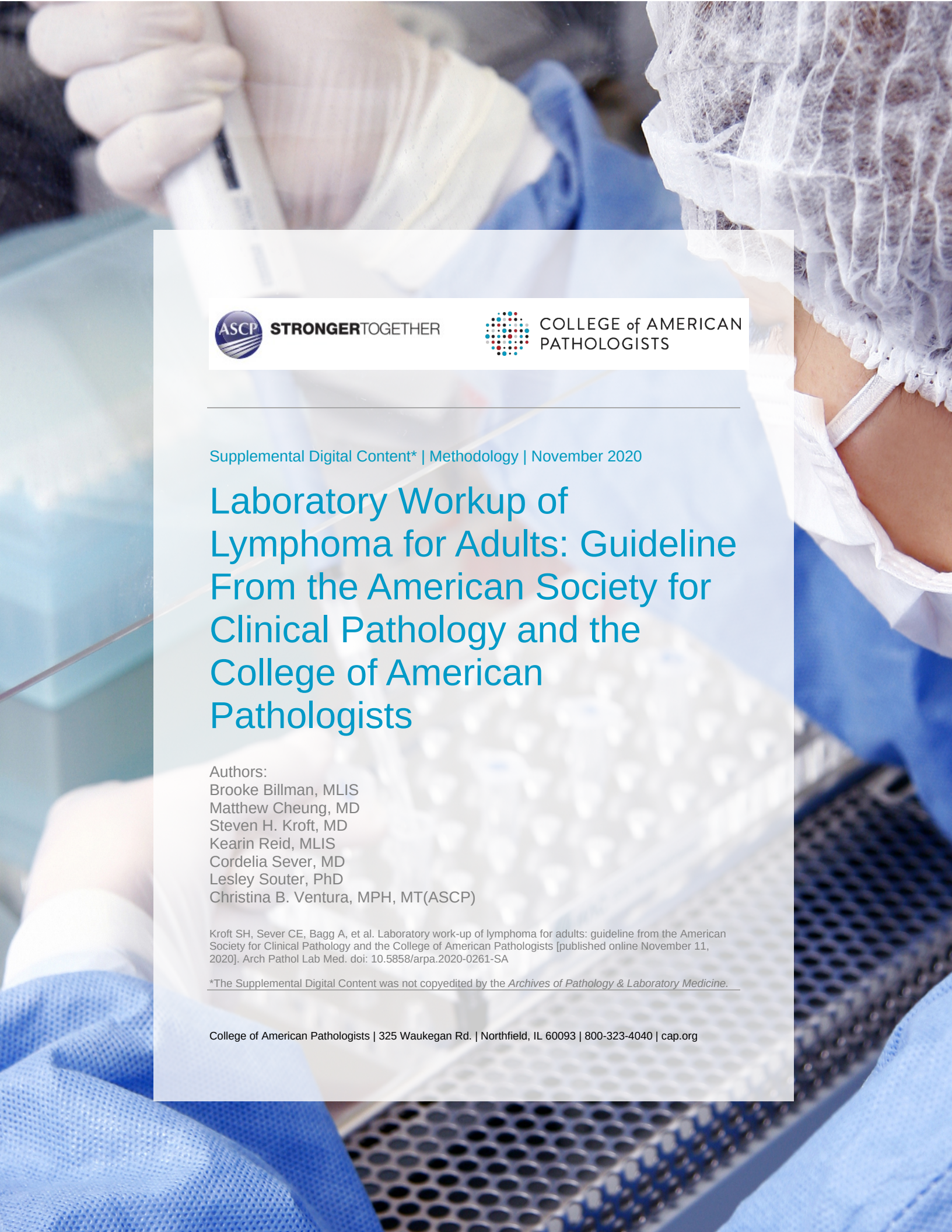

Supplemental Digital Content* | Methodology | November 2020

Laboratory Workup of Lymphoma for Adults: Guideline From the American Society for Clinical Pathology and the College of American Pathologists

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SUPPLEMENTAL DIGITAL CONTENT

GUIDELINE DEVELOPMENT METHODS

Panel Composition

The American Society for Clinical Pathology (ASCP), the College of American Pathologists (CAP), and the American Society for Hematology (ASH) convened an expert panel (EP) consisting of members with experience and expertise in lymphoma diagnosis with a goal to develop evidence-based recommendations for the preanalytic phase of testing with a focus on specimen requirements. A secondary goal was to provide evidence-based guidance on which ancillary testing and clinical parameters ensure a level of diagnostic certainty to provide actionable results. The ASCP, CAP, and ASH approved the appointment of the project co-chairs and panel members. The role of the EP members was to identify key questions, perform a systematic review of the literature search results, review the evidence base, draft recommendations, and author the manuscript.

To achieve a multi-disciplinary approach to the guideline development, the EP members included hematopathologists from various settings, including academic, community, and reference laboratory practices. The EP also included clinical hematology and oncology specialists to ensure incorporation of clinical perspectives in the evaluation of the evidence related to the key questions. Patient representatives participated to ensure that the EP did not lose sight of the desires and values of that supremely important set of stakeholders in the development of its recommendations. A methodologist experienced in systematic reviews and guideline development consulted with the EP throughout the project.

An advisory panel (AP) of pathologists, hematologists, interventional radiologist, otolaryngologist, and patient representatives was also formed. The role of the AP members was to provide feedback on the key questions for the literature search, vet the draft guideline statements prior to the public comment period, and to review and provide feedback for the manuscript and supplemental digital content. They did not vote on the recommendations.

During its deliberations, the EP came to recognize that a key set of stakeholders—cytopathologists—had inadvertently been underrepresented. Input from this group was recognized as vital, particularly with respect to the recommendations related to fine needle aspiration and cytologic evaluation of body fluids. Therefore, additional cytopathologist representation was added to the AP.

Disclosure of Interest (DOI) Policy

Prior to acceptance on the expert or advisory panel, potential members completed the joint ASCP-CAP-ASH disclosure of interest (DOI) process, whose policy and form (February 2017) require disclosure of material financial interest in, or potential for benefit of significant value from, the guideline's development or its recommendations 24 months prior to appointment through the time of publication. The potential members completed the DOI form, listing any relationship that could be interpreted as constituting an actual, potential, or apparent conflict. The ASCP, CAP, and ASH agreed upon disclosure criteria was used. The joint guideline DOI policy reflects a majority of the EP members (51%) free of conflicts. Such conflicts may be allowed in a minority of EP members (49%). The majority of the EP (10 of 12 members) were assessed as having no relevant conflicts of interest. The co-chairs did not ask any of the EP members to recuse themselves during the guideline development as none of the recommendation statement discussions were directly associated industry.

Everyone was required to disclose conflicts prior to beginning and continuously throughout the project's timeline. EP members' and staff disclosures who participated in the guideline development are listed in the manuscript appendix. ASCP, CAP, and ASH 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.

Expert Panel Responsibilities

The EP met 6 times through teleconference webinars from May 17, 2017 through November 17, 2018. Additional work was completed via electronic mail. The panel met in person on June 17, 2017 to finalize the scope and key question and on April 21–22, 2018 to draft recommendations.

All EP members participated in the systematic evidence review (SER). Each level of the SER (title-abstract screening, full-text review, and data extraction) was performed in duplicate by two members of the EP or one member of the EP and a methodologist. All EP members and a methodologist performed adjudication of the conflicts.

Project Scope

The EP approved the following scope to develop evidence-based recommendations for the preanalytic phase of testing with a focus on specimen requirements and to provide evidence-based guidance on which ancillary testing and clinical parameters ensure a level of diagnostic certainty to provide actionable results.

The EP approved the following key questions for the SER:

1. To what degree do specimen types allow for accurate primary diagnosis of indolent, non-Hodgkin lymphoma (NHL), aggressive NHL, and Hodgkin lymphoma (HL)? (Hereafter all three are referred to as lymphoma).
2. For each specimen type, what are the optimum and minimum requirements for accurate primary diagnosis or exclusion of lymphoma?
3. What are the appropriate analytical triage processes by which fresh tissue can be distributed for lymphoma?
4. What are the diagnostic test characteristics of the available ancillary assays and how does additional testing of the primary specimen influence the diagnostic accuracy to enable actionable therapy for lymphoma?

In addition, the EP approved the following key questions for discussion which will not require a systematic evidence review:

1. Under what circumstances does second review by an expert in hematopathology improve the accuracy of diagnosis?
2. To what extent do pathologists use clinical characteristics and radiographic data on the formation of a pre-test probability and what is the role of this information in determining the diagnosis?
3. To achieve efficient patient management, what elements related to specimen handling should be included in the pathology report, and if a biopsy specimen is deemed suboptimal for diagnosis, what elements should be included in the report to explain why the specimen is suboptimal?

Systematic Evidence Review (SER)

The objective of the SER was to identify articles that provided data to inform the recommended testing for the workup of lymphoma. If of sufficient quality, findings from this review would provide an evidence-base to support the recommendations of the guideline. The scope of the SER and the key questions (KQs) with the PICO elements (Population, Intervention, Comparator, Outcome(s)) were established by the EP in consultation with the methodologist prior to beginning the literature search.

Outcomes Ranking and Selection

According to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, it is important for clinical guideline panels to review a comprehensive list of outcomes.[1] The EP was polled to collect information on which outcomes should be included in the PICO. These outcomes included, but were not limited to, accuracy in diagnosis (specificity, sensitivity, positive and negative predictive values), change in patient management, cost, optimal and adequacy of specimen selection, patient preference, quality of life, rates of adverse reactions, survival rates, test/assay utility, and timely communication to the clinicians.

In consideration of the limited scope and resources, the EP ranked the outcomes used in the PICO. Using the GRADE approach[1] of considering the relative importance of outcomes, the EP was polled to rate each initially identified outcome in terms of importance for decision making. The EP voted on a scale of 1 – 9: outcomes rated 1-3 were defines as “of limited importance”; outcomes rated 4-6 as “important, but not critical”; and outcomes rated 7-9 were “critical for decision making”. The EP finalized the outcomes after a discussion during the first in-person meeting.

Outcomes of Limited Importance:
These outcomes were not used for decision making.

1. Treatment response rates
2. Timely communication to the clinician
3. Trial candidacy

Important Outcomes:

1. Patient quality of life
2. Treatment complication or adverse event rates
3. Tissue collection complications (need for rebiopsy, artifacts, crush, and cautery rates)
4. Tissue archiving

Critical Outcomes

1. Accuracy of diagnosis including appropriate treatment, diagnostic change, rate of misdiagnosis/misclassification, rate of World Health Organization (WHO) classification, change of treatment, time to appropriate treatment, concordance rates
2. Diagnostic test characteristics (sensitivity, specificity, positive and negative predictive values)
3. Survival rates
4. Heterogeneity within site and within patient
5. Adequacy and viability of tissue for analysis

Search and Selection

An initial systematic literature search for relevant evidence in Ovid MEDLINE and Elsevier Embase was completed on July 28, 2017, using controlled vocabulary and keyword terms for the concepts of “lymphoma” and “specimen procurement.” Limits were set for human studies (using the Cochrane search filter) published in English between the dates of January 1, 2002 through July 28, 2017 for Key Question 1 and between January 1, 2007 and July 28, 2017 for Key Questions 2, 3 and 4. Although the EP believed a 10 year date range limit would be sufficient to inform Key Questions 2–4, it was felt that landmark papers needed to inform Key Question 1 would be missed and therefore the search limit was expanded to cover 15 years. Limits were also set to exclude the following publication types: case reports, commentaries, editorials, and letters. Conference abstract records were excluded in the Embase searches. Database searches were supplemented with a search for unpublished (grey) literature, including a review of clinical trials via ClinicalTrials.gov and a search for existing relevant guidelines, protocols, or standards on guideline repository websites (eg, Turning Research into Practice [Trip], Cochrane Library, National Guideline Clearinghouse, Guidelines International Network). Guidelines were included if they were published in English since January 1, 2012. After deduplication, 4929 unique citations were identified during the initial literature search process.

During the recommendation drafting process, EP members identified studies evaluating fluid specimens that were missed by the original systematic literature search. A targeted systematic review search was completed on May 15, 2018 in Ovid MEDINE and Elsevier Embase to ensure that all fluid specimen studies were included in the evidence base. This search included controlled vocabulary and keywords for the concepts ‘lymphoma’ and ‘fluid samples’ but removed concepts included in the original search that were resulting in the loss of these studies. Limits were set for human studies published in English from January 1, 2007 through May 15, 2018, Commentaries, editorials, letters, and case reports were excluded. An additional 1287 unique citations were identified by this targeted search process.

Systematic review searches (including targeted searches) were repeated on September 15, 2018 to identify new evidence published since the initial searches were run. In addition, EP members were surveyed for any relevant new data that may affect the recommendations on October 11, 2019. 567 unique citations were identified by the literature refresh searches. In total, 6783 unique citations were identified across all literature searches.

Selection at all levels was also based on the predetermined inclusion/exclusion criteria. The PRISMA diagram outlining the outcome of the systematic literature review is included as Supplemental Figure 1. Detailed search strategies are included as Supplemental Figure 2.

Included:

- Study population must consist of patients with clinical features raising consideration for primary indolent or aggressive, non-Hodgkin lymphoma, or Hodgkin lymphoma.
- Studies must evaluate either:
    - The use of large or small volume incisional or excisional biopsies, bone marrow biopsy, or body fluid samples, for accurate diagnosis of lymphoma;
    - Optimum or minimum lymphoma biopsy specimen collection and handling requirements;
    - Analytical triage processes for fresh tissue;
    - The diagnostic accuracy or diagnostic specificity of additional testing when using primary specimens.
- Studies must include one of the following as primary outcomes:
    - Accuracy of diagnosis, including rate of diagnostic change, rate of misdiagnosis/misclassification, rate of WHO classification, change in treatment plan, repeat procedures/biopsies, appropriate treatment, time to appropriate treatment;
    - Diagnostic test characteristics, including diagnostic sensitivity, specificity, positive predictive value, and negative predictive value;
    - Patient survival outcomes, complication rates or adverse events;
    - Concordance between collection or handling intervention and the standard of care;
    - Adequacy of tissue for analysis or diagnosis;
    - Rate of tissue artifact introduction, including crush and cautery damage;
    - Heterogeneity or tumor percentage within collected specimen;
    - Use of positron emission tomography/computed tomography (PET/CT) to identify appropriate biopsy site;
    - Appropriate utilization of tissue or testing.
- Studies must be peer-reviewed.

Excluded:

- Letters
- Commentaries
- Editorials
- Narrative reviews
- Case reports
- Studies in animal models
- Studies conducted in cell lines
- Consensus documents
- Articles not in the English language
- Meeting abstracts
- Less than 30 patients per study arm

Due to a diagnosis pathway requiring bone marrow analysis, studies evaluating the diagnostic work-up of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and hairy cell leukemia were excluded.

Data Extraction & Management

The data elements from an included article/document were extracted by one reviewer into standard data formats and tables developed using the systematic review database software, DistillerSR (Evidence Partners Inc., Ottawa, Canada); a second reviewer confirmed accuracy and completeness. Any discrepancies in data extraction were resolved by discussion between the co-chairs and the methodologist. A bibliographic database was established in EndNote (Thomson Reuters, Carlsbad, CA) to track all literature identified and reviewed during the study.

Quality Assessment Methods

An assessment of the quality of the evidence was performed for all retained studies following application of the inclusion and exclusion criteria. Using this method, studies deemed be of low quality would not be excluded from the systematic review, but would be retained, and their methodological strengths and weaknesses discussed where relevant. To define an overall study quality rating for each included study, validated study-type specific tools were used to assess the risk of bias, plus additional important quality features were extracted. Specific details for each study type are outlined below.

Systematic Reviews (SRs) and Meta-analyses:

- The following questions were assessed as per the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) 8[2] tool using Yes or No:
  1. Was an 'a priori' design provided?
  2. Was there duplicate study selection and data extraction?
  3. Was a comprehensive literature search performed?
  4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
  5. Was a list of studies (included and excluded) provided?
  6. Were the characteristics of the included studies provided?
  7. Was the scientific quality of the included studies assessed and documented?
  8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
  9. Were the methods used to combine the findings of studies appropriate?
  10. Was the likelihood of publication bias assessed?
  11. Was the conflict of interest (COI) included?
- Additional assessed items included and were assessed as Yes, No, or Unclear:
  1. Reporting of funding sources.

Randomized Control Trials (RCTs)

- The following domains were assessed using the Cochrane Risk of Bias tool[3] using low risk, unclear risk, and high risk:
  1. Random sequence generation (selection bias)
  2. Allocation concealment (selection bias)
  3. Blinding of participants and personnel (performance bias)
  4. Blinding of outcome assessment (detection bias – patient-reported outcomes)
  5. Incomplete outcome data (attrition bias)
  6. Selective outcome reporting (reporting bias)
- Additional assessed items included and were assessed as Yes, No, Unclear:
  1. Validated and reliable measures
  2. Adequately powered statistical analysis
  3. Industry funding

Prospective cohort studies (PCS), retrospective cohort studies (RCS), and case-control studies (CCS)

- The following domains were assessed using the Risk of Bias in Non-Randomized Studies – of Intervention (ROBINS-I)[4] tool using low risk, moderate risk, serious risk, critical risk, or unclear:
  1. Confounding
  2. Patient selection (selection bias)
  3. Intervention classification (performance bias)
  4. Deviation from intended intervention (performance bias)

5. Missing data (reporting bias)
6. Outcome measurements (detection bias)
7. Selection of reported outcomes (detection bias)

- Additional assessed items included and were assessed as yes, no, or unclear:
    1. Adequately powered statistical analysis
    2. Reporting of funding sources
    3. Industry funding

Assessing the Strength of Evidence

The GRADE[5] system was used to determine the aggregate strength of evidence for studies informing each recommendation statement. GRADE defines a body of evidence in relation to how confident guideline developers can be that the estimate of effects as reported by that body of evidence is correct. Evidence is categorized as high, moderate, low and very low, and assessment is based on the aggregate risk of bias for the evidence base, plus limitations introduced as a consequence of inconsistency, indirectness, imprecision and publication bias across the studies. Additionally, certainty of evidence can be downgraded if confounding across the studies has resulted in the potential for the evidence base to overestimate the effect. Upgrading of evidence is possible if the body of evidence indicates a large effect or if confounding would suggest either spurious effects or would reduce the demonstrated effect.

Assessing the Strength of Recommendations and Considered Judgement

The central question that the panel addressed in developing the guideline was: What are the specimen requirements for accurate diagnosis in all adult patients with clinical features raising consideration of lymphoma?

Development of recommendations required that the panel review the identified evidence and make a series of key judgments:

1. What are the significant findings related to each KQ or outcome? Determine any regulatory requirements and/or evidence that support a specific action.
2. What is the overall strength of evidence supporting each KQ or outcome? Strength of evidence is graded as High, Moderate, Low, and Very Low, based on published criteria (Supplemental Table 1). Strength of evidence is a key element in determining the strength of a recommendation.
3. What is the strength of each recommendation? The strength of recommendations is designated as Strong or Conditional. There are many methods for determining the strength of a recommendation based on the strength of evidence and the magnitude of net benefit or harm. According to the GRADE approach, the strength of a recommendation demonstrates the extent to which an EP is "confident that the desirable effects of an intervention outweigh undesirable effects".[5] For each statement, the panel rated each GRADE evidence to decision framework (EtD)[6] domain. With a strong recommendation designation, the EP judgements will mostly be favoring the right or left of the framework and indicate high confidence that the desirable effects of the guidance statement outweigh the undesirable effects. With a conditional recommendation, the EP judgements will be more towards the center of the framework or with a dispersed pattern indicating lower confidence.

Evidence-to-Decision Framework Domains

1. Problem Priority
    - Is the problem a priority and is a recommendation needed to address it?
    - Are there consequences that are serious if the problem is not addressed?
2. Benefits and Harms
    - Are the desirable anticipated effects large?
    - Are the undesirable anticipated effects small?
    - Are the desirable effects large relative to undesirable effects?
3. Values and preferences of stakeholders:
    - Is there certainty of how stakeholders (patients, clinicians) value the outcomes?
    - Is there variability on how patients and clinicians value the outcomes?

- Will there be different decisions from key stakeholders because of the different values placed on the outcomes?

4. Resources Required:
    - If the Recommendation is made, how large are the resource requirements?
5. Health Equity
    - Are there groups or settings that might be disadvantaged in relation to the Recommendation being considered?
    - Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the Recommendation or the importance of the problem for disadvantaged groups or settings?
    - Are there important considerations that should be made when implementing the Recommendation in order to ensure that inequities are reduced, if possible, and that they are not increased?
6. Feasibility
    - Is the option (or recommendation) feasible to implement?
    - Is the Recommendation sustainable? Are there important barriers that are likely to limit the feasibility of implementing the Recommendation? If yes, do these barriers require consideration when implementing the Recommendation?
7. Acceptability
    - Is the option acceptable to key stakeholders?
    - Are there key stakeholders that would not accept the distribution of the benefits, harms or costs?
    - Are there key stakeholders that would not accept the costs or undesirable effects in the short term for desirable effects (benefits) in the future?

Statements not supported by evidence (ie, evidence was missing or insufficient to permit a conclusion to be reached) and made based on consensus expert opinion will be included as Good Practice Statements.[7]

Articulation of Recommendations

In order to articulate statements that were clearly written and easy to implement, the EP followed GLIDES (Guidelines Into Decision Support) and accompanying BridgeWiz software (Yale University, New Haven, CT) guidance on the wording of recommendations.[8] Statements should clearly address “who is doing what to whom”, meaning the “actor” is defined within the statement to perform a specific action or intervention to a patient or population. GLIDES prioritizes the use of active voice because using the passive voice may lack the clarity and transparency of the statement. However, in some situations, the person responsible for ensuring guidance is implemented is dependent on the organization of the clinic and/or laboratory. To ensure clarity of guidance in these situations, the EP may use passive language to emphasize the recommended action. The guideline uses a two-tier system to rate the strength of recommendations (Supplemental Table 2). Supplemental Table 1 summarizes the level of evidence and considered judgment, as well as obligatory language that was used for each of the recommendation types.

Peer Review

An open comment period was held from September 27 through October 29, 2018 on the ASCP web site www.ascp.org. Fourteen draft recommendations, 2 demographic questions, and 2 questions to assess feasibility were posted for peer review. An announcement was sent to the following societies deemed to have interest:

Medical societies:

- American Association for Cancer Research (AACR)
- American Association for Clinical Chemistry (AACC)
- American College of Medical Genetics and Genomics (ACMG)

- American Society of Cytotechnologists
- American Society of Human Genetics
- American Society for Clinical Oncology (ASCO)
- Arthur Purdy Stout Society (APSS)
- Association of Community Cancer Centers (ACCC)
- Association of Directors of Anatomic and Surgical Pathology (ADASP)
- Association of Pathology Chairs (APC)
- Association for Molecular Pathology (AMP)
- Canadian Association of Medical Oncology
- Canadian Association of Pathologists (CAP-APC)
- European Society of Pathology (ESP)
- European Society for Medical Oncology (ESMO)
- Japanese Society of Medical Oncologists (JSMO)
- National Comprehensive Cancer Network (NCCN)
- Quality Initiative in Interpretive Pathology (QIIP)
- Royal College of Pathologists
- Society to Improve Diagnoses in Medicine (SIDM)
- United States & Canadian Academy of Pathology (USCAP)

Patient advocacy groups:

- American Cancer Society
- Canadian Partnership Against Cancer
- Cancer Research and Prevention Foundation
- Cancer Leadership Council
- Leukemia and Lymphoma Society
- Partnership Against Cancer
- Union for International Cancer Control

Government and other stakeholders:

- Centers for Medicare & Medicaid Services
- Centers for Disease Control and Prevention
- European Medical Agency
- US Department of Defense
- US Food and Drug Administration
- US Veteran's Affairs

"Agree as written", "Agree with suggested Modifications" and "Disagree" responses were captured for every proposed recommendation. The website also received over 900 written comments. Twelve draft statements achieved more than 90% agreement, 1 draft statement achieved more than 80% agreement, and 1 received more than 70% achievement. All draft recommendation statements have agreements that range between 74.7% - 99.16%. Each EP member was assigned 2 draft recommendation statements for which they had to review the comments and present them to the entire panel for group discussion. After consideration of the comments, 10 draft recommendations were maintained with the original language, 3 were revised for clarity, and 1 draft recommendation was combined into other statements which resulted in a total of 13 final recommendations. Resolution of all changes was obtained by majority consensus of the panel using nominal group technique (discussion during teleconference webinars, email discussion, and multiple edited recommendations) amongst the panel members. The final recommendations were approved by supermajority by the EP with a formal vote. The panel considered efficiency and feasibility throughout the entire considered judgment process. Over 80% (293 of 365) responded that all of the draft guideline was feasible, 19.5% (71 of 365) responded that parts of it were feasible, and 0.27% (1 of 365) responded that none of it was feasible. The respondents identified that barriers may impede the adoption of the final guideline. These barriers include (1) a possible lack of support from the members of

the medical team; (2) lack of resources; (3) disagreement with the recommendations; (4) and not wanting to give up personal autonomy to follow the guideline. Neither formal cost analysis nor cost effectiveness models were performed.

There were many comments for and against the use of FNA for the primary diagnosis of lymphoma. The cytopathologist stakeholders provided comments regarding the benefits of using FNA as an initial step for a lymphoma diagnosis. The use of FNA is especially useful in cases where an excisional sample may not be easily obtainable. Specimens obtained from an FNA is useful to "rule-out" lymphoma in cases when the pre-test probability for lymphoma is low. Many other comments focused on the pitfalls of the use of FNA alone. The EP weighed the benefits and the harms and decided to delete one of the draft recommendations and incorporate the statement into the discussion about the use of FNA. The final guidance statements do not recommend FNA by itself without the additional ancillary tests to get to a definitive lymphoma diagnosis.

Document Review

The guidelines were reviewed and approved for publication separately by each organization. For ASCP, the guidelines were reviewed and approved on February 11, 2020 by a special review panel representing the ASCP Executive Committee. For CAP, the guideline was reviewed and approved on February 12, 2020 by an independent review panel representing the CAP Council on Scientific Affairs. The independent review panel was masked to the EP and vetted through a DOI process. The ASH Guideline Oversight Subcommittee (GOS) and the Committee on Quality (COQ) reviewed the guideline and affirmed their value for hematologists on March 20, 2020. Despite their value, according to the ASH committees, the guidelines do not meet established ASH methodologic criteria for organizational approval of evidence-based guidelines, therefore asked that ASH's name be withdrawn from the title.

The document was revised to address pertinent comments from organizational review, but no changes were made to recommendations. After organizational review, the guidelines were subjected to peer review.

Dissemination Plans

The ASCP and CAP will issue a joint press statement announcing the release of the guideline manuscript. Each organization will host a resource page which includes a link to the manuscript and supplement, a summary of the recommendations, a teaching PowerPoint (Microsoft Corporation, Redmond, WA), a frequently asked question (FAQ) document, and an infographic along with other additional tools such as webinar recordings as applicable. The guideline is promoted and presented at various society meetings and distributed to the societies listed in the peer review.

Quality Assessment Results

A total of 42 studies informed recommendation statements. This body of evidence comprised one meta-analysis, one RCT, 6 PCSs, and 35 RCSs. The quality assessment for the meta-analysis and RCT is detailed in Supplemental Table 3, while the quality assessment for the PCSs are included in Supplemental Table 4, and the RCSs in Supplemental Table 5.

Overall, the body of evidence included in this CPG represents a methodologically rigorous and representative summary of the available evidence with an overall quality of intermediate to very low. Of the 42 studies informing recommendation statements, two were assessed as intermediate quality, five as intermediate-low quality, 27 as low quality, and eight as very low quality.

The strength of evidence assessment for each statement is detailed below and summarized in Supplemental Table 6. Evidence informing the statements ranged from moderate through very low. The judgements of the EP for each domain of the EtD are summarized in Supplemental Table 7 and detailed below for each statement.

Recommendation Statements

Statement 1. Clinical care providers should use surgical biopsy when feasible in a clinical setting where Hodgkin lymphoma is highly suspected. *Strong Recommendation.*

The strength of evidence supporting this statement is low. The evidence base is comprised of two studies which compared CNB specimens with the gold standard surgical biopsies.[9, 10] Both studies were of a retrospective cohort design and were assessed as low quality[9, 10] with a very serious aggregate risk of bias. These studies suffered from risk of bias in patient selection,[9, 10] reporting,[9, 10] and detection domains,[9, 10] as well as a lack of reported funding in one.[10] None of the studies was found to have methodological flaws that would raise concerns about the findings. Although many other identified studies used surgical biopsy as the reference standard[11-19] studies reporting on the diagnostic test characteristics of surgical biopsies were lacking. This is believed to be due to the fact that surgical biopsies are usual practice and any studies leading to establishment of surgical biopsies as the gold standard would have been published prior to our inclusion date. Refer to Supplemental Table 5 for the individual quality assessment of the included studies and Supplemental Table 6 for the aggregate strength of evidence assessment for the statement.

Based on a combination of the available evidence and usual practices, all EP members concluded that the benefits of using surgical biopsies are moderate to large, while the harms of its use are moderate to small. Additionally, the EP discussed the harms of misdiagnosed when a large volume biopsy is not feasible. Taken together, all EP members agreed the benefits of using surgical biopsy outweighed any potential adverse events from the more invasive procedure and that this statement would be acceptable to key stakeholders and feasible to implement. Refer Supplemental Table 7 for a complete summary of the EtD framework.

Statement 2. Clinical care providers should obtain excisional or core needle biopsy (CNB) specimens in patients with high suspicion of lymphoma. *Strong Recommendation.*

The strength of evidence supporting this statement is moderate. The evidence base for this statement is comprised of 11 studies, three reporting on the use of excisional biopsies and CNB specimens for diagnosing lymphoma versus non-lymphoma[20-22] and eight studies reporting on biopsy use for subclassification of lymphoma.[9-12, 15, 23-25] This included an intermediate quality systematic review with meta-analysis,[21] an intermediate quality RCT,[20]a low quality PCS,[15] seven low quality RCS,[9-12, 22, 23, 25] and one very low retrospective cohort study.[24]Although based on a systematic review, the methodology for pooling of data in the meta-analysis was not defined.[21] Additionally, the systematic review did not employ duplicate study selection or data extraction, and did not include a list of included and excluded studies, conflict of interest declarations, or funding sources.[21] The included RCT[20] was assessed as intermediate quality based on a high risk of performance and reporting bias, as well as a lack of funding reported. The low quality PCS[15] was limited by critical risk of selection and reporting bias, and moderate risk of performance and detection bias. Finally, the RCSs suffered from risk of bias in patient selection,[9-12, 22-25] (performance,[24] reporting,[9-11, 22-25] and detection[9, 10, 23-25] domains. Additionally, six cohort studies did not report on sources of funding.[10-12, 15, 23, 24] None of the studies were found to have methodological flaws that would raise concerns about the findings. The aggregate risk of bias for studies reporting on diagnosis of lymphoma versus non-lymphoma was serious and the aggregate risk of bias for the two studies reporting on subclassification was very serious. As the evidence was not downgraded for any other factors, the strength of evidence for the entire statement was defined as moderate. Refer to Supplemental Tables 3-5 for the individual quality assessment of the included studies and Supplemental Table 6 for the aggregate strength of evidence assessment for the statement.

Based on the available evidence, all EP members agreed that the moderate to large benefits of using excisional biopsies or CNBs outweighed the moderate to trivial potential harms of using a more invasive procedure than FNA. Although the EP was divided on the magnitude of costs associated with performing the biopsies, all EP members concluded this recommendation would be acceptable to key stakeholders

and feasible to implement. Refer to Supplemental Table 7 for a complete summary of the EtD framework.

Statement 3. Clinical care providers should ***not*** use fine needle aspiration (FNA) cytomorphology alone without ancillary testing to achieve a definitive diagnosis of lymphoma. *Strong Recommendation.*

- *Note:* Cytomorphology alone without ancillary studies has low sensitivity and low predictive value.
- *Note:* A defined subset of lymphoma requires architectural assessment and cannot be reliably diagnosed and subclassified by FNA.

The strength of evidence to support this guideline statement is low. The evidence base is comprised of five studies which reported low sensitivities and predictive values when FNA cytomorphology alone was used.[26-30] All five studies were of a retrospective cohort design and were assessed as low quality[26-30] with an aggregate very serious risk of bias. These studies suffered from risk of bias in patient selection,[26-30] performance,[26] reporting,[27-30] and detection domains,[26, 28, 30] as well as a lack of reported funding.[27, 28] None of the studies was found to have methodological flaws that would raise concerns about the findings. Refer to Supplemental Table 5 for the individual quality assessment of the included studies and Supplemental Table 6 for the aggregate strength of evidence assessment for the statement.

Based on the available evidence, all EP members agreed that the moderate to large benefits of not performing FNA cytomorphology alone outweighed any potential small to trivial harms of this guidance. The decision to create a strong recommendation statement was further based on the harms to patients misdiagnosed by the use of FNA cytomorphology without further ancillary testing. Although the majority of EP members deemed this guidance would be acceptable to key stakeholders, a small minority implied that some stakeholders would probably not find the guidance acceptable. However, all EP members still concluded that this recommendation would be feasible to implement. Refer to Supplemental Table 7 for a complete summary of the EtD framework.

Statement 4. Clinical care providers should follow-up patients with "negative" results for persistent signs and symptoms of lymphoma and pursue larger volume biopsy when clinical suspicion for lymphoma persists. *Strong Recommendation.*

The strength of evidence to support this guideline statement is *moderate*. Four studies which evaluated the benefits of following patients with negative results comprised the evidence base for this statement.[13, 20-22] This included an intermediate quality systematic review with meta-analysis,[21] one intermediate quality RCT,[20] and two low quality RCSs.[13, 22] Although based on a systematic review, the methodology for pooling of data in the meta-analysis was not defined.[21] Additionally, the systematic review did not employ duplicate study selection or data extraction, and did not include a list of included and excluded studies, conflict of interest declarations, or funding sources.[21] The included RCT[20] was assessed as intermediate quality based on a high risk of performance and reporting bias, as well as a lack of funding reported. Finally, both RCSs[13, 22] suffered from critical risk of selection bias, while one suffered from moderate risk of reporting bias,[22] and the other did not report on funding sources.[13] None of the studies were found to have methodological flaws that would raise concerns about the findings. Of the included four studies, three reported on diagnostic test characteristics and carried an aggregate moderate strength of evidence, while the remaining study was of low quality and reported on specimen adequacy. As the evidence was not downgraded for any factor, the strength of evidence for the entire statement was defined as moderate. Refer to Supplemental Tables 3 and 5 for the individual quality assessment of the included studies and Supplemental Table 6 for the aggregate strength of evidence assessment for the statement.

Based on the available evidence, all EP members agreed that the moderate to large benefits of following patients with negative results outweighed the small to trivial potential harms of follow-up. Although the EP was divided on the magnitude of costs associated with follow-up and the impact on health equity, all EP members deemed this recommendation would be acceptable to key stakeholders and feasible to implement. Refer to Supplemental Table 7 for a complete summary of the EtD framework.

Statement 5. Clinical care providers may use positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (FDG-PET) to identify sites for biopsy in patients with suspected transformed/aggressive-histology lymphoma. As feasible, biopsies should be directed to the site of greatest FDG avidity. *Conditional recommendation.*

The strength of evidence is low to support this guideline statement. The evidence base supporting this recommendation comprised one low quality RCS which indicated a high SUV on FDG-PET for transformed lymphoma.[31] The RCS[31] was limited by a critical risk of selection bias, and a moderate risk of reporting and detection bias, as well as a lack of reported funding. However, no methodological flaws that would raise concerns about the findings was noted. Refer to Supplemental Table 5 for the individual quality assessment of the included study. Since the statement was based on one study, the strength of evidence was defined solely on the risk of bias carried by this study (Supplemental Table 6).

Based on this limited evidence, the EP members were divided on multiple domains on the EtD framework. While all EP members agreed that the benefits of using PET to identify sites of transformed or highly-aggressive lymphoma were moderate to large, the harms of its use were considered to range from large to trivial, with a majority of the EP deem the harms to be moderate. When the benefits were compared with the harms, the majority of EP members agreed that the benefits to outweigh the harms, with a very small minority deeming that there was only a balance. Although the majority of EP members decided that using PET to identify biopsy sites would result in moderate to large costs, all EP members concluded this conditional recommendation would be acceptable to key stakeholders and feasible to implement. Refer to Supplemental Table 7 for a complete summary of the EtD framework.

Statement 6. Clinical care providers may obtain bone marrow biopsies for the primary diagnosis in select patients with suspected lymphomas. *Conditional recommendation.*

- *Note:* For certain lymphoma types (eg, splenic low-grade lymphomas, lymphoplasmacytic lymphomas), bone marrow biopsy may be preferred over more invasive surgical methods.

The strength of evidence is very low to support this guideline statement. The evidence base is comprised of three studies which evaluated the use of bone marrow biopsies for the diagnosis of lymphoma.[32-34] All three studies were of a retrospective cohort design and were assessed as low[33, 34] and very low[32] quality. These studies suffered from risk of bias in patient selection,[32-34] reporting,[32, 34] and detection domains,[32, 33] as well as a lack of reported funding.[32, 34] None of the studies was found to have methodological flaws that would raise concerns about the findings. The aggregate risk of bias across the three studies was very serious. Additionally, strength of evidence was downgraded for inconsistency and indirectness. Refer to Supplemental Table 5 for the individual quality assessment of the included studies and Supplemental Table 6 for the aggregate strength of evidence assessment for the statement.

Based on the available evidence, EP members considered the benefits of bone marrow biopsy use to range from small to large, with the majority agreeing the benefits to be moderate. Similarly, EP members considered the harms to range from moderate to trivial, with the majority judging the harms to be small. When benefits were weighed against the harms, a majority of members deemed the benefits outweighed the harms, with only a small minority believing there was a balance. The EP members were further divided when discussing resource use and health equity if recommending bone marrow biopsies and health equity. A majority of the EP members deemed that use of bone marrow biopsies would entail a negligible cost, while a minority deemed that their use could result in either moderate additional costs or moderate savings. A small majority (55%) of EP members agreed that bone marrow biopsy use would have no impact on health equity, while the remaining members of the EP agreed that health equity would probably be increased. Taken together, all EP members concluded this recommendation would be acceptable to key stakeholders and feasible to implement. Refer to Supplemental Table 7 for a complete summary of the EtD framework.

Statement 7. Clinical care providers may use cerebrospinal fluid (CSF) for the evaluation of primary or secondary central nervous system (CNS) lymphoma in select patients. *Conditional recommendation.*

The strength of evidence to support this guideline statement is very low. The evidence base supporting this recommendation comprised one very low-quality RCS which evaluated the use of CSF for the diagnosis of CNS lymphoma.[35] The RCS[35] was limited by a critical risk of selection bias, a serious risk of reporting bias, and moderate risk of performance bias and detection bias. However, no methodological flaws that would raise concerns about the findings were noted. Refer to Supplemental Table 5 for the individual quality assessment of this study. Since the statement is based solely on this study, the strength of evidence was defined by its quality (Supplemental Table 6).

Based on this limited evidence, the EP members were divided on multiple domains of the EtD framework. While all EP members agreed that the benefits of using CSF in the diagnosis of CNS lymphoma were moderate to large, the harms of its use were considered to range from large to trivial, with the majority of the EP agreed that the harms to be moderate. When the benefits were compared with the harms, the majority of EP members concluded that the benefits to outweigh the harms, with a very small minority deeming that there was only a balance. In terms of resource use, the costs of using CSF ranged from moderate costs to large savings with the majority of EP members believing the costs to be moderate or negligible. A majority of EP members believed use of CSF would result in no impact on health equity, while a minority of members deemed its use could result in either reduced or increased equity. However, when all domains were considered, all EP members decided this conditional recommendation would be acceptable to key stakeholders and feasible to implement. Refer to Supplemental Table 7 for a complete summary of the EtD framework.

Statement 8. Clinical care providers should use a combined morphologic and flow cytometric evaluation of cerebrospinal fluid (CSF) in the investigation of possible primary or secondary central nervous system (CNS) lymphoma in select patients. *Strong recommendation.*

The strength of evidence to support this guideline statement is very low. Two studies which demonstrated improved CNS lymphoma diagnostic accuracy with cytomorphology plus flow cytometry when compared with cytomorphology alone[35, 36] comprised the evidence base for this statement. Included studies were of a retrospective cohort design and assessed as low[36] and very low[35] quality with an aggregate overall very serious risk of bias. These studies suffered from risk of bias in patient selection,[35, 36] performance,[35] reporting,[35, 36] and detection[35, 36] domains. Additionally, one of the studies[36] did not report on sources of funding. None of the studies were found to have methodological flaws that would raise concerns about the findings. Refer to Supplemental Table 5 for the individual quality assessment of the included studies and Supplemental Table 6 for the aggregate strength of evidence assessment for the statement.

Although all EP members agreed that addition of flow cytometry to cytomorphology is accurate and the benefits of its use are moderate to large, the harms of adding flow cytometry ranged from large to trivial. However, even given the divide in perceived harms, all EP members agreed that providing this guidance is a priority and that the benefits of recommending flow cytometry paired with cytomorphology for CSF outweighed the harms. Due to the low predictive value of CSF cytomorphology alone, the decision to create a strong recommendation statement was further based on potential harms to patients if CSF cytomorphology alone were employed. The majority of the EP members concluded that flow cytometry paired with cytomorphology could lead to moderate cost increase, while a minority of the members agreed the added cost to negligible. When considering the available evidence combined with the knowledge that this is standard of care in some institutions already, all EP members deemed this recommendation would be acceptable to key stakeholders and feasible to implement. Refer to Supplemental Table 7 for a complete summary of the EtD framework.

Statement 9. Based on low negative predictive values, clinical care providers should follow-up patients with “negative” results for persistent signs and symptoms of CNS lymphoma and pursue repeat CSF examination or biopsy when clinical suspicion for lymphoma persists. *Strong recommendation.*

The strength of evidence to support this guideline statement is very low. The two studies which informed Statement 8 demonstrated low negative predictive values of CSF for the diagnosis of lymphoma and

comprised the evidence base for this statement.[35, 36] Included studies were of a retrospective cohort design and assessed as low[36] and very low[35] quality. These studies suffered from risk of bias in patient selection,[35, 36] performance,[35] reporting,[35, 36] and detection[35, 36] domains. Additionally, one of the studies[36] did not report on sources of funding. None of the studies were found to have methodological flaws that would raise concerns about the findings. Strength of evidence was assessed based on an aggregate very serious risk of bias plus downgrading for inconsistency as although both studies reported a low NPV, there was a large difference in the reported value. Refer to Supplemental Table 5 for the individual quality assessment of the included studies and Supplemental Table 6 for the aggregate strength of evidence assessment for the statement.

Based on the available evidence, all EP members agreed that the moderate to large benefits of following patients with negative results outweighed the moderate to trivial potential harms of follow-up. The decision to create a strong recommendation statement was further based on the harms to patients who are not followed given the low predictive value of diagnosis with CSF. Although the EP was divided on the magnitude of costs associated with follow-up and the impact on health equity, all EP members considered this recommendation to be acceptable to key stakeholders and feasible to implement. Refer to Supplemental Table 7 for a complete summary of the EtD framework.

Statement 10. Clinical care providers should use immunophenotyping by flow cytometry and/or immunohistochemistry (IHC) in addition to morphology for the evaluation of specimens for the diagnosis and subclassification of lymphomas. *Strong recommendation.*

The strength of evidence is moderate to support this guideline statement. The evidence base for this statement comprises 19 studies.[10, 11, 20, 21, 23, 24, 26, 37-48] Twelve studies reported high diagnostic test characteristics using flow cytometry on CNB and surgical biopsies[37-42] or on FNA specimens,[43-48] and one study reported high diagnostic test characteristics when using IHC on FNA specimens.[26] An additional six studies reported high diagnostic test characteristics when using IHC as part of a routine diagnosis on CNB specimens[10, 11, 20, 21, 23, 24] and were used as indirect evidence to inform the statement. The total 19 studies included one intermediate quality systematic review with meta-analysis,[21] one intermediate qualityRCT,[20] PCSs[37, 40, 41, 44, 45] and 12 RCSs.[10, 11, 23, 24, 26, 38, 39, 42, 43, 46-48] An intermediate quality assessment for the systematic review was based a lack of duplicate study selection or data extraction, no list of included and excluded studies, no conflict of interest declarations, and a lack of funding sources being reported.[21] Additionally, although based on a systematic review, the methodology for pooling of data in the meta-analysis was not defined.[21] The included RCT[20] was assessed as intermediate quality based on a high risk of performance and reporting bias, as well as a lack of funding reported. The five PCSs were all assessed as intermediate-low quality based on risk of bias in patient selection,[40, 41, 44] performance,[41, 45] reporting,[40, 41, 44, 45] and detection[37, 40, 41, 44, 45] domains. The 12 RCSs were assessed as low[10, 11, 23, 26, 38, 39, 43] and very low quality[24, 42, 46-48] based on risk of bias in patient selection,[10, 11, 23, 24, 26, 38, 39, 42, 43, 46-48] performance,[24, 26, 38, 46-48] reporting,[10, 11, 23, 24, 38, 39, 42, 43, 46-48] and detection[10, 23, 24, 26, 42, 43, 46-48] domains. Additionally, 10 of the 17 cohort studies did not report on sources of funding[10, 11, 23, 24, 39, 42, 44, 46-48] None of the studies were found to have methodological flaws that would raise concerns about the findings. Refer to Supplemental Tables 3-5 for the individual quality assessment of the included studies. The strength of evidence for the entire statement was defined as moderate. Studies reporting on diagnostic test characteristics of flow cytometry carried a moderate strength of evidence, while studies reporting on diagnostic test characteristics of IHC carried a low strength of evidence (Supplemental Table 6).

Based on the identified studies, all EP members agreed that immunophenotyping by flow cytometry and/or IHC in addition to morphology was accurate and provided large benefits. Although the EP members considered the harms to range from moderate to trivial, all EP members felt that the benefits outweighed the potential harms. The majority of EP members felt that combination flow cytometry and/or IHC with morphologic assessment would result in moderate costs and probably no impact on health equity. All EP members believe guidance in this area to be a priority at this time and feel that the recommendation statement is acceptable to key stakeholders and feasible to implement. Refer to Supplemental Table 7 for a complete summary of the EtD framework.

Statement 11. Clinical care providers may use fluorescence in situ hybridization (FISH) analysis when evaluating specimens in patients with suspected or confirmed lymphoma, or in the subclassification of lymphoma. FISH analysis is feasible on specimens obtained by FNA and may increase diagnostic yield. *Conditional recommendation.*
Note: Demonstration of the appropriate rearrangements is required for a diagnosis of high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements.

The strength of evidence is low to support this guideline statement. The evidence base supporting this recommendation comprised two studies which used FISH on FNA specimens and reported successful subclassification of lymphoma.[49, 50] Both studies were of a retrospective cohort design and were assessed as low quality[49, 50] with an aggregate very serious risk of bias. These studies suffered from risk of bias in patient selection domains,[49, 50] reporting domains,[50] and detection domains,[49] as well as a lack of reported funding.[49, 50] Neither of the studies were found to have methodological flaws that would raise concerns about the findings. Refer to Supplemental Table 5 for the individual quality assessment of the included studies and Supplemental Table 6 for the aggregate strength of evidence assessment for the statement.

Based on the available evidence, a majority of EP members agreed that the benefits of using FISH when evaluating specimens were moderate to large, while the harms of its use were moderate to small, and thus benefits of use outweighed the potential harms. Although use of FISH may carry a moderate cost, the majority of EP members deemed this recommendation would be acceptable to key stakeholders and feasible to implement. Refer to Supplemental Table 7 for a complete summary of the EtD framework.

Statement 12. Clinical care providers should *not* routinely use up-front polymerase chain reaction (PCR)-based clonality studies of antigen receptor genes (ie, T-cell receptor and immunoglobulin) in the initial investigation of lymphoma. There may be a confirmatory role in certain settings for these studies. *Conditional recommendation.*

The strength of evidence underpinning this statement is low and the base is comprised of 5 studies.[38, 48, 51-53] Two studies evaluated up-front multiplex PCR clonality assays,[51, 52] while the other three studies evaluated antigen receptor gene rearrangements (ARGR).[38, 48, 53] All studies were retrospective cohort designs and were assessed as low quality[38, 51-53] or very low quality.[48] The aggregate risk of bias was very serious for both studies that reported on the diagnostic test characteristics of PCR clonality assays, and those evaluating ARGR. These studies suffered from risk of bias in selection,[38, 48, 51-53] performance,[38, 48] reporting,[38, 48, 52, 53] and detection[48, 51-53] domains. Additionally, two studies did not report on sources of funding.[48, 51] None of the studies was found to have methodological flaws that would raise concerns about the findings. Refer to Supplemental Table 5 for the individual quality assessment of the included studies and Supplemental Table 6 for the aggregate strength of evidence assessment for the statement.

Based on the identified evidence, the EP members were divided on multiple domains of the EtD framework. When considering the accuracy of up-front PCR-based clonality and ARGR assays, only half of the members agreed that the assays to be accurate and this led to EP members assessing the benefits across a wide range from small to large. However, the harms were still considered to be small or trivial. When benefits were weighed against the harms of performing the assays, the EP members were divided with the majority believing the benefits to not outweigh the harms, and a minority deeming that there was a balance between benefits and harms. Based on the lack of evidence supporting the accuracy of these assays and the weight of benefits versus harms, the EP recommend against the routine use of these as up-front assays. All EP members agree this statement to be acceptable to key stakeholders and feasible to implement. Refer to Table Supplemental 7 for a complete summary of the EtD framework.

Statement 13. Clinical care providers may use molecular tests to aid in classification of lymphomas. For example, pathologists may use *MYD88* L265P to aid in the classification of indolent B-cell lymphoma. *Conditional recommendation.*

Note: This recommendation statement refers to non-FISH molecular tests.

The strength of evidence to support this guideline statement is low. Five studies[38, 48, 53-55] which evaluated the use of mutational analysis to aid in classifying lymphoma subtypes comprised the evidence base for this statement. All studies were of a retrospective cohort design and were assessed as low[38, 53, 55] and very low[48, 54] quality based on risk of bias in selection,[38, 48, 53-55] performance,[48, 54] reporting,[38, 48, 53-55] and detection[48, 53, 54] domains. Additionally, one study did not report on funding sources.[48] None of the studies were found to have methodological flaws that would raise concerns about the findings. Refer to Supplemental Table 5 for the individual quality assessment of the included studies. Although evidence was not downgraded for any additional factor, the aggregate risk of bias for these studies was very serious, leading to a low strength of evidence (Supplemental Table 6).

Based on the identified evidence, all EP members agree mutational analysis to be accurate when classifying lymphoma subtypes and the benefits of its use outweighed the small to trivial harms. In terms of resource use, the EP members were divided with the majority believing addition of mutational analysis will results in a moderate cost, while the minority considered the costs to range from large to negligible. Despite disagreement on resource use, all EP members conclude this statement to be acceptable to key stakeholders and feasible to implement. Refer to Supplemental Table 7 for a complete summary of the EtD framework.

Good Practice Statements

According to the GRADE approach, good practice statements (GPS) are recommendations panels may consider important but are not appropriate to be formally rated for quality of evidence.[5] In addition to the set of key questions formulated *a priori* for the SER, the EP decided to draft GPSs, which reflect expert consensus opinions supported by a limited number of studies and data that were not formally included in the evidence-base nor systematically rated and assessed for quality. The EP wanted to address the following questions:

- Under what circumstances does second review by an expert in hematopathology improve the accuracy of diagnosis?
- To what extent do pathologists use clinical characteristics and radiographic data on the formation of a pre-test probability and what is the role of this information in determining the diagnosis?
- To achieve efficient patient management, what elements related to specimen handling should be included in the pathology report, and if a biopsy specimen is deemed suboptimal for diagnosis, what elements should be included in the report to explain why the specimen is suboptimal?

Non-systematic Review Literature Searches

Two separate literature searches were designed and run in Ovid MEDLINE and Elsevier Embase databases. The first was designed to capture literature related to secondary review of pathology samples in which lymphoma was suspected. The search updated one conducted by an *a priori* identified systematic review evaluating pathology second review.[56] The search was limited to human studies published in English from January 1, 2013 to March 2, 2019. The second search was designed to capture literature related to reporting elements in pathology samples in which lymphoma is suspected. This search was limited to human studies published in English from January 1, 2002 to March 5, 2019.

The EP co-chairs reviewed the identified literature and incorporated data collected in a pre-guideline development practice survey to arrive at the GPSs. Supplemental Figure 3 details the plan for the literature review.

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Supplemental Table 1. Strength of Evidence

Designation	Description
High	There is high confidence that available evidence reflects true effect. Further research is very unlikely to change the confidence in the estimate of effect. Included studies will be of high or intermediate quality.
Moderate	There is moderate confidence that available evidence reflects true effect. Further research is likely to have an important impact on the confidence in estimate of effect and may change the estimate. Included studies will be of intermediate or low quality.
Low	There is limited confidence in the estimate of effect. The true effect may be substantially different from the estimate of the effect. Included studies will be of low quality.
Very Low	There is very little confidence in the estimate of effect. The true effect is likely to be substantially different from the estimate of effect. Any estimate of effect is very uncertain. Included studies will be of low or very low quality.

Data derived from Guyatt 2011[5]

Supplemental Table 2. Grades for Strength of Recommendations

Designation	Recommendation	Evidence-to-Decision Judgement
Strong Recommendation	Recommend for or against a particular practice (can include "must" or "should")	Supported by assessment with the GRADE EtD framework showing EP consensus of judgements directed to the far right or far left poles of the framework.
Conditional Recommendation	Recommend for or against a particular practice (can include "should" or "may")	Supported by assessment with the GRADE EtD framework showing EP consensus of judgements directed towards the center of the framework or with a dispersed pattern.

Data derived from Guyatt 2011[5] and Alonso-Coello 2016[6]

Abbreviations: EP, expert panel; EtD, Evidence-to-Decision; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

Supplemental Table 3. Quality Assessment of Included Systematic Reviews and Randomized Controlled Trials

Systematic Reviews			Randomized Controlled Trials		
Study		Novoa[21] 2012	Study		Pugliese[20] 2017
AMSTAR Assessment	A priori design	Y	Cochrane Risk of Bias Tool Assessment	Random sequence generation	LR
	Duplicate study selection and data extraction	N		Allocation concealment	HR
	Comprehensive literature search	Y		Blinding – patients and conductors	HR
	Publication status as inclusion criterion	N		Blinding – outcome assessors	LR
	List of included and excluded studies	N		Complete outcome data	LR
	Characteristics of included studies	Y		Selective outcome reporting	HR
	Study quality assessment conducted	Y		Overall Risk of Bias	Int
	Quality assessment used in formulating conclusions	Y	Validated and reliable measures		Y
	Appropriate methods to combine findings	Y	Adequately powered		Y
	Publication bias assessment	N	Reported funding sources		N
	Conflict of interest reported	N	Industry funded		N
Reported funding sources		N	Study Quality		Int
Study Quality		Int			

Abbreviations: HR, high risk; Int, Intermediate; LR, low risk; N, no; U, unclear/unsure; Y, yes.

Supplemental Table 4. Quality Assessment of Included Prospective Cohort Studies

Study		Peluso[45] 2017	He[15] 2015	Ohmoto[37] 2015	Salameire[41] 2012	Colorado[40] 2010	Maroto[44] 2009
ROBINS-I Assessment	Confounding	MR	SR	MR	MR	MR	MR
	Patient selection	LR	CR	LR	SR	SR	MR
	Intervention classification	MR	LR	LR	LR	LR	LR
	Deviation from intended intervention	MR	MR	LR	MR	LR	LR
	Missing data	MR	CR	LR	MR	MR	MR
	Outcome measurements	LR	LR	SR	MR	MR	MR
	Selection of reported outcomes	MR	MR	LR	MR	LR	LR
	Overall Risk of Bias	MR	CR	SR	SR	SR	MR
Adequately powered		Y	Y	NS	Y	Y	N
Reported funding sources		Y	Y	Y	Y	Y	N
Industry funded		N	N	N	N	N	U

Supplemental Table 4. Quality Assessment of Included Prospective Cohort Studies

Study	Peluso[45] 2017	He[15] 2015	Ohmoto[37] 2015	Salameire[41] 2012	Colorado[40] 2010	Maroto[44] 2009
Study Quality	Int-Low	Low	Int-Low	Int-Low	Int-Low	Int-Low

Abbreviations: CR, critical risk; Int, Intermediate; LR, low risk; MR, moderate risk; SR, serious risk; N, no; NS, no statistical analysis; U, unclear/unsure; Y, yes.

Supplemental Table 5. Quality Assessment of Included Retrospective Cohort Studies

Study		Kilicarslan[11] 2017	Yu[53] 2016	Loghavi[47] 2016	Bezerra[39] 2011	Roepman[51] 2016	Groneck[9] 2016	Brozic[48] 2015	Capaldi[54] 2014
ROBINS-I Assessment	Confounding	MR	MR	MR	MR	MR	MR	MR	MR
	Patient selection	CR	CR	CR	CR	CR	CR	CR	CR
	Intervention classification	LR	LR	LR	LR	LR	LR	LR	LR
	Deviation from intended intervention	LR	LR	SR	LR	LR	LR	SR	LR
	Missing data	MR	MR	MR	MR	LR	MR	MR	CR
	Outcome measurements	LR	MR	MR	LR	MR	MR	LR	CR
	Selection of reported outcomes	LR	MR	MR	LR	LR	MR	MR	LR
	Overall Risk of Bias	CR	CR	CR	CR	CR	CR	CR	CR
Adequately powered		Y	Y	Y	Y	Y	Y	N	N
Reported funding sources		N	Y	N	N	Y	Y	N	Y
Industry funded		U	N	U	U	N	N	U	N
Study Quality		Low	Low	Very Low	Low	Low	Low	Very Low	Very Low

Study		Pittman[35] 2013	Pedersen[10] 2013	Ponzoni[33] 2012	Yasuda[26] 2012	Tomo-zawa[23] 2011	Schmid[46] 2011	Da Cunha Santos 2010[49]	Paro 2010[43]	Monaco[50] 2009
ROBINS-I Assessment	Confounding	MR	MR	MR	MR	MR	MR	MR	MR	MR
	Patient selection	CR	CR	CR	CR	CR	CR	CR	CR	CR
	Intervention classification	MR	LR	LR	LR	LR	LR	LR	LR	LR
	Deviation from intended intervention	LR	LR	LR	MR	LR	MR	LR	LR	LR
	Missing data	SR	MR	LR	LR	MR	MR	LR	MR	MR
	Outcome measurements	MR	MR	LR	LR	LR	SR	LR	MR	LR
	Selection of reported outcomes	MR	MR	MR	MR	MR	MR	MR	LR	LR
	Overall Risk of Bias	CR	CR	CR	CR	CR	CR	CR	CR	CR
Adequately powered		Y	Y	Y	Y	NS	NS	Y	NS	NS
Reported funding sources		Y	N	Y	Y	N	N	N	Y	N
Industry funded		N	U	N	N	U	U	U	N	U
Study Quality		Very Low	Low	Low	Low	Low	Very Low	Low	Low	Low

Supplemental Table 5. Quality Assessment of Included Retrospective Cohort Studies (continued)

Study		Noy 2009 [31]	Kokovic [55] 2009	Seegmiller [42] 2009	El Bolkainy [34] 2008	Tam 2008 [24]	Roh 2008 [27]	Vanderveide [12] 2008	Farmer [25] 2007	Engels [52] 2007
ROBINS-I Assessment	Confounding	MR	MR	MR	MR	MR	MR	MR	MR	MR
	Patient selection	CR	CR	CR	CR	CR	CR	CR	CR	CR
	Intervention classification	LR	LR	LR	LR	LR	LR	LR	LR	LR
	Deviation from intended intervention	LR	LR	LR	LR	MR	MR	LR	LR	LR
	Missing data	MR	MR	SR	MR	MR	MR	SR	MR	MR
	Outcome measurements	MR	LR	MR	LR	MR	LR	LR	MR	MR
	Selection of reported outcomes	MR	LR	SR	LR	LR	LR	LR	LR	LR
	Overall Risk of Bias	CR	CR	CR	CR	CR	CR	CR	CR	CR
Adequately powered		NS	NS	Y	Y	N	Y	NS	Y	NS
Reported funding sources		N	Y	N	N	N	N	N	Y	N
Industry funded		U	Y	U	U	U	U	U	N	U
Study Quality		Low	Low	Very Low	Low	Very Low	Low	Very Low	Low	Low

Study		Dictor [38] 2007	Balestreri [13] 2005	Wong [28] 2002	Adhikari [29] 2016	Cesana [36] 2011	Houcine [30] 2018	Phillips [32] 2018	Han [22] 2018
ROBINS-I Assessment	Confounding	MR	MR	MR	MR	MR	MR	SR	LR
	Patient selection	SR	CR	CR	CR	CR	CR	CR	CR
	Intervention classification	MR	LR	LR	LR	LR	LR	LR	LR
	Deviation from intended intervention	SR	LR	LR	LR	LR	LR	LR	LR
	Missing data	MR	LR	MR	MR	MR	MR	SR	MR
	Outcome measurements	LR	LR	MR	LR	MR	MR	LR	LR
	Selection of reported outcomes	LR	LR	MR	LR	MR	LR	MR	LR
	Overall Risk of Bias	SR	CR	CR	CR	CR	CR	CR	CR
Adequately powered		Y	NS	NS	Y	Y	Y	Y	Y
Reported funding sources		Y	N	N	Y	N	Y	N	Y
Industry funded		N	U	U	N	U	N	U	N
Study Quality		Low	Low	Low	Low	Low	Low	Very Low	Low

Abbreviations: CR, critical risk; Int, Intermediate; LR, low risk; MR, moderate risk; SR, serious risk; N, no; NS, no statistical analysis; U, unclear/unsure; Y, yes.

Supplemental Table 6. Strength of Evidence Assessment

Number of Studies and Design	Aggregate Risk of Bias	Inconsistency	Indirectness	Imprecision	Other£	SOE Grade
Statement 1						
2 RCS	Very serious	Not serious	Not serious	Not serious	None	Low
Statement 2						
1 SR, 1 RCT, 1 PCS, 8 RCS	Serious	Not serious	Not serious	Not serious	None	Moderate
Statement 3						
5 RCS	Very serious	Not serious	Not serious	Not serious	None	Low
Statement 4						
1 MA, 1 RCT, 2 RCS	Serious	Not serious	Not serious	Not serious	None	Moderate
Statement 5						
1 RCS	Very serious	Not serious	Not serious	Not serious	None	Low
Statement 6						
3 RCS	Very serious	Serious	Serious	Not serious	None	Very Low
Statement 7						
1 RCS	Extremely serious	Not serious	Not serious	Not serious	None	Very Low
Statement 8						
2 RCS	Very serious	Not serious	Not serious	Not serious	None	Very Low
Statement 9						
2 RCS	Very serious	Serious	Not serious	Not serious	None	Very Low
Statement 10						
1 SR, 1 RCT, 4 PCS, 13 RCS	Serious	Not serious	Serious§	Not serious	None	Moderate
Statement 11						
2 RCS	Very serious	Not serious	Not serious	Not serious	None	Low
Statement 12						
5 RCS	Very serious	Not serious	Not serious	Not serious	None	Low
Statement 13						
5 RCS	Very serious	Not serious	Not serious	Not serious	None	Low

Abbreviations: PCS, prospective cohort study; RCS, retrospective cohort study; RCT, randomized controlled trial; SR, systematic review.
£ Other category includes assessment for detection of publication bias, large effect, and confounding
§ although six studies for this statement provided indirect evidence, these studies supporting the direct evidence studies. The strength of evidence for the statement was not downgraded based on this indirectness.

Supplemental Table 7. Evidence to Decision Framework

Statement 1. Clinical care providers should use surgical biopsy when feasible in a clinical setting where Hodgkin lymphoma is highly suspected.

Is the problem a priority?	No	Probably No		Probably Yes	Yes
		••		•••	••••••
How substantial are the benefits?	Trivial	Small		Moderate	Large
				•••	••••••••
How substantial are the harms?	Large	Moderate		Small	Trivial
		••		•••••••••	
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
		•		•••••••	•••
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
				••••	••••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
	•	••••••••	••		

What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
		•	•••••••	••	•
Is the intervention acceptable to key stakeholders?	No	Probably No	Probably Yes		Yes
			•••••••••		•••
Is the intervention feasible to implement?	No	Probably No	Probably Yes		Yes
			•••••••••		•••

Statement 2. Clinical care providers should obtain excisional or core needle biopsy specimens in patients with high suspicion of lymphoma.

Is the problem a priority?	No	Probably No	Probably Yes	Yes
	•		••••	••••••
How substantial are the benefits?	Trivial	Small	Moderate	Large
			•••	••••••••
How substantial are the harms?	Large	Moderate	Small	Trivial
		•	••••••	•••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes	Probably No	No
		••••	••••••	•
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
				•	••••••••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
	••	•••••	•••	•	
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
		•	•••••	•••	••
Is the intervention acceptable to key stakeholders?	No	Probably No	Probably Yes		Yes
			•••••		•••••
Is the intervention feasible to implement?	No	Probably No	Probably Yes		Yes
			•••••		•••••

Statement 3. Clinical care providers should ***not*** use fine needle aspirate (FNA) cytomorphology alone without ancillary testing to achieve a definitive diagnosis of lymphoma.

- *Note:* Cytomorphology alone without ancillary studies has low sensitivity and low predictive value.
- *Note:* A defined subset of lymphoma requires architectural assessment and cannot be reliably diagnosed and subclassified by FNA

Is the problem a priority?	No	Probably No	Probably Yes	Yes
			•	••••••••••
How substantial are the benefits?	Trivial	Small	Moderate	Large
			••••	•••••
How substantial are the harms?	Large	Moderate	Small	Trivial
			••••••	•••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes	Probably No	No
	••	•••	•••••	••
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
				••	••••••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
		•••••	•••	••••	
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
	•	•	••	•••••••	
Is the intervention acceptable to key stakeholders?	No	Probably No	Probably Yes		Yes
		•	•••••		•••••
Is the intervention feasible to implement?	No	Probably No	Probably Yes		Yes
			•••		••••••••

Statement 4. Clinical care providers should follow-up patients with "negative" results for persistent signs and symptoms of lymphoma and pursue larger volume biopsy when clinical suspicion for lymphoma persists.

Is the problem a priority?	No	Probably No		Probably Yes	Yes
		•		•••	•••••••
How substantial are the benefits?	Trivial	Small		Moderate	Large
				•••••	••••••
How substantial are the harms?	Large	Moderate		Small	Trivial
				•••••••	••••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
		••••		••••••	•
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
			•	•	•••••••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
		••••••••	••	•	
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
			••••••	••••	•
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
				••••••	•••••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
				•••••	••••••

Statement 5. Clinical care providers may use positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (FDG-PET) to identify sites for biopsy in patients with suspected transformed/aggressive-histology lymphoma. As feasible, biopsies should be directed to the site of greatest FDG avidity.

Is the problem a priority?	No	Probably No		Probably Yes	Yes
	•	•••		•••	••••
How substantial are the benefits?	Trivial	Small		Moderate	Large
				•••••	•••••
How substantial are the harms?	Large	Moderate		Small	Trivial
	•	•••••		•••	••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
		••		••••••••	•
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
			••	•••••	••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
	•••	•••••••	•		
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
		••••	••••	•••	
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
				•••••••	••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
				••••••••	•

Statement 6. Clinical care providers may obtain bone marrow biopsies for the primary diagnosis in select patients with suspected lymphomas.

- *Note:* For certain lymphoma types (e.g. splenic low-grade lymphomas, lymphoplasmacytic lymphomas), bone marrow biopsy may be preferred over more invasive surgical methods.

Is the problem a priority?	No	Probably No	Probably Yes	Yes
	•	•••	•••	••
How substantial are the benefits?	Trivial	Small	Moderate	Large
		••	•••••	••

How substantial are the harms?	Large	Moderate		Small	Trivial
		••		•••••	•••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
	•	••••		•••••	•
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
			••	•••••	••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
		••	••••	••••	
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
			••••••	•••••	
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
				•••••••••	••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
				••••	•••••••
Statement 7. Clinical care providers may use cerebrospinal fluid (CSF) for the evaluation of primary or secondary central nervous system (CNS) lymphoma in select patients.					
Is the problem a priority?	No	Probably No		Probably Yes	Yes
	•	•		•••	•••
How substantial are the benefits?	Trivial	Small		Moderate	Large
				••••	••••••
How substantial are the harms?	Large	Moderate		Small	Trivial
	•	•••••		•••	•
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
		•		•••••••••	•
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
			•	••••	••••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
		•••••	••••	•	•
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
	•		•••••••	•••	
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
				••••••	••••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
				•••	••••••••
Statement 8. Clinical care providers should use a combined morphologic and flow cytometric evaluation of CSF in the investigation of possible primary or secondary CNS lymphoma in select patients.					
Is the problem a priority?	No	Probably No		Probably Yes	Yes
				••••••	•••
If the intervention is an ancillary test, how accurate it is?	Very Inaccurate	Inaccurate		Accurate	Very Accurate
				••••••	•
How substantial are the benefits?	Trivial	Small		Moderate	Large
				•••••••	••••
How substantial are the harms?	Large	Moderate		Small	Trivial
	••	•••		••••	••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
		•		•••••••	•••
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
				••••	•••••••

How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
		•••••••	••••		
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
		••	••••••	•••	
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
				••••••	•••••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
				•••	••••••
Statement 9. Based on low negative predictive values, clinical care providers should follow-up patients with "negative" results for persistent signs and symptoms of CNS lymphoma and pursue repeat CSF examination or biopsy when clinical suspicion for lymphoma persists.					
Is the problem a priority?	No	Probably No		Probably Yes	Yes
	•	•••		•••	•
How substantial are the benefits?	Trivial	Small		Moderate	Large
				•••••	•••••
How substantial are the harms?	Large	Moderate		Small	Trivial
		••••		•••••	••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
		•••		••••••	••
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
				•••	••••••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
		•••••••	•••	•	
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
		•	••••••	•••	•
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
				••••••••	•••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
				••••••	•••••
Statement 10. Clinical care providers should use immunophenotyping by flow cytometry and/or IHC in addition to morphology for the evaluation of specimens for the diagnosis and subclassification of lymphomas.					
Is the problem a priority?	No	Probably No		Probably Yes	Yes
					••••••••••••
If the intervention is an ancillary test, how accurate it is?	Very Inaccurate	Inaccurate		Accurate	Very Accurate
				••	•••••••••
How substantial are the benefits?	Trivial	Small		Moderate	Large
					••••••••••••
How substantial are the harms?	Large	Moderate		Small	Trivial
		•••		•••••••	•
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
				••••••	•••••
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
					••••••••••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
		••••••••	•••		
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
			•••••••	•••	•
	No	Probably No		Probably Yes	Yes

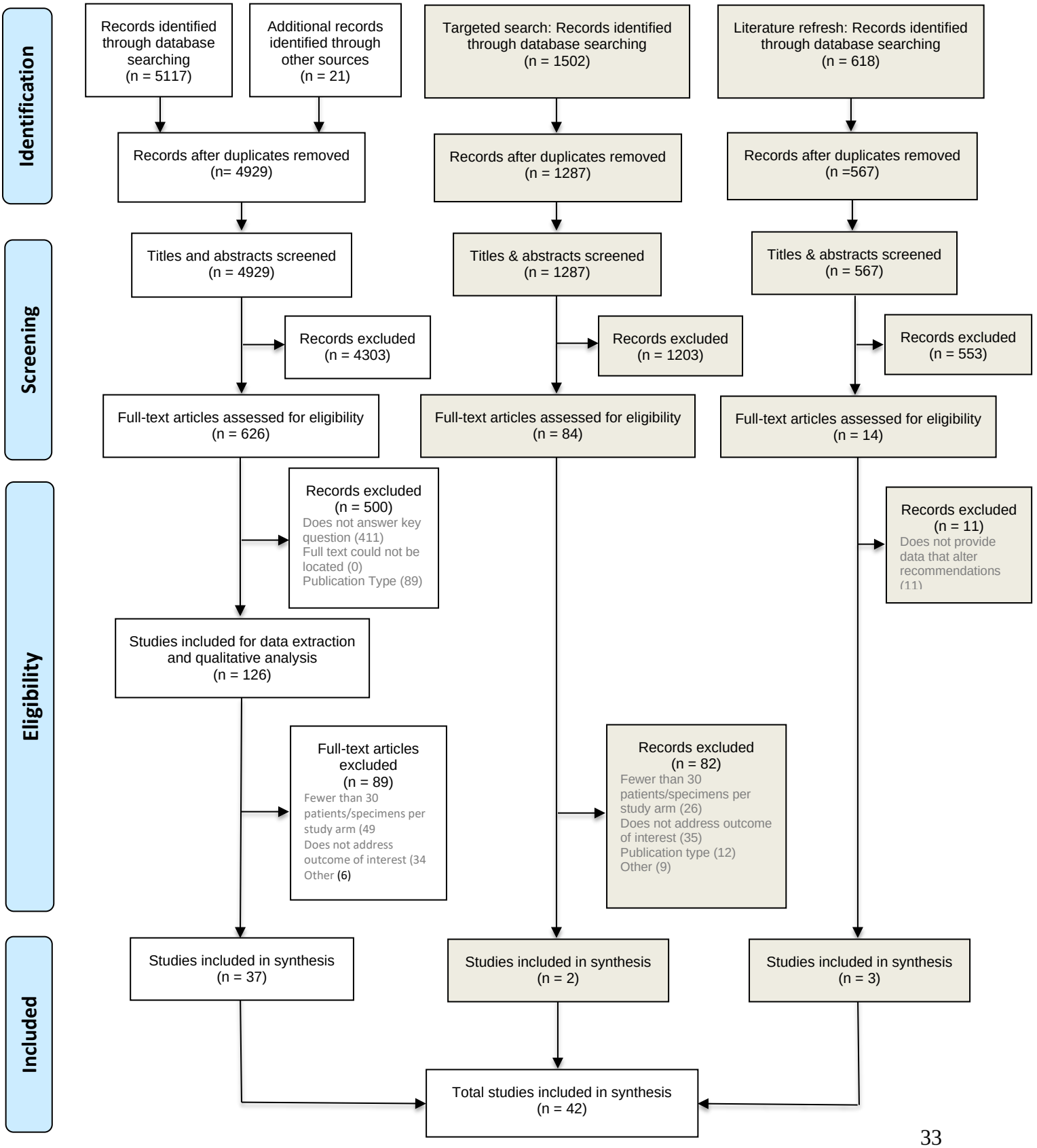
Is the intervention acceptable to key stakeholders?				•••	••••••••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
				••••	•••••••
Statement 11. Clinical care providers may use fluorescence in situ hybridization (FISH) analysis when evaluating specimens in patients with suspected or confirmed lymphoma, or in the subclassification of lymphoma. FISH analysis is feasible on specimens obtained by FNA and may increase diagnostic yield. *Note:* Demonstration of the appropriate rearrangements is required for a diagnosis of high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements.					
Is the problem a priority?	No	Probably No		Probably Yes	Yes
		••		••••••	•
If the intervention is an ancillary test, how accurate it is?	Very Inaccurate	Inaccurate		Accurate	Very Accurate
				•••••	••••
How substantial are the benefits?	Trivial	Small		Moderate	Large
		•		••••	•••••
How substantial are the harms?	Large	Moderate		Small	Trivial
	•	••••		•••••	•
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
	•	•		••••••	•••
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
			••	•••	••••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
		••••••••	••	•	
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
		•	••	••••	••••
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
		•		••••••••	••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
		•		••••••	••
Statement 12. Clinical care providers should not routinely use up-front PCR-based clonality studies of antigen receptor genes (ie, T-cell receptor and immunoglobulin) in the initial investigation of lymphoma. There may be a confirmatory role in certain settings for these studies.					
Is the problem a priority?	No	Probably No		Probably Yes	Yes
		•		•••••••••	
If the intervention is an ancillary test, how accurate it is?	Very Inaccurate	Inaccurate		Accurate	Very Accurate
		••		••	
How substantial are the benefits?	Trivial	Small		Moderate	Large
		••		•••	•
How substantial are the harms?	Large	Moderate		Small	Trivial
				••••	•
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
		•••••		••	••
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
	•••	•••	••		
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
	••	•••••	•	•	
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
	•	••••	••••		
	No	Probably No		Probably Yes	Yes

Is the intervention acceptable to key stakeholders?			•••••	•
Is the intervention feasible to implement?	No	Probably No	Probably Yes	Yes
			••••	••

Statement 13. Clinical care providers may use molecular tests to aid in classification of lymphomas. For example, pathologists may use *MYD88* L265P to aid in the classification of indolent B-cell lymphoma.
Note: This recommendation statement refers to non-FISH molecular tests.

Is the problem a priority?	No	Probably No		Probably Yes	Yes
		•		••••••••	•
If the intervention is an ancillary test, how accurate it is?	Very Inaccurate	Inaccurate		Accurate	Very Accurate
				••••	•••
How substantial are the benefits?	Trivial	Small		Moderate	Large
		•		••••••••	••
How substantial are the harms?	Large	Moderate		Small	Trivial
				••••••	•••••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
		•		•••••••••	•
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
				•••••••	••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
	•	••••••	••••		
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
		•	•••••	•••••	
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
				••••••••	•••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
				••••••	••

Supplemental Figure 1. Literature Review Flow Diagram



Supplemental Figure 2: Database Search Strings

Combined Systematic Review Literature Searches:

Ovid:
((exp composite lymphoma/ or exp hodgkin disease/ or exp immunoproliferative small intestinal disease/ or exp lymphoma, non-hodgkin/ or exp Splenomegaly/ or exp Waldenstrom Macroglobulinemia/ or (alpha-Chain Disease* or enlarged spleen or IPSID or L3 Lymphocytic Leukemia* or lymphoid neoplasm* or lymphoma* or lymphoma/ or Lymphomatoid Granulomatos* or lymphoproliferat* or Macroglobulin?emia or Splenomegaly or (Burkitt* adj (tumo?r or leuk?emia)) or (Hodgkin* adj (Granuloma or granulomas or Disease or lymphoma))).mp)
and (biopsy/ or exp biopsy, needle/ or exp image-guided biopsy/ or Lymph Node Excision/ or (cnb or fna or fnab or cytopuncture* or lymphadenectom* or trucut or tru-cut or cytologic sample* or ((ascites or blood or bone-marrow or core or csf or endoscopic or excisional or image-guided or incisional or low-volume or marrow or open or pericardial or peritoneal or pleural fluid or small or serous or spinal fluid or surgical or vacuum-assisted) adj3 biops*) or ((core or cutting or fine or skinny or wang) adj1 needle*) or (needle* adj3 (aspirat* or biops* or core*)) or (node* adj3 (biops* or excision* or dissect* or resect*))).mp)) not (comment/ or editorial/ or case reports/ or (letter/ not clinical study/) or (exp animals/ not humans/)) limit to (english language and yr="2002 -Current")

Embase:
('alpha-chain disease' OR 'b cell lymphoma'/exp OR 'brain lymphoma'/exp OR 'composite lymphoma'/exp OR 'enlarged spleen' OR 'gastrointestinal lymphoma'/exp OR 'ipsid' OR 'l3 lymphocytic leukemia*' OR 'lymphoid neoplasm*' OR 'lymphoma*' OR 'lymphoma'/de OR 'lymphomatoid granulomatos*' OR 'lymphomatosis'/exp OR 'lymphoproliferat*' OR 'macroglobulin?emia' OR 'nonhodgkin lymphoma'/exp OR 'primary central nervous system lymphoma'/exp OR 'splenomegaly' OR 'splenomegaly'/exp OR 'stomach lymphoma'/exp OR 'thymus lymphoma'/exp OR (hodgkin* NEXT/1 (granuloma OR granulomas OR disease OR lymphoma)) OR (burkitt* NEXT/1 (tumo?r OR leuk?emia))) AND ('bone marrow biopsy'/exp OR 'endoscopic biopsy'/exp OR 'image guided biopsy'/exp OR 'liquid biopsy'/exp OR 'lymph node biopsy'/exp OR 'needle biopsy'/exp OR 'percutaneous biopsy'/exp OR 'pericardial biopsy'/exp OR 'peritoneal biopsy'/exp OR 'biopsy'/de OR cnb OR fna OR fnab OR cytopuncture* OR lymphadenectom* OR trucut OR 'tru-cut' OR 'cytologic sample*' OR ((ascites OR blood OR 'bone-marrow' OR core OR csf OR endoscopic OR excisional OR 'image-guided' OR incisional OR 'low-volume' OR marrow OR open OR pericardial OR peritoneal OR 'pleural fluid' OR small OR serous OR 'spinal fluid' OR surgical OR 'vacuum-assisted') NEAR/3 biops*) OR ((core OR cutting OR fine OR skinny OR wang) NEXT/1 needle*) OR (needle* NEAR/3 (aspirat* OR biops* OR core*)) OR (node* NEAR/3 (biops* OR excision* OR dissect* OR resect*))) AND [2002-2018]/py AND [english]/lim NOT ([medline]/lim OR 'conference abstract'/it OR 'conference paper'/exp OR 'case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'note'/exp OR ('letter'/exp NOT 'clinical study'/exp) OR ('animal'/exp NOT 'human'/exp))

Non-Systematic Review Literature Searches:

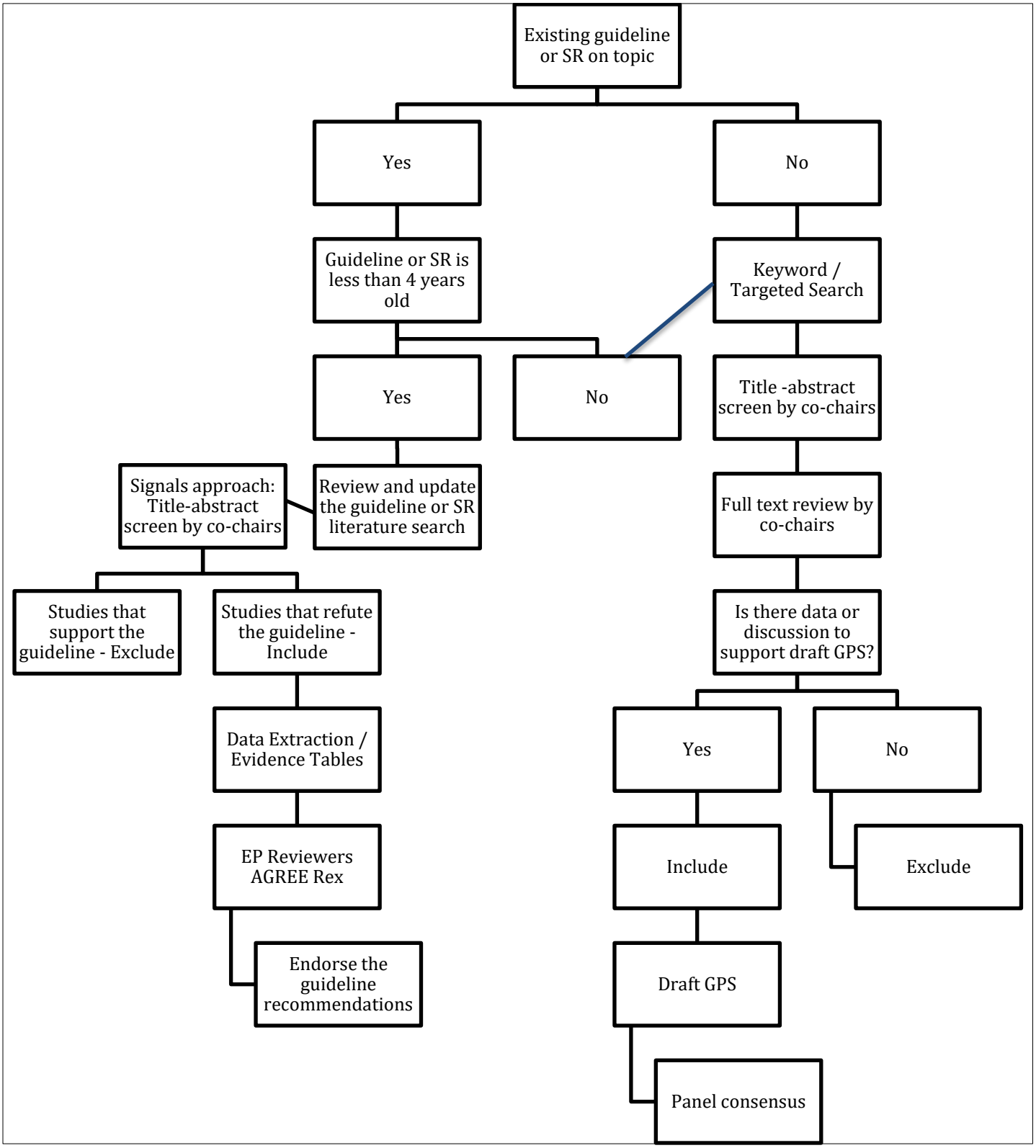
Pathology samples in which lymphoma as suspected:
((exp pathology/ or or exp histology/ or exp cytodiagnosis/ or ((pathology or pathologist: or cytopathology: or histopathology or histopathologist:? Or neuropathology or neuropathologist? Or dermatopathology or dermatopathologist?) or (cytodiagnois or histology or cytology).mp) AND (exp diagnostic errors/ or exp observer variation/ or exp “referral and consulation” or exp quality assurance, Health Care/ or exp quality control or ((diagnostic error? or observer variation or (second: adj2 (opinion? or review? or consult:)) or ((reference or second: or third or tertiary) adj (pathologist? or cytopathologist? or histopathologist? or haem??opathologist? or hem??opathologist?)) or (amend: adj2 report:) or (diagnos: adj2 (variation or disagreement or discrepancy)) or (interinstitutional adj2 (review: or consultation)) or interobserver variation or slide: review:).mp) or ((cytodiagnosis or histology or cytology.mp) or (quality control or quality assurance or interlaboratory comparison).mp) or ((diagnos: adj2 agreement).mp) or ((central: adj2 review).kw or (central: adj2 review).tw) or reproducibility.ti) limit to (english language and yr="2013 -Current")) AND (exp composite lymphoma/ or exp hodgkin disease/ or exp immunoproliferative small

intestinal disease/ or exp lymphoma, non-hodgkin/ or exp Splenomegaly/ or exp Waldenstrom Macroglobulinemia/ or (alpha-Chain Disease* or enlarged spleen or IPSID or L3 Lymphocytic Leukemia* or lymphoid neoplasm* or lymphoma* or Lymphomatoid Granulomatos* or lymphoproliferat* or Macroglobulin?emia or Splenomegaly or (Burkitt* adj (tumo?r or leuk?emia)) or (Hodgkin* adj (Granuloma or granulomas or Disease or lymphoma))).mp.)

Reporting elements in pathology samples in which lymphoma is suspected:

(((exp composite lymphoma/ or exp hodgkin disease/ or exp immunoproliferative small intestinal disease/ or exp lymphoma, non-hodgkin/ or exp Splenomegaly/ or exp Waldenstrom Macroglobulinemia/ or (alpha-Chain Disease* or enlarged spleen or IPSID or L3 Lymphocytic Leukemia* or lymphoid neoplasm* or lymphoma* or Lymphomatoid Granulomatos* or lymphoproliferat* or Macroglobulin?emia or Splenomegaly or (Burkitt* adj (tumo?r or leuk?emia)) or (Hodgkin* adj (Granuloma or granulomas or Disease or lymphoma))).mp.) and (Reporting.ti. or (report* adj5 (synoptic or standard? or uniform or format? or include? or inclusion or checklist? or template? or element? or pathology)).ti,ab,kf.)) limit to (english language and yr="2002 -Current")) not (comment/ or editorial/ or case reports/ or (letter/ not clinical study/) or (exp animals/ not humans/))

Supplemental Figure 3. Good Practice Statements Literature Review Strategy



Glossary

Acceptability - Acceptability reflects who benefits (or is harmed) and who pays (or saves); and when the benefits, adverse effects, and costs occur (and the discount rates of key stakeholders; eg, politicians may have a high discount rate for anything that occurs beyond the next election). For the Evidence to Decision (EtD) framework, the expert panel (EP) considered target users of the guideline. The less acceptable an option is to key stakeholders, the less likely it is that it should be recommended, or if it is recommended, the more likely it is that the recommendation should include an implementation strategy to address concerns about acceptability.

Accuracy - The degree of correctness or true values of a given laboratory result comparing to a gold standard. Accuracy also implies freedom from error.

Benefit – a valued or desired outcome. In EtD, the EP considers both the magnitude of the benefits as well as the importance of that benefit to both clinicians and patients.

Bone Marrow Biopsy – Removal of a sample of bone marrow.

Cerebrospinal Fluid (CSF) – Body fluid found in the brain and spinal cord.

Central Nervous System (CNS) – Part of the nervous system consisting of the brain and spinal cord.

Confidence Interval (CI) – The 95% confidence interval is a range of values that we can be 95% certain contains the point statistic.

Cost – In this guideline, the discussion on cost pertains to the use of resources for an intervention or a recommendation.

Core Needle Biopsy (CNB) – Removal of a cylinder-shaped (core) samples of tissue from a lump or mass.

Equity – Health equity is the attainment of the highest level of health for all people. For the EtD, the EP deliberated any advantages or disadvantages for any group or setting in relation to the recommendation being considered. The EP considered any differences in baseline conditions across groups or settings that affect the absolute effectiveness of the recommendation or the importance of the problem for disadvantaged groups or settings. The EP discussed any important considerations that should be made when implementing the recommendations in order to ensure that inequities are reduced or eliminated.

Excisional Surgical Biopsy – Surgical removal of an entire lump or mass.

Feasibility – is the capability of an intervention or an action to be accomplished or implemented. The less feasible an option is, the less likely it is that it should be recommended. For the EtD, the EP considered barriers that are likely to limit the feasibility of implementing the recommendation.

Fine Needle Aspirate (FNA) – Removal of a sample of cells, tissue, or fluid using a small needle.

2-deoxy-2-[fluorine-18]fluoro-D-glucose Positron Emission Tomography (FDG-PET) - 18-Fluoro-deoxyglucose positron emission tomography (FDG-PET) is a noninvasive, 3-dimensional imaging modality that has become widely used in the management of patients with malignant lymphomas.

Fluorescence in situ Hybridization (FISH) - A molecular cytogenetic technique using fluorescent probes that bind to only those parts of a nucleic acid sequence with a high degree of sequence complementarity.

Flow Cytometry (FC) - Method for simultaneous multi-parameter analysis of single cells. Laser-based technology enables analysis of cell surface and intracellular molecules expression, characterization of different cell types in a heterogeneous cell population, assessment of purity of isolated subpopulations, and analysis of cell size and volume.

Harms – a risk or injury occurring as a result of an intervention. In EtD, the EP considered both the magnitude of the harms as well as the importance of that harm to both clinicians and patients.

High suspicion – A subjective clinical impression favoring a diagnostic entity based on a set of preliminary positive and negative findings. For example, high suspicion of lymphoma in a patient with lymphadenopathy without primary tumors or clinical signs and symptoms of infection.

Incisional Surgical Biopsy - Surgical removal of a sample from a lump or mass.

Interobserver Agreement – The degree to which two or more independent observers report the same values after measuring the same events.

Meta-Analysis (MA) – Statistical procedure for combining data from multiple studies. Outcomes from a meta-analysis may include a more precise estimate of the effect of treatment or risk factor for disease, or other outcomes, than any individual study contributing to the pooled analysis.

Negative Predictive Value (NPV) - The predictive value of a negative result. This value corresponds to the percentage of true negative patients among those given a negative test result.

Negative result – In the context of this guideline this implies either the absence of lymphoma or the absence of a positive identification of an alternative diagnosis, such as infectious etiology or non-hematopoietic neoplasm.

Outcomes – Outcomes are the potential benefits or harms. Outcomes that are considered to be important to those affected by the intervention, and which are important to making a recommendation or decision. Consultation with those affected by an intervention (such as patients and their caretakers) or other members of the public may be used to select the important outcomes. A review of the literature may also be carried out to inform the selection of the important outcomes. The importance (or value) of each outcome in relation to the other outcomes should also be considered. This is the relative importance of the outcome.

Polymerase Chain Reaction (PCR) – A laboratory technique used to make multiple copies of a segment of DNA. PCR is very precise and can be used to amplify, or copy, a specific DNA target from a mixture of DNA molecules.

Pre-Test Probability – The probability of the presence of a condition before a diagnostic test result is known.

Problem – In the EtD, the EP considered the priority of the problem a recommendation is addressing. The EP considered if the consequences of the problem are serious and if addressing the problem is urgent. Serious problems are more likely that an option which addresses the problem should be a priority (e.g., diseases that are fatal or disabling are likely to be a higher priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.

Prospective Cohort Study (PCS) – Study design that enrolls a cohort of subjects and watches those subjects over a time period. A prospective study watches for outcomes during the study period and relates those outcomes to prior exposure or clinical characteristic.

Positive Predictive Value (PPV) – The predictive value of a positive result. This value corresponds to the percentage of true positive patients among those given a positive test result.

Randomized Controlled Trial (RCT) – Study design that randomly assigns subjects into an experimental group or a control group. Subjects are followed to determine effectiveness of the experimental intervention with outcomes measured at specific time-points.

Retrospective Cohort Study (RCS) – Study design that enrolls a cohort of subjects based on a known outcome and looks backwards to correlate prior exposure or clinical characteristic to that outcome.

Secondary Review – Secondary case reviews in pathology is a method of improving error detection. Pathologists may use prospective or retrospective case reviews.

Select patients – A subpopulation of patients with attributes beyond a general suspicion of lymphoma. This may pertain to a suspicion of a specific diagnosis, such as patients with splenic enlargement and suspected splenic marginal zone B-cell lymphoma, or it may pertain to clinical attributes with a specific combination of clinical findings, such as history of lymphoma and abnormal brain imaging. *Note:* In either case, the selective criteria may improve the diagnostic yield of a lower risk procedure (e.g., CSF sampling, bone marrow biopsy) before proceeding with a higher risk procedure (e.g., brain biopsy, other invasive procedure).

Sensitivity – The probability that a diagnostic test identifies patients who are in fact positive for a disease. The value corresponds to the percentage of true positive results demonstrated by an assay among those who are truly positive.

Specificity - The probability that a diagnostic test identifies patients who are in fact negative for a disease. The value corresponds to the percentage of true negative results demonstrated by an assay among those who are truly negative.

Systematic Review (SR) - A systematic review summarizes the results of available carefully designed healthcare studies and provides a high level of evidence on the effectiveness of healthcare interventions. Judgments may be made about the evidence and inform recommendations for healthcare.

Transformation – Transformation of lymphoma occurs when indolent lymphoma transforms into a more aggressive type of lymphoma.

Turnaround Time – Turnaround time is defined as the time a specimen is received in the laboratory to the time a result is reported.