American College of Medical Genetics and Genomics

Protocol Manual for Evidence-Based Guideline Development

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TABLE OF ACRONYMS

Acronym	Definition
ACMG	American College of Medical Genetics and Genomics
ACMGF	Foundation of the American College of Medical Genetics and Genomics
AHRQ	Agency for Healthcare Research and Quality
AMP	Association for Molecular Pathology
BoD	Board of Directors
CA	congenital anomalies
CAP	College of American Pathologists
CEA	cost-effectiveness analysis
CMA	chromosomal microarray
COI	Conflicts of Interest
DD	developmental delay
EBG	evidence-based guideline
ES	exome sequencing
ETD	Evidence-to-Decision
GIN	Guidelines International Network
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GS	genome sequencing
ICER	incremental cost-effectiveness ratio
ID	intellectual disability
IOM	Institute of Medicine (now superseded by the NAS)
Lab QA	Laboratory Quality Assurance Committee
MeSH	Medical Subject Headings
NAS	National Academies of Sciences, Engineering, and Medicine
NCC	National Coordinating Center
NEATS	National Guideline Clearinghouse Extent Adherence to Trustworthy Standards
NGC	National Guideline Clearinghouse (now defunct)
PICO(TS)	population, intervention, comparator, outcome (timing, setting)
PP&G	Professional Practice and Guidelines Committee
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRMD	Practice Research and Methodology Department
QALY	quality-adjusted life-year
RCT(s)	randomized controlled trial(s)
RGN	Regional Genetics Networks
SER	systematic evidence review
SIGN	Scottish Intercollegiate Guidelines Network
TSC	Topic Selection Committee
USPSTF	United States Preventive Services Task Force

FOREWORD

This first revision of the American College of Medical Genetics and Genomics (ACMG) Evidence-Based Guidelines Manual follows a substantial effort by ACMG, begun in 2012, to implement the development of Evidence-Based Guidelines. The College Board of Directors approved the first iteration of this manual, *ACMG Protocol for Development of Evidence-Based Clinical Practice Guidelines,* in October 2014, upon which this revision relies substantially.

Since 2014, ACMG has published one evidence-based guideline[1] and its corresponding systematic evidence review[2] following the process outlined in the original *Protocol*. This achievement required the creation of specific article types at the College's journal, *Genetics in Medicine*, and served as a pilot from which a dedicated Evidence-Based Guidelines Program could be developed. Many lessons were learned throughout the development of these documents. Through an iterative learning process and the opportunity to hire dedicated staff to run an Evidence-Based Guidelines program, one additional systematic evidence review has been published[3] and its corresponding guideline is nearing publication, two additional evidence reviews are in progress, and several new topics and revisions of past documents are slated to begin in the second half of 2022.

While a significant revision from the original *Protocol*, this update should be considered a living document. Future iterations will undoubtedly describe changes relevant to guideline development generally, and at ACMG, specifically. Through the dedication of countless workgroup members and ACMG staff, these guidelines will continue to support ACMG's mission.

June 27, 2022

OBJECTIVE

This manual is meant to provide relevant background on guideline development and its progress at ACMG, document the procedures by which ACMG develops systematic evidence reviews and evidence-based guidelines, and provide clarification of the integration of the Practice Research and Methodology Department within ACMG activities. The intended audiences are the ACMG Board of Directors, Committee Chairs and their members, and volunteers for ACMG evidence reviews and guidelines. Training materials, examples of operational materials (e.g., REDCap forms), and relevant resources are provided as appendices.

INTRODUCTION

In response to a request from the US Congress, the Institute of Medicine (IOM), now the National Academies of Sciences, Engineering, and Medicine (NAS), conducted a study to determine the best practices for clinical practice guideline development. The objective was to ensure that organizations developing such guidelines provide information that is objective, scientifically valid, and consistent. Following a review of international guidelines, two volumes were released in 2011: *Clinical Practice Guidelines We Can Trust*[4] and *Finding What Works in Health Care: Standards for Systematic Evidence Reviews.*[5] The IOM reviewers identified criteria to serve as guidance for the development of clinical practice guidelines (Figure 1). Although more than a decade has passed since the release of these documents, they remain relevant to guideline development and support best practices for systematic evidence reviews.

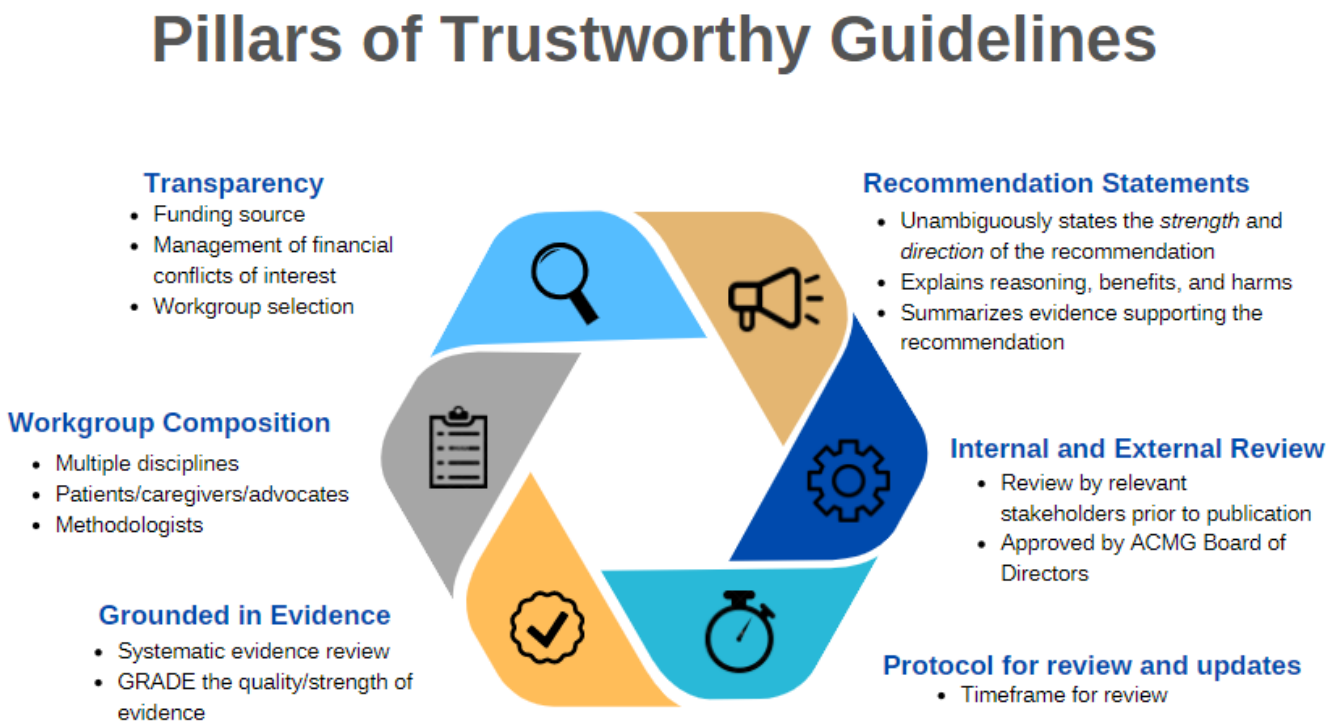


Figure 1. Pillars of Trustworthy Guidelines. Adapted from Clinical Practice Guidelines We Can Trust.[4]

Adoption of the standards for guideline development have been inconsistent: some societies continue to develop guidelines based solely on expert opinion, few guidelines undergo a true public comment period for prior to publication, and workgroup composition often fails to include a patient representative or caregiver/advocate or other relevant stakeholders.[6] Consequently, dissemination of guidelines within the affected population, implementation of guidelines by relevant health care providers, and the adoption of guideline recommendations by policymakers and payers remain challenging hurdles to overcome.

As an incentive to improve adherence to best practices (outlined in *Clinical Practice Guidelines We Can Trust*[4]) the National Guidelines Clearinghouse (NGC)[1] required that guidelines submitted for inclusion from June 2014 onward had to adhere to these standards. An assessment tool, the National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) Instrument [Appendix 18] was developed for this purpose as the AGREE II instrument, previously used for the evaluation of guidelines, was deemed insufficiently aligned to the new standards.[7] After the NGC was closed due to a lack of funding, the ECRI Institute, a not-for-profit organization, created the ECRI Guidelines Trust (https://guidelines.ecri.org) upholding the same inclusion criteria and formal assessment of submitted guidelines as the former National Guidelines Clearinghouse.

Guideline development has evolved over the last decade since the *Protocol* was written, with international societies, healthcare systems, and other guideline development organizations coalescing around the use of Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodologies. This includes more than 100 organizations, such as the Scottish Intercollegiate Guidelines Network (SIGN) (https://gradeworkinggroup.org). To address challenges faced by guideline developers, GRADE methods have been expanded to include methods to adapt or adopt existing evidence-based guidelines,[8] guidelines for diagnostic tests,[9-12] genomics,[13] rare diseases,[14,15] and those relying on qualitative evidence alone.[16-22] Additionally, in concert with the Guidelines International Network and McMaster University, there is now a certification process that requires demonstrated expertise in guideline development as well as specific training in associated topics. This is an international effort to assure the competencies for qualified individuals (methodologists) who guide panels to create evidence-based guidelines. **These and other changes now make using GRADE an appropriate choice for nearly all evidence-based guidelines, even for situations where documents of less rigor (e.g., Practice Resources) would have previously been recommended.**

[1] The National Guideline Clearinghouse (NGC) was supported by a grant through the Agency for Healthcare Research and Quality (AHRQ) beginning in 1998. Funding for the NGC ended in 2018 and the NGC was closed.

The initial project described in the 2014 *Protocol* for mucopolysaccharidosis type II (Hunter syndrome) incorporated a systematic evidence review (SER), but was published as a Practice Resource following a Delphi process to develop recommendations.[23] Shortly thereafter, a SER workgroup was convened to develop a SER that would provide an analysis of the evidence for a future recommendation for exome or genome sequencing for individuals with congenital anomalies and/or developmental delay/intellectual disability. The exome sequencing SER was published in 2020,[2] with an evidence based guideline (EBG) developed using GRADE methodology published the following year.[1]

A great many lessons have been learned since the first version of this document, many of which necessitated changes at the organizational level and for processes used to develop SERs and EBGs. This revised Protocol Manual outlines the process by which ACMG EBGs are created, describes the differences between other ACMG document types and ACMG SERs and EBGs, provides a framework for the integration of the Practice Research and Methodology Department and its methodologists with ACMG Committees and other Departments, and identifies areas of future development. The information in some appendices may be considered training materials for SER and EBG workgroups and resource materials for the Board of Directors and Committee Chairs/Members.

OVERVIEW OF THE EVIDENCE-BASED GUIDELINE DEVELOPMENT PROCESS

A schematic for the general SER and EBG development processes is presented in Figure 2. Briefly, there are two mechanisms at ACMG: 1) a new topic or an update to an existing ACMG document (of any type) is brought forward directly by a committee (for example, Lab QA, PP&G, or Therapeutics), or 2) a topic is proposed by ACMG members or others during a twice-yearly general appeal. The first step in the process, regardless of the source of the topic, is a preliminary methodological review. The specific scope of the review is described below and is determined based on the document type (i.e., Lab QA Technical Standard vs any other document type).

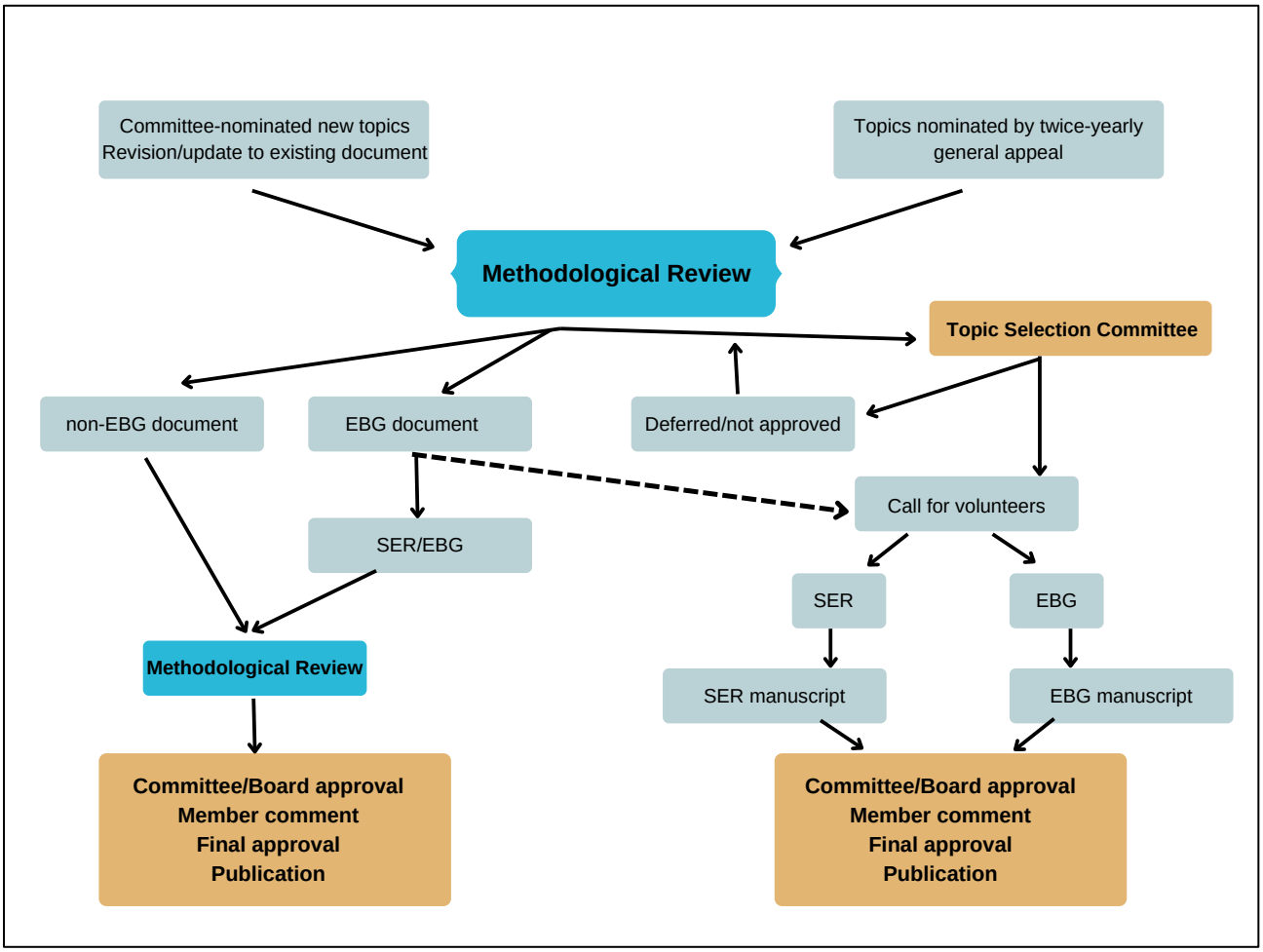


Figure 2. SER and EBG Development.

Determination of Appropriate Document Type

There are currently (June 2022) five general article types of ACMG documents:

1. ACMG Evidence-Based Guideline
2. ACMG Systematic Evidence Review
3. ACMG Practice Resource
4. ACMG Technical Standards
5. ACMG Statements
    a. Points to Consider
    b. Policy Statement
    c. Position Statement

The methodologists will make recommendations about the appropriate document type based on the results of a preliminary review. Committee and/or workgroup chairs should complete the ACMG Committee Document Methodology Review Form, which can be seen in Appendix 2. For most topics reviewed, the recommendation will be either for a SER and corresponding EBG or for a Points to Consider Statement. Laboratory-specific topics will be recommended for either a Technical Standard, Guideline, or Points to Consider. Best practice recommendations for non-EBG document types are provided in Appendix 1. As described in detail in the Evidence-Based Guidelines Section, there are now several evidence-based methods and GRADE guidance to address situations (e.g., rare diseases, sparse peer-reviewed evidence) that would previously have supported a recommendation for a Practice Resource. **For this reason, the Practice Resource Document type is not recommended for use moving forward**.

Situations in which a Points to Consider document will be recommended include, but are not limited to:

- Pubmed search <50 results
- Article types are mostly editorials and/or review articles without case reports
- Topics that are rapidly evolving
    - New therapeutics, diagnostics, or laboratory techniques are in development and are expected to be approved, cleared, or otherwise made available within the next 24 months

Initial Methodological Review

Several components are evaluated by ACMG methodologists during the preliminary review of a proposed guideline, statement, or resource, regardless of their source (i.e., committee or external submission). These components include:

- Description of an overarching research question and potential targeted key questions
- Clearly defined population, intervention, and outcomes of interest
- Identification of relevant guidelines from other organizations
    - Medline [Pubmed], Cochrane Library, ECRI Guidelines Trust, Guideline Central, International Guidelines Library
- Identification of relevant SERs
    - PROSPERO registrations
    - Medline [Pubmed], *JBI Evidence Synthesis, BMJ Systematic Reviews*, Cochrane Library
    - SER protocols and completed SERs
- Identification of potential advocacy organizations (for EBGs)
- Preliminary Medline [Pubmed] search for literature using Medical Subject Headings [MeSH terms], keywords, and excluding publication types such as reviews and editorials, filtered on English language and humans
    - Quantification of Pubmed results by article type (randomized controlled trials (RCTs), clinical trials, cohort studies, case reports, systematic evidence reviews, scoping reviews, meta-analyses)
- Anticipated feasibility to complete a SER in 9-15 months with a team of 4-7 reviewers

If the overarching question or population, intervention, and at least one outcome are not adequately described in the nomination form, the methodologists will contact the individual or committee chair for additional information. The methodologists have created an Excel workbook to manage the review process for all topics. A template can be seen in Appendix 6.

Lab QA Technical Standards will be evaluated separately from all other document types due to their unique composition and objective. Preliminary methodological assessment for Technical Standards will focus on:

- Identification of relevant documents/standards/guidelines published by others (e.g., CAP, AMP) that can be used as an evidentiary basis
- General methodology planned to ensure the final document will adhere to the description of a

technical standard:

- "**Technical standards for clinical genetics laboratories**: Developed and maintained by ACMG's Laboratory Quality Assurance Committee, these voluntary standards establish criteria for clinical genetics laboratories to provide accurate and reliable diagnostic testing that is consistent with current technologies and procedures. These documents are written by experts in the field and rely on published data and experience. ***It is expected to have a transparent, reproducible methodology, make justifiable recommendations, and discuss its limitations.***"

- If the technology is available in more than one laboratory
  - If a single laboratory offers the test/technology, methodological recommendation will be to develop the document as a *Points to Consider*, rather than a technical standard.

Workgroup Volunteers, SER and EBG processes

After the methodological review is completed and the appropriate document type has been recommended to the Committee Chair (internal revisions/updates/new topics) or approved by the Topic Selection Committee (TSC) to move forward (new topics, externally submitted), the methodologists will solicit volunteers for the SER and EBG workgroups aligning with NAS standards. The full methodological review will be shared with the workgroup chair/co-chairs for internally proposed SER/EBG topics. When applicable or desired by ACMG, the methodologists will reach out to counterparts at relevant societies to assess their interest in joint guideline development, participation in the EBG process, or potential for formal endorsement of the ACMG EBG once it has been published.

When the initial methodology review for a Committee-submitted topic (update or new) coincides with the twice-annual general call for new SER/EBG topics, it is recommended that the call for volunteers for the workgroups be included with the volunteer solicitation for new topics (see Appendix 3). This is coordinated by the Practice Research and Methodology and Communications Departments and ensures that relevant stakeholders are sought, particularly those who are not genetics professionals.

Alternatively, the topics that originate from within a Committee may be submitted for review at other times of the year, when inclusion in the general call for SER/EBG volunteers is not applicable. Committee and Project Chairs are strongly encouraged to work with the methodologists to ensure that the proposed

workgroups are sufficiently multidisciplinary and minimally include both a genetic counselor and a patient, parent of a patient, or patient advocate. For SER/EBGs, the methodologists will lead this process with input from the Committee Chair and committee liaison.

Following the call for volunteers and the formal approval for a project by the ACMG Board of Directors (BoD), the SER and EBG workgroups are provided all necessary training to complete their respective documents, as described in the SER and EBG sections that follow. Internal documents which are to be developed as non-SER/EBG document types undergo a final methodological review prior to, or alongside, review by the supporting committee or BoD review prior to member comment. All published ACMG documents undergo a multi-stage peer review process that includes committee approval, BoD approval, response to member comments, and final BoD approval prior to publication in *Genetics in Medicine*.

ACMG DOCUMENT REVISION/UPDATES

This section outlines the process for revising or updating *existing* ACMG documents, limited to the identification of topics, initiation of the projects, and methodological review. Specific details for the SER and EBG processes are provided in those sections separately.

Scheduling Of Topics

Existing Topics

On a yearly basis, the Committee chairs will meet with the Practice Research and Methodology Department staff to identify documents that need a revision. Any document published more than five (5) years (Lab QA: three (3) years) prior should be prioritized within the committee membership to be updated, revised, or retired prior to the 6th year (Lab QA: 4th year) following publication. Given the considerable number of existing ACMG documents that meet these criteria, committee chairs will work with methodologists to establish a schedule to update these documents no later than March 2023, with 1-2 projects per Committee initiated quarterly beginning in July 2023. Prioritization of these topics should be determined by Committee chairs and committee members. The Committee liaison for the project is responsible for completing the ACMG Proposal for Statement, Guideline, or Other Project form [Appendix 8].

Once an existing document or new topic is identified, the methodologists perform a preliminary assessment to identify EBGs published by other organizations, whether there are published or in-progress SERs, and consider the breadth and quality of the literature. This process is described in greater detail in the Initial Methodological Review Section.

If the evidence base is large (≥2500 returns from a preliminary Pubmed search), the methodologists will recommend delaying workgroup member solicitation until the next scheduled appeal (see Appendix 3 for the projected timeline) to obtain the largest number of potential volunteers to staff the SER and EBG workgroups. Specific non-geneticist roles (e.g., patient/advocate, non-geneticist specialists, primary care providers, nurses/physician assistants, and genetic counselors) will be identified through communications with the committee chair, methodologists, and TSC. Identification of workgroup members for topics where the anticipated evidence base is smaller (<2500 returns from a preliminary Pubmed search) can be done separately from the twice-yearly solicitation of volunteers. The authors from the original document should be contacted by the committee chair or liaison as a matter of best practice and encouraged to participate in

the new process by filling out the SER-EBG Volunteer Submission form [Appendix 4].

Project Management of SER/EBG

Documents that will be updated/revised as SERs/EBGs will be managed primarily by the methodology team with additional support provided by the committee liaison. This includes submission of the document proposal forms to the BoD for approval, development of a SER protocol with the aid of both workgroups, set-up and maintenance of a Covidence project, and training for the SER and EBG workgroups. The liaison is considered a workgroup member for both the SER and EBG, in addition to their responsibilities as the committee liaison. As workgroup members, they are expected to participate in all workgroup calls and tasks for the duration of the project. Details regarding SER and EBG processes are found in their respective sections.

Project Management of Non-EBG Documents

Documents that are determined to be ineligible for update as an SER/EBG will be managed by the host committee with assistance provided on an as-needed basis by ACMG methodologists. The results of the preliminary methodological review will be provided to the committee chair/liaison/workgroup chair(s) with recommendations for a literature search, structure of the document, and concrete suggestions to incorporate evidence-based methods where possible. Document proposals are submitted to the BoD by the committee chair/liaison/workgroup chair(s) using the electronic ACMG Proposal for Statement, Guideline, or Other Project form. The committee chair will be responsible for finding workgroup members for non-EBG documents, but they are advised to coordinate with the methodologists; volunteers for the SER/EBG who were not selected due to space constraints may be appropriate workgroup members and contribute important non-geneticist views. The authors from the original document can be contacted by the committee chair or liaison and encouraged to participate in the update.

Methodological Review of Non-EBG Documents

Prior to, or concurrent with, submission to the host committee or BoD for approval before member comment, non-EBG documents will be reviewed by at least one methodologist (Figure 2). The review will focus primarily on adherence to the document description from the Proposal form: sufficiently reported methods, including the description of how individuals were selected for the workgroup, literature search details, how the evidence was assessed/synthesized, gaps in the evidence, how and when expert opinion

was incorporated. Non-SER/EBG documents should comment on the potential risk of bias, due to the non-systematic approach to identifying evidence. It is expected that the workgroup will address comments from the methodologists similarly to those provided by their host committee or the BoD. Methodologists will NOT comment on language (i.e., wordsmithing); however, language that is specific to EBGs ("ACMG recommends…") will be highlighted with suggested wording changes to make clear that the document is not a guideline. The methodology team encourages committee chairs and/or workgroup chairs to work with methodologists early in the manuscript drafting process. Additional information regarding best practices for non-EBG documents is in Appendix 1.

NEW COMMITTEE TOPICS

This section describes the process for which new topics arising from within a committee are assessed. Specifics regarding the SER and EBG tasks are provided in their respective sections.

Preliminary Methodological Review

Similar to the process for existing documents in need of revision, new topics that emerge from within a committee undergo a preliminary assessment by methodologists to identify EBGs published by other organizations, whether there are published or in-progress SERs, and consider the breadth and quality of the literature. Additionally, new topics will be assessed by the host committee according to the same criteria used by the TSC, including feasibility of the project, alignment to current and near future ACMG priorities, and potential impact of the project. Following a determination of sufficient evidence basis for a SER/EBG by methodologists, potentially relevant patient advocacy organizations will be identified. Topics that are not approved by the committee may be reassessed in subsequent years or following revision of the proposed topic according to methodological and/or committee recommendations.

If the evidence base is large (≥2500 returns from a preliminary Pubmed search), methodologists will delay workgroup member solicitation until the next scheduled appeal (see Appendix 3 for projected timeline) to obtain the largest number of potential volunteers to staff the SER and EBG workgroups. Specific non-geneticist roles (e.g., patient/advocate, non-geneticist specialists, primary care providers, nurses/physician assistants, and genetic counselors) will be identified through communications with the committee chair, methodologists, and TSC. Identification of workgroup members for topics where the anticipated evidence base is smaller (<2500 returns from a preliminary Pubmed search) can be done separately from the twice-yearly solicitation of volunteers.

Topics which are approved by the host committee follow either a non-EBG document trajectory or an EBG document plan. Non-EBG documents are eligible for methodological assistance ***as desired*** and will undergo a formal methodological review following the drafting of the manuscript, as described in the prior section (Figure 2). Management of these documents falls to the host committee/liaison/project chair. EBG documents will be managed primarily by the methodology team with the assistance of the committee liaison. The document proposals are submitted for the SER and EBG simultaneously by the Methodology staff.

TOPIC SELECTION COMMITTEE (TSC)

The establishment of the TSC was approved by the ACMG Board of Directors in 2019 to support the process of selecting and prioritizing topics for EBG development. Members serve on the TSC for up to two 2-year terms. Solicitation for new members takes place during a call for committee volunteers, which is coordinated by the Director of Membership.

Composition of the TSC includes:

- The Chair of the PP&G, Therapeutics, and Lab QA Committees;
- Members of the ACMG BoD;
- ACMG methodologists are *de facto* non-voting members of the TSC.

PP&G, Therapeutics, and Lab QA chairs serve a single two-year term, at which point the vice-chairs of those committees replace them. Individuals unable to serve the entirety of their term may be replaced at the discretion of the TSC Chair.

Topic Nomination Process

Topics will be solicited from ACMG members, industry partners, Foundation donors, patient advocacy organizations, and other interested parties through a campaign that includes social media and ACMG communications (e.g., the ACMG in Action Ezine). The Nomination Form for new topics is created as a RedCap survey [see Appendix 5, version June 2022]. The official nomination cycles (held twice a year) are January-February and August-September. Nomination forms submitted outside of these windows are held until the next cycle begins for evaluation by the TSC. Topics not selected or deferred are periodically re-evaluated, following methodological re-assessment.

In the original *Protocol*, it was anticipated that individuals completing the nomination form would be able to sufficiently describe the population, intervention, comparator, and outcomes of interest, in alignment with the PICOTS framework. However, after multiple topic nomination cycles, it became apparent that nearly all nominations required significant input from methodologists prior to completion of the form or during the methodological review. Additionally, the highly technical form could be perceived as a barrier by patients/advocacy organizations who desire ACMG EBGs.

The new topic nomination form [Appendix 5] was developed following considerable input from ACMG methodologists and individuals submitting topics during the Fall 2021 cycle using the old form. The new document focuses on the overarching question and need for an EBG, while minimizing the more technical aspects of the previous version. In addition, it emphasizes the collaborative nature of guideline development and multidisciplinary workgroup composition by specifically asking if there are other professional societies and/or patient/advocacy organizations that may be interested in an ACMG guideline.

Scope of Topics Eligible for Consideration

Topics eligible for consideration are not restricted to specific disorders or conditions; however, emphasis is typically on the role of genetics and genomics in the screening, diagnosis, management, treatment, or risk reduction in inherited disorders. Other topics that may be considered include prognostic or pharmacogenetic tests and complex disorders.

Methodological Review of Nominations

ACMG methodologists perform an initial assessment of the topic nominations. This review follows the **Topic Selection Checklist for Methodologists** [Appendix 6]. ACMG methodologists use the overarching research question, population, intervention, and outcome(s) provided in the nomination form to draft workable PICOTS for a SER. If the nomination form lacks sufficient detail to continue a preliminary assessment, ACMG methodologists will contact the submitting individual for more information. Methodologists determine:

- If there are published SERs or SERs in progress on the same or a closely related topic;
- If there are existing EBGs published on the same or closely related topic;
- If multiple nominations are closely related and should be evaluated together;
- What patient advocacy organizations there are and if ACMG has an existing relationship with the organization; and
- The abundance of and types of studies available for a SER based on a preliminary literature search of Medline (Pubmed).

The senior methodologist will review the preliminary assessment and provide a summary to the TSC

regarding the feasibility of each project, recommendations regarding deferral of a topic, and potential patient/advocacy organizations. The number of new topics able to be started each cycle should be indicated in the summary. This information will be provided to the TSC no later than one week prior to the scheduled meeting/conference call.

Criteria for Selection of Topics

Following methodological review, the TSC will individually rank each nomination according to four domains using the Topic Selection Committee Topic Nomination Ranking Form [Appendix 7, version June 2022] using a scale of 1 (Most aligned/impactful/feasible) to 5 (Least aligned/impactful/feasible):

- Alignment to College priorities;
- Potential impact of an EBG;
- Feasibility/methodology; and
- Abundance and quality of literature.

The nominated topics are further ranked in order of priority by each TSC member. The methodology team will prepare a summary of TSC rankings to be discussed at the meeting. Overall ranking will be compared to the ranking based on domain scores. Discrepancies between overall ranking and domain scores should be highlighted and discussed.

Topics which are not approved by the TSC may be rejected as out of scope for ACMG or deferred until the time at which identified insufficiencies or misalignment to College priorities can be resolved. Following the TSC meeting, the methodologists will prepare a summary and individually contact all who submitted topics for consideration. For topics which were not approved to move forward, the rationale for deferral or rejection should be clearly stated, where appropriate. For topics that will become SER/EBGs, the TSC and methodologists should discuss the key roles needed for the EBG workgroup to ensure all relevant stakeholders are invited. The TSC may recommend other medical societies that should be contacted to potentially develop a joint guideline or formal endorsement of the ACMG EBG upon publication.

SER and EBG WORKGROUP COMPOSITION

To align with international standards for guideline development, SER and EBG workgroups should be comprised of all relevant clinical stakeholders, patients or their advocates, and appropriate researchers. Conflicts of interest (COI) must be carefully evaluated and mitigated, if necessary. Participation in SER and EBG workgroups is a benefit of membership as well as a valuable service to the field. To minimize perceived or real COI, broaden participation across ACMG membership, and include relevant non-ACMG participants, methodologists will coordinate with the Communications Department and the Community Relations Manager to solicit volunteers for the SER and EBG workgroups. Examples may include notices in the ACMG in ACTION eZine, social media posts, email blast to ACMG members, and free 'ads' on the *Genetics in Medicine* homepage.

Volunteers interested in participating are required to submit their intent on the SER-EBG Volunteer Submission form and upload a copy of their CV and/or biosketch [see Appendix 4]. This enables the methodology team to preliminarily assign volunteers to workgroups. Workgroup assignment is based on the following criteria:

1. Diversity, equity and inclusion (DEI) should be considered for all workgroups.
2. Unless otherwise requested/ineligible due to COI, the person(s) submitting the topic should be assigned to the EBG and can be asked if they would like to be the group chair/co-chair.
3. Patients/patient advocates/parents of patients are assigned to the EBG workgroup.
4. Individuals who served on one workgroup for a prior project should be prioritized to the other project type (for example, project 1 = SER workgroup, project 2 = EBG workgroup).
5. The EBG workgroup should be prioritized over the SER workgroup for multidisciplinary composition.
6. Only a single person from an institution should be on a workgroup. Two individuals from the same institution may be separated into the SER and EBG workgroups. In very rare circumstances two individuals from the same institution may be allowed.
7. Consider geography for each; try to assign international applicants (prioritize ACMG members) but remember the time zone issue for calls.
8. Trainees, early-career professionals, and student members can be assigned to either workgroup.
9. Workgroup composition should be a mix of late-stage, mid-stage, and early-stage professionals. Do NOT overload the EBG with only late-stage professionals.

10. Subject matter experts filling non-geneticist roles should be prioritized for the EBG.
11. Individuals not selected for a workgroup due to space constraints should be prioritized during the following nomination cycle.

Preliminary workgroup assignments will be shared with chairs of the host committee for the project, the TSC chair, and the BoD President and President-Elect. Workgroup members must complete Participation Agreements prior to the Board Meeting at which time the project proposals are submitted. Failure to submit a Participation Agreement by the deadline for the COI Committee review may preclude an individual from serving on a SER or EBG workgroup. Project proposals are submitted by the PRMD (SER/EBG) or by the Committee chair/workgroup chair (all other document types). The project proposal and workgroup form can be viewed in Appendix 8. Once the BoD has approved both project proposals and their associated workgroup membership, the methodology team begins preparation for the SER and EBG projects.

Conflict of Interest Assessment

All workgroup members (SER and EBG) must adhere to ACMG policies for COI as a prerequisite of participation. Participation in the EBG workgroup may necessitate the selection of a chair/co-chair without COI or other mitigation as recommended by the COI Committee. No assignment of an individual to a SER or EBG workgroup is considered final until a Participation Form is submitted by the potential workgroup member, assessed for COI by the COI Committee, and approved by the BoD.

Conflict of interest is not restricted to financial relationships. Personal, intellectual, or professional associations and relationships may affect or be perceived to affect someone's ability to make decisions in an unbiased manner. Strict rules are in place to ensure ACMG EBG and SER workgroups adhere to general ACMG COI guidelines, with the Chair (or one Co-Chair) and the majority of the workgroup (>50%) are free of potential conflicts with regard to the subject matter. Where it is necessary to ask a subject-matter expert with COI to provide a review of summary evidence for the SER, the methodologists will first obtain approval by the ACMG COI committee and the BoD.

Significant changes to the workgroup composition, including initiation or cessation of activities that represent COI (as defined by the ACMG COI committee), require a revision of the project proposal be re-approved by the COI committee and the BoD. An additional COI review takes place prior to publication in *Genetics in Medicine*; the Committee Relations Manager will coordinate this with the project methodologists and workgroup members.

SYSTEMATIC EVIDENCE REVIEW (SER)

The SER workgroup is typically composed of 5-7 members but may be larger, based on project complexity and anticipated time to complete the review. All ACMG SERs are staffed by a lead methodologist and an assistant methodologist. Medical librarians may be utilized to develop the search strategy for the SER. ACMG SERs are expected to take 9-15 months, depending on the scope of the review and the amount of literature to assess. This timeline is from the date of the first joint meeting with the SER and EBG workgroups to the submission of a draft SER manuscript to the host committee for approval. Significant deviations in the expected duration of a SER project will be justified by the Senior Methodologist to the BoD as necessary.

Prior to the formal start of the SER, methodologists draft a protocol to guide the scope of the project. This protocol [Appendix 9] is aligned to the PROSPERO database (https://www.crd.york.ac.uk/prospero/) of systematic evidence reviews and is an essential component in the SER-EBG project. This proposal is shared with members of the SER and EBG workgroups prior to the first joint call of the project and is finalized after the second call (approximately 2-4 weeks later). Once finalized, the methodologists develop the literature search queries and submit the protocol to PROSPERO.

Stages of the SER

The SER can be conceptualized as having seven phases [Figure 3]. Each step of the process is essential in the development of a rigorous SER. ACMG methodologists provide training for the SER team at the outset of the project and before each stage of the SER commences. SER workgroup members are involved in finalizing the SER protocol (with the EBG workgroup) and crafting the inclusion and exclusion criteria for the review. Methodologists and/or medical librarians develop the literature search strategy, deduplicate references from the databases using a reference manager (e.g., Endnote), and upload the citations to the software used for SER project management (e.g., Covidence). Once that is complete, the SER workgroup screens the titles and abstracts of all citations and reviews the full texts (including supplemental materials as necessary) of citations not marked irrelevant in the prior phase.

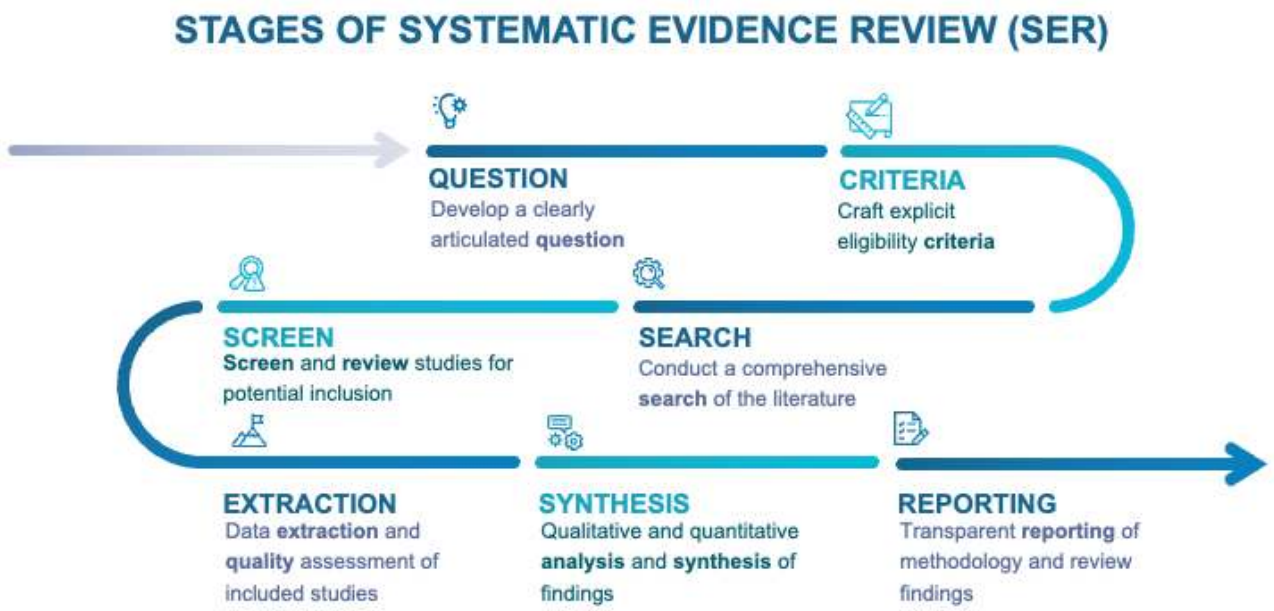


Figure 3. Stages of the systematic evidence review process.

Full texts of articles may be automatically uploaded by the SER software, by the methodologists, or by SER workgroup members. During full text review, a data extraction form is created by the methodologists, consistent with the SER protocol (Figure 4a). Quality assessment (risk of bias) forms should be developed to allow for all relevant study designs of included articles (Figure 4b). Depending on the number of articles and the structure of the SER (i.e., how many key questions), a two-stage extraction process may be desired. In the first stage, the key question(s) each article provides evidence for are identified, basic study information (e.g., study design, country, potential COI of authors and funding) is extracted, and the study's risk of bias is assessed. A secondary extraction form for detailed outcome data may be created in the same SER software, an Excel workbook, or REDCap survey.

Figure 4a. Data extraction template in Covidence.

Figure 4b. Risk of bias (quality assessment) template in Covidence.

During the SER process, all phases are performed by two reviewers, who screen/review/extract independently of the other's decisions. Where discordance arises, reviewers should discuss their decisions and come to an agreement. If an agreement cannot be reached or there remain questions about the article, a third reviewer (i.e., lead methodologist for the project) should adjudicate. After all data has been extracted and the risk of bias assessed for each study, the methodologists will export the data directly from Covidence for data analysis. Agreement between SER reviewers will be calculated using Cohen's kappa and percent agreement, exported directly from Covidence. It is expected that the methodology team perform the data analysis/synthesis according to the pre-specified analysis plan from the SER protocol and provide summaries of the results and associated figures to the SER workgroup. If members of the SER workgroup have expertise in data analysis, they are encouraged to participate in the process. Methodologists will provide the results of any analysis or synthesis to the EBG workgroup as it becomes available and create the evidence table in GRADEpro [see Appendix 15].

Reporting of the SER is aligned to the PRISMA checklist [Appendix 10] and PRISMA checklist for abstracts [Appendix 11].[24] Methodologists will provide a template manuscript and draft the methods section for the SER workgroup. Workgroup members are encouraged to write the remaining sections of the manuscript, guided by the methodology team. Figure 1 of the manuscript is typically a PRISMA flowchart which shows how the citations identified through the literature searches were eliminated until the final included number [Appendix 11]. The lead methodologist for the SER will format the manuscript (e.g., references, disclaimer) working with the Committee Relations Manager. Authorship order will be determined by the individual SER workgroup members' contributions during each phase of the process.

Internal and External Peer Review

The SER manuscript is provided to the host committee for review by the Committee Relations Manager. If the committee members approve the manuscript, the Committee Relations Manager prepares the document(s) for review by the ACMG BoD. If the committee declines approval, specific edits/comments should be conveyed to the lead methodologist for the project in a timely manner. The methodologist will work with the SER workgroup to address concerns/revise the manuscript as needed and re-submit for the following month's committee meeting. An email vote by the committee may be appropriate, depending on the timing of resubmission to the committee and the upcoming BoD meeting. If the BoD similarly declines approval, the SER workgroup and methodologists will work to revise the document as needed and re-submit in a timely manner.

Once the SER manuscript is approved by the BoD, it is sent out for general ACMG member comment for a period of no less than 30 business days, which serves as a third level of peer review for the SER prior to publication. Following the member comment period, the Committee Relations Manager prepares a document containing all comments received for the manuscript. The SER workgroup and methodologists respond to all comments and revise the manuscript as appropriate. Revisions that materially alter the interpretation of results for any outcome are communicated to the EBG workgroup at once. Once all revisions are completed, the lead methodologist coordinates with the Committee Relations Manager to resubmit the manuscript to the host committee chair and Board liaison for final review. The COI Committee reviews all authors' participation agreements prior to publication. Upon approval, the manuscript will proceed to the BoD for final review. Once approved by the BoD, the Committee Relations Manager and lead methodologist prepare the document for submission to *Genetics in Medicine*.

Communication Between the SER and EBG Workgroups

Following finalization of the SER protocol, communication between the SER and EBG workgroups should be minimized to ensure the objectivity of the SER. The host committee liaison to the SER/EBG, the Committee Relations Manager, and the methodologists are responsible for conveying information to the host committee about both groups, to the committee chairs and BoD, and the other workgroup, respectively.

EVIDENCE-BASED GUIDELINE (EBG)

The EBG workgroup is typically comprised of between 7-9 members representing a variety of stakeholder perspectives. Clinical and laboratory/molecular geneticists and genetic counselors are required for all ACMG SER and EBG workgroups. These roles are expected to be filled by ACMG members unless there is no ACMG member who is willing to participate in the SER/EBG with the requisite expertise. Patients, carers of patients, or advocates for patients are required for nearly all SER/EBG projects, with few exceptions where their inclusion would not be relevant. Additional stakeholders may include relevant specialists (non-genetics professionals) and health economists. The methodology team will work with the Communications Department and the Committee Relations Manager to plan a social media and general appeal for volunteers for each project as described previously.

Preliminary tasks that involve both the SER and EBG workgroups have been previously described. Following finalization of the SER protocol, the EBG team preliminarily ranks the outcomes as critical for decision-making, important for decision-making, or not important for decision-making. These categories align to GRADE importance ratings 7-9, 4-6, and 1-3, respectively.

For the duration of the SER, the EBG workgroup receives training in GRADE methodology for guideline development. Training culminates in a mock session to develop an EBG based on one or more systematic evidence reviews. A 12-month outline of training materials is provided in Appendix 14. ACMG methodologists input the final results from the SER into a GRADEpro evidence profile [Appendix 15] or summary of findings table [Appendix 16], complete the certainty assessment for each outcome (left side of evidence profile), and report the overall findings from the SER for each outcome separately. Data from the SER can be presented qualitatively and/or quantitatively, depending on the method used to synthesize evidence. Qualitative synthesis can be incorporated into the GRADEpro evidence profile using a narrative option for the relevant outcome(s) or isoQ (https://isoq.epistemonikos.org/) can be used to prepare an evidence table for exclusively qualitative data. Methodologists should present the data using both an evidence profile and as an interactive summary of findings (Figure 5) table to facilitate understanding of the results by lay individuals and non-experts in the workgroup.

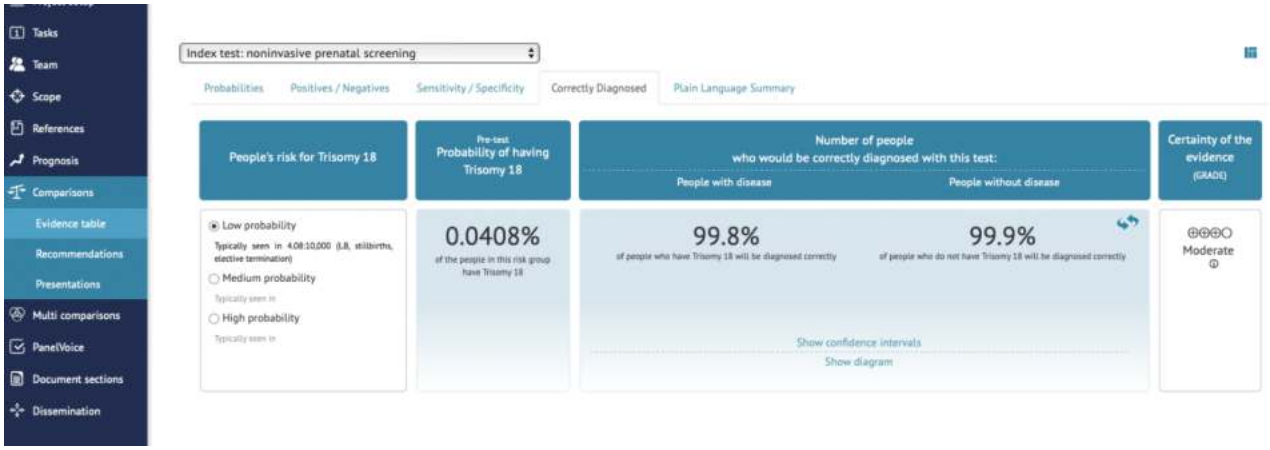


Figure 5. Interactive summary of findings table viewed in GRADEpro GDT.

Methodologists will concisely prepare a summary of the evidence from the SER, incorporate any newly identified evidence published after the SER's last search date, and relevant grey literature (when appropriate) for each of the domains in the GRADE Evidence-to-Decision (ETD) Framework. For most EBGs, there are 12 domains to be considered:

1. The priority of the problem
2. Magnitude of anticipated benefits/desirable effects
3. Magnitude of anticipated harms/undesirable effects
4. Overall certainty of the evidence
5. Values and preferences
6. Balance of effects
7. Resources required (costs)
8. Certainty of required resources
9. Cost-effectiveness
10. Potential impact on health equity
11. Acceptability of the intervention among stakeholders
12. Feasibility of implementation of the intervention

For EBGs that include a diagnostic test, additional domains to be evaluated include:

1. Test accuracy
2. Certainty of the test accuracy
3. Certainty of the evidence of the test's effects
4. Certainty of the evidence of management's effects
5. Certainty of the evidence of a link between test results and management decisions

Prior to the EBG workgroup creating their recommendation statements, each workgroup member, including the patient/carer/patient advocate vote independently on the evidence supporting each of the domains. Workgroup members do not have access to the GRADEpro project; rather they are added as team members to the software and marked as having Panel Participation. When the methodologist is confident that the EBG workgroup thoroughly understand the results from the SER and any additional evidence supporting the critical and important outcomes, voting emails are sent directly from GRADEpro to the EBG workgroup members that are eligible to vote. Expert consultants are generally disqualified from voting but unless there is a reason for exclusion, the patient/carer/patient advocate is considered a voting member. Methodologists should use the "Test" function in GRADEpro ahead of the voting to ensure all EBG members are able to receive the emails because the links are unique to each participant (Figure 6).

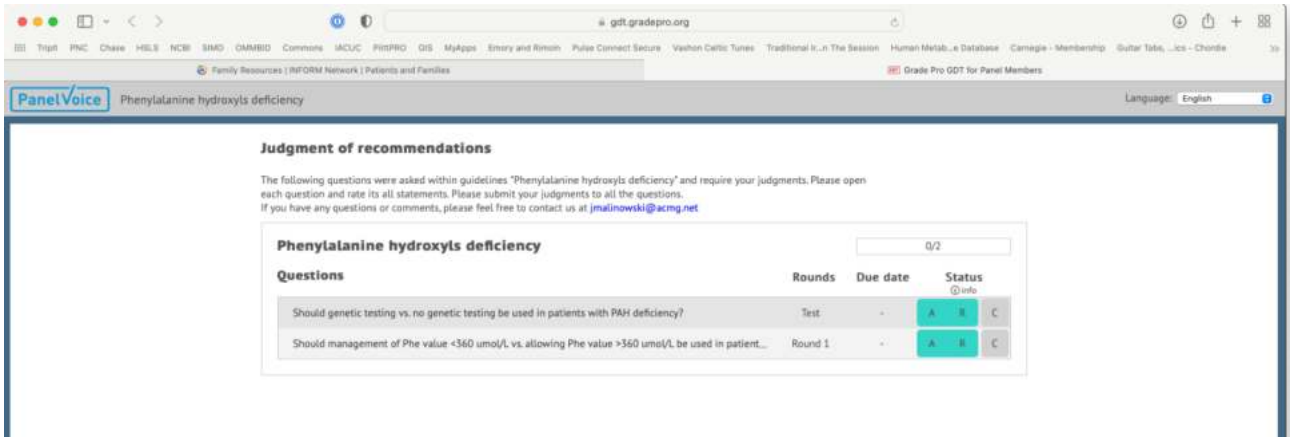


Figure 6. EBG member PanelVoice interface showing a "Test" round and "Round 1" for the final judgments. EBG members click the question to proceed to voting.

EBG members vote on each domain and have the opportunity to provide comments for each of the domains included. Once voting has been completed by all of the eligible workgroup members independently, the methodologists work with the members to attain consensus for each of the domains (Figure 7). If consensus is unable to be reached for any specific domain, there must be sufficient documentation of the rationale(s) for dissent and percent of the group dissenting. The lead methodologist should ensure that discussion points for each domain are documented either within GRADEpro or in a separate document that all workgroup members have access to.

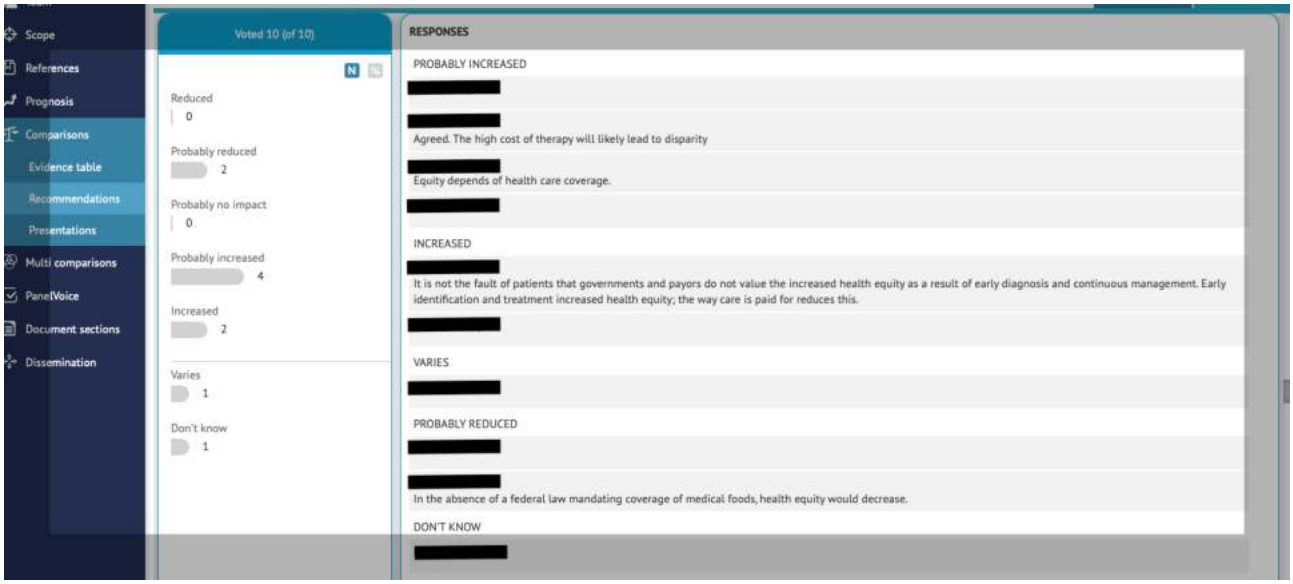


Figure 7. GRADEpro recommendations section showing individual voting responses for a domain.

After a consensus judgment has been reached for each domain, a final strength and direction for the recommendation statement(s) must be determined. The GRADEpro software presents a visual summarization of the final consensus for each ETD domain (Figure 8). If desired, but optional, specific domains that had a greater influence on the final direction and strength of the recommendation(s) can be marked. Following the determination of the strength and direction for any recommendation statements, the EBG workgroup drafts the EBG manuscript. Methodologists should provide the EBG writing leads/chair a template EBG manuscript and suggestions for how to incorporate specific requirements to align to best practices in guideline development. A copy of the NEATS [Appendix 18] or AGREE II tools may be useful for the EBG authors to understand the need to incorporate specific information. Methodologists will draft the

methods section of the EBG manuscript and offer critical appraisal of the overall draft, prepare any tables or figures that are needed, and a plain-language summary of the overall recommendation(s).

The approval process for an EBG manuscript is the same as for a SER manuscript. The host committee must first approve the document prior to review by the BoD. Following approval by the BoD, the manuscript is made available for member comment for a period of no less than 30 business days. EBG members must respond to any comments that are made during each of these peer-review processes before a final manuscript can be approved by the BoD for publication. The Committee Relations Manager will facilitate this process together with the methodologists as described previously.

Figure 8. Visual summarization of consensus judgments for Evidence-to-Decision domains.

De Novo EBGs vs ADOLOPMENT

The previously described processes are an overview for groups creating a *de novo* EBG where no existing EBG from another society addresses the desired topic. When there are EBGs that, in part or wholly, address the same overarching questions, ACMG may choose to use the GRADE-ADOLOPMENT[8] strategy to adapt or adopt that society's EBG.

The GRADE-ADOLOPMENT process maintains the rigor of GRADE. Figure 9 shows the flowchart for implementing the GRADE-ADOLOPMENT framework. Identification of potentially relevant guidelines occurs during the initial methodological review of a new topic or appraisal of the appropriate document selection for topics coming from a committee (Figure 2). Any EBG that relies on a SER and a GRADE-like process to make recommendation statements is eligible for the GRADE-ADOLOPMENT process.

When the GRADE-ADOLOPMENT process can be used, it is not necessary to convene a separate workgroup for the SER. However, all workgroup members must meet the more stringent EBG COI requirements, per ACMG policies. A list of potential key questions is drafted by the methodologists and the EBG workgroup prioritizes all desired outcomes. The very important (critical) and important outcomes are aligned to the SER(s) that served as the evidentiary basis for the existing guideline. The literature search queries from the SER are updated from the date of the last search and new evidence is incorporated into the new evidence base according to the same inclusion and exclusion criteria as the original SERs. Extraction of relevant data and appraisal of each included study's risk of bias is performed by the EBG group and/or the methodologists. As needed, meta-analyses may be performed to obtain overall effect sizes. Following data analysis, the methodologists complete an integrated GRADE evidence profile/summary of findings table and prepare the EtD summaries. The workgroup performs the voting and identifies the strength and direction of the recommendation according to the same process described previously.

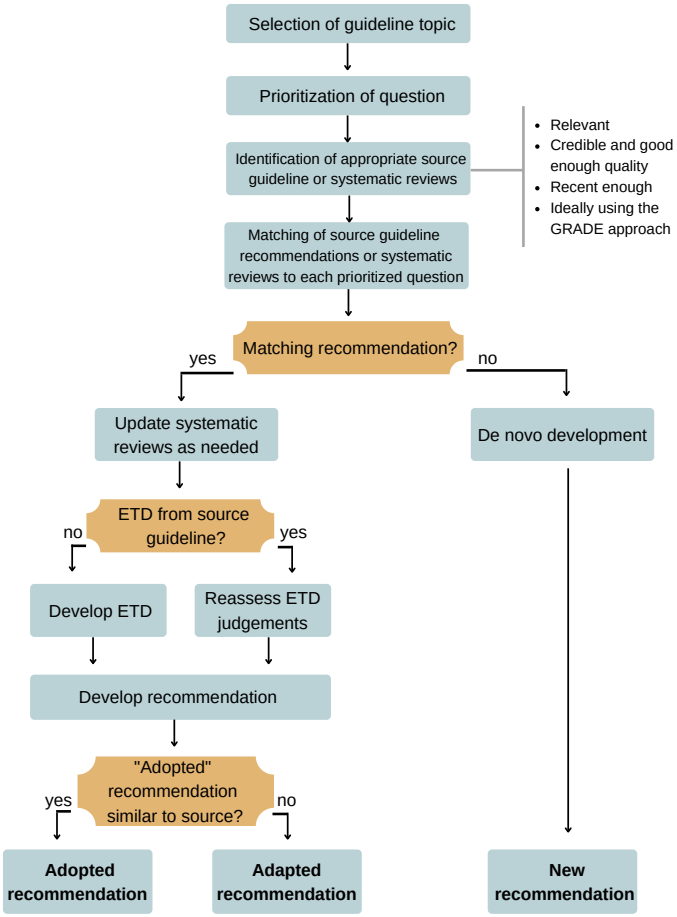


Figure 9. GRADE-ADOLOPMENT process for adoption and adaptation of existing EBGs.

If the EBG workgroup fully supports both the strength and direction of the original guideline after incorporating any new evidence, the initial guideline is said to be *adopted*. Minor disagreements with wording of the initial guideline recommendations can be accommodated with an explanation regarding the deviation. If the EBG workgroup disagrees with the strength and/or direction of the original recommendation statement(s) following consensus for the new EtD framework, the new guideline is said to be *adapted* from the original. In the case of adaptation, explicit description(s) of the rationale for changing the recommendation is required. It should not be considered a failure of GRADE-ADOLOPMENT to have an EBG panel come to a different recommendation. It is possible that based on judgments made by the ACMG EBG workgroup, values and preferences, new evidence, or other factors may result in the difference obtained.

Developing EBGs with Minimal Evidence

Historically, it has been assumed that it is not possible to create an EBG using GRADE when the evidence basis is of poor quality or indirect, when the certainty of the evidence is very low, or when there is insufficient evidence. In these situations, an expert panel consensus process, such as the Delphi method (or a modification of the Delphi method), the RAND/UCLA Appropriateness Model, or the Nominal Group Technique has been used to develop guidelines which are *informed* by evidence and blended with expert opinion. Indeed, the use of a consensus process was acknowledged by the authors of the first iteration of this manual as a need for some ACMG guidelines. However, there are ways to utilize GRADE methods even in this circumstance.

It's important to clarify that the GRADE methodology uses the ***best available*** evidence for a topic. For many disciplines, including medical genetics, RCTs are simply not available, nor are they likely to be performed in the future. Case reports and small case series, N-of-1 trials, non-controlled pre-post experimental trials, and patient registries may constitute the evidence base for many rare and very rare conditions. Furthermore, the GRADE Working Group has developed a number of guidance documents for organizations seeking to develop EBGs using GRADE in these situations, as cited in the Introduction. There are several alternatives listed below that should be utilized if necessary to follow GRADE methods, and a consensus process considered only after these options are exhausted.

Inclusion of grey literature

Many systematic evidence reviews routinely exclude grey literature (i.e., non-peer reviewed evidence) from their outset. However, though the SER workgroup may not have the capability to evaluate grey literature, it may be an important source of the most up-to-date information on a topic and considerably expand the available evidence to assess. ACMG methodologists evaluate the need for inclusion of grey literature both at the outset of the SER, and again following the completion of data analysis. At either point, if inclusion of grey literature is believed to be essential to the development of the EBG, the methodologists will work with the EBG workgroup to identify relevant conference abstracts and/or presentations, patient registries, or other unpublished and/or pre-printed (e.g., manuscripts on BioArxiv) that are relevant to the project. The EBG group will extract the needed information from these sources, transparently and consistent with the SER protocol. Although the certainty of evidence resulting from grey literature sources is nearly always low or of very low certainty, they may be the source of critical patient-focused outcomes.

Use of Indirect Evidence or Proxy Outcomes

Occasionally, there may be studies that address a key question in a closely related population, intervention, or comparator. For example, evaluation of the utility of genetic or genomic testing of a specific cancer risk variant to improve cascade testing of at-risk family members. If there is no evidence for gene *XYZ*, but there is for *ABC* which causes a similar disorder, the SER workgroup may include that study in their review, but during the certainty assessment, the judgment for the indirectness domain would be lowered. It may be necessary to first evaluate the included studies' alignment to specific key questions and identify the gaps in the literature. If there are studies that were excluded in full text review because they did not match the desired population, intervention, or comparator, the methodologists should address their feasibility to serve as indirect sources of evidence.

Similarly, the use of proxy outcomes, that is, outcomes that are highly correlated to the outcome of interest, which may be unmeasurable or not evaluated in included studies. For example, disease severity is often a very important outcome when comparing the effect of a new therapeutic for a disorder to an existing treatment. Disease severity is the desired outcome, but studies may include proxy outcomes, such as the need for additional medications to control disease symptoms or the rate of hospitalizations or other health resource utilization. Optimally, acceptable proxy outcomes should be identified at the start of the SER, with input from both the SER and EBG workgroups. If the need to include proxy outcomes is not certain until the SER is in or finished with data analysis, the methodologists should work with both SER and EBG workgroups to identify the proxy outcomes, evaluate if there were any studies excluded from full text review with relevant proxy outcome data, and integrate the data as necessary.

Expert Evidence Survey

When there is no direct or indirect evidence identified, including from grey literature, EBG members have few options available: 1) make no recommendation; 2) make recommendations based on expert opinion alone; 3) produce primary evidence that can be used to support an EBG.[25] It is typically undesirable to make no recommendation following the time- and resource-intensive process of performing a SER and the EtD evidence profile. A 'no recommendation' choice may be appropriate if there are pre-clinical or early-stage clinical trials underway without available evidence at the time of the EBG process, with the expectation that new evidence will be emerging and the EBG could be prioritized for an update of some or all of the key questions.

However, for many rare and ultra-rare disorders without novel therapeutics driving the need for new studies, the evidence base will likely remain sparse. In this situation, rather than relying on expert *opinion* to develop recommendations, the EBG workgroup can contribute to the primary evidence through a survey of expert *evidence*. The distinction between expert opinion and evidence is nuanced and can be difficult for EBG workgroup members to fully understand. The methodologist's role is essential in this process to guide the EBG workgroup.

If an expert evidence survey is used, the methodologist will prepare a questionnaire using REDCap or a similar tool with questions designed to elicit the evidence needed to support recommendation statements. Questions such as, "How many patients with XXX disorder have you managed over your career?" or "In patients you have managed who received YYY intervention, what number/percent had adverse effects due to the intervention?" may be useful. In addition to the EBG workgroup members, it may be desirable to survey other experts. Identification of relevant individuals by the EBG and SER workgroups is expected in this situation.

Following completion of the survey, the methodologists analyze the data and prepare a summary report for the EBG workgroup to assist in completion of the recommendation process. If desired by the EBG workgroup, it may be useful to consider publishing the results of the survey separately to provide the primary evidence that was previously lacking. The results of the survey, if not published as a separate manuscript, should be included in the EBG manuscript.

Expert Panel Consensus Process

Although each of the three options described in the previous section provide an opportunity for the GRADE process to be used, rather than reliance on an expert consensus process to develop recommendations, there may be situations in which a consensus process is used. There are several approaches to choose from, including the RAND/UCLA Appropriateness method,[26] the Delphi method[27] and its numerous variations, and the Nominal Group Technique.[28] The methods combine expert opinion with review of available scientific literature. If a consensus process is selected as the method used to develop a guideline, it should be considered only after the techniques described above have been assessed and a rationale for not using them explicitly stated. Brief descriptions of the above-mentioned consensus methods are provided in Appendix 17.

Drafting Recommendation Statements

Using GRADE, each recommendation statement has both a strength (strong or conditional) and a direction (for or against the intervention). Multiple recommendation statements may be developed for an EBG. All recommendations must be specific and clearly stated to avoid ambiguity that may lead to different interpretations of the guideline. The EBG manuscript should explicitly describe the patient population for whom the guideline is meant to address, the context in which the intervention or comparator is recommended (or not), and any patient subgroups or other situations in which the recommendation statement's strength or direction does not apply or differs. The methodologists play an essential role to ensure the recommendation statement(s) that are developed adhere to these criteria.

An example of the wording for a recommendation made using the GRADE process:

- We strongly recommend ES and GS as a first-tier or second-tier test (guided by clinical judgment and often clinician–patient/family shared decision making after CMA or focused testing) for patients with one or more CAs prior to one year of age or for patients with DD/ID with onset prior to 18 years of age.[1]

Note that the recommendation statement clearly defines the patient population (patients with one or more congenital anomalies prior to one year of age or patients with developmental delay/intellectual disability with onset prior to 18 years of age), the intervention (exome and genome sequencing), the timing of the intervention (first-tier or second-tier), the context in which the intervention may be used (guided by clinical judgment and shared decision making after microarray or targeted testing), and the strength and direction (strong recommendation for the intervention). A consensus (>80%) of the EBG workgroup must agree to the strength and direction of the recommendation(s); disagreements must be documented with the rationale for which the member(s) disagreed with the consensus.

Interpretation of GRADE Recommendations

The language used in crafting EBG recommendations using GRADE are specific and informs their interpretation.[29] **It is important to note that a conditional recommendation should not be interpreted as a failure of the evidence review and EBG process**. In addition, it should not be the desire to only produce

EBGs when the expectation is a strong recommendation prior to evaluating the evidence. Conditional recommendations demonstrate the careful appraisal of the evidence, illuminate areas of uncertainty, and may be revised to strong recommendations as new evidence emerges.

There are a number of domains and considerations that apply to contextualize conditional strength EBGs. ACMG EBGs should provide the interpretation for all guideline recommendations in plain-language summaries that leave no room for misunderstanding by healthcare providers, patients/patient advocates, or other stakeholders (Table 1).

Table 1. Interpretation of GRADE-developed recommendations.

Strength	Evidence-oriented interpretation	Clinician-oriented interpretation	Patient-oriented/Plain language interpretation
Strong recommendation for [the intervention]	The evidence basis is sufficiently robust and/or the balance of risks and benefits is clearly in favor of the intervention	For most patients, I can confidently recommend the intervention without need to thoroughly review the evidence with them	I would expect my healthcare provider to recommend the intervention
Conditional recommendation for [the intervention]	The evidence basis is in favor of the intervention, but the certainty is unclear, there may be variability in patients' values or preferences for the intervention, and/or the cost-effectiveness data may be incomplete or uncertain	Though many of my patients would likely prefer the intervention and there is evidence to support my recommendation of it, some patients would be better managed with the comparator, and I need to discuss with the patient the benefits and risks of both approaches	I would expect my healthcare provider to discuss with me the evidence for the intervention and whether the comparator may be more appropriate for me, based on my values and preferences and specific clinical situation
No recommendation for either the intervention or	The evidence does not favor either the	There is clinical equipoise regarding the	There is not enough evidence for my

Strength	Evidence-oriented interpretation	Clinician-oriented interpretation	Patient-oriented/Plain language interpretation
the comparator	intervention or the comparator and/or there is insufficient evidence to support a recommendation	intervention and the comparator, I need to evaluate each patient's specific clinical condition and discuss with them the risks and benefits of both approaches	healthcare provider to recommend the intervention over the comparator and shared decision making is needed
Conditional recommendation against [the intervention]	The evidence basis is in favor of the comparator, but the certainty is unclear, there may be variability in patients' values or preferences for the comparator, and/or the cost-effectiveness data may be incomplete or uncertain	Though many of my patients would likely prefer the comparator and there is evidence to support my recommendation of it, some patients would be better managed with the intervention, and I need to discuss with the patient the benefits and risks of both approaches	I would expect my healthcare provider to discuss with me the evidence for the comparator and whether the intervention may be more appropriate for me, based on my values and preferences and specific clinical situation
Strong recommendation against [the intervention]	The evidence basis is sufficiently robust and/or the balance of risks and benefits is clearly in favor of the comparator	For most patients, I can confidently recommend the comparator without need to thoroughly review the evidence with them	I would expect my healthcare provider to recommend the comparator

Adapted from Neumann et al. (2016).[29]

EBG Manuscript

Following completion of the GRADE EtD process, the EBG workgroup members should draft the EBG manuscript. As with the SER manuscript, the methodologists should provide the EBG workgroup with a template for the manuscript and a draft of the methods section. The EBG should include details consistent with the National Guideline Clearinghouse Extent of Adherence to Trustworthy Standards (NEATS, Appendix 18)[7] and AGREE II[30] guideline appraisal and reporting checklists.

Although the EBG relies heavily on the evidence generated by the SER, the focus of the EBG manuscript should be on the rationale for the recommendation statement(s). It should not simply restate the findings of the SER but should orient the reader to the specific findings that support the recommendation. Additional evidence published after the SER's completion and relevant grey literature should be included in the rationale as needed.

Peer Review and Approval Process

The peer review and approval process for the EBG manuscript mirrors that for the SER. Briefly, both the host committee(s) and BoD must approve the draft prior to a 30-day member comment period. Following member comment, the Committee Relations Manager provides a document of all received feedback for the EBG. For some EBGs, the BoD may recommend a second peer review of the manuscript by external (non-ACMG member) subject matter experts who were not involved in either the SER or the EBG. The EBG workgroup reconvenes to address all comments and incorporates all relevant suggestions. The revised EBG then is re-reviewed by the Committee Chair(s) and the BoD for final approval before publication in *Genetics in Medicine*.

It should be noted that the peer review process as described for both the SER and EBG do not fully adhere to best practices in guideline development. A public comment period, similar to what is done for USPSTF (US Preventive Services Task Force) recommendations, is ideal and would enable a greater number of stakeholders to participate in the process. The ACMG BoD should consider moving toward a fully public comment period, in addition to the member comment period which serves as peer review.

Submission of the EBG to a Guideline Repository

As described in the Introduction, the National Guideline Clearinghouse (NGC) is no longer available and the ECRI Guidelines Trust has taken its place. The Guidelines Trust uses the same criteria previously used by the NGC to critically appraise guidelines submitted to its repository (i.e., the NEATS instrument). Although not required, it is strongly encouraged to submit ACMG EBGs to the Guidelines Trust or other third-party guideline repository once published.

GUIDELINE DISSEMINATION AND IMPLEMENTATION

Dissemination

Dissemination of ACMG SERs and EBGs involves several departments at the College and *Genetics in Medicine* to reach the greatest number of stakeholders. The optimal dissemination strategy for EBGs has not yet been identified; a multi-pronged approach may lead to the best results. Dissemination may include:

- Media campaign led by the ACMG Communications Department
- Presentation of the SER results and EBG recommendations at non-ACMG conferences, including meetings of patient advocacy organizations
- Development of an educational seminar or course based on the SER and EBG recommendations
- Partnering with the National Coordinating Center (NCC) for the Regional Genetics Networks to develop educational materials and/or webinars designed for non-genetics healthcare providers
- Development of plain-language summaries of EBGs with relevant advocacy organizations
- Consider adaptations of the EBG to accommodate non-English speakers, individuals with visual, audio, or other impairments that may impact their ability to access the EBG and its recommendations
- Submission of the EBG to ECRI Guidelines Trust, the Guidelines International Guideline Library, or other international guideline repositories

Guideline Implementation

Myriad strategies have been developed to assist implementation of guidelines and can be grouped loosely into four domains: professional, organizational, financial, and regulatory.[31] A list of specific interventions for each domain can be found in Appendix 19. Although interest in implementation science has grown substantially, most guideline developers do not have an established system to measure the effects of their guidelines in these domains. It is recommended that ACMG consider formal studies of implementation strategies, led by the Practice Research and Methodology Department. Studies performed in healthcare systems or academic medical centers with robust electronic health records and billing information may enable quantitative assessment of patient impact directly following publication of an EBG. Multiple strategies could be assessed at each location to facilitate the identification of characteristics of an organization that lead to successful implementation. The ACMG BoD is strongly encouraged to support the submission of grant applications for this purpose.

UPDATING EVIDENCE REVIEWS AND GUIDELINES

Current ACMG policy is to assess published documents no later than every five years (Lab QA 3 years) to determine if they should be revised, reaffirmed, or retired. This policy is consistent with best practices in guideline development. Because many existing ACMG guidelines were not originally developed using SERs and the GRADE framework, conversion of these documents to a SER-EBG project should be anticipated. As described in the **ACMG Document Revision/Updates** Section, committee chairs should work with the methodologists to schedule this process for all existing documents.

Some topics will require more frequent review and revision based on numerous factors:

- New evidence that impacts the benefits or harms of an intervention
- Changes in the importance of outcomes
- Changes in the availability of interventions
- Evolving clinical practice
- Changes in resources or cost-effectiveness

To identify evidence that may significantly impact the strength or direction of EBG recommendations, the methodologists will proactively save the final search query strategies for all published SERs and any grey literature sources in a project folder and within the Project Settings in Covidence. Every six months, the literature search will be re-run in Medline (Pubmed) and new literature that meets inclusion criteria will be appraised for its alignment to, or deviation from, the overall strength and direction of the existing recommendation. For example, the publication of evidence from a large clinical trial may identify numerous adverse events and serious adverse events that were not identified in the prior literature.

If the studies identified from the updated search have the potential to alter any of the recommendation statements of an EBG, the methodologist will bring the study to the attention of the host Committee Chair and propose a timeframe for updating and if the update would be a comprehensive update of the entire SER/EBG, or a targeted update for one or more key questions. If no new evidence that would impact the existing recommendation is identified, the search date and results are documented, and the search is run again in six months. This scheduled framework for updating ensures that ACMG SERs and EBGs remain relevant, timely, and rigorous.

APPENDICES

Appendix 1: Best practice recommendations for non-EBG document types

Topics and/or updates to existing ACMG documents that are determined ineligible for development as SERs/EBGs should adhere as closely as possible to the following recommendations. Workgroup chairs are strongly encouraged to work with the Practice Research and Methodology Department on their document. Methodological review of the manuscripts of non-EBG documents will focus primarily on the adherence of transparent, reproducible methodology, justifiable recommendations, and acknowledgement of limitations, as described in the proposal form.

1. Explicitly stated workgroup composition.
    a. The way in which the workgroup members were selected for participation and the expertise they provide should be clearly stated.
    b. Who was responsible for determining the workgroup members? Was there a call for volunteers from the greater ACMG membership or restricted to interested Committee members?
2. Conflicts of Interest (COI).
    a. State that all workgroup participants adhered to ACMG policies for management of COI.
    b. State if any COI management precluded someone from serving as the lead author/chair of the working group or necessitated the appointment of a co-chair.
3. Methods
    a. Search terms listed in a supplement/appendix. Include:
        i. what databases were used (e.g., Pubmed, Embase)
        ii. the date of access
        iii. any truncations, alternate spellings (e.g., European vs American English)
        iv. specific headings (e.g., MeSH, Supplementary Concepts, Text words)
        v. filters (e.g., Human, English language, date of publication)
    b. Any additional sites searched for information
        i. URL
        ii. Date of access
        iii. Search terms (any that were different from databases)
    c. What information was sought
    d. Brief description of any exclusion criteria
        i. This should be sufficient to help a reader understand why any article that was found in the literature search was excluded as evidence
    e. What method(s) (quantitative, qualitative) was used to synthesize the evidence
        i. Why was that method chosen
        ii. Which outcomes were analyzed differently
        iii. How conflicting evidence was handled
    f. What method was used to establish a recommendation where there was no evidence identified?

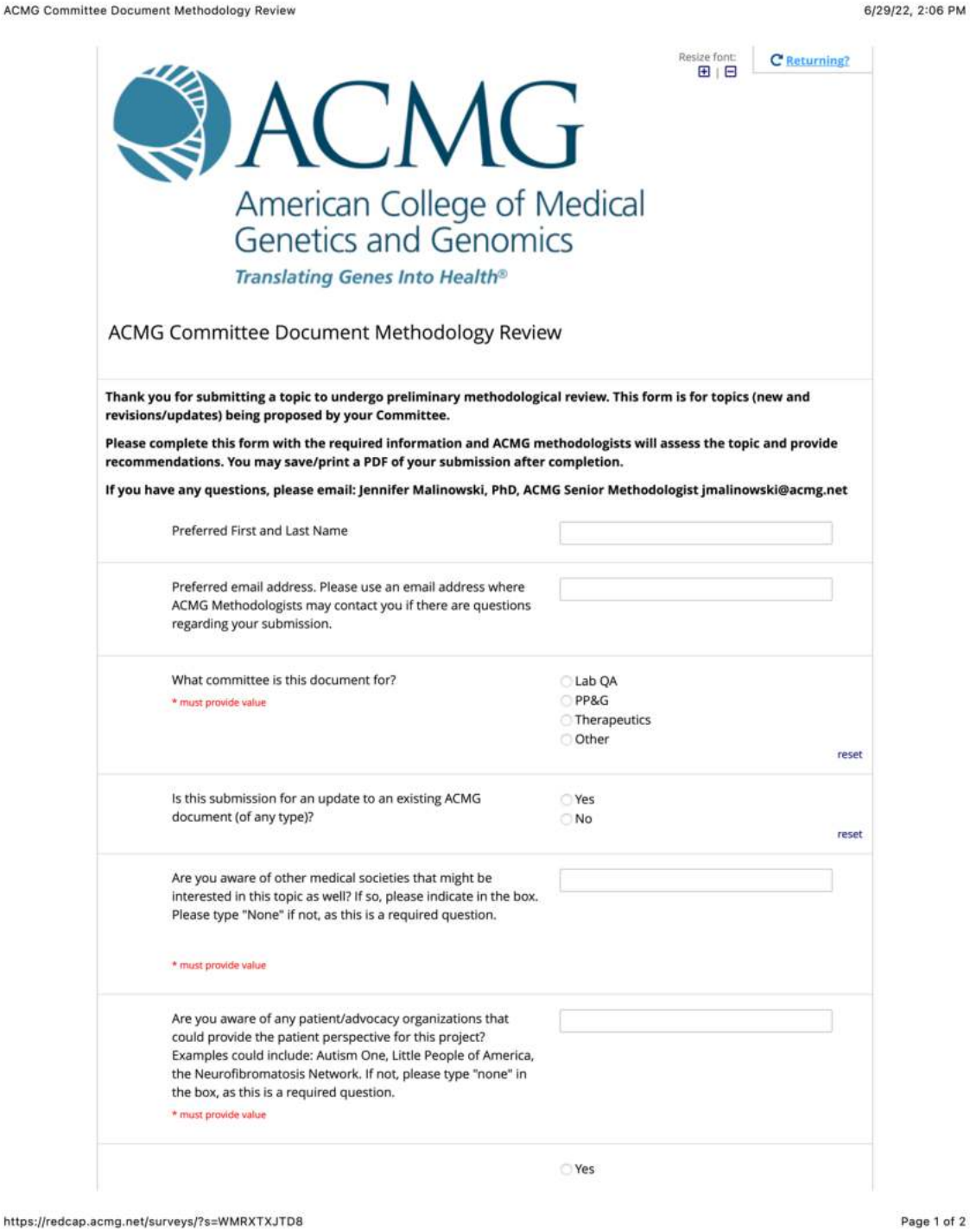
        i. If consensus, was there a minimal % agreement that was needed? (e.g., simple majority or 75% or …)
4. Results
    a. Provide a list (supplement/appendix is fine) of all studies/evidence sources used
    b. Indicate what evidence goes along w/what recommendation/section
        i. This could be a simple check mark for each section in the list of all studies
    c. Make it explicitly clear for each recommendation if it is derived from a synthesis of the evidence or expert opinion.
        i. If expert opinion, note why evidence was not used and a clear rationale for the recommendation (e.g., improve patient outcomes, avoidance of harms, optimize diagnostic yield)
5. Conclusions/Statements
    a. Avoid language that mirrors EBG (e.g., "ACMG *recommends…*").
    b. Be specific about the population and intervention the document pertains to (e.g., "Pregnant individuals **at low risk** of fetal trisomy…" instead of "All pregnant individuals.."; "Exome or genome sequencing as a first-tier test…" instead of "Exome or genome sequencing [**without any qualifier**]…").
    c. Clearly state the limitations:
        i. Lack of evidence.
        ii. Rapidly evolving evidence.
        iii. Remaining questions to be answered (i.e., research gaps).
        iv. Limitations due to the workgroup's processes

Not needed (but always useful):

1. Specific search query/queries
2. PRISMA flow chart **note these are REQUIRED for practice resources and EBGs
3. Exhaustive inclusion/exclusion criteria
4. Specific data/evidence extracted from every source of evidence

Appendix 2: ACMG Committee Methodological Review Form

*Note that this form uses logical dependencies; questions shown online are determined by the answers given.



ACMG Committee Document Methodology Review 6/29/22, 2:06 PM

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ACMG Committee Document Methodology Review

Thank you for submitting a topic to undergo preliminary methodological review. This form is for topics (new and revisions/updates) being proposed by your Committee.

Please complete this form with the required information and ACMG methodologists will assess the topic and provide recommendations. You may save/print a PDF of your submission after completion.

If you have any questions, please email: Jennifer Malinowski, PhD, ACMG Senior Methodologist jmalinowski@acmg.net

Preferred First and Last Name

Preferred email address. Please use an email address where ACMG Methodologists may contact you if there are questions regarding your submission.

What committee is this document for?
* must provide value
- Lab QA
- PP&G
- Therapeutics
- Other

reset

Is this submission for an update to an existing ACMG document (of any type)?
- Yes
- No

reset

Are you aware of other medical societies that might be interested in this topic as well? If so, please indicate in the box. Please type "None" if not, as this is a required question.
* must provide value

Are you aware of any patient/advocacy organizations that could provide the patient perspective for this project? Examples could include: Autism One, Little People of America, the Neurofibromatosis Network. If not, please type "none" in the box, as this is a required question.
* must provide value

- Yes

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Would you like a methodologist to contact you for more information ***prior*** to completing the review? If yes, someone will reach out to you via email for more information.

Methodology reviews for updates to existing ACMG documents are prioritized. A report will be provided to the Committee Chair and the person submitting this form.

* must provide value

○ No

reset

Submit

Save & Return Later

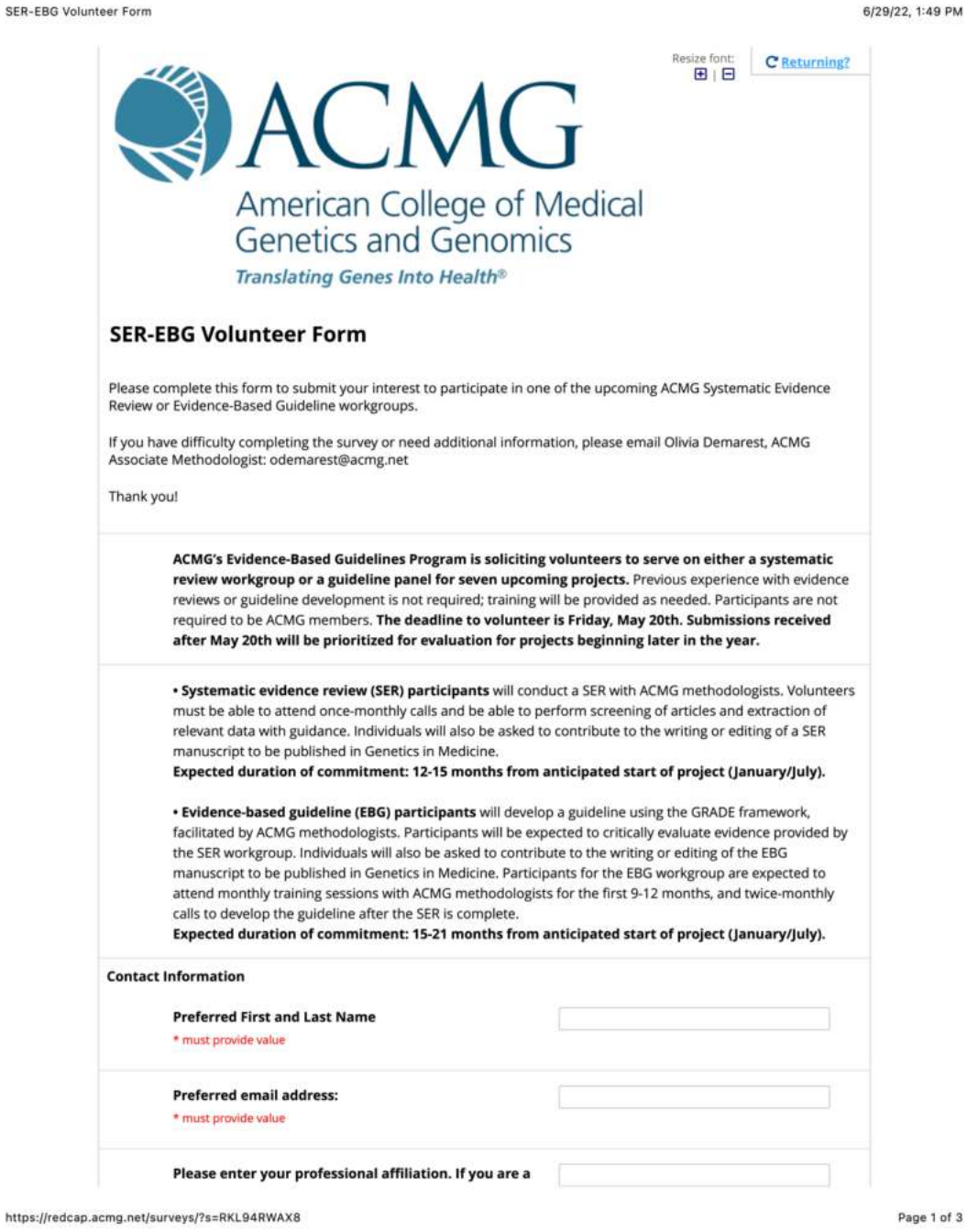
Appendix 3: Practice Research and Methodology (PRM) Department Timeline for Volunteer and Topic Nomination Requests

MONTH	TASK	STAFF COORDINATION
January	Solicit for new SER-EBG topics for TSC review New SER-EBG projects commence	PRM Department, Communications Department, Committee Relations Manager
February	Methodological review of submitted topics	PRM Methodologists
March	TSC meeting to determine **new** SER-EBG projects (at annual conference time)	Senior Methodologist/Methodologist
April	Call for project-specific volunteers (within 1 month of annual conference)	PRM Department, Communications Department, Committee Relations Manager
May	Submit workgroup composition and SER-EBG proposals to Board	PRM Methodologists, Committee Relations Manager, Committee Chairs, Board of Directors
June	Annual planning with Committee Chairs for Scheduled Updates	
July	New SER-EBG projects commence	Methodology team, Covidence, GRADEpro, Chief Operating Officer
August	Solicit for new SER-EBG topics for TSC review	Methodology team, Communications (e-zine appeal August, September)
September	Methodological review of submitted topics	PRM Department
October	TSC meeting to determine **new** SER-EBG projects (at/around ASHG)	Senior Methodologist/Methodologist
November	Call for project-specific volunteers (within 1 month of annual conference)	PRM Department, Communications Department, Committee Relations Manager
December	Submit workgroup composition and SER-EBG proposals to Board	PRM Methodologists, Committee Relations Manager, Committee Chairs, Board of Directors

***Note that topics originating from within Committees may be submitted and reviewed at any time**. Methodologists strongly encourage Committees to consider the above timing for the twice-annual calls for volunteers (April, November).

Appendix 4: SER-EBG Volunteer Submission Form

*Note that this form will change to accommodate new project topics/desired roles as needed. The form uses logical dependencies, so the specific questions will vary based on project needs and responses by the submitter.



SER-EBG Volunteer Form 6/29/22, 1:49 PM

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SER-EBG Volunteer Form

Please complete this form to submit your interest to participate in one of the upcoming ACMG Systematic Evidence Review or Evidence-Based Guideline workgroups.

If you have difficulty completing the survey or need additional information, please email Olivia Demarest, ACMG Associate Methodologist: odemarest@acmg.net

Thank you!

ACMG's Evidence-Based Guidelines Program is soliciting volunteers to serve on either a systematic review workgroup or a guideline panel for seven upcoming projects. Previous experience with evidence reviews or guideline development is not required; training will be provided as needed. Participants are not required to be ACMG members. **The deadline to volunteer is Friday, May 20th. Submissions received after May 20th will be prioritized for evaluation for projects beginning later in the year.**

• **Systematic evidence review (SER) participants** will conduct a SER with ACMG methodologists. Volunteers must be able to attend once-monthly calls and be able to perform screening of articles and extraction of relevant data with guidance. Individuals will also be asked to contribute to the writing or editing of a SER manuscript to be published in Genetics in Medicine.
Expected duration of commitment: 12-15 months from anticipated start of project (January/July).

• **Evidence-based guideline (EBG) participants** will develop a guideline using the GRADE framework, facilitated by ACMG methodologists. Participants will be expected to critically evaluate evidence provided by the SER workgroup. Individuals will also be asked to contribute to the writing or editing of the EBG manuscript to be published in Genetics in Medicine. Participants for the EBG workgroup are expected to attend monthly training sessions with ACMG methodologists for the first 9-12 months, and twice-monthly calls to develop the guideline after the SER is complete.
Expected duration of commitment: 15-21 months from anticipated start of project (January/July).

Contact Information

Preferred First and Last Name
* must provide value

Preferred email address:
* must provide value

Please enter your professional affiliation. If you are a

https://redcap.acmg.net/surveys/?s=RKL94RWAX8 Page 1 of 3

patient, patient advocate, or parent, please indicate if you are a member of a specific organization. If you are otherwise unaffiliated, please type "unaffiliated."

* must provide value

What state are you located/your primary employer located? If located outside of the US, please indicate your country.

* must provide value

Please enter your job position (examples: Methodologist at ACMG; Student at Meharry Medical College; Clinical Fellow at NIH; Laboratory Director at XYZ Laboratories; Pediatrician in Private Practice)

Expand

Are you a member of ACMG? If so, please indicate your membership and if you are a fellow. ***It is not a requirement to be a member to participate in our evidence-based guidelines process.***

* must provide value

Which project are you volunteering for? Workgroup assignment (systematic evidence review or evidence-based guideline) will be determined by ACMG methodologists in accordance with ACMG DEI principles and best-practices.

* must provide value

- ○ Pompe disease
- ○ No preference, willing to volunteer on any project
- ○ New project 1

reset

Would you fill one of the following roles that are desired for all ACMG SER-EBGs?

* must provide value

- ○ No
- ○ Clinical geneticist
- ○ Laboratory/molecular geneticist
- ○ Genetic counselor
- ○ Patient with a genetic condition
- ○ Parent of a patient/patient advocate
- ○ Representative from another professional society (e.g., ACOG, AAN, AAP, SIMD)

reset

Please upload your most recent CV, NIH Biosketch, or resume

* must provide value

Upload document

If you are not selected for one of the projects listed above, are you willing to be contacted for future projects?

- ○ Yes
- ○ No

reset

Do you have any additional comments or questions? A member of the ACMG methodology team will reach out to you via email.

Expand

Submit

Save & Return Later

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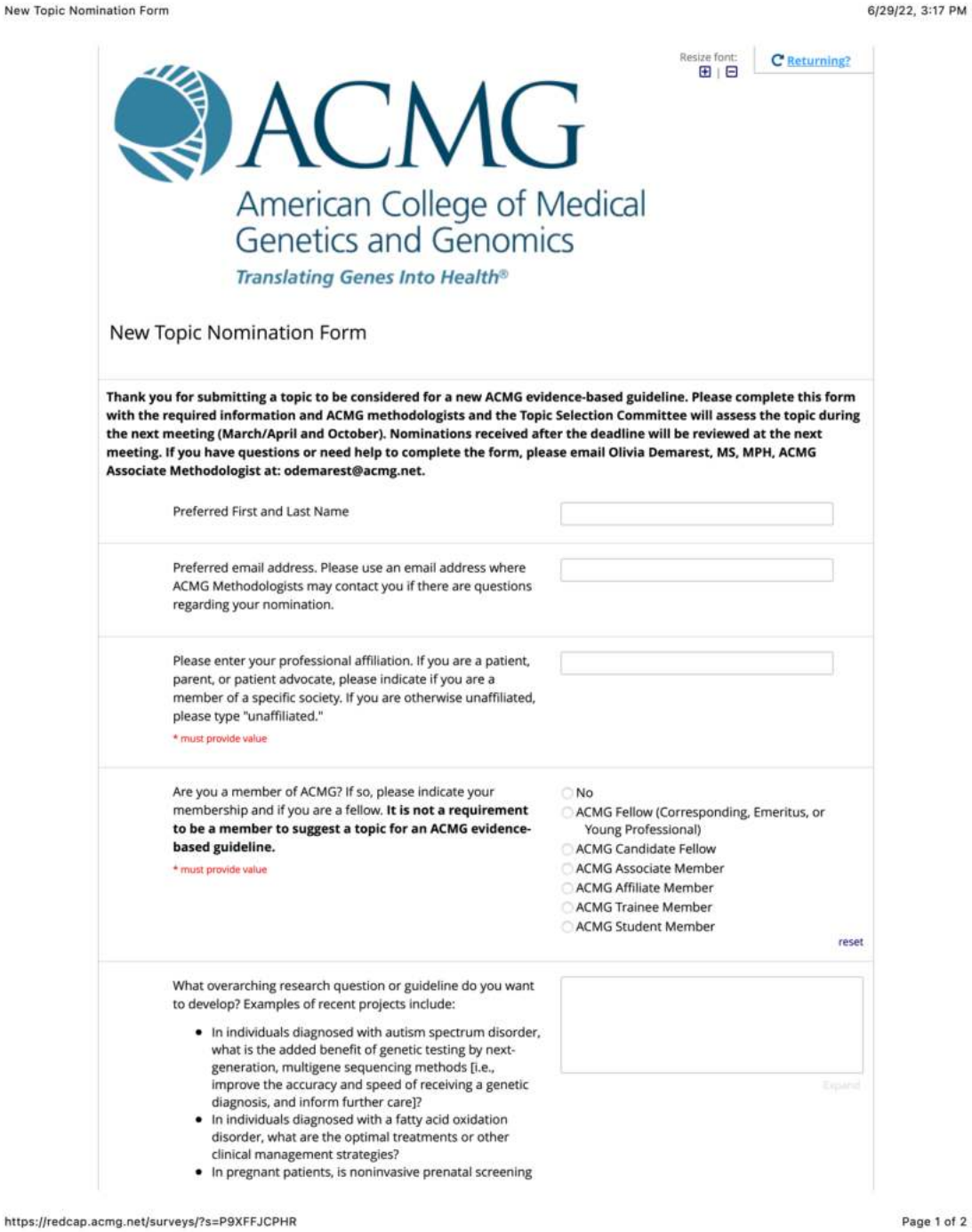
Appendix 5: New Topic Nomination Form

This form is for topics originating externally to ACMG that will be approved by the Topic Selection Committee (TSC). The TSC will meet twice yearly to decide which submitted topics should move forward; however, forms may be submitted at any time.



New Topic Nomination Form 6/29/22, 3:17 PM

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New Topic Nomination Form

Thank you for submitting a topic to be considered for a new ACMG evidence-based guideline. Please complete this form with the required information and ACMG methodologists and the Topic Selection Committee will assess the topic during the next meeting (March/April and October). Nominations received after the deadline will be reviewed at the next meeting. If you have questions or need help to complete the form, please email Olivia Demarest, MS, MPH, ACMG Associate Methodologist at: odemarest@acmg.net.

Preferred First and Last Name

Preferred email address. Please use an email address where ACMG Methodologists may contact you if there are questions regarding your nomination.

Please enter your professional affiliation. If you are a patient, parent, or patient advocate, please indicate if you are a member of a specific society. If you are otherwise unaffiliated, please type "unaffiliated."

* must provide value

Are you a member of ACMG? If so, please indicate your membership and if you are a fellow. **It is not a requirement to be a member to suggest a topic for an ACMG evidence-based guideline.**

* must provide value

- No
- ACMG Fellow (Corresponding, Emeritus, or Young Professional)
- ACMG Candidate Fellow
- ACMG Associate Member
- ACMG Affiliate Member
- ACMG Trainee Member
- ACMG Student Member

reset

What overarching research question or guideline do you want to develop? Examples of recent projects include:

- In individuals diagnosed with autism spectrum disorder, what is the added benefit of genetic testing by next-generation, multigene sequencing methods [i.e., improve the accuracy and speed of receiving a genetic diagnosis, and inform further care]?
- In individuals diagnosed with a fatty acid oxidation disorder, what are the optimal treatments or other clinical management strategies?
- In pregnant patients, is noninvasive prenatal screening

Expand

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superior to existing 1st- and 2nd-trimester screening methods to detect Down syndrome or other chromosomal anomalies?
- What is the clinical utility of exome or genome sequencing in patients with congenital anomalies and/or intellectual disability/developmental delay?

* must provide value

What are the PICOTS (population/disorder, intervention, comparator, outcomes, timing, and setting) for your research question?

Please be as specific as possible. Please include at least one outcome of interest. Examples of outcomes may include:

- cost effectiveness or other economic metrics
- diagnostic yield
- changes to morbidity or mortality
- psychosocial outcomes like depression or anxiety
- change in clinical management

* must provide value

Expand

Are you aware of other medical societies that might be interested in this topic as well? If so, please indicate in the box. You may leave this response blank if necessary.

Are you aware of any patient/advocacy organizations that could provide the patient perspective for this project? Examples could include: Autism One, Little People of America, the Neurofibromatosis Network. If not, please type "none" in the box, as this is a required question.

* must provide value

Do you have any additional information you would like to share with the ACMG methodology team to help us in our assessment of this topic? If so, someone will reach out to you shortly.

Please note that nominations will be considered by the Topic Selection Committee twice/year, around the time of the annual ACMG meeting (March/April) and in October. You will be notified about the decision of the committee shortly thereafter.

* must provide value

○ Yes
○ No

reset

Submit

Save & Return Later

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Appendix 6: Topic Selection Checklist for Methodologists

This is the template used by the methodologists to conduct a preliminary methodological assessment of proposed new topics and for updates to existing ACMG documents.

Methodologist reviewing nomination:	
Last name of nominee:	
Type of SER project (1):	
Type of SER project (2), if applicable:	
Proposed committee assignment (1):	
Proposed committee assignment (2), if applicable:	
SER topic and brief rationale:	
Methodological review	
Are PICOS complete? (Y/N) If NO, reach out to nominator for details	
Are there any closely related nominations? (Y/N) If YES, note which and assess together.	
Relevant clinical guideline from another organization? (Y/N) If YES, note year published, organization, and methodology used (i.e., GRADE/other evidence-based method, consensus).	
Is there least one patient advocacy group for the condition? (Y/N) If YES, specify.	
Relevant SERs? (Y/N) Search PROSPERO, Cochrane, Pubmed. If YES, document and indicate the group/lead authors.	
Conducted preliminary research in Pubmed? (Y/N)	
Search string	
Hits	
Quality of evidence completed? (Y/N) Filter Pubmed results by publication type.	
Scope of project:	
Can project be completed in 12-15 months? (Y/N)	
Note complexity of topic.	
Did nomination form include suggested workgroup members? (Y/N)	
Interest in joint EBG development with one or more organizations? (Y/N) [from nomin	

Appendix 7: Topic Selection Committee Topic Nomination Ranking Form

The second part of this form will be revised twice yearly to accommodate the specific topics that are to be ranked by the Topic Selection Committee.

October 2022

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Please complete the survey below.

Thank you!

How closely does the topic align to current or near future College priorities?

	Most closely aligned				Least aligned	
1) New topic 1	○	○	○	○	○	reset
2) New topic 2	○	○	○	○	○	reset
3) New topic 3	○	○	○	○	○	reset

What do you think the potential impact of an ACMG EBG would be? Take into consideration if the EBG could be jointly-developed with another organization or if formal endorsement of an ACMG EBG will be sought.

	Highest possible impact				Lowest possible impact	
4) Topic 1	○	○	○	○	○	reset
5) Topic 2	○	○	○	○	○	reset
6) Topic 3	○	○	○	○	○	reset

Please assess how feasible it will be to complete the SER within 9-15 months and the EBG in <2 years (includes the SER time plus 3-9 months)

	Most feasible				Least feasible	
7) Topic 1	○	○	○	○	○	reset
8) Topic 2	○	○	○	○	○	reset
9) Topic 3	○	○	○	○	○	reset

Based on the preliminary methodological review, what is the quality and quantity of evidence available for the SER?

	Best quality and abundance of evidence				Poorest quality and scarcity of evidence	
10) Topic 1	○	○	○	○	○	reset
11) Topic 2	○	○	○	○	○	reset
12) Topic 3	○	○	○	○	○	reset

Please rank the topics against each other, from your top choice to your last choice.

(One selection allowed per column)

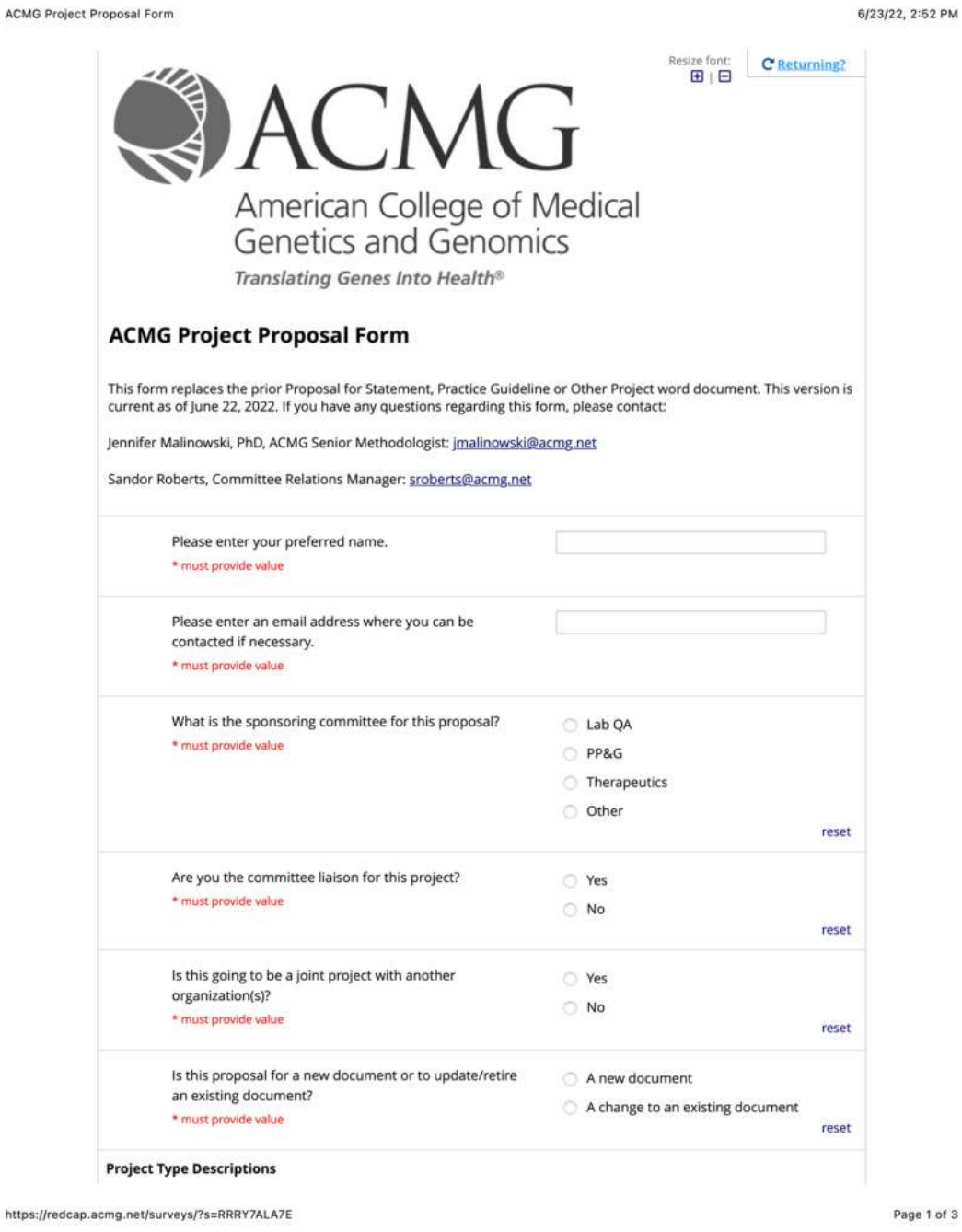
First-ranked choice	As many options as number of topics	Last-ranked choice

13) Topic 1	○	○	○	reset
14) Topic 2	○	○	○	reset
15) Topic 3	○	○	○	reset

Submit

Appendix 8: ACMG Proposal for Statement, Guideline, or Other Project Form

This form replaces the existing Word proposal form. The REDCap survey construction streamlines the proposal process, ensures all committees are working from the most recently approved document, and allows easy revisions as needed.



ACMG Project Proposal Form 6/23/22, 2:52 PM

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ACMG Project Proposal Form

This form replaces the prior Proposal for Statement, Practice Guideline or Other Project word document. This version is current as of June 22, 2022. If you have any questions regarding this form, please contact:

Jennifer Malinowski, PhD, ACMG Senior Methodologist: jmalinowski@acmg.net

Sandor Roberts, Committee Relations Manager: sroberts@acmg.net

Please enter your preferred name.
* must provide value

Please enter an email address where you can be contacted if necessary.
* must provide value

What is the sponsoring committee for this proposal?
* must provide value
- Lab QA
- PP&G
- Therapeutics
- Other

reset

Are you the committee liaison for this project?
* must provide value
- Yes
- No

reset

Is this going to be a joint project with another organization(s)?
* must provide value
- Yes
- No

reset

Is this proposal for a new document or to update/retire an existing document?
* must provide value
- A new document
- A change to an existing document

reset

Project Type Descriptions

https://redcap.acmg.net/surveys/?s=RRRY7ALA7E Page 1 of 3

Systematic evidence review/Evidence-based guideline (laboratory OR clinical): These projects incorporate BOTH a systematic review of the literature AND development of an evidence-based guideline using GRADE methodology. **These projects are guided by ACMG Methodologists** to ensure adherence to best practices, inclusion of relevant stakeholders (e.g., patients/patient advocates), and potential development with additional professional societies.

Technical standards for clinical genetics laboratories: Developed and maintained by ACMG's Laboratory Quality Assurance Committee, these voluntary standards establish criteria for clinical genetics laboratories to provide accurate and reliable diagnostic testing that is consistent with current technologies and procedures. These documents are written by experts in the field and rely on published data and experience. **It is expected to have a transparent, reproducible methodology, make justifiable recommendations, and discuss its limitations**. It is strongly encouraged to work with a methodologist at the outset of this project to ensure the methods will be adequately described in accordance with the above.

Statements: A statement about a timely issue that represents the opinions, beliefs, and/or best professional judgments of the College. **Policy statements** outline how the College intends to act in specific circumstances. **Position statements** discuss where the College stands on a topic or a debatable issue and are often used to describe the goals of a positioning strategy. **Points to Consider** statements represent an assessment of emerging issues or new technologies in practice and are reviewed regularly for accuracy. ACMG Methodologists are able to assist Statement workgroups if desired.

Practice Resource: A practice resource document addresses an important and timely topic in clinical genetics, including laboratory practice algorithms. It is informed by a non-systematic evidence review of the literature and other information sources, including expert opinion. Use of an expert panel is encouraged, but not required. These documents are expected to have **a transparent, reproducible methodology, make justifiable recommendations, and discuss its limitations, including the potential for bias given the non-systematic approach.** It is strongly encouraged to work with a methodologist at the outset of this project to ensure the methods will be adequately described in accordance with the above.

What type of project are you proposing?

Please note that for revisions to existing documents, you should select the project type that is appropriate **NOW,** rather than the document type that may have been used in the past.

* must provide value

- ○ Systematic evidence review
- ○ Evidence-based guideline
- ○ Technical standards (LabQA)
- ○ Practice Resource
- ○ Points to Consider Statement
- ○ Position Statement
- ○ Policy Statement

reset

Project Details

It is expected that the proposal have clearly defined key questions that support an overarching research question. The population of interest, intervention, comparator, and outcomes should be clearly defined in the scope of the project. It should be clear why there is a need for the project, how it aligns to current College priorities, and how the results may inform clinical or laboratory practice.

What is the overarching intent of the project? Please describe why there is a need for the project and the anticipated impact(s) on patients/clinical/laboratory practice.

* must provide value

Expand

What are the population, intervention, comparator, outcomes, [timing/setting] of interest for this project? Please describe as specifically as possible.

Examples of relevant outcomes include: diagnostic yield, test accuracy metrics, cost effectiveness, percent of patients with a change to clinical management over 5 years after diagnostic testing

* must provide value

Expand

What is the target audience for this document? Select all that apply.

* must provide value

- [ ] Clinicians
- [ ] Educators
- [ ] General public/patients/patient advocacy organizations
- [ ] Laboratorians
- [ ] Media
- [ ] Public policy makers
- [ ] Regulatory bodies
- [ ] Third-party payers
- [ ] Other

Proposed Workgroup Members

After responding to the following question, please click "Submit" to enter proposed workgroup members.

Each member will be required to complete the ACMG Participation Agreement before the proposal will be considered.

How have you considered principles of diversity, equity, and inclusion for any proposed workgroup members and the content of the proposed document?

* must provide value

Expand

Submit

Save & Return Later

Workgroup Members

Resize font: ⊞ | ⊟

Please enter each workgroup member proposed.

Thank you!

1) Name of Workgroup Member and Credentials
* must provide value

2) Email of workgroup member
* must provide value

3) Is this workgroup member a chair or co-chair?
* must provide value

- ○ Yes
- ○ No

reset

4) Title and Affiliation of Workgroup Member
* must provide value

5) Expertise or role in the project
* must provide value

6) ACMG Fellow and/or Membership
* must provide value

- ☐ ACMG Fellow
- ☐ ACMG Associate member
- ☐ ACMG Affiliate member
- ☐ Trainee member
- ☐ Student member
- ☐ Applicant for membership
- ☐ Non-member

7) Do you have another workgroup member to add?
* must provide value

- ○ Yes
- ○ No

reset

Submit and

Add another workgroup member

– or –

Submit

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Appendix 9: Systematic Evidence Review Protocol Template

Title [from approved proposal]:

PROSPERO RECORD:

Anticipated/actual start date:

Anticipated/actual completion date:

Overarching research question:

KQ1:

KQ2:

KQ3:

KQ4:
[additional as needed]

Participants/population:
Subpopulations (for analysis; for EBG):

Intervention(s)/Exposure(s):

Comparator(s)/control:

Outcome(s) [measure of effect(s)]:

Timing/Setting (if relevant):

Databases for literature search:

Literature search peer-reviewed (PRESS document, Excel spreadsheet)

Inclusion criteria:

Exclusion criteria:

Risk of bias tool(s):

Extraction details:

Analysis plan by KQ:

Proposed tables/figures:

Revisions to protocol:

Date:
Details:

[add as needed]

Appendix 10: PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	

Section and Topic	Item #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	

Section and Topic	Item #	Checklist item	Location where item is reported
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Appendix 11: PRISMA 2020 checklist for abstracts

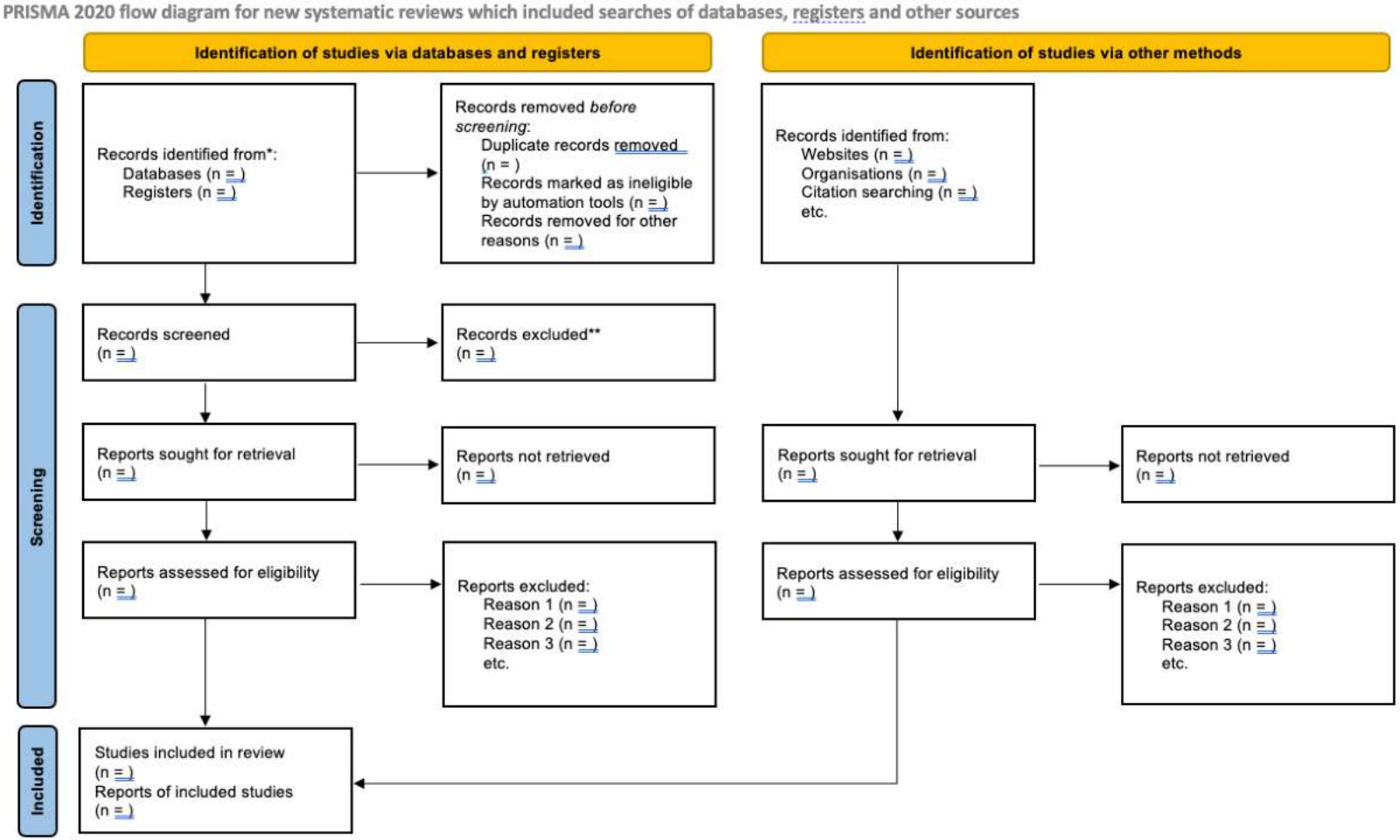
PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	
Synthesis of results	6	Specify the methods used to present and synthesise results.	
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	
Interpretation	10	Provide a general interpretation of the results and important implications.	
OTHER			
Funding	11	Specify the primary source of funding for the review.	
Registration	12	Provide the register name and registration number.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Appendix 12: PRISMA Flowchart for Systematic Evidence Reviews



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

Appendix 13: Economic Studies Extraction Template

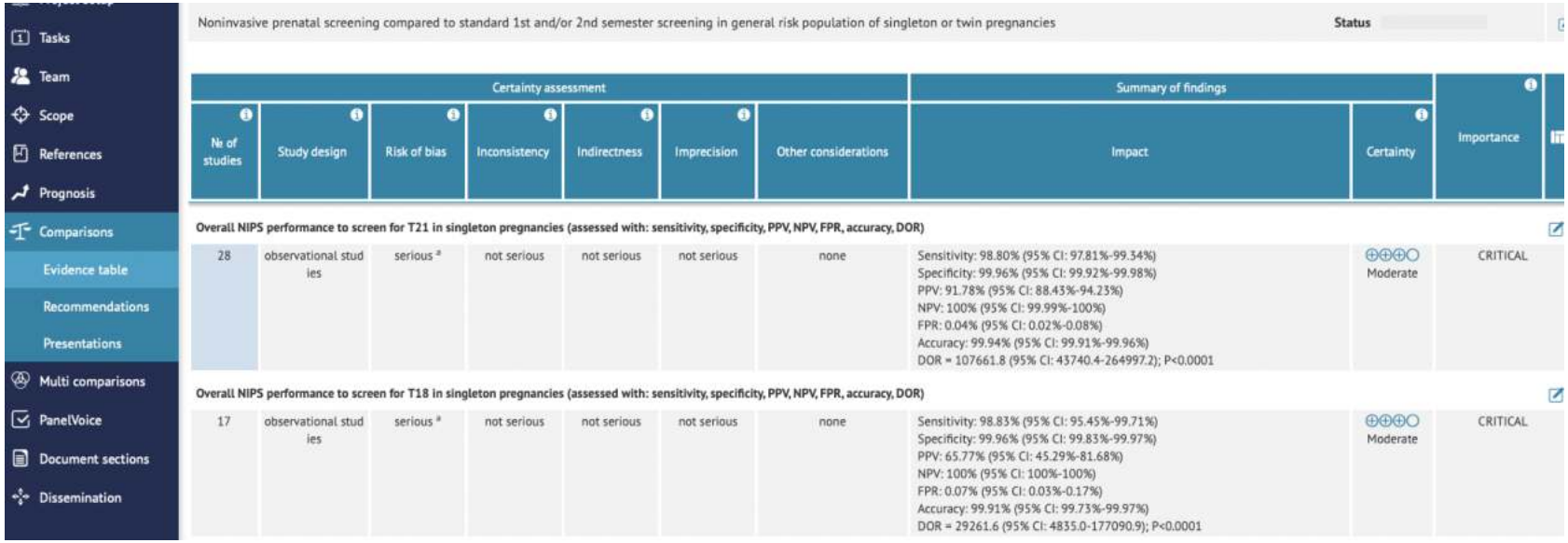
When it is not feasible to include the extraction of economic data within the larger extraction form in Covidence, this template may be used both to extract the data and as a supplemental table for the SER manuscript.

Author, Year, Country	Study Characteristics	Population Characteristics	Analysis Parameters	Results	
				Outcomes	Interpretation/Limitations
Author, Year **Country:** **Setting**: **Funding**: **Conflicts of interest**:	**Study objective:** **Perspective**: **Currency, year:** **Time Horizon**: **Discount rate:**	**Source**: **N** = **Risk**: **Age**:	**Intervention (I):** **Comparator(s) (C):** **Source of data inputs:** **Model:** **Sensitivity analyses**: **Measure of effectiveness:** **Outcomes:**	**Cost**: **QALYs:** **ICER:**	**Limitations:**
Abbreviations: CEA, cost-effectiveness analysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.					

Appendix 14: EBG Workgroup Training Plan with Publications

- Month 1: Intro/Setting the Expectations
    - GRADE #2: Framing the question and deciding on important outcomes
    - Review the SER protocol, address any remaining questions/comments
    - Set the stage for the following months
    - Q&A, training schedule
- Month 2: What will the data look like?
    - Interpreting the results of meta-analyses
    - GRADE #1: Intro to evidence profiles/summary of findings tables
    - GRADE #26: Communicating the findings of SERs
- Month 3: Risk of bias
    - GRADE #18: ROBINS-I
    - GRADE #4: Risk of bias [study limitations]
    - GRADE #17: Risk of bias with missing outcomes data
    - Murad 2018 case series quality
- Month 4: Remaining certainty domains
    - GRADE #6: Imprecision
    - GRADE #7: Inconsistency
    - GRADE #8: Indirectness
    - GRADE #5: Publication bias
- Month 5: Test accuracy studies
    - GRADE #21, part 1 and part 2
    - GRADE #22: GRADE for tests & strategies
- Month 6: Overall certainty of evidence (per outcome/overall)
    - GRADE #9: Rating up
    - GRADE #11: Overall confidence rating
- Month 7: Evidence-to-decision framework
    - Demo GRADEpro
    - GRADE #14: EtD overview
    - GRADE #15: EtD direction & strength
    - GRADE #16: EtD framework
- Month 8: Additional domains & alternate methods
    - GRADE #10: Resource use & economic evidence
    - Incorporating grey literature & surveys
- Month 9: Role of health equity
    - GRADE Equity #1-4
- Month 10: Mock recommendation part 1
    - SER, determining overall certainty
- Month 11: Mock recommendation part 2
    - Use EtD, create recommendation
- Month 12: Writing the guideline manuscript
    - Assign writing selections
    - Walk through structure of manuscript

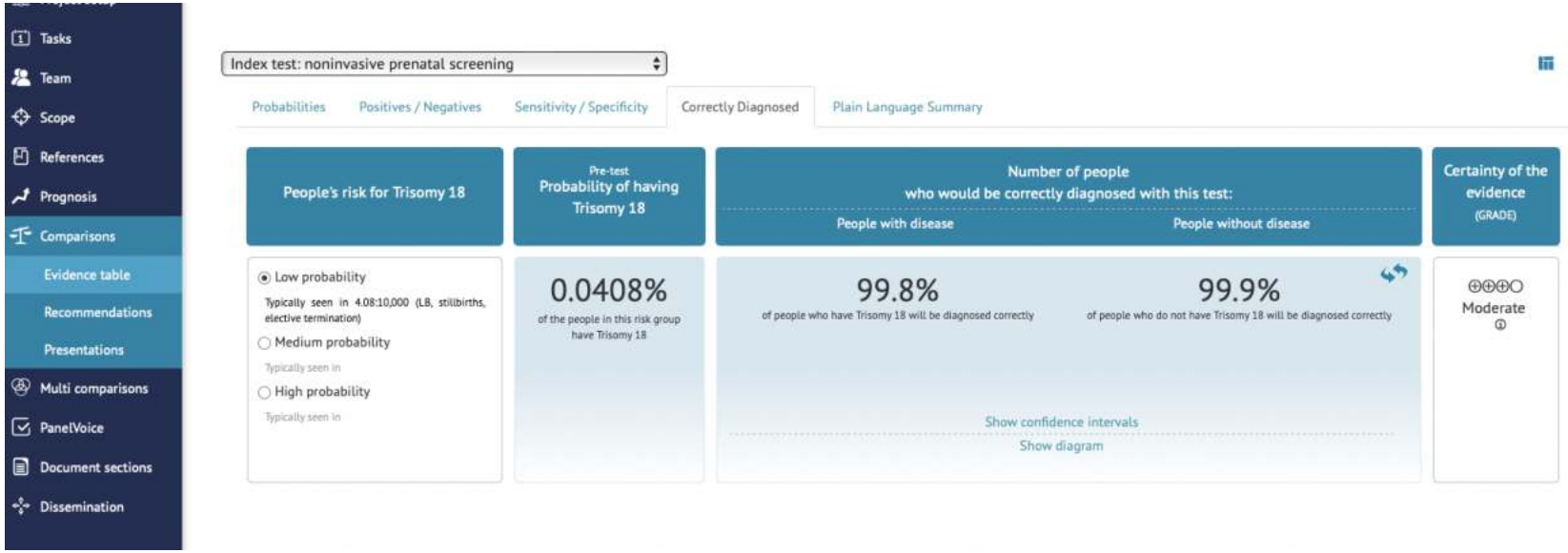
Appendix 15: GRADEpro Evidence Profile Example



Noninvasive prenatal screening compared to standard 1st and/or 2nd semester screening in general risk population of singleton or twin pregnancies **Status**

Certainty assessment							Summary of findings			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Impact	Certainty	Importance	
Overall NIPS performance to screen for T21 in singleton pregnancies (assessed with: sensitivity, specificity, PPV, NPV, FPR, accuracy, DOR)										
28	observational studies	serious [a]	not serious	not serious	not serious	none	Sensitivity: 98.80% (95% CI: 97.81%-99.34%) Specificity: 99.96% (95% CI: 99.92%-99.98%) PPV: 91.78% (95% CI: 88.43%-94.23%) NPV: 100% (95% CI: 99.99%-100%) FPR: 0.04% (95% CI: 0.02%-0.08%) Accuracy: 99.94% (95% CI: 99.91%-99.96%) DOR = 107661.8 (95% CI: 43740.4-264997.2); P<0.0001	⨁⨁⨁◯ Moderate	CRITICAL	
Overall NIPS performance to screen for T18 in singleton pregnancies (assessed with: sensitivity, specificity, PPV, NPV, FPR, accuracy, DOR)										
17	observational studies	serious [a]	not serious	not serious	not serious	none	Sensitivity: 98.83% (95% CI: 95.45%-99.71%) Specificity: 99.96% (95% CI: 99.83%-99.97%) PPV: 65.77% (95% CI: 45.29%-81.68%) NPV: 100% (95% CI: 100%-100%) FPR: 0.07% (95% CI: 0.03%-0.17%) Accuracy: 99.91% (95% CI: 99.73%-99.97%) DOR = 29261.6 (95% CI: 4835.0-177090.9); P<0.0001	⨁⨁⨁◯ Moderate	CRITICAL	

Appendix 16: GRADEpro Summary of Findings Table Example



Appendix 17: Selected Consensus Methods Descriptions and Citations

This section was written by the authors of the first version of this manual and updated with new citations as needed. In general, consensus-based methods are modifications of the Delphi technique[27] which has been used to make decisions within a group. Based upon extensions to GRADE methodology for diagnostic accuracy studies, qualitative research, rare disorders, and sparse evidence, these methods will not typically be used for an ACMG guideline.

RAND/UCLA Appropriateness Method

The RAND/UCLA appropriateness method is a method used to determine criteria of appropriateness for a medical intervention for specific clinical scenarios or indications when sufficient evidence regarding efficacy and effectiveness is not available.[26] The method combines expert opinion with review of the scientific literature. The method quantitatively assesses the expert judgment of a multidisciplinary group of clinicians concerning a comprehensive series of clinical indications on a risk-benefit scale ranging from 1 to 9. Each panelist has equal weight in determining the final result. Results yield an appropriateness rating for clinically detailed patient scenarios that can be used as the basis to develop practice guidelines, to evaluate practice patterns, and to identify areas of uncertainty. The method is described below.

- **Panel selection**. Each panel consists of nine clinicians from various specialties relevant to the topic. Clinical leaders from prominent medical organizations suggest names for the panel. The panelists are required to perform two rating tasks; the first done before the panel meeting and the second done at the meeting.
- **Initial list of indications**. Project staff members compile the initial lists of clinical indications for a particular intervention, using reviews of the medical literature on each intervention as a guide. The indications categorize patients in terms of their symptoms, past medical history, and the results of previous diagnostic tests. The indications list should be detailed and comprehensive, yet manageable.
- **Initial ratings**. Panelists are sent literature reviews, rating sheets and instructions that asked them to rate the appropriateness of each indication using their own best judgment (rather than their perceptions of what other experts might say), and considering an average group of patients presenting to an average US physician who would use the medical intervention or procedure. *Appropriate* was defined as the expected health benefit (i.e., increased life expectancy, relief of pain, reduction in anxiety, improved functional capacity) exceeded the expected negative consequences (i.e., mortality, morbidity, anxiety of anticipating the procedure or test result, pain from the procedure, time lost from work) by a sufficiently wide margin that the intervention or procedure was worth doing. *Inappropriate* meant the opposite; the negative consequences outweighed the expected benefits. Using the 1 to 9 scale, extremely inappropriate = 1; equivocal, neither clearly appropriate nor clearly inappropriate = 5; and extremely appropriate = 9. Cost is generally not considered in assessing appropriateness. The instructions also include definitions of medical terms.
- **Panel meetings**. The process is iterative with at least two rounds of anonymous ratings by nine panelists and group discussion (face-to-face, by video-teleconferencing or telephone) between rounds. Panelists discuss indications for each intervention one at a time. During the discussion, the panelists have printouts in front of them that summarize their initial ratings with a caret below the rating, and numbers above each rating show the distribution of how many panelists assigned each rating. During the discussions, the clinical indications under review may be changed; for example: splitting one indication into two or more; changing boundaries between indications; dropping some indications and adding others. After discussing each chapter, the panelists marked their final

ratings directly on the printouts.

- **Measures used to rate indications.** The 1 to 9 point-scale is an ordinal scale ranking the excess or deficiency of benefit compared to risk. A 9 is always more appropriate than an 8, and an 8 is more appropriate than a 7, but the difference between a 9 and an 8 is not necessarily the same as the difference between an 8 and a 7. Therefore, measures like means and standard deviations that treat the intervals as though they were equal should be avoided. Using the median to measure the central tendency of the nine panelists' ratings is preferable. In addition, special measures of agreement and disagreement indicate the dispersion of the ratings.
- **Agreement and disagreement**. The 9-point scale meaningfully divides into three 3-point regions. Ratings from 1 to 3 indicate that the risks outweigh the benefits, and the intervention or procedure should not be done. Ratings from 4 to 6 say that the risks and benefits are roughly equal and doing the intervention or procedure is questionable. Ratings from 7 to 9 indicate that the benefits outweigh the risks and the intervention or procedure should be done.
    - Four definitions of agreement are: (1) All nine of the ratings fell within a single 3-point region – 1 to 3, 4 to 6, or 7 to 9. (2) All nine of the ratings fell within any 3-point range. (3) After discarding one extreme high and one extreme low rating, the remaining seven ratings all fell within a single 3-point region – 1 to 3, 4 to 6, or 7 to 9. (4) After discarding one extreme high and one extreme low rating, the remaining seven ratings all fell within any 3-point range.
    - Four definitions of disagreement are: (1) Considering all nine ratings, at least one was a 1 and one was a 9. (2) Considering all nine ratings, at least one fell in the lowest 3-point region (1 to 3) and at least one fell in the highest region (7 to 9). (3) After discarding one extreme high and one extreme low rating, at least one of the remaining seven ratings was a 1 and at least one was a 9. (4) After discarding one extreme high and one extreme low rating, at least one of the remaining seven ratings fell in the lowest 3-point region (1 to 3) and at least one fell in the highest region (7 to 9).
- **Categorization of rated indications.** Each indication can fall into one of three categories – clearly appropriate, equivocal, or clearly inappropriate. "Equivocal" is defined when the benefits and risks of doing the procedure are roughly the same (a median rating of 4 to 6), or the panelists disagreed on the proper rating (according to one of the definitions discussed above). "Clearly appropriate" is when the panelist assign a median rating in the 7 to 9 range without disagreement, and it is "clearly inappropriate" if they assign a 1 to 3 rating without disagreement.

Nominal Group Technique

The nominal group technique uses a rank ordering process. While similar in many ways to other consensus-based processes, the nominal group technique is ideal when there is concern that one or more stakeholder voices will overpower the others, or when the goal is a plethora of initial ideas that can be distilled into the most important ones over time.[28] As with most consensus-models of decision making, the Nominal Group Technique is recommended for in-person use, with each small group consisting of 5-9 individuals.

Appendix 18: National Guideline Clearinghouse Extent of Adherence to Trustworthy Standards (NEATS) Instrument

The Agency for Healthcare Research and Quality's National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) Instrument

The numbered domain items that follow reflect standards from the Institute of Medicine (IOM) report *Clinical Practice Guidelines We Can Trust.* The standard from the IOM report is listed in the first box of each domain item, and it is the principle that underpins the actual rating criteria that appear in the box immediately underneath, which is highlighted light-green. For several domain items, the rating criteria are based on the IOM principle but take either a broader or a more simplified approach. Although we value the IOM standards for their ambition, comprehensiveness, and attention to detail, we tailored the rating criteria as necessary for practical implementation of the NEATS Instrument for assessing the many guidelines represented on the NGC Web site.

The stated rating criteria are what raters should consider when selecting the response; response options are either Yes/No or points on a Likert scale of 1 to 5. For the scale, 1 reflects the least adherence to the criteria listed and 5 reflects the most adherence to the criteria listed.

1. Disclosure of Guideline Funding Source

Reference IOM Standard *The processes by which a clinical practice guideline (CPG) is funded should be detailed explicitly and publicly accessible.*
Please rate on this criterion: **The clinical practice guideline (CPG) discloses and states explicitly its funding source.**

Please review the description and guidance below and then choose one option:

YES	NO
○	○

Description
This standard asks for information regarding the funding of the guideline's development. Implicit in this standard is the notion that transparency of funding "gives users confidence that guidelines are… largely free from bias… and therefore trustworthy." (IOM 2011, p. 77) The clinical practice guideline (CPG) or supporting documents should list the funding source(s) for its development. This information should be publically available.

2. Disclosure and Management of Financial Conflicts of Interests (COIs)

Reference IOM Standard

- *Prior to selection of the guideline development group (GDG), individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity, by written disclosure to those convening the GDG. Disclosure should reflect all current and planned commercial (including services from which a clinician derives a substantial proportion of income), non-commercial, intellectual, institutional, and patient–public activities pertinent to the potential scope of the CPG.*
- *Disclosure of COIs within GDG: All COI of each GDG member should be reported and discussed by the prospective development group prior to the onset of his or her work. Each panel member should explain how his or her COI could influence the CPG development process or specific recommendations.*

Please rate on this criterion:

Financial conflicts of interest of guideline development group (GDG) members have been disclosed and managed.

Please review the description and guidance below and then choose one option:

Lowest Adherence				Highest Adherence
1	2	3	4	5
○	○	○	○	○

Description

This standard addresses the issue of actual or potential relationships between members of the GDG and entities, commercial or otherwise, with financial or intellectual interests in the CPG topic.

The CPG or supporting documents should provide a detailed disclosure of actual or potential financial COIs of each GDG member AND if any COIs are present, the document should describe how these conflicts may have affected the guideline process and any steps taken to manage and minimize their effect (e.g., recusal, divestment).

3a. Guideline Development Group (GDG) Composition: Multidisciplinary

Reference IOM Standard

The GDG should be multidisciplinary and balanced, comprising a variety of methodological experts, clinicians, and populations expected to be affected by the CPG.

Please rate on this criterion:

The guideline development group (GDG) includes individuals from a variety of relevant clinical specialties and other professional groups.

Please review the description and guidance below and then choose one option:

YES	NO	UNKNOWN
○	○	○

Description

This standard seeks to reduce the potential for bias that can sometimes result from a homogeneous GDG by encouraging a GDG comprising members from multiple disciplines. While each CPG will have a different set of clinical specialties that are relevant, a multidisciplinary GDG can include subject matter experts from a variety of professional backgrounds, paraprofessionals, statisticians, program managers, and members of the public. The GDG is multidisciplinary if more than one relevant clinical specialty is represented, based on stated disciplines (e.g., it includes representatives of more than one clinical specialty or professional group). This includes the situation when a GDG member is a nonclinical specialist.

3b. Guideline Development Group (GDG) Composition: Methodologist

Reference IOM Standard *The GDG should be multidisciplinary and balanced, comprising a variety of methodological experts, clinicians, and populations expected to be affected by the CPG.*
Please rate on this criterion: **The guideline states that it included a methodological expert in the guideline development group (GDG) and it identifies the methodologist.**

Please review the description and guidance below and then choose one option:

YES	NO	UNKNOWN
○	○	○

Description

This standard seeks to ensure that the guideline was developed with the participation of a methodological expert. As described by the IOM, "methodologists (e.g., epidemiologists, biostatisticians, health services researchers) perform much of the research on the conduct of systematic reviews (SRs) and are likely to stay up-to-date with the literature on methods. Their expertise includes decisions about study design and potential for bias and influence on findings, methods to minimize bias in the SR, qualitative synthesis, quantitative methods, and issues related to data collection and data management." (IOM [Institute of Medicine]. *Finding What Works in Health Care: Standards for Systematic Reviews.* Washington (DC): The National Academies Press. 2011)

The CPG or supporting documents should make clear that methodologists were involved in the CPG development process, specifically listing methodologists and detailing their specific roles.

4. Patient and Public Perspectives

Reference IOM Standard

Patient and public involvement should be facilitated by including (at least at the time of clinical question formulation and draft CPG review) a current or former patient, and a patient advocate or patient/consumer organization representative in the GDG.

Please rate on this criterion:

The guideline development group (GDG) sought the views, perspectives, and preferences of patients, patient surrogates (parents, caretakers), patient advocates, and/or the public intended to represent those who have experience with the disease, its treatments, or complications, or those who could be affected by the guideline.

Please review the description and guidance below and then choose one option:

Lowest Adherence				Highest Adherence
1	2	3	4	5
○	○	○	○	○

Description

This standard seeks that the perspectives of the target population be included in the guideline development process. The target population includes patients, patient surrogates (parents, caregivers), patient advocates, and/or the public, i.e., those who have experience with the disease, its treatments, or complications, or those who could be impacted by the guideline. While the original IOM standard prioritizes patient or surrogate representation in the GDG, we have broadened our assessment to encompass incorporation of patient perspectives in other ways and at various points in the guideline development process, as well.

Inclusion of patient perspective can take many forms: a patient representative on the GDG, consultation with patients to set priorities for topics, and external review by stakeholders, the public, or consumers, including drafts available for public comment (Please note for drafts for public comment, it must be clear that public comment specifically involved patients and that those comments were addressed). In addition, incorporating literature published on patient preferences and perspectives that relate to the guideline's recommended care is also acceptable.

The GDG or companion documents should include at least one patient, surrogate (parents, caretakers) or advocate AND the CPG should be clear about how those individuals contributed (e.g., clinical question formulation, review of draft CPG). If utilized, the CPG should also provide detailed information about how patient perspectives (i.e., studies regarding patient preference) were incorporated.

5a. Use of a Systematic Review of Evidence – the Search Strategy

Reference IOM Standard

Clinical practice guideline developers should use systematic reviews that meet standards set by the Institute of Medicine's Committee on Standards for Systematic Reviews of Comparative Effectiveness Research.

Please rate on this criterion:

The CPG or a related companion document describes a search strategy that includes a listing of database(s) searched, a summary of search terms used, the specific time period covered by the literature search including the beginning date (month/year) and end date (month/year).

Please review the description and guidance below and then choose one option:

Lowest Adherence				Highest Adherence
1	2	3	4	5
○	○	○	○	○

Description

This standard expects that guidelines based on a systematic review of the evidence describe in detail the search strategy. This should include a listing of database(s) searched, a summary of search terms used, the specific time period covered by the literature search including the beginning date (month/year) and end date (month/year).

The CPG or companion documents should provide a detailed description of the search strategy that includes a listing of database(s) searched, a summary of search terms used, the specific time period covered by the literature search including the beginning date (month/year) and end date (month/year). The information should be well-described and complete, with multiple databases searched and specific search terms. The CPG may include additional details such as extensive search terms, MeSH terms, key questions, or other specific details of the search strategy.

5b. Use of a Systematic Review of Evidence – the Study Selection

Reference IOM Standard

Clinical practice guideline developers should use systematic reviews that meet standards set by the Institute of Medicine's Committee on Standards for Systematic Reviews of Comparative Effectiveness Research.

Please rate on this criterion:

The CPG or a related companion document describes the study selection that includes the number of studies identified, the number of studies included, and a summary of inclusion and exclusion criteria.

Please review the description and guidance below and then choose one option:

Lowest Adherence				Highest Adherence
1	2	3	4	5
○	○	○	○	○

Description

This standard expects that guidelines based on a systematic review of the evidence describe in detail the study selection. This should include the number of studies identified by search, the number of studies included, and a summary of the inclusion and exclusion criteria.

The CPG or companion documents should provide a description of study selection that includes the number of studies identified, the number of studies included, and a detailed summary of inclusion and exclusion criteria. The number of documents identified and included may be listed in the results section and may also be displayed in a flowchart (e.g., PRISMA flowchart).

5c. Use of a Systematic Review of Evidence – the Synthesis of Evidence

Reference IOM Standard

Clinical practice guideline developers should use systematic reviews that meet standards set by the Institute of Medicine's Committee on Standards for Systematic Reviews of Comparative Effectiveness Research.

Please rate on this criterion:

The CPG or a related companion document provides a synthesis of evidence from the selected studies, i.e., an analysis of individual studies and the body of evidence, in the form of a detailed description or evidence tables, or both.

Please review the description and guidance below and then choose one option:

Lowest Adherence				Highest Adherence
1	2	3	4	5
○	○	○	○	○

Description

This standard expects that guidelines based on a systematic review of the evidence describe in detail the synthesis of evidence from the studies that were selected. This means that the CPG or a related companion document should include an analysis of individual studies and also an analysis the body of evidence taken as a whole. This could take the form of a detailed narrative description of the nature and quality of studies or evidence tables that capture such details about the studies, or both.

The CPG or companion documents should provide a synthesis of the evidence from the selected studies that includes well-crafted, detailed evidence tables and a thorough narrative description and discussion of the evidence.

6. Grading or Rating the Quality or Strength of Evidence

Reference IOM Standard

For each recommendation, the following should be provided:

- *A rating of the level of confidence in (certainty regarding) the evidence underpinning the recommendation.*

Please rate on this criterion:

The CPG provides a grading or rating of the level of confidence in or certainty regarding the quality or strength of the evidence for each recommendation.

Please review the description and guidance below and then choose one option:

Lowest Adherence				Highest Adherence
1	2	3	4	5
○	○	○	○	○

Description

This standard asks that evidence be graded or rated according to a scheme that takes into account the quality of and level of confidence or certainty regarding the evidence. Note that this domain item is a grading or rating of the strength of evidence underpinning recommendations.

The CPG's recommendations should be accompanied by a grade or rating of the evidence derived from a clear and well-described scheme of the level of confidence in (or certainty regarding) the evidence. The grade or rating should be linked clearly and directly to the recommendation(s).

7. Benefits and Harms of Recommendations

Reference IOM Standard

For each recommendation, the following should be provided:

- *An explanation of the reasoning underlying the recommendation, including a clear description of potential benefits and harms*

Please rate on this criterion:

The potential benefits and harms of recommended care are clearly described for the recommendations.

Please review the description and guidance below and then choose one option:

Lowest Adherence				Highest Adherence
1	2	3	4	5
○	○	○	○	○

Description

This standard expects developers to consider and describe explicitly the potential benefits and harms as they arrive at the CPG's recommendations. Potential harms may include risk of side effects or complications.

The CPG should describe clearly and in detail the potential benefits and harms of recommendations AND also link explicitly this information to specific recommendations.

8. Evidence Summary Supporting Recommendations

Reference IOM Standard

For each recommendation, the following should be provided:

- *An explanation of the reasoning underlying the recommendation, including a summary of relevant available evidence (and evidentiary gaps), description of the quality (including applicability), quantity (including completeness), and consistency of the aggregate available evidence.*

Please rate on this criterion:

A summary of the relevant supporting evidence is explicitly linked to recommendations.

Please review the description and guidance below and then choose one option:

Lowest Adherence				Highest Adherence
1	2	3	4	5
○	○	○	○	○

Description

This standard seeks that recommendations have an explicit link to a summary of the relevant evidence underlying the recommendation. This differs from the synthesis of the evidence in that it ties specific evidence to specific recommendations and will generally be much briefer.

The CPG or supporting documents should provide a thoughtful summary of the relevant supporting evidence (e.g., in an explicit discussion of the evidence) AND link this information directly to recommendations.

9. Rating the Strength of Recommendations

Reference IOM Standard

For each recommendation, the following should be provided:

- *A rating of the strength of the recommendation in light of [benefits and harms, available evidence, and the confidence in the underlying evidence].*

Please rate on this criterion:

The CPG gives a rating of the strength of the recommendation for each recommendation that takes into account benefits and harms, available evidence, and the confidence in the underlying evidence.

Please review the description and guidance below and then choose one option:

Lowest Adherence				Highest Adherence
1	2	3	4	5
○	○	○	○	○

Description

This standard expects that the CPG provides a rating for key recommendations according to a scheme that takes into account the confidence in that evidence (e.g., quantity, quality, and consistency of the available evidence), and the balance of benefits and harms.

The CPG should provide a rating for the strength of each recommendation that is based on a clear and well-described grading scheme that takes into account the confidence in the evidence and the balance of benefits and harms.

10. Specific and Unambiguous Articulation of Recommendations

Reference IOM Standard
Recommendations should be articulated in a standardized form detailing precisely what the recommended action is and under what circumstances it should be performed.

Please rate on this criterion:

The recommendations are specific and unambiguous, stating what action should or should not be taken in what situations and for what population groups. Where the CPG recommendations are intentionally vague or underspecified, the CPG clearly describes the rationale behind those recommendations.

Please review the description and guidance below and then choose one option:

Lowest Adherence				Highest Adherence
1	2	3	4	5
○	○	○	○	○

Description
This standard expects that a CPG's recommendations are clear, concrete, and precise to facilitate its implementation. The recommendations should not be vague or open to interpretation, but instead they should say directly what action should or should not be taken in what situations and for what population groups.

The CPG's recommendations should provide a concrete and precise description of (1) what is being recommended, (2) for whom, and (3) under which circumstances. The CPG should give a clear rationale for any intentional vagueness or under-specification.

11. External Review

Reference IOM Standard

External reviewers should comprise a full spectrum of relevant stakeholders, including scientific and clinical experts, organizations (e.g., health care, specialty societies), agencies (e.g., federal government), patients, and representatives of the public.

Please rate on this criterion:

The guideline has been reviewed by relevant stakeholders, including scientific and clinical experts, organizations, agencies, and patients.

Please review the description and guidance below and then choose one option:

Lowest Adherence				Highest Adherence
1	2	3	4	5
○	○	○	○	○

Description

This standard expects that reviewers who were not involved in the guideline's development review it before publication so that the GDG can ensure "the balance, comprehensiveness, and quality" of the guideline. Reviewers can include experts in the clinical area, methodologists, and members of the public. The CPG or supporting documents should describe an external review process by specific relevant stakeholders who are outside the guideline development process and organization. This can include scientific and clinical experts, health care specialty societies, public sector agencies, and patients. Stakeholders should be named or types of stakeholders described, and the process of external review should be described.

12. Updating

Reference IOM Standard *The CPG publication date, date of pertinent systematic evidence review, and proposed date for future CPG review should be documented in the CPG.*
Please rate on this criterion: **The CPG describes a procedure to update the guideline.**

Please review the description and guidance below and then choose one option:

Lowest Adherence				**Highest Adherence**
1	**2**	**3**	**4**	**5**
○	○	○	○	○

Description

This standard expects that the developers have a process in place to keep the guideline current. The CPG or supporting documents should provide a timeframe for review and updating AND should describe the process by which a decision is made to update and how the update will be conducted. These items do not need to be specific to the guideline.

Appendix 19: Mazza Taxonomy of Implementation Strategies for Guidelines

PROFESSIONAL
Identify barriers
Distribute guideline material
Advertise guideline material
Present guideline materials at meetings
Educate individuals about guideline intent/benefits
Educate groups about guideline intent/benefits
Recruit an opinion leader who recommends implementation
Achieve consensus that guideline should be implemented
Provide reminders to individuals/groups about intent/benefits
Provide alerts when practice deviates
Provide feedback on compliance
Provide feedback about patients (outcome data, self-report)
Provide feedback from patients
Provide feedback from healthcare professionals
Print material (summary, algorithm, referral forms, etc.)
Tailor guideline
Enable self-audit (training, material)
PATIENT/CONSUMER
Education (single or group)
Counseling
Group interaction (via social media)
Print material (summary, etc.)
Reminder
FINANCIAL
Health professional
Incentive (individual financial reward or benefit for compliance)
Incentive (group or institutional financial reward or benefit)
Grant or allowance to individual (not tied to compliance)

Grant or allowance to group/institution (not tied to compliance)
Penalty (individual, for non-compliance)
Penalty (group/institution, for non-compliance)
Change in reimbursement (add/remove/substitute)
Patient
Incentive (individual financial reward/benefit for compliance)
Grant or allowance (not tied to compliance)
Penalty (for non-compliance)
Incentive (individual non-financial reward/benefit for compliance)
ORGANIZATIONAL
Health professional
Additional human resources (number/type)
Reallocated or new role
Create an implementation/multidisciplinary team
Communication between distant health professionals
Improve health professional satisfaction (non-financial)
Patient
Consumer participation in governance
Consumer feedback, suggestions, complaints
STRUCTURAL CHANGES
Organizational structure (including reorganization)
Setting/site of service delivery
Physical structure, facilities or equipment
Information/communication technology
Quality improvement, performance measurement system
Method of service delivery
Integration of services
Risk management provisions (including insurance coverage)
REGULATORY

Legislation or regulation (which enforces or mandates)
Ownership or affiliation
Licensing, credentialing or accreditation
Modified from Mazza et al. 2013.[31]

REFERENCES

1. Manickam K, McClain MR, Demmer LA, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(11):2029-2037.
2. Malinowski J, Miller DT, Demmer L, et al. Systematic evidence-based review: outcomes from exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability. Genet Med. 2020;22(6):986-1004.
3. Rose NC, Barrie ES, Malinowski J, et al. Systematic evidence-based review: The application of noninvasive prenatal screening using cell-free DNA in general-risk pregnancies. Genet Med. 2022.
4. Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice G. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US)

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5. Institute of Medicine Committee on Standards for Systematic Reviews of Comparative Effectiveness R. Finding What Works in Health Care: Standards for Systematic Reviews. Washington (DC): National Academies Press (US)

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6. Armstrong MJ, Bloom JA. Patient involvement in guidelines is poor five years after institute of medicine standards: review of guideline methodologies. Research Involvement and Engagement. 2017;3(1):19.
7. Jue JJ, Cunningham S, Lohr K, et al. Developing and Testing the Agency for Healthcare Research and Quality's National Guideline Clearinghouse Extent of Adherence to Trustworthy Standards (NEATS) Instrument. Ann Intern Med. 2019;170(7):480-487.
8. Schünemann HJ, Wiercioch W, Brozek J, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol. 2017;81:101-110.
9. Schünemann HJ, Mustafa RA, Brozek J, et al. GRADE guidelines: 21 part 1. Study design, risk of bias, and indirectness in rating the certainty across a body of evidence for test accuracy. J Clin Epidemiol. 2020;122:129-141.
10. Schünemann HJ, Mustafa RA, Brozek J, et al. GRADE guidelines: 21 part 2. Test accuracy: inconsistency, imprecision, publication bias, and other domains for rating the certainty of evidence and presenting it in evidence profiles and summary of findings tables. J Clin Epidemiol. 2020;122:142-152.
11. Trenti T, Schünemann HJ, Plebani M. Developing GRADE outcome-based recommendations about diagnostic tests: a key role in laboratory medicine policies. Clin Chem Lab Med. 2016;54(4):535-543.
12. Yang B, Mustafa RA, Bossuyt PM, et al. GRADE Guidance: 31. Assessing the certainty across a body of evidence for comparative test accuracy. J Clin Epidemiol. 2021;136:146-156.
13. Rafiq M, Boccia S. Application of the GRADE Approach in the Development of Guidelines and Recommendations in Genomic Medicine. Genomics Insights. 2018;11:1178631017753360.
14. Legault K, Schunemann H, Hillis C, et al. McMaster RARE-Bestpractices clinical practice guideline on diagnosis and management of the catastrophic antiphospholipid syndrome. J Thromb Haemost. 2018.
15. Pai M, Yeung CHT, Akl EA, et al. Strategies for eliciting and synthesizing evidence for guidelines in rare diseases. BMC Med Res Methodol. 2019;19(1):67.
16. Booth A, Lewin S, Glenton C, et al. Applying GRADE-CERQual to qualitative evidence synthesis findings-paper 7: understanding the potential impacts of dissemination bias. Implement Sci. 2018;13(Suppl 1):12.
17. Colvin CJ, Garside R, Wainwright M, et al. Applying GRADE-CERQual to qualitative evidence

synthesis findings-paper 4: how to assess coherence. Implement Sci. 2018;13(Suppl 1):13.
18. Glenton C, Carlsen B, Lewin S, et al. Applying GRADE-CERQual to qualitative evidence synthesis findings-paper 5: how to assess adequacy of data. Implement Sci. 2018;13(Suppl 1):14.
19. Lewin S, Bohren M, Rashidian A, et al. Applying GRADE-CERQual to qualitative evidence synthesis findings-paper 2: how to make an overall CERQual assessment of confidence and create a Summary of Qualitative Findings table. Implement Sci. 2018;13(Suppl 1):10.
20. Lewin S, Booth A, Glenton C, et al. Applying GRADE-CERQual to qualitative evidence synthesis findings: introduction to the series. Implement Sci. 2018;13(Suppl 1):2.
21. Munthe-Kaas H, Bohren MA, Glenton C, et al. Applying GRADE-CERQual to qualitative evidence synthesis findings-paper 3: how to assess methodological limitations. Implement Sci. 2018;13(Suppl 1):9.
22. Noyes J, Booth A, Lewin S, et al. Applying GRADE-CERQual to qualitative evidence synthesis findings-paper 6: how to assess relevance of the data. Implement Sci. 2018;13(Suppl 1):4.
23. McBride KL, Berry SA, Braverman N. Treatment of mucopolysaccharidosis type II (Hunter syndrome): a Delphi derived practice resource of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine. 2020;22(11):1735-1742.
24. Brennan SE, Munn Z. PRISMA 2020: a reporting guideline for the next generation of systematic reviews. JBI Evid Synth. 2021;19(5):906-908.
25. Mustafa RA, Garcia CAC, Bhatt M, et al. GRADE notes: How to use GRADE when there is "no" evidence? A case study of the expert evidence approach. J Clin Epidemiol. 2021;137:231-235.
26. Brook RH, Chassin MR, Fink A, Solomon DH, Kosecoff J, Park RE. A method for the detailed assessment of the appropriateness of medical technologies. Int J Technol Assess Health Care. 1986;2(1):53-63.
27. Moscovice I, Armstrong P, Shortell S, Bennett R. Health services research for decision-makers: the use of the Delphi technique to determine health priorities. J Health Polit Policy Law. 1977;2(3):388-410.
28. Horton JN. Nominal group technique. A method of decision-making by committee. Anaesthesia. 1980;35(8):811-814.
29. Neumann I, Santesso N, Akl EA, et al. A guide for health professionals to interpret and use recommendations in guidelines developed with the GRADE approach. J Clin Epidemiol. 2016;72:45-55.
30. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. Cmaj. 2010;182(18):E839-842.
31. Mazza D, Bairstow P, Buchan H, et al. Refining a taxonomy for guideline implementation: results of an exercise in abstract classification. Implement Sci. 2013;8:32.