Myeloproliferative neoplasms (MPN)

Guide to the completion of the EBMT data collection form: MPN_v1.0

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EBMT Registry

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Introduction

Myeloproliferative neoplasms (MPNs) include a group of haematological disorders originating from a pluripotent stem cell of haematopoiesis that typically present with a hypercellular bone marrow with fibrosis, hepatomegaly, splenomegaly, and increased blood cell counts (cytopenias are possible). With advanced disease the cellularity may decrease, fibrosis becomes predominant, blood counts may be low and the patient may be transfusion dependent. The transformation from one entity to another is not uncommon, as is the case with the transition from polycythaemia or thrombocythaemia to myelofibrosis. Moreover, all these conditions have an inherent tendency to progress to acute leukaemia.

In addition, myeloproliferative neoplasms have specific mutations: to distinguish these forms from CML, all forms should be BCR::ABL1 negative. More than 90% of polycythaemia vera patients and about 50% of primary myelofibrosis and essential or primary thrombocythaemia patients carry the JAK2 V617F mutation. FIP1L1-PDGFRA mutation can be found in hyper eosinophilic syndrome, whereas c-kit mutation is found in systemic mastocytosis in around 85% of cases.

This form must be completed for all patients whose primary disease for which the reported treatment is being given is MPN. In addition, the form can be completed if it was requested for specific studies.

No data items should be left blank unless specifically stated in the definition.

Disease

1. Date of diagnosis

Report the date of the first pathological diagnosis of the disease. Add the date when the sample was collected for examination or (in its absence) the date indicated by a physician within the patient's medical record.

2. MPN Classification (WHO 2016)

Select the subclassification that is appropriate for the MPN and check the box next to it (1).

Name	Diagnostic criteria
Primary myelofibrosis (overt PMF)	*Meeting all three major criteria and at least one minor criterion* Major criteria: 1. Megakaryocyte proliferation and atypia[1] and ≥ grade 2 reticulin/collagen fibrosis 2. Not meeting WHO criteria for other myeloid neoplasms 3. Presence of JAK2, CALR, or MPL mutation or presence of another clonal marker or absence of evidence for reactive bone marrow fibrosis Minor criteria: 1. Anaemia not otherwise attributed 2. Leukocytosis ≥ 11 × 10^9/L 3. Palpable splenomegaly 4. Increased lactate dehydrogenase (LDH), above upper limit 5. Leukoerythoblastosis
Primary myelofibrosis (prePMF)	*Meeting all 3 major criteria, and at least 1 minor criterion* Major criteria: 1. Megakaryocytic proliferation and atypia, without reticulin fibrosis > grade 1 (MF-1), accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis 2. Not meeting the WHO criteria for BCR::ABL1$^+$ CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms 3. Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker,[2] or absence of minor reactive BM reticulin fibrosis[3] Minor criteria: Presence of at least 1 of the following, confirmed in 2 consecutive determinations:

[1] Megakaryocytes with aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering

[2] In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1) are of help in determining the clonal nature of the disease.

[3] Minor (grade 1) reticulin fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

	a. Anemia not attributed to a comorbid condition b. Leukocytosis ≥ 11 × 10^9/L c. Palpable splenomegaly d. LDH increased to above the upper normal limit of institutional reference range
Polycythaemia vera (PV)	*Meeting all three major criteria or the first two major criteria and one minor criterion* Major criteria: 1. Haemoglobin (Hb) > 16.5 g/dL/16 g/dL (men/women) or Haematocrit (Hct) > 49%/48% (men/women) or elevated red cell mass > 25% above mean 2. Bone marrow (BM) tri-lineage myeloproliferation with pleomorphic mature megakaryocytes[4] 3. Presence of JAK2 mutation Minor criteria: 1. Subnormal serum erythropoietin level
Essential or primary thrombocythaemia (ET)	*Meeting all four major criteria or first three major criteria and one minor criterion* Major criteria: 1. Platelet count ≥ 450 × 10^9/L 2. BM megakaryocyte proliferation with large and mature morphology and hyper-lobulated nuclei, Reticulin fibrosis grade should be ≤ 1 3. Not meeting WHO criteria for other myeloid neoplasms 4. Presence of JAK2, CALR or MPL mutation Minor criteria: 1. Presence of a clonal marker or absence of evidence for reactive thrombocytosis
Hyper eosinophilic syndrome (HES)	1. Peripheral blood hypereosinophilia – defined as > 1.5 eosinophils×10^9/L blood [>1500/mcl] on two examinations at an interval of 1 month or greater– and/or – • Tissue hypereosinophilia defined by the following: • Percentage of eosinophils in BM section exceeds 20% of all nucleated cells– and/or – • Pathologist is of the opinion that tissue infiltration by

[4] BM biopsy may not required if Hb > 18.5 g/dL in men or 16.5 in women (Hct > 55.5 in men and 49.5 in women).

	eosinophils is extensive– and/or – • Marked deposition of eosinophil granule proteins is found in the absence or presence of major tissue infiltration by eosinophils 2. Organ damage and/or dysfunction attributable to tissue hypereosinophilia 3. Exclusion of other disorders or conditions as a major reason for organ damage
Chronic eosinophilic leukaemia (CEL)	1. Eosinophilia ≥ 1.5×10^9/L. 2. Absence of the Ph chromosome, BCR::ABL1 fusion gene, and exclusion of other myeloproliferative (polycythaemia vera, essential thrombocytosis, primary myelofibrosis) or myelodysplastic-myeloproliferative (chronic myelomonocytic leukaemia, atypical chronic myelogenous leukaemia) neoplasms. 3. Absence of t(5;12)(q31-35;p13) or other PDGFRB gene rearrangements. 4. Absence of the FIP1L1-PDGFRA fusion gene or other PDGFRA gene rearrangements. 5. Absence of FGFR1 gene rearrangements. 6. Less than 20% blasts in peripheral blood and BM, absence of inv(16)(p13q22), t(16;16)(p13;q22), or other features that warrant the diagnosis of AML. 7. Presence of a clonal or cytogenetic abnormality, > 2% blasts in peripheral blood, or > 5% blasts in BM.
Chronic neutrophilic leukaemia (CNL)	1. PB WBC ≥ 25×10^9/L: Segmented neutrophils plus band forms ≥ 80% of WBCs Neutrophil precursors (promyelocytes, myelocytes, and metamyelocytes) < 10% of WBC Myeloblasts rarely observed Monocyte count < 1×10^9/L No dysgranulopoiesis 2. Hypercellular BM: Neutrophil granulocytes increased in percentage and number Neutrophil maturation appears normal Myeloblasts < 5% of nucleated cells 3. Not meeting WHO criteria for *BCR::ABL1*$^+$ CML, PV, ET, or PMF 4. No rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or *PCM1-JAK2* 5. Presence of *CSF3R* T618I or other activating *CSF3R* mutation or In the absence of a *CSFR3R* mutation, persistent neutrophilia (at least 3 months), splenomegaly, and no identifiable cause of reactive neutrophilia including the absence of a plasma cell neoplasm or, if present, demonstration of clonality of myeloid cells by cytogenetic

	or molecular studies
Systemic mastocytosis	*Meeting at least 1 major and 1 minor or 3 minor criteria* Major criteria: 1. Multifocal dense infiltrates of MCs (≥ 15 MCs in aggregates) in BM biopsies and/or in sections of other extracutaneous organ(s) Minor criteria: 1. >25% of all MCs are atypical cells (type I or type II) on BM smears or are spindle-shaped in MC infiltrates detected on sections of visceral organs 2. *KIT* point mutation at codon 816 in the BM or another extracutaneous organ 3. MCs in BM or blood or another extracutaneous organ exhibit CD2 and/or CD25 4. Baseline serum tryptase level >20 ng/mL (in case of an unrelated myeloid neoplasm, item 4 is not valid as an SM criterion)
Mast cell leukaemia	Meets criteria for Systemic mastocytosis (SM). BM biopsy shows a diffuse infiltration, usually compact, by atypical, immature MCs. BM aspirate smears show 20% or more MCs.
Mast cell sarcoma	Local mast cell tumor with immature atypical mast cells and aggressive (invasive) growth pattern Cutaneous mastocytosis (CM) and SM criteria not fulfilled (CM and SM/Mast cell leukaemia excluded). High rate of recurrence/relapse. Resistance to therapy.
MPN not otherwise specified	Includes **MPN**-like neoplasms that cannot be clearly classified as one of the other subcategories of MPNs.
Myeloid and lymphoid neoplasms with FGFR1 abnormalities (Stem cell leukaemia-lymphoma syndrome, 8p11 syndrome)	Evidence of FGFR1 abnormalities
Myeloid and lymphoid neoplasms with PDGFRA rearrangement	Evidence of PDGFRA rearrangement
Myeloid and lymphoid neoplasms with PDGFRB rearrangement	Evidence of PDGFRB rearrangement

Myeloid and lymphoid neoplasms with PCM1-JAK2 rearrangement	Evidence of PCM1-JAK2 rearrangement

Table 1, WHO 2016 diagnostic criteria for Myeloproliferative neoplasms subclassification.

If the subclassification is not listed, check the box **Other** and specify the MPN classification (for example, Myeloid and lymphoid neoplasms with FLT3 rearrangement).

Note: If the disease has transformed to myelofibrosis from ET or PV, then ET or PV should be registered as the diagnosis subclassification with the ET or PV date as the diagnosis date.

3. Therapy-related MPN

Indicate if MPN developed in response to medical treatment (therapeutic agents or radiation). If the diagnosis of MPN is therapy-related, answer **Yes**. Otherwise, check **No**. If it is unknown whether or not the diagnosis of MPN was therapy-related, check **Unknown**.

MPN Assessments

4. Spleen size

Indicate the size of the spleen in centimetres, measured below the costal margin as assessed by physical examination. Select **Not evaluated** if the spleen size was not assessed. If the value is unavailable, check **Unknown**.

5. Spleen span in ultrasound or CT scan

Indicate the maximum diameter of the spleen in centimetres, as assessed by ultrasound or CT scan. Select **Not evaluated** if the spleen span was not assessed. If the value is unavailable, check **Unknown**.

6. Transfusion dependency

Transfusion dependence is defined as the transfusion of at least 6 units of RBC in a 12-week period for a Hb level of <8.5 g/dL, in the absence of bleeding or treatment-induced anaemia

(according to the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report).

Select **Yes** if the patient was transfusion dependent during his/her MPN diagnosis. Otherwise, check **No**. If the transfusion dependency status is unavailable, check **Unknown**.

7. Bone marrow fibrosis

Bone marrow fibrosis represents the continuous replacement of blood-forming cells with excessive scar tissue diagnosed in a bone marrow trephine examination.

Indicate the degree of bone marrow fibrosis according to the European Consensus.

Grading	**Description**
Grade 0 (MF-0)	Scattered linear reticulin with no intersections corresponding to normal bone marrow
Grade 1 (MF-1)	Loose network of reticulin with many intersections, especially in perivascular areas
Grade 2 (MF-2)	Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis
Grade 3 (MF-3)	Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis

Table 2, Bone marrow fibrosis grading.

If the grade of bone marrow fibrosis was not assessed during the pathology examination, select **Not evaluated**. If the bone marrow fibrosis grading is unavailable, check **Unknown.**

8. Blast count (peripheral blood)

Indicate peripheral blood blasts count in %. Select **Not evaluated** if the blast count was not assessed. If the value is unavailable, check **Unknown**.

9. IPSS risk score (all myelofibrosis subtypes)

International Prognostic Scoring System (IPSS) (2) estimates prognosis based on the following risk factors present at diagnosis:

- Age > 65 years
- Haemoglobin (Hb) < 10 g/dL
- WBC > 25×109/L
- Peripheral blood blasts ⩾ 1%
- Constitutional symptoms

IPSS score is defined based on the total number of points of the patient (1 risk factor present = 1 point) as follows:

IPSS score	**Total number of points**	**Proportion of patients, %**	**Median OS (years)**
Low risk	0	22	11.25
Intermediate-1	1	29	7.9
Intermediate-2	2	28	4.0
High risk	≥ 3	21	2.25

Table 3, IPSS Risk Scoring System for Myelofibrosis Subtypes.

If the IPSS risk score was not assessed, select Not evaluated. If the score is unavailable, check Unknown.

10. DIPSS score (all myelofibrosis subtypes)

The Dynamic International Prognostic Scoring System (DIPSS) (3) risk score places a time-dependent risk evaluation over the original IPSS evaluation, generating a new prognostic score.

Prognostic factors	Points		
	0	**1**	**2**
Age (years)	≤ 65	> 65	
WBC (x 10^9/L)	≤ 25	> 25	
Haemoglobin (g/dL)	≥ 10		< 10
% Peripheral blood blasts	< 1	≥ 1	
Constitutional symptoms	No	Yes	

Table 4, DIPSS Prognostic Factors in Myelofibrosis Subtypes.

DIPSS score	Total number of points	Median OS[5] (years)
Low risk	0	Not reached
Intermediate-1:	1-2	14.2
Intermediate-2	3-4	4
High risk	5-6	1.5

Table 5, DIPSS Risk Assessment in Myelofibrosis Subtypes.

If the DIPSS score was not assessed, select Not evaluated. If the score is unavailable, check Unknown.

11. MIPSS70 score (Primary myelofibrosis only)

The Mutation-Enhanced International Prognostic Scoring System (MIPSS70) is based on three genetic variables and six clinical risk factors present at diagnosis:

[5] Overall survival

- Haemoglobin (Hb) < 10 g/dL
- WBC > 25×109/L
- Platelets < 100×109/L
- Peripheral blood blasts ⩾ 2%
- Bone marrow fibrosis grade ⩾ 2
- Constitutional symptoms
- Absence of CALR type 1/like mutation
- Presence of any high molecular risk [HMR] mutation, specifically ASXL1, SRSF2, EZH2, IDH1, or IDH2
- Presence of ⩾2 HMR mutations

MIPSS70 score	Total number of points	Median OS (years)
Low risk	0-1	27.7
Intermediate	2-4	7.1
High risk	≥ 5	2.3

Table 6, MIPSS70 Risk Score for Primary Myelofibrosis.

You can visit http://www.mipss70score.it/ for the MIPSS70 score calculation.

If the MIPSS70 score was not assessed, select **Not evaluated**. If the score is unavailable, check **Unknown.**

Chromosome analysis

12. Chromosome analysis done before treatment (all methods including FISH)

In this section describe the results of all chromosome analyses (performed at/after diagnosis but before the treatment).

Not done or failed - the chromosome analysis has not been done or failed;

Yes, abnormal results - the chromosome analysis has been performed and at least one of the results has been found to be abnormal. In addition, indicate the total number of different abnormalities present in all analyses with abnormal results (**number of abnormalities present**).

Yes, normal results - the chromosome analysis has been performed and all the results have been found normal;

Unknown - it is unknown whether the chromosome analysis has been done or not.

12.1. Date of chromosome analysis (if tested)

Indicate the date of the chromosome analysis. If the results were normal, add the date of the first test with normal results.

12.2. Chromosome analysis details

See the cytogenetics form or ask the cytogenetics team and consult your physician.

If chromosome analysis was performed, indicate for each abnormality in the table whether it was **Absent** or **Present**. If a chromosome abnormality was not evaluated, report **Not evaluated**.

If a chromosome abnormality was checked, but not listed as an option in the table, select **Other** and specify the abnormality, marking whether it was **Absent** or **Present**.

12.3. Transcribe the complete karyotype

if it is not possible to report the chromosome analysis results as per the abnormalities table. Preferably the table above with abnormalities should be completed. If the result of the chromosome analysis is too complex, the complete karyotype should be described here. Describe all abnormalities according to the ISCN karyotype nomenclature. This notation includes the total number of chromosomes, the sex chromosomes, and any extra or missing autosomal chromosomes. For example, **47, XY, +18** indicates that the patient has 47 chromosomes, is a male, and has an extra autosomal chromosome 18.

Molecular marker analysis

13. Molecular marker analysis done before treatment

Indicate if molecular marker analysis was done or not before the treatment. Check **Unknown** if it is not known whether it was performed.

13.1. Date of molecular marker analysis (if tested)

Indicate the date of the molecular analysis. If there were multiple molecular tests done on different dates, the results can be registered separately along with the test date. For example, if the test date of the MPN driver mutations (JAK2, CALR, MPL) and the test date of additional somatic mutations (ASXL1, SRSF2 etc.) do not coincide.

13.2. Molecular marker analysis details

If molecular marker analysis was performed, indicate for each marker in the table whether it was **Absent** or **Present**. If a molecular marker was not evaluated, report **Not evaluated**.

If a molecular marker is detected, but not listed as an option in the table, select **Other** and specify the marker, mark whether it was **Absent** or **Present**.

If Calreticulin (CALR) mutation is present, indicate the mutation type if known. If the lab report does not specify the type, select **Present but type unknown**.

Bibliography

1. Campo E, Harris NL, Pileri SA, Jaffe ES, Stein H, Thiele J. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Who Classification of Tum; 2017. 586 p.
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3. Passamonti F, Cervantes F, Vannucchi AM, Morra E, Rumi E, Pereira A, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood. 2010 Mar 4;115(9):1703–8.