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

Genetics and Genomics are not just in our name, they are part of our mission

# EVIDENCE-BASED GUIDELINES PROGRAM

## SEMI-ANNUAL UPDATE[1] ON DEVELOPMENT and WORK GROUP ACTIONS
## January 2022

### INTRODUCTION

This January publication of the ACMG Foundation for Genetic and Genomic Medicine (ACMG Foundation) is the next in a series of semi-annual updates on our Evidence-Based Guidelines (EBG) Program. You may also be interested in similar updates published in September 2020, February 2021 and June 2021.

To offer feedback or learn how you can support our work, please contact Karl Moeller at kmoeller@acmgfoundation.org. For science-based inquiries, please contact Jennifer Malinowski at jmalinowski@acmg.net. Finally, those in the media are asked to reach out to Kathy Moran at kmoran@acmg.net. Please mention "EBG Program" in the subject line.

**Development Efforts**

Since founding this new program in 2019, the ACMG Foundation has raised nearly $1,000,000 in support of this priority initiative. We are particularly thankful to our lead donor, Illumina, Inc., for their steadfast support of the EBG Program. We are also grateful to our other critical corporate and philanthropic donors. [2]

To ensure scientific integrity, all donations are directed to an EBG Fund. This fund is used by our sister organization, the American College of Medical Genetics and Genomics (the College). As 2022 began, three highly technical staff members are managing the systematic evidence reviews necessary for guideline development. Reviewing scientific evidence on these genetic and genomic topics is a laborious, highly technical, and time-consuming endeavor. Luckily, ACMG's staff are not alone. The EBG Program also depends on the voluntary contributions of

[1] The ACMG Foundation will work to publish and update this document semi-annually with a goal of making this a quarterly report once the program is fully staffed. We will clearly release an update at those times when the work of the related committees or work groups warrants an update to our EBG constituency.

[2] Special thanks to Illumina, BioMarin, Invitae, Horizon Pharmaceuticals, Ultragenyx and Evan and Cindy Jones for their EBG Program contributions in 2020 and 2021. Unrestricted contributions from PerkinElmer in 2018 and Natera in 2021 also played a crucial role in the program's successes.

several dozen active ACMG members across multiple committees and work groups who represent several disciplines within the genetic and genomic medical field.

The ACMG Foundation's development team is focused on expanding the EBG Program this year, particularly in the first half of 2022. Due to longstanding funding cycles, bolstering our Graduate Student Fellowship Program was a high priority last year. Multiple Fellowship grants were awarded in 2021 – and with those funds secure, the Foundation is now following up on past EBG Program requests, finding new program sponsors, and renewing past donors to ensure continued guideline development.

**Expanding the EBG Guideline Team**

Corporate support has enabled us to build a great team. Our Senior Methodologist, Dr. Jennifer Malinowski, first worked with ACMG in 2017 as a consultant and helped with our ad-hoc evidence-based guideline work before the launch of the formal EBG Program. Jennifer later joined the organization as a full-time employee in July 2021 and is an INGUIDE/McMaster University certified Guideline Methodologist. A second full-time staff member, Gabrielle Jenkins, MSPH, joined the EBG team in 2021. Gabrielle serves as our Methodologist and is slated to earn a doctorate in Epidemiology from the University of North Carolina, Chapel Hill in the near future. Most recently, Olivia Demarest, MS, MPH, joined the EBG team.

The team is imperative to the program's success and acts as a resource for the EBG work groups. Methodologists provide our volunteers with hours of manuscript evaluation and ranking, project planning, and data analysis. The team also 1) coordinates outreach to other medical societies for future projects involving non-geneticist stakeholders and 2) provides education to ACMG committees and work group members about a.) conducting systematic evidence reviews and b.) evidence-based guideline development.

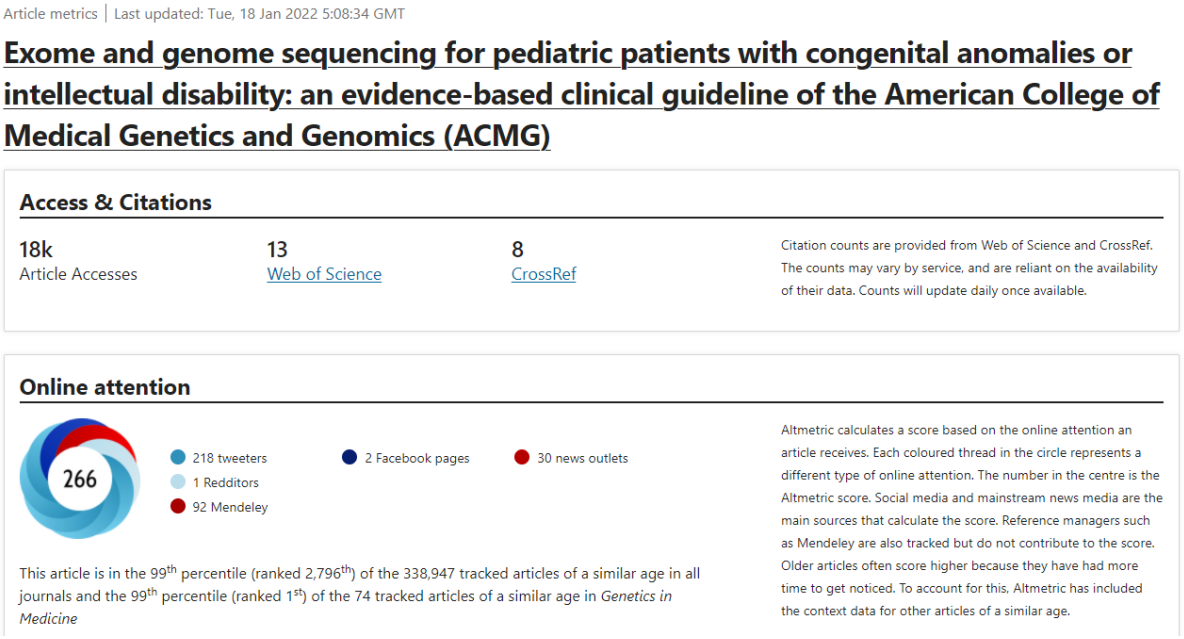
## RECENTLY PUBLISHED GUIDELINES

**The "Peds ES/GS (CA, DD, ID)" Guideline**

The first guideline published under the official[3] 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.

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

The publication was a “chart topper” in scientific media once released – as seen in the screen shot of the “Altmetric score,” which found it to be in the 99th percentile of similar published articles.




## GUIDELINE DEVELOPMENT:

## ONGOING PROJECTS

### The NIPS Guideline

A guideline for Noninvasive Prenatal Screening (NIPS) has been in development with ACMG since September 2020. Two groups of ACMG member volunteers and ACMG staff members continue to research the issues through the formal process determined by the Evidence-Based Guidelines Program at ACMG.

For the NIPS Systematic Evidence Review (SER) work group,[4] the relevant diagnostic accuracy and clinical utility data was considered from 87 studies that were ultimately included in the evidence review. Once that process was complete in October 2021, the NIPS SER compiled and

[4] Members: Jennifer Malinowski (ACMG Senior Methodologist/Chair), Danielle LaGrave, Elizabeth Barrie, Marco Leung, Nancy Rose, Monica McClain (former ACMG Methodologist), Gabrielle Jenkins (ACMG Methodologist).

released their work to ACMG's membership for a member comment period. That exercise was left open for nearly two months and the feedback received was incredibly favorable.

The NIPS EBG work group also finished working through developing their recommendations using the GRADE framework and has begun drafting the guideline manuscript. They anticipate a draft document will be reviewed by internal ACMG committees in the winter and will be released for member comment in March or April of this year. This is the final step before the document is proofed for submission to (and publication in) *Genetics in Medicine*.

The NIPS EBG work group[5] continues to meet twice monthly and adheres to guideline development standards set out by the Institute of Medicine (now the National Academies).

**Phenylalanine hydroxylase deficiency (PKU) Guideline**

During the summer of 2021, the PKU SER and EBG work groups were restructured after several group members had to step down due to personal or professional reasons. After significant updating of the literature search to address critical outcomes, the SER ultimately included 293 studies.

ACMG Methodologists are completing data analysis and have already delivered the first half of the results to the EBG work group. The EBG work group is simultaneously preparing for the manuscript and GRADE recommendation process while the SER team is preparing the SER manuscript.

A patient advocate was identified and added to the team in July 2021. This is an essential participant in the guideline process and their inclusion adheres to both Institute of Medicine (now the National Academies) standards and best practices for guideline development.

Note that the PKU SER Group members include Jennifer Malinowski (Senior Methodologist/Chair), Moises Fiesco-Roa, Judith Hobert, April Dione Adams, Paul Rothberg, Lawrence Wong, and Gabrielle Jenkins (ACMG Methodologist).

The PKU EBG panel is comprised of Jerry Vockley (Chair), Wendy Smith (co-chair), Jennifer Malinowski (Senior Methodologist), Kim McBride, Susan Berry, Barbara Burton, John Mitchell, Henry Mroczkowski, Christine Brown (patient representative), and Gabrielle Jenkins (ACMG Methodologist).

[5] Members: Jeff Dungan (Chair), Kristin Monaghan, Susan Klugman, Bob Best, Yassmine Akkari, Angelika Erwin, Sandra Darilek, Shelly DeGreef (patient representative), Jennifer Malinowski (ACMG Senior Methodologist), Gabrielle Jenkins (ACMG Methodologist).

## GUIDELINE DEVELOPMENT:

## NEW PROJECTS

Two new SER/EBG projects will begin moving through the Program's process[6] in early January 2022:

- The diagnosis and clinical management of patients with fatty acid oxidation disorders, and
- Diagnostic and clinical utility of genetic testing for patients with autism spectrum disorder.

Work group composition has been finalized and the teams will have their initial planning calls in early February. The ACMG Foundation is excited that more than 80 ACMG members and other volunteers applied to be part of these two projects.

Once volunteers are identified, ACMG's Senior Methodologist will provide the EBG work group with training in the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) methodology – a key technique used by the EBG Program to translate evidence into recommendation statement(s). ACMG's methodology team similarly provides in-depth training for the SER team.

Like the topics chosen above, all potential guideline topics submitted to ACMG by the public through our online submission form undergo methodological review and assessment by the ACMG Topic Selection Committee (TSC). Factors that influence when a nominated topic moves forward are the topic's alignment to College priorities, the potential impact on patient care of any EBG, the feasibility and methodology to support both an SER and an EBG, and the available evidence. As these are constantly evolving, topics may be deferred and revisited periodically.

New topics for review in March are currently being solicited from ACMG members and the public.

Other topics submitted to date include:

- Use of rapid genome sequencing in the intensive care unit,
- Reanalysis of exome or genome sequencing results,
- Expanded exome or genome sequencing for hereditary retinal dystrophies,
- Transfer of mosaic embryos during IVF,
- Pharmacogenomics, and
- RNA sequencing.

[6] Please see page 2 of our September 2020 update found here: https://www.acmgfoundation.org/PDFLibrary/EBG_SemiAnnualupdate_Aug_2020.pdf

## NEXT STEPS

The next meeting of the TSC will be held during the Annual Meeting in March. The TSC will review new submissions as well as revisit nominations that were deferred during previous sessions.

The methodology team will be moderating and presenting a session entitled “The ACMG Evidence-Based Guideline Program: Our Roadmap from Evidence to Recommendations and the Impact on Patient Care” on Thursday, March 24th in Nashville.

New topics are currently being sought from ACMG members, Foundation partners, and relevant patient advocacy organizations. While the Topic Selection Committee will review submissions twice yearly, we encourage submissions throughout the year. With enough staff and with the necessary resources, ACMG would like to address ALL submitted topics.

## LINKS AND HELPFUL BACKGROUND INFORMATION

The ACMG Foundation is encouraging the public to visit the EBG Program website and, if interested, 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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