ACMG
American College of Medical Genetics and Genomics
Translating Genes into Health®

February 4, 2015

Recent Activities of The American College of Medical Genetics and Genomics

The American College of Medical Genetic and Genomics (ACMG) is the professional home to over 1750 members, nearly 80% of whom are board certified clinical and laboratory geneticists and genetic counselors; it is the only nationally recognized medical organization dedicated to improving health through the practice of medical genetics and genomics. The College's mission includes the following major goals: 1) to define and promote excellence in the practice of medical genetics and genomics and to facilitate the integration of new research discoveries into medical practice; 2) to provide medical genetics and genomics education to fellow professionals, other healthcare providers, and the public; 3) to improve access to medical genetics and genomics services and to promote their integration into all of medicine; and 4) to serve as advocates for providers of medical genetics and genomics services and their patients. This report highlights key activities of the ACMG between September 2014 and January 2015.

Leadership, Advocacy and Practice Updates

Changes to the Board of Directors Coming this Spring: The following individuals will begin new terms on the ACMG Board of Directors on April 1, 2015: Gerald Feldman, MD, PhD, FACMG (President); Gail E. Herman, PM, PhD, FACMG (Past President); Louanne Hudgins, MD, FACMG (President-Elect); Tina Cowan, PhD, FACMG (Biochemical Genetics Director) Mary E. Norton, MD, FACMG (Clinical Genetics Director); Mary C. (Katy) Phelan, PhD, FACMG (Cytogenetics Director) and Amy Roberts, MD, FACMG (Clinical Genetics Director).

Secondary Findings and Clinical Genome-Scale Sequencing — ACMG Issues a New Policy Statement Informed by Results of Member Survey: As follow-up to ACMG's March 2013 "Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing," in January 2014 we surveyed our membership to learn more about their opinions and practices related to the reporting of incidental (secondary*) findings when pursuing clinical genome-scale sequencing. The member survey corroborated many of the original ACMG recommendations about secondary findings. Most agreed that seeking and reporting of secondary findings in the ACMG list of genes is consistent with medical standards, has sufficient evidence, and for adults, the benefits generally outweigh potential harms. However, there was lack of agreement regarding benefits versus harms for children, and lack of agreement about the potential impact on healthcare resources. Contrary to the original 2013 ACMG recommendations, the majority of respondents agreed that patient preferences regarding seeking and reporting of secondary findings should be considered when clinical exome or genome sequencing is pursued, including the ability for patients to opt out of receiving a sequencing report with such findings. (Earlier in 2014, ACMG did, in fact, update its initial recommendations to include an "Opt Out" option.) The ACMG Survey Results article concluded that, "according to its membership, the ACMG should continue to update a minimal list of medically, actionable genes to be assessed when clinical exome or genome sequencing is performed, but informed consent is necessary and reporting of secondary findings should be optional. More research is needed to understand the multi-level factors that may influence optimal implementation of reporting secondary findings."

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A new policy statement, "Updated Recommendations Regarding Analysis and Reporting of Secondary Findings in Clinical Genome-Scale Sequencing," is also published in the January 2015 issue of *Genetics in Medicine.* Key points of the statement include:

- When clinical genome-scale (e.g. WES, WGS) sequencing is performed, written informed consent should be obtained by a qualified genetics healthcare professional, describing the nature of the test and addressing such points as interpretive uncertainty, privacy, possible impact on other family members and the inevitable generation of data not immediately relevant to the clinical indication for sequencing. At the time of testing, the patient should be made aware that, regardless of the specific indication for testing, laboratories will routinely analyze the sequence of a set of genes deemed to be highly medically actionable so as to detect pathogenic variants that may predispose to a severe but preventable outcome.
- Patients should be informed during the consent process that, if desired, they may "opt out" of such analysis. However, they also should be made aware at that time of the ramifications of doing so.
- In accordance with the recent recommendations of the Presidential Commission for the Study of Bioethical Issues, as well as a lack of clear consensus in the ACMG membership survey, the board recommends that the same policy should be adhered to in children as in adults; i.e., routine analysis of a set of selected genes to identify pathogenic variants associated with severe but preventable disease should be routinely performed. Parents should have the option during the consent process to opt out of such analysis in their children.
- At this time, given the practical concerns and inherent difficulty of counseling patients about the features of each disorder and gene on an ever-changing list, it is not feasible for patients to be offered the option of choosing only a subset of medically actionable genes for analysis. Thus, the decision regarding routine analysis should apply to the entire set of genes deemed actionable by the ACMG.

The ACMG Policy Statement concludes, "The ACMG recognizes the complex nature of policies surrounding genome-scale testing and that positions will continue to evolve and change in response to new knowledge, new technologies, and ongoing input and discussion with our membership and the broader medical community. The ACMG will continue to explore these issues in the best interest of patients. A multidisciplinary working group has been formed to develop a process for updating and maintaining the list of genes to be routinely analyzed for secondary findings."

* ACMG is adopting the use of the term Secondary Findings instead of Incidental Findings based on the Presidential Commission for the Study of Bioethical Issues report, *Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research and Direct-to-Consumer Contexts* and the subsequent *Clinician Primer: Incidental and Secondary Findings.* ACMG will use the term "Secondary Findings" in the future while not retroactively changing earlier documents and recommendations, which had used the term "Incidental Findings."

Advocacy Updates: A very large amount of seemingly coordinated activity is occurring with regard to regulatory oversight and legislation related to genetic and genomic testing. FDA has recently proposed bringing laboratory developed tests (LDTs) under its control by declaring clinical laboratories providing LDT-based testing as manufacturers, though there are significant questions about whether their regulatory authority extends to services and procedures developed and provided locally by clinical laboratories and how this would impinge on practice of medicine exemptions that exist for this in regulatory programs. A coalition of medical associations, including ACMG, working with the American Medical Association (AMA) recently requested that FDA withdraw their guidance. It is widely accepted in the laboratory community that FDA has not provided sufficient information to even judge many of their proposals, including how they would regulate test development and delivery within their quality systems program that includes elements such as good manufacturing practices, which transfer poorly from a classical manufacturer's model to a clinical laboratory environment. In addition to responding directly to FDA, ACMG has also been involved in discussions with the House Energy and Commerce Committee that has broader interest in FDA oversight as relates to the 21st Century Cures Act, which seeks to incentivize innovation to get therapeutics for rare diseases into the marketplace and also deals with FDAs legislative authorizations. ACMG's letters and public comments can be found at: https://www.acmg.net/ACMG/Advocacy/Regulations_and_Legislation/FDA_Laboratory_Developed_Tests__LDTs_/ACMG/Advocacy/Regulation_and_Legislation/FDA_Laboratory_Developed_Tests__LDTs_.aspx?hkey=96383854-318c-4ac8-bb77-b5f81fd9463b

ACMG Guidelines Accepted into National Guidelines Clearinghouse: As the trusted experts in setting standards for the practice of genetic and genomic medicine an ACMG priority has been for our guidelines to be accepted by the National Guidelines Clearinghouse (NGC). NGC is a public resource for evidence-based clinical practice guidelines that is part of the Agency for Healthcare Research and Quality within the U.S. Department of Health and Human Services. The following five ACMG clinical practice guidelines have been accepted into the NGC, and can be found on the ACMG website or at http://www.guideline.gov:

- Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors.
- Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions.
- Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities.
- ACMG practice guideline: lack of evidence for MTHFR polymorphism testing.
- Evaluation of the adolescent or adult with some features of Marfan syndrome.

Grant and Contract Updates

The Clinical Genome Resource Project (ClinGen)

ClinGen's GenomeConnect Gives Patients a Role in Genomic Data Sharing Efforts: As ACMG moves into the second year of its role in the Clinical Genome Resource (ClinGen) — an NIH-funded project to increase the amount of genotype and phenotype data available for research and patient care — ClinGen is broadening its data capturing efforts through the launching of "GenomeConnect," an initiative that involves patients in the gathering and sharing of phenotypic and genotypic data. Using an online "patient portal" individuals can register for an account, fill out a health questionnaire and upload a copy of their genetic test reports for the GenomeConnect coordinator to deidentify, curate and prepare for sharing with genomic databases, such as ClinVar, the central public database used by the ClinGen project, and dbGAP.

To date, a key challenge has been the difficulty of obtaining detailed phenotypic data from individuals with particular genomic variants; GenomeConnect was designed to help overcome this challenge. There is also the ability for GenomeConnect team members to re-establish contact with patients and request additional information about their health information that is critical for the clinical interpretation of genome-based testing. Enrollment in GenomeConnect is open to anyone who has undergone genetic testing or has a particular genetic diagnosis, as well as their family members. Participants create an account, provide consent online and participate using their computer, smartphone or tablet. Using patient-friendly terminology, the initial health questionnaire, developed by ClinGen investigators, is a general review of systems intended to capture a broad snapshot of the participant's health. Over time, participants may be offered additional questionnaires in order to obtain more specific information about anything on their original questionnaire.

GenomeConnect is expected to increase the pace of genomic discoveries by bringing information together from a large number of patients. The project will be ongoing, enrolling an unlimited number of participants. Additional information, including a copy of the consent form, health questionnaire and outreach materials for providers to share with patients, is available at www.clinicalgenome.org.

ClinGen /DECIPHER Public Meeting to be held in May: Formerly known as the International Collaboration for Genomics Annual Meeting, this year the ClinGen Project will be collaborating with colleagues from DECIPHER to co-host a two-day meeting, "Advancing Genomic Medicine through Collaboration and Data Sharing. The meeting will be held at the Renaissance Washington, DC Downtown hotel, May 27-28, 2015. More information can be found at http://www.clinicalgenome.org/events-news/events-conferences/2015-clingen-meeting/. (DECIPHER, the **D**atabas**E** of genomi**C** var**I**ation and **P**henotype in **H**umans using **E**nsembl **R**esources, is an interactive web-based database supported by the Sanger Institute in the UK, which incorporates a suite of tools designed to aid the interpretation of genomic variants.)

Data Acquision and Dissemination: Data is rapidly accumulating in ClinVar and ClinGen-DB. Clinical domain curation is now able to engage in their tasks. Curation groups are now in place for cardiological genetics, metabolic disease, and cancer susceptibility genetics. Somatic cancer is rolling out over the next 2-4 weeks.

The Newborn Screening Translational Research Network (NBSTRN)

Now in its seventh year at ACMG, the mission of the NICHD-NIH funded Newborn Screening Translational Research Network (NBSTRN) is to improve the health outcomes of newborns with genetic or congenital disorders through an infrastructure that allows investigators access to robust resources for newborn screening research. The NBSTRN infrastructure includes three tools; the Virtual Repository of Dried Blood Spots (VRDBS), the Longitudinal Pediatric Data Resource (LPDR), and the Region 4 Stork Database (R4S). Recently, the NBSTRN launched the ELSI Advantage, a new resource for NBS researchers that addresses ethical, legal and social issues. This tool is comprised of an interactive website that contains information on IRB's, NBS related FAQ's, and templates to customize your own Consent Forms. Visit the NBSTRN.org for more information.

The National Coordinating Center for the Regional Genetic Service Collaboratives (NCC)

NCC is now in its 10th year; program evaluation continues, along with work related to the inclusion of quality genetic services into the Essential Health Benefits in the Affordable Care Act. A 2-year non-competitive renewal was just submitted to MCHB/HRSA, with movement towards more direct service support models for genetics care (providers and patients.) In addition, work continues on developing telegenetics service capacity, ACT Sheet clinical decision support tools for primary care, and transition of genetics patients from pediatric to adult care, a problem not faced previously for many genetics patients who lacked interventions that increased their likelihood of surviving to experience transition. We are also in the process of assessing whether genetic services are adequately addressed in the Affordable Care Act (ACA) and the integrated delivery systems like accountable care organization (ACOs) to ensure quality genetics services.

Details on several current projects that meet the objectives described above follow: 1) The Medical Home Excellent Care Coordination Qualitative Interview Project focuses on 24 clinical settings (a mix of primary, specialty, community care settings) nominated as excellent care coordination practices. Each of the 24 clinical settings was interviewed and a forthcoming qualitative report will highlight the components excellent care coordination. 2) The Medical Home Information and Resources Project interviewed individuals and families to better understand what type(s) and at what time point(s) (diagnosis, school age, etc.) information and specific resources would be most useful. A follow-up survey to a broader cohort of individuals with genetic conditions will be fielded in the spring 2015. 3) The Second Year Evaluation Report was provided to HRSA and two follow-up surveys are planned, one of genetics professionals, the other of consumers. These will provide the beginning of a longitudinal cohort of data on the experience of individuals with genetic conditions and their providers. 4) ACA Implementation work continues around components of genetic conditions in integrated care systems and ACOs (as mentioned above), and a 7-10 state analysis of coverage elements of three model conditions (PKU, fragile X, syndrome and sickle cell disease) will be completed by June 2015.

***Genetics in Medicine* Updates**

The following College-generated papers were published in ACMG's monthly journal, *Genetics in Medicine (GIM),* between September 2014 and January 2015. Two publications on this list are indicated as "online only" but associated with a specific issue of *GIM.* Due to the generation of an increasing number of clinical and laboratory guidelines, as well as the frequent need for updates, *GIM* is now publishing many revised guidelines, as well as some longer ones, as "online only." These are listed in the Table of Contents of the relevant issue of *GIM,* indexed, citable and searchable in PubMed, and posted on both the ACMG and *GIM* websites.

Kishnani P, Austin SL, Abdenur JE, Arn P, Bali DS, Boney A, Chung WK, Dagli AI, Dale D, Koeberl D, Somers MJ, Wechsler SB, Weinstein DA, Wolfsdorf, JI, and Watson MS. **Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics.** *Genet Med* 16(11): online only (November 2014) PMID: 25356975
https://www.acmg.net/docs/ACMG_Practice_Guideline_for_GSD_Type_I_GIM_online_Nov2014.pdf

Bean L and Pinar Bayrak-Toydemir; on behalf of the ACMG Laboratory Quality Assurance Committee. **American College of Medical Genetics and Genomics Standards and Guidelines for Clinical Genetics Laboratories, 2014 edition: technical standards and guidelines for Huntington disease.** *Genet Med* 16(12): online only (December 2014) PMID: 25356969
https://www.acmg.net/docs/ACMG_Revised_SG_for_HD_testing_GIM_OO_Dec2014.pdf

Hampel H, Bennett RL, Buchanan A, Pearlman R and Wiesner GL; for a Guideline Development Group of the American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee and of the National Society of Genetic Counselors Practice Guidelines Committee. **A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment.** *Genet Med* 17(1):70-87 (January 2015) [PMID: 25394175]

ACMG Board of Directors. **ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing.** *Genet Med* 17(1):68-69 (January 2015) [PMID: 25356965]

Scheuner MT, Peredo J, Benkendorf J, Bowdish B, Feldman G, Fleisher L, Mulvihill JJ, Watson M, Herman GE and Evans J. **Reporting genomic secondary findings: ACMG members weigh in.** *Genet Med* 17(1):27-35 (January 2015) [PMID: 25394173]

Use the URL http://feeds.nature.com/gim/podcast/current to access *Genetics in Medicine's* monthly Podcast, know as *GenePod,* to hear live a discussion of a timely (and often controversial) article from the most recent published journal.

Meetings and Education Updates

ACMG Monthly Live Online Genomics Case Conferences Continue to Grow in Popularity: Case Conferences provide a valuable opportunity to learn from an exchange of ideas by a multidisciplinary team of experts, all of whom bring unique perspectives to solving a clinical problem. But what if the issue is clinical genome-based sequencing and one does not work at center that is already versed in offering this service? To make these cutting-edge clinical discussions accessible to everyone, in November 2014, ACMG launched a very popular series of monthly live genomics case conferences, reaching physicians, geneticists, laboratory personnel, genetic counselors and other healthcare professionals via a live, interactive webcast. Each conference features a team from a selected institution leading a discussion, and answering viewer questions about intriguing, complex or difficult patient cases with a main focus on the adaptation of exome or genome sequencing technology in clinical care — from pediatric to cancer, adult, cardiac and reproductive genetics. Case Conferences to date have included:

Detecting Complex Disease Mechanisms and Unusual Disease Presentation Using Whole Exome Sequencing, hosted by GeneDx

Ending Diagnostic Odysseys: Clinical and Research Experiences with Genomic Sequencing, hosted by Partners Healthcare

Clinical Exome Sequencing Solving Medical Mysteries, hosted by Baylor Medical Center

The Case Conferences are held on the third Wednesday of each month from 2:00-3:00 PM ET. The next session, slated for February 18th, will be presented by the University of North Carolina at Chapel Hill School of Medicine. Online attendance is free and ACMG members are given first access to registration. Those unable to attend the live Case Conference can view a tape of the session at a later date on the ACMG Learning Center at www.acmg.net/education. *ACMG is grateful to QIAGEN Bioinformatics and the Ingenuity Clinical Decision Support Platform for their support of this educational series.*

The 2015 Annual Clinical Genetics Meeting, to be held March 24-28 in Salt Lake City, UT, is once again surpassing all prior records — from scientific abstracts submitted to registered participants and exhibitors. Meeting highlights include:

- The 46th Annual March of Dimes Clinical Genetics Conference, "Interdisciplinary Approaches to Disorders of Sex Development: From Genes to Quality of Life"
- Two Short Courses: Cancer Genetics and Clinical Exome Sequencing
- New Sessions on Billing and Reimbursement in the Genomic Era and Prenatal/Perinatal Diagnostic Dilemmas
- Joint Plenary Session with the Society for Inherited Metabolic Disorders (SIMD) on March 28th.

Meeting details can be found at www.acmgmeeting.net.

The 2015 Genetics and Genomics Review Course will be held in Tampa, FL, June 18-21, 2015. On-site and online options will be available. Registration information can be found at https://www.acmg.net/ACMG/ACMG_Events/Genetics_and_Genomics_Review_Course_2015/ACMG/ACMG_Events/2015_Genetics_Review_Course/GRC_Hompage.aspx?hkey=5bd262fd-6bf8-4c01-b2a3-aefea5a27895.

ACMG's Learning Center, a new website dedicated exclusively to genetic and genomic education for medical geneticists and non-geneticist providers is not only up and running, but new content is being added each week. The site houses interactive and multi-media course offerings, online events, opportunities for paced learning, discussions and more. It will also be searchable for course content, including PDF files and the Knowledge Direct Direct-to-WEB content for just-in-time learning support. Users will be able to track their CME credits and view personalized reports on course activity and test scores. The URL is ACMG.net/education.

ACMG Foundation Updates

• The ACMG Foundation will present record number of awards during the 2015 Annual Clinical Genetics meeting, including the gifting of funds for fellowship and clinical research training, as well as recognizing outstanding recent and lifelong scholarly and leadership accomplishments.

• The 2015 Summer Genetics Scholars Program has been funded by several generous donations and we are in the process of matching rising second-year medical students with mentors at two-dozen institutions, for 6-8 week hands' on experiences in medical genetics and genomics.

• Fundraising efforts continue so that ACMG may continue to expand its educational initiatives in genomic medicine, with a diversity of new learning opportunities for genetics and non-genetics health professionals, trainees and a growing pipeline.

Further information about all ACMG activities and a full listing of our press releases and clinical genetics laboratory and practice guidelines can be found on our website at www.acmg.net. The ACMG website now houses an Online Learning Center, as well. ACMG uses Facebook, LinkedIn, YouTube, and Twitter to augment its educational and advocacy missions, provide news and resources related to medical genetics, and improve communication with and among its members and stakeholders.

Submitted by Michael S. Watson, MS, PhD, FACMG
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