Ontario Health
Cancer Care Ontario

Consensus Diagnostic and Prognostic Testing for Myelodysplastic Syndromes, Myeloproliferative Neoplasms, and Myelodysplastic/Myeloproliferative Neoplasms: Recommendations Report - 2024

MDS and MPN Working Group

January 10, 2024

Executive Summary

Ontario Health (Cancer Care Ontario) was advised by stakeholders that diagnostic and prognostic testing for patients with myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN) and myelodysplastic/myeloproliferative neoplasms (MDS/MPN) are inconsistently available and utilized across the province of Ontario. The *Consensus Diagnostic and Prognostic Testing for Myelodysplastic Syndromes, Myeloproliferative Neoplasms, and Myelodysplastic/Myeloproliferative Neoplasms: Recommendations Report* (the *Report*) was developed to address these issues.

The *Report* was developed by the MDS and MPN Working Group, consisting of hematologists, hematopathologists and health care administrators, under the guidance of the Complex Malignant Hematology Steering Committee. A literature review was performed to identify existing recommendations and evidence, which was reviewed and discussed by members of the Working Group. Consensus was used to develop evidence-based recommendations for the diagnostic and prognostic testing required for clinical decision making for patients with, or suspected of having, MDS, MPN and MDS/MPN in Ontario.

This *Report* addresses the following research questions:

- What are the required and recommended diagnostic and prognostic tests for patients with MDS that are needed for clinical decision-making?
- What are the required and recommended diagnostic and prognostic tests for patients with MPN that are needed for clinical decision-making?
- What are the required and recommended diagnostic and prognostic tests for patients with MDS/MPN that are needed for clinical decision-making?

This Report details testing requirements (as summarized in Table 1), turnaround times, and other testing related recommendations for these patient populations.

Table 1: High-level diagnostic and prognostic assessment and testing requirements for patients with, or suspected of having, MDS, MPN and MDS/MPN. Further details are included in the body of the *Report*.

Diagnostic and Prognostic Assessment and Testing	MDS	MPN	MDS/MPN
History and physical	Yes	Yes	Yes
Complete blood count (CBC) and peripheral blood smear	Yes	Yes	Yes
Laboratory and biochemistry tests	Yes	Yes	Yes
Bone marrow aspirate and biopsy investigations	Yes	Yes	Yes
Morphology	Yes	Yes	Yes
Flow cytometry	Yes, adjunctive tool	Yes, adjunctive tool	Yes, adjunctive tool
Cytogenetics	Yes	Yes	Yes
Karyotype	Yes	Yes, where criteria are met	Yes
Fluorescence in situ hybridization (FISH) panel[1]	Optional	Optional	Optional
Cytochemistry	Optional	Optional	Optional
Immunohistochemistry	Yes, adjunctive tool	Yes, adjunctive tool	Yes, adjunctive tool
Molecular investigations	Yes, where criteria are met	Yes, where criteria are met	Yes, where criteria are met
Human leukocyte antigen (HLA) typing	Yes, when allogeneic stem cell transplant is being considered	Yes, when allogeneic stem cell transplant is being considered	Yes, when allogeneic stem cell transplant is being considered
Germline/hereditary testing	Yes, where criteria are met	Yes, where criteria are met	Yes, where criteria are met

The recommendations in this *Report* will be used to ensure patients with, or suspected of having, MDS, MPN and MDS/MPN are able to receive the appropriate diagnostic and prognostic services required for clinical decision making and improved outcomes. This may include local, regional and/or provincial level planning, funding, and performance management approaches as needed.

[1] Recommended if karyotyping fails. See following sections for further details on diagnostic and prognostic recommendations for MDS, MPN and MDS/MPN.

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List of Acronyms

Acronym	Meaning
AML	Acute myeloid leukemia
CAP	College of American Pathologists
CBC	Complete blood count
CMML	Chronic myelomonocytic leukemia
CNL	Chronic neutrophilic leukemia
EPO	Erythropoietin
ET	Essential thrombocythemia
FISH	Fluorescence in situ hybridization
HLA	Human leukocyte antigen
JMML	Juvenile myelomonocytic leukemia
LDH	Lactate dehydrogenase
MDS	Myelodysplastic syndromes
MDS-EB2	Myelodysplastic syndromes -excess blasts-2
MDS/MPN	Myelodysplastic/myeloproliferative neoplasms
MDS/MPN-RS-T	Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis
MDS/MPN-U	Myelodysplastic/myeloproliferative neoplasm, unclassifiable
MF	Myelofibrosis
MPN	Myeloproliferative neoplasms
NGS	Next generation sequencing
NOS	Not otherwise specified
PMF	Primary myelofibrosis
PNH	Paroxysmal nocturnal hemoglobinuria
PV	Polycythemia vera
TAT	Turnaround time
TIBC	Total iron binding capacity
vWD	von Willebrand disease
WHO	World Health Organization

Introduction

Scope: This *Report* is specific to the diagnostic and prognostic testing of adult patients with, or suspected of, myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN) and myelodysplastic/myeloproliferative neoplasms (MDS/MPN), as classified per the 2017 revision to the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues [1]. For the purposes this *Report*, the diagnostic and prognostic testing of chronic myeloid leukemia (*BCR-ABL1*-positive) and pediatric diagnoses (e.g., refractory cytopenia of childhood, juvenile myelomonocytic leukemia (JMML)) are out of scope. Other myeloid neoplasms not included in the classification of MDS, MPN and MDS/MPN (e.g., mastocytosis) are also not in scope for this *Report*.

Myelodysplastic syndromes (MDS) are a group of clonal hematopoietic disorders characterized by:

- Cytopenia in at least one hematopoietic lineage,
- Dysplasia in one or more of the major myeloid lineages,
- Ineffective hematopoiesis,
- Recurrent genetic abnormalities, and
- Increased risk of developing acute myeloid leukemia (AML).

The dysplasia may be accompanied by an increase in myeloblasts (but must be less than 20% in the marrow or blood, which is the threshold for the morphologic diagnosis of AML). Although the natural course of progression of MDS may be to AML, the rate of progression is dependent on MDS subtype and other features [1].

Myeloproliferative neoplasms (MPN) are clonal hematopoietic stem cell disorders characterized by the proliferation of cells of one or more of the myeloid lineages (i.e., granulocytic, erythroid, and megakaryocytic). Initially characterized by varying degrees of age-matched hypercellularity of the bone marrow or other morphologic features, each MPN subtype has the potential to progress to marrow failure due to myelofibrosis, ineffective hematopoiesis, or transformation to an acute blast phase [1].

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN) include clonal myeloid neoplasms that at the time of initial presentation are associated with overlapping features, some which are supportive of a diagnosis of MDS and others which are supportive of diagnosis of MPN. These neoplasms are usually characterized by hypercellularity of the bone marrow due to the proliferation of one or more of the myeloid lineages. At the same time, one or more of the other lineages may exhibit ineffective maturation, so that cytopenias may also be present [1].

Ontario Health (Cancer Care Ontario) was advised by stakeholders that diagnostic and prognostic testing for patients with MDS, MPN and MDS/MPN is inconsistently available and utilized across the province of Ontario. To address these issues, the MDS and MPN Working Group was struck to review identified evidence and develop recommendations for the diagnostic and prognostic testing required for clinical decision making for patients with MDS, MPN and MDS/MPN in Ontario. Membership of the Working Group is detailed in **Appendix A**.

This work will inform next steps to support equitable access to appropriate testing services for these patients.

Research questions:

- What are the required and recommended diagnostic and prognostic tests for patients with MDS that are needed for clinical decision-making?
- What are the required and recommended diagnostic and prognostic tests for patients with MPN that are needed for clinical decision-making?
- What are the required and recommended diagnostic and prognostic tests for patients with MDS/MPN that are needed for clinical decision-making?

Ongoing Review of the Report

It is recognized that the diagnostic and prognostic testing landscape continues to evolve for MDS, MPN and MDS/MPN and this *Report* should be adapted to meet changes in practice, as needed. This *Report* will be reviewed regularly (at a minimum, every 2 years) under the oversight of Ontario Health (Cancer Care Ontario).

Methodology

To address the research questions, Ovid Medline and Ovid Embase were searched for English language articles published between January 1, 2015 and April 21, 2020. Database specific search strategies were developed using a combination of key words and free-text terms with Boolean operators (e.g., 'and' and 'or'). Search terms and search strategy are detailed in **Appendix B.1** and **B.2**, respectively. Citations were uploaded into the EndNote database for duplicate removal. Subsequently, citations were imported into *Colandr* app[1] for the title and abstract screening phase.

Additional web-based search was also conducted within the websites of key organizations (see **Appendix B.3**). A targeted jurisdictional scan of Canada, United States, United Kingdom, Australia, New Zealand, European Union, and Japan was also conducted. Using Google Advanced Search, the first five pages of results were visually scanned and potentially relevant findings were downloaded.

Articles were included if they were English language and describing recommendations and/or evidence for diagnostic and/or prognostic testing for adult patients with MDS, MPN and MDS/MPN. Detailed selection criteria are listed in **Appendix B.4**. Those studies that did not meet the inclusion criteria were excluded based on title and abstract or a limited review of the full-text in the case of web-based results.

Hematopathologists and hematologists with a special interest in MDS, MPN and MDS/MPN, and representing the diversity of Ontario centres, came forward expressing an interest in

[1] *Colandr* is an open access software for systematic reviews. (colandrapp.com)

participating on the MDS and MPN Working Group with support provided by members of Ontario Health (Cancer Care Ontario's) Specialized Services Oversight, and the Pathology and Laboratory Medicine Programs. Membership of the Working Group and conflict of interest declarations for all authors are detailed in **Appendix A**. Conflicts of interest were managed in accordance with Ontario Health (Cancer Care Ontario's) Conflict of Interest Policy.

The Working Group met once to twice a month to review and discuss the results of the literature review and data extraction, as well as emerging evidence published after the literature search was performed (i.e., after April 21, 2020). An evidence-based, consensus approach was used to develop the recommendations in this *Report*.

Prior to finalization, the *Report* was reviewed by members of the Ontario Health (Cancer Care Ontario's) Acute Leukemia Advisory Committee and Complex Malignant Hematology Pathology and Laboratory Medicine Community of Practice, and relevant Ontario Health programs and Provincial Program Heads, as well as external reviewers.

Results

The search strategy identified a total of 979 unique articles. After reviewing titles and abstracts, 76 potentially relevant articles were identified. Thirteen potentially relevant documents were also included from web search. All references were assessed by full text review for eligibility and data was extracted from 41 articles. Details of the evidence review are found in **Figure 1**, with a summary of articles from which data was extracted by disease in **Table 2**.

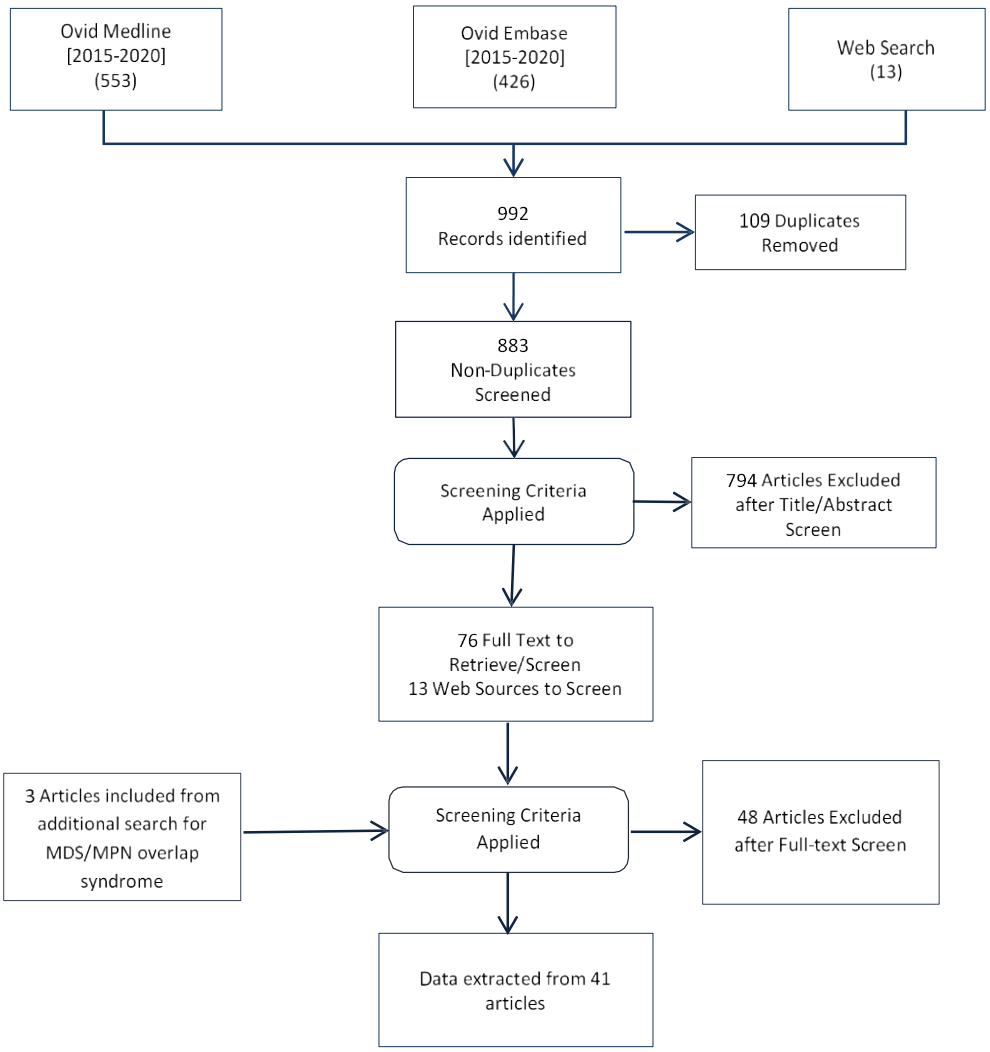

Figure 1: Flow chart of literature search and review. Through the search strategy 553 articles were identified through OVID Medline, 426 were identified through OVID Embase and 13 through web search. Totalling 992 articles of which 109 duplicates were removed. 883 non-duplicates were reviewed using the screening criteria and 794 articles were excluded after their title and abstract were reviewed. 76 full texts in addition to 13 web sources were reviewed and screening criteria was applied. Three additional articles related to MDS/MPN were identified and screened. 48 articles were excluded after the full text screen. The data was extracted from 41 articles.

Table 2: Summary of articles from which data was extracted by disease.

Disease site	Number of Articles included in Data Extraction
MDS	22
MPN	16
MDS/MPN	3

Total number of Articles	**41**

The following pages summarize the diagnostic and prognostic testing recommendations for MDS, MPN and MDS/MPN developed based on the review and discussion of evidence and clinical and laboratory experience.

Recommendations for the Diagnosis and Prognosis of Myelodysplastic Syndromes

Classification

Myelodysplastic Syndromes (MDS) should be classified per the criteria included in the 2017 revision to the World Health Organization (WHO) Classification of Tumours of Hematopoietic and Lymphoid Tissues (See **Appendix C.1**) [1]. At the time of this *Report's* release, WHO is expected to publish the 5th edition of the haemtolymphoid classification [2] [3]. The *Report* may be revised in the future to account for updates to the WHO's new classification scheme.

For the purposes this Report, the diagnostic and prognostic testing of refractory cytopenia of childhood is out of scope.

Diagnostic Workup

Upon suspicion, all patients should have:

1. **History and physical**, including family history of hematologic malignancies, familial thrombocytopenia, congenital malformations, pulmonary fibrosis and cirrhosis, and premature grey hair, as examples [4].
2. **Complete blood count (CBC) and peripheral blood smear** [4]**.**
    - The percentage of peripheral blood blasts based on morphologic assessment out of a minimum 200 counted nucleated cells should be reported [1].
3. **Laboratory and biochemistry tests**
    - Should include erythropoietin (EPO), serum ferritin, percentage iron saturation (serum iron and total iron binding capacity (TIBC)), transferrin, lactate dehydrogenase (LDH), uric acid, and vitamin B12 [4].
    - Blood paroxysmal nocturnal hemoglobinuria (PNH) flow cytometry should be done in patients who are hypocellular, with elevated LDH and iron deficiency, or with appropriate clinical indications [5].
4. **Bone Marrow Investigations** – aspirate and biopsy with a full report [1] [4].
    1. **Morphology**
        - The percentage of marrow blasts based on morphologic assessment out of a minimum 500 counted nucleated cells should be reported (aspirate smears preferred) [1] [4].
    2. **Flow Cytometry**
        - Multiparameter flow cytometry is an adjunctive tool in the diagnostic workup of patients with suspected MDS and may support MDS, as well as rule out other disorders [6] [7].

Upon initial diagnosis/suspicion of MDS from morphology, patients should receive the following:

3. **Cytogenetics**
    - Not all cytogenetic abnormalities are MDS defining [1].
        1. **Karyotype** [4]
        2. **Fluorescence in situ hybridization (FISH) panel** (option when karyotype is insufficient to determine if prognostic cytogenetic abnormalities are present) [4].
            - FISH panel should include -5/5q-, -7/7q-, +8, 17p, 20q [8].
            - Other clinically validated means of assessing these cytogenetic abnormalities (i.e., microarray, optical genome mapping) may be acceptable.
4. **Cytochemistry (optional)**
5. **Immunohistochemistry**
    - Immunohistochemistry, including CD34+ and CD117+, on bone marrow biopsy (or clot section, where available) should be used as an adjunctive tool to support or differentiate MDS from other hematological disease and assess blasts [1] [9].
6. **Molecular Investigations**
    - Requirements and scenarios in which a next generation sequencing (NGS) panel testing should be performed are detailed in Appendix D.1. Genes recommended for inclusion on an NGS panel for myeloid neoplasms are detailed in Appendix D.2.

When considering allogeneic stem cell transplant, should complete:

5. **Human Leukocyte Antigen (HLA) Typing** [4].

When considering hereditary disease:

6. **Germline/Hereditary Testing**
    - Patients being considered for germline testing should be referred to a genetics clinic as appropriate.
    - Testing criteria for hereditary hematological malignancies is being reviewed as part of the Ontario Health (Cancer Care Ontario) Provincial Hereditary Cancer Testing Program.
        - Hereditary testing panel should align with the most recent list of genes included on the forthcoming Ontario Health (Cancer Care Ontario) Hereditary Hematological Malignancies gene list (currently under development).
        - Prior to the release of malignant hematology hereditary testing guidance from Ontario Health, it is recommended that clinicians and hematologists follow Baliakas *et al*., (2019) *Nordic Guidelines for Germline Predisposition to Myeloid Neoplasms in Adults: Recommendations for Genetic Diagnosis, Clinical Management and Follow-up* [10].
    - Timelines for hereditary testing may need to be expedited as part of allogeneic stem cell transplant donor selection where there is suspected hereditary disease risk.

- Testing should be done ideally on skin fibroblasts, and not buccal swabs, blood or marrow samples.

Testing Turn-around-times (TAT) - Calendar Days

- Initial/provisional diagnosis of MDS – within 5 to 7 calendar days
- Cytogenetics: karyotype and FISH (where applicable) – within 14 to 21 calendar days
    - May be more urgently required in some patients who are transplant eligible, or suspected of being higher risk MDS (i.e., excess blasts – 2 (MDS-EB2), high risk of AML transformation) – within 7 to 14 calendar days [11]
- Complete genomic characterization – within 21 days
    - May be more urgently required in some patients who are transplant eligible, or suspected of being higher risk MDS (i.e., excess blasts – 2 (MDS-EB2), high risk of AML transformation) – within 14 calendar days [11]
- For patients being considered for intensive chemotherapy (e.g., induction), cytogenetics (including karyotype and FISH) and complete genomic characterization turnaround times should align with recommendations in Ontario Health's forthcoming *Acute Myeloid Leukemia Drug Treatment Algorithm: Recommendations Report*, which will be released in 2023.

MDS – Other Recommendations

- It is recommended that results are reported using the College of American Pathologists (CAP) Bone Marrow Checklist [12].
    - Bone Marrow reports for MDS should, at minimum, include the elements outlined in **Appendix E.1**.
    - Molecular and biomarker analysis not included in the CAP Bone Marrow checklist should be reported in a standardized way as outlined in the Ontario Health (Cancer Care Ontario) *Somatic Cancer Panel Reporting in Ontario* (2019) advice document [13].
- Patients who do not fulfill the diagnostic criteria for MDS, but have MDS-associated mutations, should be followed closely [14] [15] for the development of worsening cytopenias or the emergence of circulating blasts. If such patients are transfusion dependent or otherwise in need of therapeutic intervention, they may be treated as having presumptive lower risk MDS.

Recommendations for the Diagnosis and Prognosis of Myeloproliferative Neoplasms

Classification

Myeloproliferative Neoplasms (MPN) should be classified per the criteria included in the 2017 revision to the World Health Organization (WHO) Classification of Tumours of Hematopoietic and Lymphoid Tissues (See **Appendix C.2**) [1]. At the time of this *Report's* release, WHO is expected to publish a 5th edition of the haematolymphoid classification [2] [3]. The *Report* may be revised in the future account for updates to the WHO's new classification scheme.

For the purposes this Report, the diagnostic and prognostic testing of chronic myeloid leukemia – *BCR-ABL1*-positive is out of scope.

Diagnostic Workup

Upon suspicion, all patients should have:

1. **History and physical**, including family history of hematologic malignancies [16].
2. **Complete blood count (CBC) and peripheral blood smear** [16] [17].
    - The percentage of peripheral blood blasts based on morphologic assessment out of a minimum 200 counted nucleated cells should be reported [1].
3. **Laboratory and biochemistry tests**
    - Should include erythropoietin (EPO), serum ferritin, percentage iron saturation (serum iron and TIBC), transferrin, lactate dehydrogenase (LDH), uric acid, and vitamin B12 [16] [17].
    - Coagulation tests should be completed in patients with an elevated platelet count (>1000 x 10^9/L) to evaluate for acquired von Willebrand disease (vWD) and/or other coagulopathies in selected patients [16] [18].
4. **Bone Marrow** – aspirate and biopsy with a full report [16].
    - At the diagnosis of MPN, a bone marrow core biopsy is necessary to establish a correct diagnosis and as a baseline for follow-up examinations [17].
    1. **Morphology**
        - The percentage of marrow blasts based on morphologic assessment out of a minimum 500 counted nucleated cells should be reported (aspirate smears preferred) [1].
    2. **Flow Cytometry**
        - Multiparameter flow cytometry is an adjunctive tool in the diagnostic workup of patients with suspected MPN and can rule out other disorders [16].

Upon initial diagnosis/suspicion of MPN from morphology, patients should receive the following:

3. **Cytogenetics**
    1. **Karyotype**
        - Karyotyping should be done for all patients with:
            - Myelofibrosis, including:
                - Pre-fibrotic myelofibrosis
                - Primary myelofibrosis (PMF)
                - Post polycythemia vera (PV) myelofibrosis
                - Post essential thrombocythemia (ET) myelofibrosis
            - Selected patients with ET and PV, especially those with previous exposure to chemotherapy or radiotherapy [17].
            - All patients with non-classical MPN or other atypical clinical, laboratory or morphologic findings.
        - Karyotyping is not routinely done on patients with PV and ET but may be considered given potential prognostic value [18].
    2. **Fluorescence in situ hybridization (FISH) panel** (optional)
    - Should be considered in patients presenting with eosinophilia (i.e., eosinophilia bone marrow FISH panel, including *PDGFRA, PDGFRB, FGFR1*).
    - Other clinically validated means of assessing these cytogenetic abnormalities (i.e., microarray, optical genome mapping) may be acceptable.
4. **Cytochemistry** (optional)
5. **Immunohistochemistry**
    - Immunohistochemistry, including CD34+ and CD117+, on bone marrow biopsy should be used as an adjunctive tool to support or differentiate MPN from other hematological disease as well as support blast enumeration where aspirates are hemodilute or “dry tap” due to fibrosis [1] [16] [19].
6. **Molecular Investigations**
    - Requirements and scenarios in which a NGS panel testing should be performed are detailed in **Appendix D.1**. Genes recommended for inclusion on an NGS panel for myeloid neoplasms are detailed in **Appendix D.2**.
    - For suspected MPN:
        - Evaluation of *JAK2/CALR/MPL* and *BCR-ABL1* is required.
        - Where a specific MPN subtype, as defined by 2017 WHO criteria, is strongly supported by clinical, laboratory and bone marrow morphology; myeloid NGS may provide both diagnostic (i.e*., JAK2/CALR/MPL/BCR-ABL1*) and prognostic information if turnaround time is reasonable for clinical management [1] [17] [20].

When considering allogeneic stem cell transplant, should complete:

5. **Human leukocyte antigen (HLA) Typing** [16].

When considering hereditary disease

6. **Germline/Hereditary Testing**
    - Patients being considered for germline testing should be referred to a genetics clinic as appropriate.
    - Testing criteria for hereditary hematological malignancies is being reviewed as part of the Ontario Health (Cancer Care Ontario) Provincial Hereditary Cancer Testing Program.
        - Hereditary testing panel should align with the most recent list of genes included on the forthcoming Ontario Health (Cancer Care Ontario) Hereditary Hematological Malignancies gene list (currently under development).
        - Prior to the release of malignant hematology hereditary testing guidance from Ontario Health, it is recommended that clinicians and hematologists follow Baliakas *et al*., (2019) *Nordic Guidelines for Germline Predisposition to Myeloid Neoplasms in Adults: Recommendations for Genetic Diagnosis, Clinical Management and Follow-up* [10].
    - Timelines for hereditary testing may need to expedited as part of allogeneic stem cell transplant donor selection where there is suspected hereditary disease risk.
    - Testing should be done ideally on skin fibroblasts, and not blood or marrow samples.

Testing Turn-around-times (TAT) - Calendar Days

- Initial/provisional diagnosis of MPN – within 5 to 7 calendar days
- Cytogenetics: karyotype and FISH (where applicable) – within 14 to 21 calendar days
- Complete genomic characterization – within 21 days
- For patients being considered for intensive chemotherapy (e.g., induction), cytogenetics (including karyotype and FISH) and complete genomic characterization turnaround times should align with recommendations in Ontario Health's forthcoming *Acute Myeloid Leukemia Drug Treatment Algorithm: Recommendations Report,* which will be released in 2023.

MPN – Other Recommendations

- It is recommended that results are reported using the College of American Pathologists (CAP) Bone Marrow Checklist [12].
    - Bone Marrow reports for MPN should, at minimum, include the elements outlined in **Appendix E.2**.
    - Molecular and biomarker analysis not included in the CAP Bone Marrow checklist should be reported in a standardized way as outlined in the Ontario Health (Cancer Care Ontario) *Somatic Cancer Panel Reporting in Ontario* (2019) advice document [13].
- Patients who do not fulfill the diagnostic criteria for MPN, but have clonal hematopoiesis or MPN-associated mutations, should be followed closely for the

development of worsening cytoses, thrombotic events or the emergence of circulating blasts.

Recommendations for the Diagnosis and Prognosis of Myelodysplastic/Myeloproliferative Neoplasms

Classification

Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) should be classified per the criteria included in the 2017 revision to the World Health Organization (WHO) Classification of Tumours of Hematopoietic and Lymphoid Tissues (See **Appendix C.3**) [1]. At the time of this *Report's* release, WHO is expected to publish a 5th edition of the haematolymphoid classification [2] [3]. The *Report* may be revised in the future to account for updates to the WHO's new classification scheme.

For the purposes this Report, the diagnostic and prognostic testing of juvenile myelomonocytic leukemia (JMML) is out of scope.

Diagnostic Workup

Upon suspicion, all patients should have:

1. **History and physical**, including family history of hematologic malignancies, familial thrombocytopenia, congenital malformations, pulmonary fibrosis and cirrhosis, and premature grey hair, as examples [4].
2. **Complete blood count (CBC) and peripheral blood smear** [4] [21]**.**
    - The percentage of peripheral blood blasts based on morphologic assessment out of a minimum 200 counted nucleated cells should be reported [1].
    - Absolute monocyte count and percentage of monocytes of white blood cells (WBC) in peripheral blood should be reported [21].
3. **Laboratory and biochemistry tests**
    - Should include erythropoietin (EPO), serum ferritin, percentage iron saturation (serum iron and TIBC), transferrin, lactate dehydrogenase (LDH), uric acid, and vitamin B12 [4].
4. **Bone Marrow** – aspirate and biopsy with a full report [1] [4].
    1. **Morphology**
        - The percentage of marrow blasts based on morphologic assessment out of a minimum 500 counted nucleated cells should be reported (aspirate smears preferred) [1].
        - For diagnosis of MDS/MPN, please see **Appendix C.3.**
    2. **Flow Cytometry**

- Multiparameter flow cytometry is an adjunctive tool in the diagnostic workup of patients with suspected MDS/MPN and can rule out other disorders [6] [7] [21].

Upon initial diagnosis/suspicion of MDS/MPN from morphology, patients should receive the following:

3. **Cytogenetics**
    - All patients should have cytogenetics analysis [4] [21].
    1. **Karyotype**
    2. **Fluorescence in situ hybridization (FISH) panel** (option when karyotype is insufficient to determine if prognostic cytogenetic abnormalities are present) [4].
        - FISH may be used an adjunctive tool when diagnosing MDS/MPN depending on clinical, pathological and karyotype presentation [21].
        - FISH should be considered in patients presenting with eosinophilia (i.e., eosinophilia bone marrow panel, including *PDGFRA, PDGFRB, FGFR1*).
        - Other clinically validated means of assessing these cytogenetic abnormalities (i.e., microarray, optical genome mapping) may be acceptable.
4. **Cytochemistry** (optional)
5. **Immunohistochemistry**
    - Immunohistochemistry, including CD34+ and CD117+, on bone marrow biopsy should be used as an adjunctive tool to support or differentiate MDS/MPN from other hematological disease [1] [9].
6. **Molecular Investigations:**
    - Requirements and scenarios in which a NGS panel should be performed are detailed in **Appendix D.1.** A list of biomarkers included in NGS panel for myeloid neoplasms are detailed in **Appendix D.2**.

When considering allogeneic stem cell transplant, should complete:

5. **Human leukocyte antigen (HLA) Typing** [4].

When considering hereditary disease:

6. **Germline/Hereditary Testing**
    - Patients being considered for germline testing should be referred to a genetics clinic as appropriate.
    - Testing criteria for hereditary hematological malignancies is being reviewed as part of the Ontario Health (Cancer Care Ontario) Provincial Hereditary Cancer Testing Program.
        - Hereditary testing panel should align with the most recent list of genes included on the forthcoming Ontario Health (Cancer Care Ontario) Hereditary Hematological Malignancies gene list (currently under development).
    - Prior to the release of malignant hematology hereditary testing guidance from Ontario Health, it is recommended that clinicians and hematologists follow Baliakas *et al*., (2019)

Nordic Guidelines for Germline Predisposition to Myeloid Neoplasms in Adults: Recommendations for Genetic Diagnosis, Clinical Management and Follow-up [10].

- Timelines for hereditary testing may need to be expedited as part of allogeneic stem cell transplant donor selection where there is suspected hereditary disease risk.
- Testing should be done ideally on skin fibroblasts, and not blood or marrow samples.

Testing Turn-around-times (TAT) - Calendar Days

- Initial/provisional diagnosis of MDS/MPN – within 5 to 7 calendar days
- Cytogenetics: karyotype and FISH (where applicable) – within 14 to 21 calendar days
- Complete genomic characterization – within 21 days
- For patients being considered for intensive chemotherapy (e.g., induction), cytogenetics (including G-band karyotype and FISH) and complete genomic characterization turnaround times should align with recommendations in Ontario Health's forthcoming *Acute Myeloid Leukemia Drug Treatment Algorithm: Recommendations Report,* which will be released in 2023.

MDS-MPN – Other Recommendations

- It is recommended that results are reported using the College of American Pathologists (CAP) Bone Marrow Checklist [12].
    - Bone Marrow reports for MDS/MPN should, at minimum, include the elements outlined in **Appendix E.3.**
    - Molecular and biomarker analysis not included in the CAP Bone Marrow checklist should be reported in a standardized way as outlined in the Ontario Health (Cancer Care Ontario) *Somatic Cancer Panel Reporting in Ontario* (2019) advice document [13].
- Patients who do not fulfill the diagnostic criteria for MDS/MPN, but have MDS/MPN-associated mutations, should be followed closely [14] [15] for the development of worsening cytopenias or cytoses, thrombotic events, or the emergence of circulating blasts.

Future Considerations

The recommendations in this *Report* will be used to ensure patients with MDS, MPN and MDS/MPN are able to receive the appropriate diagnostic and prognostic testing services required for clinical decision making and improved outcomes. This may include local, regional and/or provincial level planning, funding, and performance management approaches as needed.

Recommendations in this *Report* for classifying MDS, MPN and MDS/MPN will need to be reviewed after the 5th edition of WHO haematolymphoid classifications is published. Any new recommendations should consider the classifications used to determine drug eligibility.

The diagnostic and prognostic testing landscape is continuing to evolve. It is recommended that this *Report* is reviewed and updated on a regular basis, at least every 2 years. As part of future work, the Working Group noted evolving evidence regarding repeat testing for monitoring of disease progression should be considered, as well as the use of minimal residual disease testing for patients with MDS, MPN or MDS/MPN being considered for transplant.

Further work is recommended to standardize the reporting of hematopathology of MDS, MPN and MDS/MPN. This could include the implementation of minimal reporting criteria or synoptic reporting, to address the recommendations detailed in this *Report.*

Acknowledgements

Ontario Health (Cancer Care Ontario) would like to acknowledge the efforts and contributions of the MDS and MPN Working Group members (**Appendix A**) whose valuable input and expertise made the *Report* possible.

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Dr. Rafael Bejar, MD, PhD
Associate Professor, Division of Hematology and Oncology, Director, MDS Center of Excellence, and Assistant Director, Medical Scientist Training Program, University of California San Diego Moores Cancer Center, United States

Dr. Donal McLornan MB BCh (Hons) MRCP PhD FRCPath
Consultant Haematologist, Department of Haematology, Guy's Hospital and Department of Stem Cell Transplantation, University College London Hospital, United Kingdom
Chair, Myeloproliferative Neoplasms, United Kingdom National Cancer Research Institute

Chair, Chronic Malignancy Working Party, European Society for Blood and Marrow Transplantation

David Sallman MD
Assistant Member, Myeloid Section Head, Malignant Hematology Department, Moffitt Cancer Center, United States

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Appendices

Appendix A: Members of the MDS and MPN Working Group and Conflicts of Interest

Members	Discipline	Affiliation	Conflicts of Interest
Tom Kouroukis	Hematologist	Provincial Head, Complex Malignant Hematology, Ontario Health (Cancer Care Ontario)	No relevant conflicts of interest to declare.
Aaron Pollett	Pathologist	Provincial Head, Pathology and Laboratory Medicine Program, Ontario Health (Cancer Care Ontario)	No relevant conflicts of interest to declare.
Rena Buckstein	Hematologist	Sunnybrook Health Sciences Centre	Received honorarium for advisory board from BMS/Celgene, TAIHO and AbbVie. Research funding from BMS/Celgene, TAIHO and Takeda.
Grace Christou	Hematologist	The Ottawa Hospital	Signed agreement for participation on Bristol-Myers Squibb Advisory Board, but event was cancelled due to pandemic. No payments received.
Vikas Gupta	Hematologist	University Health Network -Princess Margaret Cancer Centre	**Honorarium/Consulting Services/Advisory Board:** Provided consulting services to Novartis, BMS-Celgene, Incyte, GSK, Pfizer, AbbVie and Roche, CTI Biopharma. **Research Grant** Novartis - received research grant through institution for investigator initiated observational study – 2016-2020 ($190,000 CAD) **Member of Advocacy Group** Canadian MPN Group – Past President of the Canadian MPN

			Group, charitable group, not-for-profit organization. Canadian MPN Patient Network – Board Member for this Organization, charitable group, not for profit organization
Caroline Hamm	Hematologist	Windsor Regional Hospital	Received research grant from Apobiologix in the last 2 years. Accepted speaking engagement with BMS and Pfizer in the last 2 years.
Michael Rauh	Hematopathologist	Kingston General Hospital	Periodically provided informal feedback to Thermo Fisher over last 2 years on Oncomine Myeloid NGS panel performance. No payment. Presented talk at Thermo Fisher "Oncomine Day" in Toronto (October 24, 2019).
Catherine Ross	Hematopathologist	Hamilton Health Sciences	Accepted speaking engagement with Novartis for educational program development. Accepted speaking engagement with Celgene for education. Accepted speaking engagement with Alexion for quality improvement.
Hubert Tsui	Hematopathologist	Sunnybrook Health Sciences Centre	Honorarium from speaking engagements, educational program development and advisory board services from Novartis.
Sherrie Hertz	Healthcare Administration	Group Manager (previous), Specialized Services Oversight, Ontario Health (Cancer Care Ontario)	No relevant conflicts of interest to declare.
Cassandra McKay	Healthcare Administration	Group Manager (current), Specialized Services Oversight, Ontario Health (Cancer Care Ontario)	No relevant conflicts of interest to declare.

Lauren Chun	Healthcare Administration	Lead, Specialized Services Oversight, Ontario Health (Cancer Care Ontario)	No relevant conflicts of interest to declare.
Jennifer Hart	Healthcare Administration	Group Manager, Pathology and Laboratory	No relevant conflicts of interest to declare.
		Medicine Program, Ontario Health (Cancer Care Ontario)	
Goran Klaric	Healthcare Administration	Lead, Pathology and Laboratory Medicine Program, Ontario Health (Cancer Care Ontario)	No relevant conflicts of interest to declare.
Jaemin Kim	Healthcare Administration	Senior Research Associate, Evidence Search and Review Service, Ontario Health (Cancer Care Ontario)	No relevant conflicts of interest to declare.

Appendix B: Search terms (B.1), detailed search strategy (B.2), list of websites and jurisdictions searched (B.3) and study selection criteria for literature review (B.4)

B.1 Search terms for literature search

Myelodysplastic/myeloproliferative neoplasms	Diagnostic/Prognostic Testing	Standards/Recommendations
Myelodysplastic Syndromes [MeSH] **Myelodysplastic syndrome*** **Dysmyelopoietic Syndrome** **Hematopoetic Myelodysplasia** **"MDS" or "MDSs"** **myeloproliferative neoplasm*** **"MPN" or "MPNs"**	Hematologic tests [MeSH] Cytogenetics [MeSH] Molecular Biology [MeSH] Risk Assessment[majr] Molecular genetics/studies Diagnostic testing Prognostic testing Prognosis [MeSH] Diagnosis, differential [MeSH]	Guideline Recommend* Standard* Guidance Protocol Algorithm [MeSH] Algorithm* Health Planning Guidelines [MeSH] Practice guidelines as topic [MeSH]

B.2 Detailed Search Strategy

Ovid Medline

No.	Searches	Results
1	exp Myelodysplastic Syndromes/	20648
2	(Myelodysplastic syndrome* or Dysmyelopoietic Syndrome* or Hematopoietic Myelodysplasia or "MDS" or "MDSs" or Refractory anemia or refractory anaemia or Sideroblastic anemia or sideroblastic anaemia or Paroxysmal Hemoglobinuria or Paroxysmal Haemoglobinuria).ti,ab,kw.	19662
3	(myeloproliferative neoplasm* or "MPN" or "MPNs").ti,ab,kw.	6384
4	(MDS with multilineage dysplasia or MDS with single lineage dysplasia or MDS with ring sideroblasts or MDS with excess blasts or MDS with isolated del or MDS unclassifiable).ti,ab,kw.	75
5	(chronic myeloid leukemia or chronic neutrophilic leukemia or polycythemia vera or primary myelofibrosis or essential thrombocythemia or chronic eosinophilic leukemia-not otherwise specified or MPN unclassifiable).ti,ab,kw.	20202
6	1 or 2 or 3 or 4 or 5	54354
7	exp Hematologic tests/ or exp Cytogenetics/ or exp Molecular Biology/	290191
8	((Molecular or biomolecular or biochemical or blood) adj (genetic* or study or studies or test or testing)).ti,ab,kw.	74600
9	exp Risk Assessment/ or exp Prognosis/ or exp "Diagnosis, differential"/ or *"Diagnostic Tests, Routine"/	2191837
10	((Diagnos* or prognos* or risk) adj (test or testing or assessment*)).ti,ab.	95265
11	5 or 6 or 7 or 8	2570514
12	exp Algorithm/ or exp Health Planning Guidelines/ or exp practice guidelines as topic/ or "Reference Standards"/ or "Practice Guideline".pt.	496947
13	(Guideline* or Recommend* or Standard* or Guidance or Protocol* or algorithm or algorithms).ti,ab,kw.	2608198
14	10 or 11	2850866
15	4 and 9 and 12	1872
16	limit 15 to (english language and yr="2015 - current")	552

Ovid Embase

No.	Searches	Results
1	Myelodysplastic Syndromes/	35474
2	(Myelodysplastic syndrome* or Dysmyelopoietic Syndrome* or Hematopoietic Myelodysplasia or "MDS" or "MDSs" or Refractory anemia or refractory anaemia or Sideroblastic anemia or sideroblastic anaemia or Paroxysmal Hemoglobinuria or Paroxysmal Haemoglobinuria).ti,ab,kw.	44082
3	(myeloproliferative neoplasm* or "MPN" or "MPNs").ti,ab,kw.	11800
4	myeloproliferative neoplasm/	6118
5	1 or 2 or 3 or 4	64978
6	Blood examination/	13299
7	Cytogenetics/	37700
8	Molecular biology/	65041
9	((Molecular or biomolecular or biochemical or blood) adj (genetic* or study or studies or test or testing)).ti,ab,kw.	86604
10	risk assessment/	531400
11	cancer prognosis/	158649
12	differential diagnosis/	267565
13	diagnostic test/	72338
14	((Diagnos* or prognos* or risk) adj (test or testing or assessment*)).ti,ab.	120993
15	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	1237767
16	algorithm/	256185
17	practice guideline/	405796
18	standard/	238119
19	(Guideline* or Recommend* or Standard* or Guidance or Protocol* or algorithm or algorithms).ti,ab,kw.	3339705
20	16 or 17 or 18 or 19	3708622
21	5 and 15 and 20	2507
22	(conference abstract or "Case Reports" or editorial or comment or letter or newspaper article).pt.	5123888
23	21 not 22	1106
24	limit 23 to (human and english language and yr="2015 -Current")	426

B.3: List of websites and jurisdictions searched

Domain	Sources Searched
Websites	Cancerview Guideline Resource Centre National Comprehensive Cancer Network (NCCN) Agency for Healthcare Search and Quality (AHRQ) American Society of Clinical Oncology (ASCO) American Society of Hematology National Institute for Health Care and Excellence (NICE) Evidence Search in Health and Social Care (NHS) European Society of Medical Oncology (ESMO) Cancer Australia Cancer Care NZ Scottish Intercollegiate Guidelines Network (SIGN) European Leukemia Network (ELN)
Jurisdictions	Canada (.ca) United Kingdom (.uk) United States (.gov) Australia (.au) New Zealand (.nz) European Union (.eu) Japan (.jp)

B.4: Study selection criteria for literature review

Criteria	Details
1) Recommendations/ Evidence	• Guidelines, standards, protocols, recommendation documents, guidance documents, manuals, position papers, position statement, and review of guidelines • Any evidence found in primary research studies and/or systematic reviews • Non-systematic reviews conducted as a part of guidelines or position papers
2) Diagnostic/Prognostic Testing	• Tests performed for the purpose of diagnosis (including diagnostic criteria) and/or prognostic evaluation of MDS and/or MPN

3)
a. Myelodysplastic syndromes (MDS)
b. Myeloproliferative neoplasms (MPN)
c. Myelodysplastic/myeloproliferative Neoplasms (MDS/MPN)
	Any subtypes of MDS or MPN including:
	• MDS
	  • MDS with multilineage dysplasia (MDS-MLD)
	  • MDS with single lineage dysplasia (MDS-SLD)
	  • MDS with ring sideroblasts (MDS-RS)
	  • MDS with excess blasts (MDS-EB)
	  • MDS with isolated del(5q)
	  • MDS, unclassifiable (MDS-U)
	• MPN
	  • Chronic myeloid leukemia (BCR/ABL1+)
	  • Chronic neutrophilic leukemia
	  • Chronic eosinophilic leukemia - not otherwise specified (NOS)
	  • Essential thrombocythemia
	  • Primary myelofibrosis (PMF)
	  • PMF, prefibrotic early stage
	  • PMF, overt fibrotic stage
	  • Polycythemia vera
	  • MPN, unclassifiable (MPN-U)

Appendix C: World Health Organization classification and criteria of Myelodysplastic Syndromes (MDS) (C.1), Myeloproliferative Neoplasms (MPN) (C.2), and MDS/MPN (C.3)

C.1 World Health Organization classification and criteria of Myelodysplastic Syndromes [1]
For the purposes this Report, the diagnostic and prognostic testing of refractory cytopenia of childhood is out of scope.

Diagnostic criteria for in scope diseases can be found in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017, page 101, Table 6.01.

MDS Classification	ICD-O Code
MDS with single lineage dysplasia (MDS-SLD)	9980/3
MDS with multilineage dysplasia (MDS-MLD)	9985/3
MDS with ring sideroblasts (MDS-RS)	
MDS-RS and single lineage dysplasia (MDS-RS-SLD)	9982/3
MDS-RS and multilineage dysplasia (MDS-RS-MLD)	9993/3
MDS with isolated del(5q)	9986/3
MDS with excess blasts (MDS-EB)	
MDS-EB-1	9983/3
MDS-EB-2	9983/3
MDS, unclassifiable (MDS-U)	
With 1% blood blast	9989/3
With single lineages dysplasia and pancytopenia	9989/3
Based on defining cytogenetic abnormality	9989/3

C.2 World Health Organization classification and criteria of Myeloproliferative Neoplasms [1]

Please note, for the purposes of this Report, chronic myeloid leukemia, *BCR-ABL1*-positive is out of scope.

MPN Classification	ICD-O Code	Criteria
Chronic neutrophilic leukemia (CNL)	9963/3	Diagnostic criteria can be found in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017, page 38, Table 2.02.
Polycythemia vera (PV)	9950/3	Diagnostic criteria can be found in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017, page 39, Table 2.03.
Post-PV myelofibrosis	9950/3	Diagnostic criteria can be found in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017, page 43, Table 2.05.
Primary myelofibrosis (PMF)	9961/3	Further details regarding diagnostic criteria can be found in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017, page 44-50.
PMF, prefibrotic/early stage	9961/3	Diagnostic criteria can be found in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017, page 44, Table 2.06.
PMF, overt fibrotic stage	9961/3	Diagnostic criteria can be found in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017, page 45, Table 2.07.
Essential thrombocythemia (ET)	9962/3	Diagnostic criteria can be found in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017, page 50, Table 2.12.
Post-ET myelofibrosis	9962/3	Diagnostic criteria can be found in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017, page 53, Table 2.13.
Chronic eosinophilic leukemia, not otherwise specified (NOS)	9964/3	Diagnostic criteria can be found in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017, page 54, Table 2.14.
MPN, unclassifiable	9975/3	Diagnostic criteria can be found in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017, page 54, Table 2.15.

C.3 World Health Organization classification and diagnostic criteria of Myelodysplastic/ Myeloproliferative Neoplasms (MDS/MPN) [1]

For the purposes this Report, the diagnostic and prognostic testing of juvenile myelomonocytic leukemia (JMML) is out of scope.

MDS/MPN Classification	ICD-O Code	Criteria
Chronic myelomonocytic leukemia (CMML-0, CMML-1, CMML-2)	9945/3	Diagnostic criteria can be found in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017, page 82, Table 5.01.
Atypical chronic myeloid leukemia, *BCR-ABL1*-negative	9876/3	Diagnostic criteria can be found in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017, page 87, Table 5.02.
Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)	9982/3	Diagnostic criteria can be found in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017, page 93, Table 5.04.
Myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U)	9975/3	Diagnostic criteria can be found in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017, page 95, Table 5.05.

Appendix D: Scenarios and Recommendations for Next Generation Sequencing (D.1) and List of Biomarkers to include in Next Generation Sequencing Panel for Myeloid Neoplasms (D.2)

Appendix D.1: Scenarios and Recommendations for Next Generation Sequencing

- NGS should not be performed as a screening test.
- NGS should be done on bone marrow aspirate (where possible) examined by a hematopathologist [22].
    - When NGS on bone marrow has not been performed, molecular investigations can be done on whole blood.
- Myeloid NGS should be performed for:
    - All MF (PMF, post PV/ET-MF)
    - MDS and MPN risk stratification
    - Triple negative (*JAK2, CALR, MPL*) MPN (NGS may be required for some centres to establish 'triple negative' status)
    - Where MDS, MPN or MDS/MPN is thought to be therapy related
    - Where a clonal marker would assist with diagnostic interpretation/classification (includes unexplained cytopenias, unclassifiable cases)
    - Where NGS is required in the selection of an approved funded targeted therapy (i.e., companion biomarker)
    - Myeloid NGS should be done at diagnosis and can be repeated on change of disease status from chronic phase to accelerated or blast phase, and/or where treatment may be impacted, for example as defined by WHO criteria
- NGS should not be done if it will not influence diagnostic, prognostic, or therapeutic decisions
- The interpretation of NGS results may require cytogenetics
- Currently, not all molecular findings are of clinical relevance

Appendix D.2: List of recommended Biomarkers for Next Generation Sequencing Panel for Myeloid Neoplasms should include [11][1]

- *ABL1*
- *ASXL1*
- *BCOR*
- *BCORL1*
- *BRAF*
- *CALR*
- *CBL*
- *CEBPA*
- *CUX1*
- *CSF3R*
- *DDX41*
- *DNMT3A*
- *EZH2*
- *ETV6*
- *FLT3 (ITD/TKD)*
- *IDH1*
- *IDH2*
- *JAK2*
- *GATA2*
- *KIT*
- *KMT2A (PTD)*
- *KRAS*
- *MPL*
- *NF1*
- *NPM1*
- *NRAS*
- *PHF6*
- *PPM1D*
- *PTPN11*
- *PRPF8*
- *RAD21*
- *RUNX1*
- *SETBP1*
- *SH2B3*
- *SF3B1*
- *SRSF2*
- *STAG2*
- *TET2*
- *TP53*
- *U2AF1*
- *WT1*
- *ZRSR2*
- *ANKRD26**
- *TERC**
- *TERT**

[1] The list of useful genomic biomarkers for management of MDS, MPN and MDS/MPN continues to evolve and should be re-visited on an annual basis. A Community of Practice should determine an appropriate list of essential biomarkers for Ontario patients with MDS, MPN and MDS/MPN.

* Although these genes are not of clinical relevance for MDS, MPN and MDS/MPN at this time, the gene have been included on list based on potential relevance to other myeloid neoplasms. Labs may decide to not report on these genes base on relevance to indication.

Appendix E: Minimal Reporting Criteria for MDS (E.1), MPN (E.2) and MDS/MPN (E.3)

E.1 Minimal Reporting Criteria for MDS

There should be standardized bone marrow reporting for MDS based on WHO criteria [1], with minimal reporting criteria, including, but not limited to reporting on:

- Cellularity (age adjusted)
- Percentage of blasts (blood, aspirate)
- Lineages that meet/exceed dysplastic threshold for MDS per WHO criteria [1]
    - Percent threshold of dysplasia may be communicated (e.g., <10%, >10%, >30% megakaryocyte dysplasia
- Presence of fibrosis (as assessed by reticulin and/or collagen stains)
    - Report using WHO fibrosis grading scheme (See **Appendix F**)
- Iron stores and percentage ring sideroblasts (e.g., <5%, 5-15%, >15%)

E.2 Minimal Reporting Criteria for MPN

There should be standardized bone marrow reporting for MPN based on WHO criteria [1], with minimal reporting criteria, including, but not limited to reporting on:

- Cellularity (age adjusted)
- Percentage of blasts (blood, aspirate)
- Presence of fibrosis (as assessed by reticulin and/or collagen stains)
    - Report using WHO fibrosis grading scheme (See **Appendix F**)
- Iron stores and percentage ring sideroblasts (e.g., <5%, 5-15%, >15%)
- Megakaryocyte atypia (proportions, morphology, and distribution)
- Myeloblast description (blast clusters and percentage of blasts by CD34 immunohistochemistry on the biopsy, especially when aspirates may not be adequate or representative)
- Proportion of granulopoiesis and erythropoiesis (e.g., if describing panmyelosis) [17].

E.3 Minimal Reporting Criteria for MDS/MPN

There should be standardized bone marrow reporting for MDS/MPN based on WHO criteria [1], with minimal reporting criteria, including, but not limited to reporting on:

- Cellularity (age adjusted)
- Percentage of blasts (blood, aspirate)
- Lineages that meet/exceed dysplastic threshold for MDS/MPN per WHO criteria [1]
    - Percent threshold of dysplasia may be communicated (e.g., <10% or >10%, >30% megakaryocyte dysplasia)
- Presence of fibrosis (as assessed by reticulin and/or collagen stains)

    - Report using WHO fibrosis grading scheme (See **Appendix F**)
- Iron stores and percentage ring sideroblasts (e.g., <5%, 5-15%, >15%)
- Megakaryocyte atypia (proportions, morphology, and distribution)
- Myeloblast, or blast equivalent, description (i.e., blast clusters and percentage of blasts by CD34 immunohistochemistry on the biopsy, especially when aspirates may not be adequate or representative)
- Proportion of granulopoiesis and erythropoiesis [17].

Appendix F: WHO Fibrosis Grading Scheme

Semi quantitative bone marrow fibrosis grading system proposed by Thiele J et al. with minor modifications concerning collagen and osteosclerosis[1] can be found in WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017, Page 47, Table 2.09 [1] [23]. Adequate decalcified control material may be required to ensure staining performance.

Appendix G: Funding

This Recommendations Report was conducted with the support of Ontario Health (Cancer Care Ontario) through funding provided by the Ontario Ministry of Health. Funding to assist with open access publishing fees was provided by the Ontario Health (Cancer Care Ontario) Research Office.

Appendix H: Copyright

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Appendix I: Disclaimer

Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Ontario Health (Cancer Care Ontario) makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

Appendix J: Contact Information

For further information about this report, please contact the Specialized Services Oversight Program (OH-CCO_SSOInfo@ontariohealth.ca). For information about Ontario Health – Ontario Health (Cancer Care Ontario) and the most current version of all reports, please visit the Ontario Health (Cancer Care Ontario) website.

[1] Fibre density should be assessed only in hematopoietic areas; if the pattern is heterogeneous, the final grade is determined by the highest grade present in ≥ 30% of the marrow area.