



Cancer Predisposition Clinic

Constitutional mismatch repair deficiency syndrome (CMMRD)

Alternate names: Biallelic mismatch repair deficiency syndrome (BMMRD)

What is constitutional mismatch repair deficiency syndrome?

Constitutional mismatch repair deficiency syndrome is a rare condition that makes a child more likely to develop the following:

- Brain tumors
- Cancers in blood and lymph systems
- Polyps (abnormal growths in the intestinal tract) and cancers in the gastrointestinal tract
- Cancers in the female reproductive organs (for example, the uterus and ovaries)
- Certain skin or physical findings, for example café au lait spots (flat brown colored areas on the skin) or patches of skin that are lighter than the overall skin tone
- Other rare pediatric cancers

A child with constitutional mismatch repair deficiency syndrome can develop more than one type of cancer at a time or more than one cancer during the person's lifetime.

What causes constitutional mismatch repair deficiency syndrome?

Constitutional mismatch repair deficiency syndrome is related to changes in the genes *MLH1*, *MSH2*, *MSH6*, or *PMS2* and rarely in a gene called *EPCAM*. Genes carry information telling cells within the body how to function. The *MLH1*, *MSH2*, *MSH6* and *PMS2* genes help to repair a specific type of DNA damage through a process called "mismatch repair" or MMR. It is harder for people with constitutional mismatch repair deficiency syndrome to repair the damage that naturally occurs in their genes. This can lead to the growth of polyps and tumors at an early age.

Most people have two working copies of each of the MMR genes in their cells. One copy is inherited from the mother and one from the father. A change in the gene that causes it to not work properly is called a mutation. When someone inherits an MMR gene mutation from the mother and another mutation in the same MMR gene from the father, they have constitutional mismatch repair deficiency syndrome. In other words, this person has a mutation affecting each of the 2 copies of an MMR gene.

Most children with constitutional mismatch repair deficiency syndrome inherit the MMR gene mutations from their parents. Parents of a child with constitutional mismatch repair deficiency syndrome have a 25% or 1 in 4 chance for each pregnancy of having a child with the same syndrome.

All children of a person with constitutional mismatch repair deficiency syndrome will inherit one MMR mutation. To understand the chances of having a child with this syndrome, the partner of a person with the syndrome might consider genetic testing to see if he or she also carries an MMR gene mutation.

Note: Please see below for information regarding Lynch syndrome. This is a condition where people have **one** MMR gene mutation.

What is the cancer risk for children with constitutional mismatch repair deficiency syndrome?

For people with this syndrome the exact risk of developing cancer during their lifetime is not known at this time. It is expected to be very high in these people. Because constitutional mismatch repair deficiency syndrome can cause a wide variety of cancers, it is hard to predict what type of cancer a child with this condition may develop and when that cancer will occur.

How are people with constitutional mismatch repair deficiency syndrome screened for cancer?

In general, tumor screening involves undergoing certain tests to check for tumors before symptoms occur. The goal is to detect tumors at the earliest and most treatable stage. The tumor screening tests should be discussed with a health care provider who knows this syndrome well.

Screening tests may include the following:

- Semi-annual full physical exams
- Gastrointestinal tract screening, including colonoscopy, esophagogastroduodenoscopy (EGD) and video capsule endoscopy (VCE)
- MRI exam of the brain
- Abdominal imaging
- Chest X-rays
- Routine blood tests, such as complete blood count

How is genetic testing done for constitutional mismatch repair deficiency syndrome?

The health care provider may suspect this syndrome after looking at a person's medical history, physical findings and family history. In most cases, a health care provider or genetic counselor will ask questions about a person's health and physical findings and the health of other family members.

The genetic counselor or health care provider will record which family members have developed tumors, what types of tumors and at what ages tumors occurred. From this information they will create a family tree. Health care providers and genetic counselors will look at the family tree to find out the following:

- If there are more cancers than normal
- If cancers occurred at younger-than-expected ages
- If the types of tumors match up with what might be seen in those with MMR mutations

Please note, it is not uncommon for a patient with constitutional mismatch repair deficiency syndrome to not have many cases of cancer in the family.

Diagnostic genetic testing

If a health care provider suspects that a person may have constitutional mismatch repair deficiency, diagnostic testing may take place as follows:

- A blood sample is collected.

- DNA is isolated from the cells in the sample. A person's genes are made of DNA.
- Both copies of the person's MMR genes are checked for possible changes. A genetic specialist compares the two copies of the patient's gene to normal MMR genes. If there are differences, the specialist decides if they might cause a condition such as constitutional mismatch repair deficiency.
- If MMR gene mutations are found, the genetic counselor will work with the family in the following ways:
 - To help the family understand the cancer risks of constitutional mismatch repair deficiency
 - To find out if other family members should consider testing for the mutation
 - To help with decisions about prenatal genetic testing

In some cases tests may be performed on the person's tumor sample to better direct genetic testing.

Prenatal genetic testing

Parents may undergo prenatal testing to find out if the pregnancy is affected with known MMR mutations in the family. Testing may take place either before pregnancy occurs or during pregnancy.

People considering prenatal testing should work with a genetic counselor to review the pros and cons of the testing. The genetic counselor can also help parents consider how they wish to handle the results of the testing.

Testing that occurs before pregnancy—

Testing that happens before pregnancy is called preimplantation genetic testing (PGT). This special type of genetic testing is done along with in vitro fertilization (IVF). PGT offers a way to test embryos for known MMR mutations before placing them into the uterus.

Testing that occurs during pregnancy—Testing can be used to see if a pregnancy is affected with known MMR mutations. A doctor gathers cells from the pregnancy in one of two ways:

- **Chorionic villus sampling (CVS)**—during the first trimester (first three months)
- **Amniocentesis**—during the second trimester or later (last six months)

Collected tissue can be checked for the presence of the MMR mutations identified in the family.

Both of these tests carry minor risks and should be discussed with an experienced health care provider or genetic counselor.

Special concerns

Genetic testing for constitutional mismatch repair deficiency syndrome is a complex process. Those thinking about testing should take time to consider the benefits and risks. They should discuss the process with a genetic counselor before testing is done. If they choose testing, they



should review the test results with the health care provider or genetic counselor to be sure they understand the meaning of the results.

Sometimes families with constitutional mismatch repair deficiency syndrome can feel sad, anxious, or angry. Parents who pass on MMR mutations to one or more of their children can feel guilty. Some people with MMR mutations could have trouble getting disability coverage, life insurance or long-term care insurance in some states. More information about genetic discrimination can be found at www.ginahelp.org.

Are there other special health care needs for a patient with constitutional mismatch repair deficiency syndrome?

Children with constitutional mismatch repair deficiency syndrome are at risk of developing multiple types of cancer during their lifetimes. They should monitor their health and adopt healthy habits throughout life. It is important to continue to have regular physical checkups and screenings. That way, any cancer can be found early at the most treatable stage.

People with this syndrome should watch closely for general signs or symptoms that could signal cancer:

- Unexplained weight loss
- Tiredness
- Fever that does not go away
- Night sweats
- Loss of appetite
- Aches, pains, lumps or swelling that cannot be explained
- Headaches, vomiting, changes in vision or nerve function that do not go away
- Swollen glands
- Trouble breathing
- Blood in the stool
- Pain in the abdomen

Other ideas to reduce the risk of cancer include the following:

- Eat a healthy diet with lots of fruits and vegetables
- Get regular exercise
- Avoid smoking or using tobacco products
- Avoid secondhand smoke
- Avoid excess sun exposure and always wear sunscreen, hat and protective clothing when out in the sun Avoid radiation exposure when possible

Lynch Syndrome: Inheritance and Healthcare Considerations

If a person has one working copy and one non-working copy of an MMR gene, they have a condition known as hereditary non-polyposis colorectal cancer or Lynch syndrome. Generally, when a child has constitutional mismatch repair deficiency, both parents are assumed to have Lynch syndrome.

People with Lynch syndrome are more likely to develop colon polyps and certain types of cancer, such as colon, uterine, ovarian and small bowel cancer, most commonly as adults.

A person with Lynch syndrome will need to be followed closely by a health care provider (a gastroenterologist who knows the condition well would be best). There are well-established cancer screening guidelines for Lynch syndrome. Starting in adulthood, regular screening exams, known as colonoscopies, are recommended to look for and remove any polyps and to detect colon cancer if it is present. Women with Lynch syndrome can consider screening of the reproductive organs. Screening for other cancers may be considered depending on the gene involved and the family history.

What other information and resources are there for children with constitutional mismatch repair deficiency syndrome and their families?

Resources about colon cancer and MMR genes:

- Lynch Syndrome, Genetics Home Reference (ghr.nlm.nih.gov/condition/lynch-syndrome)
- Hereditary Colon Cancer Takes Guts (www.hcctakesguts.org)
- CCARE Lynch Syndrome (fightlynch.org)
- Colon Cancer Alliance (www.ccalliance.org)

Other resources:

- Making Sense of Your Genes: A Guide to Genetic Counseling (www.ncbi.nlm.nih.gov/books/NBK115508/)
- Young People with Cancer: A Parent's Guide (www.cancer.gov/publications/patient-education/young-people)
- Gene Ed (geneed.nlm.nih.gov)

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