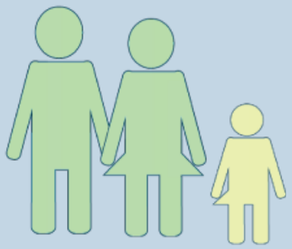
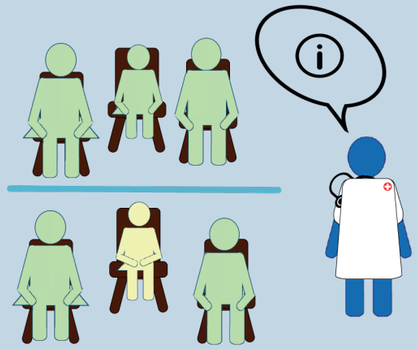
ERN GENTURIS patient journey: Constitutional Mismatch Repair Deficiency (CMMRD) syndrome

Parents and their child affected by cancer with unknown genetics for CMMRD



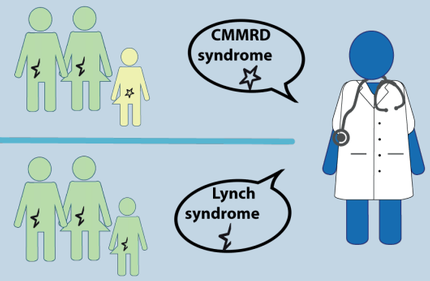
Suspicion of CMMRD syndrome - eligible for constitutional genetic testing

Genetic counselling

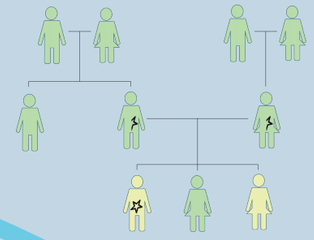


Constitutional genetic testing

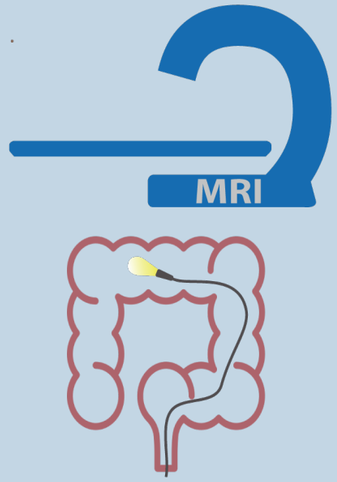
Disclosure of the results



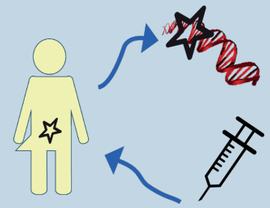
Cascade testing (testing of blood relatives) for CMMRD and Lynch syndrome*



Cancer surveillance and cancer prevention for CMMRD patients

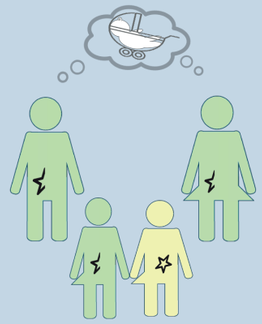


Personalised cancer treatment

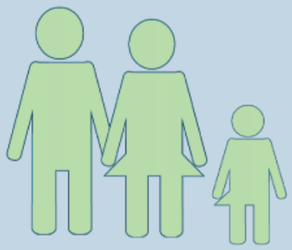


Cancer Diagnosis

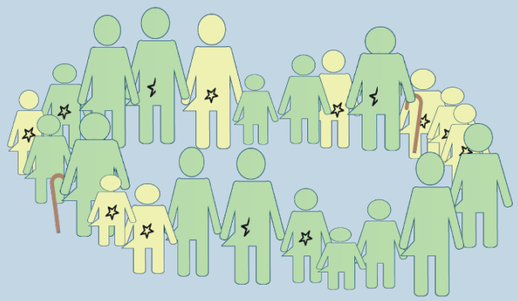
Reproductive decision-making



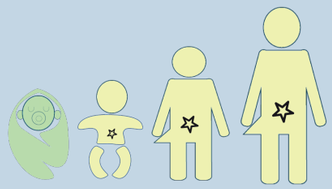
Parents and their child unaffected by cancer with unknown genetics for CMMRD



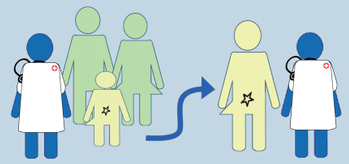
Peer support and emotional support



CMMRD care throughout life



with emphasis on healthcare transition to adult care



European Reference Network

Genetic Tumour Risk Syndromes (ERN GENTURIS)

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Disclaimer: This patient journey is intended as a general overview of the clinical and diagnostic pathway for CMMRD or its suspicion. It should not replace an individual clinical and genetic counselling at an expertise centre. It also does not intend to address all specific challenges of the complex condition of CMMRD. Specific clinical guidelines, diagnostic criteria and nomenclature may change at short notice and, therefore, are only referred to in this patient journey.

Parents and their child affected by cancer with unknown genetics for CMMRD

A child or young adult who is diagnosed with cancer and should undergo evaluation of eligibility for genetic testing because of CMMRD suspicion.

The CMMRD-associated tumour spectrum includes primarily hematologic, brain and gastrointestinal tract malignancies, but in essence any malignancy may be a CMMRD-associated one.

Parents and their child unaffected by cancer with unknown genetics for CMMRD

A person is unaffected by cancer who may be eligible for (predictive) genetic testing for CMMRD.

Suspicion of CMMRD syndrome - eligible for constitutional genetic testing

For an **affected cancer patient,** CMMRD syndrome should be suspected if:

- The patient fulfils clinical criteria by reaching a minimum of 3 scoring points according to the revised C4CMMRD indication criteria (ERN GENTURIS guidelines on constitutional mismatch repair deficiency diagnosis, genetic counselling, surveillance, quality of life, and clinical management (www.genturis.eu)) by adding scoring points of the cancer type (obligatory points) and scoring points of (non-malignant) features in the patient or the family (optional points).
- The patient's tumour or normal tissue shows characteristic features indicative of CMMRD, including a paediatric high tumour mutation burden or loss of MMR protein expression in normal cells.
- The patient is aged <18 years and is known to have a heterozygous (likely) pathogenic variant in an MMR gene even when no second pathogenic variant was found in the same MMR gene.

It is important to initiate genetic testing as soon as possible after the diagnosis of cancer to adapt treatment to the results of genetic analysis whenever possible.

An individual without cancer (**unaffected person**), is eligible for genetic testing for CMMRD syndrome if:

- The person is a child/adolescent suspected to have neurofibromatosis type 1 or Legius syndrome de novo (i.e. parents have no signs of these syndromes) with no (likely) pathogenic germline variant in *NF1* or *SPRED1* detected after comprehensive testing, and they fulfil one other CMMRD-related feature according to the ERN GENTURIS guidelines on constitutional mismatch repair deficiency diagnosis, genetic counselling, surveillance, quality of life, and clinical management (www.genturis.eu).
- CMMRD testing should be offered to siblings of a diagnosed CMMRD patient regardless of their clinical presentation.
- CMMRD testing should be offered to children, if both parents carry a pathogenic variant in the same MMR gene.

Genetic counselling

Individuals suspected of CMMRD syndrome and their family need thorough information before and after constitutional genetic testing regarding:

- clinical manifestations and natural history of CMMRD syndrome or related syndromes
- process of genetic counselling and implications of constitutional genetic testing for consult and blood relatives
- possible outcomes of genetic testing
- options of cancer surveillance and targeted treatment in CMMRD
- legal, social, insurance and financial aspects of diagnosis
- emotional support including peer support (www.genturis.eu).

Constitutional genetic testing and disclosure of the results

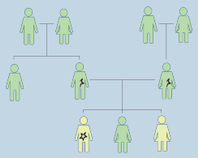
General information regarding constitutional genetic testing can be found on: https://www.coe.int/en/web/bioethics/information-brochure-on-genetic-tests-for-health-purposes

Constitutional genetic testing for CMMRD diagnosis should include a comprehensive analysis of the MMR genes (*PMS2, MSH6, MLH1* and *MSH2*) including large rearrangements and transcript analysis if necessary. It might need to include also testing for constitutional (germline) microsatellite instability (in blood), which is a hallmark of CMMRD, as it is important to come to a definite diagnosis that either confirms or refutes CMMRD in the patient. It is also important to identify the causative variants in the relevant MMR gene.

The most recent diagnostic criteria for CMMRD syndrome can be found on the ERN GENTURIS website (www.genturis.eu), section CMMRD, clinical practice guidelines, pocket guide: Guideline summary table of the ERN GENTURIS guidelines on constitutional mismatch repair deficiency diagnosis, genetic counselling, surveillance, quality of life, and clinical management.

The disclosure of the testing results should be accompanied by genetic counselling.

Given the rarity of CMMRD, collecting data on the outcomes of surveillance and treatment in all patients diagnosed with CMMRD is crucial. Your physician will propose that your information will be recorded in a registry in accordance with the legal framework applicable in your country of origin.

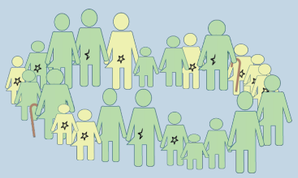


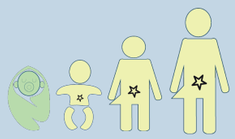
Cascade testing (testing of blood relatives) for CMMRD and Lynch syndrome*

Cascade testing is the process of performing genetic counselling and constitutional genetic testing of blood relatives at risk for inheriting CMMRD syndrome and Lynch syndrome*. The geneticist will determine for which family members constitutional genetic testing would be relevant and invite them for genetic counselling or provide a family letter that can be distributed by the index patient. **Testing of these family members and follow-up of the carriers with appropriate clinical measures where needed may save lives and improve quality of life.**

Siblings of a CMMRD patient have a 25% risk of having CMMRD syndrome and 50% risk of having Lynch syndrome.
→ Constitutional genetic testing for CMMRD should be offered to any sibling of a CMMRD patient regardless of their age and clinical presentation.

* Parents of a CMMRD patient have almost 100% risk of having Lynch syndrome. More distant family members are also at risk of Lynch syndrome. Their risk depends on their position in the pedigree.
→ Cascade testing for Lynch syndrome should be offered to parents and all adult relatives in both parental branches. More information on Lynch syndrome can be found on the ERN GENTURIS website.



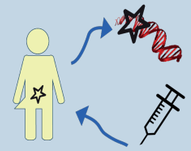


Cancer surveillance and cancer prevention for CMMRD patients

Surveillance programmes for hereditary cancer syndromes aim at early cancer detection. Early detection of cancer generally allows earlier treatment and better prognosis. Therefore, it is important to regularly participate in the provided surveillance programmes.

There are specific surveillance programmes in place for CMMRD patients (especially for gastro-intestinal tract and brain tumours). These might differ between countries.
Pre-malignant lesions should probably be resected whenever possible. The efficacy of medications aiming to reduce tumour risk in CMMRD patients is not validated.

Patients and/or their parents should ask their physicians or contact expert centres about recommendations in their country.
Current recommendations at the European level can be found on the ERN GENTURIS website: www.genturis.eu under "Guidelines and pathways".



Personalised cancer treatment

There are specific treatment recommendations for CMMRD tumours. These might differ between countries. Patients should ask their physician or contact expert centres about recommendations in their country. Current recommendations at the European level can be found on the ERN GENTURIS website: www.genturis.eu under "Guidelines and pathways".
The involvement of a multidisciplinary team covering a breadth of specialities is recommended as some treatment should probably be promoted (immune checkpoint blockade) or avoided (temozolomide in patients with CMMRD-associated high-grade glioma).
Discussions on cancer treatment should take into account the possibility of repeated treatments due to successive malignant tumours. It might be possible to participate in clinical trials.
In patients with CMMRD, a suspected relapse should prompt consideration of a second primary malignancy. Fresh tumour specimens should be collected and stored (or directly molecularly analysed) whenever possible if the CMMRD patient and/or their family approves.

Reproductive decision-making

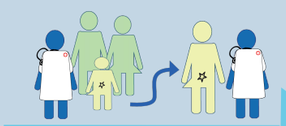
As CMMRD is characterised by a high risk of malignancies from the first years of life, discussion about prenatal or preimplantation genetic testing for subsequent pregnancies is indicated:

- with parents of a CMMRD patient that are of reproductive age.
- with a CMMRD patient of reproductive age.

Peer support and emotional support

Patients and their family might seek peer and emotional support repeatedly, at different times, for example:
- during surveillance - at diagnosis of a new cancer - when deciding on treatment options
- during ongoing cancer therapy - on how to decide about genetic testing, including genetic testing in a minor
- on how to inform family members on their genetic risk and the option to perform (predictive) constitutional genetic testing
- on how to cope with elevated tumour risk - on how to cope with the diagnosis of CMMRD in the affected child or in a sibling
- on family planning.

Details of patient organisation can be found on: https://www.genturis.eu/l=eng/patient-area/patient-associations.html.



CMMRD care throughout life with emphasis on healthcare transition to adult care

Individuals with CMMRD have a high cancer risk and need intensive heath care throughout their life.
A dedicated clinician and a structured Healthcare Transition programme are imperative for effectively transitioning adolescents and young adults with CMMRD from a paediatric to an adult care model.
The overarching goal is to foster independence, enhance quality of life, and mitigate associated medical complications.

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