ACMG issues new recommendations for reporting secondary findings in genomic sequencing

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In order to promote standardized reporting of medically actionable information from clinical genomic sequencing, the American College of Medical Genetics and Genomics (ACMG) in 2013, published a minimum list of genes to be reported as secondary findings during exome or genome sequencing. The goal was to identify and manage risks for selected highly penetrant genetic disorders through established interventions aimed at preventing or significantly reducing morbidity and mortality. Subsequently, in 2014, the ACMG established the Secondary Findings Maintenance Working Group (SFWG) to develop a process for curating and updating the list of recommended genes periodically.

Now, the ACMG has released a highly-anticipated Updated Policy Statement, "Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing, 2016 Update: a Policy Statement of the American College of Medical Genetics and Genomics," with four new genes added to the list of recommended secondary findings, along with the elimination of one of the earlier genes from the 2013 list. The new, updated secondary findings list - ACMG SF v2.0 - includes 59 medically actionable genes recommended for return in clinical genomic sequencing.

The updated policy statement is available online ahead of print in ACMG's peer-reviewed journal, *Genetics in Medicine*, at http://www.nature.com/gim/journal/vaop/ncurrent/abs/gim2016190a.html.

"The updated ACMG Secondary Findings list preserves the spirit and intent of the original list," according to David T. Miller, Medical Geneticist at Boston Children's Hospital, and co-chair of the ACMG Secondary Findings Working Group. "This new list also reflects ACMG's commitment to giving the genetics community a voice about which genes to include to further the goal of providing people information that can have a huge impact on their health outcomes," says Miller.

The ACMG Updated Policy Statement includes:

- a review of the rationale in looking for a defined, carefully considered list of genes that warrant scrutiny in individuals undergoing genome-scale sequencing;
- the development of a rigorous process that was undertaken in accepting and evaluating nominations for inclusion or exclusion of genes;
- the list of new genes being added and supporting evidence for adding or removing a gene;
- future areas of focus of the secondary findings maintenance working group, including the possibility of considering pharmacogenomic variants, expanding the nomination process and assessing the impact of secondary findings.

"Applying the new process, while upholding the core principles of the original policy statement, resulted in the addition of four genes and the removal of one gene; one gene nominated did not meet criteria for inclusion at this time in the ACMG SF v2.0," said Michael S. Watson, executive director of the ACMG.

Between March 2015 and May 2016, six nominations to the SF list were received and evaluated by the SFWG. 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. The ACMG Board subsequently reviewed and approved each of the six recommendations of the SFWG: exclusion of PTCH1, addition of BMPR1A, SMAD4, ATP7B and OTC, and removal of MYLK.

The Updated Policy Statement also discusses more details of the adjudication process such as the nomination form, determination of an actionability score, the review process, etc.

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.

According to Dr. Christa Martin, director of the Autism & Developmental Medicine Institute at Geisinger Health System and co-chair of the ACMG Secondary Findings Working Group, "The SFWG is planning on updating the list once or twice per year at most; we're sensitive to the potential burden placed on clinical laboratories who will need to make changes to their bioinformatics analysis pipelines every time the list is updated. In addition, each revision will have a new versioning number and date of implementation for easy reference."

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