FOUR YEAR LAUNCH PLAN for the EVIDENCE BASED GUIDELINE DEVELOPMENT PROGRAM

(JULY 2019 – JUNE 2023)

AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS and the ACMG FOUNDATION

Abstract

This document establishes is a comprehensive and sustainable program that develops, publishes, and regularly updates evidence-based guidelines that address the validity and utility of clinical genetic services that will inform clinical and laboratory practices.

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Evidence Based Guideline Development Program

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INTRODUCTION

Consumers, health care providers, and the companies and governments that pay for medical services are witnessing a rapidly expanding use of genetic and genomic tests in clinical care. The American College of Medical Genetics and Genomics, ACMG (the College), and its sister organization, the ACMG Foundation for Genetic and Genomic Medicine (the Foundation), believe the benefits of this expanding use of genetics and genomics in health care must be established through sound science.

Today, geneticists have uncovered as many as 7,000 rare heritable disorders that vary widely in our ability to not only establish diagnoses but also provide treatments. At the same time, technologies that once focused only on targeted genetic testing for a handful of conditions are now able to accomplish genomic sequencing that can reveal far more information about a patient. While increasing access to this greatly enhanced genetic information is largely positive for both individual diagnoses and population-level science, the clinical use of genetic and genomic test results must be seen in a framework of structured evidence-based reviews. This is especially true given that 1) the rare nature of many genetic disorders limits the robustness of available data and evidence, and 2) much of the research linking a specific condition to a gene or set of genes is ongoing.

Medical science has long depended on formal and unbiased reviews of the scientific and clinical evidence before the development of clinical practice and payer coverage policies. The efficacy of stents in cardiac patients, the benefits of a hip replacement procedure in the elderly, and the value of vaccinations in both adults and children are just a few of the hundreds of thousands of procedures that benefit from ongoing analysis through a strict and impartial review of evidence. Evidence-informed guidelines are used by millions of payers, providers, and patients all over the world to avoid futile treatments, to set payment rates, to save lives and resources.

For more than two decades, The American College of Medical Genetics and Genomics (ACMG), with the support of the ACMG Foundation, has been a leader in setting standards on the use of genetic and genomic tests and disease interventions. We have partnered with those in medical genetics services, product development, patent support services, and public health field. Our programs have leveraged our joint capacity as partner organizations to more rapidly provide evidence-based clinical and laboratory practice guidelines to the health community. We also continue to consider ways to partner with government organizations and foundations to support guideline development.

Given the pressing need for evidence-based guidelines in genetic and genomic medicine, the ACMG's new strategic plan commits to producing evidence-based practice guidelines that will inform medical geneticists and those from medical specialties who care for individuals who have (or may develop) genetic conditions. The College developed and tested a standardized process

through which evidence-based guidance in genetics and genomics can be delivered in a manner that ensures timely and science-based results.

At a January 2019 ACMG Board meeting, board members requested that Foundation staff review, refine, and further develop a draft Evidence Based Guideline (EBG) Charter with the goal of producing a formal and ongoing system for EBG development. The Board sought to "**create a comprehensive and sustainable program that develops, publishes, and regularly updates evidence-based guidelines that address the validity and utility of clinical genetic services that will inform clinical and laboratory practices."**

ACMG will “develop and publish guidelines that enhance the practice of medical genetics." The Board asked Foundation staff to seek $1,000,000 in base-year funding to support the EBG program. This document draws directly from the Board's January 2, 2019 "ACMG Charter for Evidence Based Guidelines" and from the longstanding history of ACMG’s prior accomplishments in this area.

The ACMG Board has set a goal of completing two EBG’s in the first year of the program and to “ramp up the number of published guidelines as the program progresses.”

PROGRAM DEVELOPMENT - OVERVIEW

The ACMG Foundation is leading the effort to launch the College Board’s directive in a manner that 1) supports the Board's vision, 2) builds on ACMG's proud tradition in this area, and 3) establishes a sustainable and “scalable” program that can be presented to a wide range of possible donors or funders. This four-year launch plan outlines a sustained EBG guideline development program. The Foundation draws heavily on our past and includes the 2014 process for evidence-based guideline development that was established and approved by the College Board.

An initial budget estimate for this program over the four-year launch period is $5 million. In addition to the budget breakdown for the $5 million effort, a scaled-down “minimum” budget shows the resources that would be required to support even a modest sustained effort in this area. College and Foundation Board members are aware they may need to scale the program differently and stand ready to adjust funding, staffing models, or other aspects of the program based on the outcomes achieved by the Foundation’s development efforts and the willingness of outside organizations to support the project.

ACMG's GUIDELINE DEVELOPMENT HISTORY

The College has published EBGs for more than 20 years. Through grants and support raised by the Foundation, guidelines from the College have generally fallen into two areas: technical (laboratory) guidelines and guidelines for clinical services.

Nearly 10 years ago, the ACMG Board recognized the need to establish and approve a detailed process for guideline development. ACMG's earliest guidelines were generally published when funding was available, and when a critical medical need was identified. A more formal process

was needed to ensure ACMG's expertise continued to follow protocols and ensure "trustworthy" findings.

The trustworthiness of our guidelines has always been a priority. The Foundation was established, in part, by the College Board's desire to limit the influence of donors from the programs they funded, including the development of guidelines. Specifically, a Foundation account called the *Diagnostics and Treatment Guideline Fund* (DTG Fund) was established under the banner of the Foundation's 501(c)(3) tax status. The Guideline fund serves as a pool that can provide broad support for guideline development – separate and apart from direct donor involvement. Foundation funding for guideline development is accomplished under its 501(c)(6) tax status and is free and clear of donor influence.

Foundation staff members recommend a three-pronged approach to funding the development of EBG's in the future. ACMG Foundation staff members should 1) work with policy leaders to explore government funding for guideline development that, if secured, could be directed to the College2) explore donations or direct-to-the-college grants from charitable foundations; and, 3) interested individuals or corporations who agree with the need for genetics and genomics guidelines might contribute directly to the DTG Fund.

PROCESS FOR CLEAN HANDS

The current process for guideline development was approved by the ACMG Board in 2014 after several years of study and review. A comprehensive 49-page document entitled, *"Protocol Manual for Evidence Based Guideline Development"* is posted on the EBG Program website: https://www.acmgfoundation.org/ebg

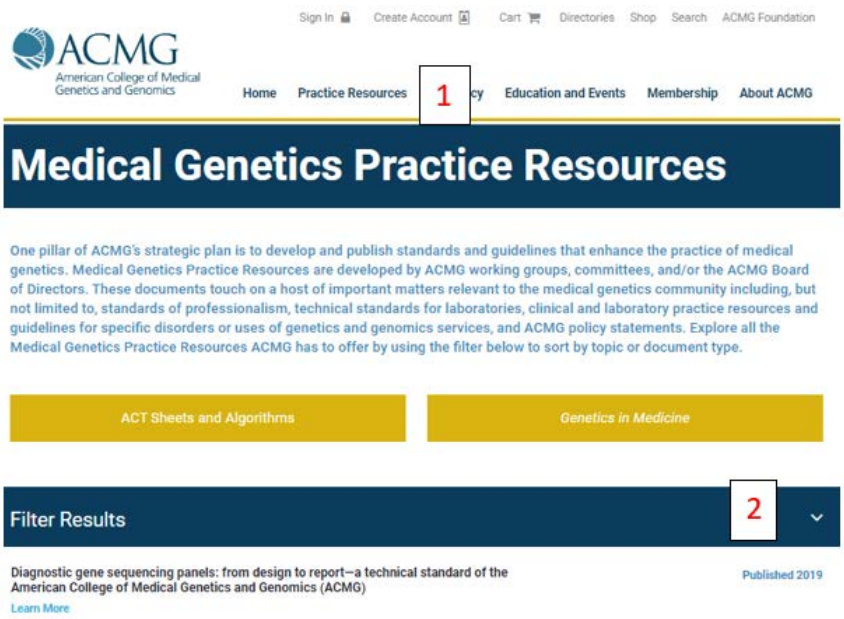
An overview of the Foundation's related Guideline Fund which serves as the clearing house for all support directed at the program is also published on that webpage.

The 2014 manual ensures that ACMG's ongoing guideline development reflects the best methods, recommended standards, and practices associated with this type of work. ACMG's current process follows the recommendations of the Institute of Medicine (IOM), the Council of Medical Specialty Societies (CMSS), and the now de-funded National Guideline Clearinghouse (NGC) at the Agency for Healthcare Research and Quality (AHRQ)[1]. During the development of the Protocol Manual, other standards and best practice considerations were offered by Board members and leaders in the genetics and genomics field.

ACMG's Technical Guidelines are voluntary standards established "as an educational resource to assist medical geneticists in providing accurate and reliable diagnostic genetic laboratory testing consistent with currently available technology and procedures in the areas of clinical cytogenetics, biochemical genetics and molecular diagnostics."

[1] Today the ECRI Institute's "Guideline Trust" is managing a "portal to expertly vet EBG briefs and scorecards" in an effort to fil the void left after AHRQ's Clearinghouse lost federal funding. See ECRI.org.

ACMG's Clinical Guidelines are also voluntary standards and serve the same educational purpose for the broader medical and patient community. Guidelines and policy statements are available at ACMG.net.



To read ACMG's past guidelines, follow the Practice Resource tab (1) on the ACMG.net webpage, then select the downward 'carrot' (2) from the blue "Filter Results" bar. Readers can select lab or clinical guidelines and statements, as well as public policy statements. Each document listed provides a hyperlink to the publication.

RENEWED EFFORT NEEDED

The National Institutes of Health has long tracked the rapidly falling cost of sequencing the human genome.[2] Lower genetic and genomic testing costs across the testing industry, the proliferation of laboratories capable of handling this once-rare capability, a new eagerness of the general public to undergo genetic and genomic tests, and new opportunities to identify emerging targeted therapies for inherited conditions are all driving an explosion of genetic and genomic testing.

Unfortunately, the results of these increasingly common tests are not always accurate, accurately interpreted, or well understood. Media outlets probed the validity of some direct-to-consumer results by submitting (perhaps unfairly) canine samples for testing and were returned reports about the sample's human traits. Moreover, some in-hospital test results have led members of the health care community to recommend unproven or unnecessary treatments. Not long ago, cardiologists did not fully appreciate the genetic science behind Brugada Syndrome and, as a result, recommended expensive and unnecessary treatments[3]. Similarly, two recent articles in Genetics in Medicine[4] [5]showed the value of determining the clinical relevance of some genes on disease hereditary.

[2] https://www.genome.gov/27541954/dna-sequencing-costs-data/

[3] Circulation. 2018 Sep 18;138(12):1195-1205.

[4] "Determining the clinical validity of hereditary colorectal cancer and polyposis susceptibility genes using the Clinical Genome Research Clinical Validity Framework" (ACMG online publication Dec. 7/2018)

[5] "Clinical validity assessment of jeans frequently tested on hereditary breast and ovarian cancer susceptibility sequencing panels" (ACMG online publication Dec. 3/2018).

ACMG's evidence-based guidelines are needed now more than ever to:

1) Inform decision-making in the medical community,
2) Help direct sound policy decisions regarding coverage of tests and resulting treatments that may be warranted for individual patients, and
3) Guide sound decision-making among stakeholders, including patients, clinicians, healthcare systems, insurance providers, and payors.

ACMG's trusted, established, and Board-approved method for systematic evidence reviews means that our guidelines can be used by policy makers, healthcare organizations, health insurers, and other payors to make informed decisions.

COSTS AND FUNDING

Successful evidence-based guideline development is both an extensive and expensive process requiring a dedicated team of staff who work closely with volunteer committees. ACMG's recent efforts in guideline development depend on expert medical staff, key partners, Board leaders, paid fellows, and volunteers — and are generally limited only by the availability of consistent funding.

A successful process develops an untainted, leading-edge recommendation for the best possible plan of action based on all available facts. The same process may also discover that not enough is known to make a science-based determination. In either case, this process includes:

- Selection of a relevant and timely topic (often from an extensive list of possible topics),
- Development of key questions that the larger community needs answered,
- Systematic evidence reviews of the literature and other information sources,
- Input from an unbiased expert panel,
- A group consensus process,
- Practice guideline development,
- Dissemination of the guidelines to the leaders in the field who will benefit from them, and,
- Continued review of guidelines and updating as needed.

While many of the ACMG Board and Committee members who helped in the development of past guidelines volunteered their time, each publication of ACMG guidelines has required significant funding and staff resources. To lead and expedite guideline development, particularly on a much larger scale than ACMG has managed in the past, new full time staff will be needed. ACMG has a total of thirty staff across all program areas, none of whom are currently engaged in guideline development beyond the CEO and a part time Methodologist. New talent, and sustained, dedicated, and predictable funding is critical if ACMG hopes to regularly publish new guidelines while updating past findings.

ACMG has successfully engaged with outside entities to develop evidence reviews and used that data to complete medical genetics and genomics guidelines in the past. The Board and staff should continue such relationships even after a formal EBG program is established. Two examples help to highlight this practice:

ACMG appointed an active member (Maren T. Scheuner, MD, MPH, FACMG) to sit on the Blue Cross Blue Shield Association's ***Technical Evaluation Center***. Through this vehicle, BC/BS Association is said to work on about 460 medical reviews each year. Dr. Scheuner has been instrumental in directing their work in the genetics area. She is now serving a third three-year term.

Though our federal connections at the Department of Health and Human Services, ACMG advised the ***Evidence-based Practice Center (EPC) Program*** of the Agency for Healthcare Research and Quality (AHRQ) to work on an evidence review for the long-term management of Phenylketonuria (PKU). AHRQ fully funded the evidence review, and ACMG then produced the guideline in short order based on the AHRQ data.

TOPIC SELECTION PROCESS

Critical to the entire program is the process of topic selection. This function remains in the College and stays separate and apart from the fundraising efforts led by the Foundation. Given the pace of medical research in the genetics and genomics field, it is likely that the need for new or updated guidelines cannot be met by the resources available to produce them.

A Topic Selection Committee of the College Board and its members will work independently from the Foundation to establish a list of high priority target topics for guideline development. Topics selected for guideline development will be generated from an ACMG nominations process managed by a Topic Selection Committee of the Board. Topics will also come by recommendation of the Technical and Laboratory Standards and Professional Practice and Guidelines Committee Chairs. These will be selected from already published guidelines, points to consider documents, Board policy statements and consensus opinions as appropriate and by consensus with the methodologist.

The topics selected will ensure the College is focused on producing or updating the most high-value and high-impact Guidelines, Clinical Practice Resources, Laboratory Practice Resources, or ACMG Position Statements.

SYSTEMATIC EVIDENCE REVIEW and GUIDELINE DEVELOPEMENT

A systematic evidence review (SER) will inform the EBG work group. A fulltime methodologist who will work collaboratively with a small group assembled to review the published data will lead a standardized SER process. Their review will focus on questions deemed to be of high value for an EBG. The EBG work group will develop PICOT questions to form the basis for a publication of the evidence. The SER work product will also be used to frame the EBG guideline and the associated clinical application of these findings. Importantly, the assembled EBG work group will remain in contact to regularly discuss new developments in the field around which their guideline was written. This will ensure the ability to reassemble and respond rapidly to changing published evidence.

FUNDING GOALS AND PURPOSE

Given the increased need for reliable, unbiased, and up-to-date guidelines, the Foundation will seek financial support from industry, private donors, foundations, federal partners and other funders who are committed to the rational use of genetic technologies. This SER and EBG program launched on August 8, 2019 and the first meeting of the new Topic Selection Committee was held soon after. The first topic selected by the Committee was Non-invasive Prenatal Screening and its value in average risk patients. The EBG work group and SER workgroups are being formed and the PICOT questions will soon be decided on. Some possible donors are aware of (and excited about) this effort.

Funding will specifically support the strengthening and professionalization of ACMG's evidence-based guidelines program through the hiring of dedicated staff. the College will be working hard to increase the production of new and updated guidelines so that the medical community has access to much-needed genetics and genomics EBG's. ACMG hopes to gain commitments for $5 million over the next four years to support the full staffing of this program.

The first budget chart can also be found at https://www.acmgfoundation.org/ebg and is listed at "*Goal Budget: ACMG Evidence Based Guidelines Program - Draft 2019 to 2022*". The document shows a detailed estimated budget outlay over the next four and a half years. This model assumes an aggressively staffed EBG program. The staffing estimates are based on our past expertise in the area of guidelines development and assume a team of staff is available by the second full grant year to shepherd 4-6 EBG guidelines through a review process annually (with Board support) while revisiting several older guidelines as needed.

The second funding chart, "*Accordion (minimum) Budget: ACMG Evidence Based Guidelines Program - Draft 2019 to 2022*" details an estimated budget outlay over the next 4 years with a minimally staffed but still credible EBG program. Under this funding model, 2-4 new guidelines could be reviewed (with significant support from Board and member volunteers), and 1-2 older guidelines could be reviewed and updated. This second funding chart more closely reflects the most recent EBG program at the College, but still expedites the effort with additional in-house staff members.

While an initial group of committed donors is needed to get the program off the ground in the first few years, success will attract additional funding possibilities. Government or foundation funds could be sent directly to the College if ACMG's EBG Program is successful in the coming years.

FUNDRAISING CONSIDERATIONS

The draft budgets give an idea of the totals needed to run the program.

In order to grow the EBG program to its largest possible capacity, both the College and the Foundation should support efforts to attract resources to this effort. While the Foundation will lead all development efforts on behalf of the College, both groups should explore ways to attract funding from as many sources as possible.