Genetics inMedicine | LETTER TO THE EDITOR

ACMG secondary findings 2.0

To the Editor: The authors of the recent American College of Medical Genetics and Genomics secondary findings recommendations[1] are to be commended for the thoughtful and helpful update they have provided to the community. As a member of the original group, I am very gratified to see that our hope for an ongoing, dynamic process of re-evaluation and evolution of that first set of recommendations[2] has been initiated. The original recommendations were viewed by the former committee as only a starting point and we fully expected (and indeed hoped) that the list would change over time. I am supportive of their recommendation to drop *MYLK* and add four other genes (*ATP7B*, *BMPR1A*, *SMAD4*, and *OTC*)—their rationale for these changes is solid.

There are two points in the 2.0 recommendations that deserve clarification and consideration going forward. The first is that the addition of *ATP7B* is notable, as Wilson disease is inherited in an autosomal recessive pattern. This has implications for opportunistic screening that deserve further explication. When clinical genome or exome sequencing (CGES) is performed on trios, phasing of *ATP7B* mutations is trivial, but necessary. If two variants are detected in a parent, phasing will unavoidably disclose that the proband is a carrier if the parent has biallelic pathogenic variants, necessarily divulging carrier status for a recessive disorder in a proband, who may be a minor. If the sequencing is performed by proband-only sequencing, it will necessary to perform reflex testing of the parents for phasing, assuming samples from both are available. If they are not available, it may be necessary and appropriate to report two variants, phase unknown, in the proband. While these consequences of opportunistic screening for Wilson disease are acceptable, it is important that they are explicit and widely recognized.

The second issue is that of the "known pathogenic" (KP) and"expected pathogenic" (EP) variant categories. These categories were supplanted by the subsequently promulgated ACMG/CAP variant interpretation recommendations.[3] The secondary findings 2.0 committee elected to continue to use the KP and EP categories for the time being, but I urge them to expedite a transition to the newer five-category system of the ACMG/CAP pathogenicity criteria.[4] This is for several reasons. The first is that the current KP/EP system potentially leads to an inconsistency in that many EP novel predicted loss of function variants would score as "likely pathogenic" in the new pathogenicity criteria, while it is unclear whether expected pathogenic missense variants should be reported as secondary findings. The second issue is that an explicit decision should be made as to the pathogenicity threshold that is appropriate for reporting secondary findings—likely pathogenic (90–99% probability of pathogenicity) and pathogenic (≥99% probability of pathogenicity), or if they should be limited to only pathogenic. The determination of the reporting threshold is a crucial decision for secondary findings—trading off the false-positive rate versus sensitivity of this opportunistic screen. This trade-off should be made in an explicit manner with the consensus of the community as it inevitably involves trading the benefits and risks of two very different kinds of screening errors.

Neither of these points should be regarded as a criticism of the secondary findings 2.0 recommendations—they are an important advance. I encourage the College and the committee to continue their work in refining and evolving the recommendations going forward.

DISCLOSURE

The author is an uncompensated adviser to the Illumina Corporation, receives royalties from Genentech Inc., and receives honoraria from Wiley-Blackwell for editing.

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