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

EVIDENCE BASED GUIDELINES PROGRAM

SEMI-ANNUAL UPDATE[1] ON COMMITTEE and WORK GROUP ACTIONS
August 2020: Key Actions One Year After Founding the EBG Program

INTRODUCTION

The ACMG Foundation would like to begin by thanking our program's founding donors, Illumina and PerkinElmer. Their early unrestricted support of our efforts to establish a formal Evidence Based Guidelines (EBG) Program made our work possible.

With their help, the ACMG Foundation was able to bring on an experienced nonprofit program development manager early in 2019 who aided the Boards of both organizations in building a professional and comprehensive EBG Program. These funds also provided the key support needed to sustain a part-time methodologist in 2019. This early EBG Program consultant was able to advance work on a new guideline related to exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disabilities. This same corporate support enabled ACMG to hire a full time staff methodologist and EBG Program staff member, Monica McClain, who began with ACMG early in 2020.

In addition to critical seed funding from both companies, Illumina has been instrumental in reaching out to other companies and organizations. ACMG Foundation Board Member and Illumina Chief Medical Officer, Dr. Phil Febbo, has helped lead the Foundation Board's outreach campaign alongside Dr. Maximilian Muenke, our recently appointed CEO.

SUMMER 2019 – JANUARY 2020

When ACMG'S Evidence Based Guidelines (EBG) Program was formalized and approved by the Boards of both ACMG and The ACMG Foundation in August of 2019, ACMG's Board quickly convened the Topic Selection Committee members under the leadership of Committee Chair and ACMG member, Laurie A. Demmer, MD, FACMG. Dr. Demmer is a specialist in pediatrics and medical genetics at Atrium Health. A full list of the Committee's current members can be found here.

Topic Selection Committee members met by phone soon after to review the goals ACMG's Board of Directors set out for the new EBG program. They discussed the systems in place to consider possible topics for new medical genetic and genomic guidelines and evaluated the on-line process for submitting topic suggestions for the committee's consideration. Guideline development is not new to ACMG, and many Board-approved practices used in past decades were reviewed, improved, and codified to guide this new program.

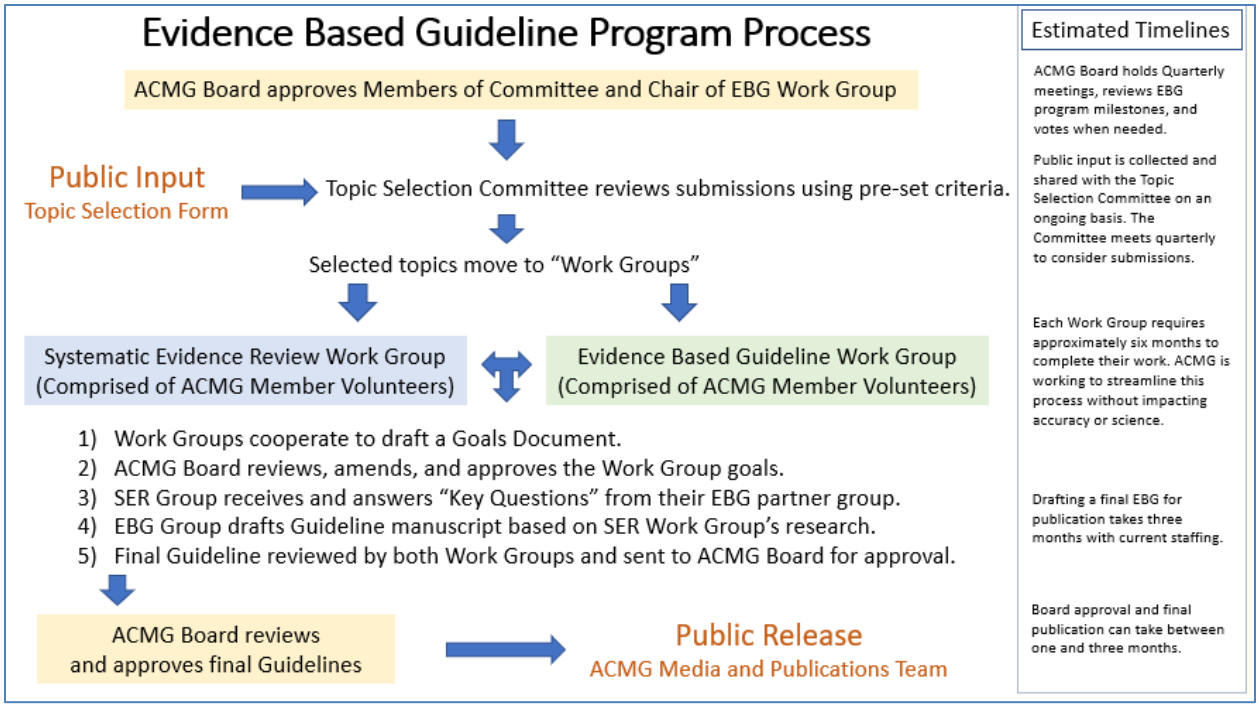
[1] The ACMG Foundation will work to publish an update to this document on a quarterly basis, or at other times when the work of the related Committees or Work Groups warrants an update to our EBG constituency.

Topic Selection Committee members quickly designed and approved a web-based Topic Submission Form in partnership with ACMG's leaders, staff, and expert consultants. ACMG is proud that this topic submission platform gives genetic leaders, concerned patients, and knowledgeable members of the public around the world an ability to suggest new topics of study. Those tendering their ideas may also suggest updates to older genetic or genomic guidelines that may require revisions.

ACMG is fortunate to have a strong membership base that represents an extensive and diverse group of medical specialists in the field from nearly all professional sectors. To help test the new submission process, thousands of ACMG members were sent a link and invited to submit guideline topic suggestions for the Topic Selection Committee to consider. Once tested, the link was made public so non-ACMG members could also propose topics for the Committee to take into consideration.

Process is Key

In these early months, ACMG Members, staff members, and the Board of Directors worked to outline the process by which guideline development would proceed. The chart below depicts that process.



ACMG's staffing resources and their roles are downplayed in this chart, but methodologists, scientific experts, and administrative staff are key players during each phase outlined. Today ACMG has one staff methodologist working on guideline development, which restricts the organization's ability to fast-track multiple efforts or investigate multiple topics simultaneously[i].

By October of 2019[2], a total of five topics were submitted in advance of the Topic Selection Committee's first face-to-face meeting in Houston. This was in addition to work already underway on the 'genome sequencing for pediatric patients' Guideline mentioned earlier.

At that meeting, the Topic Selection Committee voted to advance, "The Value of Noninvasive Prenatal Testing in Average Risk Patients" as the first topic to explore through Systematic Evidence Review. Other topics submitted by ACMG members included: Expanded Carrier Testing, the Clinical Utility of Pharmacogenomic Testing, the Clinical Utility of Prenatal Exomes, and the Clinical Utility of Pediatric Exomes. These submissions were retained for future consideration, given the EBG Program's staffing limitations. It is also worth noting that Committee members agreed more data was needed for a full review of some topics. Other topics submitted by ACMG members were already undergoing similar Systematic Evidence Reviews by other groups or organizations.

JANUARY 2020 – AUGUST 2020

New Staff, New Systems, and Work Group Membership

In addition to hiring a full time employee at the start of 2020, ACMG's EBG program obtained licenses for Covidence and GRADEpro in that same timeframe. These on-line platforms are designed to conduct systematic evidence reviews (Covidence) and develop evidence based guidelines (GRADEpro). Together they will provide much needed support to the respective Work Groups and our methodologist. ACMG is pleased these systems will help advance the Topic Selection Committee's recommendations in a transparent and efficient manner. Covidence and GRADEpro will also support documentation efforts and are designed improve our efficiency and accountability.

Each topic-specific SER Work Group is chaired by ACMG's methodologist, and SER members are identified through a "call for volunteers." The EBG Work Group Chair is selected by the ACMG Board of Directors, and members for each topic-specific EBG Work Group are chosen by that group's Chair. Each EBG Work Group Chair is approved by the ACMG Board of Directors. Also, the SER and EBG Work Groups submit the names of newly nominated members to both the Board of Directors and the ACMG Conflict of Interest Committee.

GUIDELINES IN PROGRES

Guideline Development: N.I.P.S.

After the Topic Selection Committee voted to review the production of a N.I.P.S. Guideline, our full time methodologist began shepherding this topic through the formal Evidence Based Guidelines Program at ACMG. The N.I.P.S. Working Group Chairs and other members of the teams were chosen using the guidelines passed by the ACMG Board. The members of the N.I.P.S. SER Work Group are Monica McClain (Chair), Danielle LaGrave, Elizabeth Barrie, Marco Leung, and Nancy Rose.

[2] ACMG's programs are always eager to reduce travel expenses whenever possible, so this first in-person meeting was held during the American Society of Human Genetics' Annual Meeting. Many ACMG leaders and members also attend this partner organization's important gathering each year. As a result, hotel and flight costs for participants were negligible.

The N.I.P.S. EBG Workgroup was simultaneously established and is led by Jeff Dungan as Chair. Members include Kristin Monaghan, Susan Klugman, Bob Best, Mike Bashford, Yassmine Akkari, Angelika Erwin, Sandra Darilek, and Monica McClain.

Both work teams drafted a N.I.P.S. Guideline Goals Document in May 2020. It was approved by the ACMG Board during a Board Meeting later that same month.

The N.I.P.S. SER Work Group received the "Key Questions" from the EBG work group in June of this year. The methodologist and medical librarian are now working on the medical literature database search. The first SER Work Group meeting is slated to take place on August 31. That meeting will begin the review of the identified literature and will ultimately produce a summary document used by the EBG work group to produce their recommendations and the final Guidelines.

The leadership of both ACMG and the ACMG Foundation has stated repeatedly that the EBG Program must move topics through this process as expeditiously as possible. Early estimates (pre-COVID) indicated that a final draft of the N.I.P.S. guideline could be completed in 2020. However, the cancelation of the committee's face-to-face meetings in March (originally planned for ACMG's Annual Meeting), the need to pivot in the time of COVID-19, and the need for a larger staff team have all moved a draft of this guideline back approximately six months.

Guideline Development: "Peds ES/GS (CA, DD, ID)"

An important milestone was crossed in March of this year, when ACMG's first-ever systematic evidence review from a new EBG Program Work Group was published in our Journal, Genetics in Medicine. The SER on the topic, "*Systematic evidence-based review: outcomes from exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability",* now informs the ongoing development of clinical practice guidelines by the same topic's EBG Work Group.

The Evidence Based Guideline Work Group members for the "Peds ES/GS Guideline" are Fuki Hisama (co-chair), Kandamurugu Manickam (co-chair), Sawona Biswas, Danny Miller, Laurie Demmer, Hutton Kearney, Timothy Yu, and Monica McClain. This team is meeting twice monthly and expects to have a completed draft Guideline by December 1, 2020.

Guideline Development: PKU

New topics are continuously submitted to the Topic Selection Committee, which meets quarterly to review new submissions. In March of 2020, the Topic Selection Committee was asked to consider updating an older ACMG Diagnosis and Management Guideline written in 2014, covering the topic of Phenylalanine hydroxylase deficiency. The Committee voted to advance the request, and both an SER and EBG Work Group was formed to review the PKU topic.

The SER team for PKU met in both July and August to begin their investigation of the Key Questions proposed by their counterparts on the EBG Work Group, and a manuscript is expected to be submitted for publication early in 2021. The PKU's SER Work Group members include Monica McClain (Chair),

Moises Fiesco-Roa, Judith Hobert, Pamela Arn, Jinglan Liu, April Dione Adams, Paul Rothberg, Melissa Murfin, and Lawrence Wong.

The EBG team, now waiting on the work of their PKU team counterparts, is comprised of Jerry Vockley (Chair), Wendy Smith (co-chair), Kim McBride, Susan Berry, Barbara Burton, John Mitchell, Henry Mroczkowski, and Monica McClain.

LOOKING BACK, LOOKING FORWARD

Since the launch of the Foundation's EBG Program just one year ago:

- A Topic Selection Committee of Board volunteers has been established and quickly voted to review half a dozen critical topics in the genetic and genomic medical field.
- Several topics were both prioritized and slated for review, and others were identified as needing more information for a full EBG to be developed.
- Our leadership took the important step of hiring the first full time EBG Program staff member.
- ACMG has seen the successful and ongoing use of our online Topic Submission Form. We are proud to enable the public to be involved in advancing scientific knowledge.
- Six Working Groups of volunteers began their research and are operating in partnerships to produce Evidence Based Guidelines on three separate and important topics.
- Our first EBG Program related publication was released in our medical Journal.
- The Foundation's webpage dedicated to the EBG Program continues to offer updates, providing the public, returning and potential donors, and our partner groups with an unrestricted view into the workings of ACMG and the EBG Program.

There is a great deal of work yet to do, and we must increase our capacity to push through the important studies we know are on the horizon. The program is working, the systems are in place, and our volunteers are eager and committed. Now we need donors from all sectors of the economy to help us advance the best science and understanding of genetics and genomic medicine.

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Interested parties may also 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 donors help to expand the program.

[i] The Foundation is seeking additional donors so ACMG might greatly increase our staffing for the program, Evidence Based Guideline production, and our time-to-publication. Interested companies and organizations are asked to contact Karl Moeller at kmoeller@acmgfoundation.org. To support this effort as an individual, visit the Foundation's "donate now" page and select the "Diagnosis and Treatment Guidelines" option from the list of possible designations.