



COLLEGE of AMERICAN  
PATHOLOGISTS  
Laboratory Quality Solutions

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# Evidence-based Guideline Development Methodology Manual

Pathology and Laboratory Quality Center for  
Evidence-based Guidelines

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## Introduction and Overview

The College of American Pathologists (CAP), the leading organization of board-certified pathologists, serves patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide. The CAP developed the Pathology and Laboratory Quality Center for Evidence-based Guidelines (the Center) as a forum to create and maintain evidence-based practice guidelines. Practice guidelines reflect the best available evidence and expert consensus supported in practice. This manual is intended to transparently outline the methods the CAP uses to develop laboratory practice guidelines and is intended primarily for CAP staff involved in developing guidelines, collaborating organizations, and members of the Center Guideline Committee (CGC) who have primary oversight of the guideline development projects. It may also be of interest to other stakeholders with interest in specific guidelines or in general guideline development processes.

The CAP follows standards developed by the National Academy of Medicine (formerly the Institute of Medicine [IOM])<sup>1</sup> and international recognized guideline development methodology (eg, AGREE II, GRADE).<sup>2,3</sup> It posts details about guidelines in development on the Guidelines International Network site,<sup>4</sup> completes standard reporting forms when published, and posts published guidelines on the CAP website.<sup>5</sup>

This manual outlines the guideline development process from topic selection through publication and maintenance and covers the stages illustrated in Figure I. Each stage will be discussed in detail.

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

CAP assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this statement or for any errors or omissions.

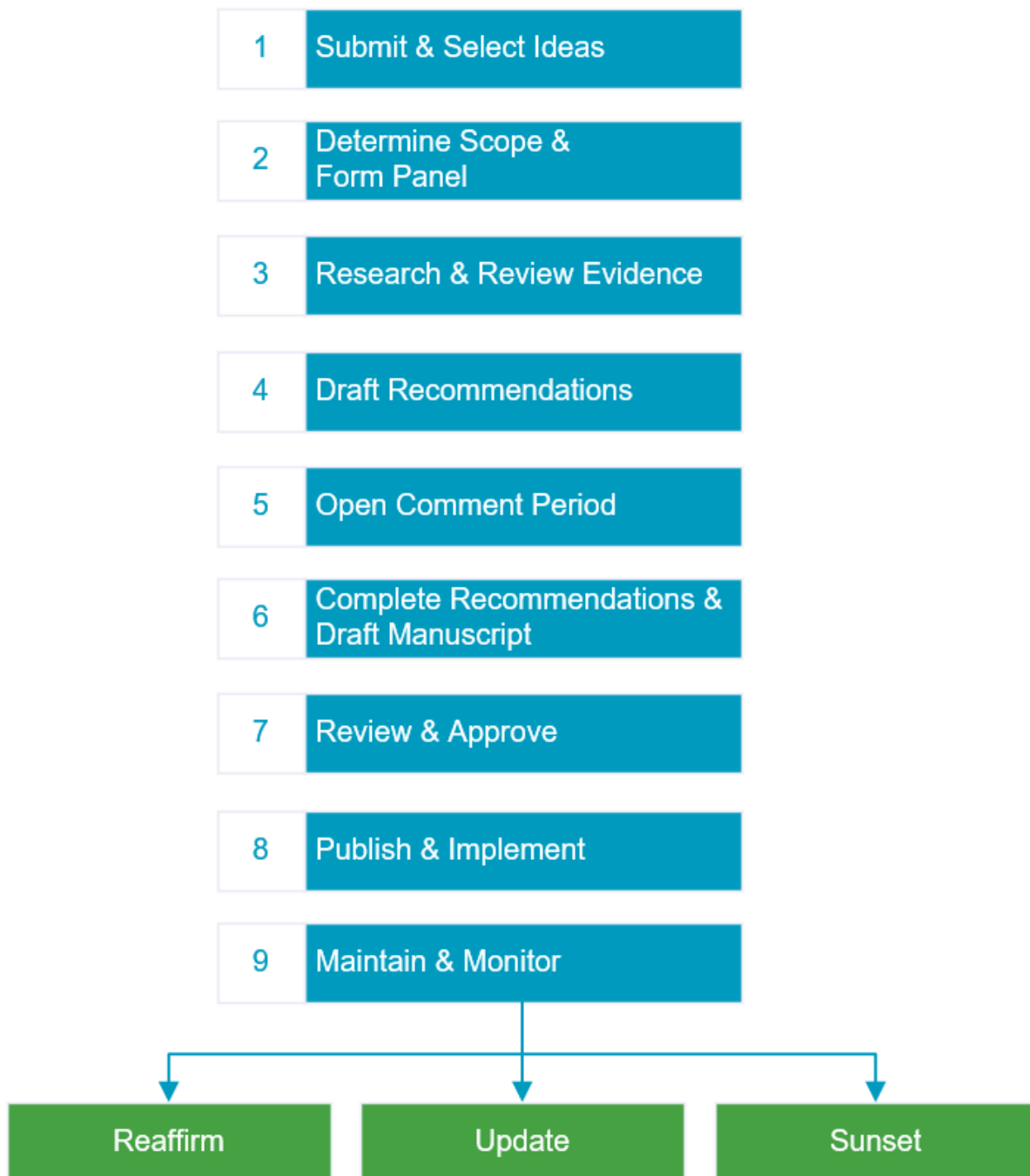


Figure 1. Overview of development stages for CAP guidelines.

## The Center's Commitment to Diversity, Equity, and Inclusion

The CAP Pathology and Laboratory Quality Center for Evidence-based Guidelines is fully committed to being inclusive and will establish diverse committee and panel members. To the greatest extent possible, we will develop interdisciplinary groups of members with various backgrounds, experiences, and expertise. In return we ask the individuals working on our groups to fully contribute to discussions and decisions by providing their unique viewpoints to develop guidelines that will benefit laboratories, hospitals, and ultimately patients.

When developing guideline panels, the Center will strive for diversity of:

- Gender
- Race/ethnicity/national origin
- Sexual orientation
- Disability status
- Age
- Years in practice
- Expertise
- Geographic location
- Practice types (eg, community practice, academic, reference laboratories, Veterans facilities, etc)
- Population the member's practice serves (eg, low socioeconomic groups, urban/rural, etc)
- Stakeholders
  - Non-pathology physicians/societies
  - Laboratory personnel (eg, medical technologist, cytotechnologists, etc)
  - Patients/Patient advocates

## 1. Submit and Select Ideas

Pathologists and others are invited to [submit](#) evidence-based guideline (EBG) ideas and topics via the [CAP website](#). Ideas may be submitted any time. The CGC reviews submissions and recommends projects to the Council on Scientific Affairs (CSA).

All topics under consideration must meet the criteria to undergo a systematic review and be developed as an EBG under the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)<sup>3</sup> for Diagnostic Tests methodology. In addition, the CGC selects topics that:

- have a major focus to reduce/mitigate patient risk, and/or improve patient safety and quality outcomes;
- define standards of care for pathology practice and aim to decrease ambiguity and increase clarity about diagnostic algorithms or testing methodology;
- include evidence that emerging technologies and/or diagnostic testing will impact the practice of pathology at large and the patients whom we serve;
- contain a risk to CAP that regulatory bodies or other professional organizations are trying to preempt, disprove or are showing an unusual interest in;
- have a potential for collaboration with partner organization(s) in development of a Center guideline to facilitate dissemination and adoption to improve probability of success;
- improve public perception of the pathologists' role in medicine.

Questions that guide topic selection:

- What problem is the guideline trying to solve?
- Who has or will have this problem?
- How is the problem being solved today?
- Why would the proposed guideline be better?
- What advantage does the Center and the CAP have in delivering this solution?



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THROUGH EVIDENCE-BASED  
GUIDELINES



## 2. Develop Scope and Form Panel

Before experts and partners are considered, a draft guideline scope must be developed. Initially, the scope is broadly defined by the CGC and then refined by an ad hoc committee of topic experts and the idea submitter. The final scope is determined by the expert (EP) and advisory (AP) panels prior to performing the literature search.

Once a draft scope is defined, partnering or collaborating organizations are considered/secured. Possible collaborations or partnerships with other organizations are discussed during scope development. A partner organization will jointly hold all rights in and to the evidence-based guideline and the associated systematic review. Each partner organization will participate in all phases of the guideline development including the approval of scope and formation of the panel. Partner organizations will have equal share of responsibilities during the guideline development, in addition, partner organizations will provide funding for the guideline. For collaborative guidelines, stakeholder organizations provide panel members to serve on the expert and advisory panel and are provided the opportunity to endorse the guideline. In a collaboration model, the CAP assumes the cost and management of the guideline and the manuscript is submitted to *Archives of Pathology & Laboratory Medicine*.

Once the scope is drafted and partner or collaborating organizations are identified, experts are nominated, beginning with the role of the chair/co-chair. The CGC usually determines if more than one chair is needed. The chair is typically a subject matter expert and a leader in the field.

The charge of the chair is to:

- a. provide leadership and support the activities of the EP and AP, from scope and key question creation through dissemination of the final guideline;
- b. serve as lead author of the guideline and assist in the development of the guideline supplement;
- c. manage Conflict of Interest (COI) disclosures together with Center staff;
- d. ensure feasibility of implementation and facilitate adoption through development of tools (eg, teaching PowerPoint, Frequently Asked Questions, webinars);
- d. participate in implementation strategy development including metrics;
- e. provide input to the EBG communication plan including being spokesperson or appointing designee; and
- f. determine initiation of guideline revision/updating.

### Chair Selection

1. During initial discussions of the guideline scope with the CGC/partnering organization staff (if applicable)/ad hoc committee, members suggest experts in the field who might serve as guideline chair. If the guideline is being developed in partnership with another organization, each

organization selects one individual to serve as co-chair. Chairs must not have COIs; in situations where there are more than 1 co-chair leading a guideline panel, there should be a balance of at least 50% of co-chairs without COI.

2. The CGC and Center staff investigate and narrow down the list.
3. The Center Guideline Development Manager (GDM), contacts the nominee(s) to discuss the guideline, the work entailed, and determine if he/she is willing to serve in the capacity of chair. If so, the GDM requests the individual to complete the conflicts of interest disclosure form.
4. The organization(s) vets the disclosures as per the conflicts of interest (COI) policy and approves the individual. (See COI section for further details)
5. The chair/co-chair nominees are vetted by the CGC and CSA for approval.
6. The GDM notifies the chair/co-chairs of the appointment.

### **Expert Panel (Figure 2)**

The charge of the EP is to develop the EBG, including full participation in systematic review process.

### **Advisory Panel (Figure 2)**

The charge of the AP is to assist the EP in the development of the guideline at key stages: scope development, review of the draft recommendations, and review of the guideline manuscript and supplement.

### **Expert and Advisory Panel Selection**

1. A CGC representative (point person), the guideline chair/co-chairs, and staff meet via conference call to identify stakeholders and determine the types of expertise needed.
2. Once a list is compiled, the Center GDM contacts candidates to discuss the guideline, the work entailed, and determine if he/she is willing to serve. If so, the GDM requests the individual to complete the conflicts of interest disclosure form.
3. The organization(s) vet the disclosures as per the COI policy and the approves the individuals. (See COI section for further details)
4. The EP nominees are vetted and approved by the CGC.
5. The GDM notifies the individuals of their appointments and requests that a commitment letter and Confidentiality/Intellectual Property (IP) agreement be signed and returned.

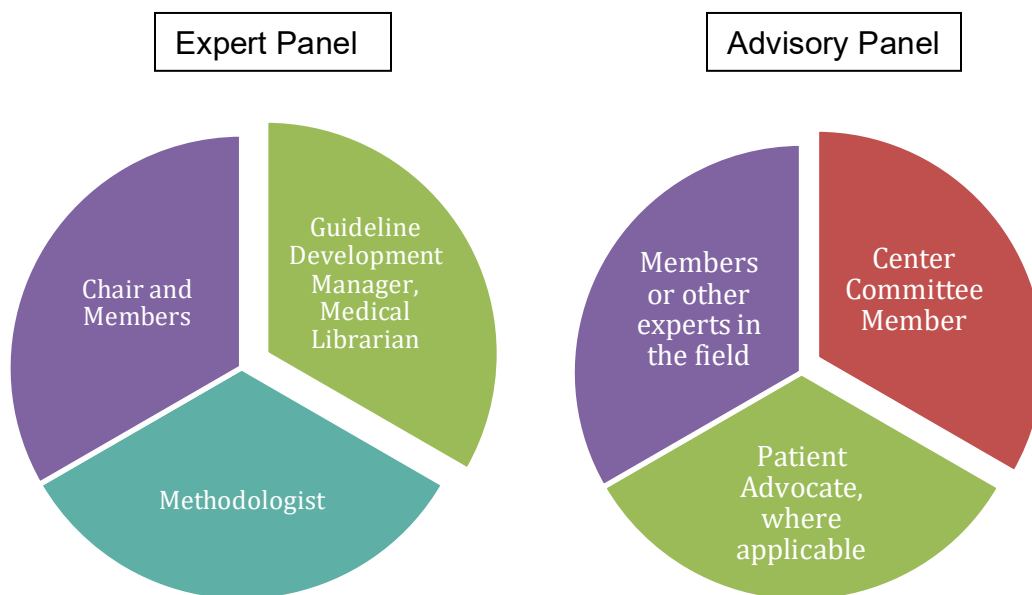
EP and AP members can be identified in various ways: the Center volunteer data base, communications with CAP Councils and Committees, a review of authors who have publications in the area of interest, etc. Generally, 10-12 members serve on the EP and 6 members serve on the AP; fewer or additional members can be appointed based on the complexity of the scope. If the guideline is being developed with a partnering organization, the EP is generally composed of an equal number of representatives from each organization. Wherever possible, the EP should consist of members from various demographic



backgrounds, practice settings, and various degrees of subject matter knowledge (basic/general knowledge to subject matter expert with several years of practice and experience). AP members are almost always subject matter experts with several years of practice and experience.

### Patient Advocate

Whenever possible, patient advocates are invited to participate as advisory panel members. Patient advocates are integral members of a guideline development group. Patient advocates will help the panel determine what factors are important to patients regarding the topic; any preferences a patient may have about certain test, treatment or outcomes; and if language used in any dissemination materials are patient friendly.



*Figure 2. Panel Composition. Expert panel members can be physicians, clinical laboratory scientists, other allied health care professionals. The expert panel may include members from other organizations/societies in joint or collaboration guideline projects.*

### Conflict of Interest (COI) Policy

Prior to acceptance on the expert or advisory panel, potential members are required to complete a disclosure form. CAP Center policy 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 through the time of publication. Any relationships that could be interpreted as constituting an actual, potential, or apparent conflict are required disclosures. When in doubt, expert or advisory panel members should disclose activities; the CAP determines if the relationship is a conflict or not. The criterion of 51% free of conflicts is set for the EP members.

## Finalizing the Scope

The EP and AP discuss and develop the key questions (KQs) the guideline will address.<sup>6</sup> Key questions follow the PICO(TS) framework:

- **Patient:** the patients or population to whom the recommendations are meant to apply
- **Intervention:** the therapeutic, diagnostic, or other intervention under investigation (e.g. the experimental intervention, or in observational studies the exposure factor)
- **Comparison:** the alternative intervention; intervention in the control group
- **Outcome:** the outcome(s) of interest
  - A survey/tool is often employed to determine and rate outcomes in terms of importance
- **Time:** the appropriate time frame in which the recommendations are applied
- **Setting:** the setting or location where the recommendations utilized or applied

The PICO framework aids the expert panel in developing focused key questions that are answerable. PICO helps to clearly define the literature search requirements. This framework ensures guideline recommendation statements are informative and flow directly from the questions. Once KQs and PICO(TS) have been developed and agreed on by the EP and AP members, the medical librarian (ML) prepares to develop the strategy and criteria for the literature search.

## Stakeholder Analysis

A stakeholder analysis and risk assessment is completed at the origination beginning of every guideline project in order to identify potential individuals, groups, or organizations who may affect, be affected, or perceive themselves to be affected by a decision, activity, or outcome of the project. This analysis helps to identify those who may provide valuable input during the development process as well as those who should be integrated into a detailed communication plan designed to periodically update interested parties regarding a guideline project's status. Participants in the stakeholder analysis and risk assessment process are dependent on guideline topic and may include CAP staff, project co-chairs, expert and advisory panel members, and representatives from partner or collaborating organizations.

### 3. Research and Review Evidence

#### Systematic Review

A standardized systematic review process (Figure 3) ensures that the resultant clinical practice guideline is objective, transparent, and scientifically valid.

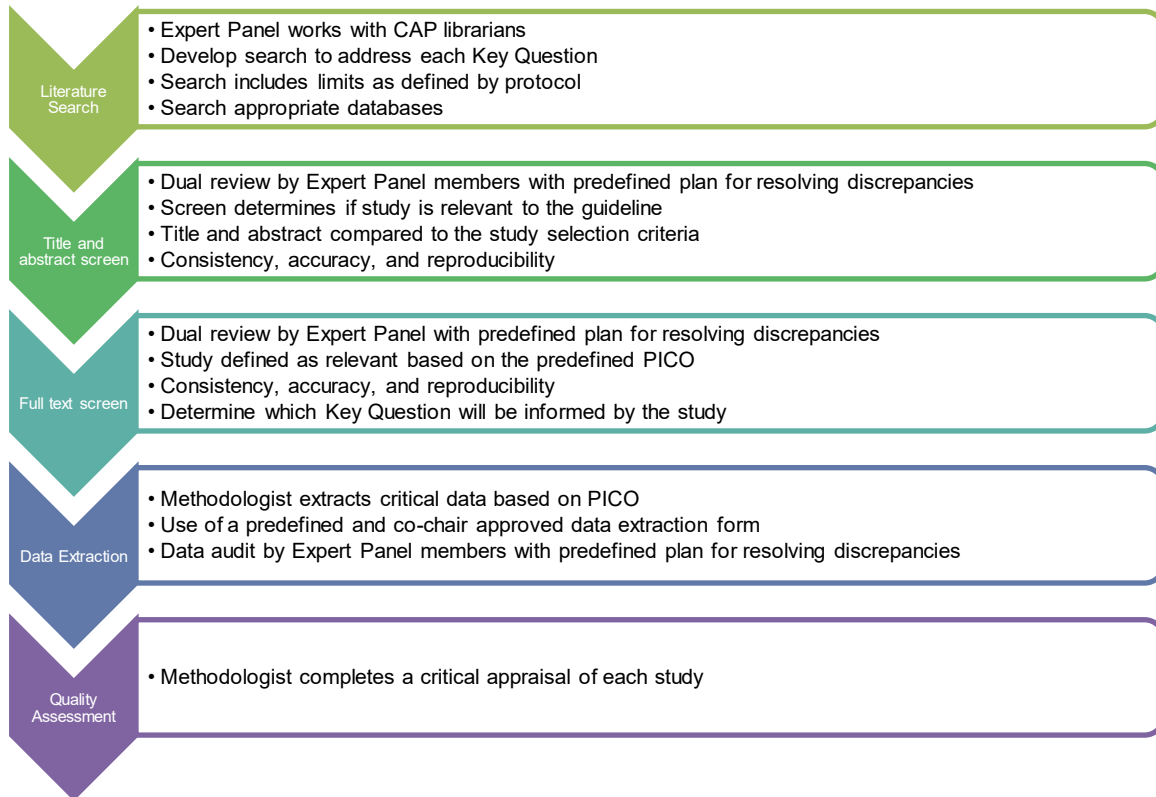


Figure 3. Phases of the systematic review

#### 4. Draft Recommendations

##### Considered Judgement Process

For each recommendation, the aggregate quality is assessed.<sup>3</sup> This helps inform the recommendation statement's quality of evidence. These studies are assessed for overall certainty, quality of pool of evidence, potential for bias and threats to validity across the group of studies. Consistency, precision, directness, and publication bias is also evaluated across all the studies included to inform the recommendations (Figure 5).<sup>3</sup>

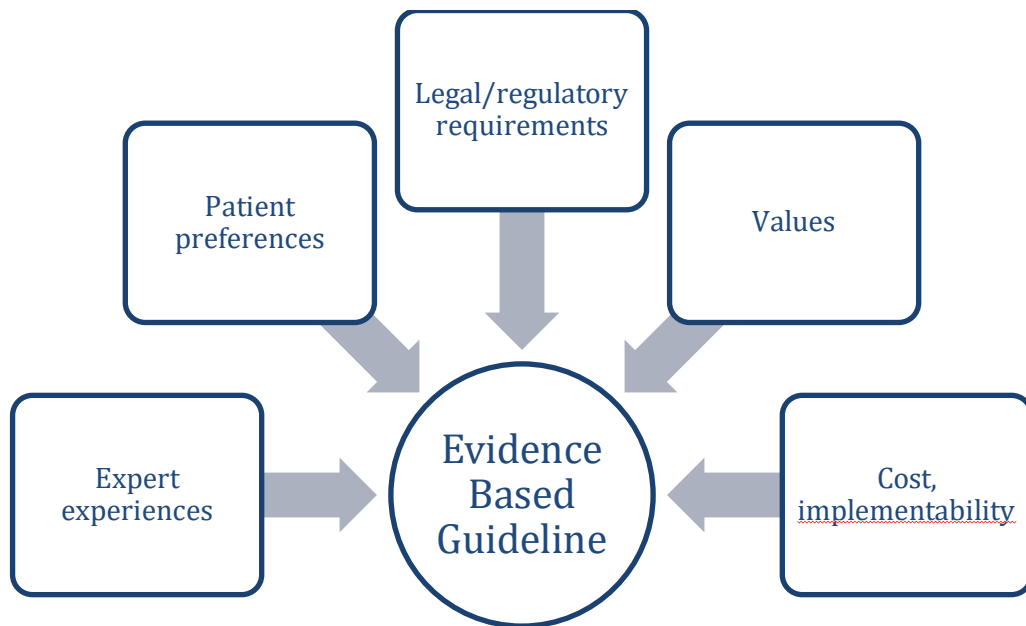


Figure 4. The Evidence Based Guideline recommendations are more than just the evidence. (mention in the text)

The expert panel uses the GRADE approach Evidence-to-Decision (EtD)<sup>3</sup> framework to look at other factors such as problem priority, balance of effects and harms versus benefits, values and preferences, acceptability, feasibility, health equity, and resources.

## 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?

## Quality Assessment

Each individual study is critically appraised for quality and potential for bias. Tests for internal and external validity, risk of bias, threats of study validity are used to appraise each study.

## Hierarchy of Evidence

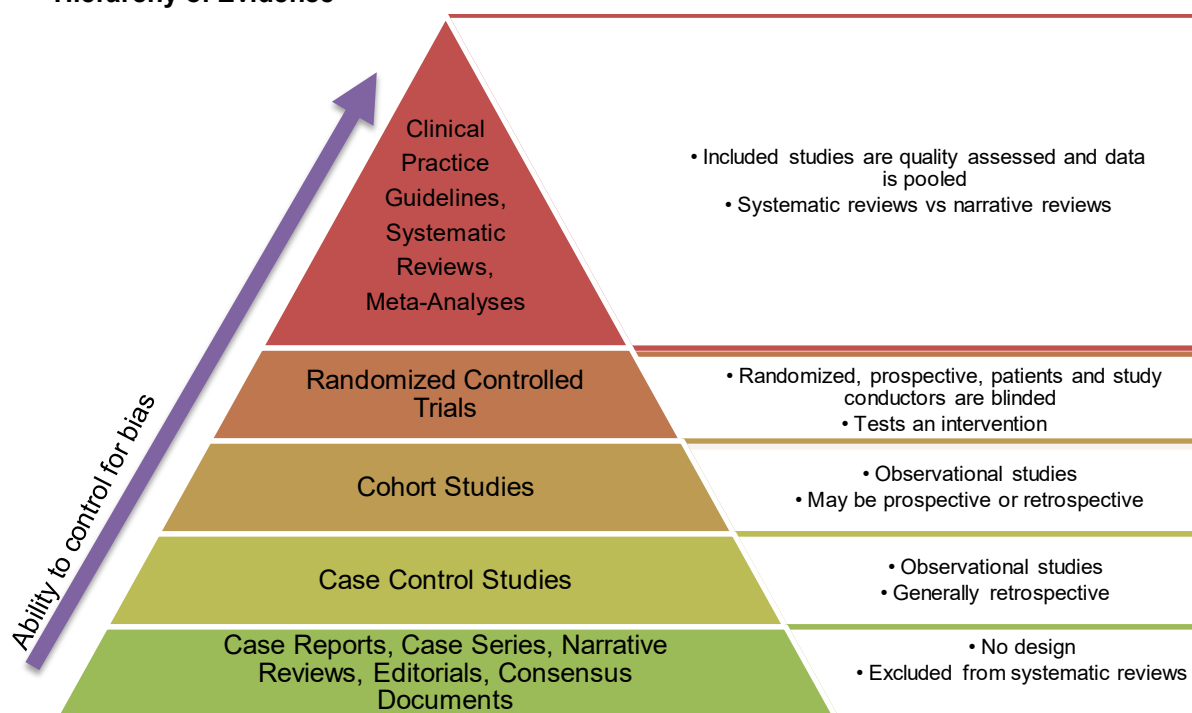


Figure 5. Hierarchy of evidence

## Overall Strength of Evidence (Table 1)

An assessment of the quality of the evidence is performed for all retained studies following application of the inclusion and exclusion criteria. Using this method, studies deemed to 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.

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.

GRADE<sup>5</sup>



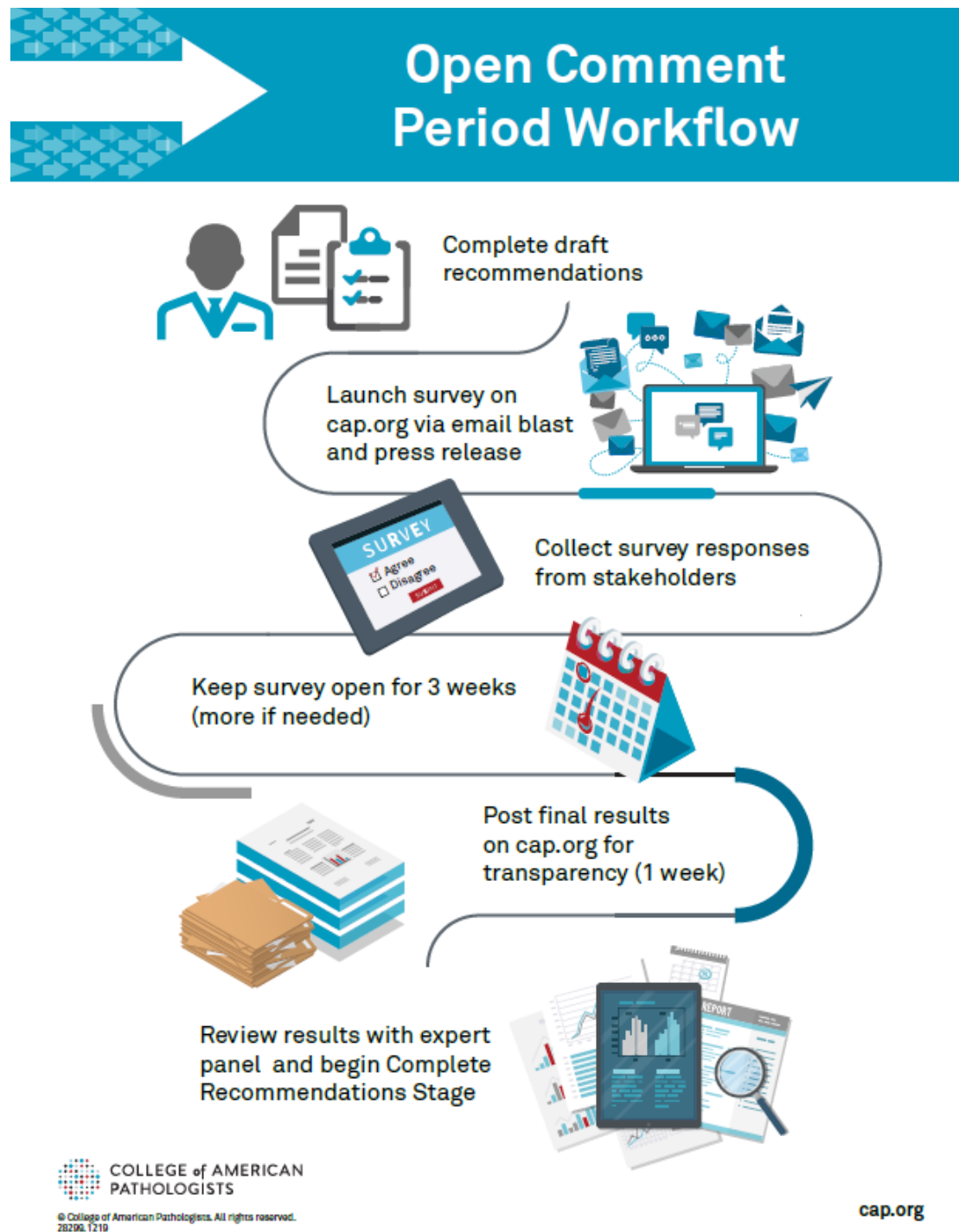
The strength of the evidence, EtD framework, and the expert panel's considered judgement process provides the designation for the strength of recommendations (Table 2).

*Table 2. Strength of Recommendations*

Designation	Rationale
Strong Recommendation (for or against an intervention)	<ul style="list-style-type: none"><li>• Convincing or adequate strength of evidence</li><li>• EtD responses to far right or far left</li></ul>
Conditional Recommendation (for or against an intervention)	<ul style="list-style-type: none"><li>• Adequate, inadequate, insufficient strength of evidence</li><li>• EtD responses to inner right or left</li></ul>

Strong recommendations may be designated despite having moderate/low quality of evidence. Higher tiered evidence (clinical practice guidelines, systematic reviews, metaanalyses, and randomized control trials) are often not available in the pathology literature. Cohort studies, either prospective or retrospective, may be used to make strong recommendations based on the quantity, quality, and consistency of the studies.

## 5. Open Comment Period

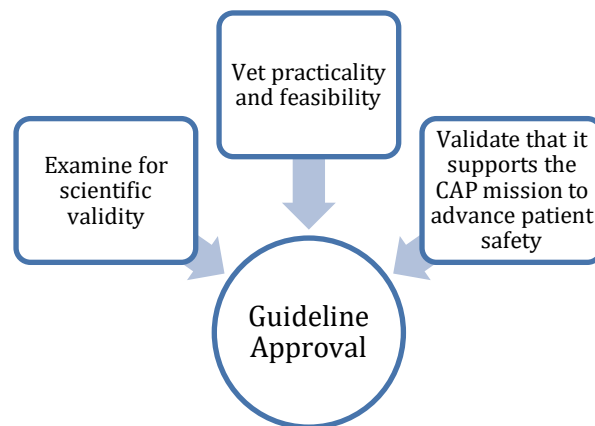


## 6. Complete Recommendations/Draft Manuscript

Following the open comment period, the EP discusses the feedback received and determines the final language of the draft recommendations based on the strength of evidence and considered judgment process.<sup>7</sup> The GDM and chair determine the writing assignments and the EP members contribute to the development of guideline manuscript which follows [Archives of Pathology & Laboratory Medicine Instructions for Authors](#). Once a draft is formed, the manuscript and methods supplement are sent to the AP for edits and feedback. The EP addresses any concerns and then prepares to submit the manuscript and methods supplement to an independent review panel for CAP-approval.

## 7. Review and Approve

An independent review panel (IRP) masked to the expert panel and comprised of 5-7 subject matter experts representing the CAP Council on Scientific Affairs is assembled to review the guideline. The IRP must include at least 1 member pathologist and a community pathologist in the panel. The IRP is vetted through the COI process and provides the approval or disapproval of the guideline. The IRP is charged with assessing the quality of the guideline development methods, its scientific validity, its support for the CAP mission to advance patient safety, and the overall quality of the guideline (Figure 6). The IRP recommends the approval or disapproval of the guideline. In addition, relevant stakeholder such as collaborators, relevant CAP committees and departments (including legal) are requested to provide a high-level review of the guideline. Collaborators are invited to endorse the final guideline.



*Figure 6. Independent Review Panel Tasks for Guideline Approval*

## 8. Publish and Implement

All newly developed CAP EBGs, substantive or non-substantive guideline revisions, and CSs, whether developed solely or in partnership, are submitted for publication in a peer-reviewed journal and are independently peer reviewed as part of the submission process. All comments from independent reviewers are seriously considered and incorporated, as deemed appropriate. All guidelines are published with a disclaimer created in consultation with the organization's legal counsel to outline the intended use of the document.

All CAP guidelines are freely available on the CAP's website<sup>5</sup> at [www.cap.org/protocols-and-guidelines/current-cap-guidelines](http://www.cap.org/protocols-and-guidelines/current-cap-guidelines). In addition, links to published guidelines are posted on the Guidelines International Network<sup>4</sup> and other guideline dissemination sites.

Once the publication date has been determined, the guideline co-chairs, guideline development manager, and CAP Communications staff prepare additional material to support the dissemination of the guideline. These may include frequently asked questions (FAQs) documents, teaching PowerPoint presentations, and glossaries.

A press release will be created to be distributed when the guideline is first published online, and additional dissemination tools may also be employed, such as email blasts, social media posts, or articles in organization publications (eg, CAP Today). Presentations at the CAP annual meeting may be created, including instructional courses, plenary presentations, platform presentations, or poster presentations. In addition, collaboration with CAP committees facilitate dissemination through webinars, participant summary report discussions, and other educational offerings.

## 9. Maintain

Guidelines will be reviewed periodically to determine if an update, revision, or reaffirmation is needed.<sup>8</sup> Decisions are based on factors such as co-chair and EP opinion, known new evidence that will change at least one recommendation in a significant way, or a request received from outside the organization that provides substantial evidence as to the necessity of an update/revision. Guidelines should be reviewed and either reaffirmed, updated/revise, or retired in 5-year increments. The CGC may determine a need to review guidelines with rapidly developing evidence more frequently. All reaffirmations, revisions, or updates will be documented by the publication of an article that outlines the process followed and the outcome of the guideline review.

Metrics will be gathered post-publication in the form of pulse/implementation surveys. Survey responses will be supplemented by the collection of guideline impact surrogate measures, such as citations by journal articles, social media mentions, and a variety of other measures detailed in the Center Guideline Impact Framework (GIF). The CAP Center GIF was adapted from similar impact frameworks used to measure publication impact in academic circles and is separated into five domains of impact: advancement of knowledge, clinical implementation, legislative and policy, community benefit, and economic impact. These indicators of potential impact, along with survey data and other available metrics data, are used to inform decisions made regarding the need to update, revise, or reaffirm a guideline.

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