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Response to Biesecker

To the Editor: We appreciate the thoughtful feedback from Dr Biesecker[1] regarding the American College of Medical Genetics and Genomics (ACMG) Secondary Findings v2.0 article.[2] Our efforts as the Secondary Findings Maintenance Working Group rest on the foundation of the first working group.[3] Our goals for SF v2.0 were (i) to engage the wider community in our shared goals of maintaining and revising the list; (ii) to facilitate these efforts through the establishment of an objective process for rendering decisions about genes to add or remove; (iii) to apply that process in the evaluation of genes to be added or removed from the original list; and (iv) to outline potential next steps in this ongoing process.

The working group was also conscious that changes in clinical practice related to the reporting of secondary findings create a challenge for clinicians and laboratories in the form of assimilating new information into consent forms and informatics workflows, not to mention the requirement that everyone involved maintain familiarity with the genes and their associated disorders. We consciously chose to keep the number of changes modest in the first revision in order to minimize the amount of effort needed to adjust to the revised list and prime laboratories and clinics to be prepared for future revisions.

We also added, for the first time, two genes related to inborn errors of metabolism (IEM). These disorders are well studied and often medically actionable. Some of these disorders are not easily detected by newborn screening and present an excellent opportunity to achieve the goal of pre-symptomatic detection. Many IEM are also autosomal recessive disorders. We share Dr Biesecker's concern that there could be confusion about how to report secondary findings in a situation where two variants are identified, but phase cannot be determined. We agree with his suggestion for how to report such results and will continue to consider genes with recessive or X-linked inheritance if they meet the same criteria for other genes currently on the list. We also note that there are orthogonal biochemical tests that could be done for many IEM as follow up to a secondary finding. In the case of Wilson disease, such tests would not require phasing for patients old enough to have evidence of copper overload.

We also considered the issue of variant classification and whether to use the classifications described in the original manuscript (KP/EP) or to modify based on the updated ACMG standards and guidelines for the interpretation of sequence variants.[4] Our working group recognizes that inclusion of some variants as secondary findings could differ between the two systems. We are currently evaluating these differences by comparing classification of several variants, particularly missense variants. Our working group is also concerned about reporting a missense variant that might receive a "likely pathogenic" classification and later be revised to "uncertain" based on new information. Dr Biesecker's point related to the "pathogenicity threshold" is particularly important. In the new ACMG classification system, a novel missense or frameshift mutation would be called likely pathogenic. If that variant was found in a gene where nonsense or frameshift mutations are a typical cause of the disorder, we would be concerned about not reporting. Our working group is eager to work with the community about the best way to approach this, and will explore options for collecting feedback so that the policy represents the genetics community. Our working group is currently discussing these issues, and we anticipate rendering a decision and update within the next year.

DISCLOSURE

C.L.M. is a consultant to The Jackson Laboratory. D.T.M. is a part-time clinical consultant to Claritas Genomics (nonequity professional services agreement).

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