American College of Medical Genetics and Genomics

Protocol Manual for Evidence-Based Guideline Development

October 13, 2014

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Table of Abbreviations

Acronym	Name and URL
AAP	American Academy of Pediatrics; http://www.aap.org
AHRQ	Agency for Healthcare Research and Quality; http://www.ahrq.gov
ACMG	American College of Medical Genetics and Genomics; http://www.acmg.net
ASCO	American Society of Clinical Oncology; http://www.asco.org
CADTH	Canadian Agency for Drugs and Technologies in Health; http://www.cadth.ca/
BOD	Board of Directors
CEBM	Oxford Centre for Evidence-Based Medicine; http://www.cebm.net/
CER	Comparative Effectiveness Review; http://www.ncbi.nlm.nih.gov/books/NBK42934/
CMSS	Council of Medical Specialty Societies; http://www.cmss.org
COCHRANE	The Cochrane Library and Database of Systematic Reviews; http://www.thecochranelibrary.com/view/0/index.html
COI	Conflict of Interest
CPG	Clinical Practice Guideline
EGAPP	Evaluation of Genomic Applications in Practice and Prevention; http://www.egappreviews.org
EMBASE	EMBASE Biomedical Database; https://www.elsevier-promo.com/embase/
EUnetHTA	European Network for Health Technology Assessment; http://www.eunethta.net/Public/Home/
FDA	United States Food and Drug Administration; http://www.fda.gov
GIN	Guidelines International Network; http://www.g-i-n.net
GRADE	A process for grading strength of bodies of evidence (e.g., by key question or specific outcome) OR strength of recommendations
IOM	Institute of Medicine; http://www.iom.edu/Reports.aspx
KQ	Key Question
Lab QA	ACMG Laboratory Quality Assurance Committee
MEDLINE	MEDLINE® is a U.S. National Library of Medicine-based database of international biomedical literature. The PubMed® portal provides free access to MEDLINE.
MeSH	Medical Subject Headings; the controlled vocabulary used by the National Library of Medicine to index articles and cataloguing books and documents.
MOC	Maintenance of Certification

NGC	AHRQ-based National Guidelines Clearinghouse; http://www.guideline.gov/
NICE	National Institute for Health and Clinical Excellence; http://www.nice.org.uk/
NR	Not reported
NSGC	National Society of Genetic Counselors; http://nsgc.org/
OpenSIGLE	Open Access to System for Information on Grey Literature in Europe; http://www.opengrey.eu/
PCORI	Patient Centered Outcomes Research Institute; http://pcori.org/
PICOTS	Patient Population, Intervention (treatment, test), Comparator/comparison (group or treatment), Outcomes, Time/timing, Setting. System used to help frame questions for systematic evidence reviews.
PP&GC	Professional Practice & Guidelines Committee
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses; http://www.prisma-statement.org/
RCT	Randomized Controlled Trial; http://www.bmj.com/content/316/7126/201
SER	Systematic Evidence Review; http://www.nhlbi.nih.gov/guidelines/about.htm
SIGN	Scottish Intercollegiate Guidelines Network; http://www.sign.ac.uk/
TEP	Technical Expert Panel
UCLA	University of California Los Angeles
UK HTA	United Kingdom Health Technology Assessment Programme; https://www.nets.nihr.ac.uk/programmes/hta
USPSTF	United States Preventive Services Task Force; http://www.uspreventiveservicestaskforce.org
WHO	World Health Organization; http://www.who.int/en/

FOREWORD

The American College of Medical Genetics and Genomics (ACMG), along with other professional societies, is investigating options for responding to the strong recommendations from the Council of Medical Specialty Societies (CMSS), the Institute of Medicine (IOM), and others regarding the need for systematic reviews of current evidence to support the development of clinical practice guidelines. The first step in this process was the establishment in late 2012 of an ad hoc work group on Evidence-Based Guideline Development. This document represents the work group's draft of an *ACMG Protocol for Development of Evidence-Based Clinical Practice Guidelines*. It was developed from an outline that was reviewed and approved by the ACMG Board of Directors in March 2013.

The outline contained several major recommendations, as well as a proposed timeline that included 3 phases. The preparation of this draft manual comprises **Phase 1**. Its intent is to provide practical advice and a general template for creating clinical practice guidelines. During **Phase 2**, two to three guidelines will be developed over a 12-14 month period using this Protocol. These "pilot guidelines" would assess the Protocol, enabling careful review of successes, barriers, and a need for any revisions and expansions. The scope of these pilot guidelines would be limited by available resources and expertise. A recommended Topics Committee (see below) would also be established in Phase 2. **Phase 3** would continue to test, refine, and expand the manual/protocol as needed.

The Topics Committee would perform proposal review and consider broadening the scope of topics to include those requiring more in-depth reviews. Budgets and resources to fund ongoing efforts would be developed. Finally, the outline strongly recommended training for those interested in developing clinical practice guidelines. To that end, a 90-minute evening workshop on "Preparing Effective Evidence-based Clinical Practice Guidelines" was presented at the ACMG 2013 annual meeting and a longer 5 hour workshop, entitled "Transition to Evidence-based Clinical Guidelines: Understanding Systematic Review and Translation of Evidence to Recommendations," will be held at the 2014 annual meeting.

The outline also described the recommended components and characteristics of a "trustworthy" clinical practice guideline. As referenced throughout this document, the work group examined similar documents from other groups and specialty societies, as well as recommendations of CMSS, IOM, and the National Guideline Clearinghouse (NGC) of the Agency for Healthcare Research and Quality (AHRQ). The work group focused on several specific areas of the guideline development process that have become the major headings/sections of this document. They include:

1. Topic selection and prioritization
2. The systematic evidence review process
3. Development of the guideline based on the systematic evidence review, including suggested guideline formatting

4. Composition and structure of the guideline development group and evidence review group

Some sections of this document are more developed than others. For example, the section on systematic evidence review has more detail and referencing in order to support the development of guidelines during the pilot phases. At the time of this writing, the first pilot guideline from the Therapeutics Committee is proceeding and involves a systematic evidence review on the treatment of mucopolysaccharidosis II (MPS II). The evidence developed will be used to write a clinical practice guideline on the *Management and Treatment of Mucopolysaccharidosis Type II (MPS II).* Further development of other protocol sections could be undertaken in parallel with this pilot study.

It is important to note that developing a protocol that satisfies the unique needs of a particular medical specialty (*e.g.,* rare disease), within available resources (*e.g.,* rapid reviews, training), is not a one-step process, but rather an evolution of thinking based on experience and changing requirements. This document is an important step in this ACMG pilot initiative. Ultimately, it is the goal of the ACMG to provide a comprehensive template for its members and committees to use in guideline preparation to augment the more general considerations addressed here.

Throughout the document, there are boxes that highlight particular sections that require more discussion, or that will not be considered for implementation until after the pilot phase.

OBJECTIVE

Clinical practice guidelines have been defined by the Institute of Medicine (IOM) as "statements that include recommendations intended to optimize patient care. They are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options." Similarly, they defined a *systematic evidence review* as, "..,a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. It may include a quantitative synthesis (meta-analysis), depending on the available data."[1,2]

This manual is meant to provide background, procedures, and templates for the production of effective evidence-based clinical practice guidelines in genetics and genomics by the ACMG.

INTRODUCTION/BACKGROUND

In response to a request from the US Congress, the Institute of Medicine (IOM) conducted a study to determine the best methods to use in developing clinical practice guidelines. The objective was to ensure that organizations developing such guidelines provide information that is objective, scientifically valid, and consistent. The IOM developed standards for developing rigorous, trustworthy clinical practice guidelines that included:[1,2]

- Ensuring a transparent process
- Management of Conflicts of Interest (COI)
- Establishing a multidisciplinary and balanced Clinical Practice Guideline Development Group with involvement of stakeholders and relevant specialists
- Clearly defining the interface between the Guideline Development Group and the Evidence Review Group on the scope, approach and output of the systematic evidence review
- Establishing the evidence, including potential benefits and harms, quantity and quality of studies, potential contextual factors (*e.g.,* values, experience), rating strength of recommendations and describing differences of opinion, and identifying evidentiary gaps
- Articulating recommendations
- Conducting external expert review of the clinical practice guideline
- Developing a process for updating the clinical practice guidelines

The Council of Medical Specialty Societies (CMSS)[3] emphasized the above standards, as well as the responsibility of Societies to serve as an independent source of evidence-based clinical practice guidelines. CMSS also considered existing methods[4-10], and developed four concepts as the Principles for the Development of Specialty Society Clinical Guidelines[3]:

1. Determinations based on an extensive, reproducible, and strong body of evidence
2. Panels consisting of knowledgeable, multispecialty/disciplinary development individuals
3. Transparent conflict of interest management
4. Broadly defined (including patient, when possible and if applicable) stakeholder involvement

Effective in June 2014, the AHRQ-based NGC began using revised criteria for inclusion of clinical practice guidelines. These new criteria are detailed and can be found at http://www.guideline.gov/about/inclusion-criteria.aspx. In addition to guideline criteria (*e.g.*, COI, systematically developed statements, assessment of benefits and harms of recommended and alternative care options), the guideline developers must provide documentation of an underlying systematic evidence review that meets another set of specific requirements. The NGC is a highly respected and widely accessed public resource. Meeting the revised criteria for inclusion in the NGC is an important goal of these efforts, since it should result in much broader dissemination of our guidelines, as well as lead to increased confidence in their value.

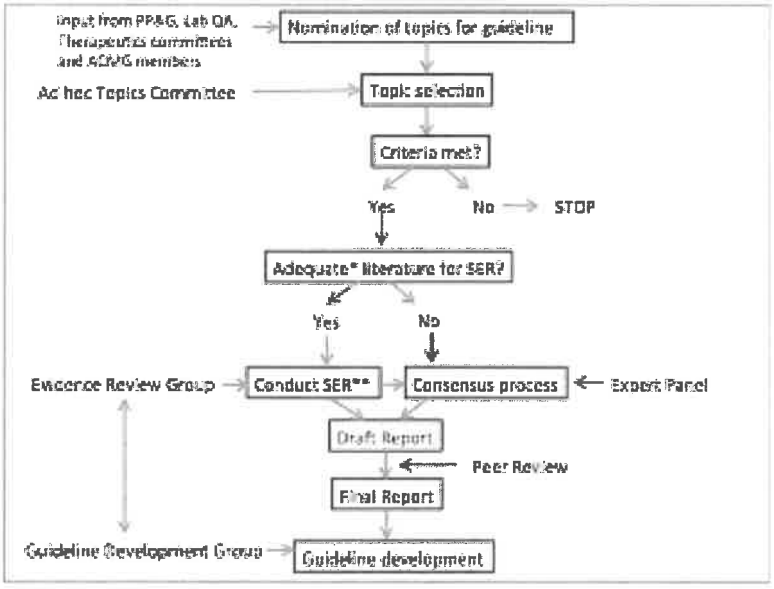
These recommended standards are intended to accelerate a needed change in the development of clinical practice guidelines for ACMG, moving from a largely expert opinion model to a more rigorous and transparent evidence-based process. As a member of CMSS, ACMG has an obligation to establish and implement guideline development procedures that are consistent with the new paradigm. To address this need, the ACMG Board of Directors has appointed an Evidence-Based Guideline Development Work Group, whose immediate goals are to: 1) recommend methods and processes that support development of evidence-based clinical practice guidelines that are feasible for ACMG to support and implement; and 2) pilot the methods and processes by producing one to two evidence-based guidelines that meet the new criteria.

Costs associated with conducting clinical trials and outcomes research are a significant concern in rare diseases. However, the Patient-Centered Outcomes Research Institute (PCORI) recently approved a two-year budget of $1.03 billion in research funding, as well as a new advisory panel on rare diseases. PCORI is an independent, non-profit organization that was authorized as part of the Affordable Care Act (http://www.pcori.org/). PCORI recognizes the need for evidence-based clinical practice guidelines, and may provide needed funding for development of evidence to support important guidelines in our field. As the US healthcare system enters a period of change, the ability to develop practice guidelines that meet CMSS and NGC requirements could impact future decisions regarding acceptance and reimbursement of genetic/genomic applications and procedures. Increased confidence in the value of evidence-based clinical practice guidelines should also result in broader dissemination and implementation. Clear and effective clinical practice guidelines will raise awareness of ACMG as the thought-leader in medical genetics and genomics, and may also provide opportunities to partner with other professional societies on guideline topics of mutual interest. Benefits of partnerships could include shared costs and raised awareness of ACMG by payers and insurers, as well as possible reduction in discrepancies between guideline recommendations.

OVERVIEW OF THE CLINICAL PRACTICE GUIDELINE DEVELOPMENT PROCESS

A summary schematic for the proposed guideline development process is presented in Figure 1. Briefly, topics for possible clinical practice guidelines will be solicited from standing committees of the college, including the Professional Practice & Guidelines Committee, the Therapeutics Committee and the Laboratory Quality Assurance Committee. Topics will also be actively solicited from ACMG members and ACMG special interest groups, and assigned for initial consideration to the appropriate ACMG committee, as per current practice. Since it is unlikely that there will be sufficient funding/resources for all suitable topics proposed for guideline development initially, a new ad hoc Topics Committee will be formed to develop criteria for topic prioritization and oversee the selection process (see pp. 8-13). For approved topics, key questions will provide the framework for a systematic evidence review by an Evidence Review Group, while the Guideline Development Group will formulate recommendations based on the evidence summary. The composition of these groups and their respective responsibilities are described on pp. 14-17. The Evidence Review Group conducts systematic evidence reviews using procedures described in detail on pp. 18-30. For important topics for which a sufficient evidence base is not available, a consensus process using an expert panel may be employed, as described on pp. 31-33. The use of expert panels is expected to be extremely important for rare disorders or where there is rapidly changing diagnostic and/or therapeutic options. Finally, the Guideline Development Group prepares the guideline following suggested formats (pp. 34-38 and see Appendix 1).

FIGURE 1 Clinical Practice Guideline Development



PPG, Professional Practice & Guidelines; Lab QA, Laboratory Quality Assurance SER, systematic evidence review
*Identifying literature of sufficient quantity and quality for the key questions of a systematic literature review may depend on the topic. In most cases, this step is part of the topic refinement prior to systematic evidence review.
**If evidence of sufficient quantity and quality is not found for one or more key questions or outcomes, a consensus process may be considered. The National Guideline Clearinghouse criteria are clear that formal consensus processes should only be employed when a systematic literature review has documented a lack of evidence.

TOPIC SELECTION AND PRIORITIZATION

This section describes proposed processes for managing the selection and prioritization of topics for evidence-based clinical practice guideline development. The establishment of a Topics Committee was recommended to the ACMG Board of Directors to support the process of selecting topics for evidence-based guideline development. A reasonable composition for this committee during the pilot phase would be 6 to 8 members, including:

- The Chair of, or a member selected by the Chair from, the Professional Practice & Guidelines Committee, the Therapeutics Committee and the Laboratory Quality Assurance Committee;
- 1 to 2 members of the ACMG Board of Directors; and
- 2 to 3 members of the ACMG at-large membership who have experience or are interested in this process.

As described by successful existing processes, proposed organizational roles of a Topics Committee would include[4-7,10]:

- promoting the nomination of topics by and through ACMG standing committees using an approved form (Proposal for Policy Statement, Practice Guideline or Other Project).
- deciding whether each nominated topic falls within the current stated scope of the process;
- documenting the receipt of each Proposal and tracking its progress through the review process to a decision. The Topics Committee could determine that: 1) a topic is a high priority and should be recommended to the ACMG Board of Directors for approval; 2) a topic is moderate priority and the Proposal should be retained for future consideration; 3) a topic is low priority and should be removed from further consideration at that time; or 4) a Proposal has been returned for additional information and will go back into the pending review list when the information is provided.
- ensuring the transparency and consistency of selection activities, including: 1) documentation of decisions on Protocols submitted, with dates and reasons; and 2) documenting changes in the review process, with dates and rationales.
- scheduling teleconferences to discuss nominated Proposals based on stated criteria and current priorities.
- compiling and maintaining a list of Proposals for potential priority topics for the ACMG Board of Directors.

Nomination of Topics for Clinical Practice Guidelines

Topics will initially be identified through discussion and input from the Professional Practice & Guidelines, Therapeutics and Laboratory Quality Assurance committees. Topic proposals from ACMG members will be solicited through these committees.

The proposal nomination form will be adapted from the current ACMG form or existing nomination forms from other groups that have been used and shown to be efficient.

Processes for soliciting topic suggestions from stakeholder groups and the public will be considered after the pilot phase of evidence-based guideline development.

Further research will also be necessary to determine the need for, or effectiveness of, search protocols to support periodic horizon scanning for emerging topics that might merit an evidence-based clinical practice guideline, or for new publications that will change the priority of a topic already proposed. **[See 2020 Update on page 13.]**

Scope of Topics Eligible for Consideration

The ACMG process will initially focus on selecting topics in clinical genetics related to the diagnosis, management, treatment, risk assessment for, or prevention of, inherited conditions. Assessment of prognostic or pharmacogenetic tests will be a lower priority unless deemed to be integral to the diagnosis, management, treatment, risk assessment for or prevention of genetic conditions, as above. The role of genetics in the prediction, treatment and prevention of common complex disorders will not be a focus during the development and piloting phase of ACMG evidence-based guideline development.

Scope of topics can be reconsidered after the pilot phase of the evidence-based guideline development process.

Criteria for Selection of Topics

The Topics Committee will utilize published criteria (modified as needed) for the selection and prioritization of topics.[4-9,11,12] Example criteria include:

Importance

- **Disease burden** is significant based on prevalence, penetrance, population, and effects on patients, families, communities and society.
- **A new diagnostic or treatment intervention** has become available that may improve health outcomes or quality of life, and for which changes in diagnosis, management and treatment protocols have been proposed or may be warranted.
- **A clinical priority area** for which there is an expressed need for guidance to inform decision making, articulated by consumers, patients, clinicians, payers, or other stakeholders.
- **Areas of clinical uncertainty** based on wide variation in practice or outcomes or controversy about what constitutes appropriate care, and with a clear potential for a guideline to reduce variation, improve health outcomes or lower costs / burden.
- **Additional information** supports consideration of proposed benefits and harms.

Appropriateness

- **Does not duplicate** an existing or planned high-quality systematic review or clinical practice guideline. Use of this criterion requires a check for existing relevant systematic evidence reviews and clinical practice guidelines, as well as assessment of their quality.

Feasibility

- Body of literature on a topic has reached sufficient size and quality to make systematic review of the evidence and guideline development realistic. This criterion requires a check on the adequacy (number and type) of studies and documents, and the availability of new evidence that makes the review possible or may change previous conclusions.
- Availability of support and resources.

Potential for Impact

- **Potential to affect change in practice**
- **Potential risk** of inaction or other unintended harms associated with lack of clinical guidance
- **Potential usefulness** of an evidence-based guideline to the genetics community to improve patient care and/or access to care by supporting reimbursement from payers.
- **Potential to resolve important dilemmas** in health care decision making.
- **Potential to improve quality of care and/or reduce cost of care** by establishing the effectiveness of an intervention or treatment and clarifying the consultative process.

Topics do not need to meet all criteria, but can be ranked or weighted based on the number of criteria met. In some cases, a guideline may be urgently needed even when the evidence is clearly inadequate. In such situations, it may be necessary to follow a systematic evidence review with an Expert Consensus Process (page 26).

Continuing assessment and revision of the ACMG selection criteria for evidence-based clinical practice guidelines is a routine and essential part of any group's development of a process for topic nomination, prioritization and selection.

Questions for a Proposal Form to Nominate a Topic

The above criteria can be translated into questions to be included in a proposal. In addition, the example below modifies a topic nomination form from the AHRQ Effective Healthcare Program that includes the use of PICOTS framework that identifies the ***P***opulation, ***I***ntervention, ***C***omparison, ***O***utcomes, ***T***iming and ***S***etting of the topic to be reviewed, as defined below.[11]

Population with the disorder, including relevant age groups, gender, race, ethnicity, and possible groups for specific exclusion.

Intervention(s) of interest (*e.g.,* risk factor, diagnostic, predictive or prognostic test, treatment) for such patients.

Comparison(s) to be made (*e.g.,* between patients receiving the specific intervention and a control, placebo or alterative treatment group).

Outcome(s) (intermediate and long-term) for which data will be sought to establish the size of any effect related to the intervention. These include health outcomes (*e.g.,* accuracy of risk assessment or diagnosis, rate of adverse outcomes, morbidity and mortality), functional health status measures (*e.g.,* general and disease-specific), and patient-centered outcomes (*e.g.,* quality of life). An important step in managing review scope is to specify the measurable outcomes of interest in advance.

Timing of intervention or time needed to demonstrate an outcome (*e.g.,* observation time, time to achieve an outcome).

Setting(s), such as primary care, specialist referral, or in-hospital.

Items 2 through 5 below are examples of how the PICOTS framework can be used.

1. Briefly describe a specific question, or series of questions, that define the health care intervention that is being proposed as the topic for an evidence-based clinical guideline.

In patients with cystic fibrosis (CF), what is the effectiveness of [a specific intervention] in improving intermediate health outcomes, such as pulmonary function and nutritional status?

2. What patients or group(s) of patients does the question apply to? (**P** of PICOTS)

Patients with CF – include information on sub-groups including age (child, adolescent, adult), clinical status (pulmonary function, nutritional status), genotype, or prior treatment(s).

3. What interventions (*e.g.*, technologies, diagnostics, treatments) will be studied and will they be compared to each other or usual care? (**I** and C of PICOTS)

Usual care for patients with CF plus [new intervention], compared to a specific [alternative intervention] or to usual management without the [new intervention].

4. What are the health-related benefits of interest (*e.g.,* intermediate or long-term outcomes)? (**O** of PICOTS)

Improvements in intermediate (e.g., pulmonary function, exercise tolerance, nutritional status, bone mineralization) and/or long-term (e.g., hospitalizations, function and health-related quality of life, survival) outcomes.

5. What are the health-related harms, risks or adverse effects, compared to care without the [new intervention]? (**O** of PICOTS)

Harms from the use of the [new intervention] include [identified adverse events].

6. What is the timing for implementing the [new intervention], and does it differ from alternative interventions or usual care? Alternatively, what is the time interval for follow-up of patient outcomes? (**T** of PICOTS)

7. What is the setting in which this [new intervention] would be utilized and assessed? (**S** of PICOTS)

8. Are you aware of controlled trials, review articles, systematic reviews, guidelines or other key primary studies that address this question (provide citations if available).

9. Explain why this topic is important.

10. Was there a specific motivation for asking this question?
    - Has new research emerged?
    - Is there uncertainty among clinicians or policy-makers?
    - Is the intervention costly?

11. Is there a timeframe in which an answer to a question or questions is needed?

12. How will the resulting clinical practice guideline be used to inform decision-making and or policy development in clinical practice? What is the likelihood of impacting or changing practice? _____

Initially, the Topics Committee would assess the clarity and completeness of each submitted proposal. They would decide if more detail is needed to complete or clarify the proposal, and return it to the submitter for clarification before moving on in the review and prioritization process.

Many guideline development and evidence review processes have validated quantitative scoring systems for ranking large numbers of suggested topics for systematic evidence reviews and clinical practice guidelines, including the United States Preventive Services Task Force[14], the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) program[7], National Institute for Health and Care Excellence (NICE)[5], AHRQ[11], and several medical societies.[6,9,11] As the numbers of potential topics for ACMG are not likely to be large in the pilot phase, the Topics Committee (or a sub-group reviewing nomination forms) may wish to utilize a more qualitative process for priority ranking.

For example, the committee may review the topic selection criteria to determine if they should have equal weight or if some will have more influence on ranking decisions than others. With that in mind, a ranked list of topics could be developed by assigning high, moderate, low or incomplete (missing information) priority rankings through discussion, with documentation of the key issues and rationales. For a high priority topic, the Topics Committee could seek additional information, such as:

- a brief online search for existing relevant systematic evidence reviews (*e.g.,* AHRQ, EGAPP, Cochrane Library, UK HTA) or clinical practice guidelines (*e.g.,* AHRQ NGC, EGAPP, Guidelines International Network, USPSTF);

- a preliminary literature search of MEDLINE® to broadly estimate the size of the available literature base; and,
- an investigation of potential sources of funding.

At this time, it is not clear who would be called upon to collection such information. Options would include the individual or committee that submitted the proposal, or a member of the Topics Committee.

A proposal form to nominate a topic for guideline development will be developed with specific questions and names of websites to support this information gathering.

Existing quantitative scoring systems could be considered for review of nominations.

A process will need to be developed and criteria specified to determine when the information obtained from a systematic review constitutes sufficient quality and strength of evidence for a key question to be used to support a recommendation. This process will need to be standardized, transparent, and adequately documented to satisfy the NGC requirement that a systematic review must be done prior to utilizing other methods, such as formal expert consensus.

2020 Update:

The Topic Selection Committee was established in 2019 and has met on several occasions. Topics for consideration may be submitted by interested members of the public online at: https://www.acmgfoundation.org/ebg.

EVIDENCE REVIEW GROUP AND GUIDELINE DEVELOPMENT GROUP

Evidence Review Group

Numerous models have been used by professional societies and expert panels to conduct systematic evidence reviews that support clinical guideline development, including:

- commissioning an outside group or agency (*e.g.,* AHRQ) to conduct systematic evidence reviews;[7,9,12,14]
- establishing staff research specialists with relevant training and experience to conduct systematic evidence reviews;[6,7]
- conducting systematic evidence reviews using a small subset of Guideline Development Group members, with consulting methodologists;[4,9] and
- combinations of the above.

Whichever model is used, the individuals chosen for the Evidence Review Group must function as a semi-independent subset of the Guideline Development Group.

1. The Evidence Review Group should typically be composed of 3-5 members, but may be larger based on the complexity and scope of the review and the available resources.
2. The Evidence Review Group should include a methodologist or experienced evidence reviewer, as well as a topic expert who may be a member of the larger Guideline Development Group, when appropriate. Access to a librarian or member with experience in guideline methodology, database management, and search strategies is not required, but highly desirable.
3. All members of the Evidence Review Group should be free of potential conflicts as determined by the ACMG Conflict of Interest Committee.
4. All members of the Evidence Review Group must be able to make a pre-determined time commitment based on the scope of the review (number of abstracts and papers and timeline).
5. As noted above, members of the Evidence Review Group may be identified through a contractual agreement with organizations and/or individuals with expertise and experience in this process. Budgets for evidence review will be developed and reviewed by the ACMG Executive Director.
6. Details of interactions between the Evidence Review Group and the Guideline Development Group are discussed below.

It is intended that one ACMG member with no conflict of interest or intellectual bias may join each Evidence Review Group as experienced reviewers or for training or experience in abstract and article review and data extraction and synthesis. Of most importance is the commitment of the Evidence Review Group members to transparency and clarity in documenting the approaches and methods used throughout the review process, as well as the rationales that supported the choices made.[1,6-9]

Guideline Development Group

In general, practice guidelines will be drafted by a workgroup, called the Guideline Development Group, under the guidance of a Sponsoring Committee of the ACMG. The Guideline Development Group is "…a panel of members with differing expertise responsible for utilizing systematic reviews to generate clinical practice guideline statements in an objective and unbiased manner."[3]

1. The Guideline Development Group should be multidisciplinary, as appropriate to the topic, and balanced between clinicians (*i.e.,* genetics and other specialties relevant to interventions and outcomes of interest) and methodological experts (*e.g.*, evidence-based medicine, statistics, economics). Members should be from different institutions, and include patient, patient advocate or consumer representation, as appropriate.
2. The Guideline Development Group should be of sufficient size (generally 6 - 12 members) to develop the work product, represent stakeholders with expertise and interest in the topic, and provide a balanced and comprehensive review based on the evidence.
3. Where there is sufficient expertise, the work group should be composed of ACMG members. It is recognized that non-members will be needed to represent other specialties, patient and/or consumer advocates, and, sometimes, methodologists.
4. The Guideline Development Group should have a Chair or 2 co-chairs. The Chair or at least one of the co-chairs must not have any potential conflicts with the proposed project. At least one of the Co-Chairs must be an ACMG member.
5. In general, one member of the Guideline Development Group should be a member of the sponsoring ACMG committee and act as liaison between the Guideline Development Group and the Committee.
6. The Guideline Development Group members must meet current ACMG guidelines for conflict of interest (see below).

Communication Between the Evidence Review Group and Guideline Development Group

There are a number of important points of interaction between the Evidence Review Group and Guideline Development Group. *However, the Guideline Development Group must understand the Evidence Review Group's need for functional separation and independence*. Note that the Guideline Development Group will also have representation from the sponsoring ACMG standing Committee (usually a Co-Chair, if there are no conflict of interest issues).

Communication between the Evidence Review Group and Guideline Development Group will occur at specific points in the review, or when the Evidence Review Group determines that content expertise or clarification is needed. The full Guideline Development Group is involved in initial in-depth discussions with the Evidence Review Group that include:

- carefully defining the disorder, potential interventions and specific outcomes of interest for the review;

- orienting the Evidence Review Group members regarding particular clinical or laboratory issues that may impact the search strategy (*e.g.,* variability in terminology or subgroup characteristics; issues of access, feasibility or acceptability of interventions); and
- developing the PICOTS, analytic framework (optional) and key questions that determine the scope and content of the review.

When the Evidence Review Group has developed a plan/protocol for the review, the Guideline Development Group is asked to:

- provide comments on search strategies;
- suggest "control articles" (*i.e.,* those key articles that should be identified by a sensitive search based on title, content and indexing) to be used to validate the search; and
- review inclusion/exclusion criteria proposed by the Evidence Review Group, and their translation to the proposed set of questions that will be used for Title, Abstract and Full Article selection.

The Guideline Development Group comments and recommendations are carefully considered, but final methodological decisions are made by the Evidence Review Group. Should the Evidence Review Group consider a protocol change (*e.g.*, modification of scope or a key question) based on preliminary evidence or methodological considerations, the members will consult with the Guideline Development Group. This will ensure that the original intent of the systematic evidence review to support the guideline is preserved.

When the initial electronic searches are completed, the Evidence Review Group will provide a general update to the Guideline Development Group on the results of the search. If existing guidelines or SERs on, or related to, this topic were identified, the Evidence Review Group will discuss with the Guideline Development Group any impact the Evidence Review Group thinks the findings could have on scope or content. If additional information is needed, the search process will continue and the Evidence Review Group will update the Guideline Development Group when this initial stage is complete, providing information on:

- the number of citations identified in the published literature;
- the proportion of the "control articles" that were identified and why articles might have been missed; and
- the number of documents/reports identified in the grey literature.

The Evidence Review Group will discuss with the Guideline Development Group whether they believe the searches are adequate, or if a change in the search strategy and further searches might be needed.

Once the Evidence Review Group moves past the initial search stage, the functional separation between the groups will be fully in place throughout the next citation identification (*e.g.,* electronic or hand searching of bibliographies) and review stages, article selection, data extraction and initial analysis and synthesis. When initial data tables and figures are completed, the Evidence Review Group will schedule a consultation with the Guideline Development Group prior to drafting the summary manuscript. The Guideline Development Group may point out

gaps in the data that might still be investigated, request clarification of data, and/or suggest additional analyses that would inform recommendation development.

The Guideline Development Group will conduct initial and subsequent reviews of manuscript drafts and provide comments to which the Evidence Review Group will formally respond.

Conflict of Interest

The Evidence Review Group is an objective team with the necessary expertise (*e.g.,* methodology, clinical content, search strategy, analysis, synthesis) to conduct the systematic evidence review. It is important to note that complete objectivity is not really an attainable goal. However, the Evidence Review Group members must disclose potential financial, professional and intellectual conflict of interest (see below). It is critical, "… to exclude individuals whose professional or intellectual bias would diminish the credibility of the review in the eyes of the intended users."[1,7]

Conflict of interest (COI) can be defined as relationships or associations, whether professional or personal, that may affect or that may be perceived to cause bias in someone's decisions, judgments, or efforts. The relationships can be compensated or uncompensated and can involve individuals or organizations. An organization may be for profit (companies) or non-profit. Full disclosure of all potential conflicts is essential so that activities and work of ACMG, including the development of clinical practice guidelines and policy statements, are trusted and utilized to the fullest extent possible.

Evidence-based clinical practice guidelines will adhere to existing ACMG-approved policies for disclosure and management of potential COI. These policies were developed to be in compliance with the CMSS regarding interactions with for-profit companies, and with their document entitled "Principles for the Development of Specialty Society Clinical Guidelines." These policies are discussed in:

1. ACMG "Proposal for Policy Statement, Practice Guideline or Other Project" revised 07-16-13
2. ACMG "Background Information and Instructions for Submitting a Policy Statement, Practice Guideline or Other Project" (revised 03-26-12)
3. ACMG policy "Conflicts that prohibit participation in an ACMG work group"

Current versions of these documents can be found in the Members portion of the ACMG website under Committees.

Briefly, each member of a Guideline Development Group or Evidence Review Group must complete an ACMG PARTICIPATION AGREEMENT that includes a disclosure of potential conflicts. Submitted proposals and participation agreements are reviewed by the COI Committee, which is a standing committee of the board that is chaired by the President-elect. If the Evidence Review Group composition is acceptable, the Proposal is forwarded to the ACMG Board of Directors for content review.

The Chair (or at least one Co-Chair) and a majority of the Guideline Development Group (>50%) must be free of potential conflicts with regard to the subject matter of the guideline. All members of the Evidence Review Group must be free of potential conflicts with regard to the subject matter of the guideline. Where proprietary data are included as part of the evidence for a guideline, the Evidence Review Group may ask an expert with a conflict to review the summary of that evidence for accuracy. This requires approval of the ACMG COI and ACMG Board of Directors as part of the Proposal review.

Any *significant* post-approval changes in the scope of the project or the membership of the work groups (Guideline Development Group and/or Evidence Review Group) must be submitted to the ACMG office for serial review by the COI Committee and the ACMG Board of Directors.

SYSTEMATIC EVIDENCE REVIEW

Key Definitions

The IOM defined a *systematic evidence review* as *"..a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. It may include a quantitative synthesis (meta-analysis), depending on the available data."*[1,2]

Evidence can be narrowly defined as *peer-reviewed publications of original data, or systematic reviews or meta-analyses of these individual studies.*[7] Invited expert opinions and editorials are not considered to be evidence.[14]

Evidence may also include grey literature, defined as *relevant materials not controlled by commercial publishers.* Grey literature is in the public domain and includes reports (*e.g.,* consensus, technical, regulatory, government agency), conference proceedings, commercial technical documentation, clinical registries and other potential sources of unpublished data.[6,7] Key criteria for determining the quality of grey documents include the level of peer review conducted, the credibility of the source, the transparency of methods and the clarity of the conclusions. Proprietary industry data submitted for review without disclosure would be excluded.

Effect size is a value that represents the impact of an intervention, also called the *magnitude of effect*. Effect size can also represent any relationship between two variables, such as the strength of relationship between a measurable outcome in individuals with different genotypes. The effect size is computed for each study, then the consistency of the effect is assessed across studies, and, in some cases, can be used to compute a summary effect size.[15]

A representative timeline for different types of systematic evidence reviews (*e.g.,* comprehensive, targeted) will be developed for the Protocol.

Type of Review

The IOM definition of a systematic evidence review is provided above. A more general description would be a transparent and consistent method for summarizing, assessing and synthesizing the evidence for the effectiveness (*e.g.*, clinical validity, clinical utility) of a clinical intervention. The characteristics of all systematic evidence reviews or comparative evidence reviews include[1,4,6-9,11,14]:

- a review protocol that guides the process;
- a pre-defined search strategy for the published and possibly grey literature;
- a validated system for assessing the quality of individual studies and the strength of evidence;
- explicit pre-defined inclusion and exclusion criteria for review and selection; and,
- explicit methods and processes for data extraction and analysis.

The current "gold standard" is commonly referred to as a *comprehensive* systematic evidence review. These reviews employ comprehensive search strategies for the published and grey literature (often in multiple languages), have a 12-18 month timeline and require significant resources.[1,4] Historically, another characteristic of comprehensive systematic evidence reviews has been a linear and rather inflexible process, with little or no allowance for modification of the search strategy or data included based on emerging findings or data analysis.

In recent years, increasingly limited resources and the need for more timely access to evidence for guideline and policy development have led to the introduction of review methods that allow for more process flexibility, shortened time frames and more streamlined products. Such reviews have many labels, such as "targeted,"[16] "focused,"[9] "focused approach to a confined topic,"[6] and "rapid."[17] Various approaches have been proposed, including:

1. limiting electronic searches (*e.g.,* by years, databases, language);
2. excluding or limiting grey literature searches;
3. limiting hand searching in relevant journals as a search strategy;
4. excluding follow-up with authors and industry to seek or clarify data;
5. limiting outside review of the systematic evidence review to selected peer reviewers and society members, and excluding public comment;
6. narrowing the scope to a single intervention or outcome, or a specific population (*e.g.,* by age, gender, race);
7. limiting the number and scope of key questions;
8. limiting to clinical outcomes (*e.g.,* versus patient-centered outcomes such as quality of life, economic factors, other social issues); and
9. using iterative searches and allowing for early course corrections based on search results.

Options 1 and 2, restrictions at the literature search phase, have been associated with increased risk of biased results, since it cannot be determined what was lost.[18] These approaches will not be used by ACMG unless a particular situation arises in which the risk of bias can be shown to be low. Options 3 to 5 are likely to be adopted by ACMG, at least in the short term, as these are high resource, low return approaches that may be offset by well-designed electronic literature searches for 3 and 4, and by appropriate expert review for 5. Hand-searching of bibliographies will be continued. Follow-up with authors may be an option in some systematic evidence reviews, if the data might resolve key gaps. Options 6 through 9 and comprehensive review methods will be considered as potential options for all systematic evidence reviews. Potential limitations of these methods will be discussed and the rationale for selection of the review type documented.

The type of systematic evidence review to be conducted will be decided early on. Criteria will minimally include the complexity of the topic and the number of key questions and outcomes to be investigated to provide the evidence to support the recommendation(s) needed to improve care.

Key Questions & Analytic Framework

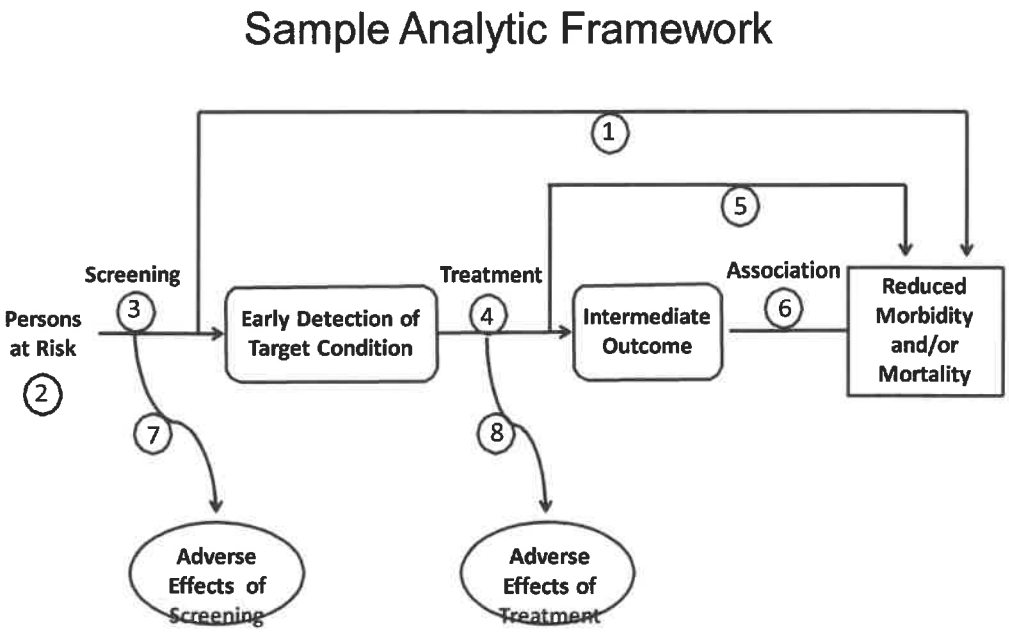
Systematic evidence reviews are framed by the scope and specificity of key questions. The first step is to clearly define the disorder of interest (*e.g.,* clinical manifestations and phenotype, associated variants and genotypes, age at onset, comorbidities). The PICOTS format[11] is again useful, in this case for identifying the information needed to structure the questions. The PICOTS can be translated into an overarching question. In this example,[19] the authors choose a general outcome (all-cause mortality) rather than a disease-specific outcome (*e.g.,* heart disease):

Population	Intervention	Comparator	Outcome
General population (primary prevention)	Fish oil supplement	Isocaloric fat placebo	All-cause mortality

What is the 5 year overall or all-cause mortality in general populations taking 1 g of fish oil supplement daily compared with those taking an isocaloric fat placebo?
Assuming that there will not be sufficient (or possibly any) evidence that directly addresses the overarching question, additional key questions would then be used to develop a chain of logic, highlight potential variables (*e.g.,* impact of age, race, ethnicity, genotype; definition of standard therapy comparator and measures of outcomes) and assess the balance of benefits and harms.

Development of an analytic framework for the defined topic is optional, but can be useful to clearly lay out the chain of logic linking the intervention to the intermediate and long-term outcomes of interest, and places into context the overarching question and other key questions to be addressed in the systematic evidence review.[14] Per the AHRQ website, "Analytic frameworks essentially provide a picture of the topic under review, helping to elucidate the ways in which the intervention under review may contribute to health outcomes in the target population in light of potential mediators and modifiers of effect." http://effectivehealthcare.ahrq.gov/slides/?pageaction=displaySlideDetails&tk=23&dpg=4

Figure 2. Analytic Framework



Modified from Harris RP, et al. *Am J Prev Med* 2001;20(Suppl):21-35

Steps in the Development of a Systematic Evidence Review

- Describe the rationale for selecting the topic for review and its potential impact
- Indicate the type of review selected and how standard methodology might be modified
- Describe the proposed timetable for conducting the review, including schedule of calls and meetings
- Define the disorder and, using the PICOTS format, describe precisely which patients and populations, interventions, comparison groups, outcome measures, time points, and settings will be addressed
- Describe the rationale for the key questions
- Describe the specific search strategies and databases to be used for published and grey literature
- Describe the title, abstract and article screening and selection process (*e.g.,* roles of reviewers, inclusion and exclusion criteria)
- Describe the data extraction strategy, including roles of reviewers, development of extraction fields and forms, and the database used (*e.g.,* Excel spreadsheets, Access, DistillerSR[20], Abstrackr[21])
- Describe the processes for audit and identifying and resolving disagreement between reviewers in study selection and data extraction decisions at each level
- For qualitative and quantitative evidence, describe the approaches and validated methods used to assess and document quality of individual documents and studies,
- For qualitative and quantitative evidence, describe the approaches and validated methods for evaluating the strength of a body of evidence by key question or outcome
- Describe planned analyses of qualitative information
- Describe and justify planned quantitative analyses of effect size for each intervention and each specific outcome studied for that intervention
- Describe potential covariates (*e.g.,* age, gender, race, ethnicity, variants/genotypes, comorbidities, intervention protocols, metrics for outcomes) to be considered if heterogeneity is identified or suspected based on clinical/scientific knowledge or observed data
- Test for publication bias
- Provide ongoing documentation (*e.g.,* summary notes for calls and meetings, decisions made through discussion and deliberation with the Guideline Development Group)

Search Strategy

- Design the search strategy to address each key question
- If needed, use an independent librarian or other information specialist to peer review the search strategy
- Use an iterative approach: searches should begin by identifying relevant guidelines or systematic reviews:
    - Standard databases with *systematic review, meta-analyses* filters– MEDLINE®, EMBASE®
    - Systematic reviews web sites or search engines

        - Cochrane Library Database of Systematic Reviews (http://www.thecochranelibrary.com/view/0/index.html)
        - AHRQ (http://www.ahrq.gov/research/findings/evidence-based-reports/index.html)
        - EGAPP (http://www.egappreviews.org/)
        - UK Health Technology Assessment Programme (http://www.nets.nihr.ac.uk/programmes/hta)
    - Guideline websites or search engines
        - National Guideline Clearinghouse (https://www.google.com/#q=national+guideline+clearinghouse);
        - Guidelines International Network International Guideline Library (http://www.g-i-n.net/library/international-guidelines-library), NICE
- Second level search
    - Standard databases (MEDLINE®, EMBASE®, Web of Science™Core Collection) using database-specific search terms (*e.g.*, MeSH for MEDLINE) and text word terms that are specific for disease, intervention(s) and outcome(s) of interest. To specify a study design, for example, terms such as randomized controlled trial or controlled clinical trial can be selected as the filter or MeSH terms for clinical trials as a publication type
    - Alternatively, leave the basic initial search open to clinical trials and observational studies (*e.g.,* cohort, case-control, case)
    - Search subject-specific databases if other databases are unlikely to provide all the relevant evidence
    - Hand search literature cited by eligible studies
    - Update the search as needed based on the timeline of the SER and CPG
- Grey-literature
    - Grey literature databases
        - New York Academy of Medicine Grey Literature Report (http://www.greylit.org/)
        - GreyNet International/ The Grey Journal (http://www.greynet.org/)
        - System for Information on Grey Literature in Europe (OpenSIGLE) (http://www.opengrey.eu/)
    - Clinical trial registries and other sources of unpublished information about studies
        - ClinicalTrials.gov (http://clinicaltrials.gov/)
        - WHO International Trials Registry (http://apps.who.int/trialsearch/)
    - Books
    - Track manufacturer submissions through the FDA website search engine (http://www.fda.gov/), and also obtain any posted data analysis reports or meeting review notes publicly posted by the FDA or other government agencies
    - Conduct web searches using search engines and document the descriptive terms used
        - Google Scholar (http://scholar.google.com/)
        - LexisNexis ® (https://www.lexisnexis.com/hottopics/lnacademic/)

- Citations identified through search engines (*e.g.,* MEDLINE) should be uploaded into commercial software applications (*e.g.,* EndNote, RefMan) or internally developed databases (*e.g.*, Access or Excel) designed to manage and track this information throughout the selection process
- Review of initial full search results with the Guideline Development Group. After the results have been evaluated, questions may be refined and subsequent searches focused based on what has been learned, with careful documentation

Inclusion and Exclusion Criteria

- The inclusion and exclusion criteria should be predetermined and clearly defined to avoid inconsistency and bias in selection
- These criteria may be:
    - general (*e.g.,* English only, range of publication dates)
    - topic specific (*e.g.,* patients with a specific disorder and phenotype or genotype, age, gender, clinical history, family history)
    - key question specific (*e.g.,* include only specific intervention(s) or outcomes)
    - different for studies and qualitative information
- The criteria may be expressed in the database as a list of questions, with automatic inclusion/exclusion based on the answers checked

Review and Selection

- Document each step of the search
    - Provide a line-by-line description of the search strategy for each search, along with the date of every search for each database or web browser
    - Include the range of dates included in each search
    - Document the disposition of each citation and article identified and reviewed including reasons for exclusions, and report using a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Appendix III) (http://www.prisma-statement.org/statement.htm)
- Include or exclude citations/abstracts or full articles based on the protocol's pre-specified inclusion and exclusion criteria
- Title and abstract screening: If dual independent review, specify who will review and the process for conflict resolution. If single review with full audit or comprehensive spot checking, audit or spot check should be performed by a methodologist or other Evidence Review Group member
    - Screen titles and abstracts using questions based on basic inclusion and exclusion criteria (*e.g.,* English language, type publication)
    - To improve accuracy and consistency, the database screens must be piloted to ensure acceptable performance, and screeners/reviewers must be trained in the use of the database, and written documentation completed
    - Any article or document with possibly relevant title, but lacking abstract or summary, moves to full article and document review

- Full text article and document review: In most cases, selection will be done using dual independent review; specify who will review and the process for conflict resolution. If single review, a full audit should be performed by a methodologist or an Evidence Review Group member with experience in systematic evidence review. The rationale for exceptions to this protocol should be documented
    - Articles and documents included at the citation/abstract screening must be read in full and selected using a new set of questions based on more specific inclusion and exclusion criteria
    - With particular focus on risk of bias, review observational studies to address the lack of randomized control trials or gaps in the evidence

Data Abstraction

- Use computer application-based standard data extraction forms developed for the specific systematic evidence review. These may be commercially available applications (*e.g.,* DistillerSR[20]), applications available free on line (*e.g.,* Brown Univ/AHRQ Abstrackr[21]) or databases developed in-house (*e.g.,* using Microsoft Access or Excel).
- One or more experienced reviewers should pilot test the computer application-based data extraction forms and process to ensure adequate performance before database training and extraction begins. Those doing data entry at any level should be familiar with or trained in the use of the data application.
- All reviewers performing data abstraction should pilot abstract the same small initial group of articles and review the results together for agreement to ensure complete understanding of the material requested and clarity of the abstraction forms.
- Use two or more reviewers to independently extract quantitative and other critical data or information from each article or document. Alternatively, one reviewer could extract the data while a second independently checks for accuracy and completeness (*e.g.,* performs an audit). The full audit of the data for accuracy and completeness should be performed by a methodologist or an Evidence Review Group member experienced in systematic evidence review.
- Resolution of important discrepancies should be done by discussion within the reviewers, with final decision by the methodologist, who may request clarification from a content expert.
- Use stratification by research sites, authors and dates, and source databases to discover links between publications to ensure that data do not overlap between studies and are not included more than once.

Assessing Quality of Individual Studies

- The methodologist or experienced reviewer should be consulted with regard to these steps.
- Systematically assess factors such as the study design and implementation; the risk of bias; the relevance of the study populations, interventions, and outcome measures; and the appropriateness of analytic methods. Select predefined criteria from validated methods and tools that are the best fit for the topic, such as:

    - QUADAS2[22]
    - AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (http://effectivehealthcare.ahrq.gov/ehc/products/60/318/CER-Methods-Guide-140109.pdf)
    - EGAPP Working Group Methods[7,23]
- If not a good fit or data are qualitative, then develop a topic-specific quality questionnaire using published methods and/or pre-validated questions from different sources. Topic-specific quality items of high importance may be added to validated criteria.
- Describe the clinical and methodological characteristics of the included studies, including their size, inclusion and exclusion of important subgroups, timeliness, and other relevant factors:
    - Describe the strengths and limitations of individual studies
    - Describe, in plain terms, how flaws in the design or execution of the study could bias the results.

Quantitative and Qualitative Analysis and Data Synthesis

- Describe the types of studies and the relationships between the characteristics of the individual studies and their reported findings and patterns across studies
- Use narrative and summary tables/figures to present the key data
- Use summary measures to estimate effect size (e.g., clinical sensitivity and specificity, odds ratio, risk ratio, difference in means)
- Provide all estimates with measures of statistical certainty (*e.g.,* confidence intervals)
- Explain why a pooled estimate might be useful to decision makers
    - If meta-analysis is possible, identify the method and software used
    - Address statistical and actual heterogeneity among study effects, and investigate publication bias
- Assess the sensitivity of conclusions to changes in the protocol, assumptions, and study selection (sensitivity analysis)[24]

Grading Strength of Evidence by Key Question and/or Specific Outcomes – GRADE Methods

- The GRADE approach[25,26] considers the factors that collectively determine how confident we are in the results (*e.g.,* accuracy of point estimate, magnitude of effect, quality of evidence) and ensures a systematic and transparent process. Grades for strength (or overall quality) of evidence using the GRADE process are high, moderate, low and very low. Randomized controlled trials (RCTs) start as high, but can be downgraded based on methodological problems. Observational studies start as low, but may be upgraded based on other factors.
- GRADE provides detailed methods and forms for reviewing strength of evidence by key question and/or specific outcome to assess the following characteristics of the body of evidence (Appendix II, Table 1; detailed methods can be found on the GRADE web site):
    - Risk of bias – limitations of study design and execution

    - Inconsistency – heterogeneity
    - Imprecision – number of events and confidence intervals
    - Indirectness – PICOTS and applicability
    - Reporting bias – publication bias
- For observational studies, systematic assessment of the following characteristics for each key question or outcome may allow upgrading
    - Dose–response association
    - Plausible confounding that would change the observed effect
    - Strength of association
- Useful forms (*e.g.,* Summary of Outcomes) and a software application, GRADEpro, can be found at www.ims.cochrane.org/revman/gradepro
- For each key question or outcome specified in the protocol, use consistent language to characterize the level of confidence in the estimates for the effect of an intervention

Grading Strength of Evidence by Key Question or Specific Outcomes – Other Methods

- The GRADE system is highly validated, and most commonly used, but not applicable to all situations. GRADE is not a good fit for some evidence (*e.g.,* qualitative data, analytic and clinical validity). Other published methods are available.
- A published method from EGAPP that works particularly well for analytic and clinical validity questions uses study design and number and quality of studies to determine the adequacy of the evidence to answer key questions as Convincing, Adequate or Inadequate.[7]
- The USPSTF[28] uses a GRADE-based process (Appendix II, Table 2) to assess the strength (or overall quality) of evidence as:
    - **Good -** Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.
    - **Fair -** Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.
    - **Poor -** Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Standard Content for a Systematic Evidence Review

Systematic evidence reviews will be directly formatted as manuscripts for submission to *Genetics in Medicine*. The sections will be:

- *Introduction*
- *Methods*
- *Results*
  - Organize around key questions; minimally describing the following for each key question (and possibly for different outcomes)
    - Study selection process
    - List of excluded studies and reasons for their exclusion
    - Appraisal quality of individual studies
    - Qualitative synthesis (*e.g.*, narrative, descriptions, and themes)
    - Statistical analyses
    - Meta-analysis – if done, should also assess heterogeneity and look for possible publication bias
    - Tables and figures that clearly present the results
- *Discussion*
  - Summary of the evidence
  - Strengths and limitations of the systematic review
  - Conclusions for each key question
  - Gaps in knowledge by key question
  - Future research needs
- *Funding sources and COI*

Peer review of the draft evidence report

The peer review process is an important check on the accuracy and comprehensiveness of the selection, analysis, and interpretation of the scientific evidence.

- The draft report will be reviewed for completeness and accuracy of content, including the analyses.
- More peer and expert reviewers than needed should be contacted well in advance of the predicted timeline for the draft review, as not all will agree to participate. In accordance with ACMG COI guidelines, they should complete ACMG Participation Agreements to disclose COI.
- In some cases, however, a COI may not make it impossible for them to take part. A representative of a company or laboratory with a financial conflict of interest could also be a useful reviewer of the presentation and/or analysis of data they produced or funded. While the COI has to be carefully kept in mind, it can be important that their comments be considered to ensure that the study details or data are accurately reported and interpreted.
- Potential reviewers should be made aware of the objectives of the review and the length of the comment period and should respond in writing if they wish to be reviewers.
- The peer review comments are returned to the Evidence Review Group. Designated members will collate all comments by key question and enter in a table (commenters can

be named or numbered, usually the latter). In most cases, the Evidence Review Group adds responses to comments in the table. Examples of common responses include:

  - A simple statement such as "This comment was noted" can be used for comments that do not require a response.
  - Clarifications are provided for questions about why an approach or statistical method was used, or why a certain conclusion was made. "No revision" or the content of any revisions are also documented in the master table.
  - Suggested missed references are obtained and reviewed using the article selection form. If the article appears relevant, it may be extracted and added to the evidence report, or a response in the table will explain why the article is not eligible.

- It is important to remember that reviewers without substantial COI might also have an intellectual bias, so keep that in mind as you read comments.
- The Evidence Review Group will have a specified time from the end date for comments to review the comments and formally reply to all in a master table, making revisions to the draft review as appropriate.
- Revisions become part of the permanent record of the systematic evidence review.
- The revised draft report and the master table with the comments and responses will be returned to the Guideline Development Group for review.
- After discussion with the Guideline Development Group about the comments and responses, the Evidence Review Group will finalize the evidence review manuscript and submit to the Guideline Development Group to support recommendation development.

EXPERT PANEL CONSENSUS PROCESS

A challenge that ACMG will encounter is the development of a needed guideline when the systematic evidence review reveals insufficient, inconsistent, indirect or poor quality evidence for some or all key questions that need to be developed into recommendations for a particular guideline. In this situation, a formal consensus methodology can be utilized to continue the development of recommendations and a guideline. The methods combine expert opinion with review of available scientific literature. Approaches commonly used are the RAND-UCLA method, the American Society of Clinical Oncology process, and Guideline International Network process. Each of these consensus methods is a modification of the Delphi method, which was developed at the RAND Corporation in an attempt to obtain expert opinion in a systematic manner.[29-31]

What all these methods have in common is the utilization of an expert panel. Developed initially for the social sciences, expert panel methods have been used in healthcare to develop clinical guidelines.[32] Historically, panel methodology has involved inviting experts with varying relevant backgrounds to participate in a consensus building exercise, typically beginning with distribution of available relevant literature followed by a three-round panel process involving: a Round 1 survey with ranking of action priorities by each panelist; a Round 2 meeting (in-person, via video-teleconferencing or by telephone only) to discuss survey results and come to consensus on initial rankings; and a Round 3 follow-up survey for final rankings of top-rated priorities. Panel methods lend themselves to adaptation for use in a variety of contexts requiring multiple stakeholder perspectives and expertise in the selection and development of action priorities.

The 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.[30] The method combines expert opinion with review of the scientific literature. The method quantitatively assesses the expert judgment of 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.[30]

- **Panel selection**. Each panel consists of nine clinicians from various specialties relevant to the topic from throughout the United States. 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**. Panelist are sent literature reviews, rating sheets and instructions that asked panelists 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 9 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 in front of them printouts 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 8 and 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 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 feel 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 (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 (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.

The ASCO Consensus Process

The ASCO consensus process is a modification of the more detailed RAND-UCLA Appropriateness Method. The ASCO Steering Committee drafts recommendations and describes a rationale for each. When complete, the draft is circulated among the Guideline Development Group, who meet to discuss the recommendations, clinical considerations and any supporting evidence, as well as specific areas of uncertainty. The draft is then sent to members of a Consensus Group for the first round of rating and review of agreement with each recommendation using a 5-point LIkert scale. Raters are provided with the evidence review, are asked to use their best judgment, and can provide feedback beyond the rating. Ratings are reviewed and the all recommendations that did not meet the consensus threshold (≥ 75%) are revised. Iterations of this review process continue until all recommendations meet the consensus threshold or it is determined that consensus cannot be reached.[32]

The Guidelines International Network (GIN) Consensus Statements.

Each member of the guideline development panel determines their agreement with recommendations using a 5-point scale ranging from "strong, definitely do it" to "strong, definitely do NOT do it", with a text field for comments for each item. A response rate of ≥ 75% of the panel is required per item reviewed, and first round non-responders are dropped from the panel. The panel may do two more iterations, and also consider an online survey of suggestions. Consensus is achieved when≥ 80% of the panel vote either "strong support" or "weak support" for the positive response or the negative response. If the minimum response rate is not achieved, then the guidance item is revised or dropped. This group believes that consensus-based suggestions should not carry grades for evidence or suggestion and are clearly labeled as consensus-based. There is a lack of confidence in the magnitude of the effect, so the balance of benefits and harms is subject to variation.[33]

A process for review of expert consensus panel reports and for their use in developing guidelines will need to be developed similar to that for formal evidence review.

DEVELOPMENT OF GUIDELINES

Steps in Developing Conclusions and Recommendations for a Guideline

- If possible, one in-person meeting is planned, perhaps at the American Society of Human Genetics or ACMG annual meetings. Whether in person or by teleconference or webinar, all relevant documents are distributed prior to the meeting. For systematic evidence reviews, presentations on the methods used and the review content are made by Evidence Review Group members, focusing on concepts and evidence synthesis. Similar procedure is followed for expert panel work.
- General open discussion by the Guideline Development Group follows. Effective group facilitation is generally needed to encourage full participation, identify what the group needs to move forward, and keep the group on task to accomplish set goals. Common reminders are that this is a debate, not argument; that members represent points of view not advocacy; that all members should participate; that good evidence tops existing intellectual biases; and that all decisions need to be made in a timely fashion. The process continues via teleconference or webinars.
- Development of conclusions from the evidence. Evidence Review Group members and the facilitator of the expert panel process remain on call to provide clarification of the evidence and analyses as the Guideline Development Group develops conclusions.
- Determination of the number of recommendations that may be supported by the evidence, and draft of the recommendation statements.
- Levels of evidence and grades of recommendation are determined for each. Note that systems for grading recommendations are well developed and protocols for ACMG can be selected (see below).
- Judgments on the potential impact of each recommendation
- Gaps in knowledge and current areas for development

Drafting Recommendation Statements

Drafting key action statements that are clear and effective requires skills that can be supplemented by available software and methods. Options for training should be considered.

- Action verbs have been well-defined for developing action statements. Examples include:[34] *conclude, should, diagnose, identify, prescribe, refer, consult, perform, discuss, educate, counsel, monitor, document.* Words to avoid: *consider* and *may*.
- Software applications are becoming available to lead guideline developers through this process in real time. An example is BRIDGE-Wiz (Yale University),[9,35] in which the screens can be projected so that all can participate in the process. This software ensures key action statements through a stepwise process of:
    - choosing action types from a dropdown list (test, perform, educate) and verbs from the dropdown list for that action type;

- completing action clauses, then linking them using AND or OR; and,
- providing checks on the quality of the statements:
  - Executability – Is each action stated specifically and unambiguously?
  - Decidability – Among the precisely defined conditions under which the action is performed, does the action statement determine if a condition was consistently met?
  - Leading the users through benefits and risks/harms to judge the balance of benefits and harms.
  - Helping to determine the strength of evidence that supports the recommendation.
  - Based on strength of recommendation, helps select a term for level of obligation (should, must) in action statements.
  - Allows the user to choose a preset recommendation style
- The process of group review in real time and speaking the statements out loud can be very effective in identifying ambiguous or unclear statements.
- 2011 versions of BRIDGEWiz are now available online. One version now uses the GRADE system, and other versions are those used for ASCO and AAP that include their active verb sets and Guideline Quality Appraisal Forms.[35]

The Clinical Practice Guideline Peer Review and Approval Process

The peer review process is an important check on the accuracy, and comprehensiveness, and balance of the presented scientific evidence. The review process provides perspectives on the validity of the rationale for the recommendations, as well as feedback on the clarity and feasibility of the recommendation statements. This process also helps to engage stakeholders.

ACMG has a well-established policy for review of Clinical and Laboratory Practice Guidelines. The policy is summarized on the final page of the "Proposal for Policy Statement, Practice Guideline or Other Project" that is available in the members section of the ACMG website. The draft Clinical Practice Guideline, accompanying systematic evidence review (with the master table of expert reviewer comments and responses) or expert panel consensus report should be reviewed together. It is expected that review of the Clinical Practice Guideline will focus on the recommendations and the rationales that support them, based on the accompanying evidence.

- The draft Clinical Practice Guideline is first reviewed and approved by the Sponsoring Committee.
- It is then submitted to the ACMG Board of Directors (BOD) for review. The BOD can give initial approval or request changes.
- Once BOD approval is given, the Clinical Practice Guideline document is submitted electronically to the ACMG membership for a 30-day comment and review.
- Comments are collected in the ACMG office and sent back to the lead author(s) in the Guideline Development Group for incorporation into the document. The authors incorporate comments as appropriate, using track changes, and then send the document back to the ACMG Staff Liaison, the Sponsoring Committee Chair and the designated

Board Liaison. The authors must include an annotated list of all comments received and the response or action(s) taken for each comment.

- The final revision of the Clinical Practice Guideline and the summary of comments with author responses are presented for final approval to the Board of Directors. Once approved, the manuscript is finalized. Outside expert reviewers are cited individually and thanked in the Acknowledgments section of the papers if a Participation Agreement has been completed and approved by the BOD.
- The paper is submitted to the ACMG Office for publication in *Genetics in Medicine.* The document is posted on-line, published ahead of print, on the ACMG website.

It is anticipated that modifications of the current ACMG clinical practice guideline review process may be needed to comply completely with CMSS and National Guideline Clearinghouse guidance.

While public review of Clinical Practice Guidelines is recommended by CMSS and other guidance, it is very resource intensive. The current ACMG review process incorporates peer review and ACMG member review, with written response to all comments by the Guideline Development Group authors. It is recommended that current ACMG review procedures be continued during the pilot phase. Public review should be seriously considered as a future goal.

Final Steps and Joint Publication of the Evidence Review and Guideline

- The summary manuscript for the systematic evidence review will highlight key messages.
- The manuscript or Clinical Practice Guideline may include discussion of key gaps in knowledge and recommendations for future research.
- The objective will be simultaneous publication of the Clinical Practice Guideline and the systematic evidence review or expert panel consensus report, both for clarity and to increase impact.
- Submission to the NGC of AHRQ - Preparation of document for submission will be performed by the ACMG Staff Coordinator and approved by the Medical Director and the Guideline Development Group Chair. As previously noted, the Guideline Development Group may decide to provide a separate informational piece for patients/consumers.

Dissemination of Guidelines

- Consider broad goals of: 1) Increasing the reach of the information to a variety of audiences across many settings (email, social media, provision of short, user-friendly summaries for different audiences); 2) increase motivation to use and apply the information using "champions," and thought leaders; and 3) increasing the ability to use and apply information (add to existing strategies such as CME or media summaries).[36-38]
- Develop practical steps to support dissemination of guidelines
    - Email alerts to genetics organizations (*e.g.,* ACMG, American Society of Human Genetics, NSGC, Society of Inherited Metabolic Disorders)

- Email alerts to other Societies relevant to the disorder (*e.g.,* American Academy of Pediatrics, American College of Cardiology)
- Email alerts to relevant advocacy and support groups
- Submit the Clinical Practice Guideline to the National Guidelines Clearinghouse and the European Guidelines International Network to increase awareness and credibility
- Send out an ACMG press release

Implementation of Guidelines

Many guideline development processes do not have the resources to actively promote guideline implementation or its evaluation. This will probably be the case for ACMG at this phase in development. However, it is important to be aware of proposed strategies to support guideline uptake.

- These include: 1) early identification of potential barriers to implementation and considering solutions; 2) use of formats and dissemination approaches based on preferences of the target group; and 3) development of educational resources adapted to the needs of target groups.[36-38]
- Monitoring and evaluating implementation is a resource intensive process that may need to be delayed to a later phase of development
- However, monitoring of ACMG members through MOC to determine awareness and use of the CPG is not resource intensive and may be useful.

Updating Guidelines

The ACMG currently has a policy that Clinical Practice Guidelines should be revised, reaffirmed, or retired at least every 5 years. This is also the stated policy of CMSS[3] and the NGC. It is recognized that Clinical Practice Guidelines may require more frequent review, depending on the topic. The questions and factors below can form a framework that helps ensure appropriate and timely updating.

- What situations may require the updating of a clinical practice guideline?[38]
  - Changes in the evidence on existing benefits and harms of interventions
  - Changes in outcomes of interest or of particular importance
  - Change in the available interventions
  - Changes in the evidence supporting current practice
  - Changes in the values placed on specific outcome
  - Changes in resources available for translation research or health care
- What factors should be addressed soon after the publication of the CPG?[38]
  - A general updating strategy should be devised, including the need for yearly or more frequent literature reviews or updates to determine whether there is important, new information that warrants consideration of a revision.
    - Action requires a choice between a full and comprehensive update, update of one or more key questions, or other specific or partial update approaches.[39]

- Determine who is responsible for monitoring, updating literature searches and organizing the assessment of new evidence.
- Consider basic search strategies for interim limited searches or a systematic monitoring system (scheduled automatic searches) based on available resources.
- Consider how ACMG will handle input from guideline users that an update may be needed.

Developing an update process that meets the needs and available resources of ACMG will take time but will be considered as part of pilot projects.

REFERENCES

1. IOM (Institute of Medicine). 2011. *Finding What Works in Health Care: Standards for Systematic Reviews.* Washington, DC: The National Academies Press.
2. IOM (Institute of Medicine). 2011. *Clinical Practice Guidelines We Can Trust.* Washington, DC: The National Academies Press.
3. Council of Medical Specialty Societies, Principles for the Development of Specialty Society Clinical Guidelines, September, 2012. Available at: http://www.cmss.org/uploadedFiles/Site/CMSS_Policies/CMSS%20Principles%20for%20the%20Development%20of%20Specialty%20Society%20Guidelines%20-%20September%202012.pdf; accessed November, 2013.
4. SIGN 50: A guideline developer's handbook, 2011. Scottish Intercollegiate Guidelines Network (SIGN), Edinburgh, Scotland. ISBN 978 1 905813 25 4. www.sign.ac.uk, accessed July 9, 2013.
5. National Institute for Health and Clinical Excellence (NICE). The Guidelines Manual: The Scope - Factors to consider when identifying key clinical issues. (January 2009) http://www.nice.org.uk/media/5F4/91/The_guidelines_manual_2009_-_Chapter_2_The_scope.pdf.
6. Jacobs AK, Kushner FG, Ettinger SM, et al. ACCF/AHA clinical practice guideline methodology summit report: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;61:213-265.
7. Teutsch SM, Bradley LA, Palomaki GE, et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: methods of the EGAPP Working Group. *Genet Med* 2009;11:3-3.
8. Qaseem A, Forland F, Macbeth F, et al. Guidelines International Network: toward international standards for clinical practice guidelines. *Ann Intern Med* 2012;156:525-531.
9. Rosenfeld RM, Shiffman RN, Robertson P, Department of Otolaryngology State University of New York D. Clinical Practice Guideline Development Manual, Third Edition: a quality-driven approach for translating evidence into action. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery* 2013;148:S1-55.
10. Begolka WS, Elston DM, Beutner KR. American Academy of Dermatology evidence-based guideline development process: Responding to new challenges and establishing transparency. *Am J Acad Dermatol* 2011;64:e105-e112.
11. Agency for Healthcare Research and Quality, Effective Health Care Program. *Developing and Selecting Topic Nominations for Systematic Reviews,* Methods Guide for Effectiveness and Comparative Effectiveness Reviews. November, 2013. In http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1321#6824.
12. Calonge N, Green NS, Rinaldo P, et al. Committee report: Method for evaluating conditions nominated for population-based screening of newborns and children. *Genet Med* 2010;12:153-159.
13. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001;20:21-35.
14. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Introduction to Meta-Analysis. West Sussex, United Kingdom:John Wiley & Sons, Ltd., 2009.
15. Bradley LA, Palomaki GE, Bienstock J, Varga E, Scott JA. Can Factor V Leiden and prothrombin G20210A testing in women with recurrent pregnancy loss result in improved pregnancy outcomes?: Results from a targeted evidence-based review. *Genet Med* 2012;14:39-50.
16. McClain MR, Palomaki GE, Piper M, Haddow JE. A rapid-ACCE review of CYP2C9 and VKORC1 alleles testing to inform warfarin dosing in adults at elevated risk for thrombotic events to avoid serious bleeding. *Genet Med* 2008;10:89-98.
17. Ganann R, Ciliska D, Thomas H. Expediting systematic reviews: methods and implications of rapid reviews. *Implement Sci* 2010;5:56.

18. Lichtenstein AH, Yetley EA, Lau J. Application of Systematic Review Methology to the Field of Nutrition. Technical Reviews, No. 17, Agency for Healthcare Research and Quality. http://www.ncbi.nlm.nih.gov/books/NBK44075/table/A29833/?report=objectonly.
19. DistillerSR Web-Based Systematic Review Software. http://systematic-review.net/.
20. Abstrackr: Software for Semi-Automatic Citation Screening, http://abstrackr.cebm.brown.edu.
21. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003;3:25.
22. Botkin JR, Teutsch SM, Kaye CI, et al. Outcomes of interest in evidence-based evaluations of genetic tests. *Genet Med* 2010;12:228-235.
23. Sun X, Ioannidis JP, Agoitsas T, Alba AC, Guyatt G. How to use a subgroup analysis: user's guide to the medical literature. *JAMA* 2014;311:405-411.
24. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-926.
25. Mustafa RA, Santesso N, Brozek J, et al. The GRADE approach is reproducible in assessing the quality of evidence of quantitative evidence syntheses. *J Clin Epidemiol* 2013;66:736-742; quiz 742 e731-735.
26. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines 3: Rating the quality of evidence: introduction. *J Clin Epidemiol* 2011;64:401-406.
27. U.S. Preventive Services Task Force Grade Definitions, February 2013. http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm#post.
28. Dalkey NC: The Delphi Method: An Experimental Study of Group Opinion. RM-5888-PR. Santa Monica: Rand Corp, 1969
Brown BB: Delphi Method: A Methodology Used for the Elicitation of Opinion of Experts. Los Angeles: Rand Corp, 1968.
29. 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;2:53-63.
30. Fink A, Kosecoff J, Chassin M, Brook RH. Consensus methods: characteristics and guidelines for use. Am J Public Health 1984;74(9):979-983.
32 Loblaw DA, Prestrud AA, Somerfield MR, et al. American Society of Clinical Oncology Clinical Practice Guidelines: formal systematic review-based consensus methodology. *J Clin Oncol* 2012;30:3136-3140.
33. Guidelines International Network (GIN) Webinar Series. Nov 19, 2013. How to Provide Reliable Guidance When Evidence is Insufficient: Developing Trustworthy Consensus Statements. https://kponline.webex.com/kponline/lsr.php?AT=pb&SP=MC&rID=80250497&rKey=f5559fe9a7a8c232.
34. Essaihi A, Michel G, Shiffman RN. Comprehensive Categorization of Guideline Recommendations: Creating an Action Palette for Implementers. *AMIA Annu Symp Proc* 2003;2003:220-224.
35. BRIDGE Wiz: Building Recommendations In a Developer's Guideline Editor. Yale University. http://gem.med.yale.edu/BRIDGE-Wiz/.
36. Communication and Dissemination Strategies to Facilitate the Use of Health-Related Evidence. November, 2013. Agency for Healthcare Research and Quality Evidence Report/Technology Assessment No. 213. http://www.effectivehealthcare.ahrq.gov/ehc/products/433/1757/medical-evidence-communication-report-131120.pdf.
37. Gagliardi AR. "More bang for the buck": exploring optimal approaches for guideline implementation through interviews with international developers. *BMC Health Serv Res* 2012;12:404.
38. Shekelle P, Woolf S, Grimshaw JM, Schunemann HJ, Eccles MP. Developing clinical practice guidelines: reviewing, reporting, and publishing guidelines; updating guidelines; and the emerging issues

of enhancing guideline implementability and accounting for comorbid conditions in guideline development. *Implementation science : IS* 2012;7:62.
39. Becker M, Neugebauer EAM, Eikermann M. Partial updating of clinical practice guidelines often makes more sense than full updating: a systematic reviw on methods and the development of an updating procedure. *J Clin Epidemiol* 2014;67:33-45.
40. GRADE Working Group. Factors panels should consider in deciding on a strong or weak recommendation. http://www.gradeworkinggroup.org/FAQ/factors_rec.htm. .
41. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist GE. GRADE guidelines 1: Introduction - GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383-394.
42. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS medicine* 2009;6:e1000100.
43. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine* 2009;6:e1000097.

APPENDIX I - ACMG EVIDENCE-BASED PRACTICE GUIDELINE

Draft Review Format

Title: XXXX, an Evidence-Based Clinical Practice Guideline of the American College of Medical Genetics and Genomics

Authors; for a Guideline Development Group of the American College of Medical Genetics and Genomics, Professional Practice and Guidelines Committee

(Disclaimer)

A. ABSTRACT

An abstract should be brief and boxed or otherwise formatted to stand out. Alternatively, a brief summary of recommendations only could appear above the abstract. The abstract should minimally include the following elements:

1) Objectives –1 to 2 concise statements describing the purpose of the guideline
2) Methods - 1 to 2 sentences regarding the literature search strategy
3) Results - Brief summary of the evidence, strength of evidence for KQs or specific outcomes, conclusions of the Guideline Development Group and any gaps in knowledge
4) Recommendations - Clear synopsis of recommendations with a grade for each

B. SCOPE AND PURPOSE

This section should describe the rationale for development of the guideline, as well as background information on the condition and intervention addressed. It should also include a list of the key questions included in the SER (choice of format may depend on the number of key questions). The introduction section should only be a few pages long, and include the following elements:

1. Status of guideline - New or revised guideline
2. Brief description of disease/condition, including frequency/prevalence, natural history, and current management (e.g., diagnosis, counseling, prognosis, management, available interventions/treatments, and genotype-phenotype associations).
3. Guideline introduction - The rationale for the guideline (*e.g.,* change in current practice, new intervention, new evidence or a need to address existing gaps in knowledge); important points about scope, and a brief statement regarding what the guideline does not include, such as cost analyses.
4. The key clinical questions – The SER key questions are often used directly, but may be reworded or reorganized to better fit the guideline; some may be combined or dropped.
5. Reference recommendations from related existing clinical practice guidelines (this can also be addressed later in the discussion)

6. Target audience - Who are the intended users of the guideline (*e.g.,* geneticists, primary practice and specialist physicians, genetic counselors, nurse counselors, policy makers, health care systems and payers)
7. Settings in which guideline is to be used (*e.g.,* inpatient, outpatient)
8. Goals of guideline – What the guideline is meant to accomplish (*e.g.*, reduce numbers of inappropriate tests, provide appropriate treatments) and how the recommendations might impact current management protocols.

C. METHODS

This section describes the process the Guideline Development Group used to create the guideline and should be detailed and transparent. Key information from the SER should be included. However, much of this information can be referenced to the SER co-publication and/or provided in an appendix of the publication or as an online supplement. Each of the elements below should be included, if appropriate:

Guideline Development Group and the Evidence Review Group

1. Description of the Guideline Development Group, including the selection process for members (with reference to ACMG policies on COI), disciplines represented and their defined roles (*e.g.*, participation as the technical expert panel for the SER, reviewing and commenting on SER drafts, overseeing outside review comments and responses, reviewing SER data and developing conclusions, writing/editing the guideline document).
2. Description of the Evidence Review Group, including the selection process (with reference to ACMG policies on COI), identifying the members acting as the methodologist and statistician, and brief comments on their working process and interaction with Guideline Development Group.
3. Brief description of key SER methods and/or reference to the SER. Key tables or figures from the SER may be included, or combined in new tables/figures to present the points relevant to the guideline recommendations. For such key points, provide quality and strength of evidence and reference SER and/or methods used.

Practice Guideline Development

1. Description of the method used to develop conclusions and recommendations
    - Guideline Development Group working process (*e.g.,* conference calls, face to face meetings)
    - Guideline Development Group voting process and how difficult issues were resolved
    - Process for writing assignments (*e.g.,* individuals, teams) and who provides editorial review tasks
2. Review process for guideline drafts and disposition of comments (refer to current ACMG policies)

D. RECOMMENDATIONS

This section presents the recommendations developed based on the evidence or, in some cases, from expert consensus or expert opinion. As noted previously, the guideline may follow the SER key questions (as below) or choose a different approach (e.g., clinical validity, clinical utility).

Numbered or bulleted list of recommendations followed by narrative sections as below OR narrative sections by recommendation

1. Recommendation 1
2. Recommendation 2

Recommendations

1. Narrative summary of the evidence related to the key question or outcome(s) of interest

1) Include evidence tables and figures, where appropriate
2) Quality and strength of evidence by key question and/or specific outcome(s)
3) Strength of recommendations, and rating scheme to determine strength of recommendations
4) Potential or evidence-supported benefits and harms associated with a recommendation and the balance of benefits and harms
5) Potential contextual issues to be considered
6) Qualifying statements, including whether certain patient groups should be excluded
7) Results of Guideline Development Group votes on recommendation – how any conflicts were resolved or is an alternative or minority opinion included
8) Acknowledgement of guidelines from other groups, including consistencies and possible explanations for differences

Limitations of Evidence
Identified Gaps in Knowledge

E. Dissemination Strategy

This section should include ACMG's generic plan for dissemination as well as additional approaches for the particular guideline topic (e.g., physician specialty groups, support groups).

F. Guideline Development Group

This section should contain a description of members of the working group, including all conflicts of interest disclosures.

G. References

Genetics in Medicine *limits the number of references for practice guidelines to 45 and the SER is limited to 75 references. When necessary, additional groups of references (e.g., those excluded) can be listed in an online supplement.*

APPENDIX II – GRADE Working Group

Table 1. GRADE Method for Determining Strength of Evidence by KQ or Outcome[25]

Study Design	Quality of Evidence	Lower if	Higher if
Randomized trial →	High	Risk of bias -1 Serious -2 Very serious Inconsistency -1 Serious -2 Very serious Indirectness -1 Serious -2 Very serious Imprecision -1 Serious -2 Very serious Publication bias -1 Likely -2 Very likely	Large effect +1 Large +2 Very large Dose response +1 Evidence of a gradient All plausible confounding +1 Would reduce a demonstrated effect or +1 Would suggest a spurious effect when results show no effect
	Moderate		
Observational study →	Low		
	Very low		

Table 2. GRADE-based US Preventive Services Task Force Methods for Grading Recommendations, Updated July, 2012[28]

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Table 3. US Preventive Services Task Force Levels of Certainty Regarding Net Benefit[28]

Level of Certainty*	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: • The number, size, or quality of individual studies. • Inconsistency of findings across individual studies. • Limited generalizability of findings to routine primary care practice. • Lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: • The limited number or size of studies or important flaws in study design or methods. • Inconsistency of findings across individual studies. • Gaps in the chain of evidence. • Findings not generalizable to routine primary care practice. • Lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

Table 4. GRADE Guideline Development Checklist, December 2013

The Checklist is 23 pages long, but can be viewed at http://cebgrade.mcmaster.ca/guidelinechecklistprintable.pdf.

Table 5. GRADE – Factors to Consider in Grading Recommendations[40]

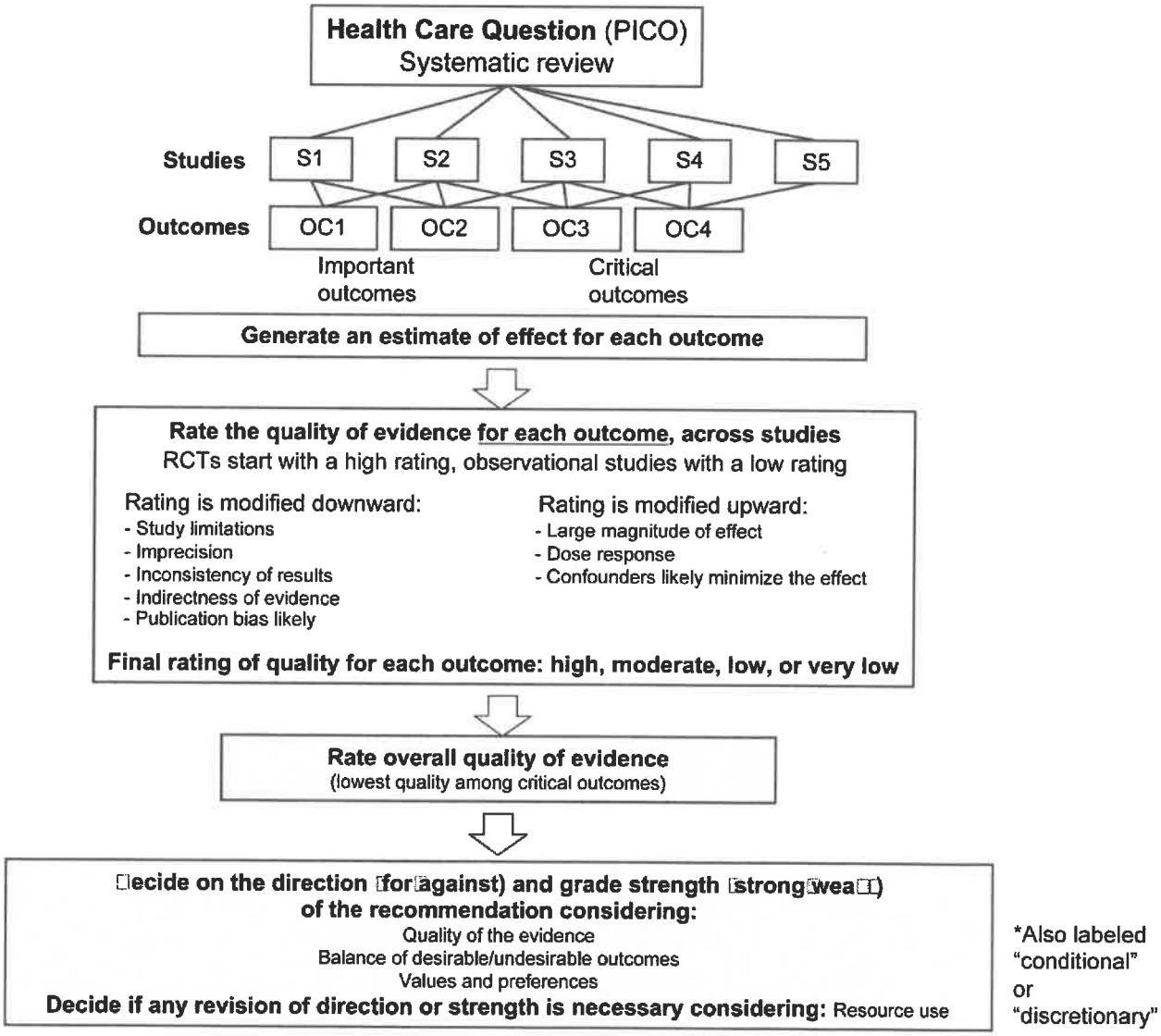
Factors
Uncertainty in the estimates of likely benefit, and likely risk, inconvenience, and costs
Importance of the outcome that treatment prevents
Magnitude of treatment Effect
Precision of estimate of treatment Effect
Risks associated with therapy
Burdens of Therapy
Risk of target event
Costs
Varying Values

Figure 1. Schematic View of GRADE's Process for Developing Recommendations[41]

GRADE has only two grades for recommendations, Strong and Weak. Selection is based on criteria in Table 5 and the bottom blue box in this schematic.

Weak Recommendation: Based on the available evidence, if clinicians believe that benefits and risks and burdens are finely balanced, or appreciable uncertainty exists about the magnitude of benefits and risks, they must offer a weak recommendation. In addition, clinicians are becoming increasingly aware of the importance of patient values and preferences in clinical decision making. When, across the range of patient values, fully informed patients are liable to make different choices, guideline panels should offer weak recommendations

Strong Recommendation: Based on the available evidence, if clinicians are very certain that benefits do, or do not, outweigh risks and burdens they will make a strong recommendation.



*Also labeled "conditional" or "discretionary"

APPENDIX III – PRISMA Flow Diagram[42,43]

PRISMA 2009 Flow Diagram