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

February 1, 2017

Summary of Recent Activities of The American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG) is the only nationally recognized medical organization dedicated to improving health through the practice of medical genetics and genomics. ACMG represents approximately 2000 members, nearly 80% of which are board certified clinical and laboratory geneticists and genetic counselors. ACMG's mission, as redefined in the 2015 Strategic Plan, is to "develop and sustain genetic and genomic initiatives in clinical and laboratory practice, education and advocacy." Three guiding pillars underpin ACMG's activities: 1) Clinical and Laboratory Practice: Establish the paradigm of genomic medicine by issuing statements and evidence-based or expert clinical and laboratory practice guidelines and through descriptions of best practices for the delivery of genomic medicine. 2) Education: Provide education and tools for medical geneticists, other health professionals and the public and grow the genetics workforce. 3) Advocacy: Work with policymakers and payers to support the responsible application of genomics in medical practice. This report highlights key activities of the ACMG between September 2016 and January 2017.

ACMG Elects New Directors for Terms Beginning April 1, 2017

Fellows of the College recently elected the following individuals to the ACMG Board of Directors. They will take office at the end of the 2017 ACMG Annual Meeting in March in Phoenix, with a formal news release to be distributed at that time.

President-Elect: Anthony R. Gregg, MD, MBA, FACOG, FACMG
Director, Clinical Genetics: Laurie Demmer, MD, FACMG
Director, Molecular Genetics: Elaine Lyon, PhD, FACMG
Director, Cytogenetics: Catherine Rehder, PhD, FACMG

As part of our Board transition, Louanne Hudgins, MD, FACMG will assume the role of President and Gerald (Jerry) Feldman, MD, PhD will become Past President.

Advocacy, Policy and Practice Activities

• *ACMG issues new position statement, "Laboratory and Clinical Genomic Data Sharing is Crucial to Improving Genetic Health Care",* which advocates for extensive sharing of laboratory and clinical data derived from individuals who have undergone genomic testing. ACMG believes that this "…ensure[s] that our patients receive the most informed care possible; information that underpins healthcare service delivery should neither be treated as intellectual property nor as a trade secret when other patients may benefit from the knowledge being widely available." Recognizing that information about genetic diseases is accumulating rapidly and information science is empowering the use of 'big data' with the goal of improving patient care and advancing personalized medicine, our Statement maintains that responsible sharing of data will provide both a resource for clinical laboratories and treating physicians who interpret test results, and also clinical validity data that can benefit laboratories and manufacturers who are developing new tests and testing platforms. Contributing research and clinical laboratory data to public databases for clinical curation is essential before advances can make it to patients. (A copy of the Statement can be found here, http://www.nature.com/gim/journal/vaop/ncurrent/pdf/gim2016196a.pdf, and is appended to this Report.)

• *ACMG SF v2.0 is Released:* To promote standardized reporting of medically actionable information from clinical genomic sequencing, in 2013 ACMG published a minimum list of genes to be reported as secondary findings (SF) during exome or genome sequencing. Shortly thereafter, a working group (SFWG) was established to develop a process for curating and updating the list of recommended genes. Our new Policy Statement, "Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing, 2016 Update" adds four new genes to the SF list of recommended secondary findings and eliminated one of the earlier genes. The new secondary findings list – *ACMG SF v2.0* – includes 59 medically actionable genes recommended for return in clinical genomic sequencing.

To attain ACMG SF v2.0, between March 2015 and May 2016 six nominations to the SF list were received and evaluated. One of these, *PTCH1* associated with Gorlin syndrome/nevoid basal cell carcinoma syndrome, did not achieve SFWG consensus for addition due to insufficient evidence that knowledge of a known or expected pathogenic variant in the gene would alter medical management. Four other genes: *BMPR1A* and *SMAD4*, associated with juvenile polyposis; *ATP7B* associated with Wilson disease; and *OTC* associated with ornithine transcarbamylase deficiency received a unanimous vote from SFWG members for addition to the list. One gene currently on the list, *MYLK* associated with familial thoracic aortic aneurysm and dissection, was removed.

Moving forward, the SFWG plans to accept nominations from other medical specialty organizations. The ACMG also intends to develop resources to assist clinicians in medical management based on specific Secondary Findings. (This updated Policy Statement can be found at http://www.nature.com/gim/journal/vaop/ncurrent/pdf/gim2016190a.pdf.)

• *Genome Editing in Clinical Genetics, Points to Consider:* The newest Statement released by the ACMG Board of Directors notes that genome editing, including CRISPR/Cas9, is an important new technology that enables geneticists and researchers to edit parts of the human genome. It acknowledges that genome editing offers great promise for the future treatment of individuals and families with genetic disorders, but it also raises major technological and ethical issues that must be resolved before clinical application. With the potential for the rapid advance of this approach, the pressure to apply it clinically should not be underestimated. In its Statement, the ACMG Board of Directors strongly encourages broad public debate regarding the clinical application of genomic editing and is appointing an *ad hoc* committee to recommend specific areas where it can contribute to this debate. (A copy of ACMG's Point to Consider is appended to this report, and can also be found at *http://www.nature.com/gim/journal/vaop/ncurrent/pdf/gim2016195a.pdf*)

• *ACMG's NCC Publishes State Statutes and Regulations on Dietary Treatment of Disorders Identified Through Newborn Screening:* In 2008, a report, "State Statutes and Regulations on Dietary Treatment of Disorders Identified Through Newborn Screening", was published by ACMG that detailed each state's statues and regulations on coverage of medical food. With funding support from the Health Resources Services Administration (HRSA), the National Coordinating Center for the Regional Genetic Service Collaboratives (NCC) recently partnered with the Catalyst Center to update this report. The 2016 Report details how individuals with genetic conditions, identified through newborn screening, who require Modified Low Protein Foods (MLPFs), medical foods, dietary supplements, enteral feeding supplies, or other dietary treatments may receive coverage (http://www.nccrcg.org/docs/NCC/ACA/Products/Dietary_Treament_Supplements_2016.pdf).

Due to the complex nature of the healthcare payment system, the report breaks down state-specified mandated coverage of medical foods by employer-sponsored health insurance, Medicaid, and other related services (such as WIC, Title V, or relief funds).

This project is supported by the Health Resources and Services Administration (HRSA) of the US Department of Health and Human Services (HHS) under Cooperative Agreement #U22MC24100, The National Coordinating Center for the Regional Genetic Service Collaboratives, $799,999 (6/15-5/17).

• *ACMG's PKU Practice Guideline is Now Available in Six Foreign Languages:* The ACMG Foundation for Genetic and Genomic Medicine, with generous support from BioMarin Pharmaceutical Inc., recently published translations of ACMG's "Phenylalanine Hydroxylase Deficiency: Diagnosis and Management Guideline" in Spanish, French, Turkish, German, Portuguese (Br) and Italian. All six translated guidelines are available on the ACMG website at (http://www.acmg.net/ACMG/Publications/Practice_Guidelines/ACMG/Publications/Practice_Guidelines.aspx?hkey=b5e361a3-65b1-40ae-bb3e-4254fce9453a). The original guideline was written by members of ACMG's Therapeutics Committee, who advocated for the translations to be undertaken to expand outreach to international providers and patients, and to ensure global access and readability of these important practice guidelines for the treatment of patients with PKU worldwide.

• *National Quality Forum Taps ACMG Medical Director for TeleHealth Committee:* ACMG Medical Director, Dr. David Flannery, has been appointed to the National Quality Forum's (NQF) Telehealth Committee. This multistakeholder Committee is charged with conducting a review of existing and potential telehealth quality measures over the next year and identifying the most appropriate way to ensure clinical measures are applied to telehealth encounters to measure quality of care and to guide the future development of telehealth related measures. ACMG has long promoted the importance of telehealth as an effective way to improve access to clinical genetic services — especially when bringing these services to areas lacking in an adequate number of medical genetic service providers. ACMG applauds the NQF in appointing a clinical geneticist with extensive experience in providing telemedicine services to this important Committee.

• *ACMG Reaffirms Recommendations on Genetic Testing Through the* Choosing Wisely® *Campaign: Five Things Patients and Providers Should Question:* ACMG reaffirmed its list of five things patients and providers should discuss regarding genetic testing as part of *Choosing Wisely*®, an initiative launched by the ABIM Foundation in 2012. With the growing number and complexity of genetic tests, the ACMG's *Choosing Wisely*® list provides patients and providers with recommendations on ordering certain genetic tests and for specific clinical scenarios, promoting well-informed genetic testing discussions. The ACMG's *Choosing Wisely*® list, first published in 2015, serves as a valuable patient resource. In reaffirming its recommendations, ACMG also added updated references (http://www.choosingwisely.org/wp-content/uploads/2015/07/ACMG-Choosing-Wisely-List.pdf) . Below are the five topics that address genetic test ordering in ACMG's *Choosing Wisely*® list:

1. Don't order a duplicate genetic test for an inherited condition unless there is uncertainty about the validity of the existing test result.
2. Don't order APOE genetic testing as a predictive test for Alzheimer disease.
3. Don't order MTHFR genetic testing for the risk assessment of hereditary thrombophilia.
4. Don't order HFE genetic testing for a patient without iron overload or a family history of HFE-associated hereditary hemochromatosis.
5. Don't order exome or genome sequencing before obtaining informed consent that includes the possibility of secondary findings.

Note: The items on the ACMG list are provided solely for informational purposes and are not intended as a substitute for consultation with a medical professional. In determining the propriety of any specific procedure or test, patients should consult with their individual clinicians and clinicians should apply their own professional judgment to the specific clinical circumstances presented by each individual patient.

Grant and Contract Updates, plus New NIH-ACMG Fellowship in Genomic Medicine Program Management

ACMG is increasingly integrating the activities of shared interest among the several national projects that it either leads or in which it participates.

• *The National Coordinating Center for the seven HRSA-funded Regional Genetic Service Collaboratives (NCC*) is developing a collaboration with the states and Regional Collaboratives to collect long-term follow-up data on their patients identified in newborn screening programs. Public health programs value data sharing that informs all such programs.

• *The Clinical Genome (ClinGen) Resource*
  - *Curating the Clinical Genome*, the 2016 ClinGen/DECIPHER public meeting was held on the Wellcome Genome Campus, Hixon, Cambridge, UK, June 22-24, 2016 and will return to the U.S. on June 28-30, 2017.
  - Collaborations between ClinGen and state newborn screening laboratories that generate and store genomic variant level and limited clinical data are also in development. States currently acquire their clinical and laboratory information on patients identified through their public health programs, under their Public Health Authorities. Ascertainment of asymptomatic or presymptomatic individuals can provide a novel perspective on penetrance that is not available through clinically ascertained populations.

• *The Newborn Screening Translational Research Network (NBSTRN)* continues multistate newborn screening pilot studies of Pompe disease and MPS-1. Adrenoleukodystrophy pilots began in November 2016.

• *The NIH-ACMG Fellowship in Genomic Medicine Program Management* was just established for physicians interested in acquiring experience in managing research and implementation programs in "genomic medicine". Two

two-year fellowships will be available each year, with an initial application deadline of March 1, 2017. Questions should be directed to Dr. Eric Green at edgreen@mail.nih.gov.

Genetics in Medicine Updates/ACMG Publications

Genetics in Medicine (GIM), ACMG's official journal, has published the following documents of the College since our last Report:

Gregg AR, Skotko BG, Benkendorf JL, Monaghan KG, Bajaj K, Best RG, Klugman S, and Watson MS; on behalf of the ACMG Noninvasive Prenatal Screening Work Group. **Noninvasive screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics.** *Genet Med* 18(10):1056-1065 (October 2016)

Kalia SS, Adelman K, Bale SJ, Chung WK, Eng C, Evans JP, Herman GE, Hufnagel SB, Klein TE, Korf BR, McKelvey KD, Ormond KE, Richards CS, Vlangos CN, Watson M, Martin CL and Miller DT; on behalf of the ACMG Secondary Findings Maintenance Working Group. **Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics.** *Genet Med*, *advance online publication* (November 17, 2017) http://www.nature.com/gim/journal/vaop/ncurrent/pdf/gim2016190a.pdf

Sharer JD, Bodamer O, Longo N, Tortorelli S, Wamelink MMC, and Young S; a Workgroup of the ACMG Laboratory Quality Assurance Committee. **Laboratory diagnosis of creatine deficiency syndromes: a technical standard and guideline of the American College of Medical Genetics and Genomics.** *Genet Med advance online publication* (January 5, 2017) http://www.nature.com/gim/journal/vaop/ncurrent/pdf/gim2016203a.pdf

ACMG Board of Directors. **Laboratory and clinical genomic data sharing is crucial to improving genetic health care: a position statement of the American College of Medical Genetics and Genomics.** *Genet Med, advance online publication* (January 5, 2017) http://www.nature.com/gim/journal/vaop/ncurrent/pdf/gim2016196a.pdf

ACMG Board of Directors. **Genome editing in clinical genetics: points to consider—a statement of the American College of Medical Genetics and Genomics.** *Genet Med, advance online publication* (January 26, 2017) *http://www.nature.com/gim/journal/vaop/ncurrent/pdf/gim2016195a.pdf*

The following ACMG documents are in preparation:

- Points to Consider in Genomic Screening of Asymptomatic Individuals
- Laboratory Guideline: Selection of Genes in a Gene Panel
- Diagnostic Cytogenetic Testing Following Positive Noninvasive Prenatal Screening Results: An ACMG Clinical Laboratory Practice Resource
- Joint Hypermobility Syndrome: Differential Diagnosis and Recommendations for Management
- ACMG/CGC Joint Standards and Guidelines for Interpretation and Reporting of Acquired Copy Number Variants and Copy-Neutral Loss of Heterozygosity in Neoplastic Disorders

Meetings and Education Updates

• *2017 Annual Clinical Genetics Meeting to be held March 21-25, 2017 in Phoenix, AZ:* At the time of this Report, ACMG has received a record-breaking number of submitted abstracts and conference registrants. The 2017 Annual Meeting will include the 48th Annual March of Dimes Clinical Genetics Conference, "The Undiagnosed Diseases Network: Changing the Paradigm of Rare Disease Diagnosis, Treatment and Research". Among other program highlights are: Two Pre-Conference Short Courses (NAMA at ACMG 2.0 and Variant Interpretation from the Clinician's Perspective); Poster Sessions; Special Exhibit Hall Events; Satellite Symposia; Exclusive Trainee Sessions; an All-New Student Day; and for the first time in 2017, live streaming video of selected sessions. Visit www.acmgmeeting.net for program information and ongoing updates, meeting registration and hotel reservations.

• *The 2017 ACMG Genetics and Genomics Review Course (GGRC)* will be held May 4-7, 2017 in Tampa, Florida. Designed for individuals preparing for the ABMGG certification examinations, the GGRC is also an excellent refresher course for practitioners looking to update their skills and knowledge, and those seeking medical genetics CME. Provided as a live face-to-face course and offered in streaming live video, attendees have two ways to participate in this popular educational update. Course information and registration can be found by using the GGRC link on the right side of the Education page on the ACMG website at http://www.acmg.net/ACMG/Education/ACMG/Education/Home.aspx?hkey=b43f18f0-61b9-485c-a87c-b3b2c547f255.

• *ACMG's Live Monthly Case Conferences*: There are two ongoing series, with all conferences are delivered via webinar and then archived in the On-Line E-Learning section of the ACMG Genetics Education (http://www.acmg.net/ACMG/Education/ACMG/Education/Home.aspx?hkey=b43f18f0-61b9-485c-a87c-b3b2c547f255).

- Genomics Case Conferences occur on the third Wednesday of each month at 2:00 PM ET.

- Adult Genomics Case Conferences occur on a quarterly basis (February, May, August and November), on the first Tuesday of the month.

- Plans are underway to begin a Carrier Screening Genomic Case Conference in 2017, with support from the Claire Altman Heine Foundation. Additional details will be posted on the ACMG Genetics Education website as they become available.

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
ACMG Liaison to the National Advisory Council for the National Human Genome Research Institute, NIH

ACMG STATEMENT | Genetics inMedicine

Laboratory and clinical genomic data sharing is crucial to improving genetic health care: a position statement of the American College of Medical Genetics and Genomics

ACMG Board of Directors[1]

Genet Med advance online publication 5 January 2017

Key Words: genomic data sharing; genomic databases; gene variant databases; genotype:phenotype correlations

There exist 5,000–7,000 rare genetic diseases, each of which harbors considerable clinical variability. None are common individually. In addition, more common diseases with genetic influences may have rare variants associated with them. Vast allelic heterogeneity lies at the foundation of most genetic diseases, the effects of which are compounded by background genomic variation that may further affect clinical presentation.

The considerable variation in clinical presentation and molecular etiology of genetic disorders, coupled with their relative individual rarity, makes it clear that no single provider, laboratory, medical center, state, or even individual country will typically possess sufficient knowledge to deliver the best care for patients in need of care. Even in the relatively rare situation in which pathogenic variants are few (e.g., sickle cell anemia), variants in other alleles may contribute to the genomic variation and clinical manifestations of disease. For more genetically complex conditions such as cystic fibrosis, in spite of decades of study, as many as 10% of cases have a *CFTR* variant so rare that it is represented in only one or two people in current databases, a situation paralleled in many genetic diseases.[1,2]

To ensure that our patients receive the most informed care possible, the American College of Medical Genetics and Genomics advocates for extensive sharing of laboratory and clinical data from individuals who have undergone genomic testing. Information that underpins health-care service delivery should be treated neither as intellectual property nor as a trade secret when other patients may benefit from the knowledge being widely available. It is similarly important for understanding the risks associated with genetic test results that place asymptomatic/presymptomatic individuals at high risk of developing a genetic disease. Sharing data in this precompetitive space will provide both a resource for clinical laboratories interpreting test results and clinical validity data that can benefit device manufacturers developing new tests and testing platforms. Contributing to public clinical databases in the precompetitive space recognizes that information about genetic diseases is dense and accumulating rapidly, and that information science is empowering the use of "big data." Further, the shift to public databases being populated by de-identified case-level information from electronic health records will speed the time to "publication" of what are essentially case reports in real time. This process can also reduce the time period during which one might be able to protect trade secrets. Recognizing the importance of data sharing for both research and clinical care, the National Institutes of Health has established a genomic data-sharing policy for its funded investigators.[3]

Responsible sharing of genomic variant and phenotype data will provide the robust information necessary to improve clinical care and empower device and drug manufacturers that are developing tests and treatments for patients.

- Broad data sharing is necessary and will improve care by making available the best data possible by which:
  - Key clinical attributes of the phenotype of those with genetic diseases can be described
  - The qualitative strength of the association between genetic diseases and the underlying causative genes can be established

[1]American College of Medical Genetics and Genomics, Bethesda, Maryland, USA. Correspondence: Michael S. Watson (mwatson@acmg.net)
The Board of Directors of the American College of Medical Genetics and Genomics approved this statement on 26 September 2016.

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  - The classification of genomic variants across the range of benign to pathogenic can be established
  - Differences in variant interpretation among laboratories can be reconciled
  - The appropriate classification of variants of uncertain significance can be made
  - Standards used in variant classification can be improved
- Data sharing will provide the scientific community, health-care providers, and industry with the best data on which:
  - Web-based systems for integrated clinical decision support are based
  - Secondary studies using these data are powered
- Data sharing will offer significant financial benefits by which:
  - More standardized approaches to coverage and reimbursement policies can be made
  - The expensive duplication of previously resolved, but unpublished, research efforts currently occurring among pharmaceutical companies can be reduced

The analytical challenges of migrating and integrating clinical and laboratory data across the genome are daunting. Standardization of laboratory and clinical information will enable:

- Data compatibility
- Interoperability between information systems

Importantly, broad data sharing is compatible with the critical imperative of protecting the privacy of individual health-care information and the security of data systems holding that information. For data to be shared safely for patients and providers, systems are required that:

- Ensure the security of databases, whether centralized or federated
- Ensure the privacy of patient and family medical information
- Provide transparency in the documentation of data-sharing transactions

Clinical-grade standards by which claims about gene/disease associations and the clinical significance of variants are made (e.g., data provenance, database versioning, and expert information curation) are central to a shared genomics data system. However, the need to deliver safe and effective care for those with or at risk for rare diseases, despite weak data for most variants and inevitable conflicts in data interpretation, requires balancing regulatory oversight with the need to provide services regardless of how well a rare disease is understood.

Due to the vast amount of data now being generated by genomic testing, genetic diseases will offer the opportunity to develop the framework for a national learning health-care system because the shared experiences of those caring for these patients continually contribute to improvements in delivering services to this population. A learning health-care system that facilitates access to diagnostic, treatment, and outcomes data to inform the care of today's patients requires a paradigm shift in how we share data to be used in research and clinical practice. Academic medical centers have already begun to address how providers within their systems can use information about their patients to benefit other patients. This approach could be made national in scope to the benefit of patients everywhere. The National Institutes of Health has already made such data sharing a priority in the research that it funds. However, to accomplish these goals, and to ensure that the tremendous amounts of information now being generated are not wasted, our community must both demonstrate the will to share data broadly and develop the mechanisms to do so easily. These efforts will require support and participation from clinical laboratories, clinicians, regulatory agencies, researchers, and patients to ensure success in improving patient care through genomic medicine.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

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2. Rehm HL, Berg JS, Brooks LD, et al.; ClinGen. ClinGen–the Clinical Genome Resource. *N Engl J Med* 2015;372:2235–2242.
3. National Institutes of Health. *NIH Genomic Data Sharing Policy*. http://gds.nih.gov/03policy2.html. Accessed 8 November 2016.

ACMG STATEMENT | Genetics inMedicine

Genome editing in clinical genetics: points to consider—a statement of the American College of Medical Genetics and Genomics

ACMG Board of Directors[1]

Genet Med advance online publication 26 January 2017

Key Words: biotechnology; CRISPR/Cas9; gene editing; genetic engineering; gene drives

Medical geneticists provide diagnosis, counseling, management, and treatment for individuals and families affected by genetic disorders. These disorders are due to genetic variations that may range from gain or loss of entire chromosomes to alterations involving only a single DNA base pair. Management options have typically included anticipatory guidance, surveillance for complications, surgery, dietary management, medications, and, in some recent instances, gene replacement therapy. Progress in these areas has brought comfort, hope, and relief to many patients and families who live with genetic conditions, some of which have devastating effects on health and well-being.

Because the underlying causes of these conditions may be changes in the structure of a gene or a region of the genome, the question has been raised as to whether it is possible to alter the genetic code in an affected individual to alleviate the pathology. In principle, this could be done in somatic cells to restore function at the tissue level, or it could be done in the embryo, both to treat that individual and to remove the variant from the germline of that individual. Until recently, this kind of approach was technologically out of reach, but with the advent of genome editing approaches, especially CRISPR/Cas9, it is becoming increasingly feasible. CRISPR/Cas9 is an RNA-guided nuclease system of bacterial origin that can be engineered to target a specific sequence in the genome where the Cas9 protein causes a precise double-strand break. Subsequent DNA repair by the cellular machinery results in either imprecise repair by the nonhomologous end-joining or precise repair by template-driven homology-directed repair. Genome editing is an area of very rapid technological change, so what is not possible today could well become a reality in the very near future. As a consequence, although the American College of Medical Genetics and Genomics (ACMG) is focused on current clinical practice, the ACMG Board of Directors feels compelled to issue these points to consider regarding the potential clinical application of genome editing.

Points to consider

1. ACMG applauds the research applications of genome editing technologies, which are proving to be of great value in developing disease models and studying disease mechanisms. However, the current limitations in these technologies—such as off-target effects—must be overcome prior to any clinical application.
2. Application of genome editing technologies to alter pathogenic variants in somatic cells offers promise in the treatment of individuals with disorders due to single-gene variants that primarily affect specific tissues, such as liver or blood cells. As with any new clinical intervention, clinical application of genome editing technology will require stringent medical and genetic review. Among the concerns that must be addressed are the needs to ensure that:
   a. The underlying pathogenic variant has been corrected to a form that will not be pathogenic.

[1]American College of Medical Genetics and Genomics, Bethesda, Maryland, USA. Correspondence: Michael S. Watson (mwatson@acmg.net)
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   b. No other genetic variations have been introduced in the process of editing the pathogenic variant.
   c. The cells that have been edited have not acquired other genetic variants as part of the process of treatment, for example, during cell culture.
   d. The cells treated do not have epigenetic marks that will result in abnormal function if transplanted back into an individual.
3. Application of genome editing at the level of the embryo raises many technical and ethical concerns, including:
   a. The risk of off-target effects of genome editing may have unpredictable consequences to the embryo and, because the germ line is involved, to future generations as well. Any potential adverse effects could have far-reaching consequences that could take years or even decades to recognize.
   b. The consequences of editing a pathogenic variant may have unknown epigenetic effects that may alter normal patterns of gene expression in some tissues.
   c. The decision as to which specific genetic variants should be subject to genome editing needs further discussion at a societal level. Some variants that are associated with highly penetrant disorders with major adverse effects on health and quality of life might seem like compelling candidates for therapeutic editing. It is inevitable, however, that consideration will also be given to editing variants associated with phenotypes that are not fully penetrant and for which effects on quality of life are less clear. Ultimately, one can foresee efforts to edit variants that are associated with nondisease traits or contribute to multifactorial disorders in unpredictable ways. Such issues are not typically of concern in the management of children or adults with genetic conditions, but will become critical if gene editing in the embryo is contemplated.

In light of these potentially serious and far-reaching concerns, the ACMG Board of Directors believes that genome editing in the human embryo is premature and should be subject to vigorous ethical debate and further refinement of technological issues.

CONCLUSION

Genome editing offers great promise for the future treatment of individuals and families with genetic disorders, but also raises major technological and ethical issues that must be resolved before clinical application. The potential for rapid advance of this approach, and the pressure to apply it clinically, should not be underestimated. The ACMG Board of Directors strongly encourages broad public debate regarding the clinical application of genomic editing and will appoint an *ad hoc* committee to recommend specific areas where it can contribute to this debate.

DISCLOSURE

The authors declare no conflict of interest.