Primary Myelofibrosis (PMF) & Myeloproliferative Neoplasms (MPNs)
Chronic myelogenous leukemia, polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis are myeloproliferative disorders characterized by clonal expansion of abnormal hematopoietic stem/progenitor cells. The term ‘myeloproliferative disorders’ was replaced by ‘chronic myeloproliferative diseases’ in 2001, and now ‘myeloproliferative neoplasms’ (MPNs) is standard terminology according to 2008...
World Health Organization (WHO) criteria. MPNs are characterized by the dysregulated proliferation of myeloid cells including megakaryocytes and myeloid and erythroid progenitors in the bone marrow resulting in ineffective erythropoiesis, the production of cytokines within the marrow microenvironment, and the reactive deposition of fibrous connective tissue (reticulin or collagen) in the bone marrow, often with osteosclerosis. In later fibrotic stages, the peripheral blood demonstrates teardrop-shaped red cells (ie, dacrocytes), nucleated red blood cells, and early myeloid forms (ie, a triad termed leukoerythroblastosis), and extramedullary hematopoiesis results in hepatomegaly and splenomegaly. Most patients with PMF present with anemia, marked splenomegaly, early satiety, and hypercatabolic symptoms including severe fatigue, low-grade fever, night sweats, bone pain, and weight loss. During the clinical course, massive splenomegaly, some hepatomegaly, along with progressive anemia requiring frequent red blood cell transfusions is frequently seen. Portal hypertension might accompany marked splenomegaly and could contribute to variceal bleeding or ascites. The median age for diagnosis is 64-67 years of age and approximately 50-65% of patients are positive for the Janus2 kinase (JAK2 V617F) mutation and 26%-35% with mutations in CALR (calreticulin). At the current time, allogeneic hematopoietic cell transplantation (HCT) constitutes the only treatment modality with a curative potential in PMF. Other treatment modalities are only palliative and include ruxolitinib as first-line therapy for management of disease-related symptoms. Hydroxyurea considered first-line therapy for control of hyperproliferation manifestations of myelofibrosis (constitutional symptoms, hepatosplenomegaly, and reduction of leukocytosis and thrombocytosis).

Management of patients with PMF is determined by the risk of disease progression and estimated overall survival as calculated by prognostic scores. The International Prognostic Scoring System (IPSS), the Dynamic International Prognostic Scoring System (DIPSS) and the Dynamic International Prognostic Scoring System Plus (DIPPS-Plus) score are the three most common scores used for risk stratification. IPSS should be used at time of diagnosis and DIPSS-Plus incorporates karyotyping and is used during the course of treatment. DIPSS can be used if karyotyping is not available. The following table outlines the DIPSS and DIPSS-Plus scoring systems:

Dynamic International Prognostic Scoring System (DIPSS) and DIPSS-Plus for primary myelofibrosis.

<table>
<thead>
<tr>
<th>The DIPSS score assigns points for the following five variables:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Age &gt;65 years: 1 point</td>
</tr>
<tr>
<td>- Leukocyte count &gt;25,000/microL (&gt;25 x 109/L): 1 point</td>
</tr>
<tr>
<td>- Hemoglobin &lt;10 g/dL (&lt;100 g/L): 2 points</td>
</tr>
<tr>
<td>- Circulating blast cells ≥1%: 1 point</td>
</tr>
<tr>
<td>- Constitutional symptoms*: 1 point</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The resulting score is interpreted as follows:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 0 points – low risk</td>
</tr>
<tr>
<td>- 1 to 2 points – intermediate-1 risk</td>
</tr>
<tr>
<td>- 3 to 4 points – intermediate-2 risk</td>
</tr>
<tr>
<td>- 5 to 6 points – high risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The DIPSS-Plus score assigns points for the following variables:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- DIPSS low risk: 0 points</td>
</tr>
</tbody>
</table>
### Stem Cell Transplantation

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells or platelets). HSCs are created in the bone marrow and are found in the bone marrow and peripheral blood. There is also a high concentration of HSCs in umbilical-cord blood. Hematopoietic stem-cell transplantation (HSCT) can be either autologous (using the person’s own stem cells) or allogeneic (using stem cells from a donor). In allogeneic HSCT, it is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. Matching is performed on the basis of variability at three of more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase.

### Pretransplant Evaluation

The goal of the pretransplant evaluation is to assess the ability of a patient to tolerate the surgery, post-operative immunosuppression, and transplant care. An extensive cardiopulmonary evaluation, screening for occult infection or cancer, and psychosocial evaluation is standard. Specific testing varies depending upon the patient's age, medical history, and transplant center practice. In addition, while a certain battery of tests may initiate the work up, more testing may be indicated depending upon the condition of the patient or the initial test results. In addition to a standard medical evaluation the initial assessment should include a psychological and social support evaluation to identify issues that may impair a successful outcome after transplantation. These include a lack of information about the nature of the transplant procedure and post-transplant care, drug or alcohol dependence, compliance with complex medical and behavior regimens. The assessment includes education of the family and the support network of the patient because compliance with complex medical and behavior treatment is critical after any organ transplant procedure. Recipients must be able to incorporate complicated medications, follow-up appointments, and frequent laboratory visits into their schedules. Having an adequate support network aware of these requirements will encourage patient compliance and long-term success.
All pretransplant evaluations require prior authorization from the Corporate Transplant Department. Solid organ transplant requests will be reviewed by the Corporate Medical Director or qualified clinical designee. All other transplants will be by the Corporate Medical Director or covering Medical Director. If the criteria are met using appropriate NCD and/or LCD guidelines, state regulations and/or MCP policies the Corporate Medical Director’s designee can approve the requested transplant.

Members must meet UNOS/OPTN policies and guidelines for pretransplantation evaluation and listing criteria and the diagnosis must be made by a Specialist in the Disease and or Transplant Surgeon.

**Pre-Transplant Evaluation:** Please see MCP-323 Pre-Transplant Evaluation for additional criteria and information.

Criteria for transplant evaluation include all of the following:

- History and physical examination
- Psychosocial evaluation and clearance:
  - No behavioral health disorder by history or psychosocial issues:
    - if history of behavioral health disorder, no severe psychosis or personality disorder
    - mood/anxiety disorder must be excluded or treated
    - member has understanding of surgical risk and post procedure compliance and follow-up required
  - Adequate family and social support
- EKG
- Chest x-ray
- Cardiac clearance in the presence of any of the following:
  - chronic smokers
  - > 50 years age
  - those with a clinical or family history of heart disease or diabetes
- Pulmonary clearance if evidence of pulmonary artery hypertension (PAH) or chronic pulmonary disease
- Neurological exam and clearance for transplant: [ONE]
  - Normal exam by H&P
  - Abnormal neurological exam with positive findings: [ONE]
    - Lumbar puncture normal cytology
    - Lumbar puncture with cytological exam abnormal: CNS disease treated prior to clearance
- Performance Status: [ONE]
  - Karnofsky score 70-100%; or
  - Eastern Cooperative Oncology Group (ECOG) grade 0-2
- Lab studies:
Complete blood count, Kidney profile (blood urea nitrogen, creatinine), electrolytes, calcium, phosphorus, albumin, liver function tests, Coagulation profile (prothrombin time, and partial thromboplastin time)

*Serologic screening for HIV, Epstein Barr virus (EBV), Hepatitis virus B (HBV), and Hepatitis C (HCV), cytomegalovirus (CMV), RPR and/or FTA:

- If HIV positive all of the following are met:
  - CD4 count >200 cells/mm-3 for >6 months
  - HIV-1 RNA undetectable
  - On stable anti-retroviral therapy >3 months
  - No other complications from AIDS (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioides mycosis, resistant fungal infections, Kaposi’s sarcoma, or other neoplasm)

  - If abnormal serology need physician plan to address and/or treatment as indicated

UDS (urine drug screen) if patient is current or gives a history of past drug abuse

*Colonoscopy (if indicated or if patient is 50 ≥ older should have had an initial screening colonoscopy, after initial negative screening requires follow up colonoscopy every ten years) with complete workup and treatment of abnormal results as indicated

*GYN examination with Pap smear for women ≥ 21 to ≤ 65 years of age or indicated (not indicated in women who have had a TAH or TVH) with in the last three year with complete workup and treatment of abnormal results as indicated

Within the last 12 months:

- Dental examination or oral exam showing good dentition and oral care or no abnormality on panorex or plan for treatment of problems pre or post-transplant

- *Mammogram (if indicated or > age 40) with complete workup and treatment of abnormal results as indicated

- *PSA if history of prostate cancer or previously elevated PSA with complete workup and treatment of abnormal results as indicated

*Participating Centers of Excellence may waive these criteria

**Criteria for Hematopoietic Allogeneic Stem Cell transplantation (HSCT) Transplantation:**

1. **Hematopoietic Allogeneic stem-cell transplantation (HSCT) ablative or non-myeloablative** from a human leukocyte antigen (HLA)-matched donor (i.e., at least six out of eight match of the HLA-A, HLA-B, HLA-C and HLA-DRB1 markers) or from cord blood when there are no matched sibling or unrelated donors (i.e. at least four out of six match of the HLA-A, HLA-B and HLA-DRB-1 markers) may be authorized in adults and children for the treatment of for Primary Myelofibrosis (Myeloproliferative Neoplasms MPS) when ANY of the following criteria are met:

- All pre-transplant criteria are met; and

- For age < 45 years, conventional intensity conditioning (CIC) allo-HSCT is recommended; or

- For age > 45 years, reduced intensity conditioning allo-HSCT is recommended; and

- Any of the following clinical indications:
High risk disease defined as the following:

- DIPSS-Plus score of 4-6 points; or
- DIPSS score of 5-6 points

OR

Intermediate risk disease defined as the following:

- DIPSS-Plus score of 1 point for intermediate-1 risk (INT-1), or
- DIPSS-Plus score of 2-3 points for intermediate-2-risk (INT-2); or
- DIPSS score of 1-2 points for intermediate-1 risk (INT-1), or
- DIPSS score of 3-4 points for intermediate-2-risk (INT-2); or

Any PMF-MPS disease with poor prognostic features including any of the following:

- Dependent on transfusions of red blood cells
- Dependent on transfusions of platelets or has frequent infarctions; or
- Has an absolute neutrophil count less than 1000/mm³; or
- Resistant to conservative therapy with poor initial response or at progression of disease; and

The requesting transplant recipient should not have any of the following absolute contraindications:

- Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery
- Malignant neoplasm with a high risk for reoccurrence, non-curable malignancy (excluding localized skin cancer)
- Systemic and/or uncontrolled infection
- AIDS (CD4 count < 200 cells/mm³)
- Unwilling or unable to follow post-transplant regimen
  - Documented history of non-compliance
  - Inability to follow through with medication adherence or office follow-up
- Chronic illness with one year or less life expectancy
- Limited, irreversible rehabilitation potential
- Active untreated substance abuse issues, requires documentation supporting free from addiction for minimally 6 months if previous addiction was present
- No adequate social/family support

The requesting transplant recipient should be evaluated carefully and potentially treated if the following relative contraindications are present:

- Irreversible lung disease patients require consultation and clearance by a Pulmonologist prior to consideration of transplantation, this includes the following:
- Smoking, documentation supporting free from smoking for 6 months
- Active peptic ulcer disease
- Active gastroesophageal reflux disease
- CVA with long term impairment that is not amendable to rehabilitation or a patient with CVA/transient ischemic attack within past 6 months
- Obesity with body mass index of >30 kg/m² may increase surgical risk
o Chronic liver disease such as Hepatitis B/C/D, or cirrhosis which increases the risk of death from sepsis and hepatic failure requires consultation by a gastroenterologist or hepatologist

o Gall bladder disease requires ultrasound of the gall bladder with treatment prior to transplantation

Criteria for Subsequent Hematopoietic Stem Cell Transplantation:

2. A second or repeat *Hematopoietic Allogeneic stem cell transplantation* (ablative or non-myeloablative) may be authorized only one time for members with PMF-MPS who meet all of the above criteria for transplant and have any of the following: [ONE]

- primary graft failure indicated by no signs of engraftment* by 42 days after the transplant; or
- failure to engraft*
- late relapse (greater than 18 months after HCT) as salvage therapy

*Note: *Engraftment is defined as the first 3 consecutive days on which the absolute neutrophil count (ANC) exceeds $5 \times 10^9/L$ or $> \text{ANC}500$ at any time after transplantation.*

CONTINUATION OF THERAPY

When extension of a previously approved transplant authorization is requested, review using updated clinical information is appropriate.

- If Molina Healthcare has authorized prior requests for transplantation, the following information is required for medical review: [ALL]
  - Presence of no absolute contraindication as listed above;
  - History and physical within the last 12 months;
  - Kidney profile within the last 12 months;
  - Cardiac update if history of cardiac disease within two years ($\geq 50$ years of age);
  - Psychosocial evaluation or update within the last 12 months;
  - Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

- If authorized prior requests for transplantation were obtained from another insurer, the following information is required for medical review: [ALL]
  - Authorization letter/documentation from previous insurer;
  - Presence of no absolute contraindication as listed above;
  - History and physical within the last 12 months;
  - Cardiac update if history of cardiac disease within two years ($\geq 50$ years of age);
  - Psychosocial evaluation or update within the last 12 months;
  - Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

LIMITATIONS 2-9

1. Allogeneic (ablative or non-myeloablative) stem cell transplantation when the above criteria are not met.
2. A second or repeat autologous or allogeneic (ablative or non-myeloablative) transplant due to persistent, progressive or early relapsed disease.

3. Autologous stem cell transplantation

4. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant is not covered

---

**SUMMARY OF MEDICAL EVIDENCE**

Peer reviewed publications regarding the efficacy of allogeneic HCT in PMF include retrospective analyses of highly selected populations and small single arm prospective trials. In these groups, estimated survival rates at three to four years range from 40 to 60 percent. The best evidence in support for the use of HCT in this population comes from a retrospective analysis of 438 younger adults (age <65 years) who received HCT (190 patients) or conventional therapies (248 patients), which noted a significant difference in the relative risk (RR) of death after allogeneic HCT versus pre-JAK2 inhibitor conventional therapies according to DIPSS score. Among patients at low risk per the Dynamic International Prognostic Scoring System (DIPSS) model, the relative risk of death after allogenic SCT vs those treated with nontransplant modalities was 5.6 (95% CI, 1.7-19; P = .0051); for intermediate-1 risk it was 1.6 (95% CI, 0.79-3.2; P = .19), for intermediate-2 risk, 0.55 (95% CI, 0.36-0.83; P = .005), and for high risk, 0.37 (95% CI, 0.21-0.66; P = .0007). Thus, patients with intermediate-2 or high-risk PMF clearly benefit from allogenic SCT. Patients at low risk should receive nontransplant therapy, whereas individual counseling is indicated for patients at intermediate-1 risk.

Results from a retrospective report using registry data on HCT results in 147 patients with either primary or secondary myelofibrosis showed that four-year OS, PFS and NRM survival were 39%, 32% and 39%, respectively.

In summary, the published, peer-reviewed scientific literature supports the safety and effectiveness of allogeneic HSCT for the treatment of PMF-MPS in selected individuals. However, improved outcomes have not been demonstrated for autologous HSCT compared with conventional chemotherapy in individuals with PMF-MPS therefore the role of autologous HSCT for this indication has not been established.

**Professional Organizations**

The European LeukemiaNet (ELN) and European Blood and Marrow Transplantation Group (EBMT) have developed consensus recommendations for HCT in PMF [11]. They suggest HCT for patients <70 years of age with intermediate-2 or high-risk DIPSS Plus scores and patients <65 years of age with intermediate-1 DIPSS Plus score with refractory, transfusion-dependent anemia, or a percentage of blasts in the peripheral blood >2, or adverse cytogenetics.

**National Comprehensive Cancer Network (NCCN):** The NCCN Guidelines (2020) for the treatment of myeloproliferative neoplasms (MPN) indicate that allo-HCT should be based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver. These guidelines include recommendations for Allo-HCT and classify the following by Prognostic Category:

- Low risk or asymptomatic patients should be observed. Ruxolitinib or interferons should be used for if symptomatic patients.
- Intermediate risk (INT-1): Evaluation for allo-HCT is recommended for patients with low platelet counts or complex cytogenetics.
- Intermediate risk (INT-2) and High risk: Evaluation for allo-HCT is recommended for all patients who are candidates for transplant. Consider allo-HCT immediately or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant.

**Coding Information:** The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
</tr>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
</tbody>
</table>

**Cell Processing Services**

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing</td>
</tr>
<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing</td>
</tr>
<tr>
<td>38210</td>
<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>Transplant preparation of hematopoietic progenitor cells; tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>Transplant preparation of hematopoietic progenitor cells; platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, oruffy coat layer</td>
</tr>
</tbody>
</table>

**Cell infusion codes**

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38240</td>
<td>Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic</td>
</tr>
<tr>
<td>38241</td>
<td>Bone marrow or blood-derived peripheral stem cell transplantation; autologous</td>
</tr>
<tr>
<td>38242</td>
<td>Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions</td>
</tr>
<tr>
<td>38243</td>
<td>Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic hematopoietic cellular transplant boost</td>
</tr>
</tbody>
</table>

**HCPCS**

<table>
<thead>
<tr>
<th>HCPCS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood derived stem-cell transplantation, allogeneic</td>
</tr>
<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage; marrow ablative therapy; drugs; supplies; hospitalization with outpatient</td>
</tr>
</tbody>
</table>
follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of
days of pre-and post-transplant care in the global definition

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Description: [For dates of service on or after 10/01/2015]</th>
</tr>
</thead>
<tbody>
<tr>
<td>D47.1</td>
<td>Chronic myeloproliferative disease</td>
</tr>
<tr>
<td>D75.81</td>
<td>Myelofibrosis</td>
</tr>
</tbody>
</table>

**RESOURCE REFERENCES**

**Government Agency**


**Professional Society Guidelines**

2. American Society for Blood and Marrow Transplantation (ASBMT).
3. National Bone Marrow Donor Program:
   - Patient Eligibility for HCT. Accessed at: [https://bethematchclinical.org/Transplant-Indications-and-Outcomes/Eligibility/](https://bethematchclinical.org/Transplant-Indications-and-Outcomes/Eligibility/)
   - Recommended Timing for Transplant Consultation. Accessed at: [https://bethematchclinical.org/](https://bethematchclinical.org/)

Peer Reviewed Publications


Other Resources
33. UpToDate [website]: Waltham, MA: Walters Kluwer Health; 2020
   - Tefferi A. Management of primary myelofibrosis.
   - Negrin C. Immunotherapy for the prevention and treatment of relapse following hematopoietic cell transplantation.
   - Deeg HJ, Sandmaier B. Determining eligibility for allogeneic hematopoietic cell transplantation.
   - Chao NG. Selection of an umbilical cord blood graft for hematopoietic cell transplantation.


Review/Revision History:
12/19/2018: New Policy.
9/18/2019 & 9/16/2020: Policy reviewed, no changes to criteria. Updated references and added TOC.