ERN GENTURIS Plain Language Summary:

CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS, TREATMENT, MANAGEMENT AND SURVEILLANCE OF PEOPLE WITH CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY

INTRODUCTION

Constitutional mismatch repair deficiency (CMMRD) is a rare cancer syndrome. Affected individuals have differences in their DNA (the instructions that determine how the cells of their body work) compared to the general population. These differences (or variants) disrupt a mechanism in their cells called mismatch repair (MMR) that normally prevents mutations (changes to the DNA and to the proteins of the cell). People with CMMRD acquire mutations in their cells faster than the general population, and these mutations can cause normal, healthy cells to become cancer cells.

CMMRD is associated with a high risk for many types of cancer starting from early childhood and throughout life. The most common are cancers of the intestine, brain, and blood. People with CMMRD often have other physical features, such as dark or light patches of skin, as well as tumour growths that have not become cancerous, such as polyps in the bowel. Some of these features are also present in other tumour syndromes, in particular neurofibromatosis type 1 (NF1). Therefore, a diagnosis of CMMRD cannot be made based on the cancer diagnosis or any other physical feature, and requires DNA testing to detect the disease-causing variants that are disrupting MMR. Unfortunately, these DNA tests sometimes give uncertain results, but this can be compensated for by other "ancillary" tests that look for evidence of MMR deficiency in a patient's normal (non-tumour) tissues, such as healthy blood.

The different types of cancer and early age of disease onset in CMMRD is associated with a high disease burden and mortality. Individuals with CMMRD benefit from cancer surveillance, which can detect tumours before they become cancer and can improve survival as the earlier a cancer is detected the easier it is to treat. For example, colonoscopy (the visualisation of the bowel using a camera) can be used to find, and sometimes remove, bowel tumours. Individuals with CMMRD may also benefit from cancer prevention strategies.

The disruption of MMR found in CMMRD cancers has important implications for cancer treatment. In particular, the MMR system needs to be working for some chemotherapy drugs to have an effect. Also, cancers that do not have a functional MMR system produce mutant proteins that can cause an

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immune response in the same way that viral or bacterial proteins cause an immune response. Therefore, a new class of immunotherapy drugs, called immune checkpoint inhibitors, have recently been shown to be highly effective against some CMMRD cancers.

Individuals who have CMMRD may also have a family history of cancer. All humans have two copies of DNA, one inherited from their mother, and one from their father. In CMMRD, both copies of DNA contain a disease-causing variant disrupting the MMR system. Family members who have only one of these disease-causing MMR variants also have a cancer syndrome, called Lynch syndrome. Lynch syndrome is less severe than CMMRD with a lower risk of cancer, an average age at first cancer diagnosis in adulthood, and with fewer associated cancer types. Most CMMRD patient's parents have Lynch syndrome, as may other family members on both their mother's and father's sides. However, not all people with Lynch syndrome develop cancer and in a large proportion of CMMRD families there is no history of cancer. A CMMRD patient's siblings may have either CMMRD, Lynch syndrome, or no cancer syndrome depending on whether they have inherited both, only one, or no, respectively, disease-causing MMR variants from the parents.

Previous clinical guidelines recommend testing for CMMRD in cancer patients fulfilling specific criteria based on the known features of CMMRD. There are also guidelines for when to test for CMMRD in patients suspected of NF1 who do not have cancer and have been proven to not have NF1 by comprehensive testing. However, our understanding of CMMRD features have advanced and new ancillary tests to complement DNA testing are now available, so the guidelines for CMMRD diagnosis need to be updated. Similarly, we have new evidence on the effectiveness of different cancer surveillance strategies and, therefore, previous clinical guidelines on surveillance and prevention in CMMRD need to be revised.

Genetic counselling, that is the explanation of the disease and how it might be inherited within a family, allows CMMRD patients and their family, particularly the parents, to make informed health care decisions. However, whilst genetic counselling is standard practice for cancer syndromes, no CMMRD-specific guidelines have previously been published. Similarly, there are no CMMRD-specific clinical guidelines on cancer treatment despite the significance of MMR deficiency on disease management. The impact of CMMRD on quality of life has not been addressed previously, and so guidelines with respect to psychological support for CMMRD patients and their families are needed.

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GUIDELINE AIMS

This guideline aims to deliver the most up to date recommendations for the diagnosis, surveillance, and clinical management of people with CMMRD.

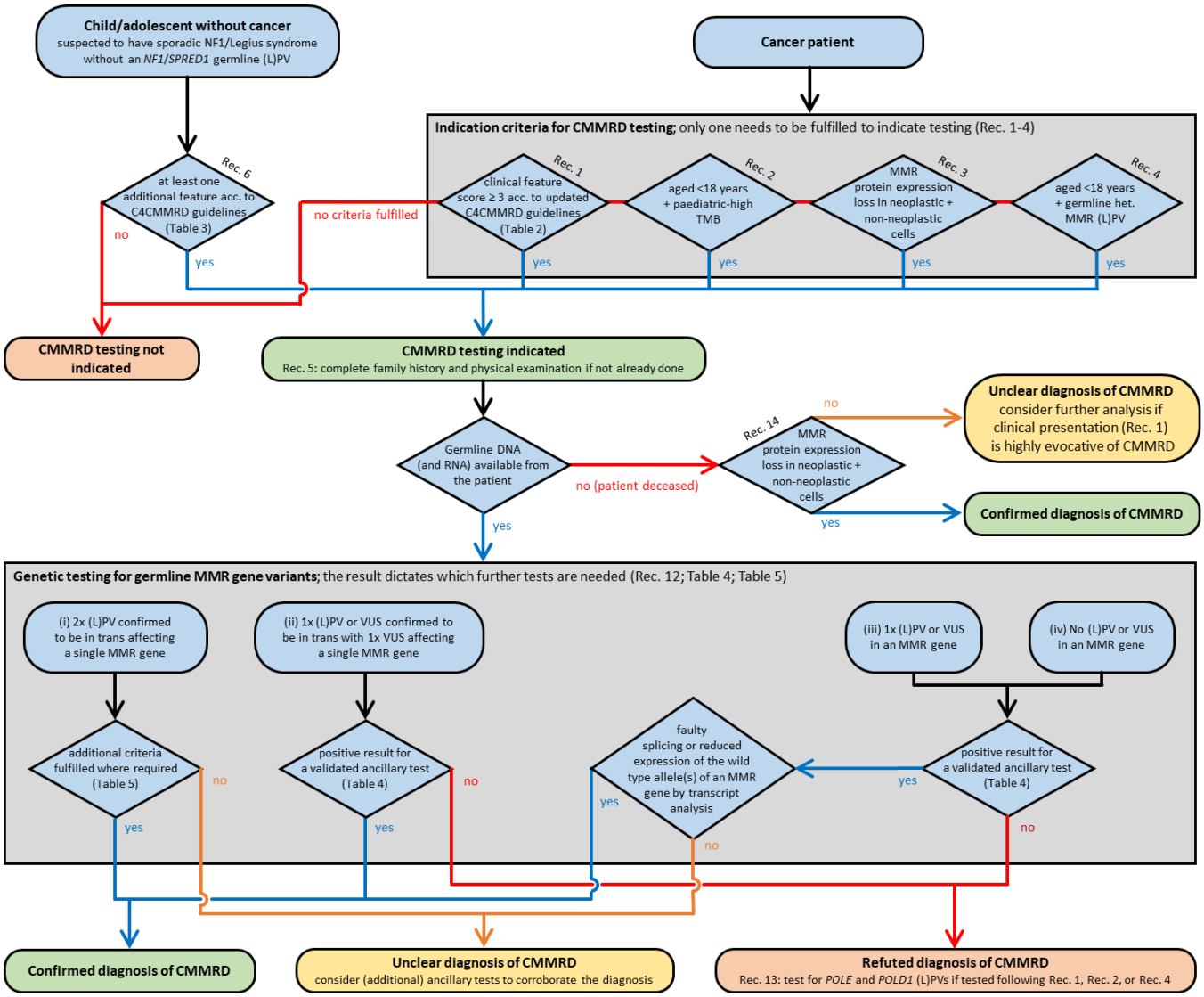
SCOPE & PURPOSE OF THE GUIDELINE

Before this guideline, there were different and limited guideline recommendations for the diagnosis and management of CMMRD and there is substantial variability in clinical practice. The guideline covers the diagnosis, genetic counselling, surveillance, clinical management, and quality of life of people with CMMRD to provide health care practitioners with a comprehensive set of recommendations for the optimal diagnosis and management of CMMRD and to help standardise practice. The genetic counselling section also addresses recommendations for the relatives of people with CMMRD. This guideline does not address the diagnosis and management of Lynch syndrome.

Clinical guidelines are statements to support decision making, based on systematically evaluated evidence for a specified clinical setting. Whilst these clinical guidelines are based on the latest published evidence, care of each individual remains primarily the responsibility of their treating medical professionals. Decisions for care should always be based on the needs, preferences and circumstances of each patient. Clinical guidelines should support clinical decision making, but never replace clinical professionals. Guidelines present recommendations based on expert opinion and published evidence and are not mandates. These guidelines do not signify nor intend to be a legal standard of care.

GUIDELINE SUMMARY

Diagnosis protocol for the detection of CMMRD



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Surveillance protocol for people diagnosed with CMMRD

Exam		Frequency	Period	Evidence*
Clinical examination		Every 6 months	From diagnosis	Strong
Brain MRI		Every 6 months	2 – 20 years	Strong
		Annually	From 20 years	Moderate
Colonoscopy		Annually**	From 6 years	Strong
Upper gastrointestinal endoscopy		Annually**	Simultaneously with colonoscopy or at least from age 10 years	Weak
Video capsule endoscopy		Annually	From 10 years	Moderate
Gynaecologic	Surveillance (clinical examination & transvaginal ultrasound)	Annually	From 20 years	Strong
	Prophylactic surgery	Not applicable	Discuss once family planning is completed	Moderate
Abdominopelvic ultrasound for gynaecological and urinary tract cancer screening		Annually	From 20 years	Strong
Whole body MRI		At least once	At diagnosis or when anaesthesia is no longer required	Strong
		Discuss optional annual imaging		Moderate

*This grading is based on published articles and expert consensus.

**Interval should be increased to once every 6 months once polyps are detected.

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KEY RECOMMENDATIONS

Recommendations for diagnosis

The decision of whether to offer CMMRD testing to a cancer patient uses an update of the clinical criteria established by the Care for CMMRD consortium (C4CMMRD). These criteria cover the age at diagnosis and type of cancer, the presence of non-cancer related features such as darker or lighter skin spots similar to those seen in NF1, and a family history of cancer.

CMMRD testing should also be offered to cancer patients based on their age along with molecular features of the cancer or presence of a single disease-causing MMR variant in their DNA.

CMMRD testing may also be offered in children/adolescents without cancer for whom a diagnosis of NF1 was suspected but disproven and who display clinical features suggesting CMMRD.

Any testing strategy should aim to come to a definite diagnosis that either confirms or refutes CMMRD in the patient, and to identify the disease-causing MMR variants in the patient's DNA. Comprehensive criteria for a CMMRD diagnosis based on DNA test results, ancillary test results, and other tests are provided.

Recommendations for genetic counselling

Genetic counselling should be offered to parents and siblings of a confirmed CMMRD patient, preferentially by a multidisciplinary team with knowledge of CMMRD, consisting of a medical geneticist, a paediatric oncologist and a psychologist.

Testing for CMMRD should be offered to siblings of the CMMRD patient, and testing for Lynch syndrome should be offered to adult relatives.

Offering preimplantation genetic diagnosis should be considered in specific circumstances where there is considerable risk of the offspring having CMMRD.

Recommendations for surveillance

CMMRD patients and/or their parents should be educated about tumour risks associated with CMMRD as well as about symptoms related to the main tumours.

The pros and cons of surveillance should be discussed among the CMMRD patient and/or their parents and clinician to make a joint decision to participate in a surveillance program.

A clinical examination should be performed every 6 months.

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Surveillance for cancers of the blood cells should probably not be performed due to limited efficacy.

Surveillance for cancers of the brain, digestive tract, female reproductive organs, and urinary tract are recommended.

Recommendations for quality of life

Psychological support should be offered to the CMMRD patient and their family.

Recommendations for clinical management

For several cancer types, no CMMRD specific treatment recommendations exist. Treatment of cancer patients with CMMRD should, therefore, be discussed in a multidisciplinary board with a treating physician, an expert for the patient's cancer type as well as a CMMRD expert.

Immunotherapy should be discussed and encouraged within a specialised centre for any CMMRD-associated tumour at any time during treatment (diagnosis or relapse), especially if standard therapeutic guidelines offer only low chance of cure.

Temozolomide should probably be avoided in CMMRD patients with brain cancer.

PSYCHOLOGICAL NEEDS

Health professionals need to understand and address the psychosocial implications of testing for CMMRD to best offer psychological support to the patient and their family and to avoid refusal of medical care. For this, psychological support should be offered to the patient and the family during the entire process of diagnostic evaluation. The family needs to be aware of the implications of the test result and of the high risk of multiple cancers in a CMMRD patient. Moreover, because surveillance does not guarantee prevention of a new cancer, it may cause a great psychological burden in the patient and their family.