MASSACHUSETTS

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Medical Policy

# Allogeneic Hematopoietic Cell transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

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## Policy Number: 155

BCBSA Reference Number: 8.01.21 (For Plan internal use only)

## Related Policies

- Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia, #212
- Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia, #150

## Policy

### Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Myeloablative allogeneic hematopoietic cell transplantation (allo-HCT) may be **MEDICALLY NECESSARY** as a treatment of:

- Myelodysplastic syndromes **or**
- Myeloproliferative neoplasms.

Reduced-intensity conditioning allo-HCT may be **MEDICALLY NECESSARY** as a risk-adapted treatment of:

- Myelodysplastic syndromes **or**
- Myeloproliferative neoplasms in individuals who are at high-risk of intolerance of a myeloablative conditioning regimen.

Myeloablative allo-HCT or reduced-intensity conditioning allo-HCT for myelodysplastic syndromes and myeloproliferative neoplasms that do not meet the criteria in the Policy Guidelines section is considered are **INVESTIGATIONAL**.

**Myeloid Neoplasms**

Myeloid neoplasms are categorized according to criteria developed by the World Health Organization (WHO). Neoplasms are risk-stratified using the International Prognostic Scoring System (IPSS).

**2022 WHO Classification Scheme for Myeloid Neoplasm and Histiocytic/Dendritic Neoplasms**

**Clonal hematopoiesis (CH)**

- CH of indeterminate potential (CHIP)

- Clonal cytopenia of undetermined significance (CCUS)

**Myeloproliferative neoplasms (MPN)**

- Chronic myeloid leukemia (CML), BCR-ABL1$^{+}$
- Chronic neutrophilic leukemia (CNL)
- Polycythemia vera
- Primary myelofibrosis (PMF)
- Essential thrombocythemia
- Chronic eosinophilic leukemia
- MPN, not otherwise specified
- Juvenile myelomonocytic leukemia

**Mastocytosis**

- Cutaneous mastocytosis
- Systemic mastocytosis
- Mast cell sarcoma

**Childhood MDS**

- Childhood MDS with low blasts
    - Hypocellular
    - Not otherwise specified
- Childhood MDS with increased blasts

**Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLN-TK)**

**Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)**

- Chronic myelomonocytic leukemia (CMML)
- MDS/MPN with neutrophilia
- MDS/MPN with *SF3B1* mutation and thrombocytosis
- MDS/MPN, otherwise specified

**Myelodysplastic neoplasms (MDS)**

- MDS with defining genetic abnormalities
    - MDS with low blasts and isolated 5q deletion (MDS-5q)
    - MDS with low blasts and *SF3B1* mutation (MDS-*SF3B1*), or MDS with low blasts and ring sideroblasts
    - MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)
- MDS, morphologically defined
    - MDS with low blasts (MDS-LB)
    - MDS, hypoplastic (MDS-h)
    - MDs with increased blasts (MDS-IB)
        - MDS-IB1
        - MDS-IB2
        - MDS with fibrosis (MDS-f)

**Acute myeloid leukemia (AML)**

- AML with defining genetic abnormalities
- AML, defined by differentiation

**Secondary myeloid neoplasms**

- Myeloid neoplasms post cytotoxic therapy
- Myeloid neoplasms associated with germline predisposition

**Dendritic cell and histiocytic neoplasms**

- Plasmacytoid dendritic cell neoplasms
- Langerhans cell and other dendritic cell neoplasms
- Histiocytic neoplasms

**Acute leukemias of ambiguous lineage (ALAL)**

- ALAL with defining genetic abnormalities
- ALAL, immunophenotypically defined

**Genetic tumor syndromes with predisposition to myeloid neoplasia**

**Risk Stratification of Myelodysplastic Syndromes**

Risk stratification for MDS is performed using the IPSS (Table PG1). This system was developed after pooling data from 7 studies that used independent, risk-based prognostic factors. The prognostic model and the scoring system were based on blast count, degree of cytopenia, and blast percentage. Risk scores were weighted relative to their statistical power. This system is widely used to group individuals into either low-risk or high-risk groups (Table PG2). The low-risk group includes low-risk and intermediate-1 IPSS groups; treatment goals in low-risk MDS individuals are to improve quality of life and achieve transfusion independence. In the high-risk group, which includes intermediate-2 and high-risk IPSS groups, treatment goals are slowing disease progression to AML and improving survival. IPSS is usually calculated on diagnosis. The role of lactate dehydrogenase, marrow fibrosis, and $\beta_2$-microglobulin also should be considered after establishing IPSS. If elevated, the prognostic category worsens by 1 category change.

**Table PG1. International Prognostic Scoring System: Myelodysplastic Syndrome Prognostic Variables**

| Variable | 0 | 0.5 | 1.0 | 1.5 | 2.0 |
|---|---|---|---|---|---|
| Marrow blasts, % | <5 | 5 to 10 | NA | 11 to 20 | 21 to 30 |
| Karyotype | Good | Intermediate | Poor | NA | NA |
| Cytopenias | 0/1 | 2/3 | NA | NA | NA |

NA: not applicable.

**Table PG2. International Prognostic Scoring System: Myelodysplastic Syndrome Clinical Outcomes**

| Risk Group | Total Score | Median Survival, y | Time for 25% of patients to Progress to AML |
|---|---|---|---|
| Low | 0 | 5.7 | 9.4 years |
| Intermediate-1 | 0.5 to 1.0 | 3.5 | 3.3 years |
| Intermediate-2 | 1.5 to 2.0 | 1.2 | 1.12 years |
| High | ≥2.5 | 0.4 | 0.2 years |

AML: acute myelocytic leukemia.

## Prior Authorization Information

**Inpatient**

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

**Outpatient**

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

| | Outpatient |
|---|---|
| **Commercial Managed Care (HMO and POS)** | Prior authorization is **required**. |
| **Commercial PPO and Indemnity** | Prior authorization is **required**. |

**Requesting Prior Authorization Using Authorization Manager**

Providers will need to use Authorization Manager to submit initial authorization requests for services. Authorization Manager, available 24/7, is the quickest way to review authorization requirements, request authorizations, submit clinical documentation, check existing case status, and view/print the decision letter. For commercial members, the requests must meet medical policy guidelines.

To ensure the service request is processed accurately and quickly:

- Enter the facility's NPI or provider ID for where services are being performed.
- Enter the appropriate surgeon's NPI or provider ID as the servicing provider, *not* the billing group.

**Authorization Manager Resources**

Refer to our Authorization Manager page for tips, guides, and video demonstrations.

## CPT Codes / HCPCS Codes / ICD Codes

*Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.*

*Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.*

*The following codes are included below for informational purposes only; this is not an all-inclusive list.*

**The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:**

## CPT Codes

| CPT codes: | Code Description |
|---|---|
| 38240 | Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic |

## HCPCS Codes

| HCPCS codes: | Code Description |
|---|---|
| S2150 | Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services) |

## ICD-10 Procedure Codes

| ICD-10-PCS procedure codes: | Code Description |
|---|---|
| 30233G1 | Transfusion of Nonautologous Bone Marrow into Peripheral Vein, Percutaneous Approach |
| 30233X1 | Transfusion of Nonautologous Cord Blood Stem Cells into Peripheral Vein, Percutaneous Approach |
| 30233Y1 | Transfusion of Nonautologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach |
| 30243G1 | Transfusion of Nonautologous Bone Marrow into Central Vein, Percutaneous Approach |
| 30243X1 | Transfusion of Nonautologous Cord Blood Stem Cells into Central Vein, Percutaneous Approach |
| 30243Y1 | Transfusion of Nonautologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach |
| 30263G1 | Transfusion of Nonautologous Bone Marrow into Central Artery, Percutaneous Approach |
| 30263X1 | Transfusion of Nonautologous Cord Blood Stem Cells into Central Artery, Percutaneous Approach |
| 30263Y1 | Transfusion of Nonautologous Hematopoietic Stem Cells into Central Artery, Percutaneous Approach |
| 3E03305 | Introduction of Other Antineoplastic into Peripheral Vein, Percutaneous Approach |
| 3E04305 | Introduction of Other Antineoplastic into Central Vein, Percutaneous Approach |
| 3E05305 | Introduction of Other Antineoplastic into Peripheral Artery, Percutaneous Approach |
| 3E06305 | Introduction of Other Antineoplastic into Central Artery, Percutaneous Approach |

## Description

**Myelodysplastic Syndromes**
Myelodysplastic syndrome (MDS) can occur as a primary (idiopathic) disease or can be secondary to cytotoxic therapy, ionizing radiation, or other environmental insults. Chromosomal abnormalities are seen in 40% to 60% of patients, frequently involving deletions of chromosome 5 or 7 or an extra chromosome as in trisomy 8. Most MDS diagnoses occur in individuals older than age 55 to 60 years, with an age-adjusted incidence of 62% among individuals older than age 70 years. Patients succumb either to disease progression to acute myeloid leukemia (AML) or to complications of pancytopenias. Patients with higher blast counts or complex cytogenetic abnormalities have a greater likelihood of progressing to AML than do other patients.

**Myelodysplastic Syndrome Classification and Prognosis**
The French-American-British system was previously used to classify MDS into 5 subtypes: (1) refractory anemia; (2) refractory anemia with ringed sideroblasts; (3) refractory anemia with excess blasts; (4) refractory anemia with excess blasts in transformation; and (5) chronic myelomonocytic leukemia. The French-American-British system was supplanted by that of the World Health Organization (WHO), which differentiates between MDS defined by genetic abnormalities or by morphologic features (in the form of dysplastic cell lineages), and reduces the threshold maximum blast percentage for the diagnosis of MDS from 30% to 20%.[1]

The most commonly used prognostic scoring system for MDS is the International Prognostic Scoring System (IPSS), which groups patients into 1 of 4 prognostic categories based on the number of cytopenias, cytogenetic profile, and the percentage of blasts in the bone marrow. This system underweights the clinical importance of severe, life-threatening neutropenia and thrombocytopenia in therapeutic decisions and does not account for the rate of change in critical parameters (eg, peripheral blood counts, blast percentage). However, the IPSS has been useful in a comparative analysis of clinical trial results, and its utility confirmed at many institutions. An updated 5-category IPSS has been proposed for prognosis in patients with primary MDS or secondary AML to account for chromosomal abnormalities frequently seen in MDS.[2] This system stratifies patients into 5 categories: very poor, poor, intermediate, good, and very good. There has been an investigation into using the 5-category IPSS to better characterize risk in MDS. A second prognostic scoring system incorporates the WHO subgroup classification that accounts for blast percentage, cytogenetics, and severity of cytopenias as assessed by transfusion requirements. The WHO classification-based Prognostic Scoring System uses a 6-category system, which allows more precise prognostication of overall survival (OS) duration, as well as risk for progression to AML.

**Myelodysplastic Syndrome Treatment**
Treatment of nonprogressing MDS has previously involved best supportive care, including red blood cell and platelet transfusions and antibiotics. Active therapy was given only when MDS progressed to AML or resembled AML with severe cytopenias. An array of therapies are now available to treat MDS, including hematopoietic growth factors (eg, erythropoietin, darbepoetin, granulocyte colony-stimulating factor), transcriptional-modifying therapy (eg, U.S. Food and Drug Administration (FDA) approved hypomethylating agents, nonapproved histone deacetylase inhibitors), immunomodulators (eg, lenalidomide, thalidomide, antithymocyte globulin, cyclosporine A), low-dose chemotherapy (eg, cytarabine), and allogeneic hematopoietic cell transplantation (allo-HCT). Given the spectrum of treatments available, the goal of therapy must be decided upfront whether it is to improve anemia, thrombocytopenia, or neutropenia, to eliminate the need for red blood cell transfusion, to achieve complete remission, or to cure the disease.

Allo-HCT is the only approach with curative potential, but its use is governed by patient age, performance status, medical comorbidities, the patient's preference, risk category, and severity of MDS at presentation. Allo-HCT is discussed in more detail in a subsequent section.

**Chronic Myeloproliferative Neoplasms**
Chronic myeloproliferative neoplasms are clonal bone marrow stem cell disorders; as a group, approximately 8,400 myeloproliferative neoplasms are diagnosed annually in the United States. Like

MDS, myeloproliferative neoplasms primarily occur in older individuals, with approximately 67% reported in patients aged 60 years and older.

Myeloproliferative neoplasms are characterized by the slow but progressive expansion of a clone of cells with the potential evolution into a blast crisis similar to AML. Myeloproliferative neoplasms share a common stem cell-derived clonal heritage, with phenotypic diversity attributed to abnormal variations in signal transduction as the result of a spectrum of variants that affects protein tyrosine kinases or related molecules. The unifying characteristic common to all myeloproliferative neoplasms is effective clonal myeloproliferation resulting in peripheral granulocytosis, thrombocytosis, or erythrocytosis that is devoid of dyserythropoiesis, granulocytic dysplasia, or monocytosis.

**Myeloproliferative Neoplasm Classification**
Myeloproliferative neoplasms are a subdivision of myeloid neoplasms that includes 4 classic disorders: chronic myeloid leukemia, polycythemia vera, essential thrombocytopenia, and primary myelofibrosis. The WHO classification also includes chronic neutrophilic leukemia, chronic eosinophilic leukemia not otherwise specified, and myeloproliferative neoplasm unclassifiable. In the 2016 classification, mastocytosis is no longer considered a subgroup of the myeloproliferative neoplasms due to its unique clinical and pathologic features.

**Myeloproliferative Neoplasm Treatment**
In indolent, nonprogressing cases, therapeutic approaches are based on relief of symptoms. Supportive therapy may include prevention of thromboembolic events. Hydroxyurea may be used in cases of high-risk essential thrombocytosis and polycythemia vera, and intermediate- and high-risk primary myelofibrosis.

The FDA (2011) approved the orally administered selective Janus kinase 1 and 2 inhibitor ruxolitinib for the treatment of intermediate- or high-risk myelofibrosis. Ruxolitinib has been associated with improved OS, spleen size, and symptoms of myelofibrosis compared with placebo.[3,] The Randomized Study of Ruxolitinib Tablets Compared to Best Available Therapy in Subjects With Primary Myelofibrosis, Post-Polycythemia Vera-Myelofibrosis or Post-Essential Thrombocythemia Myelofibrosis (COMFORT-II trial [2013]) compared ruxolitinib with best available therapy in patients who had intermediate- and high-risk myelofibrosis, and demonstrated improvements in spleen volume and OS.[4,] In a randomized trial comparing ruxolitinib with best available therapy (including antineoplastic agents, most commonly hydroxyurea, glucocorticoids) with no therapy for treatment of myelofibrosis, Harrison et al (2012) reported improvements in spleen size and quality of life, but not OS.[5,] In 2019, the FDA also approved fedratinib (Inrebic®) for adults with intermediate-2 or high-risk primary or secondary myelofibrosis based on results from a double-blind, randomized, placebo-controlled trial that found improvement in spleen volume and myelofibrosis-related symptoms.[6,]

Myeloablative allo-HCT has been considered the only potentially curative therapy, but because most patients are of advanced age with attendant comorbidities, its use is limited to those who can tolerate the often-severe treatment-related adverse events of this procedure. However, the use of reduced-intensity conditioning (RIC) for allo-HCT has extended the potential benefits of this procedure to selected individuals with these disorders. Allo-HCT is discussed in more detail in the next section.

**Hematopoietic Cell Transplantation**
Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients who receive bone marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allo-HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplantation, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. Human leukocyte

antigen refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

**Conditioning for Hematopoietic Cell Transplantation**

**Conventional Conditioning**
The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease (GVHD), which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

**Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation**
RIC refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose MAC treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this review, the term RIC will refer to all conditioning regimens intended to be nonmyeloablative.

## Summary

**Description**
Myelodysplastic syndromes (MDS) and myeloproliferative neoplasms refer to a heterogeneous group of clonal hematopoietic disorders with the potential to transform into acute myelocytic leukemia. Allogeneic hematopoietic cell transplantation (allo-HCT) has been proposed as a curative treatment option for patients with these disorders.

**Summary of Evidence**
For individuals who have myelodysplastic syndrome (MDS) who receive myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (allo-HCT), the evidence includes systemic reviews, randomized controlled trials (RCTs), and numerous case series, which are often heterogeneous in terms of diseases included. Relevant outcomes are overall survival (OS), disease-specific survival, and treatment-related mortality and morbidity. Primarilyuncontrolled, observational studies of hematopoietic cell transplantation (HCT) for MDS have reported a relatively large range of overall and progression free survival (PFS) rates, which reflect the heterogeneity in patient populations, conditioning regimens, and other factors. Reported estimates for 3- to 5-year OS of 40% to 50% are typical. Evidence from randomized and nonrandomized comparisons has suggested that RIC

may be used as a risk-adapted strategy in high-risk patients who are older and with more comorbidities without significantly worsening OS. RIC appears to be associated with lower rates of nonrelapse mortality but higher cancer relapse than MAC HCT. At present, HCT is the only potentially curative treatment option for patients with MDS. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have myeloproliferative neoplasms who receive MAC or RIC allo-HCT, the evidence includes a systematic review and retrospective observational series. Relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. Evidence has suggested that RIC may be used as a risk-adapted strategy in high-risk patients who are older and have more comorbidities without significantly worsening OS. RIC appears to be associated with lower rates of nonrelapse mortality but higher cancer relapse than myeloablative HCT. At present, HCT is the only potentially curative treatment option for patients with myeloproliferative neoplasms. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

## Policy History

| Date | Action |
|---|---|
| 3/2024 | Annual policy review. References updated. Policy statements unchanged. |
| 9/2023 | Policy clarified to include prior authorization requests using Authorization Manager. |
| 3/2023 | Annual policy review. Minor editorial refinements to policy statements; intent unchanged. |
| 2/2022 | Annual policy review. Description, summary, and references updated. Policy statements unchanged. |
| 3/2021 | Annual policy review. Description, summary, and references updated. Policy statements unchanged. |
| 1/2021 | Medicare information removed. See MP #132 Medicare Advantage Management for local coverage determination and national coverage determination reference. |
| 6/2020 | Annual policy review. Policy statement for RIC allo-HCT changed to specify it as a risk-adapted strategy for patients at high-risk of MAC intolerance, which is meant to encompass both older age and medical co-occurring conditions. Effective 6/1/2020. |
| 4/2020 | Bone marrow harvesting codes were removed. Outpatient prior authorization is not required. |
| 3/2019 | Annual policy review. Description, summary, and references updated. Policy statements unchanged. |
| 1/2019 | Outpatient prior authorization is required for all commercial products. Effective 1/1/2019. |
| 2/2018 | Annual policy review. New references added |
| 2/2018 | Clarified coding information. |
| 5/2017 | Annual policy review. New references added |
| 6/2017 | Annual policy review. New references added |
| 3/2017 | Annual policy review. Title changed. New references added. |
| 3/2016 | Annual policy review. New references added. |
| 9/2015 | Clarified coding language. |
| 12/2014 | Annual policy review. New references added. |
| 6/2014 | Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015. |
| 2/2014 | Annual policy review. New references added. |
| 12/2012 | Updated to add new CPT code 38243. |
| 11/2011-4/2012 | Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements. |
| 7/2011 | Reviewed - Medical Policy Group – Hematology and Oncology. No changes to policy statements. |
| 1/1/2010 | Medical policy 155 effective 1/1/2010describing covered and non-covered indications. |

## Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

## References


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