Bone Marrow Synoptic Reporting for Hematologic Neoplasms

Guideline From the College of American Pathologists Pathology and Laboratory Quality Center

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• ***Context.***—**There is ample evidence from the solid tumor literature that synoptic reporting improves accuracy and completeness of relevant data. No evidence-based guidelines currently exist for synoptic reporting for bone marrow samples.**

Objective.—**To develop evidence-based recommendations to standardize the basic components of a synoptic report template for bone marrow samples.**

Design.—**The College of American Pathologists Pathology and Laboratory Quality Center convened a panel of experts in hematopathology to develop recommendations. A systematic evidence review was conducted to address 5 key questions. Recommendations were derived from strength of evidence, open comment feedback, and expert panel consensus.**

Results.—**Nine guideline statements were established to provide pathology laboratories with a framework by which to develop synoptic reporting templates for bone marrow samples. The guideline calls for specific data groups in the synoptic section of the pathology report; provides a list of evidence-based parameters for key, pertinent elements; and addresses ancillary testing.**

Conclusion.—**A framework for bone marrow synoptic reporting will improve completeness of the final report in a manner that is clear, succinct, and consistent among institutions.**

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Agreement on the diagnosis of hematologic neoplasms generally exists among pathologists, based on widely adopted classification schemes, such as the World Health Organization (WHO) *Classification of Tumours of Haematopoietic and Lymphoid Tissues*.[1] However, bone marrow pathology reports are highly variable, with diagnostic statements ranging from a one-line diagnosis of *acute leukemia* to lengthy narratives with the term *acute leukemia* buried in extensive textual paragraphs. The significant variability in reporting of bone marrow specimens may result in incomplete information or misleading information that is ill-defined and difficult to find in the report. This, in turn, may result in suboptimal care, including inappropriate treatment or incorrect prognostic information. There is ample evidence that synoptic reporting improves the accuracy and completeness of relevant data elements in solid tumors, such as colorectal cancer and breast cancer.[2–8] To address the challenges of bone marrow synoptic reporting, the College of American Pathologists (CAP) Pathology and Laboratory Quality Center (*the Center*) convened an expert panel to systematically review and evaluate scientific literature pertaining to the various

*Inactive guidelines are no longer updated with systematic literature reviews, but the recommendations may still be useful for educational, informational, or historic purposes.

elements informative for the diagnosis, prognosis, and treatment of neoplastic bone marrow disease. Disease categories addressed included acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndromes (MDSs), myeloproliferative neoplasms (MPNs), plasma cell disorders, Hodgkin lymphoma, and non-Hodgkin lymphoma (NHL). Although aplastic anemia (AA) is not neoplastic, it was also addressed because of its overlap with MDSs.

The CAP Cancer Protocols have previously established a reporting foundation by adopting synoptic reporting principles as a key element. As currently defined by the CAP, synoptic reporting includes the following elements: reporting of scientifically validated data elements that influence clinical outcome and therapeutic decisions, display of each data element in a "variable:result" format on a single line, and display of data elements on separate lines. This report format ensures that critical information is transmitted consistently and succinctly in every report. It does not exclude incorporation of additional information, such as detailed differential counts, panels of immunohistochemical and special stains needed for pathologic workup, or explanatory narratives interpreting the clinical relevance of complex findings.

In recent years, the CAP has introduced evidence-based guidelines for specific high-impact topics, based on a comprehensive, systematic literature search with rigorous grading of evidence, supplemented by the considered judgment of a panel of experts.[9] The CAP Center guideline development process follows the Institute of Medicine's *Clinical Practice Guidelines We Can Trust*.[10] Rather than dictating a "one size fits all" approach to patient care, the CAP guidelines offer evaluation of the quality of the relevant scientific literature and an assessment of the likely benefits and harms of a particular practice.

In that spirit, the expert panel formulated key questions and organized the findings and recommendations presented in this guideline. This guideline is not intended to replace the *Protocol for the Examination of Specimens From Patients With Hematopoietic Neoplasms Involving the Bone Marrow*, that is included in the CAP Cancer Protocols (Cancer Protocol—Hematologic: Bone Marrow, version 3.0.1.1, posted June 15, 2012).[11] That particular checklist includes instructions on reporting specimen attributes and a comprehensive list of hematopoietic neoplasms based on the WHO classification. It also includes required reporting of immunophenotyping and cytogenetic analysis, whereas other additional testing, such as fluorescence in situ hybridization (FISH), molecular studies, and other pathologic findings, are optional. The explanatory notes of the checklist contain detailed information on recommended specimen preparation, fixation, and recording, as well as staging information for NHL and plasma cell myeloma. This proposed bone marrow reporting guideline does not include evidence-based analysis of specimen requirements because the topic was deemed out of the scope of the project. The practitioner is referred to existing recommendations, such as those outlined in the CAP Cancer Protocols.[12]

It became clear during the work on this guideline that one uniform set of data elements for all hematopoietic neoplasms was impractical. In addition, diagnostic bone marrow reporting poses unique challenges, particularly at initial diagnosis. Unlike solid tumors with identifiable, often single, mass lesions, bone marrow neoplasms may declare themselves indirectly via peripheral blood abnormalities that can be mimicked by a wide variety of secondary, often nonneoplastic, causes. A particular challenge to bone marrow diagnostics is that an accurate diagnosis may require consideration of ancillary data, which are often not available at the time of morphologic evaluation, and the need for incorporation of clinical information and data from other testing modalities (such as radiology). Gathering this information may be extremely challenging given diverse practice settings, limitations of access to patient medical records, difficulties in reaching clinicians, and the time constraints of a busy practice. Nevertheless, there is little doubt that incorporation of clinical and ancillary information represents good medical practice and further promotes the concept of a diagnostic management team as the optimal approach to patient care by helping to reach a clinicopathologic diagnosis relevant for treatment and outcome.

Consequently, the list of important data elements found in our query is somewhat lengthy, but only subsets are relevant for different diagnostic categories of neoplasms. A single reporting template for all bone marrow diseases is, therefore, unlikely to solve the complexity of bone marrow disease reporting without introducing an excessive amount of elements. A synoptic format does not preclude additional components in the bone marrow report. Narrative comments may follow the synoptic portion to clarify results, suggest further work, or discuss unusual features of a case, among others. However, for each major class of bone marrow neoplasms, there are data sets that are essential for clinical decisions, and these should be reliably reported every time in the structured format of a synoptic report.

The recommendations presented below provide a framework for evidence-based bone marrow synoptic reporting. The primary target audience for this guideline is pathologists reporting results from bone marrow examinations. Clinicians are the secondary target audience but should be involved in report design in the spirit of the diagnostic team effort. We have attempted to develop the recommendations presented herein to address diverse patient populations and diagnostic teams encountered in different practice environments.

METHODS

This evidence-based guideline was developed following the standards endorsed by the Institute of Medicine. A detailed description of the methods and a systematic review (including the quality assessment and complete analysis of the evidence) used to create this guideline can be found in the supplemental digital content available at www.archivesofpathology.org in the September 2016 table of contents.

Panel Composition

The CAP's Center convened an expert panel consisting of members with expertise in hematopathology. Panel members included 7 pathologists, 1 hematologist/oncologist, 1 methodologist consultant, and CAP staff. The CAP approved the appointment of the project chair and panel members. These panel members served as the expert panel for the systematic evidence review.

Conflict of Interest Policy

Before acceptance on the expert panel, potential members completed the CAP conflict of interest disclosure process, whose policy and form (in effect April 2010) requires disclosure of material financial interest in, or potential for benefit of significant value from, the guideline's development or its recommendations from 12 months before through the time of publication. Potential members completed the conflict of interest disclosure form, listing any

relationship that could be interpreted as constituting an actual, potential, or apparent conflict. Everyone was required to disclose conflicts before beginning and continuously throughout the project at each virtual and face-to-face meeting. Disclosed conflicts of the expert panel members are listed in the Appendix. The CAP provided funding for the administration of the project; no industry funds were used in the development of the guideline. All panel members volunteered their time and were not compensated for their involvement, except for the contracted methodologist. Please see the SDC for full details on the conflict of interest policy.

Objective

The scope of the panel was to develop a series of evidence-based recommendations to standardize the basic components of a synoptic report template for bone marrow samples that would address the following domains: bone marrow morphologic descriptors, possible tests (by category) to be performed on the primary sample, relevant clinical and laboratory information, necessary components (regulatory, legal, financial, among others), and layout.

The key questions were as follows:

1. Considering the possible primary bone marrow morphologic descriptors, which ones are required on a synoptic report if completeness is the outcome of interest?
2. Considering the possible ancillary studies that could be ordered on a bone marrow specimen, which ones are required on a synoptic report if completeness is the outcome of interest?
3. What sequence of results reporting should be followed?
   a. Considering the options available, is there an optimal report format that should be used if ease of use, error reduction, and fewer incompletes are the outcomes of interest?
   b. Is there an optimal presentation for the elements of the minimum data set if the outcomes of interest are clarity and ease of use?
4. Which components required for correct coding and data repositories should be included in the report?
   a. Coding
   b. Registries
   c. National guidelines (eg, National Comprehensive Cancer Network[13])
   d. Physician payment incentive requirements (eg, Physician Quality Reporting System[14])
5. What clinical or laboratory information should be included in the report?

There is an absence of recommendations pertaining to the quality of the primary bone marrow specimen. Although a high-quality specimen is desirable for optimal diagnostic workup, the minimum requirements depend on clinical circumstances and diagnostic needs. Because high-level evidence is not readily available for all scenarios, this was considered out of the scope for formal evidence-based recommendations at this time. The reader is referred to the CAP Cancer Protocols and existing guidelines pertaining to specimen quality.[15,16]

Literature Search and Selection

The systematic literature review for relevant evidence included a search using both OvidSP (http://ovidsp.ovid.com, accessed November 30, 2012; Ovid Technologies, New York City, New York) and PubMed (http://www.ncbi.nlm.nih.gov, accessed December 5, 2012; National Library of Medicine, Bethesda, Maryland) for articles published from January 2002 through November 2012. Medical subject headings and key words were selected to capture the concepts of bone marrow samples, ancillary testing, pathology reporting, and benign and malignant hematologic diagnostic entities. The searches were limited to human studies published in English, and a publication filter was applied to exclude less-rigorous study designs, as well as letters, commentaries, and editorials. A separate search for literature using PsycINFO (http://www.apa.org/pubs/databases/psycinfo, accessed November 26, 2012; American Psychological Association, Washington, DC) was completed to identify articles that addressed the concepts of reading comprehension, communication, and clarity. Database searches were supplemented by a search for grey literature using Cochrane Library (http://www.cochranelibrary.com, accessed January 3, 2013; Cochrane Collaboration, London, England), TRIP database (http://www.tripdatabase.com, accessed January 3, 2013; Trip Database Ltd, Newport, Wales), Grey Literature Report (http://www.greylit.org, accessed January 2, 2013; New York Academy of Medicine Library, New York), and Google Scholar (https://scholar.google.com, accessed January 2, 2013; Google, Mountain View, California), a review of relevant meeting abstracts (2011–2012), and a hand-search of selected relevant journals. A refresh of the Ovid and PsycINFO searches was completed (July 9, 2014) to capture studies published through June 2014. Detailed information regarding the literature search strategy can be found in the SCD.

Inclusion Criteria

Published studies were selected for full text review if they met each of the following criteria:

1. Human studies,
2. Original research addressing bone marrow synoptic reporting and elements of the report that provided data or information relevant to 1 or more key questions,
3. English language articles of any study design,
4. Studies from the years of 2002 to 2012.

Exclusion Criteria

1. Noncomparative studies;
2. Studies that address conditions outside of this list:
   a. *Neoplastic:* Multiple myeloma, amyloidosis, acute myeloid leukemia/acute lymphoblastic leukemia, chronic myelogenous leukemia, primary myelofibrosis, myeloproliferative neoplasms, myelodysplastic syndromes-clinical terms (eg, low risk, high risk, WHO-refractory anemias), myelodysplastic/myeloproliferative neoplasms, Hodgkin lymphoma, NHL, chronic lymphocytic leukemia (CLL);
   b. *Nonneoplastic:* Anemia of chronic inflammation, parvovirus B19, iron deficiency anemia, vitamin B12 deficiency, folate deficiency, Paget disease of the bone, idiopathic immune thrombocytopenia, AA;
3. Studies that do not address reporting or factors that aid in reporting: text, font, order of elements, optimal presentation of data, document design, ease of use, clarity, error reduction (accuracy), minimizing incomplete reports, other important aspects of synoptic reporting;
4. Studies that do not address morphologic descriptors, flow cytometry, FISH cytogenetics, molecular studies, other important ancillary studies;
5. Editorials, letters, commentaries, invited opinions, or articles that did not address any key question were also excluded.

Quality Assessment

An assessment of the quality of the evidence (risk of bias assessment) was performed for all retained studies following application of the inclusion and exclusion criteria by a contracted methodologist. Using this method, studies deemed to be of low quality were not excluded from the systematic review but were retained and their methodological strengths and weaknesses were discussed where relevant. Studies were assessed by confirming the presence of items related to both internal and external validity, which are all associated with methodological rigor and a decrease in the risk of bias. (Refer to the SDC for items relating to internal and external validity.) The quality assessment of the studies was performed by determining the risk of bias by assessing key indicators, based on study design, against known criteria.

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Table 1. Levels of Evidence	
Designation	**Description**
Level I	Evidence derived from systematic reviews of appropriate level-II studies and/or clinical practice guidelines
Level II	Evidence derived from randomized control trials
Level III	Evidence derived from comparative studies (eg, prospective cohort studies, retrospective cohort studies)
Level IV	Evidence without a comparator (eg, case reports, case series, narrative reviews)

Data derived from National Health and Medical Research Council. *A guide to the development, implementation and evaluation of clinical practice guidelines*. https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp30.pdf. 1999. Accessed February 9, 2016.

For strength of the evidence, the panel considered the level of evidence, its quantity, and the quality of included studies. The level of evidence was based on the study design as follows:

- Level I was evidence from systematic reviews or clinical practice guidelines of appropriate level II studies;
- Level II was evidence from good-quality, randomized, controlled trials;
- Level III was evidence from low-quality comparative studies;
- Level IV was evidence from studies without a comparator (Table 1).[71]

In general, evidence from levels I and II is considered most appropriate for answering clinical questions, but in the absence of such high-quality evidence, the panel considered data from lower-quality studies. The quantity of evidence refers to the number of studies and the number of cases included for each outcome in the recommendation. The quality of studies reflects how well the studies were designed to eliminate bias and threats to validity.

The appropriateness of the study design and data collected, the relevance and clarity of the findings, and the adequacy of the conclusions were evaluated. Each study was assessed individually (refer to the SDC for individual assessments and results) and then summarized by study type. Components such as generalizability and applicability were also considered when determining the strength of evidence. A summary of the overall quality of the evidence was given after considering the evidence in totality. Ultimately, the designation (ie, rating or grade) of the strength of evidence is a judgment by the expert panel of their level of confidence that the evidence from the studies informing the recommendations reflects true effect. Table 2 describes the grades for strength of evidence.

Assessing the Strength of Recommendations

Development of recommendations required that the panel review the identified evidence and make a series of key judgments. Grades for strength of recommendations were developed by the CAP Center and are described in Table 3.

Guideline Revision

This guideline will be reviewed every 4 years, or earlier in the event of publication of substantive and high-quality evidence that could potentially alter the original guideline recommendations. If necessary, the entire panel will reconvene to discuss potential changes. When appropriate, the panel will recommend revisions of the guideline to the CAP for review and approval.

Disclaimer

The CAP developed the Center as a forum to create and maintain evidence-based practice guidelines and consensus statements. Practice guidelines and consensus statements reflect the best-available evidence and expert consensus supported in practice. They are intended to assist physicians and patients in clinical decision-making and to identify questions and settings for further research. With the rapid flow of scientific information, new evidence may emerge between the time a practice guideline or consensus statement is developed and when it is published or read. Guidelines and statements are not continually updated and may not reflect the most-recent evidence. Guidelines and statements address only the topics specifically identified therein and are not applicable to other interventions, diseases, or stages of diseases. Furthermore, guidelines and statements cannot account for individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge, to determine the best course of treatment for the patient. Accordingly, adherence to any practice guideline or consensus statement is voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances and preferences. The CAP makes no warranty, express or implied, regarding guidelines and statements and specifically excludes any warranties of merchantability and fitness for a particular use or purpose. The CAP assumes no responsibility for any injury or damage to persons or property arising out of, or related to, any use of this statement or for any errors or omissions.

RESULTS

Of the 1731 unique studies identified in the systematic review, 103 were selected for inclusion. These included 102 published peer-reviewed articles and 1 meeting abstract. Among the extracted documents, 8 articles did not meet

Table 2. Grades for Strength of Evidence		
Designation	**Description**	**Quality of Evidence**
Convincing	High confidence that available evidence reflects true effect. Further research is very unlikely to change the confidence in the estimate of effect.	High/intermediate quality evidence
Adequate	Moderate confidence that available evidence reflects true effect. Further research is likely to have an important effect on the confidence in the estimate of effect and may change the estimate.	Intermediate/low quality of evidence
Inadequate	Little confidence that available evidence reflects true effect. Further research is very likely to have an important effect on the confidence in the estimate of effect and is likely to change the estimate.	Low/insufficient evidence; expert panel uses formal consensus process to reach recommendation
Insufficient	Evidence is insufficient to discern net effect. Any estimate of effect is very uncertain.	Insufficient evidence; expert panel uses formal consensus process to reach recommendation

Adapted by permission from BMJ Publishing Group Limited. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Guyatt GH, et al; GRADE Working Group. 2008;336(7650):924–926.[74]

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Table 3. Grades for Strength of Recommendations		
Designation	**Recommendation**	**Rationale**
Strong recommendation	Recommend for or against a particular bone marrow synoptic reporting practice (Can include must or should)	Supported by convincing (high) or adequate (intermediate) quality of evidence and clear benefit that outweighs any harms
Recommendation	Recommend for or against a particular bone marrow synoptic reporting practice (Can include should or may)	Some limitations in quality of evidence (adequate [intermediate] or inadequate [low]), balance of benefits and harms, values, or costs, but panel concludes that there is sufficient evidence and/or benefit to inform a recommendation
Expert consensus opinion	Recommend for or against a particular bone marrow synoptic reporting practice (Can include should or may)	Serious limitations in quality of evidence (inadequate [low] or insufficient), balance of benefits and harms, values or costs, but panel consensus is that a statement is necessary
No recommendation	No recommendation for or against a particular bone marrow synoptic reporting practice	Insufficient evidence or agreement of the balance of benefits and harms, values, or costs to provide a recommendation

Data derived from [74].

minimum quality standards, presented incomplete data or data that were not in usable formats, or included only information based on expert opinion. These articles were not included in analyses or narrative summaries. The 95 remaining articles underwent data extraction and qualitative analysis.

The expert panel met 21 times through teleconference webinars from February 2, 2012, through March 31, 2015. Additional work was completed via electronic mail. The panel met in person November 2, 2013, to review evidence to date and to draft recommendations. An open comment period was held from April 21, 2014, through May 19, 2014, on the CAP website. Ten draft recommendations and 2 demographic questions were posted for peer review.

Agree and *disagree* responses were captured for every proposed recommendation. The website also received 178 written comments. All 10 draft recommendations achieved more than 80% agreement. Each expert panel member was assigned 3 pages of comments to review and summarize. After consideration of the comments, 2 draft recommendations were maintained with the original language; 6 were revised, and 2 draft recommendations were combined into one for 9 final recommendations. Resolution of all changes was obtained by unanimous consensus of the panel members using nominal group technique (rounds of teleconference webinars, email discussions, and multiple, edited recommendations). Final expert panel recommendations were approved by a formal vote. The panel considered laboratory efficiency and feasibility throughout the entire process although neither cost nor cost-effectiveness analyses were performed.

An independent review panel, masked to the expert panel and vetted through the conflict of interest process, provided a review of the guideline and recommended approval by the CAP Council on Scientific Affairs. The final recommendations are summarized in Table 4.

GUIDELINE STATEMENTS

1. Strong Recommendation.—Laboratories should adopt synoptic reporting as a component of bone marrow pathology reports for clearly defined neoplasia or widely applied classification schemes and receive appropriate institutional support.

The strength of evidence was *convincing* to support the superiority of synoptic reports over unstructured, narrative reports.

This recommendation is evidence-based and was supported by 11 studies,[2–8,17–20] all of which met the inclusion criteria for the systematic review. These studies comprised one randomized control trial[3] and 10 retrospective cohort studies (RCSs).[2,4–8,17–20] All 11 studies found statistically significant improvements for completeness associated with synoptic-reporting methods compared with nonsynoptic-reporting methods at $P < .05$, with reported values ranging from 4.1% to 100% for synoptic reports compared with values ranging from 0.2% to 97.3% for nonsynoptic reports. All studies were assessed for risk of bias, and none were found to have methodological flaws that would raise concerns about the studies' findings. Refer to Supplemental Table 12 in the SDC for the summary of studies' findings in support of the superiority of synoptic reporting over unstructured, narrative reports.

Levels I and II evidence demonstrated significant improvement of the completeness of reporting of required data elements for prostate cancer,[17] colorectal cancer,[2–6] pancreatic cancer,[18] breast cancer,[3,7,8] and melanoma.[20] In these studies, the required data fields were based on widely accepted clinical staging systems, including TNM staging,[6,17,18] nationally adopted guidelines based on specialty society clinical requirements,[2,3,5,7,8,20,21] and CAP Cancer Protocols.[4,6,18,19] In all reports that included a statistical analysis, the difference in completeness of required data elements was highly significant with *P*-values ranging from $P < .05$ to $< .001$. (Refer to Supplemental Table 12 in the SDC.) None of the available studies specifically addressed the completeness of bone marrow pathology reporting; however, the strength of evidence in favor of synoptic or checklist based reporting was preserved across multiple different organ systems.

Concerns that were raised in the open comment period revolved around 2 issues. There was the perception that synoptic reporting precludes the use of free text. This perception is incorrect because free text, such as explanatory narrative comments, may be critical to elucidating complex findings and to helping weigh the importance of particular data elements in the context of a specific clinical case. The other concern was that bone marrow synoptic reporting would place an unnecessary burden on community and nonexpert pathologists. Although this was not explicitly addressed in the studies, there are data to support that standardization through a synoptic format improves the nonexpert report and essentially equalizes the completeness

Table 4. Guideline Statements and Strength of Recommendations

Guideline Statement	Strength of Recommendation
1. Laboratories should adopt synoptic reporting as a component of bone marrow pathology reports for clearly defined neoplasia or widely applied classification schemes and receive appropriate institutional support.	Strong recommendation
2. When reporting on peripheral blood specimens for bone marrow synoptic reports, laboratories should report clinically and diagnostically pertinent elements, if available. These key elements may include one or more parameters from complete blood cell count, absolute cell counts, and relevant morphologic descriptors.	Strong recommendation
3. When reporting bone marrow aspirate results, laboratories should report clinically and diagnostically pertinent elements in the synoptic section. These key elements may include the evidence-based parameters, such as blast percentage, dysplasia, myeloid to erythroid ratio, morphology of myeloid/lymphoid elements, and enumeration of lymphoid elements and plasma cells; additional elements may be included in nonsynoptic sections of the report.	Strong recommendation for blast percentage; recommendation for all other parameters
4. When reporting bone marrow core biopsy results, laboratories should report clinically or diagnostically pertinent elements in the synoptic section. These key elements may include the evidence-based parameters, such as fibrosis, cellularity, distribution pattern of hematopoietic elements, morphology of lymphoid elements, and enumeration of lymphoid elements and plasma cells; additional elements may be included in nonsynoptic sections of the report.	Strong recommendation for fibrosis; recommendation for all other parameters
5. If relevant ancillary testing studies are performed on the primary sample (blood or bone marrow), laboratories should report the results, general methodology, performance site, and interpretation site or have the data readily available. If the results are not available, pending status should be explicitly stated.	Strong recommendation
6. Laboratories should include in the synoptic section of the report data groups for diagnosis, supporting studies, and ancillary data that are critical for diagnosis. Key morphologic descriptors should be included and may be in the diagnosis line if critical or if a component of the disease classification. The diagnosis (or diagnosis group) should head the synoptic section when possible. A narrative, interpretative comment should immediately follow the synoptic section, if required.	Strong recommendation for inclusion of data groups for diagnosis, supporting studies, and ancillary data; recommendation for the layout of the data groups
7. Laboratories should consider the integrity of electronic data transmission for formatting and data presentation of synoptic reports.	Strong recommendation
8. No recommendation is made regarding the inclusion of coding terms in a synoptic report because coding terms are distinct from scientific terms and vary considerably among health authorities, payers, and different countries.	No recommendation
9. Laboratories should include clinical and laboratory data required for a definitive diagnosis in the synoptic section, along with its source(s), if applicable.	Recommendation

of nonexpert to expert reports for common neoplastic conditions.[6] The expert panel recognized that building the synoptic report template required initial effort and information technology resources to implement successfully; therefore, appropriate institutional support is essential for implementation.

Based on these findings, the expert panel concluded that synoptic reporting should be adopted for clearly defined bone marrow neoplasia and AA classifiable by widely adopted classification schemes, such as the WHO classification.

2. Strong Recommendation.—When reporting on peripheral blood specimens for bone marrow synoptic reports, laboratories should report clinically and diagnostically pertinent elements, if available. These key elements may include one or more parameters from complete blood cell count, absolute cell counts, and relevant morphologic descriptors.

The strength of evidence was *convincing* to support this recommendation.

This recommendation is evidence-based and supported by 6 studies,[22–27] all of which met the inclusion criteria for the systematic review. These 6 studies comprise 2 prospective cohort studies (PCSs)[22,26] and 4 RCSs.[23–25,27] All studies were assessed for risk of bias, and none were found to have methodological flaws that would raise concerns about the studies' findings. One RCS[23] reported clinical significance for data on white blood cell counts in patients with Philadelphia-positive (Ph^+) ALL and polycythemia vera. Four studies, comprising 2 PCSs[22,26] and 2 RCS,[24,27] reported clinical significance for data on hemoglobin in patients with MDS and AA. Four studies, comprising 1 PCS[22] and 3 RCSs,[24,25,27] reported clinical significance for data on platelets in MDS, myeloproliferative disease, adult T-cell leukemia/lymphoma patients. Two RCSs[24,27] reported clinical significance for data on absolute neutrophil count in patients with AA, and 1 RCS[26] reported clinical significance for data on reticulocyte count and red cell distribution width in patients with AA and MDS. Refer to Table 5 for study data by outcome of significance for peripheral blood specimens.

Peripheral blood parameters are required for the correct classification of numerous bone marrow disorders and constitute an integral component of any hematologic evaluation. There was high-level evidence demonstrating significantly different clinical outcomes for white blood cell counts in Ph^+ ALL and polycythemia vera[23,25]; hemoglobin levels in myelodysplasia and AA[26–28]; platelet counts in myelodysplasia, myeloproliferative disease, adult T-cell leukemia/lymphoma[22,24,25,27]; absolute neutrophil count in myelodysplasia[24,27]; and red cell distribution width and reticulocyte counts in AA.[26] Other parameters, such as red blood cell morphologic descriptors, percentage of blasts, and white blood cell dysplasia, may be pertinent for diagnosis, clinical management, and documentation but showed insufficient statistical strength to inform clinical outcomes.

In the open comment period, there was a broad consensus among 91% of respondents that peripheral blood

Table 5. Key Elements of Synoptic Reports for Peripheral Blood Specimens

Element With Significant Outcome Difference	Relevant Disease or Diagnosis	Studies Reporting Significant Differences, No.	Source, y
WBC count	Ph^+ ALL	1	Gandemer et al,[23] 2009
Hgb	Myelodysplasia, AA	2	Kao et al,[24] 2008
			Greenberg et al,[27] 2012
Plt	Myelodysplasia, myeloproliferative disease, adult T-cell leukemia/ lymphoma	5	List et al,[22] 2006
			Kao et al,[24] 2008
			Kvasnicka and Thiele,[25] 2006
			Wang et al,[26] 2011
			Greenberg et al,[27] 2012
Absolute neutrophil count	Myelodysplasia	2	Kao et al,[24] 2008
			Greenberg et al,[27] 2012
Reticulocyte count	AA	1	Wang et al,[26] 2011
RDW	AA, MDS	1	Wang et al,[26] 2011

Abbreviations: AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; EFS, event free survival; Hgb, hemoglobin; Int-1/Int-2, intermediate-1/intermediate-2; IPSS, International Prognostic Scoring System; MCV, mean corpuscular volume; MDS, myelodysplastic syndrome; OS, overall survival; Ph^+, Philadelphia-positive; Plt, platelet; RDW, red cell distribution width; WBC, white blood cell count.

parameters constituted an integral component of bone marrow evaluation. Concerns that were raised included duplication of data and cluttering of reports, in particular, when the bone marrow report is embedded in an electronic medical record in which complete blood cell count data are readily available. On the other hand, in particular outpatient settings or as part of documentation sent for consultative examination, these data may not be readily available and need to be supplied by the clinician requesting the bone marrow evaluation. This is especially critical at a first diagnosis, when it is not yet known whether bone marrow is neoplastic. This is further addressed in statement 9.

3. Strong Recommendation for Blast Percentage; Recommendation for All Other Parameters.—When reporting bone marrow aspirate results, laboratories should report clinically and diagnostically pertinent elements in the synoptic section. These key elements may include the evidence-based parameters, such as blast percentage, dysplasia, myeloid to erythroid ratio, morphology of myeloid/lymphoid elements, and enumeration of lymphoid elements and plasma cells; additional elements may be included in nonsynoptic sections of the report.

The evidence was *convincing* for blast percentage, but *adequate* for all other parameters (ie, strength of the evidence varied among the different key elements suggested in this recommendation).

This recommendation is evidence-based and supported by 13 studies,[23,24,26,29–38] all of which met the inclusion criteria for the systematic review. These 13 studies comprise 2 nonrandomized control trials (NRCTs),[32,33] 4 PCS,[26,29,31,35] and 7 RCS.[23,24,30,34,36–38] All studies were assessed for risk of bias, and none were found to have methodological flaws that would raise concerns about the studies' findings. Seven studies,* comprising 1 NRCT,[32] 3 PCSs,[26,29,35] and 3 RCSs,[23,24,34] reported clinical significance for data on blast percentage in ALL, AML, MDS, MPN, and AA. Five studies,[26,30,34,36,37] comprising 1 PCS[26] and 4 RCSs,[30,34,36,37] reported clinical significance for data on dysplasia in patients with MDS and MPN. Two studies,[33,38] comprising 1 NRCT[33] and 1 RCS,[38] reported clinical significance for data on lymphocyte percentage and/or lymphocyte morphology in patients with non-Hodgkin lymphoma and CLL. One PCS study[31] reported clinical significance for data on plasma cell percentage in patients with plasma cell myeloma. Refer to Table 6 for study data by outcome of significance for bone marrow aspirates.

The strongest support was for inclusion of the key element of blast percentage.† The evidence for reporting blast percentage was mainly with regard to diagnoses of ALL,[32] MDS,[24] MPN,[34] and AA.[26] Blast percentage also has relevance in determining response to therapy for acute leukemia, including at days 7 and 21 after induction therapy

* *References 23, 24, 26, 29, 32, 34, 35.*
† *References 23, 24, 26, 29, 32, 34, 35.*

Table 5. Extended

Results Summary	Comparison Favors/Shows Benefit/ Difference for (Outcome)	*P* Value
Peripheral blood WBC < 100 000 and bone marrow blast < 5% on d 21 (low risk) was associated with significantly better EFS and OS in Ph^+ pediatric ALL	EFS: 55% low risk, 18% high risk; OS: 79% low risk, 27% high risk	.002 (EFS) .003 (OS)
Hgb level has additive prognostic value in MDSs for Int-1 and Int-2 categories	Hgb > 10 g/dL is associated with better OS in Int-1 and Int-2 MDS	<.001
In MDS, significantly different survival and evolution to AML was associated with Hgb < 10 g	In MDS, significantly different survival and evolution to AML was associated with Hgb < 10 g, Plt < 100 000, absolute neutrophil count < 0.08	<.001
Plt count < 100 000 at baseline significantly associated with reduced probability of transfusion independence and cytogenetic response in lenalidomide treatment in MDS with 5q31 deletion	Thrombocytopenia < 100 000 at baseline was associated with 39% transfusion independence versus 73% without thrombocytopenia; odds ratio for decreased cytogenetic response with, versus without, thrombocytopenia was 4.78	.001 transfusion independence .02 cytogenetic response
Plt count < 100 000 was significantly associated with IPSS categories, OS, and AML evolution in MDS	Plt > 100 000 was associated with 63% overall y-median survival versus 5% <20 000	χ^2 test 3.6 versus 1.4
Plt counts have prognostic effect in idiopathic myelofibrosis	Plt counts have prognostic effect in idiopathic myelofibrosis	Not given, references quoted
Peripheral blood parameters Plt, MCV, reticulocyte count, and percentage of lymphocytes are significantly different in severe AA versus hypoplastic MDS in adults	Plt count, MCV, reticulocyte counts, and percentage of lymphocytes were significantly different between severe AA and hypoplastic MDS	<.01
In MDS, significantly different survival and evolution to AML was associated with Plt < 100 000	In MDS, significantly different survival and evolution to AML was associated Plt < 100 000,	<.001
Absolute neutrophil count > 1500 was significantly associated with IPSS categories, OS, and AML evolution in MDS	Absolute neutrophil count > 1500 had 62% median OS versus 6% y-median OS	χ^2 test 3.9 versus 0.9
In MDS, significantly different survival and evolution to AML was associated with absolute neutrophil count < 0.8	In MDS, significantly different survival and evolution to AML was associated with absolute neutrophil count < 0.8	<.001
Reticulocyte count is significantly different in severe AA as compared with nonsevere AA and MDS	Mean reticulocyte count severe AA, 13.5; versus nonsevere AA, 35.7; MDS 55.5 $\times 10^9$/L	<.01
RDW is significantly different in severe and nonsevere AA versus hypoplastic MDS	Mean RDW, 16.8% severe AA; 17.4% nonsevere AA; versus 20.4% MDS	<.05

for ALL,[23,29] day 14 after induction therapy for AML,[35] and for prognosis in myelodysplastic neoplasms.[24]

Dysplasia of erythroid, myeloid, and megakaryocytic lineages also received considerable support,[26,30,34,36,37] primarily in the diagnosis of MDS and myelodysplastic/myeloproliferative neoplasms. A prospective study of patients with AML linked dysplasia with high-risk cytogenetics but did not demonstrate independent prognostic value in multivariate analysis.[39] Distribution and morphology of megakaryocytes is of particular relevance in MPN,[34] and morphology of megakaryocytes is relevant in determining response to therapy for chronic myelogenous leukemia.[34] Myeloid to erythroid ratio, as a specific element, received the least attention in the literature reviewed, with its relevance stated specifically only in chronic MPN,[34] although, by expert panel consensus, erythroid enumeration is also relevant to current diagnosis and classification of specific subtypes of AML, such as acute erythroblastic leukemia.

Of the lymphoid neoplasms, only 2 publications met criteria for high-level evidence with statistical differences in outcome. Bone marrow involvement with NHL was associated with a significantly different outcome in follicular lymphoma.[33] In low-grade NHL, the positive-predictive value of bone marrow aspirate was significantly higher than it was in aggressive NHL, when compared with bone marrow biopsy.[38] Because the literature search was restricted to years 2000–2012, earlier high-quality studies addressing bone marrow staging were not represented in this guideline.

Although the supporting publications did not meet the criteria for systematic review, by expert opinion consensus, additional parameters merit consideration because they can be useful for diagnosis and disease monitoring: morphology and enumeration of lymphoid cells in NHL and CLL,[40–43] with cell size[41] and distribution pattern[38,40,41] being frequently cited, relevant morphologic parameters. Enumeration of lymphoid cells was also reported as being relevant to disease monitoring, particularly in CLL.[43] Multiple studies emphasized complementarity of aspirate and core biopsies in lymphoma evaluations,[38,42] although aspirate evaluation is reported as having relatively limited utility in Hodgkin lymphoma.[42] There was high-level evidence to support plasma cell enumeration for diagnosis and monitoring of plasma cell myeloma.[31]

Given the variety of neoplastic and nonneoplastic disorders that are encountered in bone marrow aspirate evaluation, not all of the evidence-based elements are applicable to all reports. Although the literature search produced an evidence-based, minimum data set, incorporation of applicable elements into specific reporting templates depends on the patient populations at different institutions and may be weighted toward different types of cases; for example, transplant centers may see a predominance of follow-up bone marrow evaluations for leukemia and myeloma, whereas pathologists in outpatient settings may see more nonneoplastic disease and primary diagnostic evaluations. Most of the comments received during the open comment period dealt with what elements should or should not be included. In particular, many took issue with the proposed examples "morphology of lymphoid elements and enumeration of lymphoid cells and plasma cells." Following the open

*Inactive guidelines are no longer updated with systematic literature reviews, but the recommendations may still be useful for educational, informational, or historic purposes.

Table 6. Key Elements of Synoptic Reports for Bone Marrow (BM) Aspirate Specimens

Element With Significant Outcome Difference	Relevant Disease or Diagnosis	Studies Reporting Significant Differences, No.	Source, y
Percentage of blasts	ALL, AML, MDS, MPN, AA	7	Basso et al,[29] 2009
			Gandemer et al,[23] 2009
			Jabbour et al,[32] 2006
			Kao et al,[24] 2008
			Lugli et al,[34] 2005
			Rowe et al,[35] 2010
			Wang et al,[26] 2011
Dysplasia	MDS, MDS/MPN	5	Baumann et al,[30] 2012
			Lugli et al,[34] 2005
			Wang et al,[26] 2011
			Liu et al,[36] 2009
			Thiele et al,[37] 2011
Percentage lymphocytes, morphology	NHL, CLL	2	Lombardo et al,[33] 2002
			Musolino et al,[38] 2010
Percentage of plasma cells	Plasma cell myeloma	1	Fernandez de Larrea et al,[31] 2011

Abbreviations: 95% CI, 95% confidence interval; AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BACOP, bleomycin, epidoxorubicin, cyclophosphamide, vincristine, and prednisone; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CR, complete remission; ET, essential thrombocythemia; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; MPN, myeloproliferative syndrome; NHL, non-Hodgkin lymphoma; NPV, negative predictive value; OS, overall survival; PPV, positive predictive value; RFS, relapse-free survival; T-ALL, T-cell lymphoblastic leukemia.

comment period, the expert panel concluded that each institution should have discretion in deciding how to incorporate the key elements of the aspirate evaluation into particular templates to best fit the needs of their patients and their clinicians. Reporting these key elements in synoptic format will provide clinicians with easy access to necessary diagnostic information in a familiar template and will facilitate comparison of data between sequential bone marrow evaluations of an individual patient; however, such templates may vary across institutions.

4. Strong Recommendation for Fibrosis; Recommendation for All Other Parameters.—When reporting bone marrow core biopsy results, laboratories should report clinically or diagnostically pertinent elements in the synoptic section. These key elements may include the evidence-based parameters, such as fibrosis, cellularity, distribution pattern of hematopoietic elements, morphology of lymphoid elements, and enumeration of lymphoid elements and plasma cells; additional elements may be included in the nonsynoptic sections of the report.

The strength of evidence was *convincing* for fibrosis, but *adequate* for all other parameters (that is, the strength of the evidence varied among the different key elements suggested in the recommendation).

This recommendation is evidence-based and supported by 12 studies,‡ comprising 2 NRCTs,[33,47] 4 PCSs,[26,35,45,48] and 6 RCSs,[25,27,34,37,44,46] which reported on fibrosis, cellularity, involvement by lymphoma, or blast percentage. All studies were assessed for risk of bias, and none were found to have methodological flaws that would raise concerns about the studies' findings. Six studies, comprising 1 NRCT,[47] 1 PCS,[45]

‡ *References 25–27, 33–35, 37, 44–48.*

*Inactive guidelines are no longer updated with systematic literature reviews, but the recommendations may still be useful for educational, informational, or historic purposes.

Table 6. Extended

Results Summary	Comparison Favors/Shows Benefit/ Difference for (Outcome)	*P* Value
Residual disease of BM blasts in d 15 childhood ALL is predictive of relapse	BM blasts: <0.1%, <10%, ≥10% measured by flow cytometry was associated with 5-y cumulative relapse in 7.5%, 17.5%, and 47.2%, respectively	<.001
BM blast percentage at d 21 is associated with prognosis	95% CR ≤ 5% blasts; 75% CR > 5% blasts	<.001
Marrow involvement in T-ALL associated with OS; CR defined as ≤ 5% blasts	OS BM^+, 85%; OS BM^-, 37%	.01
Uses IPSS cytogenetic group blast percentage definitions	Significant correlation with blast percentage and cytopenias	<.001
BM blast percentage is morphologic indicator of response in CML	BM blast percentage associated with cytogenetic response	.001
BM blast percentage as response criterion, residual disease postinduction portends worse prognosis, but similar long-term outcome with 1 or 2 cycles to CR	Various, including >10% blasts d-6 CR, 54%; <10% blasts d-16 CR, 84%	None given, reference cited
$CD34^+$ blasts lower in AA than in hypocellular MDS	Severe AA, 0; nonsevere AA, 0.12; MDS, 2.2	<.05
Morphologic criteria can distinguish refractory cytopenia of childhood versus severe AA with high interobserver reliability	Patchy erythropoiesis with defective maturation and micromegakaryocytes were the most significant discriminators (no statistical values provided)	κ = 0.79, indicates substantial interobserver agreement
Decrease of abnormal megakaryocytes correlates with cytogenetic response of CML on imatinib treatment	Reduction of abnormal megakaryocytes to ≤10%, significantly correlates with cytogenetic response	<.001
Dyserythropoiesis is a key finding in MDS in distinction to severe AA	Erythropoietic pathologic hemogenesis in 0% of severe AA versus 95.5% of MDS	None given
Incidence of specific dysplasia for granulocyte and megakaryocyte lineage was significantly different for abnormal karyotype MDS versus normal karyotype MDS or non-MDS cytopenias	Incidence of specific dysplasia for granulocyte and megakaryocyte lineage was significantly different for abnormal karyotype MDS versus normal karyotype MDS or non-MDS cytopenias	<.05
Morphologic BM features distinguish ET versus early primary myelofibrosis	Megakaryocyte morphologic features, increased granulopoiesis and erythropoiesis can distinguish ET versus primary myelofibrosis with high interobserver concordance	Concordance κ = 0.739 (*P*<.001), 95% CI, 0.651–0.827
Response rate and RFS in follicular lymphoma treated with BACOP was significantly different in patients with BM involvement	Response rate and RFS in follicular lymphoma treated with BACOP was significantly worse in patients with BM involvement	Response rate difference, <.001; RFS, <.001
BM aspirate staging correlates with BM biopsy but has a different sensitivity, specificity, NPV, and PPV when compared with BM biopsy	BM aspirate staging significantly correlates with BM biopsy results; BM aspirate PPV is 82% and NPV is 85% in indolent NHL versus 29% PPV and 89% NPV in aggressive NHL	<.001 for correlation of BM aspirate and biopsy
BM plasma cells > 1.5% after autologous transplantation had an increased risk of progression	BM plasma cells > 1.5% after autologous transplantation had an increased risk of progression	.02

and 4 RCSs,[25,27,34,44] were obtained that all reported clinical significance for data on fibrosis outcomes for patients with MPN and MDS. One PCS[26] and 2 RCSs[34,37] were obtained that reported clinical significance for data on cellularity outcomes for patients with MPN, AA, and myeloproliferative disease. Three studies, comprising 1 NRCT,[33] 1 PCS,[48] and 1 RCS,[46] were obtained that reported clinical significance for data on cellularity involvement in lymphoma for patients with Hodgkin lymphoma and NHL. One PCS[35] was obtained that reported clinical significance for data on bone marrow blast percentage in patients with AML. Refer to Table 7 for study data by outcome of significance for bone marrow core biopsies.

The strongest support was regarding the key elements of fibrosis,[25,27,34,44,45,47] which was most applicable to patients with myeloid neoplasms, in particular MPN[25,34,44,45,47] and MDS.[27] The cellularity estimates and identification of involvement was relevant for lymphomas,[33,46,48] in the workup of AA versus hypocellular myelodysplastic processes,[26] and for evaluation of treatment effects or prognosis in MPN.[34,37] Of the lymphoid neoplasms, adverse outcomes were significantly associated with involvement by follicular lymphoma, peripheral T-cell lymphoma, and acute T-cell lymphoblastic leukemia/lymphoma.[33,46,48] Although, in the time period of publications searched for this guideline, no high-level evidence study was identified, determination of bone marrow involvement in Hodgkin lymphoma is standard practice in appropriately selected patients; it is well known that the bone marrow aspirate is insensitive compared with the trephine biopsy (no detection in bone marrow aspirates versus 5.2% positivity in biopsies).[49] Similar to reporting of bone marrow aspirate, enumeration and morphology of lymphoid neoplasms on the biopsy are valuable for diagnostic classification and treatment decisions, but the screened publications did not meet the systematic review criteria for high-level evidence regarding clinical outcomes.

There was substantial agreement during the comment period with this statement. Concerns that were raised, similar to those raised for reporting of the bone marrow aspirate, focused primarily on which key or essential elements should be included or were not required.

*Inactive guidelines are no longer updated with systematic literature reviews, but the recommendations may still be useful for educational, informational, or historic purposes.

Table 7. Key Elements of Synoptic Reports for Bone Marrow (BM) Core Biopsies			
Element With Significant Outcome Difference	**Relevant Disease or Diagnosis**	**Studies Reporting Significant Differences, No.**	**Source, y**
Fibrosis	MPN, MDS	6	Barbui et al,[44] 2012
			Campbell et al,[45] 2009
			Hultdin et al,[47] 2007
			Kvasnicka and Thiele,[25] 2006
			Lugli et al,[34] 2005
			Greenberg et al,[27] 2012
Cellularity	MPN, AA, MPD	3	Wang et al,[26] 2011
			Thiele et al,[37] 2011
			Lugli et al,[34] 2005
Cellularity/involvement by lymphoma	NHL and Hodgkin lymphoma	3	Lombardo et al,[33] 2002
			Gallamini et al,[46] 2004
			Takasaki et al,[48] 2007
Blast %	AML	1	Rowe et al,[35] 2010

Abbreviations: 95% CI, 95% confidence interval; AA, aplastic anemia; AML, acute myeloid leukemia; ATLL, adult T-cell leukemia/lymphoma; BM, bone marrow; CML, chronic myeloid leukemia; ET, essential thrombocythemia; HR, hazard ratio; HYA, hyaluronan acid; IMF, idiopathic myelofibrosis; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; NHL, non-Hodgkin lymphoma; PCV, polycythemia vera; PMF, prefibrotic primary myelofibrosis; RFS, relapse-free survival.

Suggestions as to inclusion of information regarding the presence of nonhematopoietic elements, such as bone trabeculae were most frequent. It is the consensus of the expert panel that this information would be important in a subset of cases but was not pertinent to many bone marrow tests, in particular bone marrow tests performed for diagnosis of hematologic processes. When appropriate, these elements should be included in the nonsynoptic portion of the report. Another issue raised during the open comment was the need for inclusion of a comment on the adequacy of the bone marrow biopsy as part of the synoptic report. The panel agreed on the importance of this element, in particular for staging of lymphoma; however, specimen requirements were determined to be out of the scope of this project and were not addressed at this point. Similarly, the presence of a metastatic, nonhematopoietic tumor on a bone marrow biopsy (or aspirate) is not specifically addressed in this guideline but is of obvious importance to the clinician.

5. Strong Recommendation.—If relevant ancillary testing studies are performed on the primary sample (blood or bone marrow), laboratories should report the results, general methodology, performance site, and interpretation

Table 7. Extended

Results Summary	Comparison Favors/Shows Benefit/ Difference for (Outcome)	*P* Value
Fibrosis at diagnosis in PCV significantly associated with splenomegaly, decreased thrombosis, postpolycythemic myelofibrosis	Palpable splenomegaly, thrombosis 1.1 versus 2.7 per 100 patient-y; postpolycythemic myelofibrosis 2.2 versus 0.8 per 100 patient-y	.01–.03
Elevated reticulin fibrosis at presentation of ET predicted higher rates of arterial thrombosis, major hemorrhage and myelofibrotic transformation	Arterial thrombosis HR 1.8, 95% CI, 1.1 to 2.9; major hemorrhage HR, 2.0; 95% CI, 1.0–3.9; myelofibrotic transformation HR, 5.5; 95% CI, 1.7–18.4	<.001–.05
After 2 y of anagrelide therapy, the reticulin and HYA scores were significantly higher than before treatment ($P = .02$ and $P = .002$, respectively); indicating progression of disease	Reticulin and HYA scores were significantly higher than before treatment	.002
Included ≥grade 2 fibrosis or cases with increase of 1 grade in <12 mo follow-up; survival rates in IMF: prefibrotic and early fibrotic stages of IMF display significantly higher 5- and 10-y relative survival rates than advanced (classical) stages with prominent myelofibrosis (IMF-2/3 or myeloid metaplasia). Myelofibrosis survival rates in polycythemia rubra vera: 10%–20% of patients present with mild to moderate reticulin fibrosis at onset; development of marked collagen myelofibrosis occurred in <20% of patients and displayed strong time-related progression	Patients with ET has better survival than those with prefibrotic and early IMF (IMF0, IMF1)	<.001
Reduction of fibrosis significantly associated with cytogenetic response	Fibrosis ≤grade 2 associated with higher rate of complete or other cytogenetic response	.01
Significantly different survival and evolution to AML were associated ($P < .001$) with marrow fibrosis	Patients with associated BM fibrosis had poorer survival and higher incidence of transformation to AML than those who did not have associated bone marrow fibrosis	<.001
Cellularity of <20%–30% is defining hypoplastic MDS	Hypoplastic MDS requires BM biopsy cellularity <30% age <60 y, <20% age ≥60 y	<.05
Cellularity determination can help, in addition to other morphologic features, to distinguish between ET and early PMF.	Normal or slightly increased cellularity present in ET is significantly different from marked increase in age-matched cellularity in early prefibrotic stage of PMF with high diagnostic concordance of 74%	<.001
Normalization of cellularity was significantly associated with cytogenetic response in CML on imatinib treatment	Age-adjusted normal cellularity was significantly associated with complete or other cytogenetic response	.001
BM involvement by follicular lymphoma is significantly associated with adverse response rate and RFS	BM involvement by follicular lymphoma is significantly associated with adverse response rate and RFS	.001 response rate and RFS
BM involvement by peripheral T-cell lymphoma is associated with poorer outcome (increased relative risk 95% CI, 1.454; $P = .03$) in multivariate analysis and worse overall survival in univariate analysis ($P < .001$)	BM involvement by peripheral T-cell lymphoma is associated with worse outcome after therapy and worse overall survival	.03 <.001
BM involvement is strongly associated with adverse outcome in ATLL (HR, 1.9)	Presence of BM involvement in ATLL is associated with increased risk of death when compared with patients with no marrow involvement	.001
BM blast percentage as response criterion for AML, residual disease postinduction portends worse prognosis, but similar long-term survival if complete remission is achieved with 2 cycles of induction chemotherapy	Significant improvement of complete remission if patients with residual leukemia after first induction received second induction chemotherapy	<.001

site or have the data readily available. If the results are not available, pending status should be stated explicitly.

The strength of evidence was *convincing* to support this recommendation.

This recommendation is evidence-based and supported by 20 studies,[50–69] 19 of which met the inclusion criteria for the systematic review.[50–64,66–69] These studies comprise one quasi-randomized control trial,[54] 3 NRCTs,[56,67,69] 13 PCSs,[§] and 2 RCSs.[63,66] All studies were assessed for risk of bias, and none were found to have methodological flaws that would raise concerns about the studies' findings. Eight studies, comprising 1 QRCT[54] and 7 PCSs[50,51,53,58–60,68] were obtained that all reported clinical significance for data on flow cytometry in patients with AML, ALL, MDS, lymphoma, and CLL. Three PCSs[52,55,62] were obtained that all reported clinical significance for data on cytogenetics in patients with AML, MDS, and ALL. One of these PCSs[62] also reported clinical significance for FISH in a cohort of unspecified patients. One NRCT[69] reported clinical significance for immunohistochemistry in patients with CLL. Two studies,[64,65] comprising 1 PCS[64] included in the systematic review, reported clinical significance for bone marrow–isolated tumor-cell detection in a cohort of breast cancer patients. Six studies, comprising 2 NRCTs,[56,67] 2 PCSs,[57,61] and 2 RCSs,[63,66] reported clinical significance for data on molecular analysis in patients with AML, CLL, chronic myeloid leukemia, and lymphoma. Refer

[§] *References 50–53, 55, 57–62, 64, 68.*

*Inactive guidelines are no longer updated with systematic literature reviews, but the recommendations may still be useful for educational, informational, or historic purposes.

to Supplemental Table 16 in the SDC for the table summarizing the studies' findings.

Ancillary tests are, by definition, performed to supplement morphologic evaluation. Those performed on bone marrow samples typically include flow cytometry, immunohistochemistry, molecular studies, FISH, and conventional cytogenetics. Other ancillary tests used more sparingly include immunofluorescence, array comparative genomic hybridization, and mass spectrometry–based proteomic analysis, among others. Live cells are required for flow cytometry, conventional cytogenetics, and metaphase FISH, whereas air-dried or formalin-fixed, paraffin-embedded materials can be used for most other ancillary tests. In certain situations, some of these tests might be performed on a concurrent peripheral blood sample.

Inclusion of ancillary testing results is supported by strong evidence. This is not surprising because morphology currently comprises only one aspect of bone marrow evaluation, which increasingly relies on ancillary techniques for accurate diagnosis and is required in all current classification systems (such as WHO) for many hematolymphoid diseases. However, whereas incorporation of ancillary test results into the diagnostic bone marrow report is supported by high-level evidence, the inclusion of information regarding methodology and the laboratory or the site where testing and interpretation is performed is based on expert consensus. The panel contends that inclusion of the latter information in the bone marrow report provides context for the diagnosis, serves as a reference point for future follow-up, and creates transparency for testing location. Adequate evidence for including ancillary testing results exists for flow cytometry,[||] cytogenetics,[52,55,62] FISH,[62] immunohistochemistry,[69] and molecular testing.[56,57,61,63,66,67] The association with clinical outcome was particularly strong for measurement of minimal residual disease by flow cytometry in lymphoma and AML,[50,51,53,58] for cytogenetic risk groups in AML,[52,55,62] and for *BCR-ABL* to *ABL* ratios by real-time polymerase chain reaction in chronic myeloid leukemia.[56,57,61,63,66] Supporting evidence for FISH studies demonstrated the high concordance of FISH and cytogenetic analysis in AML.[62] In some studies, detection of isolated metastatic tumor cells in the bone marrow of patients with breast cancer was significantly associated with adverse outcomes.[64,65] Although metastatic disease was not specifically addressed in the literature search and scope, these studies emerged based on the key questions and are retained as an example of ancillary studies that show statistical significance but have not found widespread adoption.

During the open comment period, the need to include relevant ancillary studies in the bone marrow synoptic was broadly supported. However, concerns were raised regarding the report timing of such studies because the results may not be available at the time of diagnosis. Other remarks indicated that some ancillary testing may not be essential for diagnosis and, thus, is not essential for report accuracy. Finally, a few commented on the difficulty of obtaining details about ancillary test methodology from external sources. This feedback informed the final wording of this statement, which provides additional flexibility for pathologists to address some of these challenges that may be specific to their practices or clinical situations.

6. Strong Recommendation for Inclusion of Data Groups for Diagnosis, Supporting Studies, and Ancillary Data; Recommendation for the Layout of the Data Groups.—Laboratories should include in the synoptic section of the report data groups for diagnosis, supporting studies, and ancillary data that are critical for diagnosis. Key morphologic descriptors should be included and may be in the diagnosis line if they are critical or a component of the disease classification. The diagnosis (or diagnosis group) should head the synoptic section when possible. A narrative, interpretative comment should immediately follow the synoptic section if required.

The strength of evidence was *convincing* to support this recommendation.

This recommendation is evidence-based and supported by 42 studies,[#] 40 of which met the inclusion criteria for the systematic review,[**] comprising one systematic review,[70] 1 quasi-randomized control trial,[54] 6 NRCTs,[32,33,47,56,67,69] 19 PCSs,[††] and 13 RCSs.[‡‡] Six studies,[22–27] comprising 1 NRCT,[22] 1 PCS,[26] and 4 RCSs,[23–25,27] were obtained that reported clinical significance for data on peripheral blood parameters in patients with all hematopoietic neoplasms. Thirteen studies,[23,24,26,29–38] comprising 2 NRCTs,[32,33] 4 PCSs,[26,29,31,35] and 7 RCSs,[23,24,30,34,36–38] were obtained that reported clinical significance for data on bone marrow aspirate in patients with all hematopoietic neoplasms. Twelve studies,[§§] comprising 2 NRCTs,[33,47] 4 PCSs,[26,35,45,48] and 6 RCSs,[25,27,34,37,44,46] were obtained that reported clinical significance for data on bone marrow biopsies in patients with all hematopoietic neoplasms. Twenty studies,[50–69] 19 of which met the inclusion criteria for the systematic review,[50–64,66–69] comprising 1 quasi-randomized control trial,[54] 3 NRCTs,[56,67,69] 13 PCSs,[||||] and 2 RCSs,[63,66] were obtained that reported clinical significance for data on ancillary testing in patients with all hematopoietic neoplasms. All studies were assessed for risk of bias, and none were found to have methodological flaws that would raise concerns about the studies' findings.

Synoptic reporting ensures the pathologist that she or he is reporting all pertinent diagnostic information in a standardized and consistent manner. The variability in findings in hematopathologic diseases and the complexity of information assimilated and integrated into hematopathology results, impedes the creation of a single synoptic template applicable to all disease processes. Similarly, disease-specific checklists are impractical considering the many diagnostic entities, such as those in the WHO classification system. However, systematization of reports and a consistent grouping of data across disease entities in a synoptic format is an achievable goal. The results of our literature search and expert opinion support inclusion of the following data groups of studies supporting the diagnosis: peripheral blood findings, bone marrow aspirate findings, bone marrow biopsy findings, and ancillary testing on the primary specimen. These data groups are further detailed in statement 2, peripheral blood[22–27]; statement 3, bone marrow aspirate[23,24,26,29–38]; statement 4, bone marrow core biopsy[##]; and statement 5, ancillary testing studies.[50–69] Specific components and ancillary supporting studies, such

[||] *References 50, 51, 53, 54, 58–60, 68.*

[#] *References 22–27, 29–38, 44–48, 50–70.*

[**] *References 23–27, 29–38, 44–48, 50–64, 66–70.*

[††] *References 26, 29, 31, 35, 45, 48, 50–53, 55, 57–62, 64, 68.*

[‡‡] *References 23–25, 27, 30, 34, 36–38, 44, 46, 63, 66.*

[§§] *References 25–27, 33–35, 37, 44–48.*

[||||] *References 50–53, 55, 57–62, 64, 68.*

[##] *References 25–27, 33–35, 37, 44–48.*

as special stains, within these data groups include the evidence-based elements, as outlined in the respective statements. Composition of the data groups may vary in different disease templates; however, consistency of overall layout and sequence of data groups would enhance reader comprehension.

The panel concluded that the diagnosis should head the synoptic section of the report. This is supported by adequate level evidence provided by a review by Valenstein,[70] with a recommendation for diagnostic headlines, and agreed upon by the expert panel. Additional useful principles outlined in this reference include maintenance of layout, optimization of information density, and reduction of extraneous information; these principles are derived from a thorough review of pertinent literature, which represents the best-available evidence.

The recommendation for inclusion of a narrative, interpretative comment immediately after the synoptic section is based on the expert opinion of the panel. In particular, if ancillary data, such as cytogenetics, molecular diagnostics, or critical radiographic and laboratory results, are not yet available at the time of sign-out of a morphology report, a narrative is often necessary to communicate differential diagnostic considerations and the effect of the pending tests on the diagnosis. Placement of the narrative comment after the synoptic portion should ensure that this important component does not get buried in other report elements. However, the choice of placement of the narrative comment should be consistent with other reports issued by individual institutions and other practices so clinicians can expect to find the comments in similar portions of all reports.

7. Strong Recommendation.—Laboratories should consider the integrity of electronic data transmission for formatting and data presentation of synoptic reports.

The strength of evidence was *convincing* to support this recommendation.

This recommendation is evidence-based and supported by a single, systematic review,[70] assessed to have a low risk of bias.

Because most pathology reports are distributed electronically, fidelity of content and formatting becomes very important. Correct data transmission is an issue important enough to comprise specific CAP accreditation requirements for both report review and report elements; pathologists must ensure that data are received and presented in acceptable formats for the end user. This requires interface validation and verification that the final data display recapitulates the content and intent of the pathologist's original report.

There was convincing evidence to support considerations of formatting and data presentation of synoptic reports. A comprehensive review article[70] addressed the limited capabilities of the most-common health level 7 interface, which significantly restricts formatting of pathology reports. In particular, tables, font variations, images, bold face, and bullets, among others, can enhance presentation but are problematic when data are transmitted across interfaces. This statement is further supported by the CAP Diagnostic Intelligence and Health Information Technology Committee's interoperability white paper[72] and the CAP Laboratory Accreditation (LAP) Checklists,[73] which underwent data extraction, but were not included in the evidence-based references because they do not meet inclusion criteria. Although the synoptic reporting section should not include tables, bullets, and other formatting not conducive to electronic data integrity, these items can be used in a more comprehensive summary report that has validated data transmission, for example, portable document format (.pdf). In the open comment period, it became evident that specific recommendations regarding font and/or white space could not be rendered because of the wide diversity of information technology systems used in pathology, hospitals, and doctor's offices.

Based on the available evidence, the realities of electronic medical records, and expert consensus, the panel recommends that evaluation and validation of data transmission in the particular practice environment and electronic media is required.

8. No Recommendation.—No recommendation was made regarding the inclusion of coding terms in a synoptic report because coding terms are distinct from scientific terms and vary considerably among health authorities, payers, and different countries.

The strength of evidence was *insufficient* to support a recommendation; therefore, no recommendation is made.

In the United States and other countries, data extraction for payers and registries is based on coding schemes, such as the ICD9/10 (International Statistical Classification of Diseases and Related Health Problems), and SNOMED-CT (Systematized Nomenclature of Medicine—Clinical Terms). The committee considered whether harmonization with coding terminology was beneficial to diagnosis and data collection. There were no publications directly addressing coding terms in pathology reports. However, 3 of the retrieved references examined data extraction for cancer registries. Use of predefined forms led to a 28.4% (95% confidence interval [CI], 15.7–41.2) increase in complete reporting of a minimum data set required for cancer registration, and a 24.5% (95% CI, 11.0–38.0) increase in complete reporting of minimum data required for patient management.[3] Another study examining electronic transfer of required data elements uncovered incompleteness of the cancer protocols as a barrier to complete data transfer without statistical evaluation.[75] Similarly, improved reporting of key parameters to the national cancer registry was improved if the correct (national) template was used.[5] Therefore, the construction of synoptic templates should rely on scientifically proven data elements that then inform the data for coding and cancer registries. There was no significant disagreement in the open comment period.

9. Recommendation.—Laboratories should include clinical and laboratory data required for a definitive diagnosis in the synoptic section, along with its source(s), if applicable.

The strength of evidence was *convincing* to support this recommendation.

This recommendation is evidence-based and supported by 11 studies,[22–28,33,46,55,76] 10 of which met the inclusion criteria for the systematic review.[22–27,33,46,55,76] These studies comprise 2 NRCTs,[33,76] 3 PCSs,[22,26,55] and 5 RCSs.[23–25,27,46] All studies were assessed for risk of bias, and none were found to have methodological flaws that would raise concern about the studies' findings. Three RCSs[23,25,46] reported clinical significance for data on age in patients with ALL, myeloproliferative disorders essential thrombocythemia, polycythemia vera, idiopathic myelofibrosis, and peripheral T-cell lymphoma. Two studies, 1 RCS and 1 NRCT,[33,46] reported clinical significance for data on performance status in NHL and peripheral T-cell lymphoma. Four studies,[28,46,55,76] 3 of which were included in the systematic

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review,[46,55,76] comprising an NRCT,[76] a PCS,[55] and an RCS,[46] reported clinical significance for data on lactate dehydrogenase for patients with AML, peripheral T-cell lymphoma, primary bone marrow NHL, NHL, and hypoplastic MDS. Two studies, comprising an NRCT[33] and an RCS,[46] reported clinical significance for data on staging in patients with NHL and peripheral T-cell lymphoma. Two studies, comprising an NRCT[33] and an RCS,[46] reported clinical significance for data on prognostic scoring systems in patients with NHL and peripheral T-cell lymphoma. Six studies[22–27] comprising 2 PCSs,[22,26] and 4 RCSs,[23–25,27] reported clinical significance for data on peripheral blood parameters in patients with Ph^+ ALL, polycythemia vera, myelodysplasia, AA, myeloproliferative disease, and adult T-cell leukemia/lymphoma. Refer to Supplemental Table 17 in the SDC for table summarizing studies' findings.

When submitting a bone marrow specimen for interpretation, the referring institution should submit pertinent laboratory and clinical information for complete diagnostic evaluation. Initially, the clinician should provide as much detailed history and radiographic and physical findings as are available at the time of specimen submission. Specific data elements that are supported by high-level evidence include age,[23,25,46] performance status,[28,46] lactate dehydrogenase,[28,46,55,76] and staging and prognostic scoring systems.[33,46] In outpatient settings, in particular, the clinician or referring institution should submit peripheral blood parameters that may not be available to the pathologist receiving the bone marrow specimen, including hemoglobin level,[24,26,27] absolute neutrophil count,[24,27] and platelet count[22,24,25,27] (see also recommendation statement 2).

In the open comment period, there was general agreement with the necessity of including clinical and laboratory data but diverging opinions on whose responsibility it was to obtain and communicate those data and whether it was the duty of the pathologist to extract the data from the electronic medical record, if available. These responsibilities for the clinician and the pathologist are in a grey zone and are highly dependent on practice settings. In addition, this information is often not available for a first-time diagnosis and will only be generated after a diagnosis is rendered. Nevertheless, there is no doubt that communication and a collaborative effort between clinician and pathologist will improve the quality and specificity of the final diagnosis contained within the synoptic bone marrow report. In the opinion of the expert panel, pathologists and clinicians should define responsibilities as well as possible in their practice environment so that critical clinical and laboratory data are incorporated in the bone marrow report. It is equally important that clinicians recognize their responsibility in transmitting critical information to the pathologist to provide the appropriate context for bone marrow evaluation and diagnosis.

CONCLUSIONS

This evidence-based guideline has been developed during a 3-year period that has seen a dramatic increase in genomic information on hematologic neoplasms gained through whole genome sequencing and other molecular technologies. Many of the genomic studies were published after the search period for the guideline was closed or did not meet stringent review criteria and are, therefore, not represented in the final list of studies informing this guideline. On the other hand, some standard-of-care clinical practices, such as lymphoma staging or the link of cytogenetic studies to patient outcome in leukemias and myelodysplasias, were established before the search period began in 2002 and are, therefore, underrepresented. Nevertheless, inclusion of additional studies would not substantially change the list of data elements that are presented in this guideline. The genomic revolution advances our understanding and has already enabled new therapeutic interventions for hematopoietic diseases, many of which remain under active investigation in clinical trials or have just been approved by the US Food and Drug Administration within the past 1 to 2 years. The relevant ancillary, molecular testing can be incorporated in the data element of molecular tests as it applies to each institution and as it reaches maturity as standard clinical care. However, other more-traditional methods of diagnosis, prognostication, and prediction of response to therapy remain relevant for patient care and are not replaced by genomic analysis. In an environment of the increasing complexity of the diagnostic armamentarium, it becomes ever more important to work up and report bone marrow examinations in a methodical, consistent manner that clearly communicates critical information to the clinicians, to other members of the health care team, and increasingly, to patients.

This guideline advocates the use of synoptic reports for bone marrow examinations and has identified data elements that are directly relevant to patient outcomes and to reliable and complete reporting. As mentioned in statement 6, a single template for all bone marrow reporting would not fulfill the requirement for succinct data presentation that is free of clutter and irrelevant information. It is, therefore, up to individual institutions and practice environments to develop or adopt synoptic templates with the appropriate selection of evidence-based data elements outlined in statements 2 to 5 and 9. This guideline's relationship with the CAP Cancer Protocols will be discussed in the companion publications (eg, the "Frequently Asked Questions" document that the Center provides upon release of the guideline), possible journal correspondence, and in the next update of the guideline. A practical approach could be to initially determine the most commonly encountered disease categories and/or and diagnostic scenarios that cover 80% of the reports. Data elements that have not been identified in the evidence-based search but are important tools for the pathologist to arrive at a diagnosis can be reported in the nonsynoptic portion of the report; this can be standardized as well, such as bone marrow differential counts, immunohistochemistry antibodies used, and special stains performed. The most difficult recommendations to implement are statement 5, regarding ancillary testing on the primary specimen, and statement 9, regarding clinical data and test results other than the primary specimen. Because both clinical and ancillary data are often unavailable at all or within the period expected for a timely bone marrow report, it will require additional effort to implement systems to follow up on pending results, to communicate with clinicians, and to retrieve data from electronic medical records. Although this can be a daunting task, there is no doubt that it represents best practice and improves the accuracy of bone marrow diagnostics. Because it is increasingly difficult for clinicians to put together and understand correctly the complexities of all the data generated in the bone marrow diagnostic workup, it represents a great opportunity for pathologists to be

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valuable members of the diagnostic team and to strengthen collaboration with their clinician colleagues. It is our hope that, with experience and more widely practiced adoption of synoptic principles of bone marrow reports, additional guidance will emerge for future revisions of this practice guideline.

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APPENDIX
Conflicts of Interest Table; Disclosed Interests and Activities August 2011–June 2015[a]

Name	Interest/Activity Type	Entity
Charles L. Abbott, MD	Board or advisory board	NeoGenomics Medical Scientific Advisory Board
	Leadership in other associations	Massachusetts Society of Pathologists
Monica E. de Baca, MD	Consultancies	Millipore/Amnis
	Board or advisory board	Clinical Laboratory Improvement Advisory Committee
		DoveMed
Sherrie L. Perkins, MD, PhD	Royalties	American Society for Clinical Pathology
	Leadership in other associations	Society for Hematopathology
		American Society for Clinical Pathology
		Children's Oncology Group
	Lecture fees paid by entity (honoraria)	College of American Pathologists
	Grants	St. Baldrick's Foundation
		Children's Oncology Group
	Elected or appointed positions in other national/ international medical organizations	Children's Oncology Group
	Institutional financial interests	ARUP Laboratories
Kaaren Kemp Reichard, MD	Lecture fees paid by entity (honoraria)	College of American Pathologists
	Royalties	American Society for Clinical Pathology
		Amirsys Publishing Company
Cordelia Sever, MD	Elected or appointed positions in other national/ international medical organizations	Greater Albuquerque Medical Association
	Leadership in other associations	TriCore Reference Laboratories
	Grants	HORIBA Medical
Ann Taylor, MD	Ownership or beneficial ownership of stock	Utah Pathology Services, Inc
Howard R. Terebelo, DO	Board or advisory board	Celgene
	Lecture fees paid by entity (honoraria)	Celgene
		Amgen
		Millennium
		Pharmacyclics
	Ownership or beneficial ownership of stock	Pharmacyclics
R. Bryan Rumble, MSc	Consultancy	American Society for Clinical Pathology
		Association for Molecular Pathology
		American Society of Clinical Oncology
		American Society of Hematology
	Vendor to College of American Pathologists	College of American Pathologists
Nicole E. Thomas, MPH, CT(ASCP)^{cm}	Grants	Centers for Disease Control and Prevention

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*Inactive guidelines are no longer updated with systematic literature reviews, but the recommendations may still be useful for educational, informational, or historic purposes.