



**HAL**  
open science

## Report of the fifth meeting of the European Consortium 'Care for CMMRD' (C4CMMRD), Leiden, The Netherlands, July 6th 2019

M. Suerink, K. Wimmer, L. Brugieres, C. Colas, R. Gallon, T. Ripperger, P.  
R Benusiglio, Ema Bleiker, Z. Ghorbanoghli, Y. Goldberg, et al.

### ► To cite this version:

M. Suerink, K. Wimmer, L. Brugieres, C. Colas, R. Gallon, et al.. Report of the fifth meeting of the European Consortium 'Care for CMMRD' (C4CMMRD), Leiden, The Netherlands, July 6th 2019. Familial Cancer, inPress, 10.1007/s10689-020-00194-1 . hal-03034558

**HAL Id: hal-03034558**

**<https://hal.science/hal-03034558v1>**

Submitted on 1 Dec 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## Report of the fifth meeting of the European Consortium 'Care for CMMRD' (C4CMMRD) organized in Leiden, The Netherlands, July 6<sup>th</sup> 2019

M Suerink<sup>1</sup>, K Wimmer<sup>2</sup>, L Brugieres<sup>3</sup>, C Colas<sup>4</sup>, R Gallon<sup>5</sup>, T Ripperger<sup>6</sup>, PR Benusiglio<sup>7,8</sup>, EMA Bleiker<sup>9,10</sup>, Z Ghorbanoghlil<sup>11</sup>, Y Goldberg<sup>12</sup>, JCH Hardwick<sup>13</sup>, M Kloor<sup>14,15</sup>, M le Mentec<sup>4</sup>, M Muleris<sup>7</sup>, M Pineda<sup>16,17</sup>, C Ruiz-Ponte<sup>18</sup>, FH Menko<sup>19</sup>, HFA Vasen<sup>13</sup>

1. Department of Clinical Genetics, Leiden University Medical Centre, Leiden, the Netherlands.
2. Division of Human Genetics, Medical University of Innsbruck, Innsbruck, Austria.
3. Child and Adolescent Cancer Department, Gustave Roussy Cancer Campus, Villejuif, France.
4. Department of Genetics, Institut Curie, Université de Recherche Paris Sciences et Lettres, Paris, France.
5. Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK.
6. Institut für Humangenetik, Medizinische Hochschule Hannover, Hannover, Germany.
7. Sorbonne Université, Inserm, Unité Mixte de Recherche Scientifique 938, Equipe Instabilité des Microsatellites et Cancer Centre de Recherche Saint-Antoine, CRSA, Paris, France
8. Unité fonctionnelle d'Oncogénétique, Département de Génétique et Institut Universitaire de Cancérologie, Groupe Hospitalier Pitié-Salpêtrière, AP-HP, Sorbonne Université, F-75013 Paris, France.
9. Division of Psychosocial Research and Epidemiology & Family Cancer Clinic, The Netherlands Cancer Institute, Amsterdam, The Netherlands.
10. Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands.
11. The Netherlands Foundation for the Detection of Hereditary Tumours, Leiden, The Netherlands 2. Department of Gastroenterology & Hepatology, Leiden University Medical Center, Leiden, The Netherlands
12. Raphael Recanati Genetics Institute, Rabin Medical Center, Beilinson Campus, Petah Tikva, Israel
13. Department of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, The Netherlands
14. Department of Applied Tumor Biology, Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany.
15. Clinical Cooperation Unit Applied Tumor Biology, DKFZ (German Cancer Research Center) Heidelberg, Heidelberg, Germany.
16. Hereditary Cancer Program, Catalan Institute of Oncology, ONCOBELL Program, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Hospitalet de Llobregat, Barcelona, Catalonia, Spain.
17. Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain.
18. Fundacion Publica Galega de Medicina Xenomica, SERGAS, Instituto de Investigacion Sanitaria de Santiago (IDIS), Grupo de Medicina Xenomica-USC, Centro de Investigacion Biomedica en Red de Enfermedades Raras (CIBERER), 15706 Santiago de Compostela, Spain
19. Family Cancer Clinic, Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

Constitutional mismatch repair deficiency (CMMRD) is an autosomal recessive condition associated with a high risk of pediatric cancers. It is caused by homozygous or compound heterozygous pathogenic germline variants in one of four mismatch repair (MMR) genes (*i.e.*, *MLH1*, *MSH2*, *MSH6* and *PMS2*)[1]. Mono-allelic (heterozygous) MMR gene variants lead to autosomal dominant Lynch syndrome[2].

While Lynch syndrome is one of the most common cancer predisposition syndromes and leads to an increased risk of colorectal cancer, endometrial cancer and other malignancies in adults[2], CMMRD is rare and leads to an increased probability to develop brain tumors,

hematological malignancies, colorectal cancer and a wide range of other cancers in children, adolescents and young adults[1]. In addition, most patients with CMMRD have non-neoplastic features with multiple café-au-lait maculae (CALM) being the most prevalent[1,3].

This report summarizes the 5<sup>th</sup> meeting held by the 'Care for CMMRD' (C4CMMRD) consortium in Leiden, the Netherlands, on July 6<sup>th</sup> 2019. The consortium was established in 2013 and aims at improving the care of patients with CMMRD and their families by increasing knowledge and awareness of the syndrome through developing guidelines for diagnosis and clinical care, establishing a database to record clinical details of known patients with CMMRD and conducting collaborative studies. Meetings are held every one to two years and aim at updating the members with the latest results and developments of ongoing research and at initiating new study proposals. Thirty-five participants from nine countries and various medical fields (including basic and translational researchers, pediatric oncologists, clinical geneticists, gastroenterologists and molecular geneticists) attended the meeting in Leiden.

### **CMMRD-database in Paris**

For research purposes a database with CMMRD patients was established in the Gustave Roussy Cancer Campus in Villejuif, France. To start the meeting an update on its current status was given by Chrystelle Colas. At the time of the meeting, 87 patients with CMMRD from 66 families were included, 27 of whom are still alive (age range 3 – 48 years). *PMS2* is the gene which most often carries pathogenic variants (n=34), followed by *MSH6* (n=19), *MSH2* (n=8) and *MLH1* (n=4). Molecular results are lacking for one patient. All but one patient developed at least one malignancy. There is a total of 154 tumor diagnoses in 86 patients with tumors of the central nervous system being the most frequent (n=64, 41%), followed by hematological malignancies (n=45, 28%), mainly of T lymphoblastic lymphomas, and Lynch syndrome-related malignancies (n=43, 27%).

This database was used as a starting point for several studies of which (preliminary) results were discussed during the meeting.

### **Role of functional assays**

The previously developed C4CMMRD criteria for the clinical suspicion of a CMMRD diagnosis in young cancer patients[1] were designed to have high diagnostic sensitivity at the cost of specificity. Detection of pathogenic variants in both alleles of an MMR gene is required to confirm the diagnosis. A definite molecular diagnosis or, equally important, a rejection of this diagnosis is also needed when testing for CMMRD as a differential diagnosis to neurofibromatosis type 1 (NF1)/Legius syndrome in a malignancy-free child with NF1-signs without a causative *NF1* or *SPRED1* mutation[3]. Unfortunately, molecular genetic testing is not always definitive, and the diagnosis of CMMRD is frequently confounded by MMR variants of unknown significance (VUS) and *PMS2* pseudogenes.

The need to resolve diagnostic ambiguities has led to the development of functional CMMRD assays and highly sensitive microsatellite instability (MSI) assays that detect low-frequency microsatellite length variants in non-neoplastic tissues, a diagnostic hallmark of CMMRD.

Current functional approaches include assessing methylation tolerance in combination with MSI in primary lymphoblastoid cell lines[4] and assessment of the MMR capacity of protein extracts from patient cells[5]. Martine Muleris presented data of the methylation tolerance test that was performed on 85 patients with a CMMRD-like phenotype and 92 controls. Previously it was shown, in a smaller cohort, that this test can discern CMMRD patients and healthy controls and may therefore be a useful diagnostic tool in CMMRD-like patients[4]. The results of the methylation tolerance test in this larger cohort will be published elsewhere.

While being reliable, these functional assays performed in specialized laboratories may not easily be scalable. Furthermore, they require fresh patient material[4,5]. MSI assays for CMMRD detection may be applied also on ascertained patient DNA in retrospective studies, and are likely to need less specialized laboratories. The first MSI assay assessing low-level MSI in three dinucleotide repeat markers in patient peripheral blood leukocytes (PBLs) is simple, fast and scalable, but has the disadvantage of being insensitive to MSH6 deficiency due to the type of microsatellite analyzed[6].

At the meeting, Richard Gallon presented a sensitive and scalable MSI assay that detects low-level MSI in patient PBLs using 24 mononucleotide repeat markers. The assay method was developed in a pilot cohort of 5 CMMRD patients and 40 controls, and was validated by analyzing an additional 27 CMMRD patients, and 54 controls, blind to sample status, as well

as 40 Lynch syndrome patients. The assay achieved 97% sensitivity and 100% specificity, including the detection of MSH6 deficient patients, and patients with hypomorphic *PMS2* variants[7]. The single false negative result was attributed to the patient's chemotherapy-induced aplasia when this sample was collected, as additional samples of this patient collected after recovery from aplasia were correctly classified[7].

Marta Pineda presented a high sensitivity MSI (hs-MSI) assessment that can be used in non-neoplastic tissues of Lynch syndrome and CMMRD carriers using a panel of 186 mononucleotide repeat markers. This approach was applied to a training cohort including 15 blood samples from negative controls, 48 from Lynch syndrome individuals and 12 from CMMRD patients. MSI score was significantly higher in blood DNA samples from CMMRD patients compared to healthy controls, without overlapping. This finding was confirmed in a validation set including 36 blinded samples (18 controls and 18 CMMRD provided by the C4CMMRD consortium) reaching 100% specificity and sensitivity, also including the detection of MSH6 deficient patients. Moreover, high hs-MSI scores were not detected in blood from germline *TP53*, *POLE*, *POLD1* and *NF1* mutation carriers and early-onset Lynch syndrome, showing that the assay discriminates between CMMRD and other hereditary syndromes with overlapping phenotypes. The results of this approach had good correlation with the MSI assay presented by Richard Gallon. The results of this work have been recently published by González-Acosta *et al.*[8].

Patrick Benusiglio presented a proof-of-concept study of another assay detecting ultra-low MSI in leukocytes enabling rapid and accurate diagnosis of CMMRD, which will be published elsewhere.

In conclusion, several reliable MSI assays for a rapid CMMRD diagnosis are developed with the support of the C4CMMRD consortium and at least one of them is suitable for scalable screening of at-risk populations (see proposal for the assessment of *Prevalence of CMMRD in patients with T-cell acute lymphoblastic lymphoma*).

### **CMMRD-like phenotypes**

Differential diagnoses in patients with a "CMMRD-like" phenotype in whom neither identification of bi-allelic germline MMR mutations nor functional or MSI assays could confirm this diagnosis were another topic of the 5<sup>th</sup> C4CMMRD meeting.

Clara Ruiz-Ponte presented the case of a boy who fulfilled the C4CMMRD criteria for suspecting CMMRD. This boy, who had a maternal family history of Lynch syndrome, developed colorectal cancer at 12 years of age and had a skin nodule suspected of being a neurofibroma. However, he only carried the maternally inherited pathogenic *MSH2* variant and was negative for CMMRD in all functional and MSI assays that were applied. Therefore, other possible scenarios were explored that could explain the early age of tumour onset. Interestingly paternally-inherited low/moderate-penetrance variants in other cancer predisposing genes or genes described as genetic modifiers of Lynch syndrome were identified. Data of this patient suggest that the combination of several low-risk modifier alleles in addition to the pathogenic *MSH2* variant may be responsible for the CMMRD-like phenotype in this patient[9].

Katharina Wimmer presented three cases with a “CMMRD-like” phenotype likely explained by germline *POLE* pathogenic variants. These included a previously published case of a 14 year old boy with colorectal cancer, colon adenomas, a pilomatricoma and multiple CALM[10] and two unpublished cases, one being a 31 year old male with colorectal cancer, adenomatous polyposis, glioblastoma, CALM and pilomatricomas, and the other a 4 year old girl with a malignant central nervous system tumor and CALM. As it was the case for a *POLE* pathogenic variant found in a medulloblastoma patient with a “CMMRD-like” phenotype who was published after our meeting[11], the *POLE* mutations found in all three patients presented at the meeting were *de novo* and were previously seen as somatic but never as germline mutations. Taken together, these cases support the evolving notion that specific *POLE* exonuclease domain variants, typically seen as somatic mutations in hyper-mutated tumors, confer a phenotype reminiscent of CMMRD when present as a germline mutation. Katharina Wimmer also presented two siblings, diagnosed with bowel cancer as teenagers, who both had a maternally inherited, heterozygous *PMS2* pathogenic variant and a paternally inherited *POLD1* variant likely to affect POL $\delta$  exonuclease activity. This suggests that this “CMMRD-like” phenotype could be caused by digenic inheritance of MMR and polymerase proofreading inactivating mutations.

Marine Le Mentec and Chrystelle Colas presented a patient with duodenal cancer at age 17 with a maternally inherited heterozygous *PMS2* pathogenic variant as well as a paternally inherited heterozygous *POLE* variant of unknown significance.

Taken together, these cases demonstrate that sequencing of *POLE* and *POLD1* should be considered in patients with a “CMMRD-like” phenotype in whom CMMRD can’t be confirmed (neither molecularly nor functionally).

### **CMMRD and early onset systemic lupus erythematosus**

As listed in the C4CMMRD consensus guidelines, there are a number of non-neoplastic features, such as pilomatricomas, that are indicative of CMMRD in the (young) cancer patient or in a patient with suspected NF1 but without an *NF1* or *SPRED1* pathogenic variant[1,3]. At the meeting, Yael Goldberg introduced a new non-neoplastic feature by presenting two cases of young children with CMMRD and pediatric systemic lupus erythematosus (SLE). Age of onset was five years in both children. One of them did not have any cancer at the time of diagnosis[12]. Taken together with three previously published children with CMMRD and SLE[13-15], these patients indicate that pediatric onset SLE should be considered a diagnostic criterion of CMMRD and CMMRD testing should be offered if additional features are present. This may alert early diagnosis, but the treatment of SLE in those patients may be challenging. Immune checkpoint inhibitors are under investigation as a treatment for CMMRD-related cancers, but may cause SLE to flare, while steroid treatment for SLE may mitigate the effect of immune checkpoint inhibitors.

### **Psychological impact**

Eveline Bleiker was invited to the meeting to give a presentation on her experience with the psychological impact of another severe cancer predisposition syndrome, namely Li Fraumeni syndrome (LFS), and see what can be learned from this in the context of CMMRD. Based on experiences and literature on LFS it is expected that the uptake of genetic testing in those who are aware of their hereditary factor will be high, particularly for siblings of affected children. It is expected that in 20-30% of patients with a confirmed diagnosis the levels of distress will be high. The large majority of these patients might experience specific worries related to CMMRD and to coping with cancer in their family. Professional psychosocial support should be offered to all. Worries about the cancer risk in children are expected to be high and deserve attention from a counselor and, if needed and desired, from a professional psychosocial worker. The Psychological Aspects of Hereditary Cancer questionnaire can be used as a tool to identify and discuss the specific problems

experienced[16]. These expectations are based on studies with LFS. To learn more about the psychosocial issues that come with CMMRD, qualitative and quantitative studies on this topic in this population are recommended.

### **Experience with colonoscopic surveillance**

James Hardwick outlined his experience of performing colonoscopic surveillance in a CMMRD patient in Leiden. Surveillance was commenced at 26 years of age and performed yearly for four years until the patient developed a glioblastoma. At the first colonoscopy a 2cm villous adenoma with high grade dysplasia was successfully removed by piecemeal Endoscopic Mucosal Resection. A 1cm sessile serrated polyp with low grade dysplasia and 2 sub-centimeter adenomas were also removed. Subsequent colonoscopies were performed using chromoendoscopy due to the subtle flat morphology of several of the polyps, with the removal of several more sub-centimeter sessile serrated polyps and adenomas over the four year period. In conclusion the colon is at high risk in CMMRD. Both serrated polyps and classical adenomas are found. Advanced polyps can be removed successfully endoscopically. Intensive surveillance seems justified.

### **Proposals for collaborative studies and recent results**

#### *Selection criteria for CMMRD testing in children without malignancy with an NF1-like phenotype*

CMMRD is a valid differential diagnosis in children without cancer who are suspected of sporadic NF1 but in whom no causative *NF1* or *SPRED1* variant is identified. In 2019 a consensus guideline was published by the C4CMMRD consortium, advocating testing of CMMRD in preselected patients with a higher a priori chance, rather than reflex testing of all suspected sporadic NF1 children lacking causative *NF1/SPRED1* variants[3]. Manon Suerink and Katharina Wimmer presented the design of a prospective multicenter study to validate the specificity of the criteria by prospectively recording cases to whom CMMRD testing is offered.

#### *PD-1 blockade as treatment in CMMRD*

Laurence Brugieres gave a presentation on the potential of PD-1 blockade as a treatment for CMMRD-related cancer. MMR deficient cancers have been shown to respond well to this



treatment modality[17]. To evaluate the proportion of patients who could benefit from treatment with PD-1 inhibitors and to analyze indications and efficacy of immunotherapy in this first set of patients, an analysis of patients included in the C4CMMRD database was undertaken. In addition, collaborating researchers were contacted to include more patients who received immunotherapy.

Overall, 18 CMMRD patients treated with PD-1 inhibitors were identified. Indication for immunotherapy was high-grade glioma in 13 patients (2 for front-line treatment, 11 at relapse). The type of treatment was known for 17/18 patients: pembrolizumab for 5 and nivolumab for 12 patients (3 of which are included in a trial combining ipililumab and nivolumab). Ten patients had progressive disease, whereas 8 patients had a stabilization and/or a response. After the initiation of immunotherapy, 11 patients died with a median survival of 5 months (9 high-grade gliomas and 2 digestive tract cancers) and 7 patients were still alive with median follow-up of 20 months (4 high-grade glioma, 2 digestive tract cancers and one non-Hodgkin lymphoma).

It appears from this short series of patients that, despite a high mutation burden, not all CMMRD patients benefit from immunotherapy. It was proposed to include this series of patients in the SIGN'it project, an on-going project aiming to analyze biomarkers associated with response to PD-1 inhibitors (B. Georger, France). To collect more data, a specific data sheet will be sent to all investigators who have included a CMMRD patient treated with immunotherapy in the C4CMMRD database.

### *Guidelines for genetic counselling*

Tim Ripperger followed with a presentation drawing attention to the need for guidelines regarding counselling issues faced by genetic counsellors, clinical geneticists, and oncologists taking care of CMMRD families. Following the consortiums' focus on the development of surveillance guidelines [18] and clinical criteria indicating when to test for CMMRD in cancer patients [1] as well as their recent refinement regarding individuals with suspected neurofibromatosis type 1 but without an identifiable *NF1* or *SPRED1* mutation[3], we discussed and consented the crucial need of recommendations for genetic counselling of families with suspected and/or diagnosed CMMRD. Although, there is a growing body of literature dealing with CMMRD, none of the papers specifically addressed counselling

issues (e.g., ethical and legal issues of predictive testing in minor siblings, or the chance of inadequate surveillance or even risk reducing surgery in parents with formal molecular diagnosis of Lynch syndrome in the absence of a family history of Lynch syndrome-associated malignancies). Moreover, we need to address the question of whether, and if so, when and how, CMMRD has to be implemented in the counselling of Lynch syndrome patients.

#### *Vaccination*

Matthias Kloor gave an update on the role of vaccinations in the prevention of cancer in Lynch syndrome and posed questions that need to be answered about a similar vaccination for CMMRD: 1) What are the neoantigen profiles of CMMRD-associated tumors? 2) Is there a pre-existing systemic immune response in CMMRD? 3) What immune response pathways are active in CMMRD, and can auto-immune symptoms be expected? and 4) What are the mechanisms of immune evasion in CMMRD tumors?.

#### *Prevalence of CMMRD in patients with T-cell acute lymphoblastic lymphoma*

Richard Gallon proposed to use a newly developed scalable MSI assay (see above) to study the prevalence of CMMRD in children with T-cell acute lymphoblastic lymphoma (T-LBL) and high-grade gliomas in PBLs from retrospective cohorts of patients with these types of cancer.

#### *Preliminary results of surveillance according to the C4CMMRD guidelines*

Zeinab Ghorbanoghli presented the preliminary results of surveillance according to the protocol as proposed by the C4CMMRD consortium in 2014[18]. Data were collected from 22 patients including 12 females. Fifteen of these patients (68%) had bi-allelic *PMS2*-variants. Seventy-seven percent of the patients had developed a previous cancer; mainly colorectal and hematological tumors. During a follow-up time of up to 5 years, 15 malignancies developed divided over 12 patients. These malignancies were most frequently located in the digestive tract, followed by brain tumors. Twelve patients were diagnosed with (multiple) adenomas in the colon. The investigators concluded that the yield of screening was very high. The preliminary results suggest that surveillance of the digestive

tract is effective because many polyps were endoscopically removed and early cancers were detected. However, the benefit of screening of the brain is still uncertain.

Following this presentation, it was discussed whether surveillance guidelines should be adjusted in view of these findings. One of the participants suggested to recommend MRI-screening of the brain with intervals of 6 months instead of 6-12 months which is currently advised. In addition, the question arose whether a lower starting age for colonic surveillance (currently 8 years) should be considered given that patients have been reported with adenomatous polyps before this age. After the final analysis of the data, adjustment of the protocol will be re-discussed.

**Acknowledgements** We would like to thank all meeting participants for their attendance and valuable input: Felipe Andreiuolo, Amedeo Azizi, Birgit Burkhardt, Bianca Desouza, Demetra Georgiou, Lea Guerrini-Rousseau, Yvette van Ierland, Hanna IJspeert, Danuta Januszkiewicz-Lewandowska, Maria Kurnikova, Monika Morak, Enrico Opocher, Daniel Rueda, Pauline van Schouwenburg, Irene Slavc, Helen Toledano, Anja Wagner, Liudmila Yasko

1. Wimmer K, Kratz CP, Vasen HF, Caron O, Colas C, Entz-Werle N, Gerdes AM, Goldberg Y, Ilencikova D, Muleris M, Duval A, Lavoine N, Ruiz-Ponte C, Slavc I, Burkhardt B, Brugieres L, CMMRD EU-CCf (2014) Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). *Journal of medical genetics* 51 (6):355-365. doi:10.1136/jmedgenet-2014-102284
2. Kohlmann W, Gruber SB (1993) Lynch Syndrome. In: Adam MP, Ardinger HH, Pagon RA et al. (eds) *GeneReviews*((R)). Seattle (WA),
3. Suerink M, Ripperger T, Messiaen L, Menko FH, Bourdeaut F, Colas C, Jongmans M, Goldberg Y, Nielsen M, Muleris M, van Kouwen M, Slavc I, Kratz C, Vasen HF, Brugieres L, Legius E, Wimmer K (2019) Constitutional mismatch repair deficiency as a differential diagnosis of neurofibromatosis type 1: consensus guidelines for testing a child without malignancy. *Journal of medical genetics* 56 (2):53-62. doi:10.1136/jmedgenet-2018-105664
4. Bodo S, Colas C, Buhard O, Collura A, Tinat J, Lavoine N, Guilloux A, Chalastanis A, Lafitte P, Coulet F, Buisine MP, Ilencikova D, Ruiz-Ponte C, Kinzel M, Grandjouan S, Brems H, Lejeune S, Blanche H, Wang Q, Caron O, Cabaret O, Svrcek M, Vidaud D, Parfait B, Verloes A, Knappe UJ, Soubrier F, Mortemousque I, Leis A, Auclair-Perrossier J, Frebourg T, Flejou JF, Entz-Werle N, Leclerc J, Malka D, Cohen-Haguenaer O, Goldberg Y, Gerdes AM, Fedhila F, Mathieu-Dramard M, Hamelin R, Wafaa B, Gauthier-Villars M, Bourdeaut F, Sheridan E, Vasen H, Brugieres L, Wimmer K, Muleris M, Duval A, European Consortium "Care for C (2015) Diagnosis of Constitutional Mismatch Repair-Deficiency Syndrome Based on

- Microsatellite Instability and Lymphocyte Tolerance to Methylating Agents. *Gastroenterology* 149 (4):1017-1029 e1013. doi:10.1053/j.gastro.2015.06.013
5. Shuen AY, Lanni S, Panigrahi GB, Edwards M, Yu L, Campbell BB, Mandel A, Zhang C, Zhukova N, Alharbi M, Bernstein M, Bowers DC, Carroll S, Cole KA, Constantini S, Crooks B, Dvir R, Farah R, Hijiya N, George B, Laetsch TW, Larouche V, Lindhorst S, Luiten RC, Magimairajan V, Mason G, Mason W, Mordechai O, Mushtaq N, Nicholas G, Oren M, Palma L, Pedroza LA, Ramdas J, Samuel D, Wolfe Schneider K, Seeley A, Semotiuk K, Shamvil A, Sumerauer D, Toledano H, Tomboc P, Wierman M, Van Damme A, Lee YY, Zapotocky M, Bouffet E, Durno C, Aronson M, Gallinger S, Foulkes WD, Malkin D, Tabori U, Pearson CE (2019) Functional Repair Assay for the Diagnosis of Constitutional Mismatch Repair Deficiency From Non-Neoplastic Tissue. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 37 (6):461-470. doi:10.1200/JCO.18.00474
6. Ingham D, Diggle CP, Berry I, Bristow CA, Hayward BE, Rahman N, Markham AF, Sheridan EG, Bonthron DT, Carr IM (2013) Simple detection of germline microsatellite instability for diagnosis of constitutional mismatch repair cancer syndrome. *Human mutation* 34 (6):847-852. doi:10.1002/humu.22311
7. Gallon R, Muhlegger B, Wenzel SS, Sheth H, Hayes C, Aretz S, Dahan K, Foulkes W, Kratz CP, Ripperger T, Azizi AA, Baris Feldman H, Chong AL, Demirsoy U, Florkin B, Imschweiler T, Januszkiewicz-Lewandowska D, Lobitz S, Nathrath M, Pander HJ, Perez-Alonso V, Perne C, Ragab I, Rosenbaum T, Rueda D, Seidel MG, Suerink M, Taeubner J, Zimmermann SY, Zschocke J, Borthwick GM, Burn J, Jackson MS, Santibanez-Koref M, Wimmer K (2019) A sensitive and scalable microsatellite instability assay to diagnose constitutional mismatch repair deficiency by sequencing of peripheral blood leukocytes. *Human mutation* 40 (5):649-655. doi:10.1002/humu.23721
8. Gonzalez-Acosta M, Marin F, Puliafito B, Bonifaci N, Fernandez A, Navarro M, Salvador H, Balaguer F, Iglesias S, Velasco A, Grau Garces E, Moreno V, Gonzalez-Granado LI, Guerra-Garcia P, Ayala R, Florkin B, Kratz C, Ripperger T, Rosenbaum T, Januszkiewicz-Lewandowska D, Azizi AA, Ragab I, Nathrath M, Pander HJ, Lobitz S, Suerink M, Dahan K, Imschweiler T, Demirsoy U, Brunet J, Lazaro C, Rueda D, Wimmer K, Capella G, Pineda M (2020) High-sensitivity microsatellite instability assessment for the detection of mismatch repair defects in normal tissue of biallelic germline mismatch repair mutation carriers. *Journal of medical genetics* 57 (4):269-273. doi:10.1136/jmedgenet-2019-106272
9. Fernandez-Rozadilla C, Alvarez-Barona M, Schamschula E, Bodo S, Lopez-Novo A, Dacal A, Calvino-Costas C, Lancho A, Amigo J, Bello X, Cameselle-Teijeiro JM, Carracedo A, Colas C, Muleris M, Wimmer K, Ruiz-Ponte C (2019) Early Colorectal Cancers Provide New Evidence for a Lynch Syndrome-to-CMMRD Phenotypic Continuum. *Cancers (Basel)* 11 (8). doi:10.3390/cancers11081081
10. Wimmer K, Beilken A, Nustede R, Ripperger T, Lamottke B, Ure B, Steinmann D, Reineke-Plaass T, Lehmann U, Zschocke J, Valle L, Fauth C, Kratz CP (2017) A novel germline POLE mutation causes an early onset cancer prone syndrome mimicking constitutional mismatch repair deficiency. *Familial cancer* 16 (1):67-71. doi:10.1007/s10689-016-9925-1
11. Lindsay H, Scollon S, Reuther J, Voicu H, Rednam SP, Lin FY, Fisher KE, Chintagumpala M, Adesina AM, Parsons DW, Plon SE, Roy A (2019) Germline POLE mutation in a child with hypermutated medulloblastoma and features of constitutional mismatch repair deficiency. *Cold Spring Harb Mol Case Stud* 5 (5). doi:10.1101/mcs.a004499
12. Toledano H, Orenstein N, Sofrin E, Ruhrman-Shahar N, Amarilyo G, Basel-Salmon L, Shuldiner AR, Smirin-Yosef P, Aronson M, Al-Tarrah H, Bazak L, Gonzaga-Jauregui C, Tabori

- U, Wimmer K, Goldberg Y (2019) Paediatric systemic lupus erythematosus as a manifestation of constitutional mismatch repair deficiency. *Journal of medical genetics*. doi:10.1136/jmedgenet-2019-106303
13. Rahner N, Friedrichs N, Wehner M, Steinke V, Aretz S, Friedl W, Buettner R, Mangold E, Propping P, Walldorf C (2007) Nine novel pathogenic germline mutations in MLH1, MSH2, MSH6 and PMS2 in families with Lynch syndrome. *Acta oncologica* 46 (6):763-769. doi:10.1080/02841860701230217
14. Plaschke J, Linnebacher M, Kloor M, Gebert J, Cremer FW, Tinschert S, Aust DE, von Knebel Doeberitz M, Schackert HK (2006) Compound heterozygosity for two MSH6 mutations in a patient with early onset of HNPCC-associated cancers, but without hematological malignancy and brain tumor. *European journal of human genetics : EJHG* 14 (5):561-566. doi:10.1038/sj.ejhg.5201568
15. Lindsay H, Jubran RF, Wang L, Kipp BR, May WA (2013) Simultaneous colonic adenocarcinoma and medulloblastoma in a 12-year-old with biallelic deletions in PMS2. *J Pediatr* 163 (2):601-603. doi:10.1016/j.jpeds.2013.03.007
16. Eijzenga W, Aaronson NK, Hahn DE, Sidharta GN, van der Kolk LE, Velthuizen ME, Ausems MG, Bleiker EM (2014) Effect of routine assessment of specific psychosocial problems on personalized communication, counselors' awareness, and distress levels in cancer genetic counseling practice: a randomized controlled trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 32 (27):2998-3004. doi:10.1200/JCO.2014.55.4576
17. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Lubner BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA, Jr. (2017) Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 357 (6349):409-413. doi:10.1126/science.aan6733
18. Vasen HF, Ghorbanoghli Z, Bourdeaut F, Cabaret O, Caron O, Duval A, Entz-Werle N, Goldberg Y, Ilencikova D, Kratz CP, Lavoine N, Loeffen J, Menko FH, Muleris M, Sebille G, Colas C, Burkhardt B, Brugieres L, Wimmer K, CMMR-D EU-CCf (2014) Guidelines for surveillance of individuals with constitutional mismatch repair-deficiency proposed by the European Consortium "Care for CMMR-D" (C4CMMR-D). *Journal of medical genetics* 51 (5):283-293. doi:10.1136/jmedgenet-2013-102238