ACMG Foundation for Genetic and Genomic Medicine
Better Health Through Genetics™

EVIDENCE-BASED GUIDELINES (EBG) PROGRAM
SEMI-ANNUAL UPDATE[1]
October 2022

"The ACMG Foundation's Evidence-Based Guidelines Program has been running at full steam since our last update. Three full-time staff members supported by nearly 150 ACMG Members and a cadre of experts from 22 nations. People on every continent (other than Antarctica) participated in a massive effort this year." *-- Dr. Bruce Korf, President of the ACMG Foundation*

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[1] The ACMG Foundation publishes this update semi-annually to keep partners informed of our work.

INTRODUCTION

This update from the ACMG Foundation for Genetic and Genomic Medicine (ACMG Foundation) is focused on the Evidence-Based Guidelines (EBG) Program's activities from January through September of 2022.

Several EBG-related Committee and Board-level discussions took place in March of this year at the ACMG 2022 Annual Meeting. The ACMG's newly named *Practice Research and Methodology Department* (PR&M Department), several ACMG committees, and approximately 200 essential volunteers met throughout the first half of the year. As a result, Systematic Evidence Review (SER) and EBG manuscripts from four separate topics are either underway or have already been published. Up to 10 additional topics covering key genetic and genomic medical issues are slated to begin review by committees and staff as the year comes to a close.

Note that older updates and other historic and foundational documents can be found on the Foundation's EBG webpage, ACMGFoundation.org/EBG.

To offer feedback or learn how you can support our work, please contact Karl Moeller at kmoeller@acmgfoundation.org. For specific process or science-based inquiries, please contact Gabrielle Jenkins (gjenkins@acmg.net) or Olivia Demarest (odemarest@acmg.net). Those in the media with guideline development questions are asked to reach out to Kathy Moran at kmoran@acmg.net.

The Ongoing Work of the EBG Program

This update of the EBG Program's current projects is outlined in four sections:

- **Section One**: Topics that have passed through review by both the SER and EBG Workgroups and are nearing final publication (1),
- **Section Two**: Topics that are in the first phase of review by an SER Workgroup (3),
- **Section Three**: Topics that are (or will soon be) completing the SER stage and are now under review by an EBG Workgroup (3).
- **Section Four**: Topics that have been published since 2019 (either as guidelines or as SER documents) (3).

Please note, the efforts outlined in Sections Two and Three are the same three *topics* but must move separately through both the SER and EBG Workgroups in that order.

Section One: A Guideline Nearing Publication

Non-invasive Prenatal Screening (NIPS)

Staff and volunteers have worked on this complex passing topic since September 2020. During that time, the ACMG has benefited from the input of a wide range of partners and subject matter experts.

As mentioned in earlier EBG updates, the NIPS SER was opened to ACMG's membership for an extended member comment period after 770 articles were screened and 87 studies were included in the final systematic review. The SER Workgroup's systematic evidence review was published earlier this year. The EBG Workgroup completed the GRADE (Grading of Recommendations Assessment, Development and Evaluation) process to develop recommendations based on the evidence from the SER.

ACMG volunteers and PR&M Department staff are finalizing the evidence-based guideline for Board approval and publication in our peer-reviewed journal, *Genetics in Medicine* (*GIM*). The ACMG carefully considers member comments and is grateful that numerous members took the opportunity to participate in this crucial final review stage of our guideline development process.

Section Two: SER Projects Under Review

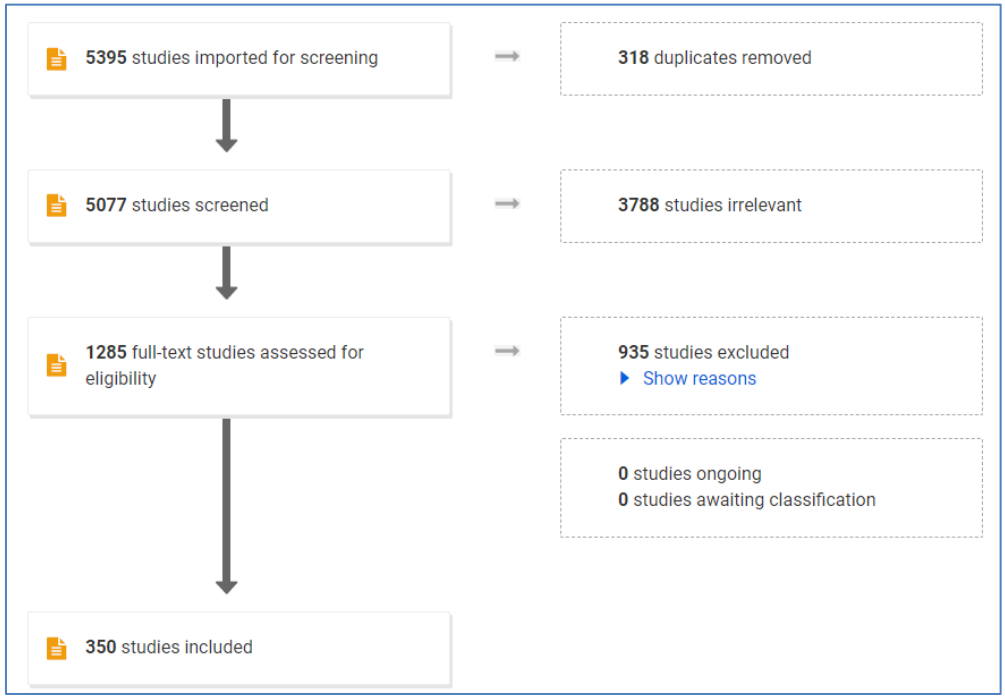
SERs are the first phase of guideline development. Staff work with volunteers to form a topic-specific SER workgroup. The SER workgroup then reviews all relevant literature to understand the key issues an EBG Workgroup (on the same topic) must consider.

#1: Update to PKU – Diagnosis and Management Guideline

The ACMG has an existing Practice Guideline on Phenylalanine Hydroxylase Deficiency (PKU) that was originally published in 2014. As treatment options expanded and best practices were updated for PKU, several partners requested that our team review the ACMG's older publication.

The SER workgroup for PKU finished drafting an SER manuscript in the summer of 2022. The manuscript was reviewed by the ACMG's Board of Directors and then released for member comment. The publication of the final SER manuscript is anticipated later this year, and the EBG workgroup is now developing guidelines based on the evidence provided from the systematic review.

Below is the PRISMA diagram detailing this SER Workgroup's literature review progress for the PKU effort. Our team and volunteers screened over 5,000 articles to find the few hundred most relevant papers and studies.



#2: Diagnosis and Management of Fatty Acid Oxidation Disorders (FAOD)

Genetic and genomic experts from both the FAOD SER Workgroup and FAOD EBG team met in March of 2022 to finalize the SER protocol and project aims. The initial literature search was completed by staff and more than 4,700 articles were reviewed for Title and Abstract screening. The SER workgroup completed this stage of the SER in August 2022. Full-text review of over 1,100 articles fitting initial eligibility criteria began later that month. Data extraction, quality analysis, data analysis, and manuscript writing will commence in the months to follow.

#3: Diagnostic Utility of Genetic Testing for Autism Spectrum Disorder

Subject matter experts in autism spectrum disorder and genetic testing who volunteered to work on the EBG or SER workgroups met in March of 2022 to finalize the SER protocol and project aims. An initial literature search completed by staff found 3,938 articles to review. The SER team finished Title and Abstract screening in July of 2022 and are currently making their way through the 1,800 articles that were determined to be worthy of a full text review. Data extraction, quality analysis, data analysis, and manuscript writing will begin in the coming months.

Section Three: EBG Workgroup Activities

In most cases, the EBG Workgroups for any topic moved forward by the Topic Selection Committee are tasked with drafting an Evidence-Based Guideline (when the evidence warrants one) after the SER team completes its work. Below is the status of all projects in this phase of our process.

#1: Update to PKU – Diagnosis and Management Guideline

The EBG Workgroup for Phenylalanine Hydroxylase Deficiency (PKU) completed a preliminary voting round using the formal "GRADE" evidence review process in the spring of 2022. Consensus voting among workgroup members was reached in August. ACMG's committees provide expertise to the organization, and the EBG Workgroup is taking advantage of this organizational strength and unique pool of subject matter experts by sharing its findings with the ACMG's Therapeutics Committee members. Upon receiving input from this internal ACMG committee, a draft EBG manuscript will be shared with the ACMG Board. It will then be sent to members of the ACMG for an open comment period. Publication of the final document is slated for early 2023, after reaching a final consensus among the ACMG's volunteer members.

#2: Fatty Acid Oxidation Disorders (FAOD) – Diagnosis and Management Guideline

Since April, the EBG team has been meeting monthly to receive training on GRADE methodology in preparation for the work they will begin once the SER Workgroup completes the systematic review. This is a global team, with members joining the effort from as far away as Australia. The ACMG staff members are working to complete this project in 2023.

#3: Diagnostic Utility of Genetic Testing for Autism Spectrum Disorder – Guideline

This guideline has followed a similar timeline to the FAOD effort above, with the EBG team and SER Workgroup meeting in Q1 of 2022 to receive training on GRADE methodology. The EBG team's final guideline development and publication is slated for 2023.

Section Four: Published Systematic Evidence Reviews or Guidelines since 2019

The application of noninvasive prenatal screening using cell-free DNA in general-risk pregnancies
Systematic Evidence Review (2022) https://doi.org/10.1016/j.gim.2022.03.019

> This recent publication has already garnered several dozen social media impressions and sparked global discussions. It is too soon to know the true impact of this SER manuscript, but the ACMG is tracking the issues and considering next steps as needed.

The "Peds ES/GS (CA, DD, ID)"
Evidence-based Guideline (2021) https://doi.org/10.1038/s41436-021-01242-6

The first full guideline published under the official[2] systems set up by the EBG Program was titled, "Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG)". The paper was published on July 1, 2021, and an ACMG press release from that date can be found here.

The publication was a "chart topper" in scientific media once released – with an "Altmetric score," showing it to be in the 99th percentile of similar published articles in terms of popularity.

The "Peds ES/GS (CA, DD, ID)"
Systematic Evidence Review (2020) https://doi.org/10.1038/s41436-020-0771-z

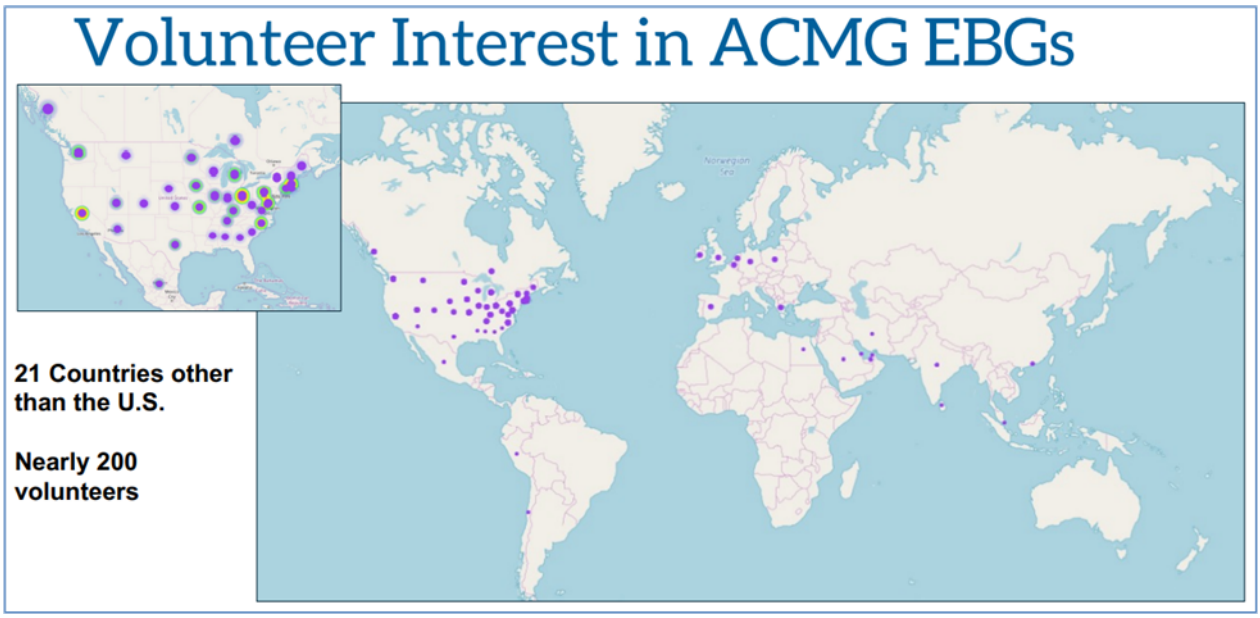
The precursor to the Peds Evidence-Based Guideline listed above, the SER on the same topic was well-received in the medical community and represented the first SER document to be passed through the full GUIDE process after the founding of our EBG Program in 2019.

Upcoming Work of the EBG Program and PR&M Department

With the implementation of a new web portal to submit guideline topic nominations [https://redcap.acmg.net/surveys/?s=P9XFFJCPHR], the pace of online topic submissions through the ACMG and ACMG Foundation's web portal has increased significantly. As a result, many new topics were considered by the Topic Selection Committee earlier this year. Several were moved into the pipeline for SER and EBG Workgroups to process with the help of ACMG staff members. The ACMG plans to carefully consider and process all topic submissions, but a ranking system is used, given the limits of existing staff. Topics moved into the full review process are generally those with the most readily available and highest quality/quantity of scientific studies available.

When the ACMG recently sent out a call for volunteers to sit on upcoming SER and EBG Workgroups, the PR&M Department was thrilled by the positive response. Hundreds of individuals stepped forward to volunteer and the global reach of ACMG's Guideline work became evident. Clearly, this new program of the ACMG and ACMG Foundation is attracting attention.

[2] ACMG has published guidelines for over two decades on an ad hoc basis, but the EBG Program formalized the effort and ensures a common scientific approach to the development and release of all EBG publications.



The Guideline Pipeline

As new volunteers step forward to serve on SER and EBG Workgroups, teams will be formed, and work will begin on several new topics. Four topics already approved by the Topic Selection Committee and approved by the ACMG Board of Directors will begin the EBG Programs review process shortly. Those topics are:

- Cancer risk in differences of sexual development/intersex,
- Rapid genome sequencing in neonatal and pediatric intensive care or units,
- Expanded exome or genome sequencing for inherited retinal dystrophies,
- Transfer of mosaic embryos during in vitro fertilization
    - To be jointly developed with the American Society for Reproductive Medicine (ASRM); anticipated state date: January 2023

The ACMG team is also beginning to undertake revisions and updates to six existing ACMG documents, thanks to topic submissions and new data provided by the medical community. These topics include:

- Marfan syndrome (first published by the ACMG in 2012)
- Advanced paternal age (first published by the ACMG in 2008)
- Osteogenesis imperfecta (first published by the ACMG in 2006)
- Fetal skeletal dysplasias (first published by the ACMG in 2009)
- Referral to genetics (first published by the ACMG in 2007)
    - Representatives from the American Academy of Pediatrics and American Academy of Family Physicians will participate. Additional specialists are being sought from other organizations (e.g., American Academy of Neurology)

- Pompe disease (first published by the ACMG in 2006)
    - To be jointly developed with the American Association of Neuromuscular & Electrodiagnostic Medicine; anticipated start is late 2022.

Topics eligible for consideration are not restricted to specific disorders or conditions; however, emphasis is typically on the role of genetics and genomics in the screening, diagnosis, management, treatment, or risk reduction in inherited disorders.

The selection of new projects will continue to change in response to various factors, such as new scientific advances, available staff resources, volunteer involvement and support, the impact of new compelling submissions, and the funding available to the program.

Future EBG Program Initiatives

The ACMG is working to gain the support of partner medical specialty organizations to involve in jointly developed evidence-based guidelines. Staff members are proactively reaching out to appropriate medical societies to explore ways we might co-release guidelines that have jurisdictional overlap. While our guidelines are very well received, they will have a greater impact with the medical and payer communities when multiple organizations publicly endorse our findings at the time of publication.

Additionally, the PR&M Department has begun working closely with the ACMG Advocacy and Government Affairs Committee to explore ways ACMG can alert payers about newly published medical guidelines. The ACMG quickly observed how important it will be to educate payers on how to use these new guidelines when making coverage decisions. As guidelines are published, the ACMG Foundation would like to build a team of volunteers and support new staff positions that work together and ensure new findings and recommendations are understood by the medical and payer communities. Developing evidence-based guidelines is an integral part of translation of medical research, and we must ensure new guidelines are used correctly to keep pace with medical discoveries and inform patient care.

Development Efforts

The EBG Program of the ACMG was launched in 2019. One part-time consultant supported several newly-formed committees and workgroups. These workgroups were comprised of volunteers who were not yet trained in evidence review methodologies.

This year, the ACMG's EBG Program hailed three full time and highly trained staff, a large roster of experienced ACMG members on several committees and workgroups, and volunteer training was ongoing. None of this would have been possible without funding from over a half dozen organizations and key individuals. Together, these leaders provided the ACMG Foundation with nearly $2 million through contributions to the Guideline Fund. Their generosity, and particularly the support of Illumina, made the successful launch of this program possible and assisted the ACMG's guideline work in reaching a global audience.

As we move into 2023, the ACMG Foundation is working to provide resources needed to fill staff postions so the College can advance the slate of guidelines already in the pipeline and address the influx of new guideline requests that we are expecting to receive in the months ahead. We are determined to maintain the enthusiasm of our past donors while adding new sponsors to the roster. This will be the development team's focus throughout 2023: keeping current friends involved while adding new sources of support. The important work of the EBG Program is now recognized and applauded globally, and we hope to widen the circle of program sponsors just as the program has expanded.

Individuals who would like to learn what they, or their organizations, can do to assist this project should connect with Karl Moeller by emal at kmoeller@acmgfoundation.org. Together, we can improve patient care and health outcomes in genetic and genomic medicine!

LINKS AND HELPFUL BACKGROUND INFORMATION

The ACMG Foundation encourages the public to visit the EBG Program website and to follow the link to the online Topic Submission Form. The EBG Program site will be updated as guidelines progress, as the selection committee makes further determinations, and as new or returning donors help expand the program.

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Supplement the October 2022 *EBG Update*

2/13/2023

Published Papers in *Genetics in Medicine*

- Systematic evidence-based review: Outcomes from exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability (June 2020)
- Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: An evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG) (November 2021)
- Systematic evidence-based review: The application of noninvasive prenatal screening using cell-free DNA in general risk pregnancies (July 2022)
- Noninvasive prenatal screening (NIPS) for fetal chromosome abnormalities in a general-risk population: An evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG) (February 2023)

Papers Accepted by *Genetics in Medicine*

- Phenylalanine hydroxylase deficiency treatment and management: A systematic evidence review (expected publication March 2023)

Papers in Development

- EBG: Update to phenylalanine hydroxylase deficiency: Diagnosis and management guideline (expected publication late Fall 2023)

Projects In-Progress

- SER and EBG: Diagnostic utility of genetic testing for patients with autism spectrum disorder (expected SER completion Summer 2023; expected EBG completion Winter 2023)
- SER and EBG: Diagnosis and management of fatty acid oxidation disorders (expected SER completion Summer 2023; expected EBG completion Winter 2023)
- SER and EBG: Living kidney donors (expected SER completion Summer 2023; expected EBG completion Winter 2023)
- SER and EBG: Diagnosis and management of patients with osteogenesis imperfecta (expected SER completion Winter 2023 2023; expected EBG completion Spring 2024)

Projects Recently Launched (Winter 2022/2023)

- Genetic implications of advanced paternal age: evaluation and recommendations
- Gonadal germ cell tumor risk in individuals with differences of sex development (DSD)/intersex
- Diagnosis and perinatal management of fetal skeletal dysplasia
- Genetic diagnosis and clinical management of Marfan syndrome
- Rapid exome and genome sequencing in the neonatal and pediatric intensive care units
- Genetic diagnosis and clinical management of inherited retinal dystrophies

Upcoming Projects to Start Late Spring 2023

- Transfer of mosaic embryos during in vitro fertilization
- Referral to genetics
- Pompe disease
- Urea cycle disorders
- Chronic kidney disease