch syndrome-spectrum cancers was low among parents, despite being obligate

heterozygotes (nine [7%] of 127 patients; table). A large proportion of patients with CMMRD had a history of parental consanguinity (104 [54%] of 193; table; appendix 1 pp 9–10). However, the majority of individuals were enrolled from countries with a low population prevalence of consanguinity (132 [69%] of 192; appendix 1 pp 9–10). In these countries, detailed analysis of homozygous patients without a history of parental consanguinity (13 [21%] of 63) revealed a predominance of minority, immigrant, and indigenous communities (10 [77%] of 13; appendix 1 pp 9–10).

Non-cancerous skin manifestations overlapping with other human syndromes were common (117 [93%] of 126 patients). Hypopigmentation (43 [33%] of 129) was associated with café-au-lait (hyperpigmented) macules (157 [89%] of 176) in all but one patient (appendix 1 pp 9–10). Combining with other manifestations, clinical criteria[21] for neurofibromatosis type 1 were fulfilled in 35 (28%) of 126 patients with CMMRD who had complete skin data (appendix 1 pp 9–10). However, no patients with available germline sequencing (n=132) harboured pathogenic variants in the *NF1* or *SPRED1* genes. A need for school accommodation for intellectual deficits was low (nine [7%] of 123 patients). Clinically significant autoimmunity[25] was uncommon (six [5%] of 120), and no patients had clinically overt immunodeficiency.[26]

A total of 339 cancers were reported in 194 (97%) of 201 individuals. CNS tumours were the most frequent (173 [51%]), followed by gastrointestinal (75 [22%]) and haematological malignancies (61 [18%]; figure 1A). Other tumour types (30 [9%]) included paediatric-type embryonal (Wilms tumour, neuroblastoma), paediatric and adolescent mesenchymal (sarcomas), and adult-type carcinomas. Importantly, even within organ systems commonly affected in CMMRD, we observed previously rare or unreported cancer types, such as optic glioma,[27] ependymoma,[28] Hodgkin lymphoma, histiocytic sarcoma, mixed-lineage leukaemia, melanoma, and pancreatic adenocarcinoma (figure 1A).

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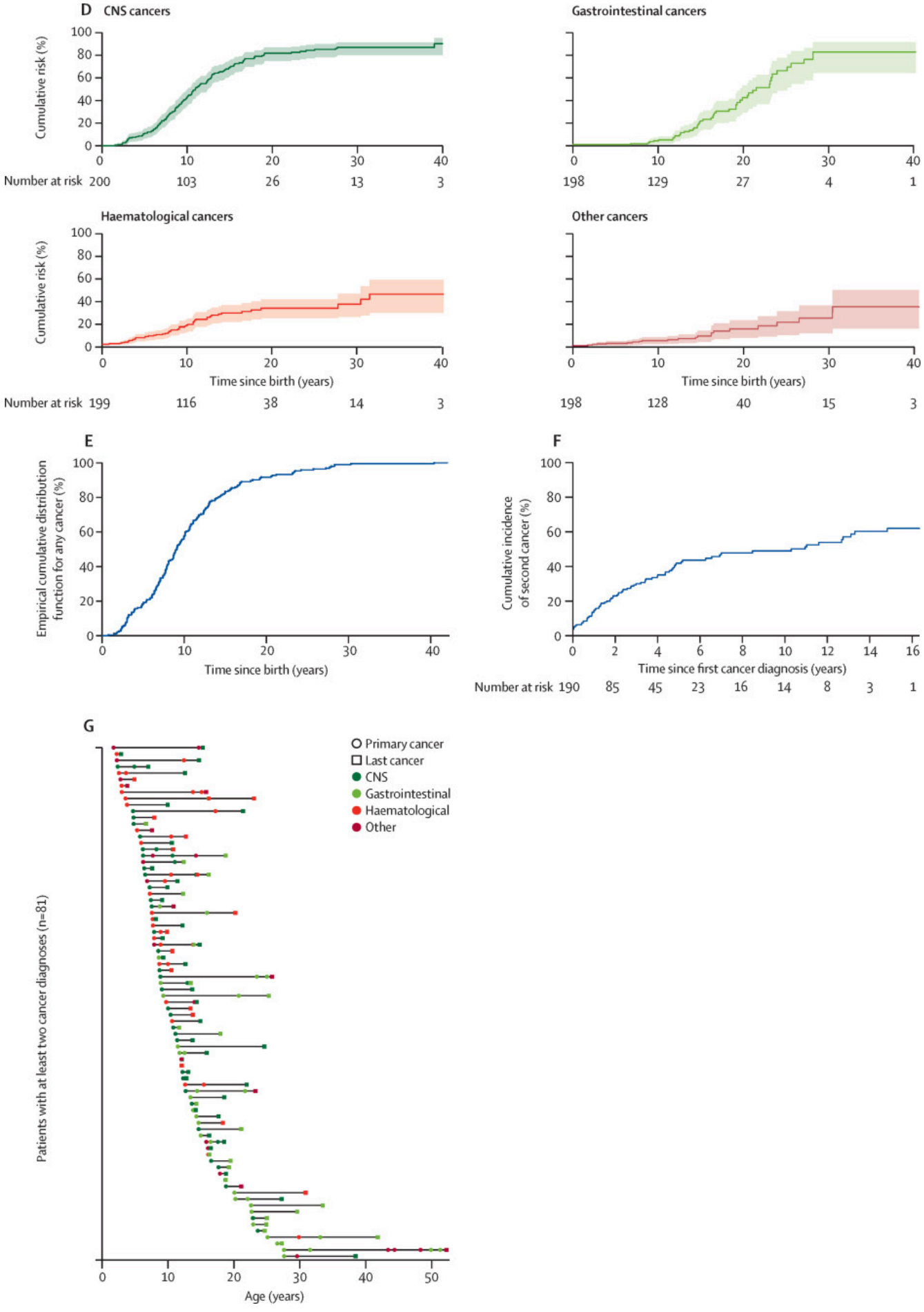


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Figure 1. Cancer spectrum and incidence in CMMRD (n=339 tumours)

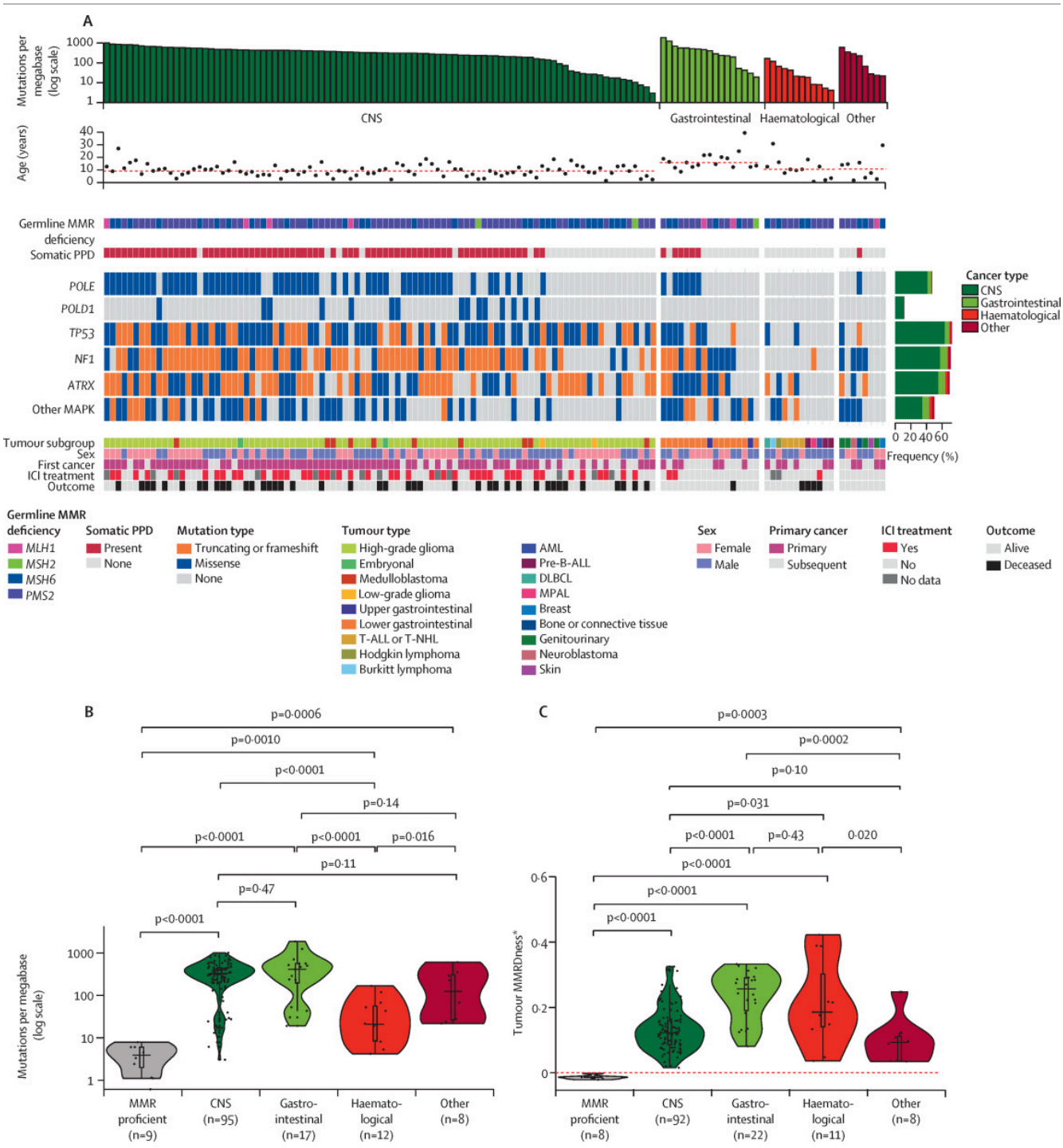
(A) Diverse tumour types detected in patients with CMMRD. (B) Kaplan–Meier curves for overall survival from diagnosis including all tumours stratified by cancer type; p value is from log-rank test. (C) Age at cancer diagnosis by cancer type; median (IQR) is shown on each graph. (D) Cumulative risk of developing each cancer type over time, starting from birth. Shaded areas are 95% CIs. (E) Cumulative incidence of any cancer in patients with CMMRD over time, starting from birth. (F) Cumulative incidence of a second cancer in patients over time from their first cancer diagnosis. (G) Patients with multiple cancers developing over time, showing the time of onset of each cancer by the patient's age and the time between cancers (n=81). Three patients had two cancers diagnosed on the same date and are not shown in this plot. Primary cancer is each new cancer, and last cancer is the last cancer recorded for the patient by the date of last follow-up (study end date) or at death. AML=acute myeloid leukaemia. B-ALL=B-cell acute lymphoblastic leukaemia. CMMRD=constitutional mismatch-repair deficiency syndrome. MPAL=mixed-phenotype acute leukaemia. PXA=pleomorphic xanthoastrocytoma. T-ALL=T-cell acute lymphoblastic leukaemia.

Overall, patients with CNS tumours had significantly worse 10-year overall survival from cancer diagnosis (39% [95% CI 30–52]) than did those with haematological cancers (67% [55–82], p=0·0036) gastrointestinal cancers (89% [81–97], p<0·0001), and other solid tumours (96% [88–100], p=0·0001; log-rank p<0·0001 across all four cancer types; figure 1B). Age at diagnosis for CNS cancers (median 9·7 years [IQR 6·9–12·9]) and haematological neoplasms (9·7 years [5·3–13·4]) was significantly earlier than for gastrointestinal cancers (20·1 years [13·9–24·9]) and other solid tumours (14·9 years [7·7–23·9]; p<0·0001, Mann–Whitney U test for CNS and haematological *vs* gastrointestinal and other cancers; figure 1C). Notably, many of the adult-type cancers observed (breast, bladder, and prostate cancers; figure 1A) developed at earlier ages than in the general population.

The cancer burden among the study population was very high. Cumulative incidence by age 20 years was 82% (95% CI 76–88) for CNS cancers, 42% (30–54) for gastrointestinal cancers, 33% (24–41) for haematological cancers, and 15% (7–23) for other cancers (figure 1D). Among 43 patients who survived to age 20 years or older, the frequency of CNS or haematological cancers (n=42) was lower than that of gastrointestinal or other cancers (n=68; p<0·0001, $\chi^2$ test), where Lynch syndrome-type cancers (gastrointestinal or genitourinary) predominated, albeit at a much earlier age than in Lynch syndrome.[3] The risk of having any cancer diagnosed was 90% (95% CI 80–99) by age 18 years and 100% (90–100) by age 40 years; among the patients diagnosed with cancer during the study period, all but one had developed at least one cancer by age 30 years (figure 1E). The 10-year cumulative incidence for a second cancer was 49% (95% CI 41–57) and for a third cancer was 61% (45–77; figure 1F; appendix 1 p 10). 84 (43%) of 194 patients developed more than one cancer with a median interval between cancer diagnoses of 1·9 years (IQR 0·8–3·9; range 0–14·8; figure 1G). At study closure, only seven (3·5%) of 201 patients (median age 3·3 years [IQR 1·2–7·2; range 0·8–25·2]) were cancer free at a median follow-up time of 4·2 years (IQR 3·5–4·6; range 2·8–6·5). Of those, four had cascade testing following the diagnosis of a CMMRD proband, one infant underwent a germline panel testing for café-au-lait macules, and two children were tested because of having parents with Lynch syndrome with no cancers diagnosed as part of familial cancer screens.

Although the median TMB (298 mutations per megabase [IQR 72–449]) was in the ultra-hypermutant range (≥100 mutations per megabase),[2] there was significant variation across cancer types (figure 2A, B). CNS and gastrointestinal cancers harboured the highest TMBs due to their acquisition of somatic DNA polymerase mutations (polymerase proofreading deficiency; p=0·0001, Fisher's exact test for CNS and gastrointestinal cancers *vs* haematological and other cancers; figure 2A).[2] Additionally, we observed enrichment for deleterious *TP53* (p=0·0001, Fisher's exact test), *RAS–MAPK* pathway (p=0·0008),[29] and

*ATRX* mutations (p=0·0009) in CNS and gastrointestinal cancers as compared with haematological and other cancers (figure 2A). Furthermore, the degree of MMRDness revealed significant differences between cancer types (figure 2C). CNS tumours, which had high TMBs, had fewer microsatellite indels than haematological malignancies (p=0·031). By contrast, gastrointestinal malignancies had both high TMBs and high MMRDness (compared with CNS tumours). Importantly, all but three tumours (2%) had mutational signatures for MMR deficiency or combined MMR deficiency and polymerase proofreading deficiency, supporting the complementary roles of TMB, microsatellite instability, and mutational signatures as surrogate functional assays for the diagnosis of MMR deficiency in cancers[11] (figure 2D; appendix 1 pp 11–12).

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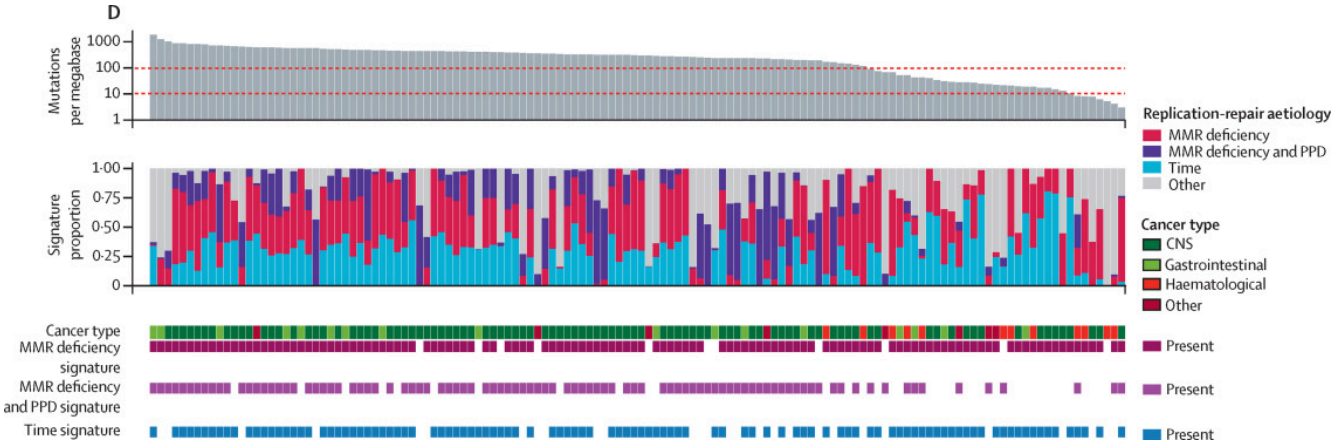


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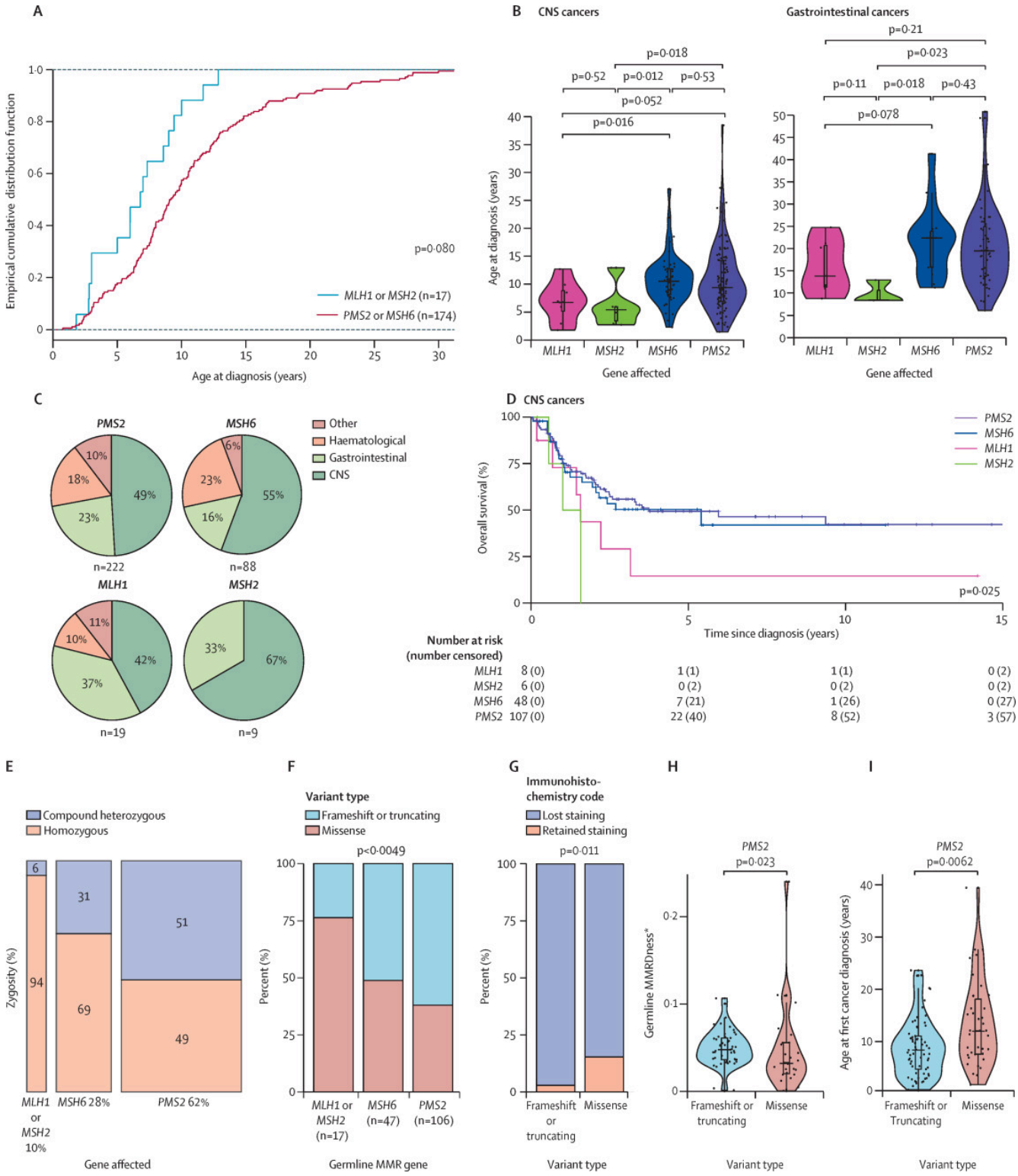
Figure 2. Genomic landscape of CMMRD tumours

(A) Whole-exome sequencing data from 132 CMMRD tumours grouped by cancer type, including number of mutations per megabase, clinical information, and genetic alterations for each sample. Frequency of mutations in each gene by cancer type are summarised on the right. (B) Mutations per megabase and (C) tumour MMRDness score from the low-coverage whole-genome sequencing (n=133) LOGIC assay; p values are from Mann–Whitney *U* tests. (D) COSMIC signatures from whole-exome sequencing, grouped by replication-repair aetiology: MMR deficiency (COSMIC signatures 6, 15, 21, and 26), MMR deficiency and PPD (COSMIC signatures 10, 14, and 20), time (COSMIC signatures 1 and 5) and others. AML=acute myeloid leukaemia. Pre-B-ALL=precursor B-cell acute lymphoblastic leukaemia. DLBCL=diffuse large B-cell lymphoma. CMMRD=constitutional mismatch-repair deficiency. ICI=immune checkpoint inhibitor. MMR=mismatch repair. MPAL=mixed-phenotype acute leukaemia. PPD=polymerase proofreading deficiency. T-ALL=T-cell acute lymphoblastic leukaemia. T-NHL=T-cell non-Hodgkin lymphoma. *MMRDness represents the degree of microsatellite indel accumulation.[11]

*PMS2* was the most frequently affected gene in our cohort, followed by *MSH6, MLH1*, and *MSH2* (table). Generally, the first cancer diagnosis was earlier for patients in whom *MLH1* or *MSH2* were affected than for those in whom *PMS2* or *MSH6* were affected (figure 3A). Differences in age of CNS and gastrointestinal cancer diagnoses by MMR gene were notable (figure 3B), with significant differences found when *MLH1* and *MSH2* were analysed in combination (appendix 1 pp 13). Haematological cancers were infrequent or absent among patients with *MLH1* or *MSH2* pathogenic variants, whereas gastrointestinal and CNS cancers were common across all four MMR genes (figure 3C). The MMR gene involved also affected patient survival, as shown among those with CNS tumours, with patients in whom *MLH1* or *MSH2* was affected having significantly lower 5-year overall survival (9% [95% CI 1–60]) than patients in whom *PMS2* (49% [40–62], p=0·015, log-rank test) or *MSH6* (50% [37–69], p=0·035) was affected (figure 3D; appendix 1 pp 13–14).

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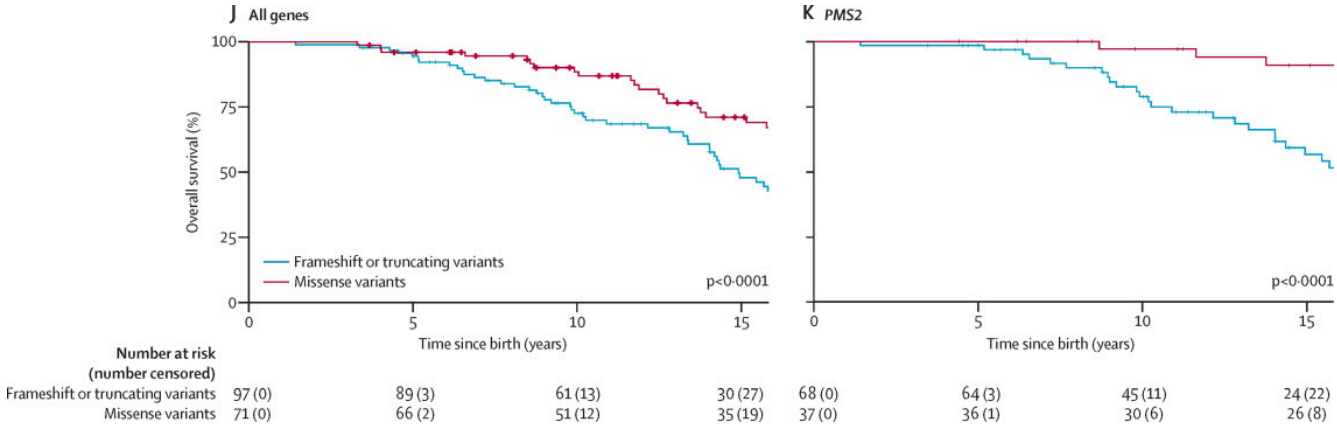


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Figure 3. Affected gene, genotype, and phenotype associations in CMMRD

(A) Cumulative incidence of first cancer stratified by MMR gene involved (*MLH1* or *MSH2 vs PMS2* or *MSH6*); p value is from Kolmogorov–Smirnov test. (B) Comparison of age at cancer diagnosis for CNS cancers (n=172) and gastrointestinal cancers (n=75) by MMR gene involved; p values are from Mann–Whitney *U* tests. (C) Proportion of each cancer type by germline gene affected in the patient. (D) Kaplan–Meier curves of overall survival for CNS cancers by MMR gene affected; p value is from log-rank test. (E) Proportion of MMR gene affected and zygosity within the germline, showing a high proportion of homozygosity in patients with *MLH1* or *MSH2* variants (p=0·0014, Fisher's exact test; total n=170). (F) Proportion of germline variant type by MMR gene affected; in this analysis, splice site, in-frame, and silent single-nucleotide variants were grouped with either frameshift or truncating variants or missense variants on the basis of the predicted protein effect; p value is from $\chi^2$ test. (G) Immunohistochemical staining results by variant type; p value is from $\chi^2$ test (n=112); staining was interpreted on each patient's tumour slide, which included both cancerous and non-cancerous (normal) cells (note: patients with CMMRD have a lack of staining in both tumour and normal cells). (H) Comparison of germline MMRDness score from LOGIC assay by variant type in patients with germline *PMS2* variants (n=76; p value is from Mann–Whitney *U* test). (I) Comparison of age at first cancer diagnosis by variant type for patients with germline *PMS2* variants (n=103); p value is from Mann–Whitney *U* test. (J–K) Kaplan–Meier curves for overall survival from birth until death or last follow-up by variant type for all genes (J) and for *PMS2* only (K); p values are from log-rank tests. CMMRD=constitutional mismatch-repair deficiency. MMR=mismatch repair. *MMRDness represents the degree of microsatellite indel accumulation.[11]

Examination of specific variants within MMR genes revealed an enrichment of germline homozygosity in *MLH1* and *MSH2* compared with *PMS2* or *MSH6* (p=0·0014; figure 3E). Furthermore, carriers of pathogenic variants in *MLH1* or *MSH2* showed enrichment for missense variants, in contrast to the higher percentage of frameshift or truncating variants observed in *PMS2* or *MSH6* (p=0·0049; figure 3F). Frameshift or truncating variants were more often associated with complete loss of MMR protein expression in tissues (as assessed by immunohistochemistry; p=0·011; figure 3G), higher MMRDness[11] in the germline (p=0·023 for *PMS2* gene; figure 3H; appendix 1 pp 14), and earlier cancer onset (p=0·0062 for *PMS2* gene; figure 3I; appendix 1 pp 14) compared with missense variants across all genes and within the *PMS2* gene (appendix 1 p 14–15). Notably, patients with frameshift or truncating variants had poorer overall survival (15-year overall survival 49% [95% CI 39–62]) than patients with missense variants (71% [60–84], p<0·0001; figure 3J), with starker differences within the largest group of patients

with germline *PMS2* variants (59% [47–74] *vs* 91% [80–100], p<0·0001; figure 3K; see appendix 1 p 15 for *MSH6* variant results).

At age 15 years, predicted overall survival by affected gene was 63% (95% CI 55–73) for *PMS2*, 49% (35–68) for *MSH6*, and 19% (6–66) for *MLH1*, with no survivors among patients in whom *MSH2* was affected (p<0·0001; appendix 1 p 16). Patients prospectively undergoing surveillance[15] had improved survival (15-year overall survival 65% [95% CI 52–81]) compared with those without surveillance (37% [23–57]; p=0·0001; appendix 1 p 17). Surveillance had the highest impact among patients in whom *MLH1* or *MSH2* was affected (15-year overall survival 40% [95% CI 14–100] with surveillance *vs* 0% without surveillance; figure 4A, B).

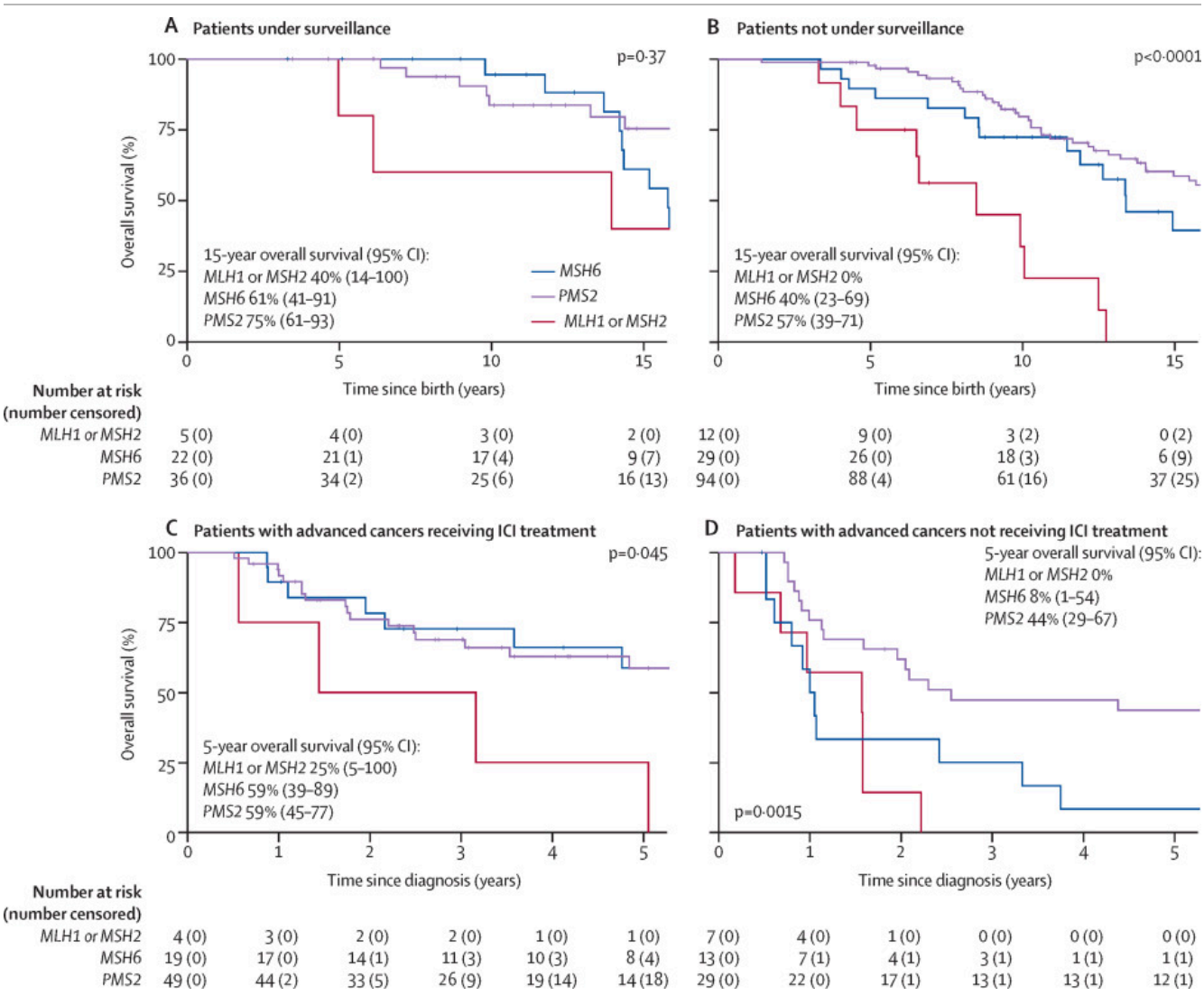


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Figure 4. Patient survival by mismatch-repair gene affected and intervention received

(A–B) Overall survival from birth until death or last follow-up in patients under surveillance (A) and not under surveillance (B). (C–D) Overall survival from cancer diagnosis until death or last follow-up for patients with advanced (recurrent or metastatic) tumours receiving ICI treatment (C) and not receiving ICI treatment (D). p values are from log-rank tests. Multivariable Cox regression analyses for overall survival are presented in the appendix 1 (pp 19–20). ICI=immune-checkpoint inhibitor.

ICI treatment improved survival[17, 18] among patients with advanced (ie, recurrent or metastatic) cancers (5-year overall survival 56% [95% CI 45–71] with ICI treatment *vs* 28% [18–45] without ICI treatment, p=0·014; appendix 1 p 18), but the maximal impact was noted for patients with germline *PMS2* or *MSH6* pathogenic variants (5-year overall survival 58% [47–73] with ICI treatment *vs* 33% [21–51] without ICI treatment in the combined group of patients with *PMS2* or *MSH6* mutations; figure 4C, D).

Multivariable analysis showed the germline MMR gene (*MLH1* or *MSH2 vs PMS2* or *MSH6*) was an independent predictor for survival for all patients (hazard ratio 2·25 [95% CI 1·20–4·22], p=0·011) and for those with advanced cancers (2·51 [1·15–5·45], p=0·020; appendix 1 pp 19–20). Age at diagnosis of CMMRD [for surveillance analysis] or cancer [for ICI analysis], region of residence (North America, Europe, or Australia *vs* others), first cancer diagnosis (CNS *vs* others), and interventions (surveillance or ICI treatment) were also independent predictors of survival in all patients; these parameters, except for region of residence were also independent predictors of survival in patients with advanced cancer (appendix 1 pp 19–20, 24–27). Sex was not an independent predictor of survival in either group of patients.

## Discussion

This large cohort of carefully annotated patients with CMMRD characterises their true clinical phenotype and the genomic spectrum of their cancers. The important associations between the gene affected and variant type in the germline and their differential effects on cancer type, onset, biology, and outcome will affect individualisation of patient care.

Examination of families with CMMRD reveals that the high homozygosity in countries with a low population prevalence of consanguinity is related to silent endogamy in isolated populations. In most instances, hidden consanguinity and founder effects were clinically apparent, suggesting that a high index of suspicion should be maintained for specific demographic populations in which adults remain healthy. Even in geographically dispersed cohorts, including Indigenous patients from Canada, we observed identical variants in individuals with CMMRD, suggesting that endogamy across generations can be missed.

Individuals with CMMRD can have several non-oncological manifestations. We observed dermatological findings in the vast majority, with a third fulfilling the clinical criteria for neurofibromatosis type 1.[21] Although none had germline pathogenic variants in *NF1* or *SPRED1*, mosaicism or organ-specific secondary hits due to obligatory mutagenesis are probable explanations for this observation. Indeed, somatic mutations in *NF1* were detected in many CMMRD cancers. Clinical distinction between CMMRD and neurofibromatosis type 1 can be aided by the higher prevalence of concomitant hypomelanotic macules and the relative paucity of neurodevelopmental issues in CMMRD, different family histories reflecting autosomal dominant inheritance (neurofibromatosis type 1) versus recessive inheritance (CMMRD), and the distinct spectrum of benign (pilomatrixoma) and multisystem malignant neoplasms in patients with CMMRD.[9] Notably, in this large cohort, we did not observe significant clinical immune dysfunction[26] or autoimmunity.[25] Furthermore, intellectual disability, vision loss, and hearing loss were rare. These manifestations should not affect the counselling of families and therapeutic decisions.

Cancer is the hallmark of CMMRD. Although we cannot ascertain the true population risk of cancers in CMMRD from our cohort, our observed rates of primary and subsequent cancers[19] at young ages are much higher than observed in other predisposition syndromes. Patients developed a new tumour every

2 years, suggesting that CMMRD is one of the most penetrant and aggressive human cancer predisposition syndromes. The cancer spectrum extended beyond the classical triad of gliomas, colorectal cancers, and T-cell lymphomas. Specifically in the CNS, we observed optic glioma,[27] ependymoma,[28] and aggressive embryonal tumours. Among haematological malignancies, we found entities not commonly associated with CMMRD, including mixed-phenotype acute leukaemia and mature B-cell lymphomas. Importantly, patients with CMMRD develop adult-type cancers (gastric and pancreatic adenocarcinoma, transitional renal cell, urological, and breast cancers) at younger ages than the general population, which are distinguished by the uniform presence of MMR-deficiency signatures.[11] As patients with CMMRD survive into adulthood, the guidelines for surveillance will need to evolve to screen for these cancers. Despite intertumoural differences possibly related to tissue-specific oncogenic processes, our pan-cancer analyses revealed universal hypermutation, microsatellite instability, and specific replication-repair deficiency signatures. These distinguish MMR deficiency-driven cancers from other tumours emerging from the same organ and can guide management decisions. Robust and inexpensive functional genomic analyses can be fast, reliable, and accessible methods globally to diagnose cancers associated with MMR deficiency and then test the germline to diagnose CMMRD.

Our data also provides valuable insights regarding somatic mutagenesis in CMMRD cancers. CNS cancers have very high TMBs but relatively lower MMRDness (reflecting microsatellite indel accumulation). By contrast, haematological cancers have lower TMBs but higher MMRDness, whereas gastrointestinal cancers have both high TMBs and MMRDness. These findings are explained by the stochastic accumulation of microsatellite indels related to the number of cell divisions, whereas TMB is affected by secondary somatic mutations in polymerase genes,[2] and the resulting ultra-hypermutation requires mutations in *TP53* for cell viability. Indeed, secondary polymerase and *TP53* mutations were enriched in CNS and gastrointestinal neoplasms. Cancers from organs with high rates of cell division (haematopoietic and gastrointestinal) tolerated a higher microsatellite indel burden. These differences could explain the divergent responses to ICI treatment across CMMRD cancers observed previously.[17] Furthermore, the scarcity of *TP53* mutations in CMMRD haematopoietic malignancies contrasts with the deleterious effect of *TP53* mutations in patients with Li-Fraumeni syndrome, and might explain the survival differences in leukaemias from these different predisposition syndromes.[30]

Our large dataset involving biallelic inheritance of MMR genes in patients allowed us to test genotype–phenotype associations. We found that *MSH2* and *MLH1* genes were more aggressive, wherein biallelic alterations result in higher penetrance, earlier cancer onset, and worse outcomes than for *PMS2* and *MSH6*. Most variants in *MLH1* or *MSH2* are homozygous rather than compound heterozygous, and missense rather than frameshift or truncating, suggesting that the repertoire of variants in these genes compatible with life might be limited due to extreme mutagenesis and microsatellite indel accumulation. Furthermore, frameshift or truncating variants were more aggressive than non-truncating missense variants, even in the same gene. Patients with missense variants retained partial expression of their gene product, had lower MMRDness in their germline, and had later onset of cancer. These effects contributed to patients with frameshift or truncating variants having inferior outcomes than those with missense variants. For *PMS2*, these effects could be related to a higher frequency of CNS cancers with poor outcomes, earlier cancer onset in each tumour type, and a higher frequency of cancer initiation in general.

Importantly, the impact of the specific MMR gene involved persisted even with implementation of robust interventions such as surveillance or immunotherapy. Although both interventions confer a

significant survival benefit, their impact varied across genes, highlighting the need for tailoring of management approaches not only to cancer type but also to the individual patient's affected germline gene.

We acknowledge classic limitations for our registry study, including potential biases, such as probable over-representation of patients with cancers, potential under-representation of some populations, familial correlations, and differences in therapies and outcomes between institutions and countries. To mitigate some of these issues, longitudinal follow-ups were conducted to collect clinical, cancer, and therapy data. Cascade testing, enrolment, and surveillance for unaffected patients enabled data collection on cancer development over time. Most patients came from distinct families, and siblings usually developed different cancer types, limiting the bias for familial relatedness. Outcomes were stratified by countries and included in multivariable analyses to reduce confounding. However, we did not address additional important questions, such as the differences in genomic landscapes and outcomes between CMMRD and non-CMMRD cancers, which should be analysed in future studies.

In summary, we have highlighted CMMRD as one of the most aggressive and penetrant disorders in terms of cancer frequency and outcomes among childhood cancer predisposition syndromes. We have provided data on rare patients who survived into adulthood but who remained at risk for new cancer types, and redefined the clinical and molecular landscape for patients with CMMRD and their related cancers. Additionally, we have generated genomic and genetic insights to assist in personalised risk assessment, potentially affecting the initiation and type of surveillance, decisions for immunotherapy and future endeavours at cancer interception and prevention. We underscore that global collaboration is needed for translating such advances for patients with CMMRD and their families across different communities, countries, and health-care systems.

**Contributors**

Study conception and design: ABE, UT, and AD. Study supervision: UT and AD. Patient enrolment and sample coordination: ME, VB, and LS. Data collection and analysis: ABE, UT, and AD. Provision of study materials and patients: MA, AA-B, ARe, ALi, AA, ALa, ATR, AFA-D, ACS, AVD, AB, ARa, ASM, BLK, BP, BH, BL-A, BC, CK, CG, CCP, DG, DSa, DSZ, DTB, DJK, DH, DB, D-AK-Q, DSt, EO, FC, HBF, HT, IW, IS, IF, JMS, JV, JS, JK, JRH, JRG-S, KB, KJB, KM, KEN, KAC, LP, MAH, MS, MJG-d-C, MJM, MMi, MLB, MMa, MA-H, MFA-J, MAC, MO, MPL, MZ, MG, NS, NM, NW, NH, NF-B, OA, OC, PR, PNP, PN, RP, RCA, RKS, RK, RD, RR, RE, RBM, RC, RN, RT, SRa, SS, SL, SPer, SCas, SRi, SCo, SA, SCha, SB, SChi, SLC, SRo, SCah, SPen, SAH, TG, UI, VL, VMI, WDF, and YYL. Radiology reporting: M-LCG and BE-W. Pathology reporting: CH and ALe. Bioinformatics analysis: ABE, NRF, YC, and AS. Microsatellite indel analysis: LN, JC, and YEM. Statistical analysis: ABE, AD, and ZAL. Data interpretation: ABE, UT, AD, MA, CD, PCN, AV, DM, and EB. Manuscript preparation: ABE, UT, and AD. Manuscript editing and final approval: all authors. UT and AD accessed and verified the data. The corresponding author is responsible for the data, analyses, and publication.

## Data sharing

All clinical data relevant to this work will be available in an anonymised format at the European Genome Phenome Archive, where we have a common repository of IRRDC data (https://ega-archive.org/datasets/EGAD00001008036↗). These data will be accessible through communication with the corresponding author from the time of publication. As some of these data can lead to patient identification for this rare subset of patients, they will not be publicly available. Researchers interested

to use these data will need to submit a brief research proposal to the IRRDC scientific committee for approval and, thereafter, necessary data sharing agreements will need to be completed.

## Declaration of interests

ALa reports payment from Alexion, support from Servier and stock from Gilead, outside of the submitted work. AV is co-lead role of the Consortium for Childhood Cancer Predisposition, outside of the submitted work. BH reports payment and stock from Invitae, outside of the submitted work. BC reports participation as data safety and monitoring board member in ReRad Study, participation in the chapter advisory board for Make a Wish Canada Nova Scotia, and participation in the medical advisory committee for Make a Wish Canada, outside of the submitted work. CCP reports grants from St Baldrick's Foundation, outside of the submitted work. DSZ reports consulting fees for Bayer, AstraZeneca, Accendatech, Novartis, Day One, FivePhusion, Alexion, Amgen, and Norgine, outside of the submitted work. DTB reports grants from MSD and Novocure, consulting fees from Nanocarry Therapeutics and Servier, and payment from Servier, outside of the submitted work. EO reports payment and support from Alexion for educational event, outside of the submitted work. EB reports grants from Roche and board participation for Novartis, Alexion and Gilead, outside of the submitted work. FC reports grants from Hall Hunter Foundation (UK), outside of the submitted work. HBF reports payments from Illumina and Sanofi Genzyme, support from Illumina, participation as scientific advisory committee for Sanofi Genzyme, International Gaucher Alliance and Igentify, stock from Igentify, and receipt of materials from Illumina, outside of the submitted work. IW reports grants from Chimerix and payment from COG Partners, outside of the submitted work. IS reports grants from Fondation Saint-Luc and FNRS-CDR, outside of the submitted work. JK reports other financial interests at Servier and PRA Health Sciences, outside of the submitted work. JRG-S reports participation on the board of the Philippine Society of Pediatric Oncology and Philippine Board of Pediatric Oncology, and stock in Macrogenics, Moderna, Mirati Therapeutics, CRISPR Therapeutics, Repligen, Quidelortho, and Shockwave Medical, outside of the submitted work. KJB reports consulting fees from US WorldMeds, Springworks Therapeutics, Alexion, and YmAbs, and payment from Alexion, outside of the submitted work. MS reports grants and support from the Swedish Childhood Cancer Fund, participation as a data safety and monitoring board member for clinical trial NCT05230758, and participation in the Swedish Pediatric CNS tumour group, outside of the submitted work. MAC reports financial support from SUNY Upstate Department of Pediatrics and board participation for Paige's Butterfly Run, outside of the submitted work. MO reports payment from Aptitude Health and participation on a data safety monitoring board or advisory board for Ultragenyx and Abeona, outside of the submitted works. MZ reports payment and support from and board participation for AstraZeneca. NW reports grants from CANSEARCH Foundation, Childhood Cancer Research Switzerland, and the Foundation for Children and Adolescents with Cancer; payment, support, and advisory board participation for Swedish Orphan Biovitrum; and board participation for Childhood Cancer Switzerland, outside of the submitted work. NH reports grants from the National Institutes of Health (NIH) and board participation for Incyte and Pfizer, outside of the submitted work. PCN reports grants from the Canadian Institutes for Health Research (CIHR) Foundation, US Department of Defense, and Garron Family Cancer Centre, outside of the submitted work. RP reports participation in the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer, outside of the submitted work. RT reports consulting fees from Fennec Pharmaceuticals and Day One Biopharmaceuticals and payment from Fennec Pharmaceuticals, outside of the submitted work. SS reports payments from Sanofi Pharmaceuticals and Mylan Pharmaceutical, and board participation for Sanofi Pharmaceuticals, outside of the submitted work. SB reports

consulting fees from Hoffmann-La Roche, YmAbs, MAP Biopharma and SERB SAS, and payment from Zschimmer & Schwarz Mohsdorf, outside of the submitted work. UI reports board participation in Pakistan Society of Pediatric Oncology, outside of the submitted work.

**Acknowledgments**

UT is supported by the CIHR (PJT-156006), the CIHR Joint Canada–Israel Health Research Program (MOP-137899); a Stand Up to Cancer–Bristol Myers Squibb Catalyst Research grant (SU2C-AACR-CT07-17); a Children's Oncology Group National Cancer Institute Community Oncology Research Program Research Base Administrative Supplement Request (3UG1CA189955-08S2); CCS/CIHR/BC Spark Grants (Novel Technology Applications in Cancer Prevention and Early Detection; SPARK-21, 707089), funded by the Canadian Cancer Society and Brain Canada); The V Foundation for Cancer Research (T2019-016); and BioCanRx (FY17/18/ES8), Canada's Immunotherapy Network (a Network Centre of Excellence). UT is also generously supported by SickKids Foundation donors Harry and Agnieszka Hall; Meagan's Walk (MW-2014-10); BRAINchild Canada; and The LivWise Foundation. AD is supported by the Kai Slockers Pediatric Cancer Research Fund St Baldrick's International Scholar Grant (grant number 697257); a Stand Up to Cancer Maverick award; a Hold'em for Life Oncology Fellowship Award; and the Garron Family Cancer Centre. DM is supported by the Canadian Imperial Bank of Commerce Children's Foundation Chair in Child Health Research. F Carceller is partly funded by The Giant Pledge via the Royal Marsden Cancer Charity and acknowledges funding from the Hall-Hunter Foundation to the Paediatric and Adolescent Neuro-Oncology & Drug Development Unit at The Royal Marsden Hospital. MZ is supported by the Ministry of Health of the Czech Republic (grant number NU21-07-00419).

## Supplementary Materials

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