



EVIDENCE BASED GUIDELINES PROGRAM

SEMI-ANNUAL UPDATE¹ ON DEVELOPMENT and WORK GROUP ACTIONS JUNE 2021

INTRODUCTION

The ACMG Foundation for Medical Genetics and Genomics publishes these semi-annual updates on the Evidence Based Guidelines (EBG) Program to keep the community informed of our progress. Be sure to read the updates from [September of 2020](#) and [February 2021](#) as well. To offer feedback and input on what you read here, or to learn how you can support our work, please contact Karl Moeller at kmoeller@acmgfoundation.org.

Development Efforts

With the help of individuals and corporate donors alike, the ACMG Foundation secured over \$500,000 in 2020 for the EBG Program. Again, special thanks to Illumina, BioMarin, Invitae, Horizon Pharmaceuticals, and Evan and Cindy Jones for their generous contributions in 2020.

Last year's funding is being used to build a highly-technical team – but maintaining that team into the future will require additional funding each year. We are working to secure new and returning donations to keep the EBG Program on track. ACMG Foundation remains committed to our goal of securing \$700,000 in 2021. This program cannot exist without highly qualified staff who can perform in a stable and predictable work environment. Plus, the growing number of requests we have received recently for new or updated guidelines is a sign this program is not only valued but gaining steam.

Building the EBG Guideline Team:

The ACMG Foundation is excited that Dr. Jennifer Malinowski agreed to return to ACMG full time as the ACMG Senior Methodologist. At this time, Jennifer has already worked with us on a part time basis for five months and will transition to a full time role in July. Those who worked with ACMG on our early guideline work in 2019 may recall working with Jennifer at that time. Because of her prior work with ACMG, Dr. Malinowski needs no introduction to our staff, ACMG's committee members, or the leadership of ACMG or the ACMG Foundation. She has hit the ground running as a seasoned methodologist with an eye for organization. We know she will be instrumental in helping to lead our EBG efforts.

Our 2020 development work and the generosity of our donors also enabled us to hire Gabrielle Jenkins, MS. Gabrielle began her role as ACMG Methodologist in mid-May. A doctoral candidate in Epidemiology

¹ The ACMG Foundation will work to publish an update to this document on a quarterly basis, or at other times when the work of the related committees or work groups warrants an update to our EBG constituency.

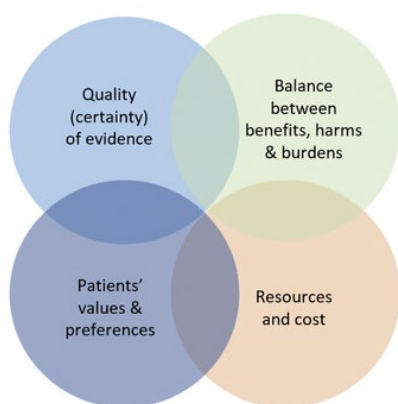
at the University of North Carolina, Chapel Hill, Ms. Jenkins first received a B.S. in Biological Sciences and a B.A. in Chemistry from North Carolina State University. She also holds a Master of Public Health in Applied Epidemiology from the University of Alabama-Birmingham. Ms. Jenkins is anticipated to defend her dissertation² and earn her Ph.D. by the fall 2021.

Complementing her extensive training in epidemiology, Ms. Jenkins most recently worked with the University of North Carolina Frank Porter Graham Child Development Institute where she performed a systematic evidence review and analyzed qualitative and quantitative data using a variety of methods. She authored a policy brief on “Best Practices for Early Childhood Program Evaluation” for the Babies First North Carolina Program Evaluation. Ms. Jenkins also has experience in the private sector, serving as a contract researcher for GlaxoSmithKline in their respiratory and oncology units and working for Merck in the area of pharmacoepidemiology. In both roles, Ms. Jenkins performed numerous systematic evidence reviews, protocols, study reports, and manuscript sections.

GUIDELINE DEVELOPMENT: CURRENT PROJECTS

The “Peds ES/GS (CA, DD, ID)” Guideline

The first guideline to be produced under the EBG program, “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)” was submitted to *Genetics in Medicine* at the end of May after review. Date of publication is currently estimated at 4-6 weeks.



In addition to the evidence from the previously-published SER and recent health technology assessment from Ontario, the EBG panel considered the overall priority of the problem, the certainty of evidence, patient values and preferences, cost-effectiveness and required resources, the acceptability and feasibility of implementing the guideline, and the impact of the guideline on health equity. These domains comprise the GRADE Evidence to Decision framework (Figure).

Figure. Considerations for evidence-based guideline recommendations.

The NIPS Guideline

Since September of 2020, two teams of ACMG member volunteers and our staff members have continued to drive the Noninvasive Prenatal Screening (NIPS) Guideline through the formal Evidence

² “Longitudinal and isotemporal associations of time spent in physical activity and sedentary behavior on anthropometric measures in pre-school age children.”

Based Guidelines Program at ACMG. For the Systematic Evidence Review (SER) Work Group,³ work has continued as the group has extracted the relevant diagnostic accuracy and clinical utility data from more than 50 studies that were ultimately included in the evidence review (Figure).

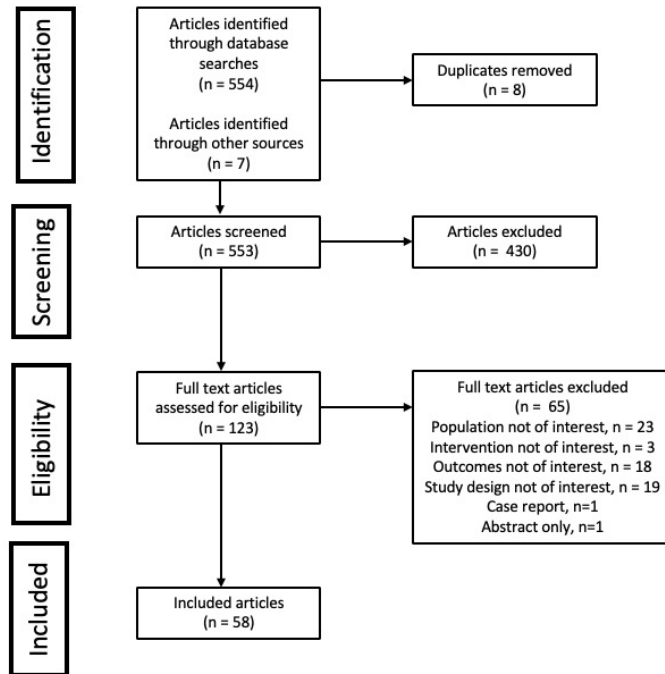


Figure. PRISMA flow diagram of studies in NIPS SER.

The group is currently working with the Senior Methodologist on meta-analyses and narrative synthesis of the evidence and simultaneously writing the SER manuscript. The SER workgroup will be presenting their results to the NIPS EBG panel at their June 22nd conference call and will finish drafting the SER manuscript at that time. After the manuscript has been drafted, it will go to the PP&G Committee for review and then out for ACMG member comment before submission to *Genetics in Medicine*.

The NIPS EBG Work Group⁴ has been meeting twice monthly. To adhere to guideline development standards set out by the Institute of Medicine (now the National Academies), a patient or patient advocate is an essential guideline panelist. At the request of the Senior Methodologist in order to adhere to this standard, the NIPS EBG panel identified a patient to serve on the panel in this capacity. They are expected to be officially added once the Board meets in mid-June. Additionally, the Senior Methodologist has been providing initial training on Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology to the panel ahead of their anticipated work developing the recommendation statement(s) which will begin in earnest in July. Additional training in

³ Members: Jennifer Malinowski (ACMG Senior Methodologist/Chair), Danielle LaGrave, Elizabeth Barrie, Marco Leung, Nancy Rose, Monica McClain (former ACMG Methodologist), Gabrielle Jenkins (ACMG Methodologist)

⁴ Members: Jeff Dungan as Chair, Kristin Monaghan, Susan Klugman, Bob Best, Mike Bashford, Yasmine Akkari, Angelika Erwin, Sandra Darilek, Shelly DeGreef (patient representative), Jennifer Malinowski (ACMG Senior Methodologist), Gabrielle Jenkins (ACMG Methodologist)

GRADE methodology will be provided in an ongoing basis for the EBG panel as they work through the GRADE Evidence to Decision framework.

Phenylalanine hydroxylase deficiency (PKU) Guideline

Since the last update, the PKU EBG Work Group has undergone some restructuring as several group members had to step down due to personal or professional reasons. This has delayed the completion of the SER; however, the group is now in the final stages of data extraction and assessing the risk of bias for more than 100 articles. Once the extraction and risk of bias assessment are complete, the methodologists will perform data analysis and provide guidance to the workgroup for the SER manuscript. The data analysis is anticipated to be completed by July 1.

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

As with the NIPS EBG panel, the Senior Methodologist strongly recommended the inclusion of a patient/patient advocate as a panelist. This individual was approved as a panelist in May. While the SER team has been working, the EBG panel has not been meeting regularly. The Chairs and Senior Methodologist have met separately for updates on the SER workgroup progress and to determine which recommendations from the previous publication should go through the GRADE process. The GRADE process (Evidence to Decision framework) should not be undertaken for statements that are considered “good practice statements,” that is, recommendations for actions that would be done for all patients as part of standard clinical management. For example, taking a patient history would be considered a good practice statement. The PKU EBG is currently assessing the statements made in the previous consensus-based guideline in anticipation of receiving the data from the SER workgroup. The full group will be meeting June 9th to introduce the patient representative and for an overview of the GRADE process by the Senior Methodologist.

The 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).

NEXT STEPS

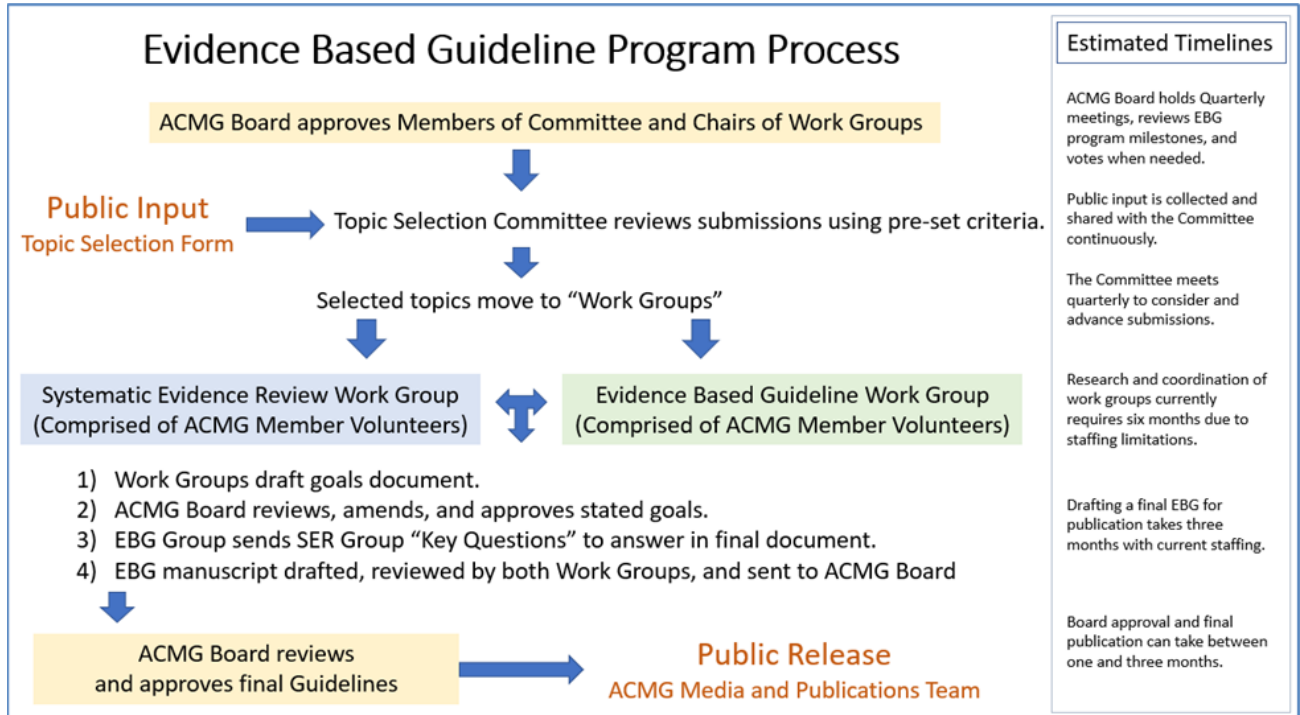
There is a lot of work ahead of us. The Topic Selection Committee currently has over a dozen proposed topics under consideration, and more submissions are expected as a June 18 deadline for online submissions draws near. ACMG and the ACMG Foundation are committed to keeping our members, donors, and partners updated on the EBG Program’s ongoing work and will continue to update the Foundation’s public webpage dedicated to the EBG Program.

Again, thanks to successful fundraising campaigns in 2019 and 2020 (and assuming the trend continues in 2021!), ACMG plans to move forward with adding a Chief Medical Officer. Our goal remains driving genetic and genomic medicine – and patient care – forward.

LINKS AND HELPFUL BACKGROUND INFORMATION

The ACMG Foundation is encouraging interested parties 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.

The Process: This chart below is republished again in this EBG Update and seeks to answer the question, “How long does it take for an idea to become a published guideline?”



Please direct any questions to Karl Moeller via email at kmoeller@acmgfoundation.org.