Waldenstrom Macroglobulinemia Early Detection, Diagnosis, and Staging

Detection and Diagnosis

Catching cancer early often allows for more treatment options. Some early cancers may have signs and symptoms that can be noticed, but that is not always the case.

- Can Waldenstrom Macroglobulinemia Be Found Early?
- Signs and Symptoms of Waldenstrom Macroglobulinemia
- How Is Waldenstrom Macroglobulinemia Diagnosed?

Stages and Outlook (Prognosis)

After a cancer diagnosis, staging provides important information about the extent of cancer in the body and anticipated response to treatment.

- How Is Waldenstrom Macroglobulinemia Staged?
- Survival Rates for Waldenstrom Macroglobulinemia

Questions to Ask About Waldenstrom Macroglobulinemia

Here are some questions you can ask your cancer care team to help you better understand your cancer diagnosis and treatment options.

- What Should You Ask Your Doctor About Waldenstrom Macroglobulinemia?

Can Waldenstrom Macroglobulinemia Be Found Early?

Waldenstrom macroglobulinemia (WM) is not common, and at this time there are no widely recommended screening tests to look for this disease in people without symptoms.

Still, many cases of WM are found early, either when people go to the doctor because of symptoms they are having, or when they have blood tests done for other reasons. The best way to find this cancer early is to see your doctor if you have signs or symptoms that might be caused by this disease.

- References

See all references for Waldenstrom Macroglobulinemia

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Signs and Symptoms of Waldenstrom Macroglobulinemia

Sometimes, Waldenstrom macroglobulinemia (WM) isn't causing any symptoms when it's first found. Instead, it's found when the person has blood tests done for some other reason. WM found this way is sometimes called *asymptomatic* or *smoldering* WM.

When WM does cause symptoms, some of them can be like those seen with other types of non-Hodgkin lymphoma (NHL). For example, weight loss, fever, night sweats, and swollen lymph nodes can be seen in many types of NHL.

Other WM symptoms are caused by the large amounts of abnormal IgM antibody (M protein) made by the cancer cells:

- In *hyperviscosity syndrome*, too much of the M protein in the blood can cause it to become too "thick." (This is not the kind of thickness that can be treated with drugs known as *blood thinners*.) When the blood gets too thick, it has trouble moving through blood vessels. This can cause problems such as poor circulation to the brain, which can lead to symptoms like those from a stroke.
- If the M protein only thickens the blood in cooler parts of the body (like in the tip of

the nose, ears, fingers, and toes), it is called a *cryoglobulin*. Cryoglobulins can cause pain or other problems in these areas if a person is exposed to cooler temperatures.
- A condition called *amyloidosis* can occur when a part of the IgM antibody (called the *light chain*) builds up in organs like the heart and kidneys. This buildup can lead to heart and kidney problems.

Not all people with WM develop hyperviscosity, cryoglobulins, or amyloidosis.

Common symptoms of WM

Weakness: This is one of the most common symptoms of WM. It can be caused by anemia (too few red blood cells), which can happen when the WM cells crowd out normal cells in the bone marrow. Some people also feel weak when the blood thickens from the buildup of the abnormal protein.

Loss of appetite: Some people with WM lose their appetite.

Fever, sweats, weight loss: WM, like other lymphomas, can cause fevers (without an infection), drenching night sweats, and weight loss (without trying). Together, these are called *B symptoms*.

Neuropathy: In some people with WM, the abnormal antibody can attack and damage nerves outside the brain. This can lead to numbness or a painful “pins and needles” sensation in the feet and legs, which is called *neuropathy*.

Other problems

Enlarged lymph nodes: These usually appear as lumps under the skin around the neck, in the groin, or in the armpits. Enlarged lymph nodes are usually about 1 or 2 inches across. They are seen less often in WM than in most other lymphomas.

Swollen abdomen (belly): WM can sometimes make the spleen or liver bigger, making the belly look swollen. In the upper part of the abdomen, the liver is on the right and the spleen on the left. When the spleen gets larger, it can press on the stomach, which makes people feel full when they eat even a small amount.

Nervous system symptoms: In hyperviscosity syndrome, the thickened blood causes poor brain circulation, leading to problems like headache, confusion, and dizziness. It can also cause symptoms like those seen with a stroke, including slurred speech and weakness on one side of the body. Patients with these symptoms should contact their

doctor right away.

Abnormal bleeding: High levels of abnormal antibody can damage blood vessels, which can lead to problems like nosebleeds and bleeding gums.

Vision problems: Bleeding around the small blood vessels inside the eyes or poor circulation in these vessels caused by thickened blood might lead to blurred vision or blind spots.

Kidney problems: High levels of the M protein can damage the kidneys directly or through the development of amyloidosis. When the kidneys don't work well, excess salt, fluid, and body waste products stay in the blood. This can cause symptoms like weakness, trouble breathing, and fluid buildup in body tissues.

Heart problems: High levels of the M protein can damage heart tissue directly or through the development of amyloidosis, in which the protein builds up in the heart muscle. This weakens the heart, affecting its ability to pump blood. In addition, because the blood of people with WM is thicker than normal, their hearts have to work harder to pump blood throughout the body. This strain can wear down the heart muscle, leading to a condition called *congestive heart failure*. Symptoms can include heart palpitations, feeling tired and weak, cough, shortness of breath, rapid weight gain, and swelling in the feet and legs.

Infections: The high levels of abnormal antibody in WM can slow the body's normal antibody production. This makes it harder for the body to resist infections.

Digestive symptoms: In some people with WM, the buildup of the M protein in the intestines can lead to problems such as diarrhea, poor absorption of vitamins, or gastrointestinal bleeding (seen as blood in the stools or dark stools).

Sensitivity to cold: In people with cryoglobulins, exposure to cold temperatures can lead to pain, itching, a bluish color, or even sores on the tip of the nose, ears, fingers, or toes due to reduced blood flow to these areas.

- References

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How Is Waldenstrom Macroglobulinemia Diagnosed?

Waldenstrom macroglobulinemia (WM) is often found when a person goes to see their doctor because of symptoms they are having, or because they just don't feel well and go in for a checkup. Sometimes it's found in people without symptoms when they have blood tests done for some other reason.

If signs or symptoms suggest that a person might have WM, exams and tests will be done to be sure. The most important ones will look for abnormal proteins in the blood and abnormal cells in the bone marrow.

This document is about WM, but it will sometimes discuss ways to diagnose non-Hodgkin lymphoma (NHL). This is because WM is a type of lymphoma. Like other lymphomas, WM can invade the bone marrow, lymph nodes, and other organs.

Medical history and physical exam

If you have signs or symptoms that suggest you might have WM (or another type of lymphoma), your doctor will want to get a thorough medical history, including information about your symptoms, possible risk factors, family history, and other medical conditions.

Next, the doctor will examine you, paying special attention to your lymph nodes and other areas of your body that might be involved, including the eyes, nerves, spleen, and liver. The doctor might also look for signs of infection, which can cause many of the same symptoms.

If the doctor suspects that WM (or another type of lymphoma) might be causing your symptoms, he or she will probably order blood tests as the next step. You might also be referred to a hematologist, a doctor who specializes in diseases of the blood.

Lab tests

WM might be suspected if your doctor finds you have low blood cell counts or unusual

protein levels on blood tests. If so, your doctor may order a blood test called *serum protein electrophoresis* to find out what the abnormal proteins are. It is usually only after these tests are done that a biopsy of either the bone marrow or a lymph node is considered.

Blood cell counts

The complete blood count (CBC) is a test that measures the levels of red blood cells, white blood cells, and platelets. If lymphoma cells occupy too much of the bone marrow, these levels will be low.

Quantitative immunoglobulins

This test measures the levels of the different antibodies (immunoglobulins) in the blood – IgA, IgE, IgG, and IgM – to see if any are abnormally high or low. In WM the level of IgM is high but the IgG level is often low.

Electrophoresis

The abnormal immunoglobulin made in WM is an IgM antibody. This antibody is *monoclonal*, meaning that it is many copies of the exact same antibody. Serum protein electrophoresis (SPEP) is a test that measures the total amount of immunoglobulins in the blood and finds any monoclonal immunoglobulin. Another test, such as immunofixation or immunoelectrophoresis, is then used to determine the type of antibody that is abnormal (IgM or some other type).

Finding a monoclonal IgM antibody in the blood is needed to diagnose WM. This abnormal protein in WM is known by many different names, including *monoclonal immunoglobulin M*, *IgM protein*, *IgM spike*, *IgM paraprotein*, *M protein*, and *M-spike*. High levels of other types of monoclonal immunoglobulins, like IgA or IgG, are seen in different disorders (like multiple myeloma and some other lymphomas).

Sometimes pieces of the IgM protein are excreted by the kidneys into the urine. These proteins can be detected with a test called *urine protein electrophoresis* (or UPEP).

Viscosity

Viscosity is a measure of how thick the blood is. If the IgM level is too high, the blood will become thick (viscous) and can’t flow freely (think about pouring honey compared to pouring water).

Cryocrit

This test measures the blood levels of cryoglobulins (proteins that clump together in cool temperatures and can block blood vessels).

Cold agglutinins

Cold agglutinins are antibodies that attack and kill red blood cells, especially at cooler temperatures. These dead cells can then build up and block blood vessels. A blood test can be used to detect these antibodies.

Beta-2 microglobulin (2M)

This test measures another protein made by the cancer cells in WM. This protein itself doesn't cause any problems, but it's a useful indicator of a patient's prognosis (outlook). High levels of 2M are linked with a worse outlook.

Biopsies

The symptoms of WM and NHL are not distinctive enough for a doctor to know for certain if person has one of them, based on symptoms alone. Most symptoms can also be caused by non-cancerous problems like infections or by other kinds of cancers. Blood tests can help point to the correct diagnosis, but a biopsy (removing samples of affected tissue to look at under a microscope) is the only way to be sure. Several types of biopsies might be used.

Bone marrow aspiration and biopsy

This is the most important type of biopsy for WM, and is needed to confirm the diagnosis. It can be done at the doctor's office or at the hospital.

The bone marrow aspiration and biopsy are usually done at the same time. The samples are taken from the back of the pelvic (hip) bone, although in some cases they may be taken from the sternum (breast bone) or other bones.

In bone marrow *aspiration*, you lie on a table (either on your side or on your belly). The doctor cleans the skin over the hip and then numbs the area and the surface of the bone by injecting a local anesthetic. This may briefly sting or burn. A thin, hollow needle is then inserted into the bone, and a syringe is used to suck out a small amount of liquid

bone marrow. Even with the anesthetic, most patients still have some brief pain when the marrow is removed.

A bone marrow *biopsy* is usually done just after the aspiration. A small piece of bone and marrow is removed with a slightly larger needle that is pushed down into the bone. This may also cause some brief pain.

Once the biopsy is done, pressure is applied to the site to help stop any bleeding. There will be some soreness in the biopsy area when the numbing medicine wears off. Most patients can go home right after the procedure.

The bone marrow samples are then sent to a lab, where they are tested to see if they have lymphoma cells (see below). For a diagnosis of WM, at least 10% of the cells in the bone marrow must be lymphoplasmacytoid lymphoma cells.

Fine needle aspiration (FNA) biopsy

In an FNA biopsy, the doctor uses a very thin, hollow needle with a syringe to withdraw a small amount of tissue from a tumor or lymph node. This type of biopsy is useful for sampling lymph nodes to see if they are enlarged because of cancer or another cause such as infection. FNA can help diagnose some lymphomas, but WM is usually diagnosed with a bone marrow biopsy instead.

For an FNA on an enlarged node near the surface of the body, the doctor can aim the needle while feeling the node. If the enlarged node (or tumor) is deep inside the body, the needle can be guided while it is seen on a computed tomography (CT) scan or ultrasound (see the descriptions of imaging tests later in this section).

The main advantage of FNA is that it does not require surgery and can often be done in a doctor’s office. The main drawback is that in some cases it might not get enough tissue to make a definite diagnosis of lymphoma. However, advances in lab tests (discussed later in this section) and the growing experience of many doctors with FNA have improved the accuracy of this procedure.

Excisional or incisional biopsy

For these types of biopsies, a surgeon cuts through the skin to remove an entire lymph node or tumor (excisional biopsy) or a just a small part of a large tumor or lymph node (incisional biopsy). These biopsies are rarely needed in people with WM because the diagnosis is usually made with a bone marrow biopsy. They are used more often for other types of lymphoma.

If the area to be biopsied is near the skin surface, this can be done using local anesthesia (numbing medicine). If the area is inside the chest or abdomen, general anesthesia or deep sedation is used (where the patient is asleep). These types of biopsies almost always provide enough tissue to diagnose the exact type of lymphoma.

Fat pad fine needle aspiration

This type of biopsy may be used in some people with WM to check for amyloid. In this procedure, a thin, hollow needle with a syringe attached is inserted into an area of fat (usually under the skin of the abdomen/belly). A small amount of fat is removed and sent to the lab for testing.

Lab tests on biopsy specimens

All biopsy specimens are looked at under a microscope by a *pathologist* – a doctor with special training in using lab tests to diagnose diseases. In some cases, a *hematopathologist*, a doctor with further training in diagnosing blood and lymph node diseases, might also look at the biopsy. The doctors look at the size and shape of the cells and how the cells are arranged. Sometimes just looking at the cells doesn't provide a clear answer, so other lab tests are needed.

Immunohistochemistry

In this test, a part of the biopsy sample is treated with special man-made antibodies that attach to cells only if they contain specific molecules. These antibodies cause color changes, which can be seen under a microscope. This test may help tell different types of lymphoma from one another and from other diseases.

Flow cytometry

In this test, cells are treated with special man-made antibodies. Each antibody sticks only to certain types of cells. The cells are then passed in front of a laser beam. If the cells now have antibodies attached to them, the laser will make them give off light, which is measured and analyzed by a computer.

This is the most common test for *immunophenotyping* – classifying lymphoma cells according to the substances (antigens) on their surfaces. Different types of lymphocytes have different antigens on their surface. These antigens also change as each cell matures.

This test can help show whether a lymph node is swollen because of lymphoma, some other cancer, or a non-cancerous disease. It has become very important in helping doctors determine the exact type of lymphoma so they can select the best treatment.

Cytogenetics

Doctors use this technique to look at the chromosomes (long strands of DNA) inside lymphoma cells. Cells (usually from the bone marrow) are first grown in the lab. Then the chromosomes are stained and looked at under a microscope. Because it takes time for the cells to start dividing, this test can take weeks.

In some lymphomas, the cells may have too many chromosomes, too few chromosomes, missing parts of chromosomes (called *deletions*), or other abnormalities. These changes can help identify the type of lymphoma. In WM, deletions are the most common type of chromosome change.

Molecular genetic tests

Molecular tests such as fluorescent in situ hybridization (FISH) and polymerase chain reaction (PCR) are not usually needed to diagnose WM, but they are sometimes used to diagnose other types of NHL. These tests look at the cells' DNA without having to grow the cells in the lab first. The tests can give results in less time than cytogenetics and can be done on cells from different sources (like lymph nodes, blood, and bone marrow). They are generally used to look for specific chromosome or gene changes, not just any change.

More testing information

See our document Testing Biopsy and Cytology Specimens for Cancer to learn more about different types of biopsies and lab tests used to diagnose cancer and what the results can tell you.

Imaging tests

Imaging tests use x-rays, magnetic fields, sound waves, or radioactive particles to produce pictures of the inside of the body. These tests are not needed to diagnose WM, but one or more of them might be done to help show the extent of the disease in the body.

Chest x-ray

An x-ray might be done to look at the chest for enlarged lymph nodes.

Computed tomography (CT) scan

The CT scan uses x-rays to make detailed cross-sectional images of your body. Unlike a regular x-ray, CT scans can show the detail in soft tissues (such as internal organs). This scan can help show if any lymph nodes or organs in your body are enlarged. CT scans are useful for looking for signs of lymphoma in the chest, abdomen, and pelvis.

Before the test, you may be asked to drink a contrast solution and/or get an intravenous (IV) injection of a contrast dye to better outline abnormal areas in the body. You might need an IV line through which the contrast dye is injected. The injection can cause some flushing (a feeling of warmth, especially in the face). Some people are allergic to the dye and get hives or a flushed feeling or, rarely, have more serious reactions like trouble breathing and low blood pressure. Be sure to tell the doctor if you have any allergies (especially iodine or shellfish) or have ever had a reaction to any contrast material used for x-rays. Medication can be given to help prevent and treat allergic reactions.

A CT scanner has been described as a large donut, with a narrow table that slides in and out of the middle opening. You need to lie still on the table while the scan is being done. CT scans take longer than regular x-rays, and some people might feel a bit confined by the ring while the pictures are being taken.

CT-guided needle biopsy: CT scans can also be used to guide a biopsy needle into a suspicious area. For this procedure, the patient lies on the CT scanning table while the doctor moves a biopsy needle through the skin and toward the area. CT scans are repeated until the needle is in the right place. A biopsy sample is then removed and sent to the lab to be looked at under a microscope.

Magnetic resonance imaging (MRI) scan

Like CT scans, MRI scans make detailed images of soft tissues in the body. But MRI scans use radio waves and strong magnets instead of x-rays. This test is rarely used in WM, but if your doctor is concerned about the brain or spinal cord, MRI is very useful for looking at these areas.

Sometimes a contrast material is injected into a vein to make some structures clearer. This contrast is not the same as the contrast used for CT scans, but allergic reactions

can still occur. Again, medicine can be given to prevent and treat allergic reactions.

MRI scans take longer than CT scans – often up to an hour. You may have to lie inside a narrow tube, which is confining and can upset some people. Newer, more open MRI machines might be another option. The machine makes loud buzzing and clicking noises that some people find disturbing. Some places provide headphones or earplugs to help block this noise out.

Ultrasound

Ultrasound uses sound waves and their echoes to make pictures of internal organs or masses.

Ultrasound can be used to look at lymph nodes near the surface of the body or to look inside your abdomen for enlarged lymph nodes or organs such as the liver, spleen, and kidneys. (It can't be used to look at organs or lymph nodes in the chest because the ribs block the sound waves.) It is sometimes used to help guide a biopsy needle into an enlarged lymph node.

For this test, a small, microphone-like instrument called a *transducer* is placed on the skin (which is first lubricated with a gel). It gives off sound waves and picks up the echoes as they bounce off the organs. A computer then converts the echoes into a black and white image on a screen.

This is an easy test to have, and it uses no radiation. For most ultrasounds, you simply lie on a table, and a technician moves the transducer over the part of your body being looked at.

Positron emission tomography (PET) scan

For a PET scan, a radioactive sugar (known as *FDG*) is injected into the blood. (The amount of radioactivity used is very low and will pass out of the body in a day or so.) Because cancer cells in the body grow quickly, they absorb large amounts of the sugar. You then lie on a table in the PET scanner for about 30 minutes while a special camera creates a picture of areas of radioactivity. The picture is not detailed like a CT or MRI scan, but it can provide helpful information about your whole body.

PET scans can help tell if an enlarged lymph node contains lymphoma or not. It can also help spot small areas that might be lymphoma, even if the area looks normal on a CT scan. These tests can be used to tell if a lymphoma is responding to treatment. They can also be used after treatment to help decide whether an enlarged lymph node still

contains lymphoma or is merely scar tissue.

Many medical centers now use a machine that combines the PET scan with a CT scan (PET/CT scan). This lets the doctor compare areas of higher radioactivity on the PET scan with the more detailed appearance of that area on the CT scan.

- References

See all references for Waldenstrom Macroglobulinemia

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How Is Waldenstrom Macroglobulinemia Staged?

For most types of cancer, determining the stage of the cancer is very important. The stage of a cancer is a summary of how far it has spread. This can be helpful in predicting outcomes and in deciding on treatment.

There is no standard staging system for Waldenstrom macroglobulinemia (WM) based on the extent of the disease in the body because this hasn't been shown to be important when looking at outcomes or deciding on treatment.

Instead, doctors look at other factors, such as age, blood cell counts, the amount of immunoglobulin (IgM) in the blood, and the level of another protein in the blood called beta-2 microglobulin (2M). People with lower levels of IgM and 2M tend to do better than those with higher levels. People with WM who are older, are anemic (based on a low blood hemoglobin level), or have a low blood platelet count tend to have a poorer outlook.

Experts have used these factors to develop a system that helps predict prognosis (outlook) for patients with WM. It is called the *International Prognostic Scoring System for Waldenstrom Macroglobulinemia* (ISSWM). This system takes into account the factors that seem to predict a poorer outcome, such as:

- Age more than 65 years old
- Blood hemoglobin level 11.5 g/dL or less
- Platelet count 100,000/mcL or less
- Beta-2 microglobulin more than 3 mg/L
- Monoclonal IgM level more than 7 g/dL

Except for age, each of these factors is worth a single point. The points are added to make a score, which is used to divide patients into 3 risk groups:

- The low-risk group includes patients 65 or younger who have no more than 1 point.
- The intermediate-risk group includes those who are older than 65 with 2 or fewer points, and those younger than 65 who have 2 points.
- The high-risk group includes those of any age who have at least 3 points.

These groups can be used to help predict survival (discussed in more detail in Survival Rates for Waldenstrom Macroglobulinemia).

- References

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Survival Rates for Waldenstrom Macroglobulinemia

Survival rates are often used by doctors as a standard way of discussing a person's prognosis (outlook).

The 5-year survival rate refers to the percentage of patients who live *at least* 5 years after their cancer is diagnosed. Of course, many people live much longer than 5 years.

Five-year *relative* survival rates assume that some people with WM will die of other causes and compare the observed survival with that expected for people without WM. This is a better way to see the impact of the cancer on survival.

To get 5-year survival rates, doctors have to look at people who were treated at least 5 years ago. There have been many improvements in the treatment of WM in recent years, so people now being diagnosed with WM may have a better outlook than would be expected based on the numbers below.

According to the National Cancer Institute's SEER database (based on people diagnosed between 2001 and 2010), the overall relative 5-year survival of people with WM is about 78%.

The group that created the International Prognostic Scoring System for Waldenstrom Macroglobulinemia (ISSWM) used data from about 600 patients with WM who were diagnosed and treated before January 2002 to develop their risk groups:

ISSWM risk group	**5-year survival rate**
Low	87%
Intermediate	68%
High	36%

Median survival

Median survival is another way to look at survival. It is the length of time at which half of the patients in a group are still alive, and half have died. By definition, half of the patients live longer than the median survival. The group that developed the ISSWM used data from WM patients diagnosed and treated before January 2002 and found the following:

ISSWM risk group	**Median survival***
Low	12 years
Intermediate	8 years
High	3.5 years

*Median survival is measured from the point that treatment is started.

Survival rates are based on previous outcomes of large numbers of people who had the disease, but they can't predict what will happen with any particular person. They don't take into account all of the factors that can affect a person's outlook, such as how well the cancer responds to treatment. Your doctor knows your situation best and can tell you how the numbers above might apply to you.

- References

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What Should You Ask Your Doctor About Waldenstrom Macroglobulinemia?

As you deal with Waldenstrom macroglobulinemia (WM) and the process of treatment, you need to have honest, open discussions with your cancer care team. You should ask about anything you don't understand or want to know more about. Among the questions you might want to ask are:

- How sure are you about my diagnosis?
- Do I need any other tests before we can decide on treatment?
- Do I need to see any other doctors?
- How much experience do you have treating this disease?
- Should I get a second opinion before starting treatment? Can you suggest someone?
- What treatment options do I have?
- Are there clinical trials I should consider?
- Do you recommend starting treatment now or waiting until later on?
- What would be the goal of treatment (to reduce symptoms, lower IgM levels, etc.)?
- Which drugs do you recommend? How would you compare their effectiveness and side effects to others?
- Is a stem cell transplant an option in my situation? What are the pros and cons of this treatment?
- What should I do to be ready for treatment?
- How long will treatment last? What will it be like? Where will it be done?
- What side effects might I expect from treatment?

- How long will it take me to recover from treatment?
- When can I go back to work or resume other activities after treatment?
- What would we do if the treatment doesn't work or if the cancer comes back?
- What is my outlook for survival?
- What type of follow-up will I need after treatment?

You will no doubt have other questions. Be sure and write them down so you remember to ask them during each visit with your cancer care team. Keep in mind, too, that doctors are not the only ones who can give you information. Other health care professionals, such as nurses and social workers, might be able to answer some of your questions. You can find out more about speaking with your health care team in The Doctor-Patient Relationship.

- References

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