| Constitutional Mismatch Repair Deficiency (CMMRD) Care pathway | | |
|---|---|---|
| *The Patient Clinical Pathway is "the whole care pathway from identification, diagnostics, and multidisciplinary case discussions to surveillance and preventive surgery", so a pathway in time, focusing on **HOW** the CMMRD patient should be managed* | | |
| | | |
| **Bi-annual (twice yearly) Review Recommended** | | |
| CMMRD syndrome is characterised by an increased tumour risk that affects multiple organs. The first time a tumour occurs is usually during childhood or adolescence. The risk is most markedly increased for haematological malignancies, brain tumours and intestinal tract adenomas and carcinomas. | | |
| At the time of diagnosis, or when CMMRD is suspected, a patient should be seen in a genetics department or by a clinician with experience in genetics.<br>Once a diagnosis of CMMRD has been made, clinical review is indicated at least twice per year. Surveillance measures depend on the age of the patient and are summarised below. | | |
| | | |
| **Review Checklist** | | |
| | **WHAT TO LOOK FOR** | **WHEN TO REFER AND WHERE TO** |
| **General assessment** | **Lifelong:** complete physical examination every 6 months, including neurological assessment.<br>**Imaging:** Whole body MRI is performed at least once. | Any sign indicative of malignancy.<br>**Refer** to appropriate specialist, preferably with expertise in cancer syndromes. |
| | | |
| **Brain** | Raise awareness of neurological symptoms that might indicate a brain tumour.<br>**Imaging:** Brain MRI (with contrast enhancement for the first one) every 6 months from the age of 2 years. Brain MRI at least annually from the age of 20 years. | **Refer** to team specialised in neurooncology if suspicious clinical symptoms or any suspicious lesion on brain MRI are present. |
| | | |
| **Gastrointestinal** | Raise awareness of gastrointestinal blood loss as a symptom of intestinal tract cancer.<br>**Surveillance** aiming at cancer detection and polyp removal: Annual colonoscopy (including gastroenterologists experienced in Lynch syndrome) from the age of 6 years. Annual upper gastrointestinal endoscopy simultaneous with colonoscopy at least from the age of 10 years. Annual video capsule endoscopy from the age of 10 years.<br>Increase frequency if adenomas are detected. | **Refer** to team specialised in digestive tract oncology when a malignancy is identified or polyposis becomes unmanageable by endoscopy. |
| | | |
| **Gynaecological** | Educate females to recognise symptoms of gynaecological cancer (e.g. abnormal uterine bleeding)<br>**Surveillance:** Yearly clinical examination and transvaginal ultrasound annually from the age of 20 years.<br>Discuss prophylactic surgery once family planning is completed. | **Refer** to gynaeco-oncologist and/or -surgeon when a tumour is identified. |
| | | |
| **Urological** | **Surveillance:** Annual abdominopelvic ultrasound from the age of 20 years. | **Refer** to urological oncologist and/or surgeon when a tumour is identified. |

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| **Psychological** | **Psychological support** should be available for the patient and family to address the stress and anxiety associated with a CMMRD diagnosis, including cancer risk and the burden of clinical interventions. | **Refer** the patient and family to psychological support, often available through clinical genetics or oncology department, at the time of CMMRD diagnosis. |
| | | |
| **Reproductive options** | **Parents** of the patient have a 25% recurrence risk of CMMRD (and an additional 50% risk of Lynch syndrome) in a future child and should be counselled appropriately about prenatal options and pre-implantation genetic testing.<br><br>**Patient with CMMRD** Children of the patient with CMMRD will be obligate heterozygous carrier of one pathogenic variant in a mismatch repair gene and will therefore have Lynch syndrome. Offspring will only be at risk of CMMRD if the partner is carrying a pathogenic variant in the same mismatch repair gene. | **Refer** parents to a clinical geneticist for counselling at the time of CMMRD diagnosis in their child.<br><br>**Refer** CMMRD patients who are planning a pregnancy to a clinical geneticist for appropriate counselling. |

**Surveillance schedule for patients with CMMRD**

According to ERN GENTURIS guideline on constitutional mismatch repair deficiency diagnosis, genetic counselling, surveillance, quality of life, and clinical management. Authors: Chrystelle Colas, Léa Guerrini-Rousseau, Manon Suerink, Richard Gallon, Christian P. Kratz, Éloïse Ayuso, CMMRD Guideline Group, Laurence Brugières, Katharina Wimmer

| Exam | Frequency | Period |
|---|---|---|
| Clinical examination | Every 6 months | From diagnosis |
| Brain MRI | Every 6 months | Age 2 years - 20 years |
| | At least annually | From age 20 years |
| Colonoscopy | Annually<br>Every 6 months in case of adenoma | From age 6 years |
| Upper gastrointestinal endoscopy | Annually | Simultaneously with colonoscopy or at least from age 10 years |
| Video capsule endoscopy | Annually | From age 10 years |
| Gynaecologic surveillance (clinical examination & transvaginal ultrasound) | Annually | From age 20 years |
| Gynaecologic prophylactic surgery | Not applicable | Discuss once family planning is completed |
| Abdominopelvic ultrasound for gynaecological and urinary tract cancer screening | Annually | From age 20 years |
| Whole body MRI | At least once | At diagnosis or when anaesthesia is no longer required |
| | Discuss optional annual imaging | - |

Any symptom indicative of a cancer between two examinations must be explored.

**ERN GENTURIS healthcare providers:** A list of healthcare providers with expertise in Thematic Group 4: Other rare - predominantly malignant - genturis can be found on the ERN GENTURIS website www.genturis.eu.

# Constitutional Mismatch Repair Deficiency (CMMRD)

## Care pathway

Faculty: .....

European Reference Network for rare or low prevalence complex diseases
Network Genetic Tumour Risk Syndromes (ERN GENTURIS)

Family name:

Given name(s)

Address:

Date of Birth: Sex: ☐ M ☐ F ☐ I

## Bi-Annual (twice yearly) Review Recommended

CMMRD syndrome is characterised by an increased tumour risk that affects multiple organs. The first time a tumour occurs is usually during childhood or adolescence. The risk is most markedly increased for haematological malignancies, brain tumours and intestinal tract adenomas and carcinomas. At the time of diagnosis, or when CMMRD is suspected, a patient should be seen in a genetics department or by a clinician with experience in genetics. Once a diagnosis of CMMRD has been made, clinical review is indicated at least twice per year. Surveillance measures depend on the age of the patient and are summarised below.

## CMMRD syndrome Review Checklist

**Clinical Presentation:**
..... ☐
..... ☐
..... ☐

Other symptoms:
.....
.....
.....

Genetic counselling completed ☐
Date Completed: .....

**Clinical diagnosis**
.....

How was the CMMRD diagnosis confirmed?
☐ DNA testing
☐ functional testing
☐ otherwise: .....

Diagnosis Date: .....

**General Health Check:**
Monitor growth, development and general health:

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.....
.....

**Notes:**
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| WHAT TO LOOK FOR | WHEN TO REFER AND WHERE TO |
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| Whole body MRI | At least once | At diagnosis or when anaesthesia is no longer required |
| | Discuss optional annual imaging | - |

Any symptom indicative of a cancer between two examinations must be explored.

**Doctor:** .....
Review date: .....
Faculty: .....

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European Reference Networks
Funded by the European Union

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