Protocol for the Examination of Hematologic Malignancies in Bone Marrow

Version: Bone Marrow 4.0.0.0   **Protocol Posting Date:** February 2019

Accreditation Requirements
The use of this protocol is recommended for clinical care purposes but is <u>not</u> required for accreditation purposes.

This protocol is intended to be used for the following procedures AND tumor types:

Procedure	Description
Bone marrow trephine biopsy	Includes specimens designated non-targeted bone marrow biopsy and touch preparations
Bone marrow aspiration	Includes non-targeted bone marrow aspiration, clot section, and aspirate smear preparations
Tumor Type	**Description**
Myeloproliferative neoplasms Mastocytosis Myelodysplastic syndromes Myelodysplastic/myeloproliferative neoplasms Myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement Myeloid neoplasms with germline predisposition Blastic plasmacytoid dendritic neoplasm Acute myeloid leukemia Acute leukemia of mixed/ambiguous lineage Acute lymphoblastic leukemia/lymphoma Mature B-cell neoplasms with leukemic presentation (excluding plasma cell myeloma) Mature T- and NK-cell neoplasms with leukemic presentation	Includes most primary myeloid malignancies, acute leukemias, and mature B-cell, T-cell, and NK-cell neoplasms with frequent leukemic presentation. Disease entities in this protocol are based on the 2017 revised fourth edition World Health Organization classification and include provisional entries.

The following should NOT be reported using this protocol:

Procedure
Extramedullary biopsy specimens
Peripheral blood smears (without bone marrow material)
Tumor Type
Plasma cell myeloma (consider the Plasma Cell Neoplasm protocol)
Histiocytic disorders involving the bone marrow
Non-neoplastic diseases of the bone marrow
Secondary marrow involvement by lymphoma or metastatic cancer (consider the Hodgkin or non-Hodgkin Lymphoma Protocols)

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The pathologist responsible for issuing the diagnostic bone marrow report included in the patient's medical record and forming the basis of treatment decisions is encouraged to fill out the synoptic report. The pathologist may need to include data elements generated at an external facility (e.g. reference lab) for inclusion in the synoptic report. In these scenarios, it is understood that the pathologist is not assuming responsibility for the technical accuracy of such external data.

CAP Bone Marrow Protocol Summary of Changes

Version 4.0.0.0

The following data elements were added:
Clinical Context
Peripheral Blood Complete Blood Cell Count
Bone Marrow Cellularity
Bone Marrow Blasts
Bone Marrow Lymphocytes
Biomarker Information

Surgical Pathology Cancer Case Summary

Protocol posting date: February 2019

BONE MARROW: Final Integrated Diagnosis

Note: This case summary is recommended for reporting hematologic malignancies in bone marrow but is NOT REQUIRED for accreditation purposes. Core data elements are bolded to help identify routinely reported elements.

Note: If the Integrated Diagnosis section is not applicable, proceed to Histological Assessment summary.

Select a single response.

Final Integrated Diagnosis (Note A)

Myeloproliferative neoplasms
___ Chronic myeloid leukemia, *BCR-ABL1* positive
___ Chronic neutrophilic leukemia
___ Polycythemia vera
___ Primary myelofibrosis
___ Essential thrombocythemia
___ Chronic eosinophilic leukemia, NOS
___ Myeloproliferative neoplasm, unclassifiable

Mastocytosis
___ Systemic mastocytosis
___ Mast cell leukemia

Myelodysplastic syndromes (MDS)
___ Myelodysplastic syndrome with single lineage dysplasia
___ Myelodysplastic syndrome with ring sideroblasts and single lineage dysplasia
___ Myelodysplastic syndrome with ring sideroblasts and multilineage dysplasia
___ Myelodysplastic syndrome with multilineage dysplasia
___ Myelodysplastic syndrome with excess blasts-1
___ Myelodysplastic syndrome with excess blasts-2
___ Myelodysplastic syndrome with isolated del(5q)
___ Myelodysplastic syndrome, unclassifiable
___ Refractory cytopenia of childhood

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
___ Chronic myelomonocytic leukemia
___ Atypical chronic myeloid leukemia, *BCR-ABL1*-negative
___ Juvenile myelomonocytic leukemia
___ Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis
___ Myelodysplastic/myeloproliferative neoplasm, unclassifiable

Myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement
___ Myeloid/lymphoid neoplasm with *PDGFRA* rearrangement
___ Myeloid/lymphoid neoplasm with *PDGFRB* rearrangement
___ Myeloid /lymphoid neoplasm with *FGFR1* rearrangement
___ Myeloid /lymphoid neoplasm with *PCM1-JAK2*

Acute myeloid leukemia (AML) and acute leukemias of ambiguous lineage
___ Acute myeloid leukemia, NOS
___ Acute myeloid leukemia with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
___ Acute myeloid leukemia with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
___ Acute promyelocytic leukemia with *PML-RARA*
___ Acute myeloid leukemia with t(9;11)(p21.3;q23.3); *KMT2A-MLLT3*
___ Acute myeloid leukemia with t(6;9)(p23;q34.1);*DEK-NUP214*
___ Acute myeloid leukemia with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
___ Acute myeloid leukemia (megakaryoblastic) with t(1;22)(p13.3;q13.1);*RBM15-MKL1*
___ Acute myeloid leukemia with *BCR-ABL1*
___ Acute myeloid leukemia with mutated *NPM1*
___ Acute myeloid leukemia with biallelic mutations of *CEBPA*
___ Acute myeloid leukemia with mutated *RUNX1*
___ Acute myeloid leukemia with myelodysplasia-related changes
___ Therapy-related myeloid neoplasm
___ Acute myeloid leukemia with minimal differentiation
___ Acute myeloid leukemia without maturation
___ Acute myeloid leukemia with maturation
___ Acute myelomonocytic leukemia
___ Acute monoblastic/monocytic leukemia
___ Pure erythroid leukemia
___ Acute megakaryocytic leukemia
___ Acute basophilic leukemia
___ Acute panmyelosis with myelofibrosis
___ Acute undifferentiated leukemia
___ Mixed phenotype acute leukemia with t(9;22)(q34.1;q11.2); *BCR-ABL1*
___ Mixed phenotype acute leukemia with t(v;11q23.3); *KMT2A* rearranged
___ Mixed phenotype acute leukemia, B/myeloid, NOS
___ Mixed phenotype acute leukemia, T/myeloid, NOS
___ Mixed phenotype acute leukemia, NOS
___ Acute leukemia of ambiguous lineage, NOS
___ Transient abnormal myelopoiesis (TAM) associated with Down syndrome
___ Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm
___ Blastic plasmacytoid dendritic cell neoplasm

Precursor lymphoid neoplasms
___ B-lymphoblastic leukemia/lymphoma, NOS
___ B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
___ B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged
___ B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
___ B-lymphoblastic leukemia/lymphoma with hyperdiploidy
___ B-lymphoblastic leukemia/lymphoma with hypodiploidy
___ B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3); *IGH-IL3*
___ B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
___ B-lymphoblastic leukemia/lymphoma, *BCR-ABL1*-like
___ B-lymphoblastic leukemia/lymphoma with iAMP21
___ T-lymphoblastic leukemia/lymphoma
___ Early T-cell precursor lymphoblastic leukemia
___ NK-lymphoblastic leukemia/lymphoma

Mature B-cell neoplasms
___ Chronic lymphocytic leukemia/small lymphocytic lymphoma
___ B-cell prolymphocytic leukemia
___ Hairy cell leukemia

___ Lymphoplasmacytic lymphoma
___ Other mature B-cell neoplasm (specify): _____

<u>Mature T and NK cell neoplasms</u>
___ T-cell prolymphocytic leukemia
___ T-cell large granular lymphocytic leukemia
___ Chronic lymphoproliferative disorder of NK-cells
___ Aggressive NK-cell leukemia
___ Systemic EBV-positive T-cell lymphoma of childhood
___ Hepatosplenic T-cell lymphoma
___ Adult T-cell leukemia/lymphoma
___ Other mature T/NK-cell neoplasm (specify): _____

<u>Other</u>
___ Other histologic type not listed (specify): _____
___ Cannot be determined

Surgical Pathology Cancer Case Summary

Protocol posting date: February 2019

BONE MARROW: Histologic Assessment

Note: This case summary is recommended for reporting hematologic malignancies in bone marrow but is NOT REQUIRED for accreditation purposes. Core data elements are bolded to help identify routinely reported elements.

Select a single response unless otherwise indicated.

Clinical

Clinical context
___ New diagnosis, untreated
___ New diagnosis, treatment status unknown
___ Follow up sample
___ Other (specify, or state if unknown): _____

Procedure (select all that apply) (Note B)
___ Bone marrow aspiration
___ Bone marrow aspirate clot
___ Bone marrow core biopsy
___ Bone marrow core touch preparation (imprint)
___ Other (specify): _____

Peripheral Blood Complete Blood Cell Count
White blood cell count: ___ x10^3 / μL
Neutrophils: ___%
Monocytes: ___%
Lymphocytes: ___%
Eosinophils: ___%
Basophils: ___%
Blasts: ___%
Other cells: ___%
            Cell type (specify): _____
Hemoglobin: ___ g/dL
Platelets: ___ x10^3 / μL

Bone Marrow Morphology (Note C)

Bone Marrow Cellularity: ___%

Bone Marrow Blasts: ___ %

Bone Marrow Lymphocytes (report for lymphoid malignancies): ___ %

Dysplasia (report for myeloid malignancies)
___ Absent
___ Present (select all that apply)
            ___ Granulocytic lineage
            ___ Erythroid lineage
            ___ Megakaryocytic lineage

Special Stains (Note D)

Iron stain (report for myeloid malignancies)
___ No ring sideroblasts detected
___ Positive for ring sideroblasts (specify percent of erythroid precursors): _____%
___ Stain not evaluable (explain): _____

Reticulin/Trichrome stains (fibrosis grade) (report if applicable)
___ MF-0
___ MF-1
___ MF-2
___ MF-3

Histologic Group
___ Myeloproliferative neoplasm
___ Mastocytosis
___ Myelodysplastic syndrome (MDS)
___ Myelodysplastic/myeloproliferative neoplasm (MDS/MPN)
___ Acute myeloid leukemia (AML)
___ Blastic plasmacytoid dendritic cell neoplasm
___ Precursor lymphoid neoplasm (acute lymphoblastic leukemia/lymphoma)
___ Mature B-cell neoplasm
___ Mature T and NK cell neoplasm
___ Other histologic group not listed (specify): _____
___ Cannot be determined

Biomarker Studies (Note D)
___ Testing performed (see Bone Marrow Biomarker Reporting Template)
___ Pending
___ Not performed
___ Not applicable

Comment(s)

Bone Marrow Biomarker Reporting Template

Protocol posting date: February 2019

BONE MARROW: Biomarker Template

Note: This case summary is recommended for reporting hematologic malignances in bone marrow but is NOT REQUIRED for accreditation purposes.

Biomarker Studies (Note D)

Immunohistochemistry
___ Immunophenotype of neoplastic cells (specify): _____
___ Not performed

Flow Cytometry (select all that apply)
___ No aberrant populations identified
___ Positive for aberrant myeloid blast population
     ___ Immunophenotype (specify): _____
___ Positive for aberrant lymphoid blast population
     ___ Immunophenotype (specify): _____
___ Positive for aberrant mixed phenotype blast population
     ___ Immunophenotype (specify): _____
___ Positive for aberrant mature B-cell population
     ___ Immunophenotype (specify): _____
___ Positive for aberrant mature T-cell population
     ___ Immunophenotype (specify): _____
___ Positive for other aberrancy (specify): _____
     ___ Immunophenotype (specify): _____
___ Not performed
Note: Specify immunophenotype or refer to separate report

Cytogenetics
___ Normal diploid karyotype
___ Abnormal karyotype
     ___ Karyotype (specify: _____
___ Not performed
Note: Specify karyotype or refer to separate report

Fluorescence in situ Hybridization
___ Normal pattern (specify panel): _____
___ Abnormal pattern (specify panel): _____
___ Not performed

Molecular Diagnostics

BCR-ABL1 Transcript by RT-PCR Testing (select all that apply)
___ Absent
___ Present
___ Present transcript type p210
___ Present transcript type p190
___ Present transcript type, other (specify): _____
___ Cannot be determined (explain): _____

CEBPA (mono-allelic) Mutation
___ Absent
___ Present (specify): _____
___ Cannot be determined (explain): _____

FLT3-ITD *(*internal tandem duplication*)* Mutation
___ Absent
___ Present (specify): _____
___ Cannot be determined (explain): _____

FLT3 p.D835 *(*tyrosine kinase domain*)* Mutation
___ Absent
___ Present (specify): _____
___ Cannot be determined (explain): _____

JAK2 p.V617F Mutation
___ Absent
___ Present (specify): _____
___ Cannot be determined (explain): _____

MYD88 p.L265P Mutation
___ Absent
___ Present (specify): _____
___ Cannot be determined (explain): _____

NPM1 Mutation
___ Absent
___ Present (specify): _____
___ Cannot be determined (explain): _____

PML-RARA Transcript by RT-PCR Testing
___ Absent
___ Present (specify): _____
___ Cannot be determined (explain): _____

RUNX1 Mutation
___ Absent
___ Present (specify): _____
___ Cannot be determined (explain): _____

SF3B1 Mutation
___ Absent
___ Present (specify): _____
___ Cannot be determined (explain): _____

Specify Other Mutations (repeat as needed)
___ Absent for other mutation(s) (specify): _____
___ Present for other mutation(s) (specify): _____

Comments:

Explanatory Notes

A. Introduction

The aim of this protocol is to improve the completeness, clarity, and portability of bone marrow reporting in routine clinical practice settings, while being mindful of the wide range of practices in which the data in the report are generated and disseminated. Diagnostic workup of hematologic neoplasms requires the integration of data from multiple sources, including microscopic evaluation, flow cytometry immunophenotyping, cytogenetic analysis, and molecular testing. These requirements are reflected in the World Health Organization (WHO) classification of hematolymphoid malignancies. While this protocol emphasizes diagnostic data elements, it should be noted that many markers considered previously to be diagnostic in nature now provide the basis for frontline treatment decisions thus obscuring the boundaries of diagnostic and biomarker testing (e.g. CD20 and CD33 expression, *BCR/ABL1* fusion, *JAK2*p.V617F and *FLT3* mutations, etc.).

This protocol is based to a large extent on the following documents:
- Revised 4th edition of the WHO classification.[1]
- CAP bone marrow synoptic reporting guidelines for hematologic neoplasms.[2]
- CAP/ASH clinical practice guidelines on initial diagnostic workup of acute leukemia.[3]
- CAP templates for reporting results of biomarker testing.[4,5]

In a disease group where complementary tests may on occasion yield results that challenge the notion of succinct reporting (e.g. complex karyotype, complex mutational profile, etc.), a midway stance was adopted in this protocol to translate complex results into simpler terms that best inform treatment decisions and risk stratification. The synoptic report might thus on occasion lack the full scope of complexity of a given patient's neoplasm, requiring reliance on source documentation. Previously published templates for reporting biomarker testing for myeloproliferative neoplasms (MPN) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) provide more in-depth details compared to the corresponding generic entries in the present protocol. The choice between the generic entries and the more detailed MPN and CLL/SLL templates, where applicable, is left to local discretion.

Integrated Diagnosis

It is understood that the preferred timepoint at which this synoptic report is to be completed might vary by practice patterns and could be influenced by myriad factors, including the information technology environment. Notwithstanding, in the interest of medical record clarity and to avoid effort redundancy, *it is recommended that this synoptic report be completed when all tests required for definitive WHO classification are completed*. In other words, the use of this protocol would be most appropriate as a template for an "integrated report" in cases with hematologic malignancy, rather than for use as a standard template for morphology-based reporting. To this end, this protocol is structured in a "layered" reporting format as follows:

Layer 1: Integrated diagnosis (incorporating all tissue-based information)
Layer 2: Histological assessment
Layer 3: Biomarker studies

References
1. Swerdlow HS, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thele J eds. *World Health Organization Histological Classification of Tumors of Haematopoietic and Lymphoid Tissues* (ed 4th (rev)). Lyon, France: IARC Press; 2017.
2. Sever C, Abbott CL, de Baca ME, et al. Bone Marrow Synoptic Reporting for Hematologic Neoplasms: Guideline From the College of American Pathologists Pathology and Laboratory Quality Center. *Arch Pathol Lab Med.* 2016;140(9):932-949.
3. Arber DA, Borowitz MJ, Cessna M, et al. Initial Diagnostic Workup of Acute Leukemia: Guideline From the College of American Pathologists and the American Society of Hematology. *Arch Pathol Lab Med.* 2017;141(10):1342-1393.

4.   Kelley TW, Arber DA, Gibson C, et al. Template for Reporting Results of Biomarker Testing of Specimens From Patients With Myeloproliferative Neoplasms. *Arch Pathol Lab Med.* 2016;140(7):675-677, www.cap.org/cancerportocols.
5.   Duncavage E, Advani RH, Agosti S, et al. Template for Reporting Results of Biomarker Testing of Specimens From Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Arch Pathol Lab Med. 2016, www.cap.org/cancerportocols.

B.   Sample Type and Clinical Data

Bone marrow evaluation is a critical part of the evaluation of patients suspected of having a hematologic malignancy. At initial presentation, sampling should ideally entail a core (trephine) biopsy and aspiration, with procurement of sufficient material for microscopic evaluation, flow cytometry immunophenotyping, cytogenetics, and molecular studies. It is advisable that a portion of the aspirate material be used to prepare a formalin-fixed paraffin-embedded clot sample (cell block). While this protocol is intended primarily for reporting of bone marrow specimens, applicable elements can be used for reporting extramedullary hematologic neoplasms if needed.

Although the availability of clinical and laboratory data may be limited in certain practice settings, efforts to ensure that the pathologist has at their disposal as much pertinent information as possible to inform their diagnostic assessment are highly encouraged. This premise has been endorsed jointly by the College of American Pathologists and the American Society of Hematology.[1] Inclusion of pertinent clinical and laboratory data in the bone marrow synoptic report is an evidence-based strong recommendation[2], which often also serves as a basis for classification or subclassification on certain hematologic malignancies.

References
1.   Arber DA, Borowitz MJ, Cessna M, et al. Initial Diagnostic Workup of Acute Leukemia: Guideline From the College of American Pathologists and the American Society of Hematology. *Arch Pathol Lab Med.* 2017;141(10):1342-1393.
2.   Sever C, Abbott CL, de Baca ME, et al. Bone Marrow Synoptic Reporting for Hematologic Neoplasms: Guideline from the College of American Pathologists Pathology and Laboratory Quality Center. *Arch Pathol Lab Med.* 2016;140(9):932-949.

C.   Morphology

Bone marrow aspirate smears stained with Wright Giemsa or May-Grunwald-Giemsa stain should be used to perform a 500-cell differential count to enumerate bone marrow blasts (including promonocytes where pertinent) and other marrow cellular elements excluding megakaryocytes. Adequate aspirate smears are also a prerequisite for optimal evaluation for dysplasia. If aspirate smears are limited, touch preparations might provide an alternative; on these a 300-cell differential is recommended. A 200-cell differential is recommended on peripheral blood smears. In instances where sample adequacy does not permit an adequate manual count, the number of blasts and other elements in the bone marrow may be estimated based on ancillary studies, particularly immunohistochemistry, and this would be specified in the pathology report. Descriptors for sample adequacy should be included in the bone marrow report. In this protocol, entries for dysplasia and the percentage of bone marrow blasts and lymphocytes are recommended, as applicable. For instance, reference to dysplasia or the percentage of blasts might not be necessary in a sample involved by chronic lymphocytic leukemia/small lymphocytic lymphoma.

Age-matched bone marrow cellularity should be estimated on 3-4 µm thick sections of formalin-fixed paraffin-embedded tissue sections of the core biopsy and/or clot preparation stained with hematoxylin and eosin, whichever is deemed most representative in a given sample. Normal ranges of bone marrow cellularity vary with age, as described in Table 1.[1]

Table 1. Normal ranges of bone marrow cellularity.

Age (years)	% Hematopoietic area
20-30	60-70
40-60	40-50
≥70	30-40

References
1. Thiele J, Kvasnicka HM, Facchetti F, Franco V, van der Walt J, Orazi A. European consensus on grading bone marrow fibrosis and assessment of cellularity. *Haematologica*. 2005;90(8):1128-1132.

D. Ancillary and Biomarker Studies
Special Stains

A number of cytochemical stains may be utilized in the evaluation of hematologic neoplasms. An iron (Prussian blue) stain is required for assessment of stainable iron in erythroid precursors and the identification of ring sideroblasts.[1] Stainable iron is best evaluated on an aspirate smear or a touch preparation in cases for which such preparations are available. Evaluation of stainable iron on biopsy specimens should be avoided because of limited visualization of ring sideroblasts and the impact of decalcification on iron content. Aberrant cytoplasmic periodic acid-Schiff (PAS) positivity, either diffuse or granular, is a characteristic of dysplasia in erythroid precursors. Cytochemical detection of myeloperoxidase is a rapid and cost-effective tool in the initial workup of acute myeloid leukemia. Notwithstanding, although useful and practical for lineage determination in some instances, cytochemical stains are no longer required for the diagnostic workup of most hematologic neoplasms.

The assessment of bone marrow fibrosis requires a good-quality reticulin stain.[2] The WHO classification recommends the use of trichrome stain in samples with moderate or severe fibrosis (see below). Bone marrow fibrosis grading scheme is summarized in Table 2.

Table 2. Semi-quantitative grading of bone marrow fibrosis.

Myelofibrosis grade	Description
MF-0	Scattered linear reticulin with no intersections (crossovers) corresponding to normal BM.
MF-1	Loose network of reticulin with many intersections, especially in perivascular areas.
MF-2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibers mostly consistent with collagen, and/or focal osteosclerosis.
MF-3	Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibers consistent with collagen, usually associated with osteosclerosis.

Fiber density should be assessed only in hematopoietic areas.
In grades MF-2 or MF-3 an additional trichrome stain is recommended.

Immunophenotyping

Immunophenotyping of bone marrow specimens can be performed by flow cytometry or immunohistochemistry for diagnostic evaluation and for biomarker assessment.[3] Both techniques provide diagnostic, prognostic, and therapy-guiding data elements, and each technique has advantages and disadvantages. Flow cytometry is rapid (hours), quantitative, and allows multiple antigens to be evaluated on the same cell simultaneously. Flow cytometry is the gold standard for minimal residual disease detection in patients with acute leukemia.

Immunohistochemistry permits correlation of antigen expression with architecture and cytomorphology, and it can be performed on archival material.

Cytogenetics, Fluorescence in situ Hybridization, and Molecular Genomics Studies

Cytogenetic and molecular data are integral to the evaluation of patients with primary bone marrow neoplasms. Cytogenetic analysis typically entails conventional karyotyping and FISH. Conventional karyotyping requires viable cells. FISH may be performed on metaphase spreads from karyotyping studies or on air-dried, fresh unfixed aspirate or touch preparation slides. Array comparative genomic hybridization (aCGH) is used as an adjunct tool to detect copy number changes in certain conditions. Unlike conventional karyotyping, aCGH does not require viable cells.

The WHO classification recognizes certain cytogenetic abnormalities as sufficient for a diagnosis of acute myeloid leukemia with myelodysplasia-related change if the bone marrow blast percentage is greater than 20% and the patient has no history of antecedent cytotoxic therapy. These abnormalities are summarized in Table 3.

Table 3. Myelodysplasia-related cytogenetic changes.

Complex karyotype (3 or more abnormalities)
Unbalanced abnormalities
-7/del(7q) del(5q)/t(5q) i(17q)/t(17p) -13/del(13q) del(11q) del(12p)/t(12p) idic(X)(q13)
Balanced abnormalities
t(11;16)(q23.3;p13.3) t(3;21)(q26.2;q22.1) t(1;3)(p36.3;q21.2) t(2;11)(p21;q23.3) t(5;12)(q32;p13.2) t(5;7)(q32;q11.2) t(5;17)(q32;p13.2) t(5;10)(q32;q21.2) t(3;5)(q25.3;q35.1)

The advent of next-generation sequencing (NGS) has altered the landscape of molecular diagnostics. Mutation profiling using gene panels that range from tens to hundreds of genes is increasingly becoming widespread, providing valuable diagnostic, prognostic, and therapy-guiding data. Mutation profiling may be done at initial diagnosis or at subsequent timepoints such as at transformation or relapse. There are no definitive approaches to synoptic reporting of NGS-based mutation profiling results. In this protocol, entries for mutation data on key genes are included in the generic portion of the document. Inclusion of mutation results for other genes is kept at the discretion of the pathologist completing the synoptic report.

References
1. Della Porta MG, Travaglino E, Boveri E, et al. Minimal morphological criteria for defining bone marrow dysplasia: a basis for clinical implementation of WHO classification of myelodysplastic syndromes. *Leukemia* 2015;29: 66–75.
2. Thiele J, Kvasnicka HM, Facchetti F, Franco V, van der Walt J, Orazi A. European consensus on grading bone marrow fibrosis and assessment of cellularity. *Haematologica*. 2005;90(8):1128-1132.
3. Khoury JD, Wang WL, Prieto VG, et al. Validation of Immunohistochemical Assays for Integral Biomarkers in the NCI-MATCH EAY131 Clinical Trial. *Clin Cancer Res*. 2018;24(3):521-531.

Sample synoptic reports
Pathologists may use synoptic reporting tools incorporated into pathology informatics systems or use custom template forms to incorporate the data elements and responses into cancer pathology reports. The following are examples of synoptic reports using this version of the protocol.

<u>Example 1</u>

Integrated Diagnosis:	Hairy cell leukemia
Procedure:	Bone marrow aspiration, clot, and core biopsy
Peripheral blood complete blood cell count:	
White blood cell count:	2.3 x 10^3/µL
Hemoglobin:	10.4 g/dL
Platelets:	112 x 10^3/µL
Bone Marrow Cellularity:	20%
Bone Marrow Lymphocytes:	30%
Immunohistochemistry:	Positive for annexin A1 and BRAF p.V600E
Flow cytometry:	Aberrant B-cell population: Positive for CD11c, CD19, CD20, CD22, CD25, CD103, CD123, kappa; negative for CD5, CD10, lambda
Cytogenetics:	Normal diploid karyotype
Molecular Diagnostics:	Other mutation testing performed:
	Positive: *BRAF* p.V600E

<u>Example 2</u>

Integrated Diagnosis:	Chronic myelomonocytic leukemia-1
Procedure:	Bone marrow aspiration, clot, and core biopsy
Peripheral blood complete blood cell count:	
White blood cell count:	13.7 x 10^3/µL
Monocytes:	21%
Blasts:	1%
Hemoglobin:	11.3 g/dL
Platelets:	68 x 10^3/µL
Bone Marrow Cellularity:	70%
Bone Marrow Blasts:	6%
Dysplasia:	Present; erythroid, megakaryocytic
Flow cytometry:	Positive for other aberrancy: CD56+monocytes
Cytogenetics:	Normal diploid karyotype
Fluorescence in situ hybridization:	Negative for *BCR/ABL1* fusion
Molecular Diagnostics:	Negative for *JAK2* p.V617Fmutation
	Other mutation testing performed:
	Positive: *NRAS* p.G12D