# About Waldenstrom's Macroglobulinemia Fact Sheet

## Waldenstrom's Macroglobulinemia What is it?

Waldenstrom's macroglobulinemia (WM) is a lymphoma, or cancer of the lymphatic system. The disease occurs in a type of white blood cell called a B-lymphocyte or B-cell, which normally develops into a plasma cell whose job is to manufacture immunoglobulins (antibodies) to help the body fight infection. In WM, there is a malignant change to the B-cell in the late stages of development, and it continues to proliferate into a clone of identical cells, primarily in the bone marrow but also in the lymph nodes and other tissues and organs of the lymphatic system. These clonal cells over-produce an antibody of a specific class called IgM.

Under the microscope, WM cells have characteristics of both B-lymphocytes and plasma cells, and they are called lymphoplasmacytic cells. For that reason, WM is classified as a type of non-Hodgkin's lymphoma called lymphoplasmacytic lymphoma (LPL). About 95% of LPL cases are WM; the remaining 5% do not secrete IgM and consequently are not classified as WM. WM is a very rare disease – only about 1,500 patients are diagnosed with WM each year in the US. WM is usually indolent (slow growing) and can be managed as a chronic disease for a number of years. However, it is not yet curable.

As a result of proliferation in the bone marrow and other sites, the lymphoplasmacytic cells of WM may interfere with normal functioning. In the bone marrow where blood cells are produced, the WM cells "crowd out" the normal blood cells and may lead to a reduction in normal blood counts; in the lymph nodes and other organs, the WM cells may lead to enlargement of these structures and other complications.

The over-production of IgM may also cause many of the symptoms associated with the disease. IgM is a large antibody and tends to make the blood thicker than normal, a condition called hyperviscosity. Sometimes the IgM may incorrectly recognize the body's tissues as "foreign" and attach to them, causing inflammation and injury.

## Causes and risk factors

There is no definitive cause of WM. As is the case with most cancers, there are probably multiple risk factors involved – some may be inherited predisposing genetic factors and some may be due to environmental or occupational exposures acquired during one's lifetime.

There are several known risk factors that increase the chance of developing WM. These include the following:

- **Male sex** – The incidence of WM is significantly greater in men than in women.
- **Increasing age** – The median age at diagnosis is approximately 65 years, although patients as young as 18 have been reported. The annual incidence increases dramatically as age increases.
- **Caucasian race** – The incidence is higher in whites than in blacks, but reliable figures for other races are not available.
- **IgM monoclonal gammopathy of undetermined significance (IgM MGUS)** – This refers to a condition in which the presence of a monoclonal IgM has been detected from blood tests, but there is no evidence of malignancy in the bone marrow. In one long-term study of IgM MGUS, the incidence

of progression to WM and other B-cell malignancies was 10% at 5 years, 18% at 10 years, and 24% at 15 years – a progression rate of approximately 1.5% each year.

- **Familial susceptibility** – Several studies report an element of familial susceptibility, as approximately 20% of patients have family members with WM or other B-cell malignancies.

Environmental factors such as radiation exposure, Agent Orange exposure, and occupational exposure to leather, rubber, paints, dyes, and solvents have also been implicated in some studies, as have certain autoimmune diseases and viruses such as hepatitis C. However, none of these environmental factors has consistently been determined to increase risk.

## Prognosis

There are no treatments that can cure WM, although in most cases the disease is slow growing and can be effectively managed with appropriate therapies. Much of the older literature on WM quotes a survival rate of 5-7 years after diagnosis, and this number still shows up from time to time. Patients should be aware that this was based on studies conducted before many of the newer treatments, especially monoclonal antibodies, proteasome inhibitors, and now the targeted therapies to the B-cell signaling pathways, were widely used. Noted WM researchers are reporting that survival is much better today given the rapid improvements in therapeutic options for WM patients. This, plus the fact that people with WM tend to be older when diagnosed, puts their survival rates closer to those expected for the general population. It is important to keep in mind that published survival rates are based on how groups of people with WM respond to treatment. These statistics are less useful in characterizing the prognosis for any given individual with WM, whose outlook can be affected by many factors, such as their overall health, access to therapy, and tolerance or side effects. Patients should speak with their health care team to get an individualized assessment of their long-term outlook.

## Signs and symptoms of disease

Because WM is slow growing, there may be no signs or symptoms of disease for years before and even after diagnosis. Because there are currently no treatments that cure WM or that halt its progression, patients who are asymptomatic or who have mild symptoms should be placed on "watch and wait," a period during which they are not treated but instead are regularly monitored by their health care team for changes in their disease status.

When signs or symptoms do occur, there may be no correlation between the level of monoclonal IgM and/or the amount of bone marrow infiltration with the degree of symptom severity. Patients with similar laboratory test results can have markedly different types and degrees of symptoms.

The following are conditions along with typical signs or symptoms that can occur in WM patients – depending on their severity, they may indicate the need for treatment. It is important to note that several of these signs and symptoms are also associated with other conditions, and one should not necessarily assume that WM is the only cause.

**Anemia** – decreased production of red blood cells, which carry oxygen from the lungs to the tissues. Although anemia has many causes, it is the most common manifestation of lymphoplasmacytic cell infiltration in the bone marrow, and its symptoms often initiate the process leading to a WM diagnosis. These symptoms include pallor, weakness, fatigue, lightheadedness, palpitations of the heart, and shortness of breath.

**Lymphadenopathy, splenomegaly, and hepatomegaly** – enlargement of the lymph nodes, spleen, and liver, respectively. Unless the enlargement is significant, it is frequently not noticeable.

**Hyperviscosity** – increased thickness of the blood, which in WM is caused by a high IgM level. Signs and symptoms of hyperviscosity include chronic bleeding from the nose, gums, and less commonly, the gastrointestinal tract; headache; ringing in the ears; dizziness; loss of coordination or balance, impaired hearing; blurring or loss of vision; distended, sausage-shaped veins in the retina; and swelling of the optic disk at the back of the eye. In severe cases, heart failure, sleepiness, stupor, and coma can develop. Symptoms of hyperviscosity occur most commonly at IgM concentrations greater than 4,000 mg/dL. However, such concentrations are not necessarily associated with hyperviscosity, as there is considerable variability in the amount of IgM that produces hyperviscosity symptoms in an individual.

**Constitutional symptoms (also called B symptoms)** – these include recurring fever, night sweats, weight loss, and fatigue.

**Peripheral neuropathy** – characterized by numbness, tingling, burning, or prickling sensations that are commonly first noticed in the feet. The sensations are usually symmetrical, affecting both feet equally, and slowly progress to the knees before beginning to affect the hands and arms. Weakness of the legs and arms may develop. Peripheral neuropathy is seen in approximately 25% of WM patients and can occur because the monoclonal IgM targets specific components of the nerves, thereby affecting nerve conduction. It can also be caused by treatments that include bortezomib or other neurotoxic agents.

**Cold agglutinin disease** – characterized by the presence of a high concentration of circulating antibody directed against the red blood cells. The antibody typically binds to the cells at low body temperatures and can cause hemolytic anemia (destruction of red blood cells). Signs and symptoms vary according to the severity of the disease and may include painful fingers and toes upon exposure to the cold, anemia, fatigue, shortness of breath, jaundice, Raynaud's phenomenon (whiteness of the fingers, toes, nose, and/or ears) when cold, and dark urine caused by the presence of hemoglobin.

**Cryoglobulinemia** – a condition in which the circulating IgM has the properties of a cryoglobulin, which is a protein that precipitates at low body temperatures. When the IgM concentration reaches high levels, the precipitated antibody physically obstructs smaller blood vessels, leading to blueness of the fingers and toes when cold; Raynaud's phenomenon; purpura (purple skin marks); and bleeding, ulcers, and gangrene of the fingers, toes, nose, and ears.

**Thrombocytopenia** – decreased production of platelets, which are important in blood clotting. Typical symptoms are bleeding, usually from the gums and nose, pinpoint flat red discolorations on the skin called petechiae, and easy bruising.

**Amyloidosis** – a group of rare diseases caused by the deposition of an abnormal protein called amyloid in various tissues and organs of the body. The amyloid protein forms fibrils that may injure these body parts or interfere with their normal functioning. The protein may be deposited in a localized area or throughout the body. The most common tissues and organs involved are the kidneys, heart, gastrointestinal tract, peripheral nerves, and liver. Symptoms can vary widely based on which tissues and organs have the abnormal fibril deposits. Signs and symptoms of amyloidosis may be vague, such as weakness, fatigue, weight loss, shortness of breath, abnormal sensation in the feet, enlarged liver and/or spleen, bleeding under the skin, or anemia. More specific signs and symptoms might include swelling of the extremities, an enlarged tongue,

carpal tunnel syndrome, food malabsorption, skin thickening, unexplained congestive heart failure, and unexplained kidney failure.

**Bing-Neel syndrome** – characterized by the infiltration of lymphoplasmacytic cells in the central nervous system (brain and spinal cord). This is a very rare condition which can result in mental deterioration, confusion, visual disturbances, irritability, personality changes, convulsions, and coma.

**Other signs and symptoms** – recurring infections, particularly of the sinuses and upper respiratory tract, may occur more often in WM patients than in the normal population. Occasionally the lymphoplasmacytic cells of WM can infiltrate the lung and produce masses or pleural effusions (fluid in the chest). Involvement of the kidneys and lesions in the bones are rare. Occasionally patients will have a rash or hives, and rarely the lymphoplasmacytic cells may infiltrate the skin. A small number of patients may exhibit masses of WM cells in various parts of the body, including the extremities, the spine, the breast, and the eye socket.

## Common medical tests used for diagnosis and disease monitoring

The physical examination is the process by which a health care professional examines the body of a patient for signs of disease. It follows the taking of a medical history, which is an account of the symptoms experienced by the patient as well as questions regarding the patient's current and past health history.

The frequency of physical examinations to monitor the disease after diagnosis depends on disease status. Patients with smoldering WM who are stable may not need to see a hematologist-oncologist more than once or twice a year. Newly diagnosed patients or those with progressing disease will be followed at more frequent intervals, perhaps once every 2-3 months. Patients in treatment may be monitored even more frequently (possibly even weekly) because of side effects that need to be recognized early to be effectively managed.

Various tests are performed to establish a WM diagnosis. Many of these same tests are used to monitor the status of the disease, before, during, and after treatment.

**Bone marrow biopsy** – The bone marrow biopsy (BMB) is the definitive test for confirming the diagnosis of WM. While necessary for diagnosis, it is infrequently used to monitor the disease. This procedure can be performed in a physician's office or in a monitored setting (such as a hospital) under local anesthetic or light sedation. The specimen is usually obtained from the posterior iliac crest (back of the hip bone) by using a large-bore needle, although in rare cases it may be taken from the sternum (breastbone) or other bones. Both a liquid bone marrow sample (bone marrow aspiration) and a solid bone sample (bone marrow biopsy) may be taken during the procedure.

A pathologist examines the bone marrow cells under a microscope and may request additional testing with special stains, flow cytometry, polymerase chain reaction techniques, genome sequencing, or FISH analysis to further identify the type of cancer cells present. In WM, the pathologist will note an increased amount of lymphoplasmacytic cells (which have features of both lymphocytes and plasma cells) and estimate the amount of infiltration of these cells into the bone marrow. The pathologist will also examine the marrow to determine how healthy it is, and whether it appears capable of generating adequate amounts of normal blood cells.

Even with light sedation, a patient may experience brief discomfort during the procedure and some soreness in the biopsy area afterwards when the numbing medicine wears off. Most patients can go home right after the procedure.

One of the primary means to assess a WM patient's disease status is through periodic blood tests. Among

the more common test sets are the Complete Blood Count (CBC), Comprehensive Metabolic Panel (CMP), and Immunoglobulins. Other tests listed below may be added as needed.

**Complete Blood Count** – This panel measures the number and percentage of white blood cells, red blood cells, and platelets in the blood and provides other useful information about the structure of these cells. This test also determines the amount of hemoglobin in the blood. Hemoglobin is the molecule in red blood cells that is responsible for carrying oxygen throughout the body. In WM patients, the red cell count and hemoglobin may be lower than normal, leading to anemia. This is one of the most common conditions occurring in WM patients and frequently leads to the need for treatment.

**Comprehensive Metabolic Panel** – This test provides an overall picture of your body's chemical balance and metabolism. The panel measures the blood levels of albumin, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, glucose, potassium, sodium, total bilirubin, total protein, and liver enzymes (alanine aminotransferase, alkaline phosphatase, and aspartate aminotransferase).

**Immunoglobulins** – These are antibodies (proteins) produced by the body to help fight infection. Monoclonal immunoglobulin M (IgM) is over-produced by the WM cancer cells and, along with results from the bone marrow biopsy, its presence in the serum is necessary to establish a WM diagnosis. IgM is also one of the most common markers used to monitor the disease. The other immunoglobulins, such as IgG and IgA, are frequently lower than normal in WM patients, potentially leading to an increased risk of infections. Immunoglobulin testing includes serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), and serum immunofixation electrophoresis (SIFE).

**Imaging Tests** – Computed tomography (CT) scans of the chest, abdomen, and pelvis, preferably with contrast, are an essential part of the diagnostic workup of WM, particularly if patients have enlarged lymph nodes or an enlarged spleen or if infiltration of WM cells into other parts of the body is suspected. X-rays, MRIs, ultrasounds, and PET scans may be useful in specific clinical situations.

**Dilated eye examinations** – These are suggested if the IgM is equal to or greater than 3,000 mg/dL, or if hyperviscosity (excessive thickening of the blood) is suspected. It is preferable to have an ophthalmologist who is knowledgeable about WM and its effects on the eye perform the examination.

## Treatments and side effects

WM patients should be treated when they have symptoms and not on the basis of blood test results alone. This applies not only to consideration of initial (frontline) treatment but also to treatment following relapse. Many therapies have toxic side effects and treating patients who don't yet have symptoms may potentially have an adverse effect on quality of life and health.

Ibrutinib alone and in combination with rituximab has been approved for the treatment of WM by the US Food and Drug Administration (FDA) and the European Medicines Agency. Zanubrutinib has also been approved by the FDA, Health Canada, European Medicines Agency,and Australia for the treatment of WM. Zanubrutinib has also been conditionally approved by the China National Medical Products Administration (NMPA) for the treatment of WM in patients with relapsed or refractory WM. Prior to these approvals, most treatments used for WM were approved for the related cancers of follicular lymphoma, chronic lymphocytic leukemia, and multiple myeloma. Once Phase 1 and Phase 2 clinical trials established that these treatments had an acceptable safety profile and were effective for WM patients, they were prescribed for "off label" use in WM. The process of "off label" prescription is still in use and valid today.

There is no single standard of therapy to treat WM. Many treatment options are available to WM patients, and a full discussion of each is beyond the scope of this fact sheet. For more information about these therapeutic

options, please see the Treatment Options Guides and specific treatment Fact Sheets on the IWMF website at IWMF & Affiliate Publications. Currently available treatment options may include one or more of the following:

- **Chemotherapy** with alkylating agents such as cyclophosphamide and bendamustine or with nucleoside analogs such fludarabine and cladribine;
- **Biologic therapy** with monoclonal antibodies such as rituximab and ofatumumab;
- **Proteasome inhibitors** such as bortezomib, carfilzomib, and ixazomib;
- **Targeted therapies** to the B-cell signaling pathways, including BTK inhibitors such as ibrutinib;

**Surgical or other procedures**, including splenectomy (surgical removal of the spleen), plasmapheresis to temporarily remove IgM from the serum (especially in the presence of hyperviscosity), targeted radiation to reduce the size of lymph nodes or WM cell masses, and stem cell transplantation.

Newer targeted therapies being tested (including the BCL2 inhibitor venetoclax and the second generation BTK inhibitors (acalabrutinib, zanubrutinib, and tirabrutinib) and combinations of these drugs with older therapies are being added to the treatment options. Supportive therapy such as transfusions or growth factors to boost the production of red blood cells, white blood cells, and platelets may be needed during treatment regimens for WM.

When treatment is being considered, a WM patient may want to ask the health care team to consult with a WM expert at a major medical center for a second opinion about the necessity for treatment and the various treatment options available. This can be very helpful because few health care providers have a great deal of experience with a rare disease like WM. A recent study by Mayo Clinic has demonstrated that better outcomes are achieved when WM patients are treated by health care teams at facilities that see a larger volume of patients.

Many of the older, established treatments are still appropriate for WM patients. While the newer drugs that target B-cell signaling pathways represent a very important step forward in treatment, they are not a cure for WM and not everyone responds to them or can tolerate their side effects.

Treatment can usually be administered in an outpatient setting or at home and may be oral, by intramuscular or subcutaneous injection, or by intravenous therapy. Some treatments require that certain medications be taken the day before or the day of treatment in order to minimize associated side effects. Traditionally, treatment has been done in cycles that may take several weeks to months, depending on the course of therapy chosen. It is not unusual to have a round of therapy and then wait a week or a month before another round of treatment. Some of the newer oral therapies such as ibrutinib require daily dosing instead, until relapse or significant toxicities develop.

A relapse or recurrence after treatment occurs when laboratory values and physical signs and symptoms begin to trend in a deteriorating direction. These signs and symptoms may be quite similar to those that led to initial treatment. At this point, patients and their health care team are confronted with choosing the next appropriate course of action, be it continued periodic monitoring or re-treatment.

The severity of symptoms, overall health condition, quality of life, and candidacy for future stem cell

transplantation will factor into the decision of when to begin re-treatment. The question becomes: Which treatment to choose? In general, if a patient has had good results with a prior therapy that led to a significant period of response (2 years or more), then a repeat treatment with the same therapy may be appropriate. If a prior therapy was not very effective or the response period was short, a different type of therapy is indicated.

The IWMF also encourages patients to consider participating in clinical trials if they are thinking about treatment. Information on currently available clinical trials can be searched for on the US government website www.clinicaltrials.gov.

Most treatments for WM come with side effects, which can include one or more of the following: nausea or vomiting, constipation, diarrhea, low blood counts, hair loss, fatigue, infusion reactions, increased risk of infections, and neuropathy.

Patients in treatment should ask for written information on potential side effects and how to manage them. There are supportive therapies to help manage many of these side effects. Patients should discuss with their health care team any changes in symptoms or any possible side effects they are experiencing, even if they are not sure a problem is related to treatment.

## Recent developments

Research into the genetics of WM made a major leap forward in 2011 with the discovery of a single mutation in a gene called MYD88 at a frequency of 90% or more in WM patients. This was the first time that the entire genome, or complete set of DNA, of patients with WM was sequenced, with the goal to determine which genes were present in the cancer cells of these patients that were not seen in their normal cells. The same study also reported that the MYD88 mutation, designated MYD88 L265P, was not nearly as prevalent in most other types of lymphoma or in multiple myeloma. Subsequent follow-up studies by WM investigators around the world have validated these findings.

Researchers are continuing to study the mutation's effects on complex downstream cellular pathways and how these pathways might in turn promote the growth and proliferation of WM cells. Current guidelines recommend AS-PCR testing for the presence of MYD88 L265P in the bone marrow cells of suspected WM patients and have characterized the test as essential for the diagnosis of WM. Not only does the presence of the mutation help to confirm the diagnosis, but the absence of a mutation in MYD88 (called wild-type MYD88) can negatively impact response to BTK inhibitor therapy in WM patients.

Several other genetic mutations appear to be fairly common in WM patients, although not to the extent of the MYD88 L265P mutation. One such group of mutations occurs in the gene CXCR4 at a frequency of about 30-40%. Studies have shown that mutations in this gene have an impact on the clinical presentation of WM and negatively affect response to ibrutinib therapy. At this time, it is technically difficult in clinical practice to reliably detect the numerous possible CXCR4 mutations, but studies are ongoing to refine and standardize detection methods.

The IWMF has played a major role in funding these recent genetic studies and intends to expand its research role in the near future. Since its incorporation in 1998, the IWMF has raised over $18 million USD for research and has built strong relationships with many institutions in the US, Canada, and abroad. All potential IWMF-funded research projects are reviewed by an independent committee that includes members of our prestigious Scientific Advisory Committee (SAC), co-chaired by Stephen M. Ansell, MD, PhD, of Mayo Clinic and Steven P. Treon, MD, PhD, of Dana-Farber Cancer Institute. This committee provides feedback to researchers and recommends the most promising research projects to the IWMF Board of Trustees for funding consideration.

In 2014, the Foundation decided that the time was right to update its research strategy and enlist the

cooperation of many of the major players in the WM research community. To this end, the IWMF partnered with the Leukemia & Lymphoma Society (LLS) to sponsor a Strategic Research Roadmap Summit in May 2015. The Roadmap Summit was attended by a number of WM researchers and resulted in the identification of key priority areas where concentrated research is needed. The Summit's work has continued, and these are the currently identified key priority areas:

- **Genomics and Epigenomics** – The genetic basis for unmutated MYD88 (also called wild-type) disease remains unknown, and one important priority should be the use of improved laboratory genetic sequencing techniques to identify this basis. The epigenome consists of chemical compounds and proteins that can attach to DNA and turn genes on or off, thereby controlling the production of proteins in cells. The epigenome has undergone extensive study in other B-cell malignancies. A comprehensive analysis of the epigenome of WM cells whose MYD88 and CXCR4 status are known will provide insights into potential therapeutic targets.

- **Signaling** - Studies are needed to identify signaling pathways and downstream proteins associated with mutated MYD88 and mutated CXCR4 in order to advance future WM treatments;

- **Immunotherapy** – The mechanism whereby a WM patient's own immune system can be manipulated or triggered to recognize and subsequently attack the offending WM cells remains unknown. Research to understand the biology of the immune response in WM is vitally important;

- **Bone marrow/tumor microenvironment** – Focused research is needed into the role of the bone marrow and tumor microenvironment (the "neighborhood" around WM cells) in supporting malignant cell growth in WM. Studies are required to better characterize the components of the microenvironment, as well as its contribution to disease progression and resistance to treatment;

- **IgM monoclonal gammopathy of undetermined significance (IgM MGUS)** – While many patients with the precursor condition called IgM MGUS harbor MYD88 mutations, the presence of mutated MYD88 alone is unlikely to explain progression to WM, given findings from animal models of the disease. An understanding of the genetic and other changes that occur during progression to smoldering and then active WM may identify patients at risk of progression and interventions that may prevent or suppress progression.

Beginning in 2015 and continuing until the present, an IWMF Request for Proposals under the Research Roadmap guidelines has been issued annually to almost 300 researchers, and a number of important and promising proposals have been funded.

## Survivorship

Advances in the treatment of WM have led to an improved life expectancy for people living with the disease. Some patients are experiencing extended responses from treatment, and others continue to manage the disease with ongoing therapies. Living longer with WM presents new challenges…managing long-term treatment-related side effects (fatigue, increased risk of infections, neuropathy, chemo brain, etc.) and coping with the emotional, social, employment, and financial issues that may persist.

Maximizing quality of life throughout the WM journey is key to overall well-being and requires active

participation by the WM patient/caregiver and health care professionals. Essential areas to target may include healthy lifestyles (nutrition, physical activity, relaxation, etc.), support system, counseling, pain management,

and use of financial/employment resources. Ideally, the goal is to thrive, not just survive, within the scope of each person's unique WM experience.

## About the IWMF

The International Waldenstrom's Macroglobulinemia Foundation (IWMF) is a patient-founded and volunteer-led, nonprofit 501(c)(3) organization with an important vision, "A World Without WM," and a mission to "Support and educate everyone affected by WM while advancing the search for a cure."

The IWMF and its international Affiliates provide a wide variety of services to help patients and their caregivers understand and cope with WM. These include a network of Support Groups, our Internet group discussion forums, our volunteer-based telephone and email LIFELINE, and our quarterly magazine, the *IWMF Torch*.

We offer Information Packets (Info Paks) for patients and for medical professionals that have been designed to provide very readable information about WM and about membership in the IWMF. Info Paks are available free of charge, in several languages in addition to English, and can be immediately downloaded from our website or mailed upon request through our website or through our Office.

We encourage WM patients and caregivers to attend our annual Educational Forum, which provides a unique opportunity to hear about the latest research and treatments in WM. It's also a great way to network with other patients. The Educational Forum has typically rotated to various regions around the US. Several of our Affiliates also hold periodic country-specific educational forums.

More information about Waldenstrom's macroglobulinemia and these and other services offered by the IWMF can be found on our website, www.iwmf.com. Our international Affiliates and their websites/contact information can be found at www.iwmf.com/about-us/international-affiliates.

The IWMF relies on donations to continue its mission, and we welcome your support. The Foundation maintains a Business Office at 6144 Clark Center, Ave., Sarasota, FL 34238. The Office can be contacted by phone at 941-927-4963, by fax at 941-927-4467, or by email at info@iwmf.com.

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